Title: Gut microbiota is associated with obesity and cardiometabolic disease in a population in the midst of Westernization

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Supplementary Results

Prevotella-Bacteroides co-exclusion.

A pattern commonly observed in microbiome studies has been the co-exclusion of *Prevotella* and *Bacteroides*¹⁻⁵, which has been suggested to suffice for describing enterotypes⁶. We took advantage of the curatedMetagenomicData⁷ package to analyze the breadth of this co-exclusion in 16 benchmark metagenomic studies. This meta-analysis confirmed the co-exclusion between these two taxa, with the co-exclusion being stronger in Western (Spearman’s rho=−0.32, p=0.002) than in non-Western populations (rho=−0.21, p<0.001). We observed that the negative correlation between *Prevotella* and *Bacteroides* in the Colombian cohort was intermediate between Western and non-Western populations (Spearman’s rho=−0.26, p<0.0001); this co-exclusion did not distinguish clear types of microbiota (Fig. SR1).

![Principal coordinate analysis (PCoA) based on weighted UniFrac distances.](image)

**Fig. SR1.** Principal coordinate analysis (PCoA) based on weighted UniFrac distances. Samples are colored by their *Prevotella-Bacteroides* ratio (PB ratio) using the relative abundances of all OTUs classified as *Prevotella* (174 OTUs) and *Bacteroides* (101 OTUs). The *Prevotella-Bacteroides* ratio was calculated as the relative abundances of *Prevotella*/*(Bacteroides + Prevotella)*; red indicates no *Prevotella* and purple no *Bacteroides*. Percentages on the axes represent the proportion of the explained variation of each component of the PCoA.
Replicability of the CAG clustering.

We explored the replicability of the five detected CAGs underscored in the Colombian dataset using genus-level abundance in most of the benchmark metagenomic studies available in the curatedMetagenomicData\textsuperscript{7} package (11 countries comprising 1600 individuals; we excluded datasets from Austria, Germany, Luxembourg, Peru and Tanzania since they considered few individuals for robust CAG inference); note that OTU abundance was unavailable in these datasets.

For each dataset, we applied the methodology employed for CAG definition in the Colombian dataset (see Methods in the main text), and compared the species composition of each CAG with those underscored in the Colombian cohort. In this way, we counted the number of times taxa clustered with “expected” microbes and the number of times there were “unexpected” associations. As an example, consider stool data from the Human Microbiome Project. In this dataset, we detected a CAG containing \textit{Bifidobacterium}, \textit{Collinsella}, \textit{Coprococcus}, \textit{Dorea}, \textit{Faecalibacterium}, \textit{Ruminococcus} and \textit{Streptococcus}. All these microbes, except \textit{Streptococcus}, clustered within the Lachnospiraceae-CAG in our Colombian cohort; \textit{Streptococcus} was expected to cluster within the Pathogen-CAG. We counted the first six cases as checked (1 point was given to each taxon) while \textit{Streptococcus} counted as unchecked (0 points). The replicability of a given CAG was calculated as the sum across datasets of all checked cases for the taxa “expected” to cluster in that CAG over the sum of checked and unchecked cases.

This analysis indicated that most datasets formed well-defined CAGs, some of which overlapped with the five CAGs uncovered in the Colombian cohort. In particular, the Akkermansia-Bacteroidales-, Pathogen- and Lachnospiraceae-CAGs were 70-80% replicable across datasets, whereas the Prevotella- and Ruminococcaceae-CAGs were less common (Table SR1). This is not surprising given that important taxa aggregating within the latter CAGs are enriched in non-Western populations (e.g., \textit{Prevotella}, Ruminococcaceae) while the datasets for comparison originated mostly from Westernized populations, where these taxa are rarer. Even though co-abundance patterns are fundamentally dataset-dependent, several of the CAGs that we underscored in the Colombian cohort were partly replicable and might represent general ecological associations in the human gut microbiota.
Table SR1. Replicability of the “Colombian” CAGs in publicly available datasets (see Methods in the main text).

| CAG                | Taxa “expected” to cluster within the CAG | Taxa found at least once in public datasets | Checked* | Checked + unchecked | Replicability of CAGs |
|--------------------|------------------------------------------|---------------------------------------------|----------|---------------------|-----------------------|
| Prevotella         | 6                                        | 4                                           | 7        | 16                  | 43.75%                |
| Akkermansia-       | 17                                       | 14                                          | 75       | 94                  | 79.79%                |
| Bacteroidales      |                                          |                                             |          |                     |                       |
| Ruminococcaceae    | 11                                       | 2                                           | 1        | 4                   | 25.00%                |
| Lachnospiraceae    | 18                                       | 9                                           | 58       | 84                  | 69.05%                |
| Pathogen           | 10                                       | 7                                           | 27       | 38                  | 71.05%                |

*Number of times the taxa found in at least one public dataset clustered in the “expected” CAG across all datasets.

Supplementary References

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**Fig. S1.** CAG-defining correlation heatmap. Dendrograms obtained by hierarchical Ward-linkage clustering based on Spearman’s correlation coefficients of the relative abundances of the 100 OTUs that had median abundances $\geq 0.01\%$. Color bars on top and left of the heatmap show the defined CAGs.
Fig. S2. Boxplot of α-diversity metrics of each co-abundance group (CAG) calculated in the subset of participants forming high-abundance poles (HAPs; n=114). (A) Species richness, (B) Shannon diversity index, (C) Pielou's J, (D) KEGG ortholog (KO) richness. Notches represent the 95% confidence intervals of the median.
Table S1. Foods most commonly ingested by the participants of the study.

| Food       | Individuals (%) | Mean daily consumption (g) | Notes                                                                 |
|------------|-----------------|----------------------------|----------------------------------------------------------------------|
| Rice       | 77.8            | 150.2                      |                                                                      |
| Vegetable oil | 76.5          | 14.9                       |                                                                      |
| Sugar      | 76.0            | 16.5                       |                                                                      |
| Coffee     | 65.8            | 171.3                      |                                                                      |
| Whole milk | 62.3            | 228.1                      |                                                                      |
| Tomatoes   | 58.4            | 57.5                       |                                                                      |
| Potatoes   | 54.0            | 179                        |                                                                      |
| Bread      | 48.6            | 70.9                       |                                                                      |
| Eggs       | 47.7            | 79.4                       |                                                                      |
| Beef       | 46.4            | 77.3                       |                                                                      |
| Soda       | 44.2            | 336.9                      |                                                                      |
| Arepa      | 43.1            | 96.4                       | Grilled patty of soaked, ground kernels of maize or maize flour       |
| Cheese     | 41.0            | 52.9                       |                                                                      |
| Vegetable fat | 40.3        | 6.9                        |                                                                      |
| Chicken    | 39.9            | 90.1                       |                                                                      |
| Carrot     | 38.6            | 28.5                       |                                                                      |
| Bulb onion | 36.8            | 29.2                       |                                                                      |
| Plantain   | 34.9            | 114.9                      |                                                                      |
| Panela     | 30.3            | 46.3                       | Unrefined whole cane sugar                                           |
| Cookies    | 30.3            | 33.1                       |                                                                      |
| Lime       | 29.2            | 45.4                       |                                                                      |
| Lunch meat | 26.1            | 44.9                       |                                                                      |
| Fish oil   | 24.4            | 8.8                        |                                                                      |
| Tea        | 23.1            | 186.3                      |                                                                      |
| Chocolate  | 21.4            | 9.9                        |                                                                      |
| Lettuce    | 19.8            | 22.4                       |                                                                      |
| Welsh onion| 19.6            | 7.1                        |                                                                      |
| Pea        | 18.3            | 32.8                       |                                                                      |
| Green bean | 15.7            | 31.1                       |                                                                      |
| Pasta      | 15.7            | 133.6                      |                                                                      |
| Banana     | 14.8            | 98                         |                                                                      |
| Mango      | 14.8            | 138.7                      |                                                                      |
| Papaya     | 14.4            | 98.6                       |                                                                      |
| Bean       | 14.4            | 141.7                      |                                                                      |
| Pork       | 14.4            | 81.3                       |                                                                      |
| Coriander  | 13.3            | 0.9                        |                                                                      |
| Garlic     | 12.9            | 2.1                        |                                                                      |
| Tamarillo  | 12.4            | 77.7                       | Solanum betaceum                                                      |
| Blackberry | 12.2            | 56.2                       |                                                                      |
| Manioc     | 12.2            | 55.3                       |                                                                      |
| Ketchup    | 11.8            | 12.9                       |                                                                      |
| Snack foods| 11.5            | 41.6                       |                                                                      |
| Bell pepper| 11.5            | 13.2                       |                                                                      |
| Avocado    | 11.3            | 43.2                       |                                                                      |
| Apple      | 10.7            | 141.3                      |                                                                      |
| Cake       | 10.5            | 101.8                      |                                                                      |
| Guava      | 10.2            | 115.3                      |                                                                      |
| Orange     | 10.0            | 257.7                      |                                                                      |
| Lentil     | 9.4             | 189.5                      |                                                                      |
| Corn       | 9.2             | 38                         |                                                                      |
| Lulo       | 9.2             | 91.3                       | Solanum quitoense                                                     |
| Pineapple  | 9.2             | 110.2                      |                                                                      |
| Chorizo    | 8.7             | 33.2                       |                                                                      |
| Breakfast cereal | 8.3         | 30.2                       |                                                                      |
| Oatmeal    | 8.1             | 66.6                       |                                                                      |
| Toast      | 8.1             | 32.9                       |                                                                      |
| Fish       | 7.8             | 141.6                      |                                                                      |
| Cabbage    | 7.8             | 24.5                       |                                                                      |
| Sugar candy| 7.2             | 17.5                       |                                                                      |
| Tangerine  | 7.2             | 252.4                      |                                                                      |
| Empanada   | 7.0             | 149.6                      | Stuffed and fried pastry made of maize meal                           |
| Vinaigrette| 6.5             | 4.5                        |                                                                      |
| Animal fat | 6.5             | 9                          |                                                                      |
| Powdered milk | 6.5         | 15.1                       |                                                                      |
For each food, the proportion of individuals who reported having eaten it in the last 24 hours and the mean intake in grams is given. Macronutrient intake in the studied population, expressed as the percentage of calories contributed by total carbohydrates, protein and total fat, was (mean ± SD) 55.4 ± 3.0%, 15.7 ± 1.4% and 28.7 ± 2.5%, respectively. Fiber intake was 17.7 ± 5.1 g.
Table S2. Proportions of enrolled participants according to the city of origin, sex, age range and BMI.

| City of origin   | N (%)  | Sex (%male | %female) | Age range (%18-40 yrs | %41-62 yrs) | BMI (%Ln | %Ow | %Ob) |
|------------------|--------|------------|-----------|------------------------|--------------|---------|------|------|
| Barranquilla     | 89 (20%) | 50 | 50 | 43 | 57 | 26 | 39 | 35 |
| Bogota           | 85 (19%) | 40 | 60 | 49 | 51 | 31 | 42 | 27 |
| Bucaramanga     | 79 (18%) | 52 | 48 | 62 | 38 | 38 | 39 | 23 |
| Cali             | 89 (20%) | 43 | 57 | 43 | 57 | 31 | 37 | 31 |
| Medellin         | 99 (22%) | 52 | 48 | 40 | 60 | 31 | 36 | 32 |
| **Total**        | 441 (100%) | 48 | 52 | 47 | 53 | 31 | 39 | 30 |

Ln=lean; Ow=overweight; Ob=obese
Table S3. Marker taxa associated with Westernization.

| Country | Subjects | Lifestyle | Prevotella | Treponema | Bacteroides | Bifidobacterium | Barnesiella |
|---------|----------|-----------|------------|------------|-------------|----------------|-------------|
| AUT     | 6        | Western   | 0.1 ± 0.2  | 0 ± 0      | 4.9 ± 4.9   | 12.1 ± 5.2     | 0.5 ± 0.5   |
| CAN     | 36       | Western   | 3.3 ± 13.1 | 0 ± 0      | 36 ± 18.3   | 1.3 ± 2.4      | 1.7 ± 2.5   |
| CHN     | 278      | Western   | 11.2 ± 21  | 0 ± 0      | 36 ± 21.3   | 1.2 ± 3        | 0.5 ± 1     |
| DEU     | 5        | Western   | 1.7 ± 3.8  | 0 ± 0      | 17.2 ± 10.2 | 7.5 ± 7.5      | 0.8 ± 0.6   |
| DNK     | 163      | Western   | 8 ± 16.4   | 0 ± 0      | 21.6 ± 14.6 | 1.1 ± 1.4      | 2.2 ± 2.7   |
| ESP     | 63       | Western   | 4.6 ± 12.7 | 0 ± 0      | 24 ± 13.8   | 3.1 ± 3.9      | 1.7 ± 1.5   |
| FJI     | 112      | Non-Western | 31.5 ± 16.7 | 2.2 ± 9.1 | 1.7 ± 3.3   | 3.4 ± 6        | 0.1 ± 0.4   |
| FRA     | 41       | Western   | 3.1 ± 9.7  | 0 ± 0      | 15.1 ± 11.1 | 4.6 ± 5.5      | 0.8 ± 1.1   |
| GBR     | 178      | Western   | 1.3 ± 5.1  | 0 ± 0      | 21.6 ± 15.2 | 5.7 ± 7.7      | 2.5 ± 2.7   |
| ITA     | 27       | Western   | 5.1 ± 13.3 | 0 ± 0      | 11.7 ± 14.1 | 17.9 ± 25.1    | 0.5 ± 1     |
| LUX     | 7        | Western   | 0 ± 0      | 0 ± 0      | 19.6 ± 8.9  | 1.2 ± 1.1      | 3.2 ± 2.2   |
| MNG     | 45       | Western   | 17.1 ± 16.6 | 0 ± 0    | 5.2 ± 8.6   | 18.1 ± 17.4    | 0.2 ± 0.7   |
| MNG     | 65       | Non-Western | 16 ± 14.3  | 0 ± 0      | 5.1 ± 10.1  | 17.8 ± 15.5    | 0.2 ± 0.4   |
| NLD     | 393      | Western   | 3.7 ± 7.7  | 0 ± 0      | 8.9 ± 7.8   | 15 ± 12.2      | 0.8 ± 1.1   |
| PER     | 16       | Non-Western | 5.2 ± 4   | 8.8 ± 19.2 | 0.2 ± 0.3   | 2.9 ± 7.1      | 0 ± 0       |
| TZA     | 21       | Non-Western | 27.6 ± 19.4 | 3.1 ± 3.5 | 0.1 ± 0.2   | 0 ± 0          | 0 ± 0       |
| USA     | 199      | Western   | 3.9 ± 11.6 | 0 ± 0      | 39.7 ± 24.6 | 1.1 ± 3.2      | 1.6 ± 3.1   |

**Sample size, Westernization status and relative abundances of the marker taxa of the countries included in the analysis of publicly available datasets.**

*The values in parentheses exclude the particular Mongolian populations.

**From Wilcoxon rank sum tests, testing the null hypothesis that the abundance of each marker taxa is not significantly different between Western and non-Western populations.

| Markers |
|---------|
|         |
| Western |
| Non-Western |
| P-value** |

|          |          |          |          |          |
|----------|----------|----------|----------|----------|
|          | 4.85 ± 4.80 | 0 ± 0 | 20.12 ± 11.52 | 6.92 ± 6.61 (5.98 ± 5.94)* | 1.31 ± 0.92 |
|          | 20.08 ± 11.90 | 3.52 ± 3.75 | 1.78 ± 2.33 | 6.02 ± 7.99 (2.10 ± 1.84)* | 0.08 ± 0.10 |
| P-value** | 0.01 | 0.001 | 0.005 | 0.69 (0.35)* | 0.004 |
Table S4. OTUs correlated with the PCoA axes of weighted UniFrac distances.

| OTU     | Taxonomy (k = kingdom; p = phylum; c = class; o = order; f = family; g = genus; s = species)                                                                                       | Spearman's rho          |
|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| OTu00001| k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Prevotellaceae;g__Prevotella;s__copri;                                                                           | PCo1 (16.30%)           |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | PCo2 (13.71%)           |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | PCo3 (11.82%)           |
| OTu00002| k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Prevotellaceae;g__Prevotella;s__copri;                                                                           | -0.56                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.13                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.45                    |
| OTu00003| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Gemmiger;s__formicilis;                                                                           | -0.65                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.15                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.51                    |
| OTu00004| k__Bacteria;p__Proteobacteria;c__Gammaproteobacteria;o__Enterobacteriales;f__Enterobacteriaceae;g__Escherichia;s__coli;                                                             | -0.35                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.07                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.63                   |
| OTu00006| k__Bacteria;p__Verrucomicrobia;c__Verrucomicrobiae;o__Verrucomicrobiales;f__Verrucomicrobiaceae;g__Akkermansia;s__muciniphila; | 0.48                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.54                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.28                   |
| OTu00007| k__Bacteria;p__Actinobacteria;c__Actinobacteria;o__Bifidobacteriales;f__Bifidobacteriaceae;g__Bifidobacterium;s__adolescentis; | 0.33                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.19                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.14                    |
| OTu00008| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Faecalibacterium;s__prausnitzii;                                                               | 0.42                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.48                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.07                    |
| OTu00009| k__Bacteria;p__Proteobacteria;c__Gammaproteobacteria;o__Enterobacteriales;f__Enterobacteriaceae;g__Enterobacter;s__hormaechei; | -0.38                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.23                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.38                   |
| OTu00010| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Clostridium;s__celatum;                                                                         | 0.05                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.30                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.06                    |
| OTu00012| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Oscillospira;unclassified;                                                                   | 0.16                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.18                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.35                    |
| OTu00020| k__Bacteria;p__Firmicutes;c__Bacilli;o__Lactobacillales;f__Streptococcaceae;g__Streptococcus;unclassified;                                                                       | 0.18                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.46                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.09                   |
| OTu00021| k__Bacteria;p__Firmicutes;c__Bacilli;o__Lactobacillales;f__Streptococcaceae;g__Streptococcus;unclassified;                                                                       | 0.10                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.35                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.14                   |
| OTu00030| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Blautia;s__obeum;                                                                               | 0.34                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.42                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.10                    |
| OTu00032| k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Prevotellaceae;g__Prevotella;s__stercorea;                                                                    | -0.38                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.02                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.19                    |
| OTu00033| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Oscillospira;unclassified;                                                                  | -0.02                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.20                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.32                    |
| OTu00037| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Blautia;unclassified;                                                                     | 0.00                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.35                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.05                    |
| OTu00041| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Oscillospira;unclassified;                                                                   | 0.22                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.01                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.32                    |
| OTu00043| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Ruminococcaceae;g__Oscillospira;unclassified;                                                                  | -0.01                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.17                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.32                    |
| OTu00046| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Blautia;unclassified;                                                                     | 0.30                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.37                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.06                    |
| OTu00052| k__Bacteria;p__Actinobacteria;c__Coriobacteriia;o__Coriobacteriales;f__Coriobacteriaceae;unclassified;                                                                  | 0.13                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.04                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.30                    |
| OTu00058| k__Bacteria;p__Actinobacteria;c__Actinomycetales;o__Actinomyces;unclassified;                                                                                                    | 0.34                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.37                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.04                    |
| OTu00060| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Blautia;unclassified;                                                                    | 0.36                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.06                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.20                    |
| OTu00083| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Dorea;s__formigenerans;                                                                     | 0.17                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.46                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.18                    |
| OTu00097| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Mogibacteriaceae;unclassified;unclassified;                                                                  | 0.31                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.29                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.17                    |
| OTu00108| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Coprococcus;unclassified;                                                                  | -0.10                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.01                   |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.34                    |
| OTu00126| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Clostridium;s__clostridiforme;                                                              | 0.37                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.20                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.02                   |
| OTu00197| k__Bacteria;p__Firmicutes;c__Bacilli;o__Gemellales;f__Gemellaceae;g__Gemella;unclassified;                                                                               | 0.12                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.36                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | -0.13                   |
| OTu00284| k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Coprococcus;unclassified;                                                                | 0.22                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.30                    |
|         |                                                                 ------------------------------------------------------------------------------------------------------------------ | 0.24                    |

Spearman’s correlation coefficients of the operational taxonomic units (OTUs) that had a median abundance ≥0.01% and that were significantly correlated (q-value<0.05) with one of the first three axes of the weighted UniFrac principal correspondence analysis (PCoA). Rho<-0.3 or rho>0.3, and q-value<0.05 are highlighted in bold. The percentages of explained variations are given for each PCoA axis.
| CAG | OTU | Median relative abundance | Taxonomy (k = kingdom; p = phylum; c = class; o = order; f = family; g = genus; s = species) | SparCC-based CAG | Mean decrease accuracy |
|-----|-----|---------------------------|---------------------------------------------------------------------------------|------------------|---------------------|
| Prevotella | 0.033 | Bacteroidetes:p Bacteroidetes;o Bacteroidales:f Prevotellaceae,g Prevotella;s copri | Prevotella | 0.698 |
| | 0.02974 | Bacteroidetes:p Bacteroidetes;o Bacteroidales:f Prevotellaceae,g Prevotella;s copri | Prevotella | 0.457 |
| | 0.0101 | Bacteroidetes:p Actinobacteria:o Coriobacteria:o Coriobacteriales:f Coriobacteriaceae,g Adlercreutzia:unclassified | Prevotella | 0.52 |
| | 0.01128 | Bacteroidetes:p Firmicutes:o Erysipelotrichi:o Erysipelotrichales:f Erysipelotrichaceae,g Catenibacterium:unclassified | Prevotella | 0.13 |
| | 0.03852 | Bacteroidetes:p Firmicutes:o Erysipelotrichi:o Erysipelotrichaceae,g [Eubacterium]:unclassified | Prevotella | 0.85 |
| | 0.0018 | Bacteroidetes:p Actinobacteria:o Coriobacteria:o Coriobacteriales:f Coriobacteriaceae,g Adlercreutzia:unclassified | Lachnospiraceae | 0.62 |
| | 0.00241 | Bacteroidetes:p Actinobacteria:o Coriobacteria:o Coriobacteriales:f Coriobacteriaceae,g Adlercreutzia:unclassified | Lachnospiraceae | 0.69 |
| | 0.01034 | Bacteroidetes:p Actinobacteria:o Coriobacteria:o Coriobacteriales:f Coriobacteriaceae,g Adlercreutzia:unclassified | Lachnospiraceae | 0.113 |
| | 0.01433 | Bacteroidetes:p Clostridia:o Clostridiales:f Ruminococcaceae,g Gemmiger:s formicilis | Lachnospiraceae | 0.113 |
| Lachnospiraceae | 0.0102 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Faecalibacterium:s prausnitzii | Pathogen | 0.12 |
| | 0.00972 | Bacteroidetes:p Actinobacteria:o Bifidobacteria:o Bifidobacteriales:f Bifidobacteriaceae,g Bifidobacterium:s adolescentis | Lachnospiraceae | 0.266 |
| | 0.01286 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Faecalibacterium:s prausnitzii | Lachnospiraceae | 0.352 |
| | 0.00383 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Clostridiaceae,g Clostridium:s cellulatum | Lachnospiraceae | 0.043 |
| | 0.00804 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Roseburia:s faecis | Pathogen | 0.031 |
| | 0.00514 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Cellulosibacter:s alkalithermophilus | Prevotella | 0.031 |
| | 0.01072 | Bacteroidetes:p Actinobacteria:o Coriobacteria:o Coriobacteriales:f Clostridiaceae,g Collinsella:s aerofaciens | Lachnospiraceae | 0.103 |
| | 0.00453 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Ruminococcus:s gnavus | Lachnospiraceae | 0.022 |
| | 0.00962 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Bulryanococcus:s paulceorum | Lachnospiraceae | 0.022 |
| | 0.0047 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Ruminococcus:s albus | Lachnospiraceae | 0.136 |
| | 0.00149 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Ruminococcus:s lactaris | Lachnospiraceae | 0.004 |
| | 0.0084 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Blautia:s ubuminumin | Lachnospiraceae | 0.071 |
| | 0.00036 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Ruminococcus:s gnavus | Pathogen | 0.013 |
| | 0.01178 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Ruminococcus:s albus | Lachnospiraceae | 0.031 |
| | 0.00387 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Ruminococcus:s albus | Pathogen | 0 |
| | 0.00254 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Blautia:s obum | Lachnospiraceae | 0.136 |
| | 0.00049 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Ruminococcus:s lactaris | Lachnospiraceae | 0.014 |
| | 0.00148 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Blautia:s ubiquitim | Lachnospiraceae | 0.032 |
| | 0.00149 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Roseburia:s inulinivorans | Pathogen | 0.007 |
| | 0.00088 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Dorea:s unclassified | Lachnospiraceae | 0.037 |
| | 0.00012 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Enterococcaceae,g Enterococcus:s casseliflavus | Pathogen | 0.007 |
| | 0.00039 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Coprococcus:unclassified | Pathogen | 0.018 |
| | 0.00114 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Dorea:s formigenicola | Lachnospiraceae | 0.117 |
| | 0.00157 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Clostridiaceae,g Clostridium:unclassified | Lachnospiraceae | 0.031 |
| | 0.00051 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f [Mogibacteriaceae]:unclassified | Lachnospiraceae | 0.044 |
| | 0.00126 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Clostridium:s distridiforme | Pathogen | 0.057 |
| | 0.0004 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Ruminococcus:s infantilis | Pathogen | 0.038 |
| | 0.00012 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Dorea:unclassified | Lachnospiraceae | 0.005 |
| | 0.00011 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Ruminococcaceae,g Ruminococcus:s mosora | Lachnospiraceae | 0.087 |
| | 0.00013 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Coprococcus:unclassified | Lachnospiraceae | 0.036 |
| | 0.0002 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Ruminococcus:s mosora | Pathogen | 0.006 |
| | 0.00218 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Ruminococcus:s mosora | Lachnospiraceae | 0.018 |
| | 0.00082 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Ruminococcus:s mosora | Pathogen | 0.023 |
| | 0.00034 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Ruminococcus:s mosora | Lachnospiraceae | 0.008 |
| | 0.00027 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Ruminococcus:s mosora | Pathogen | 0.011 |
| | 0.00017 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Ruminococcus:s mosora | Lachnospiraceae | 0.031 |
| | 0.00015 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Ruminococcus:s mosora | Pathogen | 0.009 |
| Pathogen | 0.00014 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Ruminococcus:s mosora | Pathogen | 0 |
| | 0.00019 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Ruminococcus:s mosora | Pathogen | 0 |
| | 0.00011 | Bacteroidetes:p Firmicutes:o Clostridia:o Clostridiales:f Lachnospiraceae,g Ruminococcus:s mosora | Lachnospiraceae | 0.015 |
The 95th percentile of the distribution of each CAG is shown. In addition, for each OTU, the median relative abundance, the taxonomy, the alternative grouping proposed by the compositional network reconstruction analysis (SparCC) and the decreasing mean accuracy to discriminate CAGs by the Random Forest machine-learning algorithm are shown.
| Metabolic module ID | Metabolic module name | Hierarchy level 1 | Hierarchy level 2 | Prevotella-CAG | Lachnospiracea-CAG | Pathogen-CAG | Akkermansia-Bacteroidales-CAG | Ruminococcaceae-CAG | q-value (Benjamini-Hochberg) | q-value (Kruskal-Wallis) |
|---------------------|----------------------|------------------|------------------|---------------|-------------------|--------------|-----------------------------|------------------|-----------------------------|-----------------------------|
| MF0001              | ethanol production (formate pathway) | alcohol metabolism | ethanol metabolism | 0.001895 | 0.002039124 | 0.001441904 | 0.00122 | 0.00142 | 5.63E-09 | 6.86E-09 |
| MF0003              | acetylglucosaminuria degradation | amines and polyamines degradation | acetylglucosamine degradation | 0.0003715 | 0.000729 | 0.00033 | 0.000314 | 0.001014 | 4.15E-12 | 2.93E-12 |
| MF0005              | acetylmannosamine degradation | amines and polyamines degradation | biacetyl acid degradation | 0.000187 | 0.000273 | 0.000177 | 0.000205 | 0.000203 | 4.52E-13 | 3.94E-14 |
| MF0007              | acetylneuraminic acid degradation | amines and polyamines degradation | acetylneuraminic acid degradation | 0.000351 | 0.000465 | 0.000339 | 0.000254 | 0.000254 | 6.3E-12 | 3.94E-14 |
| MF0008              | acetylglucosamine degradation | amines and polyamines degradation | acetylglucosamine degradation | 0.0000517 | 0.00008049 | 0.0000169 | 0.0000374 | 0.000046 | 4.5E-09 | 3.59E-09 |
| MF0009              | acetylglutamic acid degradation | amines and polyamines degradation | acetylglutamic acid degradation | 0.000029 | 0.000039 | 0.000036 | 0.000026 | 0.000026 | 6.4E-14 | 2.57E-13 |
| MF0010              | acetylpyruvic acid degradation | amines and polyamines degradation | acetylpyruvic acid degradation | 0.00001184 | 0.00001574 | 0.000015 | 0.0000152 | 0.0000152 | 7.12E-08 | 7.18E-08 |
| MF0011              | acetylglutamate degradation | amines and polyamines degradation | acetylglutamate degradation | 0.000017 | 0.0000217 | 0.0000187 | 0.0000187 | 0.0000187 | 5.15E-12 | 9.23E-12 |
| MF0012              | acetylglutamate degradation | amines and polyamines degradation | acetylglutamate degradation | 0.00003 | 0.00003 | 0.00003 | 0.00003 | 0.00003 | 5.15E-12 | 9.23E-12 |
| MF0014              | acetylglutamate degradation | amines and polyamines degradation | acetylglutamate degradation | 0.000029 | 0.000039 | 0.000036 | 0.000026 | 0.000026 | 6.4E-14 | 2.57E-13 |
| MF0015              | acetylglutamate degradation | amines and polyamines degradation | acetylglutamate degradation | 0.00001184 | 0.00001574 | 0.000015 | 0.0000152 | 0.0000152 | 7.12E-08 | 7.18E-08 |
| MF0016              | acetylglutamate degradation | amines and polyamines degradation | acetylglutamate degradation | 0.00001184 | 0.00001574 | 0.000015 | 0.0000152 | 0.0000152 | 7.12E-08 | 7.18E-08 |
| MF0017              | acetylglutamate degradation | amines and polyamines degradation | acetylglutamate degradation | 0.00001184 | 0.00001574 | 0.000015 | 0.0000152 | 0.0000152 | 7.12E-08 | 7.18E-08 |

Table S6. Metabolic modules present in the gut microbiota of individuals with single-CAG dominated microbiota.
| Metabolic module ID | Metabolic module name | Hierarchy level 1 | Hierarchy level 2 | Prevotella- CAG | Lachnospiraceae-CAG | Pathogen- CAG | Akkermansia- Bacteroidales-CAG | Ruminococcaceae- CAG | B-value (Kruskal-Wallis) | B-value (Benjamini-Hochberg) |
|---------------------|-----------------------|------------------|------------------|----------------|------------------|-------------|-------------------------------|--------------------------|--------------------------|--------------------------|
| MF0069              | succinate degradation  | carbohydrate degradation | sugar degradation | 0.0001245 | 0.0003455 | 0.000118 | 0.0000513 | 0.000185 | 1.8E-12 | 3.8E-12 |
| MF0107              | succinate degradation  | carbohydrate degradation | sugar degradation | 0.0000685 | 0.0002011 | 0.000118 | 0.0000513 | 0.000185 | 1.8E-12 | 3.8E-12 |
| MF0111              | Z-galacturonate degradation | carbohydrate degradation | sugar degradation | 0.00032 | 0.0001313 | 0.000369 | 0.000106 | 0.000191 | 1.7E-06 | 2.1E-06 |
| MF0114              | methyl degradation | carbohydrate degradation | sugar degradation | 0.000167 | 0.000067 | 0.2967 | 0.000118 | 0.000229 | 1.3E-11 | 2.5E-11 |
| MF0134              | sorbitol degradation (dehydration) | carbohydrate degradation | sugar degradation | 0.0001715 | 0.0001218 | 0.000184 | 0.0000517 | 0.000119 | 1.8E-12 | 3.8E-12 |
| MF0136              | sorbitol degradation (phosphoformate):sorbitose degradation | carbohydrate degradation | sugar degradation | 0.0000506 | 0.000352 | 0.000154 | 0.0000803 | 0.000206 | 1.9E-12 | 2.4E-12 |
| MF0140              | succinate degradation | carbohydrate degradation | sugar degradation | 0.000166 | 0.000237 | 0.000118 | 0.0000513 | 0.000185 | 1.8E-12 | 3.8E-12 |
| MF0157              | succinate degradation | carbohydrate degradation | sugar degradation | 0.0003235 | 0.000222 | 0.000274 | 0.0000803 | 0.000206 | 1.9E-12 | 2.4E-12 |
| MF0165              | threonine degradation | carbohydrate degradation | sugar degradation | 0.000447 | 0.000424 | 0.000368 | 0.00015 | 0.000333 | 2.22E-06 | 2.39E-06 |
| MF0062              | sorbose phosphate pathway (oxidative branch) | carbohydrate degradation | energy metabolism | 0.000175 | 0.000036 | 0.000407 | 0.000118 | 0.000229 | 1.3E-11 | 2.5E-11 |
| MF0063              | xylulose dehydrogenase complex | carbohydrate degradation | energy metabolism | 0.0004895 | 0.000424 | 0.000368 | 0.00015 | 0.000333 | 2.22E-06 | 2.39E-06 |
| MF0066              | MF0070 galactonate degradation carbohydrate degradation | 0.00000513 | 0.0000165 | 1.52E-12 | 3.82E-12 |
| MF0067              | MF0071 sorbitol degradation carbohydrate degradation | 0.00000513 | 0.0000165 | 1.52E-12 | 3.82E-12 |
| MF0068              | MF0072 threonine degradation carbohydrate degradation | 0.00000513 | 0.0000165 | 1.52E-12 | 3.82E-12 |
| MF0069              | MF0073 xylulose dehydrogenase complex carbohydrate degradation | 0.00000513 | 0.0000165 | 1.52E-12 | 3.82E-12 |
| MF0070              | MF0074 threonine degradation carbohydrate degradation | 0.00000513 | 0.0000165 | 1.52E-12 | 3.82E-12 |
| MF0071              | MF0075 xylulose dehydrogenase complex carbohydrate degradation | 0.00000513 | 0.0000165 | 1.52E-12 | 3.82E-12 |

Abundances of inferred metabolic modules for each co-abundance group (CAG) of microbes in the subset of participants having high abundance pols (HAPs; n=114, P-values (from Kruskal-Wallis tests) and q-values (Benjamini Hochberg correction) denote differences in the functional potential among CAGs.
Table S7. Correlations between relevant metabolic modules and co-abundance groups (CAGs) of microbes in the complete dataset.

| Modules Figure 5A | Prevotella-CAG | Lachnospiraceae-CAG | Pathogen-CAG | Akkermansia-Bacteroidales-CAG | Ruminococcaceae-CAG |
|-------------------|----------------|---------------------|--------------|-----------------------------|--------------------|
|                   | Rho | q value | Rho | q value | Rho | q value | Rho | q value | Rho | q value |
| Lipopolysaccharide biosynthesis | 0.02 | 0.06 | -0.17 | 0.05 | 0.50 | 0.0002 | -0.03 | <0.0001 | -0.41 | <0.0001 |
| Mucus degradation | -0.18 | <0.0001 | 0.35 | <0.0001 | -0.09 | <0.0001 | 0.33 | <0.0001 | -0.49 | 0.04 |
| Methanogenesis | 0.20 | <0.0001 | -0.15 | <0.0001 | -0.13 | <0.0001 | -0.27 | <0.0001 | 0.58 | 0.004 |

| Modules Figure 5B | Prevotella-CAG | Lachnospiraceae-CAG | Pathogen-CAG | Akkermansia-Bacteroidales-CAG | Ruminococcaceae-CAG |
|-------------------|----------------|---------------------|--------------|-----------------------------|--------------------|
|                   | Rho | q value | Rho | q value | Rho | q value | Rho | q value | Rho | q value |
| Lipopolysaccharide biosynthesis | 0.21 | <0.0001 | 0.15 | <0.0001 | -0.18 | 0.0002 | -0.34 | <0.0001 | 0.41 | <0.0001 |
| Mucus degradation | 0.13 | <0.0001 | 0.25 | <0.0001 | 0.29 | <0.0001 | -0.37 | 0.04 | -0.26 | <0.0001 |
| Methanogenesis | -0.24 | 0.0002 | -0.25 | <0.0001 | 0.14 | 0.0003 | 0.47 | 0.04 | -0.31 | 0.03 |

| Modules Figure 5C | Prevotella-CAG | Lachnospiraceae-CAG | Pathogen-CAG | Akkermansia-Bacteroidales-CAG | Ruminococcaceae-CAG |
|-------------------|----------------|---------------------|--------------|-----------------------------|--------------------|
|                   | Rho | q value | Rho | q value | Rho | q value | Rho | q value | Rho | q value |
| Lipopolysaccharide biosynthesis | 0.41 | <0.0001 | 0.07 | <0.0001 | 0.29 | <0.0001 | -0.67 | 0.01 | 0.01 | 0.09 |
| Mucus degradation | -0.05 | 0.006 | -0.73 | <0.0001 | 0.05 | <0.0001 | 0.19 | <0.0001 | 0.24 | <0.0001 |
| Methanogenesis | -0.05 | 0.0008 | 0.70 | <0.0001 | -0.10 | <0.0001 | -0.05 | <0.0001 | -0.24 | <0.0001 |

Correlations between the relative abundances of metabolic modules depicted in Fig. 5 and CAG abundances in the complete dataset (n=441). Spearman's rho and q-values are shown.