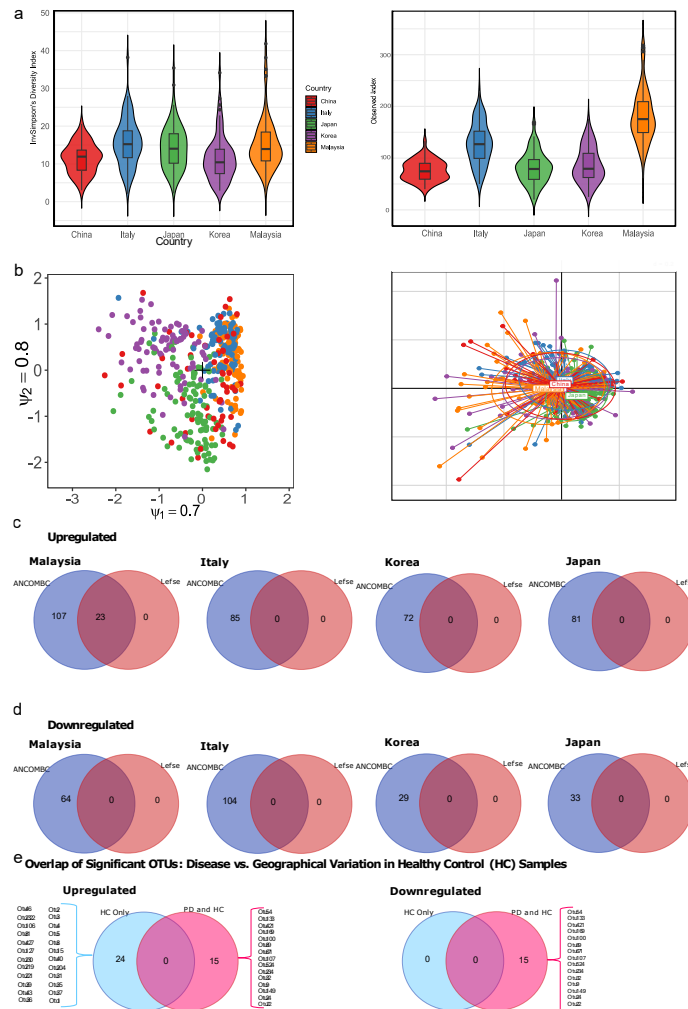


Supplementary Materials

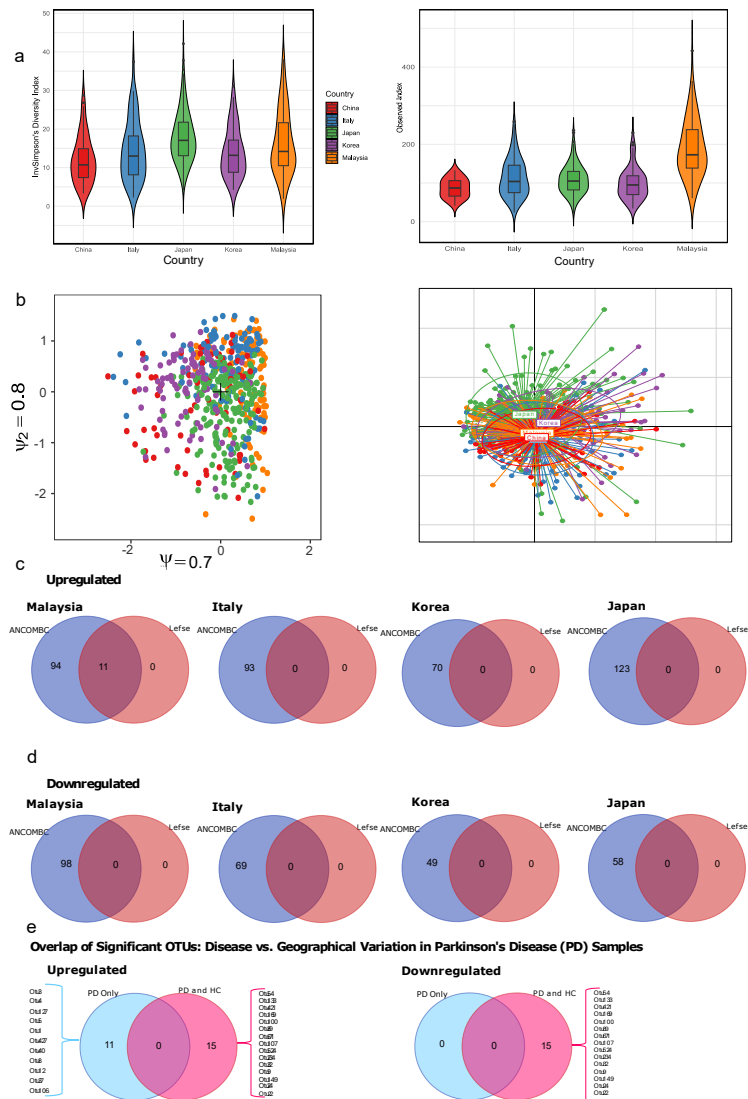
Proinflammatory and GABA Eating Bacteria in Parkinson Disease Gut Microbiome From a Meta-analysis Prospective

Supplementary Figure 1: Microbial Difference Between Geographical Location Within Healthy Control (HC) Samples



a Inverse Simpson richness Diversity Index and Observed Richness Index for species diversity within each study in Healthy Control (HC) samples. b Beta diversity analysis using Residual Variance–Covariance Modelling (RCM) and Rhea of microbial composition within geographical regions in HC samples. c Common upregulated significant species from ANCOM-BC and Lefse results across countries. d Common downregulated significant species from ANCOM-BC and Lefse results across countries. e Common significant species between the main meta-analysis and the HC-specific meta-analysis

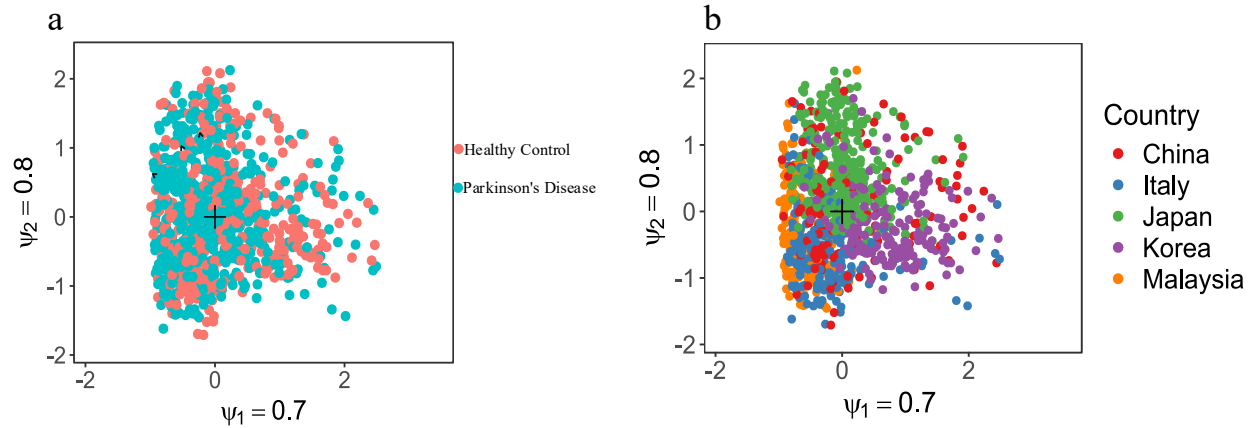
Supplementary Figure 2: Microbial Difference Between Geographical Location Within Parkinson's Disease (PD) Samples



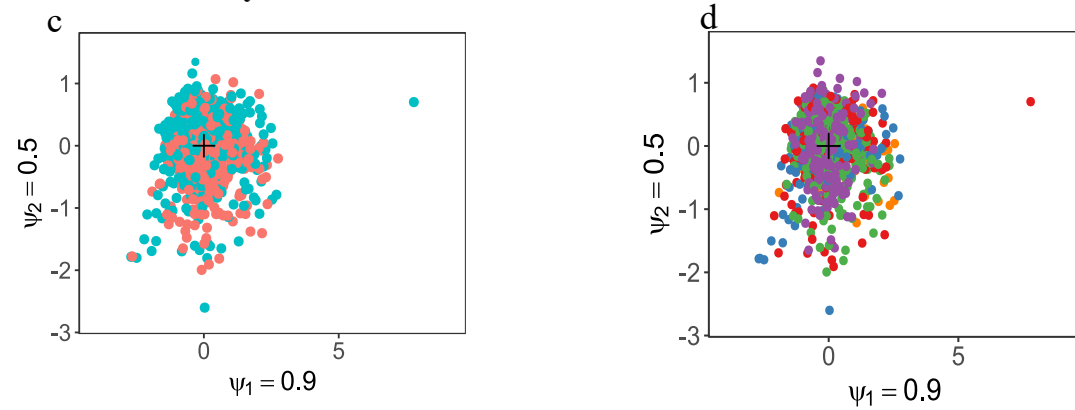
a Inverse Simpson Richness Diversity Index and Observed Richness Index measuring species diversity across studies in Parkinson's Disease (PD) samples. b Beta diversity analysis with Residual Variance–Covariance Modelling (RCM) and Rhea, exploring microbial composition by geographical region in PD samples. c Shared upregulated significant species identified by ANCOM-BC and Lefse across countries. d Shared downregulated significant species detected by ANCOM-BC and Lefse across countries. e. Overlapping significant species between the main meta-analysis and the HC-specific meta-analysis.

Supplementary Figure 3: Residuals and Covariance Modelling Analysis Results

RCM for Country and Conditoin Classification

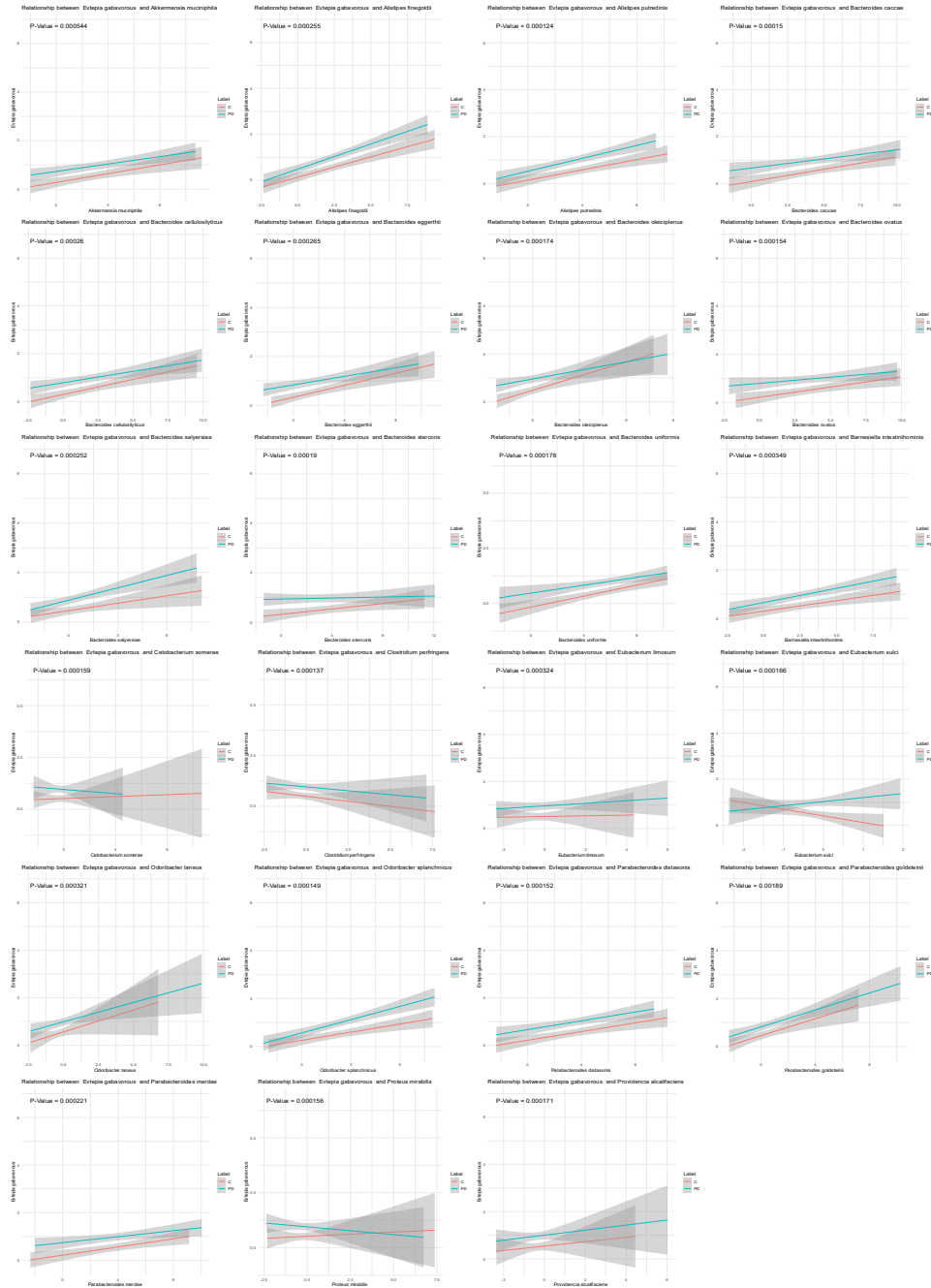


RCM for Country and Conditoin Classification with Confounder Effect



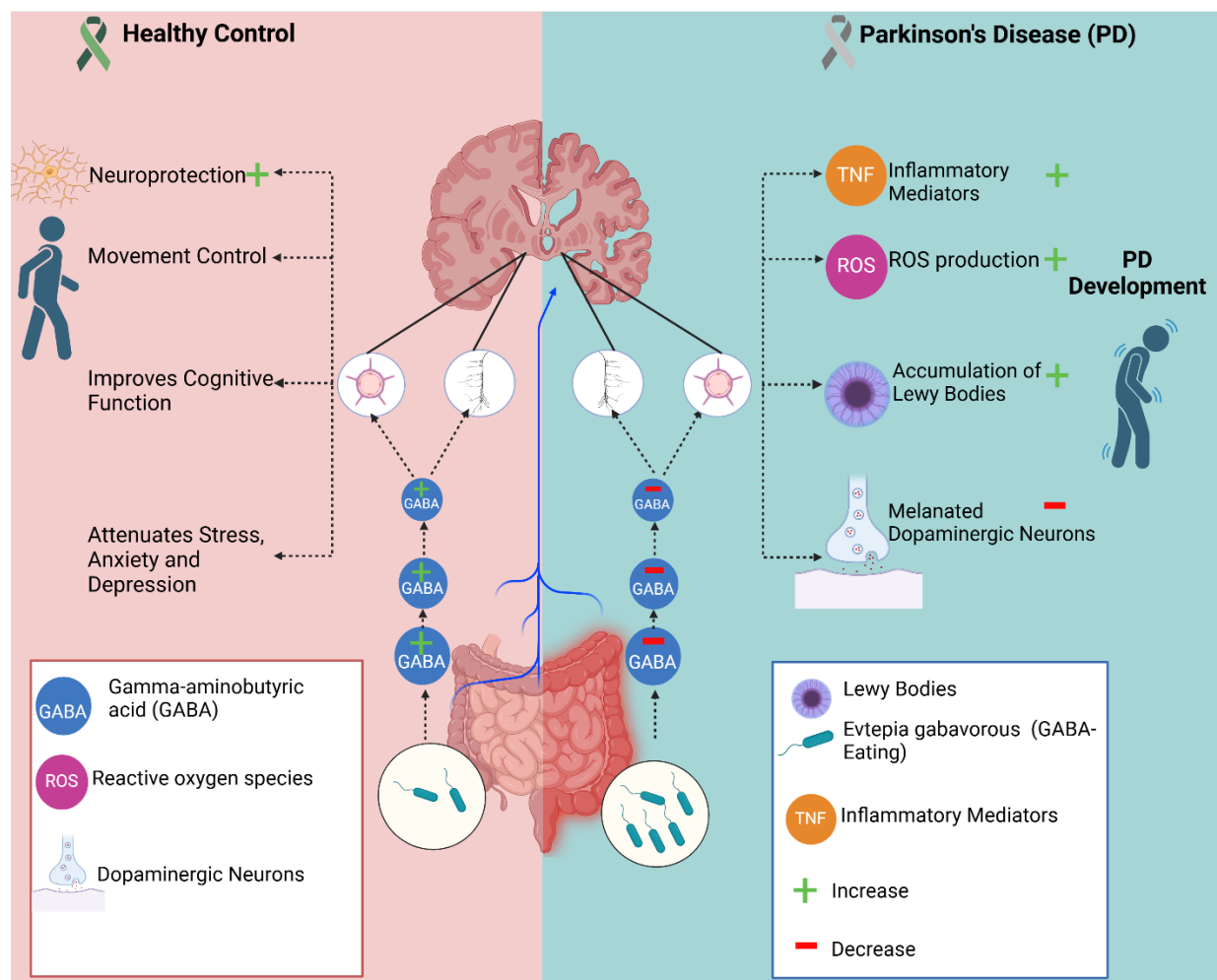
a Residuals and Covariance Modelling (RCM) plot for comparing between Parkinson's disease patients and healthy controls. **b** RCM plot comparing Parkinson's Disease across different countries. **c** RCM plot for comparing between Parkinson's disease across different countries taking the geographical region as a confounder effect. **d** RCM plot for comparing Parkinson's Disease Across Different Countries

Supplementary Figure 4: Linear Model Results for GABA-Eating and GABA-Producing Bacteria



The results of all the linear models to identify the correlation between *Etetepia gabavorous* and all the GABA-producing bacterial species separately

Supplementary Figure 5: Gut-Brain Axis in Parkinson's Disease (PD): Role of GABA and Microbiome Dysbiosis



This illustration compares the gut-brain axis in healthy individuals versus Parkinson's disease (PD) patients. In a healthy state (left), Gamma-aminobutyric acid (GABA) produced in the gut supports neuroprotection, movement control, cognitive function, and emotional well-being. Conversely, in PD (right), reduced GABA levels, driven by the presence of *Evtepia gabavorous* (a GABA-eating bacteria), lead to increased inflammatory mediators and reactive oxygen species (ROS), contributing to Lewy body accumulation, loss of melanated dopaminergic neurons, and PD development. This disruption in the gut-brain communication pathway highlights the significant role of GABA-eating bacteria in neurodegenerative diseases. Created with [BioRender.com](https://www.biorender.com).

Supplementary Table 1: Selection of Studies for Meta-Analysis Using PRISMA. Studies were included based on specific criteria, while exclusions were due to factors such as the use of animal models, lack of associated publications, absence of V3-V4 region coverage, unavailable metadata, or non-16S rRNA sequencing methods.

ID	Included/Excluded	Excluded
PRJNA822998	Included	_____
PRJNA742875	Included	_____
PRJDB8639	Included	_____
PRJNA510730	Included	_____
PRJNA494620	Included	_____
PRJNA915969	Excluded	animal model
PRJNA914678	Excluded	animal model
PRJNA905333	Excluded	animal model
PRJEB56556	Excluded	animal model
PRJEB55464	Excluded	animal model
PRJNA895962	Excluded	animal model
PRJNA881840	Excluded	no paper
PRJNA852512	Excluded	not covering v3-v4 region
PRJEB52086	Excluded	meta-data unavailable
PRJNA838759	Excluded	not 16s
PRJNA834801	Excluded	not 16s
PRJDB12032	Excluded	no paper
PRJDB12031	Excluded	no paper
PRJNA822715	Excluded	meta-data unavailable
PRJNA821099	Excluded	animal model
PRJNA808166	Excluded	not case-control
PRJNA790457	Excluded	not case-control
PRJNA769968	Excluded	not 16s
PRJNA765486	Excluded	animal model
PRJNA764337	Excluded	not case-control
PRJNA762484	Excluded	not 16s
PRJNA756556	Excluded	not 16s
PRJNA753493	Excluded	animal model
PRJEB45549	Excluded	not 16s
PRJNA725395	Excluded	animal model
PRJNA720771	Excluded	no paper
PRJNA673724	Excluded	animal model
PRJNA662100	Excluded	irrelevant topic
PRJNA658581	Excluded	animal model
PRJEB32920	Excluded	not case-control
PRJEB32682	Excluded	animal model

PRJNA601994	Excluded	not covering v3-v4 region
PRJEB30615	Excluded	not covering v3-v4 region
PRJNA594156	Excluded	antibiotic
PRJNA588359	Excluded	animal model
PRJNA574851	Excluded	animal model
PRJNA564818	Excluded	animal model
PRJNA561023	Excluded	meta-data unavailable
PRJNA559904	Excluded	animal model
PRJEB27564	Excluded	antibiotic
PRJNA530401	Excluded	no paper
PRJEB30401	Excluded	meta-data unavailable
PRJNA454894	Excluded	animal model
PRJNA433459	Excluded	not 16s
PRJNA387564	Excluded	irrelevant topic
PRJEB14928	Excluded	not covering v3-v4 region
PRJNA381395	Excluded	mentioned before
PRJEB14674	Excluded	not covering v3-v4 region
PRJNA362482	Excluded	irrelevant topic
PRJEB17694	Excluded	animal model
PRJEB4927	Excluded	454 GS FLX Titanium
PRJNA268515	Excluded	only one sample

Supplementary Table 2: Significant Taxonomic Levels. The microbial taxa enrichment between Parkinson's Disease (PD) samples and Healthy Control (HC) samples

Taxonomic Level	PD Enriched Taxa	HC Enriched Taxa
Phylum	Actinobacteria, Bacteria_unclassified, Synergistetes, Verrucomicrobia, Bacilli, Coriobacteriia, Firmicutes_unclassified, Synergistia, Verrucomicrobiae, Bifidobacteriales, Clostridia_unclassified, Eggerthellales, Lactobacillales, Synergistales.	Bacteroidetes, Alphaproteobacteria, Bacteroidia, Betaproteobacteria, Clostridia, and Negativicutes
Order	Bifidobacteriales, Clostridia_unclassified, Eggerthellales, Lactobacillales, Synergistales	Aeromonadales, Alphaproteobacteria_unclassified, Bacteroidales, Burkholderiales, Clostridiales, Pasteurellales, Selenomonadales.
Family	Akkermansiaceae, Bifidobacteriaceae, Clostridiales_Incertae_Sedis_XIII, Clostridiales_unclassified, Eggerthellaceae, Enterococcaceae, Lactobacillaceae, Synergistaceae.	Bacteroidaceae, Burkholderiales_unclassified, Lachnospiraceae, Pasteurellaceae, Prevotellaceae, Selenomonadaceae, Succinivibrionaceae, Sutterellaceae.
Genus	Bifidobacterium, Cloacibacillus, Clostridium_IV, Desulfovibrio, Eisenbergiella, Enterococcus, Hungatella, Intestinimonas, Lactobacillus, Ligilactobacillus, Limosilactobacillus, Longicatena, Merdimonas, Ruthenibacterium, Parabacteroides, Dysosmobacter, Streptococcus, Negativibacillus,	Acidaminococcaceae_unclassified, Agathobacter, Agathobaculum, Blautia, Clostridiaceae_1_unclassified, Coprococcus, Dialister, Dorea, Faecalibacterium, Fusicatenibacter, Gemmiger, Haemophilus, Lachnospira, Lachnospiraceae_unclassified,

	Flintibacter, Akkermansia, Alistipes, Eggerthella, Neglecta, Clostridiales_Incertae_Sedis_XIII_unclassified.	Lawsonibacter, Megamonas, Muribaculaceae_unclassified, Oscillibacter, Phocaeicola, Prevotella, Roseburia, Ruminococcus, Ruminococcus2, Succinivibrio, Terrisporobacter, Weissella, Anaerotignum, Ruminococcaceae_unclassified, Parasutterella.
Species	Bifidobacterium longum, Streptococcus anginosus, Lactobacillus acidophilus, Evtepia gabavorous, Bifidobacterium bifidum, Mordavella massiliensis, Eubacterium siraeum, Bifidobacterium pseudocatenulatum, Klebsiella variicola, Parabacteroides goldsteinii.	Lachnoclostridium edouardi, Clostridium fessum, Dialister invisus, Coprococcus eutactus, Agathobaculum butyriciproducens, Jutongia huaianensis, Haemophilus parainfluenzae, Clostridium porci, Lactobacillus rogosae.

Supplementary Table 3: Differential abundance analysis results of OTUs using MetaDE.

The table presents the effect size and variance for each dataset, Z-values (zval), p-values (pval), and false discovery rate (FDR) for each OTU identified by MetaDE.

	ind.ES.M alaysia	ind.ES.K orea	ind.ES.Ja pan	ind.ES.I taly	ind.ES.C hina	ind.Var.Mal aysia	ind.Var.K orea	ind.Var.J apan	ind.Var.I taly	ind.Var.C hina	zval	pval	FDR
Otu1	-0.2	-0	-0.1	-0.3	0.13	0.02	0.01	0.02	0.03	0.02	-1.2	0.2	0.35
Otu10	-0.7	0.12	-0.2	-0.3	-0.1	0.02	0.01	0.02	0.03	0.02	-1.7	0.07	0.18
Otu100	0.37	0.13	0.22	0.27	0.29	0.02	0.01	0.02	0.03	0.02	3.78	0	0
Otu102	-0.5	0	-0.2	0.09	0.24	0.02	0.01	0.02	0.03	0.02	-0.7	0.46	0.63
Otu104	0.08	-0.3	0.03	-0.1	0.01	0.02	0.01	0.02	0.03	0.02	-1	0.26	0.42
Otu106	-0.2	0.25	-0.1	-0.2	-0	0.02	0.01	0.02	0.03	0.02	-0.5	0.58	0.71
Otu107	0.08	0.25	0.17	0.25	0.35	0.02	0.01	0.02	0.03	0.02	3.36	0	0
Otu108	-0	0.04	-0	0	-0.1	0.02	0.01	0.02	0.03	0.02	-0.4	0.62	0.74
Otu109	-0	0.02	-0.1	0.6	0.49	0.02	0.01	0.02	0.03	0.02	1.24	0.18	0.32
Otu11	-0.3	0.29	-0.2	-0.3	-0.2	0.02	0.01	0.02	0.03	0.02	-1.2	0.18	0.32
Otu110	0.11	-0.2	0.1	0.31	0.07	0.02	0.01	0.02	0.03	0.02	0.65	0.47	0.64
Otu111 2	-0	0.25	-0.1	0.13	0.14	0.02	0.01	0.02	0.03	0.02	1.5	0.1	0.25
Otu117	-1.2	0.06	0.15	0.31	0.12	0.02	0.01	0.02	0.03	0.02	-0.4	0.66	0.77
Otu12	0.09	0.19	-0	-0.2	0.47	0.02	0.01	0.02	0.03	0.02	1.05	0.25	0.41
Otu120	0.33	-0.1	-0	0.01	-0.1	0.02	0.01	0.02	0.03	0.02	0.25	0.78	0.88
Otu122	-0.4	0.01	-0.3	0	-0.1	0.02	0.01	0.02	0.03	0.02	-1.8	0.05	0.16
Otu122 5	0.1	0.19	-0.2	0.23	0.3	0.02	0.01	0.02	0.03	0.02	1.37	0.14	0.29
Otu122 8	-0.4	-0.3	-0.4	0.05	-0.1	0.02	0.01	0.02	0.03	0.02	-3	0	0.01
Otu124	-0.3	-0	-0.2	-0.4	0.05	0.02	0.01	0.02	0.03	0.02	-2	0.04	0.12
Otu125	-0	0.08	0.21	0.01	0.02	0.02	0.01	0.02	0.03	0.02	1	0.27	0.42
Otu125 4	-0.3	-0.2	-0.4	0.25	-0.1	0.02	0.01	0.02	0.03	0.02	-1.4	0.12	0.27
Otu126	0.03	-0.2	-0	0.17	0.08	0.02	0.01	0.02	0.03	0.02	-0.4	0.67	0.77
Otu128	-0.3	0.1	-0.1	-0	0.19	0.02	0.01	0.02	0.03	0.02	-0.2	0.83	0.92
Otu129	0.67	0.21	0.15	0.22	-0	0.02	0.01	0.02	0.03	0.02	2.18	0.02	0.08
Otu13	-0.4	-0.2	-0.4	-0.3	-0.2	0.02	0.01	0.02	0.03	0.02	-4.7	1e-20	2.562 5e-19
Otu130	-0.1	-0.4	-0.3	0.51	-0.4	0.02	0.01	0.02	0.03	0.02	-0.9	0.31	0.46
Otu131	0.19	0.14	-0.2	0.27	-0	0.02	0.01	0.02	0.03	0.02	0.98	0.28	0.43
Otu132	0	0.43	-0	0.22	0.52	0.02	0.01	0.02	0.03	0.02	2.07	0.03	0.1
Otu133	0.38	0.23	0.14	0.32	0.32	0.02	0.01	0.02	0.03	0.02	4.18	1.463414 63415078 e-05	0
Otu136	-0.3	-0.1	-0.3	0.07	0.1	0.02	0.01	0.02	0.03	0.02	-1.3	0.16	0.3

Otu14	-0	0.18	-0.2	-0.4	0.23	0.02	0.01	0.02	0.03	0.02	-0.2	0.86	0.92
Otu142	-0.4	-0.3	-0.2	0.08	-0.1	0.02	0.01	0.02	0.03	0.02	-2.8	0	0.02
Otu144	-0.2	-0	0.1	0.21	-0	0.02	0.01	0.02	0.03	0.02	-0.2	0.85	0.92
Otu144 9	0.15	0.19	0.05	0.56	0.08	0.02	0.01	0.02	0.03	0.02	2.05	0.03	0.1
Otu145	-0.6	-0.3	-0.5	-0.4	-0.3	0.02	0.01	0.02	0.03	0.02	-5.8	1e-20	2.562 5e-19
Otu145 7	-0.5	0.06	-0.5	-0.2	-0.1	0.02	0.01	0.02	0.03	0.02	-2.3	0.01	0.06
Otu149	-0.1	0.42	0.26	0.16	0.43	0.02	0.01	0.02	0.03	0.02	2.68	0.01	0.03
Otu15	-0	-0	-0.3	-0.5	0.26	0.02	0.01	0.02	0.03	0.02	-0.8	0.39	0.55
Otu150	0.48	0.21	-0.2	0.24	-0.1	0.02	0.01	0.02	0.03	0.02	1.14	0.21	0.37
Otu152	-0.3	0.04	0.07	0.15	0.29	0.02	0.01	0.02	0.03	0.02	0.55	0.54	0.7
Otu156	-0.1	0.04	-0.1	-0.3	-0.2	0.02	0.01	0.02	0.03	0.02	-1.6	0.09	0.23
Otu157	0.4	0.13	-0.2	-0.1	0.44	0.02	0.01	0.02	0.03	0.02	1.02	0.26	0.42
Otu158	-0.1	-0.1	-0.1	-0.1	0	0.02	0.01	0.02	0.03	0.02	-1.4	0.13	0.27
Otu16	-0.4	-0.1	-0.3	0.12	-0	0.02	0.01	0.02	0.03	0.02	-1.7	0.08	0.2
Otu160	-0.1	-0.2	-0.4	0.09	-0.5	0.02	0.01	0.02	0.03	0.02	-2.2	0.02	0.07
Otu163	0.14	0.13	0.01	-0.1	-0.1	0.02	0.01	0.02	0.03	0.02	0.61	0.5	0.65
Otu165	-0.1	0.21	0.01	-0.4	0.3	0.02	0.01	0.02	0.03	0.02	0.09	0.92	0.96
Otu166	-0.2	0.06	-0.3	0.03	-0.1	0.02	0.01	0.02	0.03	0.02	-1.4	0.12	0.27
Otu168	0.14	0.12	0.13	0.22	-0	0.02	0.01	0.02	0.03	0.02	1.77	0.06	0.17
Otu169	0.4	0.35	0.23	0.06	0.11	0.02	0.01	0.02	0.03	0.02	3.91	5.853658 53658093 e-05	0
Otu17	-0.1	-0.2	-0	0.08	-0.1	0.02	0.01	0.02	0.03	0.02	-1.3	0.15	0.3
Otu170	-0.2	0.27	0.09	-0.1	0.26	0.02	0.01	0.02	0.03	0.02	0.66	0.47	0.64
Otu171	-0.3	-0.1	-0.2	-0.4	-0.2	0.02	0.01	0.02	0.03	0.02	-3.1	0	0.01
Otu173 3	-0.2	-0	-0.2	-0	-0.1	0.02	0.01	0.02	0.03	0.02	-1.6	0.08	0.2
Otu175	0.22	0.29	0.09	0.16	0.16	0.02	0.01	0.02	0.03	0.02	3.05	0	0.01
Otu178	-0.1	0.14	-0.1	0.18	0.48	0.02	0.01	0.02	0.03	0.02	1.04	0.25	0.41
Otu182	-0.1	0.41	-0.3	0.11	0.34	0.02	0.01	0.02	0.03	0.02	0.85	0.35	0.51
Otu192	0.14	0.1	-0.2	0.06	-0.1	0.02	0.01	0.02	0.03	0.02	-0	0.97	0.98
Otu194	-0.2	0.17	0.14	0.16	0.38	0.02	0.01	0.02	0.03	0.02	1.36	0.14	0.29
Otu194 9	-0.6	-0	-0.5	-0.2	-0.2	0.02	0.01	0.02	0.03	0.02	-2.7	0	0.03
Otu195	0.01	0.11	-0.3	0.18	0.19	0.02	0.01	0.02	0.03	0.02	0.44	0.62	0.74
Otu199	-0.2	-0	-0.2	0.4	-0.2	0.02	0.01	0.02	0.03	0.02	-0.5	0.59	0.72
Otu199 1	-0.3	0.11	-0.3	-0.1	-0	0.02	0.01	0.02	0.03	0.02	-1.5	0.12	0.27
Otu2	-0.6	-0	-0	0.2	-0.4	0.02	0.01	0.02	0.03	0.02	-1.2	0.19	0.33

Otu20	-0.1	0.02	-0.2	-0.3	0.15	0.02	0.01	0.02	0.03	0.02	-0.9	0.34	0.5
Otu200	-0.2	0.2	0.16	0.16	0.18	0.02	0.01	0.02	0.03	0.02	1.68	0.07	0.19
Otu201	0.31	0.05	0.07	0	0.14	0.02	0.01	0.02	0.03	0.02	1.8	0.05	0.16
Otu202 0	0.2	-0	0.1	-0.1	0.01	0.02	0.01	0.02	0.03	0.02	0.71	0.44	0.6
Otu204	-0.8	-0	-0.1	0.16	-0.5	0.02	0.01	0.02	0.03	0.02	-1.4	0.12	0.27
Otu208 0	-0.1	-0	-0.3	0.15	-0.3	0.02	0.01	0.02	0.03	0.02	-1.5	0.09	0.23
Otu21	0.16	-0	-0.3	0.01	0.07	0.02	0.01	0.02	0.03	0.02	-0.4	0.68	0.78
Otu210	-0.5	-0.2	-0.4	-0.1	-0.2	0.02	0.01	0.02	0.03	0.02	-3.5	0	0
Otu214	0.02	0.53	-0.2	-0.2	0.41	0.02	0.01	0.02	0.03	0.02	0.65	0.48	0.64
Otu215	-0.3	0.22	-0.2	-0	-0.1	0.02	0.01	0.02	0.03	0.02	-1	0.29	0.43
Otu217	-0.6	-0.2	-0.5	-0.4	-0	0.02	0.01	0.02	0.03	0.02	-3.2	0	0.01
Otu219	-0.2	0.41	-0.4	0.23	0.32	0.02	0.01	0.02	0.03	0.02	0.45	0.62	0.74
Otu22	0.24	0.49	-0	0.02	0.37	0.02	0.01	0.02	0.03	0.02	2.43	0.01	0.05
Otu221	-0.1	-0.2	0.18	0.88	-0.1	0.02	0.01	0.02	0.04	0.02	0.62	0.5	0.65
Otu222 0	0.48	0.26	0.27	0.18	0.32	0.02	0.01	0.02	0.03	0.02	4.73	1e-20	2.562 5e-19
Otu225	-0	0.36	0.24	0.08	0.16	0.02	0.01	0.02	0.03	0.02	2.84	0	0.02
Otu229	0.13	0.43	-0.2	0	0.26	0.02	0.01	0.02	0.03	0.02	1.35	0.14	0.29
Otu23	-0.7	-0.1	-0.2	0.04	-0.2	0.02	0.01	0.02	0.03	0.02	-2	0.03	0.11
Otu230	-0.2	0.78	-0	-0.1	0.48	0.02	0.02	0.02	0.03	0.02	1.09	0.23	0.39
Otu232	0.16	0.16	-0.2	-0.1	0.09	0.02	0.01	0.02	0.03	0.02	0.57	0.53	0.69
Otu232 2	-0.2	0.18	-0.2	-0.2	0.43	0.02	0.01	0.02	0.03	0.02	0.05	0.95	0.97
Otu233	0.19	0.2	-0.3	0.2	0.43	0.02	0.01	0.02	0.03	0.02	1.11	0.23	0.38
Otu234	0.2	0.2	0.17	0.01	0.4	0.02	0.01	0.02	0.03	0.02	3.18	0	0.01
Otu235	-0.5	-0.3	-0.4	0.04	-0.1	0.02	0.01	0.02	0.03	0.02	-2.8	0	0.02
Otu236 6	0.08	0.4	0.1	-0.4	0.42	0.02	0.01	0.02	0.03	0.02	0.8	0.38	0.54
Otu24	0.27	0.06	0.28	0.21	0.06	0.02	0.01	0.02	0.03	0.02	2.59	0.01	0.03
Otu25	-0.4	-0.1	-0.1	-0.6	0.09	0.02	0.01	0.02	0.03	0.02	-1.7	0.06	0.18
Otu251	-0	0	-0.4	-0.1	0.08	0.02	0.01	0.02	0.03	0.02	-1	0.28	0.43
Otu26	0.03	0.1	0.21	-0.3	0.08	0.02	0.01	0.02	0.03	0.02	0.68	0.45	0.62
Otu263	0.28	0.19	-0.3	0.09	-0.1	0.02	0.01	0.02	0.03	0.02	0.24	0.79	0.88
Otu272	-0	0.18	-0.3	-0.1	-0	0.02	0.01	0.02	0.03	0.02	-0.4	0.64	0.75
Otu273	-0.5	-0.2	0.01	-0.1	-0.2	0.02	0.01	0.02	0.03	0.02	-2.3	0.02	0.06
Otu274	-0.2	-0.3	-0.5	0.06	-0.4	0.02	0.01	0.02	0.03	0.02	-3	0	0.01
Otu279	-0.2	-0	0.19	-0.1	-0.4	0.02	0.01	0.02	0.03	0.02	-1.1	0.23	0.38
Otu28	-0	-0	0.11	-0	-0.3	0.02	0.01	0.02	0.03	0.02	-0.5	0.57	0.71
Otu285	0.61	0.16	-0.1	0.2	-0.1	0.02	0.01	0.02	0.03	0.02	1.34	0.15	0.29

Otu286	-0.2	-0.3	-0.3	-0.2	-0	0.02	0.01	0.02	0.03	0.02	-3.3	0	0
Otu296	0.18	-0.2	0.16	0.03	0.18	0.02	0.01	0.02	0.03	0.02	0.85	0.35	0.51
Otu3	-0	0.09	0.1	0.06	0.24	0.02	0.01	0.02	0.03	0.02	1.39	0.13	0.28
Otu30	-0.1	-0	0.06	0.32	-0.1	0.02	0.01	0.02	0.03	0.02	0.08	0.93	0.96
Otu301	0.43	0.1	-0.1	-0	-0	0.02	0.01	0.02	0.03	0.02	1	0.27	0.42
Otu303	-0.2	-0	-0.3	-0.1	-0.4	0.02	0.01	0.02	0.03	0.02	-3	0	0.01
Otu305	0.12	0.19	-0.1	0.1	0.18	0.02	0.01	0.02	0.03	0.02	1.75	0.06	0.17
Otu31	-0.6	0.21	-0.3	0.15	-0	0.02	0.01	0.02	0.03	0.02	-0.8	0.38	0.54
Otu313	-0	0.29	0.23	0.1	0.15	0.02	0.01	0.02	0.03	0.02	2.56	0.01	0.04
Otu314	0.19	0.11	-0.1	-0.1	-0.1	0.02	0.01	0.02	0.03	0.02	0.23	0.8	0.88
Otu32	0.2	0.14	0.09	0.5	0.24	0.02	0.01	0.02	0.03	0.02	2.93	0	0.02
Otu327	-0	0.43	-0.2	0.25	0.49	0.02	0.01	0.02	0.03	0.02	1.3	0.16	0.3
Otu33	0.1	0.27	-0	0.38	0.23	0.02	0.01	0.02	0.03	0.02	2.67	0.01	0.03
Otu333	0.24	0.5	-0.1	0.09	0.22	0.02	0.01	0.02	0.03	0.02	1.98	0.03	0.12
Otu334	-0.4	0.39	0.04	-0.1	0.06	0.02	0.01	0.02	0.03	0.02	-0	0.99	0.99
Otu337	0.32	0.11	-0.3	0.33	-0.1	0.02	0.01	0.02	0.03	0.02	0.52	0.57	0.71
Otu338	0.22	0.31	0.37	-0.2	0.22	0.02	0.01	0.02	0.03	0.02	2.4	0.01	0.05
Otu340	0.31	0.41	0.27	0.37	0.07	0.02	0.01	0.02	0.03	0.02	4.55	1e-20	2.5625e-19
Otu35	-0.3	0.19	-0.5	0.08	-0.2	0.02	0.01	0.02	0.03	0.02	-1.1	0.22	0.37
Otu367	0.01	0.19	-0.2	-0.2	0.26	0.02	0.01	0.02	0.03	0.02	0.17	0.84	0.92
Otu368	0.16	0.27	-0.2	0.02	-0	0.02	0.01	0.02	0.03	0.02	0.91	0.32	0.47
Otu369	0.27	0.04	0.09	0.09	0.06	0.02	0.01	0.02	0.03	0.02	1.65	0.08	0.2
Otu37	-0.2	0.24	-0.1	-0.3	0.29	0.02	0.01	0.02	0.03	0.02	-0.1	0.93	0.96
Otu371	0.18	0.04	-0	0.15	0	0.02	0.01	0.02	0.03	0.02	0.98	0.28	0.43
Otu376	0.2	0.09	0.08	0.11	0.12	0.02	0.01	0.02	0.03	0.02	1.81	0.05	0.16
Otu38	0.04	0.09	0.02	-0.1	0.07	0.02	0.01	0.02	0.03	0.02	0.53	0.56	0.7
Otu388	0.27	0.07	-0.1	0.05	0.15	0.02	0.01	0.02	0.03	0.02	1.42	0.12	0.27
Otu39	-0	0.22	-0.1	-0.3	0.29	0.02	0.01	0.02	0.03	0.02	0.3	0.74	0.84
Otu390	-0.2	-0.1	-0.1	0.15	0.05	0.02	0.01	0.02	0.03	0.02	-1.1	0.21	0.37
Otu391	-0	-0	-0.1	0.05	0.23	0.02	0.01	0.02	0.03	0.02	0.32	0.72	0.82
Otu4	-0.1	0.62	0.12	-0.1	0.24	0.02	0.02	0.02	0.03	0.02	1.23	0.18	0.32
Otu40	0.02	0.28	-0.2	-0.2	0.15	0.02	0.01	0.02	0.03	0.02	0.52	0.57	0.71
Otu414	-0	0.03	-0.1	-0.1	-0.3	0.02	0.01	0.02	0.03	0.02	-1.3	0.17	0.31
Otu42	-0.7	-0.4	-0.3	-0.3	-0.1	0.02	0.01	0.02	0.03	0.02	-3.7	0	0
Otu421	0.38	0.35	0.1	0.55	0.19	0.02	0.01	0.02	0.03	0.02	3.92	5.36585365853437e-05	0
Otu423	-0.4	-0	-0.3	0.09	-0	0.02	0.01	0.02	0.03	0.02	-1.6	0.09	0.22
Otu427	-0.4	0.17	-0.2	-0.3	0.3	0.02	0.01	0.02	0.03	0.02	-0.6	0.48	0.64

Otu428	-0.2	0.03	-0.2	0.16	0.15	0.02	0.01	0.02	0.03	0.02	-0.3	0.75	0.84
Otu43	-0.4	-0.2	-0.2	-0.1	0.06	0.02	0.01	0.02	0.03	0.02	-2.3	0.01	0.06
Otu44	0.48	0.64	0.21	0.48	0.16	0.02	0.02	0.02	0.03	0.02	4.5	1e-20	2.5625e-19
Otu45	-0.5	-0.1	-0.2	-0.1	0.07	0.02	0.01	0.02	0.03	0.02	-1.8	0.05	0.16
Otu46	-0.5	0.2	-0.1	-0	0.19	0.02	0.01	0.02	0.03	0.02	-0.4	0.64	0.75
Otu462	0.01	0.21	0.01	0.3	0.33	0.02	0.01	0.02	0.03	0.02	2.39	0.01	0.05
Otu467	0.13	-0.2	-0.1	0.3	0.07	0.02	0.01	0.02	0.03	0.02	0.09	0.92	0.96
Otu47	-0.1	-0.2	0.11	0.13	-0.1	0.02	0.01	0.02	0.03	0.02	-0.5	0.59	0.72
Otu471	0.23	0.15	-0	0.34	0.25	0.02	0.01	0.02	0.03	0.02	2.67	0.01	0.03
Otu478	-0	0.15	-0.3	0.07	0.35	0.02	0.01	0.02	0.03	0.02	0.47	0.6	0.72
Otu48	0.05	0.51	0.08	-0.3	0.5	0.02	0.01	0.02	0.03	0.02	1.3	0.16	0.3
Otu481	0.21	-0	0.11	-0.3	-0	0.02	0.01	0.02	0.03	0.02	0.12	0.89	0.96
Otu493	0.04	0.2	-0	-0.2	-0	0.02	0.01	0.02	0.03	0.02	0.48	0.6	0.72
Otu496	-0.1	-0.3	-0.2	0.41	0.2	0.02	0.01	0.02	0.03	0.02	-0.1	0.91	0.96
Otu497	0.34	0.41	-0.1	0.19	0.43	0.02	0.01	0.02	0.03	0.02	2.33	0.01	0.06
Otu498	-0.1	0.56	-0.1	0.22	0.14	0.02	0.01	0.02	0.03	0.02	1.34	0.15	0.29
Otu5	0.21	0.02	0.35	-0.1	0.33	0.02	0.01	0.02	0.03	0.02	2.03	0.03	0.11
Otu50	0.13	0.08	-0	0.05	-0.1	0.02	0.01	0.02	0.03	0.02	0.44	0.63	0.74
Otu516	0.03	0.25	0.13	0.13	0.17	0.02	0.01	0.02	0.03	0.02	2.34	0.01	0.06
Otu524	0.5	0.63	-0	0.48	0.27	0.02	0.02	0.02	0.03	0.02	3.26	0	0.01
Otu539	0.14	0.28	0.16	0.34	-0.3	0.02	0.01	0.02	0.03	0.02	1.31	0.15	0.3
Otu54	0.43	0.26	0.16	0.16	0.54	0.02	0.01	0.02	0.03	0.02	4.2	1.46341463415078e-05	0
Otu55	-0	-0.4	-0.3	-0.1	-0.5	0.02	0.01	0.02	0.03	0.02	-2.9	0	0.02
Otu555	0.05	-0.2	-0.3	0.17	-0.3	0.02	0.01	0.02	0.03	0.02	-1.3	0.15	0.29
Otu556	0.05	0.17	0	-0	0.29	0.02	0.01	0.02	0.03	0.02	1.75	0.06	0.17
Otu56	-0.1	0.36	-0.1	0.11	0.36	0.02	0.01	0.02	0.03	0.02	1.04	0.25	0.41
Otu562	0.3	-0	-0	0.3	0.03	0.02	0.01	0.02	0.03	0.02	1.37	0.14	0.29
Otu58	-0.2	-0.2	-0.5	0.04	0.08	0.02	0.01	0.02	0.03	0.02	-1.6	0.08	0.21
Otu6	-1	-0	-0.1	-0.4	-0.1	0.02	0.01	0.02	0.03	0.02	-1.8	0.06	0.17
Otu61	-0.1	0.08	0.16	0.11	0.25	0.02	0.01	0.02	0.03	0.02	1.41	0.13	0.27
Otu610	-0.1	0.04	-0.2	-0.4	0.05	0.02	0.01	0.02	0.03	0.02	-1.4	0.13	0.27
Otu62	0.13	0.06	0.05	0.11	0.44	0.02	0.01	0.02	0.03	0.02	2.09	0.03	0.1
Otu625	-0.6	0.08	-0.2	-0.2	-0.2	0.02	0.01	0.02	0.03	0.02	-2	0.03	0.11
Otu63	0.03	0.07	-0.2	0.01	0.17	0.02	0.01	0.02	0.03	0.02	0.17	0.85	0.92
Otu638	0.15	0.23	-0.1	0.32	-0	0.02	0.01	0.02	0.03	0.02	1.47	0.11	0.26
Otu64	-0.8	0.11	-0.1	0.07	0.09	0.02	0.01	0.02	0.03	0.02	-0.7	0.42	0.59
Otu67	-0.5	-0.2	-0.1	-0	-0.1	0.02	0.01	0.02	0.03	0.02	-2.1	0.02	0.09

Otu671	0.26	0.25	0.16	0.32	0.15	0.02	0.01	0.02	0.03	0.02	3.48	0	0
Otu68	-0	0.33	-0.3	0.27	0.61	0.02	0.01	0.02	0.03	0.02	1.24	0.18	0.32
Otu69	-0.2	0.08	-0.2	-0.1	0.09	0.02	0.01	0.02	0.03	0.02	-1	0.29	0.43
Otu7	-0.7	-0.7	-0.7	-0.2	-0.6	0.02	0.02	0.02	0.03	0.02	-5.5	1e-20	2.562 5e-19
Otu70	0.03	0.28	-0.2	-0.3	0.53	0.02	0.01	0.02	0.03	0.02	0.54	0.55	0.7
Otu71	-0.4	0.05	0.11	-0	0.2	0.02	0.01	0.02	0.03	0.02	-0.1	0.94	0.96
Otu719	-0.4	-0.1	-0.6	0.1	-0.1	0.02	0.01	0.02	0.03	0.02	-1.8	0.06	0.16
Otu72	-0.6	0.03	-0.4	-0.1	-0.3	0.02	0.01	0.02	0.03	0.02	-2.5	0.01	0.04
Otu724	-0.1	0.16	-0.2	0.04	-0	0.02	0.01	0.02	0.03	0.02	-0.1	0.93	0.96
Otu76	0.07	-0.3	0.14	0.23	-0.1	0.02	0.01	0.02	0.03	0.02	-0	0.98	0.98
Otu764	-0.2	0.14	-0.1	0.01	-0.1	0.02	0.01	0.02	0.03	0.02	-0.6	0.49	0.64
Otu78	-0.6	-0.2	-0.6	0.17	-0.4	0.02	0.01	0.02	0.03	0.02	-2.4	0.01	0.05
Otu79	-0.2	0.32	0.22	-0.1	0.53	0.02	0.01	0.02	0.03	0.02	1.06	0.25	0.41
Otu8	-0	-0	-0.2	-0.1	0.31	0.02	0.01	0.02	0.03	0.02	-0.1	0.9	0.96
Otu81	-0.1	0.23	-0.1	0.06	0.42	0.02	0.01	0.02	0.03	0.02	0.89	0.33	0.48
Otu82	0.22	0.25	-0	0.24	-0	0.02	0.01	0.02	0.03	0.02	2.04	0.03	0.11
Otu826	0.31	-0.1	0.06	-0.2	-0	0.02	0.01	0.02	0.03	0.02	0.11	0.9	0.96
Otu83	0.07	0.05	0.19	-0	0.25	0.02	0.01	0.02	0.03	0.02	1.63	0.08	0.2
Otu85	0.28	0.1	0.16	0.29	0.36	0.02	0.01	0.02	0.03	0.02	3.38	0	0
Otu86	-0.3	-0.2	-0.6	-0.1	-0.5	0.02	0.01	0.02	0.03	0.02	-3.7	0	0
Otu87	-0.5	-0.3	-0.4	0.31	-0.2	0.02	0.01	0.02	0.03	0.02	-1.5	0.1	0.23
Otu89	0.48	0.21	0.35	0.02	0.28	0.02	0.01	0.02	0.03	0.02	3.77	0	0
Otu9	0.17	0.08	0.17	0.24	0.36	0.02	0.01	0.02	0.03	0.02	2.91	0	0.02
Otu92	-0.7	-0.2	-0.3	0.23	0.03	0.02	0.01	0.02	0.03	0.02	-1.2	0.21	0.36
Otu93	-0.1	-0.1	0.15	0.13	0.37	0.02	0.01	0.02	0.03	0.02	1.01	0.27	0.42
Otu932	0.03	0.14	-0.2	-0.1	0.08	0.02	0.01	0.02	0.03	0.02	-0	0.96	0.98
Otu94	0.45	0.49	0.21	0.24	0.35	0.02	0.01	0.02	0.03	0.02	5.69	1e-20	2.562 5e-19
Otu949	0.06	0.13	-0.1	0.14	0.31	0.02	0.01	0.02	0.03	0.02	1.61	0.08	0.21
Otu97	0.37	0.26	0.31	0.26	0.63	0.02	0.01	0.02	0.03	0.02	5.36	1e-20	2.562 5e-19
Otu98	-0.2	-0	-0	-0.1	0.13	0.02	0.01	0.02	0.03	0.02	-0.6	0.5	0.65
Otu99	0.05	0.13	0.02	0.06	0.38	0.02	0.01	0.02	0.03	0.02	1.97	0.04	0.12

Supplementary Table 4: Functional Pathway Analysis Results Using MicrobiomeAnalyst.

Identified metabolic pathways based on MicrobiomeAnalyst listing the pathways along with their size, observed hits, statistical scores, and multiple testing corrections (Holm and false discovery rate (FDR)).

Pathway	Size	Hits	Statistic Q	Expected Q	Pval	Holm p	FDR
Glycerolipid metabolism	17	17	0.943613	0.099404	1.43E-05	0.001447	0.000104
Toluene degradation	9	9	0.870863	0.099404	1.57E-05	0.001574	0.000107
Tryptophan metabolism	24	24	0.731475	0.099404	1.84E-05	0.001821	0.00011
Ascorbate and aldarate metabolism	23	23	0.728021	0.099404	1.90E-05	0.001859	0.00011
Valine, leucine and isoleucine degradation	23	23	0.80172	0.099404	1.92E-05	0.001866	0.00011
Glycine, serine and threonine metabolism	40	40	0.721692	0.099404	2.07E-05	0.001988	0.00011
Biosynthesis of type II polyketide products	3	3	1.589317	0.099404	2.08E-05	0.001988	0.00011
Carotenoid biosynthesis	10	10	0.929013	0.099404	2.56E-05	0.002404	0.000129
Sulfur metabolism	14	14	1.00956	0.099404	2.87E-05	0.002666	0.000139
Ubiquinone and other terpenoid-quinone biosynthesis	23	23	0.673829	0.099404	3.34E-05	0.003072	0.000149
Purine metabolism	42	42	0.773646	0.099404	3.35E-05	0.003072	0.000149
Cysteine and methionine metabolism	36	36	0.780241	0.099404	4.21E-05	0.003787	0.000181
Propanoate metabolism	34	34	0.749184	0.099404	4.93E-05	0.004388	0.000204
Lipoic acid metabolism	10	10	0.875764	0.099404	5.84E-05	0.005137	0.000227
Tyrosine metabolism	28	28	0.662626	0.099404	5.86E-05	0.005137	0.000227
Valine, leucine and isoleucine biosynthesis	4	4	0.807676	0.099404	7.70E-05	0.006619	0.000288
Glutathione metabolism	15	15	0.846876	0.099404	8.17E-05	0.006947	0.000294
Caffeine metabolism	2	2	0.962297	0.099404	8.36E-05	0.007019	0.000294
Pentose phosphate pathway	32	32	0.743873	0.099404	9.04E-05	0.007505	0.000308
Butanoate metabolism	31	31	0.723309	0.099404	0.000105	0.008646	0.000349
Lysine biosynthesis	19	19	0.699933	0.099404	0.000117	0.009487	0.000377
alpha-Linolenic acid metabolism	3	3	0.938851	0.099404	0.000127	0.010122	0.000397
Fatty acid degradation	13	13	1.060535	0.099404	0.000137	0.010857	0.000418
Phenylalanine metabolism	29	29	0.639678	0.099404	0.00014	0.010957	0.000418
Starch and sucrose metabolism	41	41	0.682611	0.099404	0.000159	0.012274	0.000448
Riboflavin metabolism	17	17	0.587332	0.099404	0.000161	0.012274	0.000448
Caprolactam degradation	6	6	0.932922	0.099404	0.000162	0.012274	0.000448
Inositol phosphate metabolism	14	14	0.644602	0.099404	0.000185	0.013702	0.000494
Carbon fixation pathways in prokaryotes	25	25	0.656982	0.099404	0.000187	0.013702	0.000494
Pyrimidine metabolism	28	28	0.731449	0.099404	0.000197	0.014156	0.000507
Biosynthesis of enediyne antibiotics	2	2	1.139609	0.099404	0.000201	0.014302	0.000508
Taurine and hypotaurine metabolism	8	8	0.551992	0.099404	0.000217	0.01521	0.000536
Cyanoamino acid metabolism	6	6	0.946689	0.099404	0.000249	0.017169	0.000601
Chloroalkane and chloroalkene degradation	8	8	0.628773	0.099404	0.000296	0.020153	0.000702
Chlorocyclohexane and chlorobenzene degradation	13	13	0.60652	0.099404	0.000351	0.023529	0.000813

Histidine metabolism	15	15	0.657097	0.099404	0.000357	0.023587	0.000813
Pinene, camphor and geraniol degradation	4	4	0.889578	0.099404	0.000366	0.023816	0.000817
D-Amino acid metabolism	13	13	0.569777	0.099404	0.000392	0.025067	0.000857
Steroid hormone biosynthesis	2	2	0.866929	0.099404	0.000478	0.030113	0.001027
Pentose and glucuronate interconversions	36	36	0.637963	0.099404	0.000521	0.032289	0.001098
Isoquinoline alkaloid biosynthesis	6	6	0.545307	0.099404	0.000587	0.035779	0.001215
Arginine biosynthesis	18	18	0.560083	0.099404	0.0008	0.047978	0.001609
Porphyrin metabolism	44	44	0.480768	0.099404	0.000814	0.048013	0.001609
N-Glycan biosynthesis	5	5	0.571708	0.099404	0.000818	0.048013	0.001609
Retinol metabolism	2	2	1.071142	0.099404	0.000843	0.04804	0.001616
Staurosporine biosynthesis	2	2	0.710369	0.099404	0.000863	0.048347	0.001616
Drug metabolism - other enzymes	11	11	0.718762	0.099404	0.000864	0.048347	0.001616
Teichoic acid biosynthesis	2	2	1.056766	0.099404	0.000969	0.052347	0.001759
Galactose metabolism	25	25	0.576553	0.099404	0.00097	0.052347	0.001759
beta-Alanine metabolism	20	20	0.506424	0.099404	0.001001	0.052347	0.001775
Aminobenzoate degradation	13	13	0.486854	0.099404	0.00101	0.052347	0.001775
Fluorobenzoate degradation	9	9	0.449945	0.099404	0.001097	0.054875	0.0019
Naphthalene degradation	4	4	0.826527	0.099404	0.00131	0.064175	0.002234
Dioxin degradation	9	9	0.605258	0.099404	0.001399	0.067166	0.002352
Tetracycline biosynthesis	2	2	0.706279	0.099404	0.001501	0.070536	0.002487
Phosphonate and phosphinate metabolism	9	9	0.715787	0.099404	0.001639	0.075398	0.002678
Lysine degradation	16	16	0.597423	0.099404	0.001918	0.086291	0.003089
Pyruvate metabolism	34	34	0.533076	0.099404	0.002051	0.090256	0.00326
Nitrogen metabolism	15	15	0.434275	0.099404	0.002392	0.102877	0.00375
Amino sugar and nucleotide sugar metabolism	61	61	0.463424	0.099404	0.002728	0.114562	0.004219
Photosynthesis	4	4	0.447671	0.099404	0.003332	0.136628	0.005086
Alanine, aspartate and glutamate metabolism	17	17	0.539743	0.099404	0.004144	0.165764	0.006243
Fructose and mannose metabolism	40	40	0.397106	0.099404	0.004424	0.172536	0.006579
Tropane, piperidine and pyridine alkaloid biosynthesis	5	5	0.422386	0.099404	0.005255	0.199694	0.007716
O-Antigen nucleotide sugar biosynthesis	29	29	0.421712	0.099404	0.005382	0.199694	0.007804
Citrate cycle (TCA cycle)	14	14	0.544199	0.099404	0.005817	0.209407	0.00833
Ether lipid metabolism	4	4	0.561241	0.099404	0.006016	0.210554	0.00851
Nitrotoluene degradation	4	4	0.456333	0.099404	0.006131	0.210554	0.008568
Biosynthesis of various antibiotics	4	4	0.499683	0.099404	0.006538	0.215755	0.008925
Selenocompound metabolism	8	8	0.620421	0.099404	0.00654	0.215755	0.008925
Carbon fixation in photosynthetic organisms	10	10	0.408026	0.099404	0.008099	0.251065	0.010924
Biosynthesis of various other secondary metabolites	4	4	0.444018	0.099404	0.008868	0.266036	0.011824
Biosynthesis of 12-, 14- and 16-membered macrolides	2	2	0.474415	0.099404	0.00902	0.266036	0.01189
Folate biosynthesis	17	17	0.402128	0.099404	0.01015	0.284199	0.013229

Biotin metabolism	11	11	0.393073	0.099404	0.010541	0.284614	0.013587
Atrazine degradation	5	5	0.47292	0.099404	0.012253	0.318565	0.015619
Styrene degradation	9	9	0.382586	0.099404	0.014569	0.364222	0.018369
Glycerophospholipid metabolism	13	13	0.390339	0.099404	0.016546	0.397096	0.020507
Glycolysis / Gluconeogenesis	26	26	0.370957	0.099404	0.016618	0.397096	0.020507
Oxidative phosphorylation	9	9	0.302385	0.099404	0.018496	0.406913	0.022585
Monobactam biosynthesis	4	4	0.37972	0.099404	0.023291	0.489114	0.028143
Other glycan degradation	3	3	0.44372	0.099404	0.02641	0.528203	0.031437
Fatty acid biosynthesis	7	7	0.335613	0.099404	0.026558	0.528203	0.031437
Primary bile acid biosynthesis	2	2	0.412556	0.099404	0.030114	0.542049	0.035285
Phenylpropanoid biosynthesis	3	3	0.337885	0.099404	0.046323	0.787486	0.053734
One carbon pool by folate	6	6	0.293231	0.099404	0.053017	0.848268	0.06089
Metabolism of xenobiotics by cytochrome P450	5	5	0.291296	0.099404	0.066861	1	0.076038
Drug metabolism - cytochrome P450	6	6	0.282668	0.099404	0.069491	1	0.078262
Novobiocin biosynthesis	3	3	0.258574	0.099404	0.072495	1	0.08086
Streptomycin biosynthesis	6	6	0.236577	0.099404	0.084969	1	0.093327
Sphingolipid metabolism	8	8	0.223359	0.099404	0.085282	1	0.093327
Photosynthesis - antenna proteins	2	2	0.196241	0.099404	0.139018	1	0.150711
Vitamin B6 metabolism	6	6	0.183587	0.099404	0.144439	1	0.155138
Sesquiterpenoid and triterpenoid biosynthesis	2	2	0.169603	0.099404	0.188799	1	0.200924
Arachidonic acid metabolism	2	2	0.147738	0.099404	0.21891	1	0.230851
Lipopolysaccharide biosynthesis	20	20	0.080997	0.099404	0.389976	1	0.407542
Glycosaminoglycan degradation	8	8	0.073503	0.099404	0.498703	1	0.516514
Various types of N-glycan biosynthesis	2	2	0.048672	0.099404	0.553885	1	0.56859
Glycosphingolipid biosynthesis - globo and isoglobo series	2	2	0.03788	0.099404	0.631498	1	0.642577
Phenazine biosynthesis	2	2	0.022335	0.099404	0.772761	1	0.77948
Linoleic acid metabolism	2	2	0.00921	0.099404	0.911356	1	0.911356
Terpenoid backbone biosynthesis	13	13	1.382153	0.099404	2.41E-07	2.77E-05	1.40E-05
Steroid degradation	6	6	1.500446	0.099404	2.00E-08	2.32E-06	2.32E-06
Thiamine metabolism	15	15	1.210224	0.099404	1.70E-06	0.000194	4.57E-05
Benzoate degradation	41	41	0.823567	0.099404	1.77E-06	0.0002	4.57E-05
Polycyclic aromatic hydrocarbon degradation	4	4	1.284818	0.099404	2.45E-06	0.000275	4.57E-05
Biosynthesis of unsaturated fatty acids	3	3	1.05181	0.099404	2.60E-06	0.000289	4.57E-05
Peptidoglycan biosynthesis	9	9	1.149397	0.099404	3.56E-06	0.000392	4.57E-05
Glyoxylate and dicarboxylate metabolism	41	41	0.88194	0.099404	3.90E-06	0.000425	4.57E-05
Phenylalanine, tyrosine and tryptophan biosynthesis	20	20	0.76523	0.099404	4.62E-06	0.000499	4.57E-05
Methane metabolism	41	41	0.787567	0.099404	4.90E-06	0.000524	4.57E-05
Arginine and proline metabolism	44	44	0.749763	0.099404	4.92E-06	0.000524	4.57E-05
Pantothenate and CoA biosynthesis	16	16	0.993638	0.099404	5.29E-06	0.000555	4.57E-05

Xylene degradation	20	20	1.199797	0.099404	5.40E-06	0.000562	4.57E-05
C5-Branched dibasic acid metabolism	8	8	0.883438	0.099404	5.51E-06	0.000568	4.57E-05
Nicotinate and nicotinamide metabolism	14	14	0.941797	0.099404	6.55E-06	0.000668	5.06E-05



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title (reported as meta-analysis)
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section 1.0 Introduction and Section 3.0 Discussion
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section 1.0 Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Figure 1 and Section 4.2 Data Pre-processing
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Section 4.2 Data Pre-processing
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Section 4.2 Data Pre-processing and Supplementary Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Figure 1 and Section 4.2 Data Pre-processing
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Section 4.2 Data Pre-processing
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Section 4.2 Data Pre-processing and Supplementary Table 1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Not applicable
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Section 4.2 Data Pre-processing and Figure 1
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Section 4.4 Biomarkers Detection
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Section 4.2 Data Pre-processing and Figure 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Section 4.2 Data Pre-processing and 4.3 Diversity analysis
	13c	Describe any methods used to tabulate or visually display results of individual studies	Section 4.2 Data Pre-

Section and Topic	Item #	Checklist item	Location where item is reported
		and syntheses.	processing
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Section 4.2 Data Pre-processing and Supplementary Table 1
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Section 4.2 Data Pre-processing
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Section 4.2 Data Pre-processing and Figure 1
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Section 4.2 Data Pre-processing and Figure 1
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Section 4.4 Biomarkers Detection
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1 and Section 2.1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary Table 1
Study characteristics	17	Cite each included study and present its characteristics.	Figure 1 and Table 1 and Section 2.1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Section 2.1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplementary Table 2 and Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1 and Section 2.2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Supplementary Table 2 and Section 2.5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figure 1 and Section 2.1 and Supplementary Table 1
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Figure 1 and Section 2.1 and 2.2
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figure 1 and Section 2.1
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Figure 1 and Section 2.1 and Supplementary Table 1
DISCUSSION			
and Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section 5.0 Discussion and Section 1.0 Introduction
	23b	Discuss any limitations of the evidence included in the review.	Section 5.0 Discussion and

Section and Topic	Item #	Checklist item	Location where item is reported
			Supplementary Table 1
	23c	Discuss any limitations of the review processes used.	Section 5.0 Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Section 5.0 Discussion and Section 1.0 Introduction
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not applicable
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Section 5 Data availability
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Section 7 Acknowledgement
Competing interests	26	Declare any competing interests of review authors.	Section 9 Competing interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Table 1 and Section 5 Data availability and Section 6 Code availability

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>



PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes (reported as meta-analysis)
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>