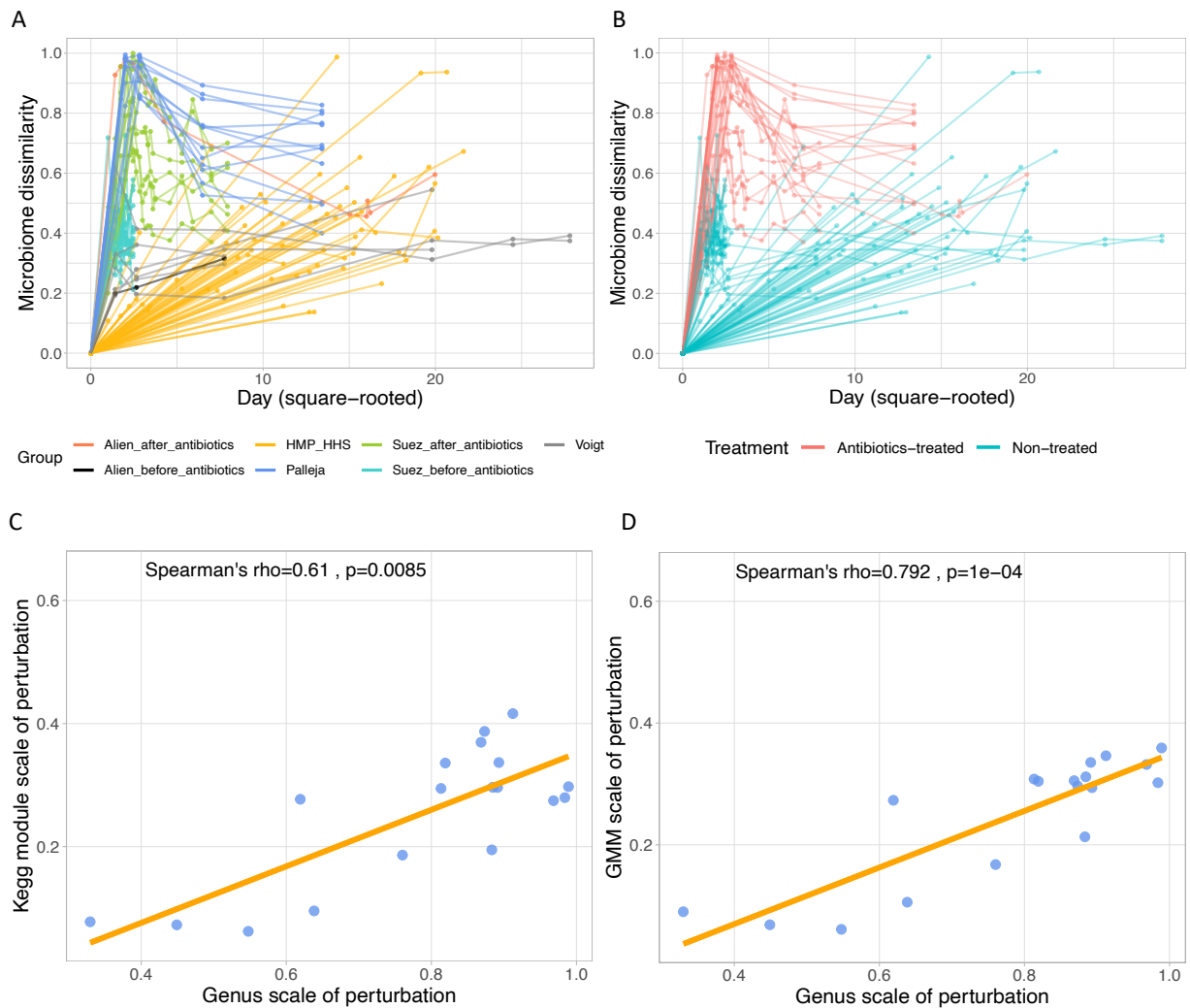


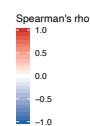
Extended Table 1. Antibiotics used in the studies.

Antibiotics	Classification	Study
Ceftriaxone	Cephalosporin	Alien (from Voigt)
Meropenem	Carbapenem	Palleja
Vancomycin	Glycopeptide	Palleja
Gentamicin	Aminoglycoside	Palleja
Ciprofloxacin	Fluoroquinolone	Suez
Metronidazole	Nitroimidazole	Suez



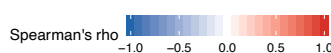
Extended figure 1. Gut microbiome shift is larger in antibiotics-treated group, and the scale of perturbation between taxa and functional profile are correlated. The plots show the microbiome dissimilarity (Bray-Curtis distance) at the species level between the baseline and each time point at subsequent days. Samples are colored by **(A)** different data source, which are Alien_before_antibiotics (n = 1), Alien_after_antibiotics (n = 1), HMP-HHS (n = 55), Palleja (n = 12), Suez_before_antibiotics (n = 21), Suez_after_antibiotics (n = 16) and Voigt (n = 6), or **(B)** different treatment, which are non-treated (n = 83) and antibiotics-treated (n = 29). Each point denotes one sample. Lines connect points of the same individual. The discrepancy between the sample size of Suez before/after antibiotics is because some of the individuals underwent further post-antibiotics intervention (i.e., probiotics supplement or autologous fecal transplant) and were excluded here. (C, D) The correlation between the scales of perturbation of genus and (C) KEGG module and (D) gut metabolic module (GMM). The orange solid lines are the linear regression fitted to the points to show the overall trend.

Number	1	2	3	4	5	6	7	8
Baseline	Species	Genus	KEGG module	Gut metabolic module	KEGG module	Gut metabolic module	Genus	Genus
Scale of perturbation	Species	Genus	KEGG module	Gut metabolic module	Genus	Genus	KEGG module	Gut metabolic module
Random Forest significance	Significant	Significant	Significant	Non-significant	Significant	Significant	Significant	Significant
Feature 1	uncultured <i>Faecalibacterium prausnitzii</i> 0.6 *	Shannon diversity -0.56 *	M00716: ArlS-ArlR two-component regulatory system -0.71 *	MF0042: 4-aminobutyrate degradation -0.48 *	M00373: Ethylmalonyl pathway 0.58 *	MF0099: methanol conversion -0.54 *	Shannon diversity -0.26	Shannon diversity -0.37
Feature 2	Shannon diversity -0.54 *	<i>Bifidobacterium</i> -0.51	M00227: Glutamine transport system -0.76 *	MF0048: lactose degradation 0.59 *	M00425: HACA ribonucleoprotein complex -0.74 *	MF0042: 4-aminobutyrate degradation -0.56 *	<i>Bifidobacterium</i> -0.67 *	<i>Anaerostipes</i> -0.49 *
Feature 3	<i>Blautia</i> sp. -0.57 *	Dehalococcoidales gen. incertae sedis -0.56 *	M00342: Bacterial proteasome -0.7 *	MF0030: threonine degradation (formate pathway) -0.46 *	M00227: Glutamine transport system -0.61 *	MF0048: lactose degradation 0.6 *	<i>Alistipes</i> 0.64 *	<i>Bifidobacterium</i> -0.58 *
Feature 4	<i>Prevotella</i> sp. CAG 520 -0.58 *	<i>Lactobacillus</i> -0.39	M00219: Al-2 transport system 0.56 *	MF0115: Crotonyl-coA from succinate -0.58 *	M00240: Iron complex transport system 0.69 *	MF0039: lysine fermentation to acetate and butyrate 0.17	<i>Anaerostipes</i> -0.37	<i>Lactobacillus</i> -0.38
Feature 5	<i>Eubacterium eligens</i> -0.36	<i>Faecalibacterium</i> 0.36	M00373: Ethylmalonyl pathway 0.71 *	MF0019: proline degradation (aminopentanoate pathway) -0.65 *	M00342: Bacterial proteasome -0.58 *	MF0116: butyrate production via transferase 0.17	<i>Bacteroides</i> 0.58 *	<i>Bacteroides</i> 0.67 *
Feature 6	<i>Ruminococcus</i> species incertae sedis -0.24	<i>Anaerostipes</i> -0.28	M00645: Multidrug resistance, efflux pump SmeABC -0.54 *	MF0084: pyruvate:ferredoxin oxidoreductase -0.47 *	M00260: DNA polymerase III complex, bacteria -0.71 *	MF0022: isoleucine degradation 0.47 *	<i>Lactobacillus</i> -0.57	<i>Succinivibrio</i> -0.55
Feature 7	<i>Lactobacillus acidophilus</i> -0.55 *	Eggerthellaceae gen. incertae sedis -0.37	M00280: PTS system, glucitol/sorbitol-specific II component -0.78 *	MF0033: cysteine degradation (mercaptopyruvate pathway) -0.28	M00646: Multidrug resistance, efflux pump AcrAD-ToiC 0.55 *	MF0097: Methanogenesis - methyl-coM -0.56 *	<i>Succinivibrio</i> -0.53 *	<i>Romboutsia</i> -0.47 *
Feature 8	<i>Ruminococcus</i> sp. CAG 254 -0.53 *	Firmicutes gen. incertae sedis -0.25	M00700: Multidrug resistance, efflux pump AbcA -0.61 *	MF0132: superoxide reductase -0.51 *	M00715: Lincosamide resistance, efflux pump LmrB -0.49 *	MF0089: Entner-Doudoroff pathway I 0.56 *	Firmicutes gen. incertae sedis -0.33	<i>Faecalibacterium</i> 0.41
Feature 9	<i>Bifidobacterium animalis</i> -0.55 *	<i>Clostridium</i> -0.33	M00715: Lincosamide resistance, efflux pump LmrB -0.79 *	MF0085: pyruvate:formate lyase -0.38	M00299: Spermidine/putrescine transport system 0.22	MF0085: pyruvate:formate lyase -0.51 *	<i>Coproccoccus</i> -0.31	Dehalococcoidales gen. incertae sedis -0.46 *
Feature 10	Dehalococcoidales species incertae sedis -0.35	<i>Bacteroides</i> 0.41	M00741: Propanoyl-CoA metabolism, propanoyl-CoA => succinyl-CoA 0.58 *	MF0011: aspartate degradation (oxaloacetate pathway) -0.25	M00390: Exosome, archaea -0.62 *	MF0030: threonine degradation (formate pathway) -0.44 *	<i>Dorea</i> -0.49 *	<i>Fusicatenibacter</i> -0.28



Extended figure 2. The result of random forest regression fitting the scale of perturbation. The random forest models were trained using leave-one-out cross-validation (LOOCV). Each column represents the scale of perturbation based on one feature predicted by the other baseline feature. RF significance is based on the permutation ($n = 1000$) result, where the negative MAE of each RF is compared to the permuted negative MAE. If a negative MAE is larger than $> 95\%$ of the permuted values, then it is regarded as significant ($p < 0.05$). Colors represent Spearman's correlation between the feature with the scale of perturbation. Text below the feature name is the Spearman's rho value. Asterisks and bold texts denote that Spearman's correlation $q < 0.1$. Benjamini-Hochberg procedure was used to adjust the p values within each column ($n = 10$).

Number	1	2	3	4
Baseline	Species	Genus	KEGG module	Gut metabolic module
Fragility index	Species	Genus	KEGG module	Gut metabolic module
Random forest significance	Non-significant	Non-significant	Non-significant	Non-significant
Feature 1	<i>Prevotella copri</i> -0.42	<i>Eubacterium</i> -0.41	M00212: Ribose transport system -0.61 *	MF0019: proline degradation (aminopentanoate pathway) -0.66 *
Feature 2	<i>Prevotella</i> sp. incertae sedis -0.18	Lachnospiraceae gen. incertae sedis 0.41	M00841: Tetrahydrofolate biosynthesis -0.52 *	MF0020: valine degradation 0.44
Feature 3	<i>Roseburia intestinalis</i> 0.64 *	<i>Prevotella</i> -0.07	M00383: ECV complex 0.39	Perturbation scale 0.64 *
Feature 4	<i>Ruminococcus</i> sp. incertae sedis -0.47	Perturbation scale 0.49	M00523: RegB-RegA (redox response) two-component regulatory system 0	MF0103: nitrate reduction (assimilatory) 0.4
Feature 5	<i>Bacteroides caecimuris</i> 0.39	Shannon diversity -0.34	M00790: Pyrroinin biosynthesis, tryptophan => pyrroinin -0.58 *	MF0091: beta-D-glucuronide and D-glucuronate degradation 0.38
Feature 6	uncultured <i>Faecalibacterium prausnitzii</i> 0.28	<i>Coprococcus</i> -0.4	M00261: DNA polymerase alpha / primase complex -0.21	MF0008: tyrosine degradation (hydroxyphenylacet-aldehyde pathway) 0.07
Feature 7	<i>Ruminococcus bicirculans</i> 0.21	Ruminococcaceae gen. incertae sedis 0.37	M00806: PTS system, maltose-specific II component -0.38	MF0076: arabitol degradation -0.37
Feature 8	Lachnospiraceae sp. incertae sedis 0.51	<i>Barnesiella</i> 0.13	M00217: D-Allose transport system -0.34	MF0011: aspartate degradation (oxaloacetate pathway) 0.01
Feature 9	<i>Bifidobacterium ruminantium</i> 0.27	<i>Holdemanella</i> -0.46	M00333: Type IV secretion system 0.26	MF0072: ribitol degradation -0.41
Feature 10	<i>Faecalibacterium</i> sp. 0.28	<i>Bifidobacterium</i> -0.32	M00202: Oligogalacturonide transport system 0.39	MF0097: Methanogenesis - methyl-coM -0.47

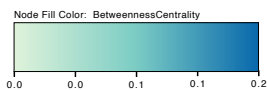
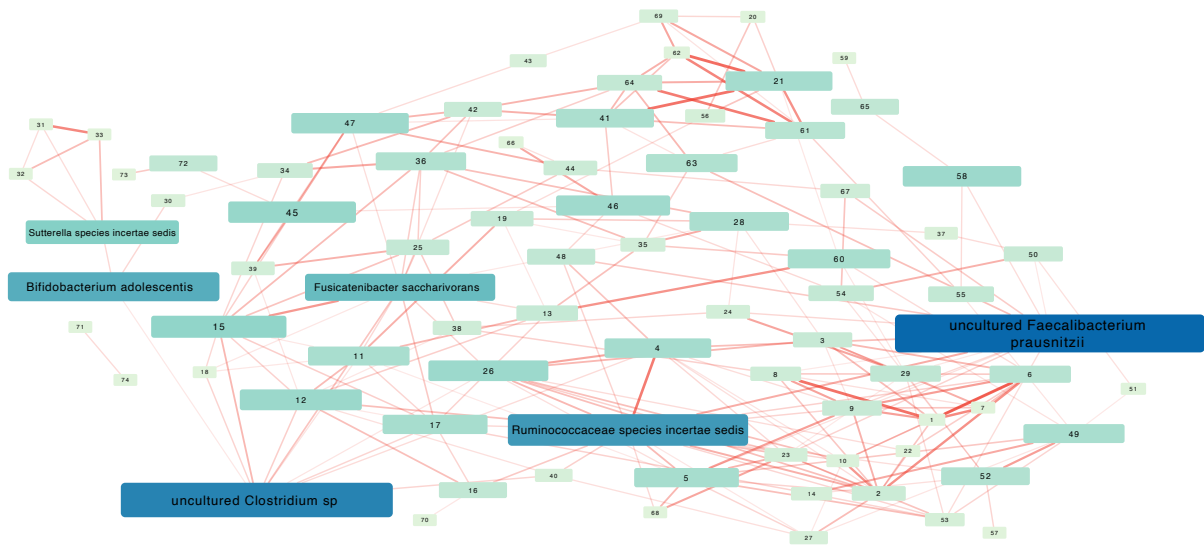


Extended figure 3. The result of random forest regression fitting the fragility index. The random forest models were trained using 5-fold cross-validation. Each column represents the fragility index based on one feature predicted by the other baseline feature. RF significance is based on the permutation ($n = 1000$) result, where the negative MAE of each RF is compared to the permuted negative MAE. If a negative MAE is larger than $> 95\%$ of the permuted values, then it is regarded as significant ($p < 0.05$). Colors represent Spearman's correlation between the feature with the fragility index. Text below the feature name is the Spearman's rho value. Asterisks and bold texts denote that Spearman's correlation $q < 0.1$. Benjamini-Hochberg procedure was used to adjust the p values within each column ($n = 10$).

Number	1	2	3	4
Baseline	Species	Genus	KEGG module	Gut metabolic module
Fragility index	Species	Genus	KEGG module	Gut metabolic module
Random forest significance	Non-significant	Non-significant	Non-significant	Non-significant
Feature 1	Ruminococcaceae species incertae sedis 0.33	Perturbation scale 0.49	M00790: Pyrrolnitrin biosynthesis, tryptophan \Rightarrow pyrrolnitrin -0.58 *	MF0019: proline degradation (aminopentanoate pathway) -0.66 *
Feature 2	<i>Prevotella copri</i> -0.42	<i>Eubacterium</i> -0.41	M00841: Tetrahydrofolate biosynthesis -0.52 *	Perturbation scale 0.64 *
Feature 3	Firmicutes bacterium CAG 341 -0.13	Lachnospiraceae gen. incertae sedis 0.41	M00449: CreC-CreB two-component regulatory system -0.54 *	MF0042: 4-aminobutyrate degradation -0.57 *
Feature 4	<i>Ruminococcus bicirculans</i> 0.21	<i>Prevotella</i> -0.07	M00489: DctS-DctR two-component regulatory system 0.49 *	MF0022: isoleucine degradation 0.47 *
Feature 5	<i>Dorea longicatena</i> -0.58 *	Shannon diversity -0.34	M00115: NAD biosynthesis, aspartate \Rightarrow NAD -0.15	MF0103: nitrate reduction (assimilatory) 0.4
Feature 6	Lachnospiraceae species incertae sedis 0.51 *	<i>Bifidobacterium</i> -0.32	M00403: HRD1/SEL1 ERAD complex -0.35	MF0072: ribitol degradation -0.41
Feature 7	<i>Roseburia intestinalis</i> 0.64 *	<i>Coprococcus</i> -0.4	M00169: CAM (Crassulacean acid metabolism), light 0.58 *	MF0089: Entner-Doudoroff pathway I 0.43 *
Feature 8	<i>Prevotella</i> sp. incertae sedis -0.18	<i>Holdemanella</i> -0.46	M00600: alpha-1,4-Digalacturonate transport system 0.44 *	MF0021: leucine degradation 0.46 *
Feature 9	<i>Blautia obeum</i> 0.2	Ruminococcaceae gen. incertae sedis 0.37	M00354: Spliceosome, U4/U6.U5 tri-snRNP 0.08	MF0008: tyrosine degradation (hydroxyphenylacetaldehyde pathway) 0.07
Feature 10	<i>Bacteroides caecimuris</i> 0.39	<i>Faecalibacterium</i> 0.26	M00212: Ribose transport system -0.61 *	MF0097: Methanogenesis - methyl-coM -0.47 *

Spearman's rho: -1.0 -0.5 0.0 0.5 1.0

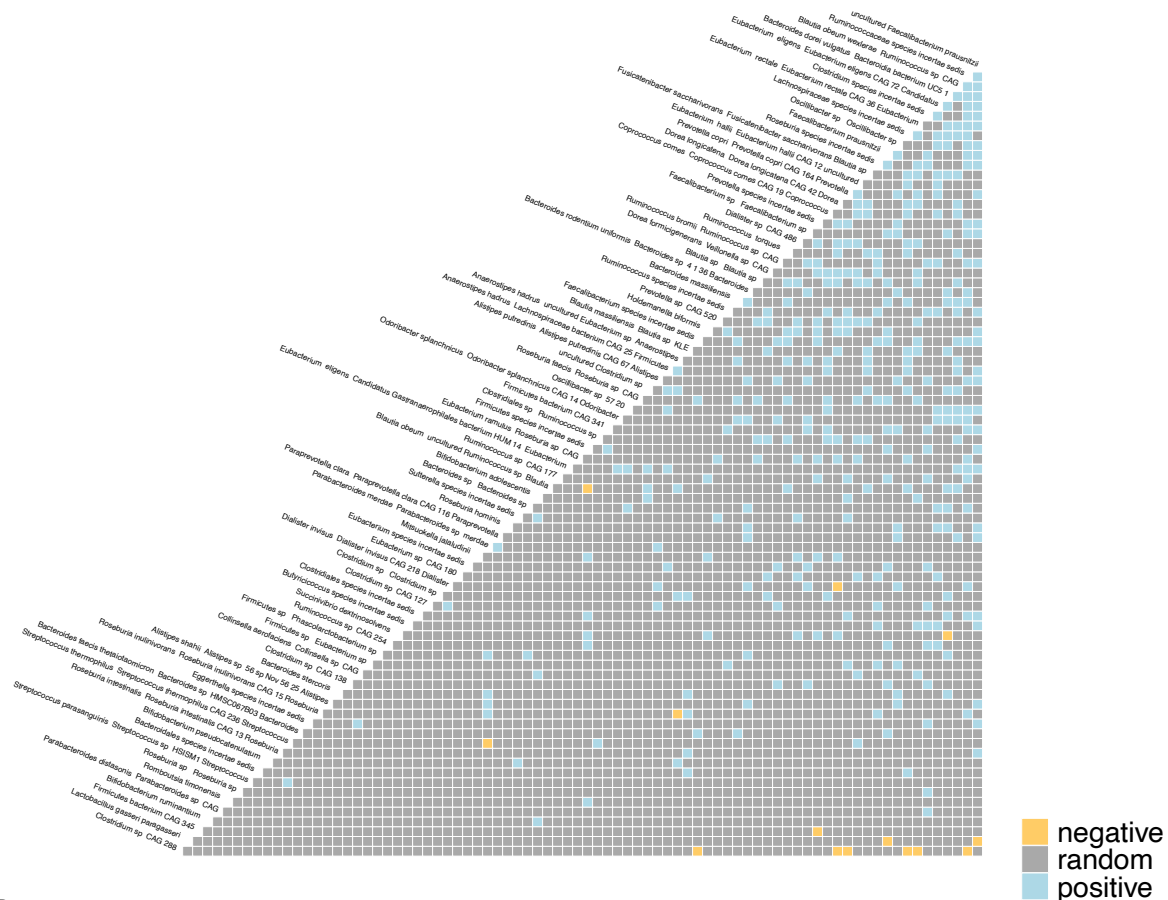
Extended figure 4. The result of random forest regression fitting the fragility index. The random forest models were trained using leave-one-out cross-validation (LOOCV). Each column represents the fragility index based on one feature predicted by the other baseline feature. RF significance is based on the permutation ($n = 1000$) result, where the negative MAE of each RF is compared to the permuted negative MAE. If a negative MAE is larger than $> 95\%$ of the permuted values, then it is regarded as significant ($p < 0.05$). Colors represent Spearman's correlation between the feature with the fragility index. Text below the feature name is the Spearman's rho value. Asterisks and bold texts denote that Spearman's correlation $q < 0.1$. Benjamini-Hochberg procedure was used to adjust the p values within each column ($n = 10$).



- | | | | |
|----|---|----|---|
| 1 | <i>Alistipes shahii</i> | 38 | <i>Bacteroides massiliensis</i> |
| 2 | <i>Bacteroides rodentiumuniformis</i> | 39 | Clostridiales sp |
| 3 | <i>Bacteroides stercoris</i> | 40 | <i>Eubacterium eligens</i> Candidatus |
| 4 | Clostridiales species incertae sedis | 41 | <i>Dialister</i> sp CAG 486 |
| 5 | <i>Faecalibacterium</i> sp | 42 | <i>Prevotella</i> sp CAG 520 |
| 6 | Firmicutes sp | 43 | <i>Romboutsia timonensis</i> |
| 7 | <i>Parabacteroides merdae</i> | 44 | <i>Roseburia faecis</i> |
| 8 | <i>Paraprevotella clara</i> | 45 | <i>Eubacterium hallii</i> |
| 9 | <i>Alistipes putredinis</i> | 46 | <i>Eubacterium</i> sp CAG 180 |
| 10 | <i>Roseburia hominis</i> | 47 | <i>Blautia</i> sp |
| 11 | <i>Anaerostipes hadrus</i> uncultured | 48 | <i>Eubacterium eligens</i> |
| 12 | <i>Blautia obeum/wexlerae</i> | 49 | <i>Clostridium</i> sp CAG 138 |
| 13 | <i>Coprococcus comes</i> | 50 | <i>Roseburia</i> species incertae sedis |
| 14 | <i>Eubacterium</i> species incertae sedis | 51 | <i>Clostridium</i> sp CAG 127 |
| 15 | Lachnospiraceae species incertae sedis | 52 | <i>Clostridium</i> species incertae sedis |
| 16 | <i>Oscillibacter</i> sp | 53 | <i>Faecalibacterium prausnitzii</i> |
| 17 | <i>Anaerostipes hadrus</i> | 54 | <i>Ruminococcus bromii</i> |
| 18 | <i>Blautia obeum</i> uncultured | 55 | <i>Ruminococcus</i> sp CAG 177 |
| 19 | <i>Clostridium</i> sp | 56 | Bacteroidales species incertae sedis |
| 20 | <i>Ruminococcus</i> sp CAG 254 | 57 | <i>Roseburia</i> sp |
| 21 | <i>Succinivibrio dextrinosolvens</i> | 58 | <i>Eggerthella</i> species incertae sedis |
| 22 | <i>Bacteroides</i> sp | 59 | <i>Eubacterium rectale</i> |
| 23 | <i>Oscillibacter</i> sp ER4 | 60 | <i>Ruminococcus</i> species incertae sedis |
| 24 | <i>Roseburia intestinalis</i> | 61 | <i>Holdemanella bififormis</i> |
| 25 | <i>Ruminococcus torques</i> | 62 | <i>Mitsuokella jalaludinii</i> |
| 26 | <i>Bacteroides dorei/vulgatus</i> | 63 | <i>Prevotella copri</i> |
| 27 | <i>Odoribacter splanchnicus</i> | 64 | <i>Prevotella</i> species incertae sedis |
| 28 | <i>Blautia massiliensis</i> | 65 | <i>Collinsella aerofaciens</i> |
| 29 | Firmicutes bacterium CAG 341 | 66 | <i>Butyrivibrio</i> species incertae sedis |
| 30 | <i>Bifidobacterium ruminantium</i> | 67 | <i>Faecalibacterium</i> species incertae sedis |
| 31 | <i>Bifidobacterium pseudocatenuatum</i> | 68 | <i>Dialister invisus</i> |
| 32 | <i>Lactobacillus gasseri/paragasseri</i> | 69 | Firmicutes species incertae sedis |
| 33 | <i>Bifidobacterium catenulatum/kashiwanohense</i> | 70 | <i>Parabacteroides distasonis</i> |
| 34 | <i>Eubacterium ramulus</i> | 71 | Firmicutes sp/ <i>Eubacterium</i> sp CAG 76 |
| 35 | <i>Dorea formicigenerans</i> | 72 | <i>Streptococcus thermophilus</i> |
| 36 | <i>Dorea longicatena</i> | 73 | <i>Streptococcus parasanguinis</i> |
| 37 | <i>Roseburia inulinivorans</i> | 74 | <i>Ruminococcus</i> sp/ <i>Eubacterium</i> sp CAG 76 incertae sedis |

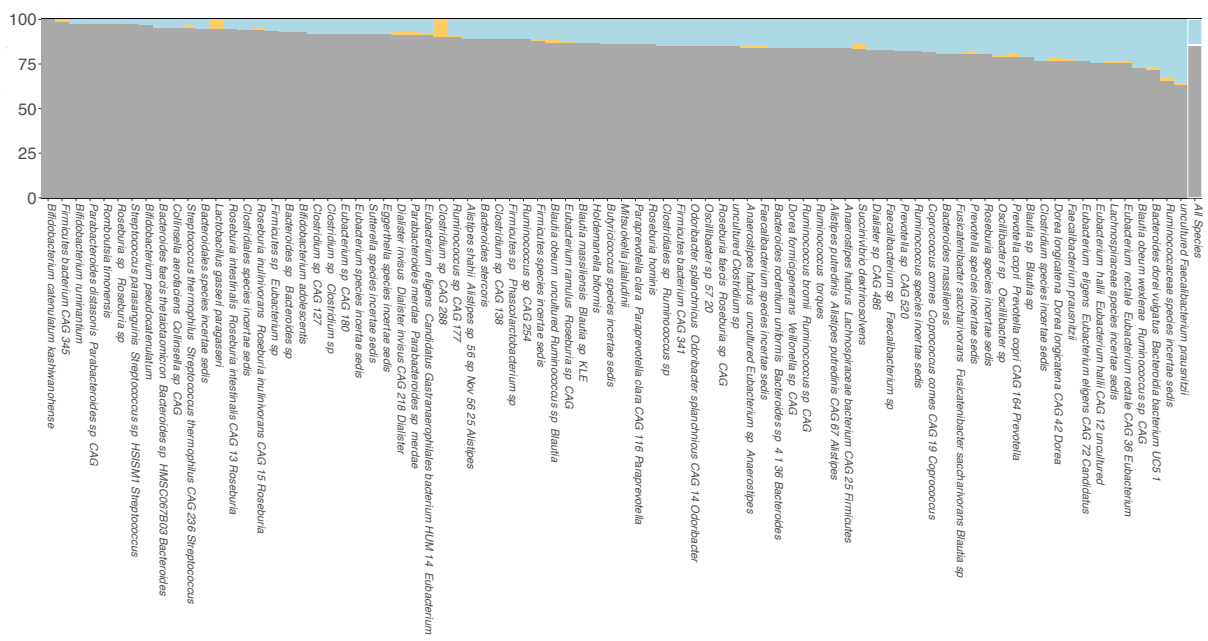
Extended figure 5. Co-occurrence network at species level. Spearman's correlations between all species were calculated, and then those significant ones (Benjamini-Hochberg corrected $q < 0.1$) were used to construct a co-occurrence network. Red and blue represent positive and negative correlation, respectively.

A

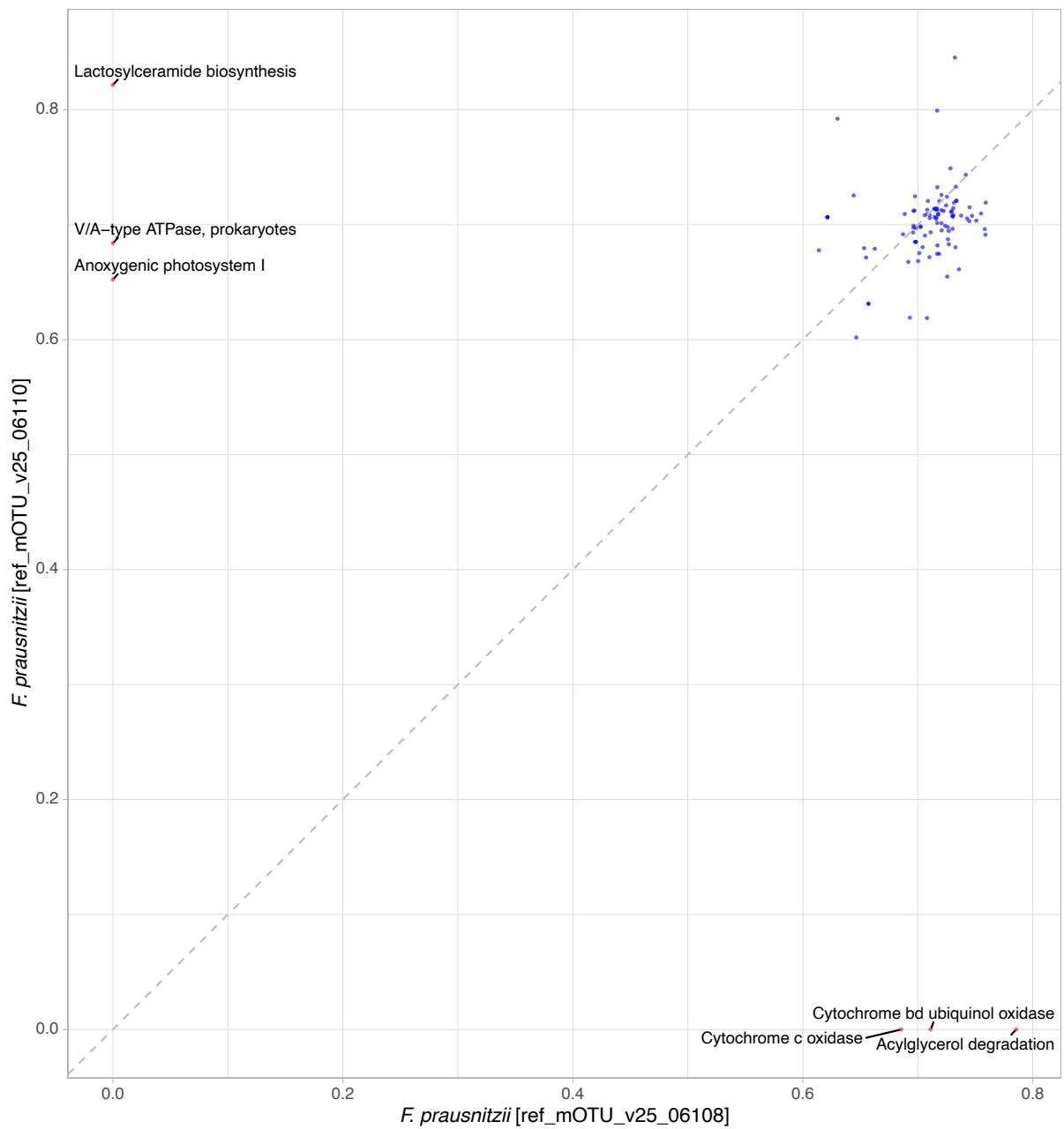


negative
random
positive

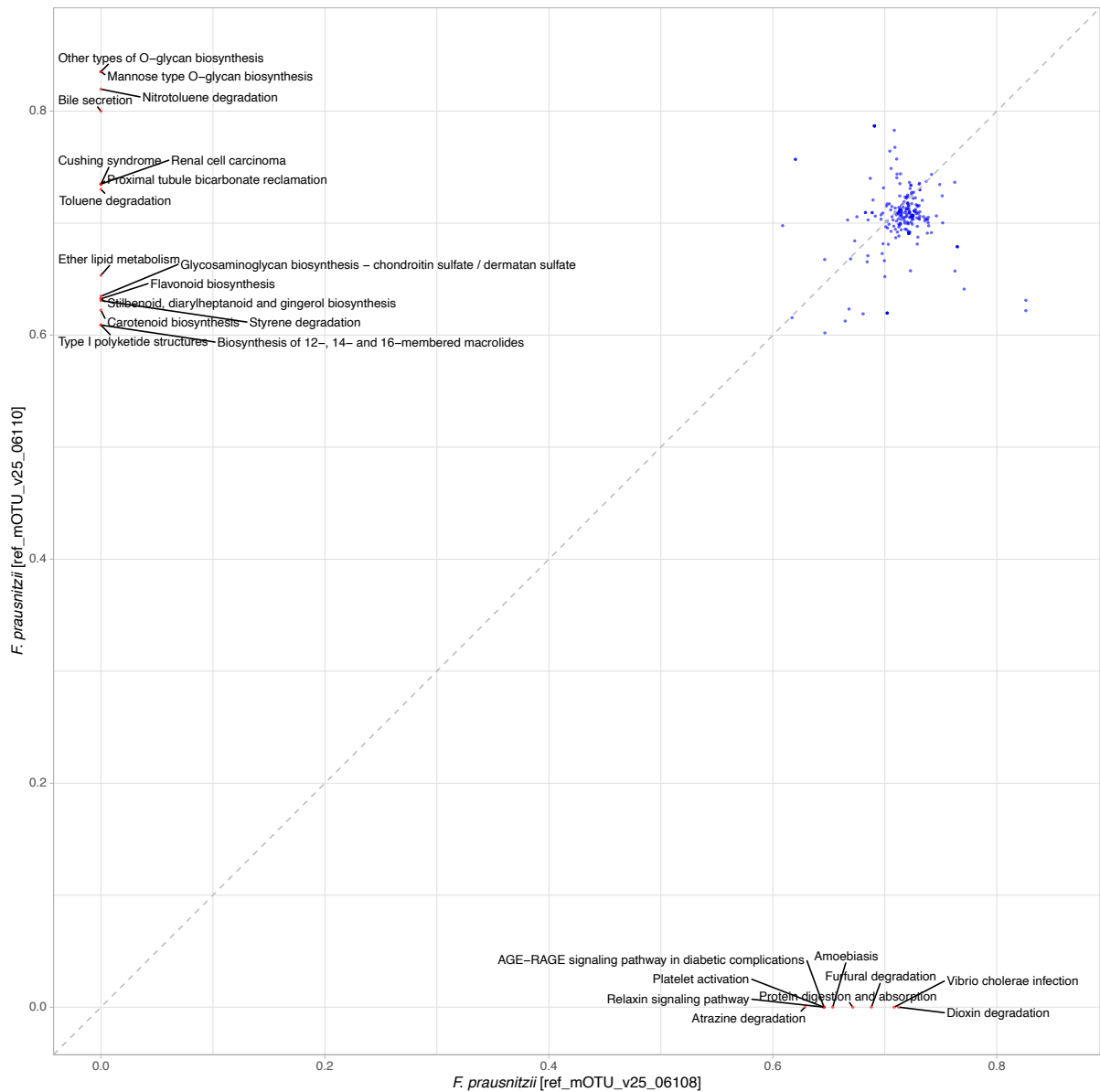
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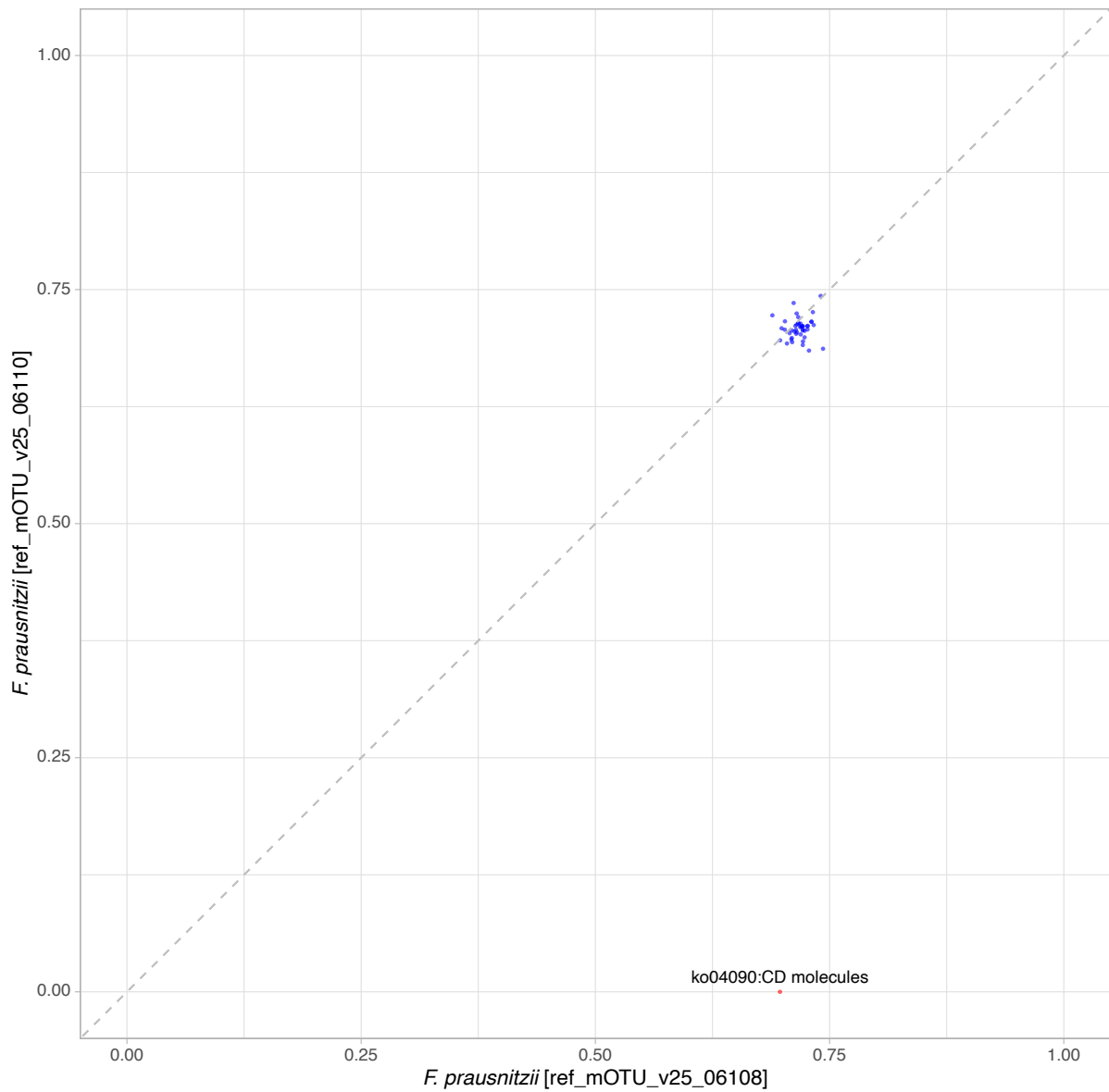
Extended figure 6. Species co-occurrence results of the microbiome community (A) Species co-occurrence Matrix (B) Species association profile. This analysis was done using the coccur R package.



Extended figure 7. The KEGG modules that are correlated with the two uncultured *F. prausnitzii* mOTUs. The x and y axes show the Spearman's rho between the modules and each mOTU (*F. prausnitzii* 06108 on the x-axis and *F. prausnitzii* 06110 on the y-axis). Significant correlations (FDR-corrected $q < 0.05$) were kept and binned into KEGG modules. Red point denotes that the rho difference between the two mOTUs is larger 0.5.



Extended figure 8. The KEGG pathways that are correlated with the two uncultured *F. prausnitzii* mOTUs. The x and y axes show the Spearman's rho between the pathways and each mOTU (*F. prausnitzii* 06108 on the x-axis and *F. prausnitzii* 06110 on the y-axis). Significant correlations (FDR-corrected $q < 0.05$) were kept and binned into KEGG pathways. Red point denotes that the rho difference between the two mOTUs is larger 0.5.



Extended figure 9. The BRITEs that are correlated with the two uncultured *F. prausnitzii* mOTUs. The x and y axes show the Spearman's rho between the BRITEs and each mOTU (*F. prausnitzii* 06108 on the x-axis and *F. prausnitzii* 06110 on the y-axis). Significant correlations (FDR-corrected $q < 0.05$) were kept and binned into BRITEs. Red point denotes that the rho difference between the two mOTUs is larger 0.5.