

Supplementary Information

Supplementary information includes:

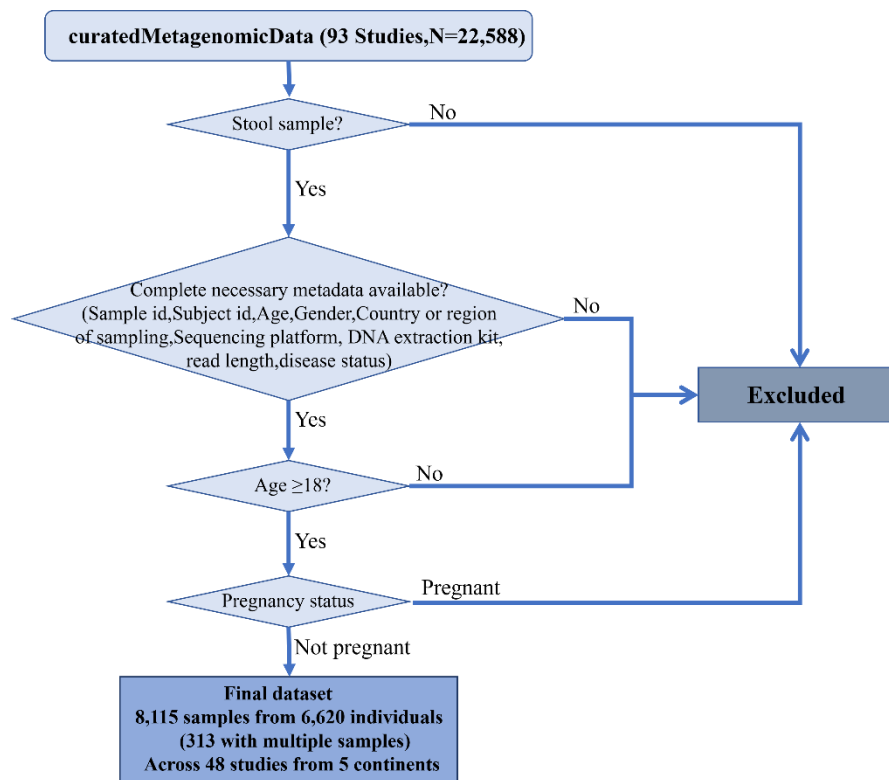
Supplementary Figures 1-8

Supplementary Tables 1-7

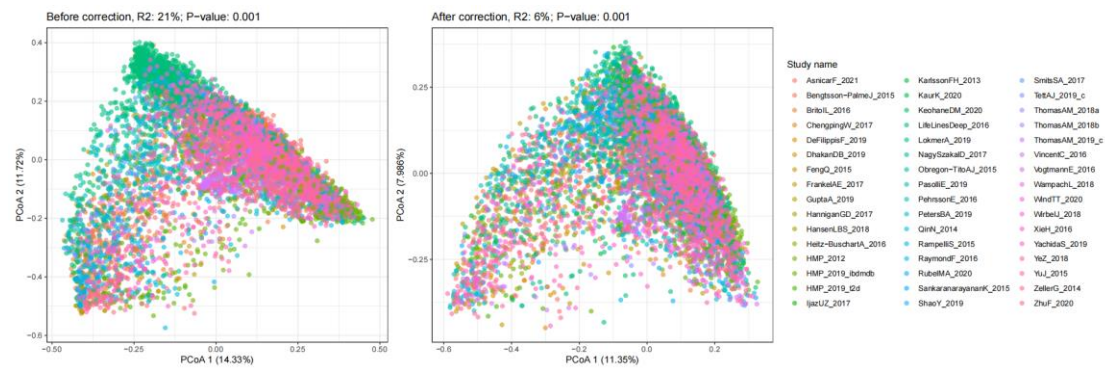
Supplementary Text

Supplementary Text Figure 1

Supplementary Text Reference

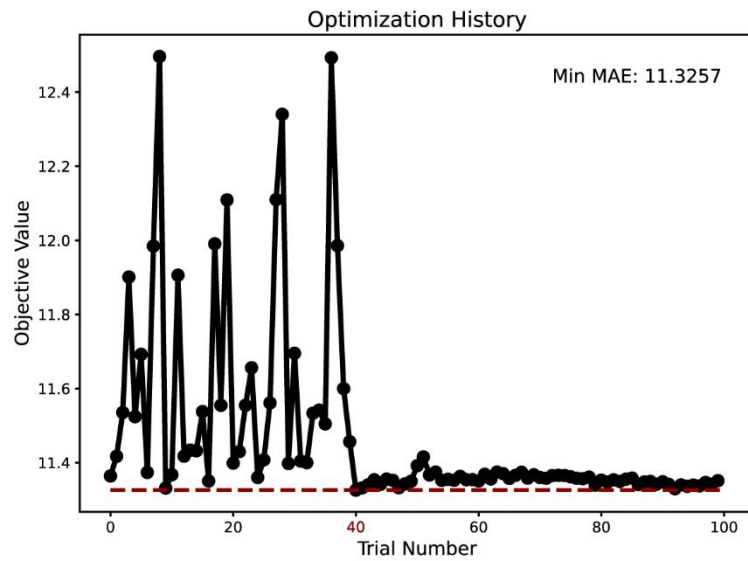
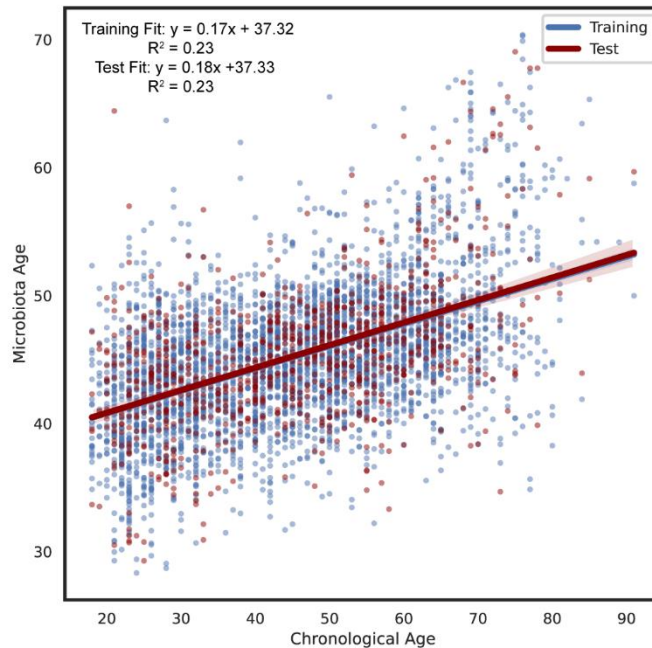


Supplementary Figure 1. Sample selection workflow. Overview of sample selection from curatedMetagenomicData. Of 22,588 samples across 93 studies, 8,115 stool samples from 6,620 individuals (48 studies) passed inclusion criteria: age ≥ 18 years, complete metadata (age, sex, geography, disease status, sequencing parameters), and non-pregnancy status. Final dataset excluded samples with incomplete metadata or non-stool sources.

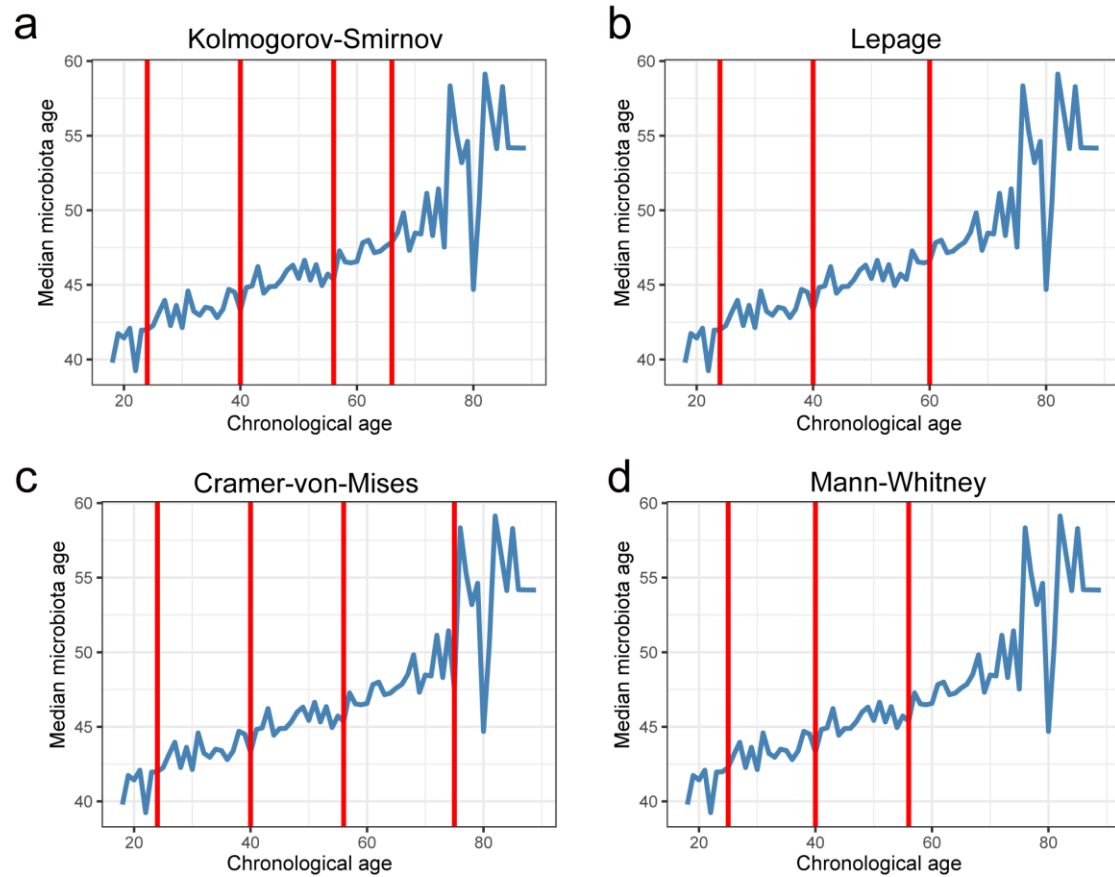


Supplementary Figure 2. Batch effects decreased after being adjusted by MMUPHin.

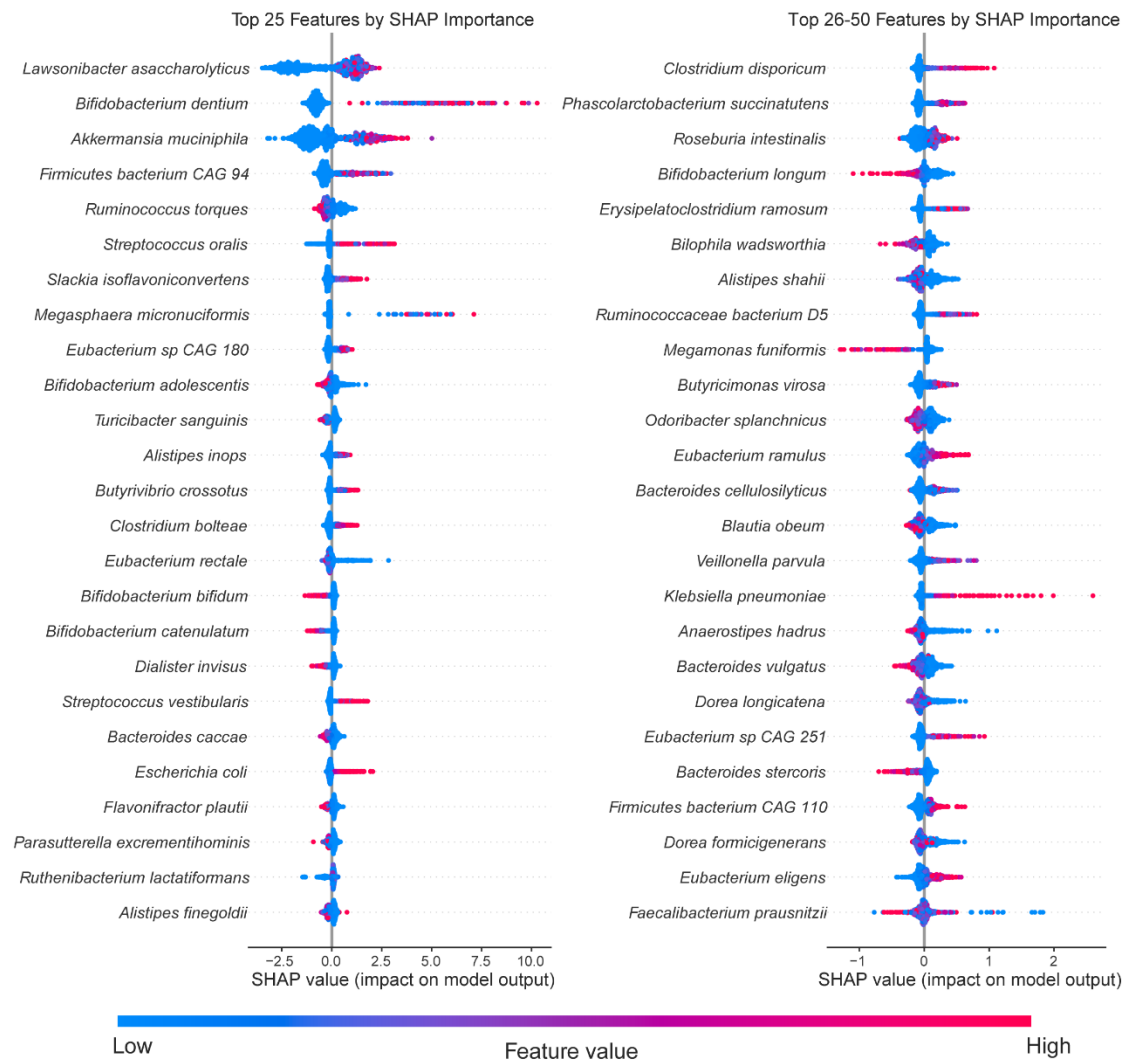
Species-level Bray–Curtis dissimilarity was utilized to perform principal coordinate analysis (PCoA) across all samples, with samples differentiated by cohorts. The proportion of variance explained by these effects was quantified using permutational multivariate analysis of variance (PERMANOVA, permutations = 999).

a**b**

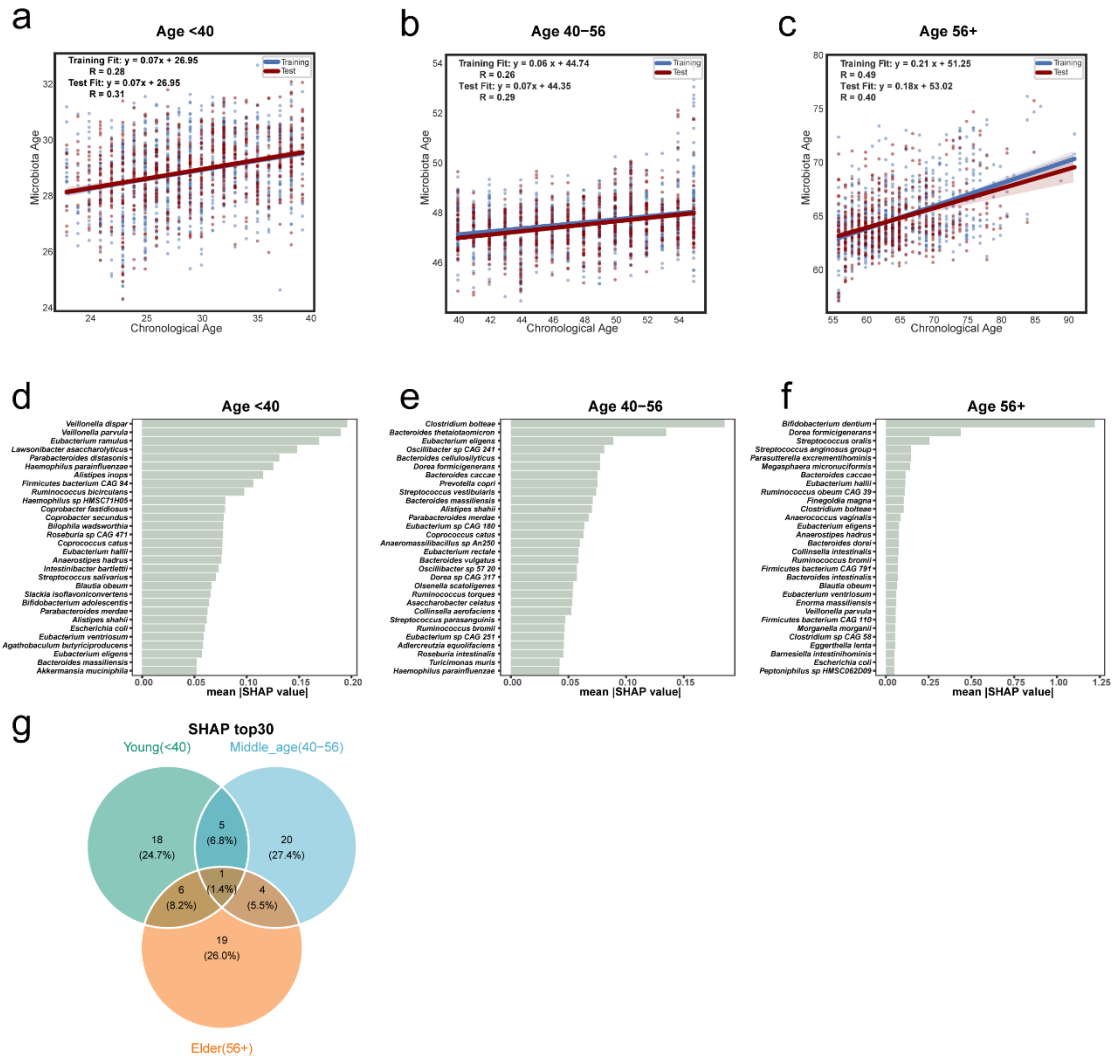
Supplementary Figure 3. Hyperparameter Optimization and model performance of gut microbiota age clock. a, Optimization History shows the process of model hyperparameter tuning. The optimal parameters were achieved at the 40th trial, where the minimum MAE (Mean Absolute Error) of 11.3257 was reached. **b,** Comparison of model performance on the training and test sets. The plot displays the relationship between microbiota age and chronological age, with separate linear fits for the training (blue) and test (red) datasets. The reported R^2 scores summarize the agreement between the model predictions and chronological age within each set, independent of any linear-regression assumption.



Supplementary Figure 4. Similar microbiota age inflection points were identified by distinct change point models. a-d, Microbiota age inflection points discovered by different approaches are signified by the red line.

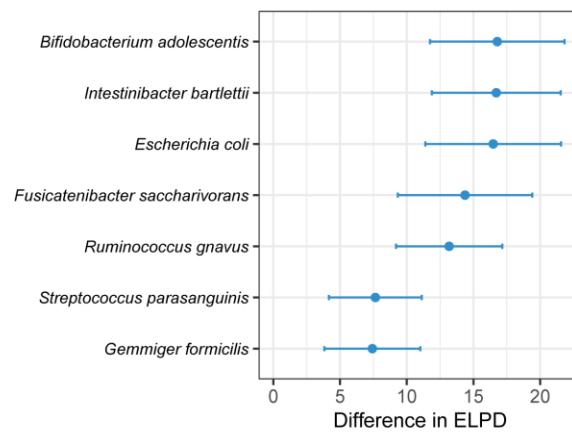


Supplementary Figure 5. Beeswarm plot of SHAP values for the top 50 important microbiota of the gut microbiota age clock. Each dot represents a participant in the study and the color designates the relative abundance of the corresponding species. The dot's position on the x-axis reflects the feature's influence on the model's prediction for that participant. When multiple dots align at the same x-coordinate, they stack to indicate data density.

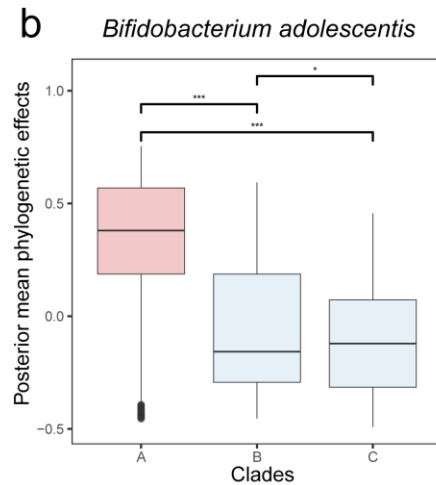


Supplementary Figure 6. Model performance of the microbiota age clock established in different age groups. **a-c**, Performance for microbiota age prediction in three age groups: <40, 40-56, and 56+. The plots show the relationship between microbiota age and chronological age, with separate linear fits for the training (blue) and test (red) datasets. **d-f**, Top 30 important features quantified by SHAP values in corresponding age group models. **g**, Venn plot shows the interaction relationship of the top 30 important species in each model among the three age groups.

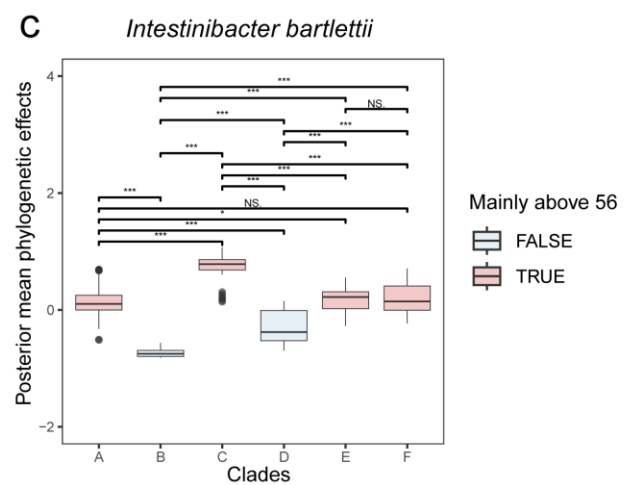
a



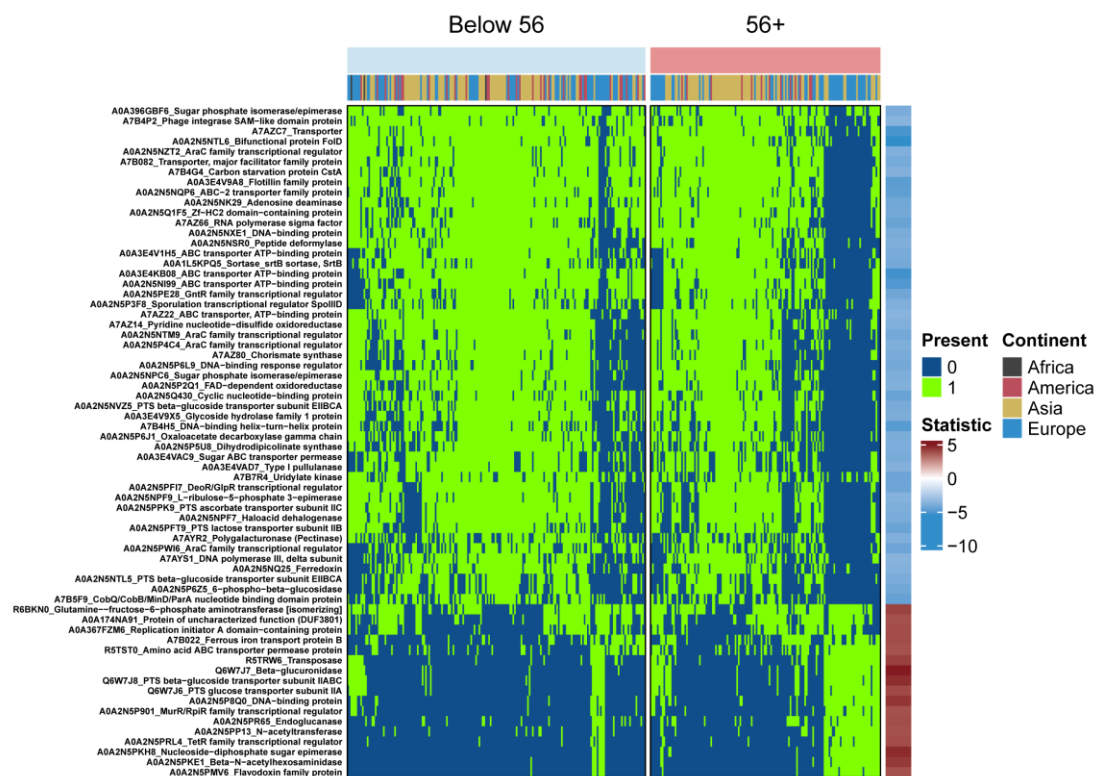
b



c



Supplementary Figure 7. Within-species phylogenetic divergence between pre- and post-transition age groups. a, The PGLMM with a binary outcome (Methods) discovered subclades within the 7 species with significant differential associations to the age group. b-c, Different subclades of *Bifidobacterium adolescentis* and *Intestinibacter bartlettii* exerted a divergent posterior mean phylogenetic effect. The differences in the effect between subclades within species were determined using the two-sided Wilcoxon rank-sum test. NS indicates $P > 0.05$, $*P < 0.05$, $***P < 0.001$.



Supplementary Figure 8. Differential gene family profile of *Ruminococcus gnavus* between pre- and post-transition age groups. In the heatmap, columns represent individual metagenomes, while rows correspond to specific UniRef90 gene families, with colors indicating presence (green) or absence (blue). The heatmap on the right side illustrates the association strength, quantified as the t-statistic from the anpan gene association model, between each gene family and age group. Red indicates gene families enriched in the older group, whereas blue denotes gene families depleted in this group.

Supplementary Table 1. Demographic and technical characteristics of participants across continents.

Characteristic	Africa	America	Asia	Europe	Oceania	p ¹
Number of participants	386	890	1562	3628	154	
Age (median [IQR])	38.00 [29.00, 50.00]	51.00 [33.25, 65.00]	53.00 [38.00, 65.00]	49.00 [38.00, 61.00]	50.00 [35.00, 55.00]	<0.001
Gender (%)						<0.001
Female	208 (53.89)	460 (51.69)	636 (40.72)	2305 (63.53)	89 (57.79)	
Male	178 (46.11)	430 (48.31)	926 (59.28)	1323 (36.47)	65 (42.21)	
Sequencing platform (%)						<0.001
IlluminaHiSeq	386 (100.00)	791 (88.88)	1414 (90.52)	2530 (69.74)	154 (100.00)	
IlluminaNextSeq	0 (0.00)	2 (0.22)	148 (9.48)	97 (2.67)	0 (0.00)	
IlluminaNovaSeq	0 (0.00)	97 (10.90)	0 (0.00)	1001 (27.59)	0 (0.00)	
DNA extraction kit (%)						<0.001
Chemagen	0 (0.00)	66 (7.93)	0 (0.00)	0 (0.00)	0 (0.00)	
Gnome	0 (0.00)	104 (12.50)	0 (0.00)	340 (10.31)	0 (0.00)	
Illuminakit	57 (15.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
KAMA Hyper Prep	0 (0.00)	100 (12.02)	0 (0.00)	0 (0.00)	0 (0.00)	
MoBio	0 (0.00)	205 (24.64)	0 (0.00)	154 (4.67)	0 (0.00)	
MPBio	0 (0.00)	0 (0.00)	0 (0.00)	147 (4.46)	0 (0.00)	
NorgenBiotek	0 (0.00)	0 (0.00)	0 (0.00)	13 (0.39)	0 (0.00)	
PowerSoil	0 (0.00)	28 (3.37)	0 (0.00)	111 (3.37)	0 (0.00)	
PowerSoilPro	0 (0.00)	97 (11.66)	0 (0.00)	1001 (30.36)	0 (0.00)	
PSP Spin Stool	156 (42.28)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
QIAamp	0 (0.00)	98 (11.78)	0 (0.00)	0 (0.00)	0 (0.00)	

Qiagen	156 (42.28)	134 (16.11)	341 (91.67)	1531 (46.44)	154 (100.00)
ZR Fecal DNA MiniPrep	0 (0.00)	0 (0.00)	31 (8.33)	0 (0.00)	0 (0.00)

¹*Kruskal–Wallis rank sum test for continuous variables; Pearson's Chi-squared test for categorical variables. All tests were two-sided.*

Supplementary Table 2. Significant age-associated gut microbiota was identified by Maaslin2. The false discovery rate was controlled by the Benjamini-Hochberg method (P.adjust) with significant threshold under 0.05

Species	Coefficient (β)	P	P.adjust	Continents presented in	Type
<i>Faecalibacterium prausnitzii</i>	-0.363044883	4.33E-13	1.98E-12	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Prevotella copri</i>	-1.045937489	6.77E-16	3.76E-15	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides uniformis</i>	0.291486195	1.42E-06	3.92E-06	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Eubacterium rectale</i>	-0.553273163	3.67E-16	2.09E-15	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bifidobacterium adolescentis</i>	-0.631463976	3.26E-10	1.23E-09	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides dorei</i>	0.379550739	0.000251407	0.000542539	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Roseburia faecis</i>	-0.368046658	6.91E-06	1.78E-05	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides stercoris</i>	-0.442021907	9.08E-06	2.30E-05	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Fusicatenibacter saccharivorans</i>	-0.34937308	1.18E-07	3.57E-07	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Akkermansia muciniphila</i>	0.96726993	9.54E-29	9.27E-28	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bifidobacterium longum</i>	-0.347961709	1.82E-06	4.96E-06	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Escherichia coli</i>	0.252305824	0.001380126	0.002742001	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Anaerostipes hadrus</i>	-0.328757605	5.92E-09	1.99E-08	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Eubacterium eligens</i>	-0.184947019	0.029267986	0.048195932	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides plebeius</i>	-0.46174475	9.36E-08	2.86E-07	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Dorea longicatena</i>	-0.576967238	6.44E-17	3.81E-16	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides caccae</i>	-0.300854379	0.000895616	0.001803235	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Ruminococcus torques</i>	-0.862922204	1.79E-23	1.43E-22	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides ovatus</i>	-0.328976667	1.37E-05	3.42E-05	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Roseburia inulinivorans</i>	-0.405854844	1.63E-10	6.28E-10	Africa, America, Asia, Europe, Oceania	Pancontinental

<i>Eubacterium</i> sp CAG 180	0.673836567	7.22E-08	2.25E-07	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Eubacterium siraeum</i>	0.296152969	0.000205387	0.000448179	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Coprococcus eutactus</i>	-0.32473627	0.000700663	0.001434375	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Ruminococcus bicirculans</i>	-0.281606119	0.001295288	0.002576066	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Lachnospira pectinoschiza</i>	-0.661089992	3.88E-11	1.57E-10	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Eubacterium hallii</i>	-0.252269757	0.001807275	0.003515546	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Coprococcus comes</i>	-0.431559519	2.72E-08	8.73E-08	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Methanobrevibacter smithii</i>	0.86863837	6.29E-19	4.25E-18	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Butyrivibrio crossotus</i>	0.355373854	3.16E-09	1.09E-08	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Blautia obeum</i>	-0.244016204	0.000368222	0.000775769	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Ruminococcus gnavus</i>	0.191011	0.010975114	0.019397646	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Blautia wexlerae</i>	-0.257212261	1.83E-07	5.44E-07	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Oscillibacter</i> sp 57 20	-0.335828135	0.000167462	0.000369553	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Phascolarctobacterium succinatutens</i>	0.400641498	9.71E-05	0.000221091	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides eggerthii</i>	0.203218899	0.015846133	0.027484456	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides cellulosilyticus</i>	0.475300413	1.68E-08	5.51E-08	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Prevotella stercorea</i>	-0.57379717	4.84E-24	3.97E-23	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Dorea formicigenerans</i>	-0.314420132	1.38E-08	4.55E-08	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bifidobacterium pseudocatenulatum</i>	-0.403793077	9.96E-08	3.04E-07	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Agathobaculum butyriciproducens</i>	-0.187090651	0.000892053	0.001797915	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Streptococcus salivarius</i>	0.159445369	0.007965849	0.014246614	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bifidobacterium bifidum</i>	-0.627920858	4.25E-16	2.38E-15	Africa, America, Asia, Europe, Oceania	Pancontinental

<i>Prevotella sp 885</i>	-0.166839809	9.15E-08	2.80E-07	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Prevotella sp CAG 520</i>	-0.197294683	5.49E-05	0.000128445	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Oscillibacter sp CAG 241</i>	0.239682147	0.001544723	0.003028959	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Klebsiella pneumoniae</i>	0.11658836	0.010827523	0.019171488	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Alistipes inops</i>	0.431700305	1.09E-11	4.59E-11	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Ruthenibacterium lactatiformans</i>	0.39889278	7.02E-15	3.63E-14	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Eubacterium sp CAG 38</i>	-0.270309495	0.000750035	0.001529038	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Prevotella sp AM42 24</i>	-0.306458978	3.91E-14	1.91E-13	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Firmicutes bacterium CAG 110</i>	0.240815662	0.000678498	0.001390457	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Prevotella sp CAG 279</i>	-0.26828433	1.36E-06	3.76E-06	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Gemmiger formicilis</i>	-0.283565453	4.74E-06	1.24E-05	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Phascolarctobacterium faecium</i>	-0.220415881	0.003566734	0.006749836	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Parasutterella excrementihominis</i>	-0.563322229	1.11E-12	4.97E-12	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Prevotella sp CAG 5226</i>	-0.118320938	0.000637699	0.001309597	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides finegoldii</i>	-0.163608333	0.01824013	0.031441282	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Dialister invisus</i>	-0.210362111	0.001439104	0.00284183	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Proteobacteria bacterium CAG 139</i>	-0.545886831	4.99E-14	2.43E-13	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Slackia isoﬂavoniconvertens</i>	0.579078134	3.51E-10	1.32E-09	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Butyrivibrio sp CAG 318</i>	0.260600658	1.40E-08	4.61E-08	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Eubacterium ventriosum</i>	-0.175743209	0.020177044	0.034505925	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Veillonella parvula</i>	0.331020875	4.74E-08	1.50E-07	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Streptococcus parasanguinis</i>	0.531052468	4.73E-18	3.00E-17	Africa, America, Asia, Europe, Oceania	Pancontinental

<i>Bifidobacterium catenulatum</i>	-0.264887416	1.59E-09	5.68E-09	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Desulfovibrio piger</i>	0.286323143	0.001204569	0.002407904	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Lactobacillus ruminis</i>	-0.340915411	4.24E-16	2.38E-15	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Intestinibacter bartlettii</i>	-0.172505562	0.006714852	0.012121737	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Eggerthella lenta</i>	0.365476809	5.39E-07	1.56E-06	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides</i> sp CAG 144	0.221446187	0.000447038	0.000933759	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Prevotella</i> sp CAG 1092	-0.061361262	0.023821636	0.040141204	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Enterococcus faecium</i>	0.070999582	0.008201758	0.014628341	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Erysipelatoclostridium ramosum</i>	0.591622092	2.21E-25	1.92E-24	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Clostridium</i> sp CAG 58	0.260691521	1.32E-05	3.31E-05	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Fusobacterium mortiferum</i>	0.089683365	0.009912619	0.017567464	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Clostridium bolteae</i>	0.405312834	2.16E-13	1.02E-12	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Firmicutes bacterium</i> CAG 170	0.179231705	0.000625681	0.001286269	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Lawsonibacter asaccharolyticus</i>	0.603273179	1.28E-23	1.04E-22	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Megasphaera elsdenii</i>	-0.079914473	0.02819292	0.046780605	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Butyrlicimonas virosa</i>	0.438359525	5.65E-10	2.09E-09	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Mitsuokella multacida</i>	-0.085352531	0.015444886	0.026884013	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Megamonas funiformis</i>	-0.333499733	2.15E-17	1.31E-16	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Gordonibacter pamelaee</i>	0.366481673	4.64E-09	1.58E-08	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Clostridium leptum</i>	0.338105173	2.56E-08	8.27E-08	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Clostridium disporicum</i>	0.327393966	8.91E-10	3.24E-09	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Firmicutes bacterium</i> CAG 95	0.23491676	6.93E-05	0.000160708	Africa, America, Asia, Europe, Oceania	Pancontinental

<i>Ruminococcus sp CAG 488</i>	-0.08322896	0.029983382	0.049332388	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Parabacteroides goldsteinii</i>	0.415824489	2.85E-16	1.63E-15	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Collinsella intestinalis</i>	0.29187373	2.75E-07	8.15E-07	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Klebsiella quasipneumoniae</i>	0.100480016	0.002002597	0.003876186	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Intestinimonas butyriciproducens</i>	0.376834458	9.13E-09	3.03E-08	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides pectinophilus</i>	0.08687362	0.002826616	0.005385737	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Prevotella bivia</i>	0.155693931	2.63E-11	1.08E-10	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Turicibacter sanguinis</i>	-0.279022849	9.08E-07	2.56E-06	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Clostridium symbiosum</i>	0.405940501	2.19E-12	9.63E-12	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Clostridium innocuum</i>	0.425147296	3.06E-13	1.42E-12	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Veillonella atypica</i>	0.29151652	6.44E-09	2.16E-08	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Ruminococcus sp CAG 330</i>	-0.117024572	0.000413442	0.000867295	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Alistipes onderdonkii</i>	0.148736423	0.000261721	0.000564173	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Sellimonas intestinalis</i>	0.159799127	0.001487228	0.00292798	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Hungatella hathewayi</i>	0.420525488	2.64E-16	1.51E-15	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bifidobacterium dentium</i>	0.841856543	2.63E-56	4.59E-55	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Enterococcus faecalis</i>	0.382620552	7.85E-32	8.52E-31	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Porphyromonas sp HMSC065F10</i>	0.231396324	4.92E-32	5.40E-31	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides sp CAG 530</i>	-0.067918449	0.006731211	0.012138555	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Eisenbergiella tayi</i>	0.409996205	1.99E-15	1.08E-14	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Lactobacillus salivarius</i>	0.170601792	3.06E-09	1.06E-08	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Firmicutes bacterium CAG 534</i>	0.05992446	0.002799496	0.005344492	Africa, America, Asia, Europe, Oceania	Pancontinental

<i>Veillonella dispar</i>	0.148468103	0.00143548	0.002837542	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Enorma massiliensis</i>	0.252840284	1.25E-06	3.46E-06	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Firmicutes bacterium CAG 238</i>	0.343856806	1.34E-15	7.36E-15	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides coagulans</i>	0.16133197	6.20E-30	6.34E-29	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Anaeromassilibacillus sp An250</i>	0.141341029	0.020313475	0.034678512	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Prevotella timonensis</i>	0.171322818	8.21E-13	3.73E-12	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Peptoniphilus lacrimalis</i>	0.217103013	5.81E-23	4.56E-22	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Streptococcus anginosus group</i>	0.594155792	5.53E-46	8.19E-45	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Streptococcus vestibularis</i>	0.435722513	6.71E-31	7.00E-30	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Prevotella buccalis</i>	0.145303115	4.44E-12	1.92E-11	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Parabacteroides sp CAG 409</i>	0.055607072	0.020863074	0.035461779	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Gardnerella vaginalis</i>	0.054156486	1.15E-06	3.22E-06	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Porphyromonas asaccharolytica</i>	0.245281383	1.42E-19	9.84E-19	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Anaerococcus vaginalis</i>	0.227555417	5.68E-32	6.19E-31	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Megamonas hypermegale</i>	-0.128662302	4.30E-05	0.000101896	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Citrobacter freundii</i>	0.05439348	0.021350484	0.036258691	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Clostridium sp CAG 590</i>	0.049120153	0.02275049	0.03846901	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Klebsiella aerogenes</i>	0.061865064	8.76E-05	0.00020115	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Coprobacillus cateniformis</i>	0.266118701	2.60E-12	1.14E-11	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Olsenella scatoligenes</i>	0.115576227	0.02832874	0.046886465	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Methanosphaera stadtmanae</i>	0.109372374	0.001397051	0.00276999	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Streptococcus infantarius</i>	-0.088247773	1.19E-05	2.99E-05	Africa, America, Asia, Europe, Oceania	Pancontinental

<i>Turicimonas muris</i>	-0.340595619	5.06E-12	2.18E-11	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Ruminococcus callidus</i>	-0.196030881	0.000180776	0.000397139	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Lactobacillus fermentum</i>	0.179791659	1.10E-14	5.64E-14	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Prevotella disiens</i>	0.074896479	0.000835847	0.00169513	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Roseburia sp CAG 309</i>	0.291253916	8.20E-10	2.99E-09	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Clostridium bolteae CAG 59</i>	0.084279989	0.025867305	0.043178502	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Ruminococcaceae bacterium D5</i>	0.401424316	1.16E-19	8.12E-19	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Anaerotruncus colihominis</i>	0.162475249	0.008898138	0.015827017	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Comamonas kerstersii</i>	-0.057175467	0.009254888	0.016431633	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Desulfovibrionaceae bacterium</i>	0.142161628	0.000116436	0.000263499	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Clostridium citroniae</i>	0.142789585	0.013291086	0.023259401	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Holdemanella filiformis</i>	0.199721879	0.000199254	0.000435771	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Lactobacillus delbrueckii</i>	0.076260679	0.028833031	0.047522201	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Dialister pneumosintes</i>	0.221186274	6.84E-19	4.61E-18	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Clostridium sp CAG 411</i>	0.056613004	0.000362371	0.000764266	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Prevotella corporis</i>	0.112320372	1.97E-05	4.83E-05	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Citrobacter youngae</i>	0.055577395	0.002121976	0.00409913	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Streptococcus oralis</i>	0.597877661	2.03E-43	2.88E-42	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Klebsiella oxytoca</i>	0.093853487	1.48E-10	5.72E-10	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Parvimonas micra</i>	0.291738137	8.90E-25	7.59E-24	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Morganella morganii</i>	0.041692832	6.47E-05	0.000150606	Africa, America, Asia, Europe, Oceania	Pancontinental
<i>Bacteroides coprocola</i>	-0.622919099	1.61E-18	1.05E-17	Africa, America, Asia, Europe	Regional

<i>Dialister</i> sp CAG 357	-0.520489716	5.01E-20	3.53E-19	America, Asia, Europe	Regional
<i>Acidaminococcus intestini</i>	0.152423921	0.003583768	0.006769595	America, Asia, Europe, Oceania	Regional
<i>Cupriavidus metallidurans</i>	0.157218751	4.99E-31	5.24E-30	America	Regional
<i>Blautia</i> sp CAG 257	0.273880394	2.11E-06	5.71E-06	America, Asia, Europe	Regional
<i>Bifidobacterium animalis</i>	0.148027862	0.002403469	0.004606452	Africa, America, Asia, Europe	Regional
<i>Bifidobacterium angulatum</i>	-0.225617898	7.57E-14	3.64E-13	Africa, America, Asia, Europe	Regional
<i>Clostridium</i> sp CAG 167	0.15404626	0.003921238	0.00737072	Africa, America, Asia, Europe	Regional
<i>Clostridium clostridioforme</i>	0.359428653	2.02E-15	1.09E-14	America, Asia, Europe	Regional
<i>Phascolarctobacterium</i> sp CAG 266	0.174667593	3.87E-05	9.26E-05	Africa, America, Asia, Europe	Regional
<i>Firmicutes bacterium</i> CAG 94	0.491182142	1.16E-19	8.12E-19	America, Asia, Europe	Regional
<i>Faecalitalea cylindroides</i>	0.257682149	1.84E-07	5.48E-07	America, Asia, Europe	Regional
<i>Anaerotignum lactatifermentans</i>	0.178444668	9.15E-05	0.000209413	Africa, America, Asia, Europe	Regional
<i>Alistipes</i> sp An31A	0.083024132	0.00169313	0.003300082	America, Asia, Europe	Regional
<i>Firmicutes bacterium</i> CAG 145	0.503452438	2.94E-19	2.02E-18	America, Asia, Europe	Regional
<i>Eisenbergiella massiliensis</i>	0.326996452	1.57E-07	4.71E-07	Africa, America, Asia, Europe	Regional
<i>Finegoldia magna</i>	0.302025788	6.30E-29	6.24E-28	America, Asia, Europe, Oceania	Regional
<i>Candida albicans</i>	0.013551224	0.023391306	0.039450104	America, Europe	Regional
<i>Dorea</i> sp CAG 317	0.378000426	5.05E-17	3.03E-16	America, Asia, Europe	Regional
<i>Stenotrophomonas maltophilia</i>	0.099817383	1.23E-18	8.03E-18	America, Asia, Europe	Regional
<i>Clostridium</i> sp CAG 242	0.280902106	3.60E-10	1.35E-09	America, Asia, Europe, Oceania	Regional
<i>Firmicutes bacterium</i> CAG 555	0.05784011	0.008782217	0.015635068	Africa, America, Asia, Europe	Regional
<i>Peptoniphilus</i> sp HMSC062D09	0.222065293	2.19E-43	3.08E-42	America, Asia, Europe, Oceania	Regional

<i>Peptoniphilus harei</i>	0.201992352	3.73E-39	4.93E-38	Africa, America, Asia, Europe	Regional
<i>Clostridium</i> sp CAG 299	-0.128752392	0.000924844	0.001860165	Africa, America, Asia, Europe	Regional
<i>Campylobacter ureolyticus</i>	0.151463211	2.25E-28	2.14E-27	America, Asia, Europe	Regional
<i>Negativicoccus succinicivorans</i>	0.112293443	1.37E-28	1.31E-27	America, Europe	Regional
<i>Megasphaera micronuciformis</i>	0.226146381	3.30E-19	2.26E-18	Africa, America, Asia, Europe	Regional
<i>Odoribacter laneus</i>	0.076054744	5.88E-05	0.000136921	America, Asia, Europe, Oceania	Regional
<i>Bacteroides</i> sp CAG 598	0.030475962	0.030113391	0.04950459	Africa, America, Asia, Europe	Regional
<i>Pseudomonas aeruginosa</i> group	0.103980579	7.34E-18	4.58E-17	America, Asia, Europe	Regional
<i>Clostridium lavalense</i>	0.258959642	1.77E-08	5.78E-08	Africa, America, Asia, Europe	Regional

Supplementary Table 3. The Mann-Kendall trend test revealed the microbiota age changing trend of different age stages identified by four change points detection approaches.

Method	Mutation interval	Statistic (Z)	N	P	Signif
Kolmogorov-Smirnov	<24	-0.345334421	289	0.729842972	ns
Kolmogorov-Smirnov	24-40	-3.468595496	1272	0.000523187	***
Kolmogorov-Smirnov	40-56	0.040984122	1467	0.967308554	ns
Kolmogorov-Smirnov	56-66	2.618336821	711	0.008835954	**
Kolmogorov-Smirnov	≥66	4.013923896	420	5.97E-05	***
Lepage	<24	-0.345334421	289	0.729842972	ns
Lepage	24-40	-3.468595496	1272	0.000523187	***
Lepage	40-60	-0.464619464	1724	0.642203991	ns
Lepage	≥60	6.850417925	874	7.36E-12	***
Cramer-von-Mises	<24	-0.345334421	289	0.729842972	ns
Cramer-von-Mises	24-40	-3.468595496	1272	0.000523187	***
Cramer-von-Mises	40-56	0.040984122	1467	0.967308554	ns
Cramer-von-Mises	56-75	4.868520141	1026	1.12E-06	***
Cramer-von-Mises	≥75	2.378476513	105	0.017384344	*
Mann-Whitney	<25	-0.298480447	360	0.765336497	ns
Mann-Whitney	25-40	-3.540819441	1201	0.000398886	***
Mann-Whitney	40-56	0.040984122	1467	0.967308554	ns
Mann-Whitney	≥56	6.290360161	1131	3.1673E-10	***

Supplementary Table 4. Age-stratified species identified by Maaslin2. The false discovery rate was controlled by the Benjamini-Hochberg method (P.adjust) with significant threshold under 0.01

Species	Group	Coefficient (β)	P	P.adjust	Mean relative abundance
<i>Akkermansia muciniphila</i>	56+	1.635746564	1.6E-12	4.9E-12	1.98%
<i>Ruminococcus torques</i>	56+	-1.17319496	2.7E-08	6.9E-08	0.92%
<i>Dorea longicatena</i>	56+	-0.861470539	5.7E-08	1.4E-07	1.01%
<i>Eubacterium</i> sp CAG 180	56+	1.792701776	6.0E-08	1.5E-07	1.05%
<i>Methanobrevibacter smithii</i>	56+	1.42897535	1.2E-07	2.8E-07	0.79%
<i>Bifidobacterium bifidum</i>	56+	-0.961033179	4.3E-06	9.2E-06	0.30%
<i>Eubacterium siraeum</i>	56+	0.980639985	5.5E-06	1.2E-05	1.12%
<i>Bacteroides uniformis</i>	56+	0.748054327	8.0E-06	1.7E-05	5.67%
<i>Eubacterium rectale</i>	56+	-0.734148193	8.2E-06	1.7E-05	3.51%
<i>Phascolarctobacterium succinatutens</i>	56+	0.698786756	1.2E-05	2.3E-05	0.58%
<i>Butyrivibrio crossotus</i>	56+	0.767816309	1.3E-05	2.7E-05	1.03%
<i>Bacteroides dorei</i>	56+	1.127122201	3.7E-05	7.3E-05	2.59%
<i>Bifidobacterium adolescentis</i>	56+	-0.998029291	1.2E-04	2.2E-04	2.49%
<i>Prevotella copri</i>	56+	-1.275691183	2.5E-04	4.6E-04	6.50%
<i>Lachnospira pectinoschiza</i>	56+	-0.905791162	7.8E-04	1.4E-03	0.84%
<i>Bacteroides cellulosilyticus</i>	56+	0.749723467	1.0E-03	1.8E-03	0.49%
<i>Escherichia coli</i>	56+	0.721022258	1.1E-03	1.8E-03	2.27%
<i>Bacteroides plebeius</i>	56+	-0.600938027	5.6E-03	8.8E-03	0.97%
<i>Bacteroides stercoris</i>	56+	-0.747845707	5.5E-03	8.8E-03	1.31%
<i>Fusicatenibacter saccharivorans</i>	40-56	0.601601956	2.5E-05	5.4E-05	1.86%

<i>Escherichia coli</i>	40-56	-0.813936849	7.0E-05	1.4E-04	1.13%
<i>Ruminococcus torques</i>	40-56	0.582387708	3.0E-03	5.4E-03	1.17%
<i>Eubacterium hallii</i>	40-56	0.468627565	3.2E-03	5.7E-03	0.89%
<i>Anaerostipes hadrus</i>	40-56	0.366650021	4.7E-03	8.1E-03	1.44%
<i>Akkermansia muciniphila</i>	<40	-1.67362535	3.7E-15	1.2E-14	1.17%
<i>Methanobrevibacter smithii</i>	<40	-1.516888808	9.6E-10	2.7E-09	0.60%
<i>Bacteroides dorei</i>	<40	-1.504477497	2.0E-09	5.5E-09	1.92%
<i>Butyrivibrio crossotus</i>	<40	-0.756344921	3.1E-06	6.9E-06	0.68%
<i>Bacteroides uniformis</i>	<40	-0.693608675	6.8E-06	1.5E-05	4.72%
<i>Bacteroides cellulosilyticus</i>	<40	-0.94130533	7.3E-06	1.6E-05	0.37%
<i>Eubacterium siraeum</i>	<40	-0.822024187	3.4E-05	7.1E-05	0.94%
<i>Bifidobacterium adolescentis</i>	<40	0.968486225	4.8E-05	9.7E-05	3.15%
<i>Eubacterium rectale</i>	<40	0.586529973	1.1E-04	2.1E-04	4.44%
<i>Bifidobacterium bifidum</i>	<40	0.738798979	1.2E-04	2.3E-04	0.41%
<i>Eubacterium sp CAG 180</i>	<40	-1.136854678	1.9E-04	3.6E-04	0.80%
<i>Phascolarctobacterium succinatutens</i>	<40	-0.540395497	2.3E-04	4.2E-04	0.66%
<i>Ruminococcus bromii</i>	<40	-0.974224115	1.7E-03	3.0E-03	3.12%
<i>Prevotella copri</i>	<40	0.93389325	3.6E-03	6.0E-03	6.90%

Supplementary Table 5. Distribution of individuals across continents and age groups, stratified by merged and original disease labels.

Age interval	Disease label merged	Original disease label	Africa	America	Asia	Europe	Oceania
<40	Healthy	healthy	157	207	239	913	45
	IBD	IBD	0	30	0	0	0
	Obesity	obesity	0	23	2	64	0
	Autoimmune diseases	BD	0	0	12	0	0
		RA	0	0	64	0	0
	Cirrhosis	ascites;cirrhosis	0	0	2	0	0
		ascites;cirrhosis;hepatitis	0	0	9	0	0
		ascites;cirrhosis;wilson	0	0	1	0	0
		cirrhosis	0	0	1	0	0
		cirrhosis;hepatitis	0	0	7	0	0
	CRC	CRC	0	4	9	4	0
		CRC;T2D	0	0	1	0	0
		carcinoma_surgery_history	0	0	2	0	0
	Diabetes	IGT	0	2	0	0	0
		T2D	0	2	0	0	0
		T1D	0	0	0	5	0
	Infectious disease	STH	43	0	0	0	0
		CMV;coeliac;gestational_diabetes	0	0	0	1	0
	Nervous and mental disorders	schizophrenia	0	0	68	0	0
40-56	Healthy	healthy	94	119	189	992	71
	IBD	IBD	0	15	0	0	0
	Obesity	obesity	9	31	4	212	0

	Autoimmune diseases	BD	0	0	8	0	0
		RA	0	0	27	0	0
	Cirrhosis	ascites;cirrhosis	0	0	3	0	0
		ascites;cirrhosis;hepatitis	0	0	29	0	0
		cirrhosis	0	0	5	0	0
		cirrhosis;hepatitis	0	0	30	0	0
	CRC	CRC	0	23	70	34	0
		CRC;T2D	0	0	7	0	0
		carcinoma_surgery_history	0	0	13	0	0
		CRC;T2D;fatty_liver;hypertension	0	0	0	1	0
		CRC;hypertension	0	0	0	1	0
	Diabetes	IGT	0	6	0	0	0
		IGT;respiratoryinf	0	1	0	0	0
		T2D	0	10	9	0	0
	Infectious disease	STH	18	0	0	0	0
		hepatitis	0	0	0	1	0
	Nervous and mental disorders	ME/CFS	0	50	0	0	0
		schizophrenia	0	0	13	0	0
		migraine	0	0	0	7	0
		migraine;asthma	0	0	0	5	0
56+	Healthy	healthy	45	104	272	673	38
	IBD	IBD	0	7	0	0	0
	Obesity	obesity	4	14	7	135	0
	Autoimmune diseases	RA	0	0	4	0	0

	Cirrhosis	ascites;cirrhosis	0	0	4	0	0
		ascites;cirrhosis;hepatitis	0	0	17	0	0
		ascites;cirrhosis;hepatitis;schistosoma	0	0	3	0	0
		ascites;cirrhosis;hepatitis;wilson	0	0	1	0	0
		ascites;cirrhosis;schistosoma	0	0	1	0	0
		cirrhosis	0	0	3	0	0
		cirrhosis;hepatitis	0	0	6	0	0
		hepatitis	0	0	1	0	0
	CRC	CRC	0	52	294	135	0
		CRC;T2D	0	0	21	0	0
		carcinoma_surgery_history	0	0	25	0	0
		CRC;T2D;fatty_liver;hypertension	0	0	0	3	0
		CRC;T2D;hypertension	0	0	0	2	0
		CRC;cholesterolemia	0	0	0	1	0
		CRC;fatty_liver	0	0	0	3	0
		CRC;fatty_liver;hypertension	0	0	0	12	0
		CRC;hypercholesterolemia	0	0	0	3	0
		CRC;hypercholesterolemia;hypertension	0	0	0	1	0
		CRC;hypertension	0	0	0	19	0
		CRC;metastases	0	0	0	1	0
		hypertension;metastases	0	0	0	1	0
		metastases	0	0	0	1	0
	Diabetes	IGT	0	11	0	49	0
		T2D	0	8	7	53	0

		T1D	0	0	0	2	0
		generic_diabetes	0	0	0	8	0
	Infectious disease	STH	16	0	0	0	0
		CDI	0	6	0	0	0
		CDI;osteoarthritis	0	1	0	0	0
		CDI;pneumonia	0	1	0	0	0
		cellulitis	0	2	0	0	0
		gangrene	0	1	0	0	0
		pneumonia	0	3	0	0	0
	Nervous and mental disorders	migraine	0	0	0	29	0
		migraine;asthma	0	0	0	7	0
		migraine;generic_diabetes	0	0	0	1	0

Supplementary Table 6. The difference of posterior mean phylogenetic effects in 17 significant phylogenetic divergence species examined by wilcoxon ran sum test between age groups. The false discovery rate was controlled by the Benjamini-Hochberg method.

Species	Group1	Group2	Sample size of group1	Sample size of group2	Statistic	P	P.adjust	Signif
<i>Bacteroides uniformis</i>	<40	40-56	546	577	59833	2.7E-72	2.7E-72	****
<i>Bacteroides uniformis</i>	40-56	56+	577	628	62299	2.2E-86	3.3E-86	****
<i>Bacteroides uniformis</i>	<40	56+	546	628	12928	8.9E-165	2.7E-164	****
<i>Bifidobacterium adolescentis</i>	<40	40-56	463	482	87150	5.7E-09	5.7E-09	****
<i>Bifidobacterium adolescentis</i>	40-56	56+	482	410	62643	4.1E-21	6.1E-21	****
<i>Bifidobacterium adolescentis</i>	<40	56+	463	410	44812	2.2E-41	6.6E-41	****
<i>Clostridium disporicum</i>	<40	40-56	49	78	577	4.0E-11	6.0E-11	****
<i>Clostridium disporicum</i>	40-56	56+	78	113	2230	6.8E-09	6.8E-09	****
<i>Clostridium disporicum</i>	<40	56+	49	113	343	9.4E-19	2.8E-18	****
<i>Coprococcus comes</i>	<40	40-56	496	561	96680	1.0E-17	1.0E-17	****
<i>Coprococcus comes</i>	40-56	56+	561	528	97585	2.1E-22	3.1E-22	****
<i>Coprococcus comes</i>	<40	56+	496	528	56669	1.4E-55	4.3E-55	****
<i>Dorea formicigenerans</i>	<40	40-56	511	542	70893	9.7E-43	9.7E-43	****
<i>Dorea formicigenerans</i>	40-56	56+	542	510	63963	2.4E-51	3.5E-51	****
<i>Dorea formicigenerans</i>	<40	56+	511	510	22952	6.2E-115	1.9E-114	****
<i>Dorea longicatena</i>	<40	40-56	561	622	147526	4.4E-06	4.4E-06	****
<i>Dorea longicatena</i>	40-56	56+	622	564	127380	3.6E-16	5.4E-16	****
<i>Dorea longicatena</i>	<40	56+	561	564	94105	6.0E-32	1.8E-31	****
<i>Faecalibacterium prausnitzii</i>	<40	40-56	602	603	107307	1.1E-34	1.1E-34	****
<i>Faecalibacterium prausnitzii</i>	40-56	56+	603	566	83255	7.6E-52	1.1E-51	****

<i>Faecalibacterium prausnitzii</i>	<40	56+	602	566	41525	9.0E-111	2.7E-110	****
<i>Flavonifractor plautii</i>	<40	40-56	180	210	7837	2.1E-23	3.2E-23	****
<i>Flavonifractor plautii</i>	40-56	56+	210	239	14426	7.5E-15	7.5E-15	****
<i>Flavonifractor plautii</i>	<40	56+	180	239	3465	6.0E-49	1.8E-48	****
<i>Fusicatenibacter saccharivorans</i>	<40	40-56	605	692	167326	4.3E-10	4.3E-10	****
<i>Fusicatenibacter saccharivorans</i>	40-56	56+	692	654	151940	1.8E-25	2.7E-25	****
<i>Fusicatenibacter saccharivorans</i>	<40	56+	605	654	100755	2.9E-51	8.7E-51	****
<i>Gemmiger formicilis</i>	<40	40-56	590	616	145198	1.5E-09	1.5E-09	****
<i>Gemmiger formicilis</i>	40-56	56+	616	566	119960	1.8E-20	2.7E-20	****
<i>Gemmiger formicilis</i>	<40	56+	590	566	87487	1.4E-44	4.2E-44	****
<i>Intestinibacter bartlettii</i>	<40	40-56	170	172	9418	1.3E-08	1.3E-08	****
<i>Intestinibacter bartlettii</i>	40-56	56+	172	210	10084	1.1E-13	1.7E-13	****
<i>Intestinibacter bartlettii</i>	<40	56+	170	210	5502	4.2E-31	1.3E-30	****
<i>Roseburia inulinivorans</i>	<40	40-56	482	427	68559	3.5E-18	3.5E-18	****
<i>Roseburia inulinivorans</i>	40-56	56+	427	482	58534	2.9E-29	4.3E-29	****
<i>Roseburia inulinivorans</i>	<40	56+	482	482	40134	3.0E-69	8.9E-69	****
<i>Ruminococcus gnavus</i>	<40	40-56	126	135	1883	1.7E-27	1.7E-27	****
<i>Ruminococcus gnavus</i>	40-56	56+	135	196	3809	3.4E-28	5.1E-28	****
<i>Ruminococcus gnavus</i>	<40	56+	126	196	368	7.1E-49	2.1E-48	****
<i>Ruminococcus torques</i>	<40	40-56	483	520	93653	3.3E-12	3.3E-12	****
<i>Ruminococcus torques</i>	40-56	56+	520	454	85255	7.1E-14	1.1E-13	****
<i>Ruminococcus torques</i>	<40	56+	483	454	54303	9.5E-41	2.9E-40	****
<i>Streptococcus parasanguinis</i>	<40	40-56	76	101	1832	2.8E-09	4.2E-09	****

<i>Streptococcus parasanguinis</i>	40-56	56+	101	174	5363	7.3E-08	7.3E-08	****
<i>Streptococcus parasanguinis</i>	<40	56+	76	174	1430	6.7E-23	2.0E-22	****
<i>Streptococcus salivarius</i>	<40	40-56	200	243	15113	7.4E-12	7.4E-12	****
<i>Streptococcus salivarius</i>	40-56	56+	243	275	16541	3.3E-23	4.9E-23	****
<i>Streptococcus salivarius</i>	<40	56+	200	275	7251	9.0E-43	2.7E-42	****
<i>Veillonella dispar</i>	<40	40-56	47	31	288	2.9E-06	2.9E-06	****
<i>Veillonella dispar</i>	40-56	56+	31	109	548	1.0E-08	1.5E-08	****
<i>Veillonella dispar</i>	<40	56+	47	109	279	1.2E-18	3.6E-18	****

Supplementary Table 7. UniRef90 gene families within species associated with age group divided by 56 years, quantified by gene model in anpan.

Species	Gene	Estimate	Standard.error	Statistic	P	q_bug_wise	q_global
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P2Q9	-2.13778131	0.375197797	-5.697744827	1.21E-08	5.88E-05	0.000562208
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NTL6	-2.216788463	0.396823314	-5.586336249	2.32E-08	5.88E-05	0.000562208
<i>Ruminococcus gnavus</i>	UniRef90_A0A3E4KB08	-1.919202434	0.358776277	-5.349301385	8.83E-08	0.000149218	0.001426985
<i>Ruminococcus gnavus</i>	UniRef90_F7JXC5	-1.886259291	0.358178876	-5.266249407	1.39E-07	0.000175652	0.001679777
<i>Ruminococcus gnavus</i>	UniRef90_A7AZC7	-1.917933141	0.368665541	-5.202366171	1.97E-07	0.000175652	0.001679777
<i>Ruminococcus gnavus</i>	UniRef90_F7JUQ7	-1.732143377	0.333607676	-5.192156845	2.08E-07	0.000175652	0.001679777
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P2S4	-1.858892306	0.360166054	-5.161209079	2.45E-07	0.000177711	0.001699468
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NI99	-1.705507775	0.337508596	-5.053227673	4.34E-07	0.000275305	0.002632769
<i>Ruminococcus gnavus</i>	UniRef90_Q6W7J7	1.281301498	0.258422929	4.958157171	7.12E-07	0.000400896	0.003833816
<i>Ruminococcus gnavus</i>	UniRef90_A7B4H5	-1.385466239	0.283148642	-4.893070395	9.93E-07	0.000503324	0.004813342
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P6T2	-1.228092511	0.252398351	-4.865691504	1.14E-06	0.000525701	0.005027335
<i>Ruminococcus gnavus</i>	UniRef90_A0A3E4V9A8	-1.776422177	0.368532517	-4.820258982	1.43E-06	0.000605747	0.005792825
<i>Ruminococcus gnavus</i>	UniRef90_A7B880	-1.227046955	0.256804441	-4.778137593	1.77E-06	0.000690013	0.00659867
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NQP6	-1.692046218	0.35863919	-4.717962419	2.38E-06	0.000838133	0.007593315
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NNV5	-1.286343173	0.273484079	-4.703539517	2.56E-06	0.000838133	0.007593315
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P7X8	1.332675116	0.28385707	4.694880827	2.67E-06	0.000838133	0.007593315
<i>Ruminococcus gnavus</i>	UniRef90_F7JZ74	-1.301085446	0.278343156	-4.674393531	2.95E-06	0.000838133	0.007593315
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PKH8	1.511358618	0.323458552	4.672495463	2.98E-06	0.000838133	0.007593315
<i>Ruminococcus gnavus</i>	UniRef90_A7B1D5	-1.346927096	0.289557198	-4.651678857	3.29E-06	0.00087856	0.007981686
<i>Ruminococcus gnavus</i>	UniRef90_A7AZ12	-1.350127189	0.292426421	-4.616980853	3.89E-06	0.000954823	0.008716038
<i>Ruminococcus gnavus</i>	UniRef90_Q6W7J8	1.192500403	0.258467243	4.613739021	3.95E-06	0.000954823	0.008716038

<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P1S5	-1.164719638	0.25369461	-4.591030281	4.41E-06	0.001016451	0.009297807
<i>Ruminococcus gnavus</i>	UniRef90_A7B5F9	-1.136369972	0.248329162	-4.576063339	4.74E-06	0.001044436	0.009571891
<i>Ruminococcus gnavus</i>	UniRef90_A7AZ66	-1.472612941	0.32733859	-4.498745298	6.84E-06	0.001353387	0.01177945
<i>Ruminococcus gnavus</i>	UniRef90_F7JZ36	1.152729093	0.256382087	4.496137406	6.92E-06	0.001353387	0.01177945
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NED8	-1.335380478	0.297047817	-4.495506787	6.94E-06	0.001353387	0.01177945
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5Q430	-1.308815138	0.29181506	-4.485084276	7.29E-06	0.001368621	0.01177945
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PMV3	1.47488675	0.330525603	4.462246609	8.11E-06	0.001438947	0.011894233
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PFT9	-1.169919992	0.262764805	-4.452346625	8.49E-06	0.001438947	0.011894233
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P2J1	-1.268745579	0.285109913	-4.450022671	8.59E-06	0.001438947	0.011894233
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P8Q0	1.199653845	0.270014284	4.442927344	8.87E-06	0.001438947	0.011901245
<i>Ruminococcus gnavus</i>	UniRef90_R5TKF4	-1.60100105	0.360752653	-4.437946716	9.08E-06	0.001438947	0.011901245
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PFB5	1.240040728	0.28120173	4.409790532	1.03E-05	0.001573034	0.013202039
<i>Ruminococcus gnavus</i>	UniRef90_A7B7R4	-1.27518654	0.29006713	-4.396177329	1.10E-05	0.001573034	0.01320858
<i>Ruminococcus gnavus</i>	UniRef90_R5TS44	1.466311708	0.333589983	4.395550775	1.10E-05	0.001573034	0.01320858
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NSS6	-1.352075291	0.307765534	-4.393199175	1.12E-05	0.001573034	0.01320858
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PWI6	-1.144641684	0.261594636	-4.375631329	1.21E-05	0.001625241	0.013689123
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PFI7	-1.238085987	0.283035228	-4.374317634	1.22E-05	0.001625241	0.013689123
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PKE1	1.388246264	0.318031486	4.365122093	1.27E-05	0.001651673	0.013689123
<i>Ruminococcus gnavus</i>	UniRef90_A7B424	-1.165351953	0.268255983	-4.344178789	1.40E-05	0.001771935	0.014261349
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PE28	-1.319729773	0.304464478	-4.334593589	1.46E-05	0.001805781	0.014449485
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P753	-1.055922583	0.244492167	-4.318840123	1.57E-05	0.00189342	0.015209876
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P6Z5	-1.092979344	0.254728836	-4.29075625	1.78E-05	0.002099519	0.01575571
<i>Ruminococcus gnavus</i>	UniRef90_UPI000C7C4C2F	1.185059857	0.276740008	4.28221372	1.85E-05	0.002132201	0.015869294

<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P4N7	-1.308425356	0.305955486	-4.276521963	1.90E-05	0.002133029	0.015869294
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NK29	-1.389213799	0.325188991	-4.272019768	1.94E-05	0.002133029	0.015918727
<i>Ruminococcus gnavus</i>	UniRef90_A7B5F6	-1.517261689	0.355544467	-4.26743159	1.98E-05	0.002133029	0.015978747
<i>Ruminococcus gnavus</i>	UniRef90_A0A3E4KAA5	-1.036577805	0.243811413	-4.251555716	2.12E-05	0.00224232	0.016873629
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P9I1	1.108884718	0.26197862	4.232729816	2.31E-05	0.002335464	0.017596735
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PFD7	1.160074162	0.274504355	4.226068339	2.38E-05	0.002335464	0.017596735
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NVE5	1.353530256	0.320377143	4.224802824	2.39E-05	0.002335464	0.017596735
<i>Ruminococcus gnavus</i>	UniRef90_F7JZ39	1.067073616	0.252595235	4.224440797	2.40E-05	0.002335464	0.017596735
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P6L9	-1.197889109	0.28403503	-4.217399205	2.47E-05	0.002364115	0.017615395
<i>Ruminococcus gnavus</i>	UniRef90_F7JYH5	-1.479960212	0.351456848	-4.210930074	2.54E-05	0.002379412	0.017615395
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5Q1F5	-1.44123576	0.342684553	-4.205721401	2.60E-05	0.002379412	0.017698014
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NTM9	-1.23944161	0.29485916	-4.203503842	2.63E-05	0.002379412	0.017698014
<i>Ruminococcus gnavus</i>	UniRef90_F7JSP5	-1.257313948	0.299467296	-4.198501689	2.69E-05	0.002389899	0.017845592
<i>Ruminococcus gnavus</i>	UniRef90_R5TRW6	1.114377631	0.266121653	4.187474476	2.82E-05	0.002446827	0.018165238
<i>Ruminococcus gnavus</i>	UniRef90_A0A1L5KPQ5	-1.273927187	0.304378402	-4.185340289	2.85E-05	0.002446827	0.018165238
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P759	-1.017242739	0.24348874	-4.177781439	2.94E-05	0.002487395	0.01853552
<i>Ruminococcus gnavus</i>	UniRef90_F7JXC9	-1.333459138	0.319965331	-4.167511318	3.08E-05	0.002559463	0.01914183
<i>Ruminococcus gnavus</i>	UniRef90_R6BKN0	1.261031307	0.303615536	4.153382019	3.28E-05	0.002678899	0.020105757
<i>Ruminococcus gnavus</i>	UniRef90_A7B082	-1.471833141	0.354904557	-4.147123822	3.37E-05	0.002709456	0.02027319
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PYN5	-1.37337038	0.333383732	-4.119488289	3.80E-05	0.002995695	0.022106654
<i>Ruminococcus gnavus</i>	UniRef90_A7AZ18	-1.500411192	0.36445493	-4.116863485	3.84E-05	0.002995695	0.022106654
<i>Ruminococcus gnavus</i>	UniRef90_R5U633	1.115021604	0.272141451	4.097213416	4.18E-05	0.003191038	0.023056738
<i>Ruminococcus gnavus</i>	UniRef90_F3AU73	1.002008151	0.244744556	4.094097813	4.24E-05	0.003191038	0.023056738

<i>Ruminococcus gnavus</i>	UniRef90_A7AZ80	-1.17373435	0.286848534	-4.091826211	4.28E-05	0.003191038	0.023056738
<i>Ruminococcus gnavus</i>	UniRef90_A0A3E4VAC9	-1.209624365	0.296274431	-4.082783525	4.45E-05	0.003269744	0.023199536
<i>Ruminococcus gnavus</i>	UniRef90_A0A3E4V1H5	-1.235044624	0.303318611	-4.07177331	4.67E-05	0.003379269	0.023812043
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NVZ5	-1.208400057	0.297710443	-4.058977719	4.93E-05	0.003468071	0.024455416
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NXE1	-1.344106028	0.33137931	-4.056095197	4.99E-05	0.003468071	0.024455416
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P545	-1.051028865	0.259133737	-4.055932192	4.99E-05	0.003468071	0.024455416
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NPF7	-1.135319846	0.280619311	-4.045765211	5.22E-05	0.00357315	0.025286132
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P9I2	1.027883827	0.255336219	4.025609174	5.68E-05	0.003717362	0.025966636
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NTL5	-1.030164942	0.256180338	-4.021249062	5.79E-05	0.003717362	0.025966636
<i>Ruminococcus gnavus</i>	UniRef90_R5TKS2	0.965194645	0.240260657	4.01728131	5.89E-05	0.003717362	0.025966636
<i>Ruminococcus gnavus</i>	UniRef90_A0A367FZM8	1.25944069	0.313562957	4.016548068	5.91E-05	0.003717362	0.025966636
<i>Ruminococcus gnavus</i>	UniRef90_A0A396GBF6	-1.467783229	0.365466295	-4.016193144	5.91E-05	0.003717362	0.025966636
<i>Ruminococcus gnavus</i>	UniRef90_A0A174N9L2	1.134454607	0.282533221	4.01529634	5.94E-05	0.003717362	0.025966636
<i>Ruminococcus gnavus</i>	UniRef90_A0A3A6GLV6	-1.242899989	0.309914272	-4.010463866	6.06E-05	0.003717362	0.025966636
<i>Ruminococcus gnavus</i>	UniRef90_F7K1C1	-1.023567576	0.255372407	-4.008136937	6.12E-05	0.003717362	0.025966636
<i>Ruminococcus gnavus</i>	UniRef90_Q6W7J6	1.025793447	0.255942007	4.00791358	6.13E-05	0.003717362	0.025966636
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P6J1	-1.091433299	0.272406338	-4.006636943	6.16E-05	0.003717362	0.025966636
<i>Ruminococcus gnavus</i>	UniRef90_A0A3E4V9X5	-1.123306895	0.28152723	-3.990047052	6.61E-05	0.003940296	0.027375455
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P9Y7	1.018409123	0.257039005	3.962080082	7.43E-05	0.004380221	0.029287939
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P5U8	-1.019933653	0.25773876	-3.957238145	7.58E-05	0.004418553	0.029646752
<i>Ruminococcus gnavus</i>	UniRef90_A7AYM0	-1.071290849	0.271167173	-3.950665706	7.79E-05	0.004490068	0.029804606
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NPC6	-1.167607429	0.295771445	-3.94766787	7.89E-05	0.004495562	0.029804606
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PPK9	-1.097169306	0.278760802	-3.93588087	8.29E-05	0.00461392	0.030454981

<i>Ruminococcus gnavus</i>	UniRef90_A0A367FZM6	1.18307286	0.300733638	3.933955872	8.36E-05	0.00461392	0.030454981
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NU67	-1.022490826	0.260173445	-3.930035319	8.49E-05	0.00461392	0.030454981
<i>Ruminococcus gnavus</i>	UniRef90_A0A174JGL0	-1.110965434	0.28273873	-3.9293005	8.52E-05	0.00461392	0.030454981
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P4C4	-1.122354571	0.285709099	-3.928312305	8.55E-05	0.00461392	0.030454981
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PRL4	1.235269224	0.314707696	3.925131927	8.67E-05	0.004626093	0.030454981
<i>Ruminococcus gnavus</i>	UniRef90_A7B022	0.959392671	0.244763914	3.919665514	8.87E-05	0.004682987	0.030929924
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PR65	1.009037817	0.257638397	3.916488494	8.98E-05	0.004696184	0.031116323
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NSR0	-1.208758782	0.309349475	-3.90742147	9.33E-05	0.004826141	0.032077933
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PPI3	-1.068160183	0.274238117	-3.895009911	9.82E-05	0.00502876	0.032609389
<i>Ruminococcus gnavus</i>	UniRef90_A0A174NAF8	1.114122182	0.286296321	3.891500173	9.96E-05	0.005048243	0.032859742
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P3F8	-1.086102044	0.279259546	-3.889220826	0.000100567	0.005048243	0.032945748
<i>Ruminococcus gnavus</i>	UniRef90_A7AZ14	-1.2282985	0.317451926	-3.869242553	0.000109174	0.005333039	0.034770062
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P901	1.112770283	0.287712081	3.867652263	0.000109888	0.005333039	0.034770062
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PMV6	1.219563023	0.315402085	3.866692958	0.000110321	0.005333039	0.034770062
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NZT2	-1.390816743	0.359913259	-3.864310941	0.000111403	0.005333039	0.034770062
<i>Ruminococcus gnavus</i>	UniRef90_F7JWU6	-1.291513359	0.334233918	-3.864100234	0.000111499	0.005333039	0.034770062
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PP13	1.112484403	0.288079686	3.861724572	0.000112589	0.005334846	0.034770062
<i>Ruminococcus gnavus</i>	UniRef90_A7AYR2	-0.937663157	0.242989475	-3.858863259	0.000113916	0.005347707	0.034956964
<i>Ruminococcus gnavus</i>	UniRef90_A0A174N8K3	1.166434282	0.302825169	3.851840605	0.000117233	0.005452963	0.035525361
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P2Q1	-1.060045809	0.276028186	-3.840353497	0.000122857	0.005642882	0.03594272
<i>Ruminococcus gnavus</i>	UniRef90_A0A174NA91	1.10328753	0.287390189	3.838988146	0.000123542	0.005642882	0.03594272
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PFF0	1.066807533	0.27864001	3.828622941	0.000128862	0.005833318	0.036537348
<i>Ruminococcus gnavus</i>	UniRef90_A7AYY3	-1.082524781	0.283516999	-3.818200623	0.000134429	0.00592505	0.037533547

<i>Ruminococcus gnavus</i>	UniRef90_A7B4G4	-1.373239818	0.359772263	-3.816969677	0.000135101	0.00592505	0.037533547
<i>Ruminococcus gnavus</i>	UniRef90_A0A3E4VAD7	-1.101658577	0.288865241	-3.813745728	0.000136876	0.00592505	0.037533547
<i>Ruminococcus gnavus</i>	UniRef90_F7JYH8	-1.049419749	0.275334196	-3.811439936	0.00013816	0.00592505	0.037533547
<i>Ruminococcus gnavus</i>	UniRef90_A7AYQ9	-0.938920173	0.246414477	-3.810328787	0.000138782	0.00592505	0.037533547
<i>Ruminococcus gnavus</i>	UniRef90_R5TST0	0.916133245	0.240450517	3.810069767	0.000138928	0.00592505	0.037533547
<i>Ruminococcus gnavus</i>	UniRef90_A0A396G8Q5	-1.007530759	0.264456412	-3.809817849	0.000139069	0.00592505	0.037533547
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NNP1	-1.086219492	0.285602803	-3.803252209	0.000142809	0.006028259	0.03804443
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NQ25	-1.041550018	0.273989786	-3.801419147	0.00014387	0.006028259	0.038117605
<i>Ruminococcus gnavus</i>	UniRef90_F7JWG3	-0.998656146	0.263061085	-3.796289923	0.000146878	0.006103853	0.038703077
<i>Ruminococcus gnavus</i>	UniRef90_A7B422	-1.425169272	0.377874357	-3.771542695	0.000162241	0.006687511	0.04118468
<i>Ruminococcus gnavus</i>	UniRef90_A0A174E9H2	-0.926680232	0.246155321	-3.764615894	0.000166805	0.006791837	0.041415755
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NZM5	-0.976439414	0.259439524	-3.763649423	0.000167452	0.006791837	0.041415755
<i>Ruminococcus gnavus</i>	UniRef90_R5GWN8	1.079806268	0.287059119	3.761616331	0.000168819	0.00679295	0.041415755
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NPF9	-1.04504179	0.27914421	-3.743734434	0.000181305	0.007237935	0.042466602
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5P758	-0.934770836	0.2506933	-3.728742802	0.000192437	0.007622327	0.044430139
<i>Ruminococcus gnavus</i>	UniRef90_A7AYL9	-0.929554541	0.249598638	-3.724197175	0.000195938	0.007700809	0.045023894
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PMW7	1.208176255	0.324638424	3.721605837	0.00019796	0.007720435	0.045262301
<i>Ruminococcus gnavus</i>	UniRef90_A0A3E4V6E2	-0.927430657	0.250803852	-3.697832591	0.000217448	0.008415744	0.047757227
<i>Ruminococcus gnavus</i>	UniRef90_A7AYI1	-1.097977205	0.297273445	-3.693492382	0.000221195	0.008448324	0.047757227
<i>Ruminococcus gnavus</i>	UniRef90_A7AYS1	-1.044719928	0.282891821	-3.69300153	0.000221623	0.008448324	0.047757227
<i>Ruminococcus gnavus</i>	UniRef90_A7AZ22	-1.13513078	0.308032362	-3.685102342	0.000228611	0.008637455	0.048402588
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5PVU5	-1.062114289	0.288338407	-3.683568549	0.000229991	0.008637455	0.048483187
<i>Ruminococcus gnavus</i>	UniRef90_A0A2N5NJF5	-0.992097819	0.269705951	-3.67844245	0.000234663	0.008748085	0.04893982

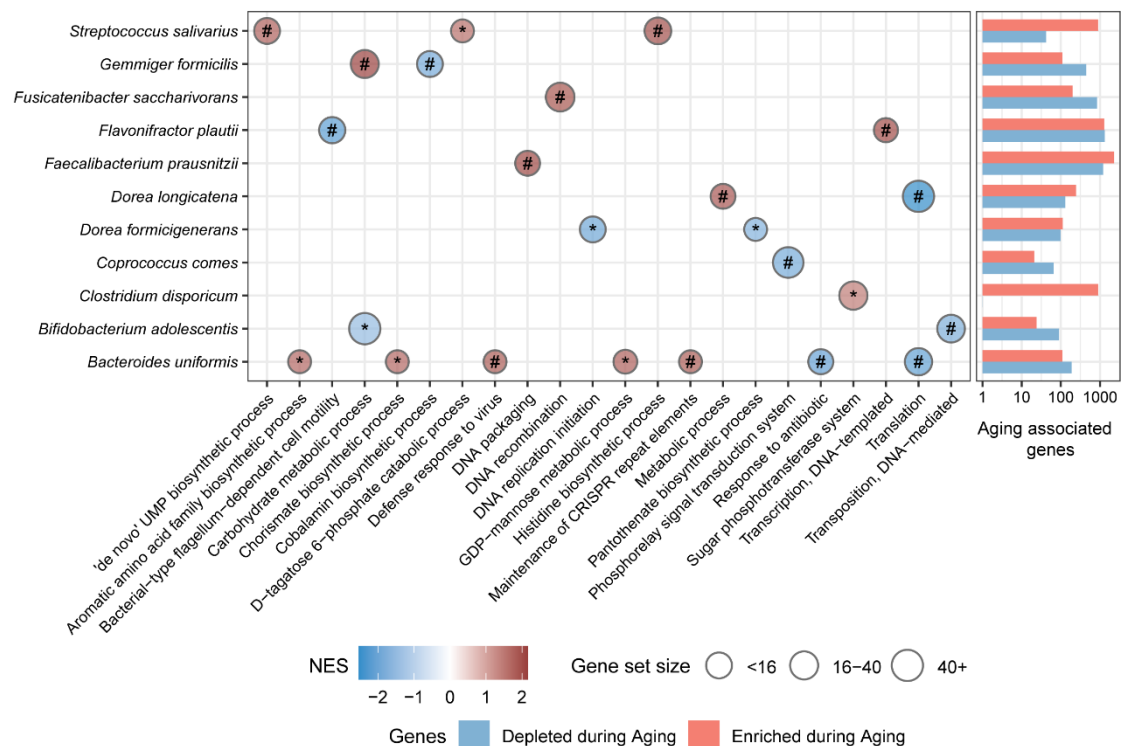
<i>Ruminococcus gnavus</i>	UniRef90_A7B4P2	-1.211704542	0.329648768	-3.675744188	0.000237157	0.008751769	0.04893982
<i>Ruminococcus gnavus</i>	UniRef90_F7JW46	-0.992465769	0.27008744	-3.674609109	0.000238214	0.008751769	0.04893982
<i>Streptococcus parasanguinis</i>	UniRef90_A0A2I1TRX2	1.41788559	0.303355353	4.674008803	2.95E-06	0.006037499	0.007593315
<i>Streptococcus parasanguinis</i>	UniRef90_E8K403	1.494798617	0.333170665	4.48658533	7.24E-06	0.007306412	0.01177945
<i>Streptococcus parasanguinis</i>	UniRef90_A0A2I1TRI8	1.328192143	0.305893585	4.342007184	1.41E-05	0.007306412	0.014261349
<i>Streptococcus parasanguinis</i>	UniRef90_K8N1X4	1.27700516	0.297152927	4.297467889	1.73E-05	0.007306412	0.01575571
<i>Streptococcus parasanguinis</i>	UniRef90_A0A380LBU7	1.603410731	0.373761387	4.289931451	1.79E-05	0.007306412	0.01575571
<i>Streptococcus parasanguinis</i>	UniRef90_I1ZLQ0	1.587012448	0.383476886	4.138482676	3.50E-05	0.011910056	0.020671773
<i>Streptococcus parasanguinis</i>	UniRef90_I2NIE6	1.264919186	0.309769481	4.083420949	4.44E-05	0.012508435	0.023199536
<i>Streptococcus parasanguinis</i>	UniRef90_V8BGB6	1.318738212	0.326797283	4.03534019	5.45E-05	0.012508435	0.025917248
<i>Streptococcus parasanguinis</i>	UniRef90_A0A2I1TU25	1.22646545	0.304109727	4.032970143	5.51E-05	0.012508435	0.025925956
<i>Streptococcus parasanguinis</i>	UniRef90_I1ZKM0	1.243001885	0.313503098	3.964879106	7.34E-05	0.014540161	0.02918366
<i>Streptococcus parasanguinis</i>	UniRef90_A0A2I1TRD0	1.209387839	0.306197437	3.949699414	7.82E-05	0.014540161	0.029804606
<i>Streptococcus parasanguinis</i>	UniRef90_I2NLH7	1.313971609	0.336516043	3.90463289	9.44E-05	0.016074106	0.032221535
<i>Streptococcus parasanguinis</i>	UniRef90_F8DIG1	1.17227401	0.303067328	3.868031621	0.000109717	0.016660955	0.034770062
<i>Streptococcus parasanguinis</i>	UniRef90_I1ZPR4	1.11653497	0.289559947	3.855971735	0.000115271	0.016660955	0.035150346
<i>Streptococcus parasanguinis</i>	UniRef90_I1ZMB2	1.116560191	0.290654695	3.841535027	0.000122267	0.016660955	0.03594272
<i>Streptococcus parasanguinis</i>	UniRef90_I1ZMI3	1.206628474	0.316322387	3.814552886	0.00013643	0.017387014	0.037533547
<i>Streptococcus parasanguinis</i>	UniRef90_A8AXT6	1.172956891	0.309352949	3.791646059	0.000149652	0.017387014	0.039010117
<i>Streptococcus parasanguinis</i>	UniRef90_E7S948	1.137694053	0.302577829	3.760004677	0.00016991	0.017387014	0.041415755
<i>Streptococcus parasanguinis</i>	UniRef90_A0A2I1TU21	1.314398062	0.349859072	3.756935775	0.000172007	0.017387014	0.041442151
<i>Streptococcus parasanguinis</i>	UniRef90_A0A359YKD7	1.095104819	0.291893821	3.7517232	0.000175623	0.017387014	0.041740666
<i>Streptococcus parasanguinis</i>	UniRef90_I1ZKT4	1.091605927	0.29129215	3.747460848	0.000178634	0.017387014	0.04206642

<i>Streptococcus parasanguinis</i>	UniRef90_F8DJX1	1.181868423	0.316913538	3.729308723	0.000192006	0.017607686	0.044430139
<i>Streptococcus parasanguinis</i>	UniRef90_K8MHT4	1.075291807	0.289019431	3.72048275	0.000198842	0.017607686	0.045262301
<i>Streptococcus parasanguinis</i>	UniRef90_A0A359YI56	1.390173985	0.376204539	3.69526107	0.000219661	0.017607686	0.047757227
<i>Streptococcus parasanguinis</i>	UniRef90_I1ZMH2	1.258650555	0.341037134	3.690655443	0.000223677	0.017607686	0.047838361
<i>Streptococcus parasanguinis</i>	UniRef90_V8BGS5	1.182552412	0.320447158	3.690319548	0.000223973	0.017607686	0.047838361
<i>Streptococcus parasanguinis</i>	UniRef90_A0A211TUF5	1.239705702	0.337285735	3.675535524	0.000237351	0.01796835	0.04893982
<i>Escherichia coli</i>	UniRef90_A0A376JPR1	1.114840381	0.22170069	5.028583266	4.94E-07	0.034167886	0.024754765
<i>Escherichia coli</i>	UniRef90_A0A376TF09	1.057029635	0.215273177	4.910178074	9.10E-07	0.034167886	0.030391297
<i>Escherichia coli</i>	UniRef90_A0A0L6XY56	1.510941741	0.312165009	4.840202131	1.30E-06	0.034167886	0.032490989
<i>Escherichia coli</i>	UniRef90_A0A376RMB2	1.214489435	0.258383548	4.700335776	2.60E-06	0.042527304	0.044933491
<i>Escherichia coli</i>	UniRef90_A0A377AMR9	1.019123301	0.220045925	4.631411828	3.63E-06	0.042527304	0.044933491
<i>Escherichia coli</i>	UniRef90_P37342	0.990488877	0.214787362	4.611485826	4.00E-06	0.042527304	0.044933491
<i>Escherichia coli</i>	UniRef90_A0A398Q5L5	1.008638615	0.220190063	4.580763546	4.63E-06	0.042527304	0.044933491
<i>Escherichia coli</i>	UniRef90_A0A376SFZ7	0.975210698	0.21295073	4.579513283	4.66E-06	0.042527304	0.044933491
<i>Escherichia coli</i>	UniRef90_A0A0Q3CU51	1.303707926	0.285637415	4.564205721	5.01E-06	0.042527304	0.044933491
<i>Escherichia coli</i>	UniRef90_POACV7	0.944005529	0.2075037	4.549343111	5.38E-06	0.042527304	0.044933491
<i>Fusicatenibacter saccharivorans</i>	UniRef90_A7VI07	-0.752277898	0.152030316	-4.948209787	7.49E-07	0.002508373	0.009028844
<i>Fusicatenibacter saccharivorans</i>	UniRef90_A0A174LBJ3	-0.713810744	0.158785752	-4.495433214	6.94E-06	0.011625794	0.030546653
<i>Fusicatenibacter saccharivorans</i>	UniRef90_A0A2A7AHN8	0.959120977	0.222510816	4.310446531	1.63E-05	0.018187885	0.036825173
<i>Fusicatenibacter saccharivorans</i>	UniRef90_D4M3L4	-0.523263022	0.125298304	-4.176138116	2.96E-05	0.020126696	0.044044165
<i>Fusicatenibacter saccharivorans</i>	UniRef90_E7GQB6	0.676920864	0.162210706	4.173096082	3.00E-05	0.020126696	0.044044165
<i>Gemmiger formicilis</i>	UniRef90_A0A1T4XBI9	0.707559745	0.138288362	5.116553069	3.11E-07	0.000418835	0.009028844
<i>Gemmiger formicilis</i>	UniRef90_A0A1T4WC00	-0.632834488	0.138659012	-4.563962182	5.02E-06	0.003378267	0.03025548

<i>Gemmiger formicilis</i>	UniRef90_A0A1T4XQP2	-0.570439906	0.133963636	-4.258169771	2.06E-05	0.007154714	0.039229832
<i>Gemmiger formicilis</i>	UniRef90_A0A1T4XFQ6	-1.336783178	0.316281287	-4.226564243	2.37E-05	0.007154714	0.040863003
<i>Gemmiger formicilis</i>	UniRef90_A0A1T4Y6B2	0.994141483	0.23839791	4.170093121	3.04E-05	0.007154714	0.044044165
<i>Gemmiger formicilis</i>	UniRef90_A0A3D4DXL0	-1.342173415	0.324765012	-4.132752505	3.58E-05	0.007154714	0.049837698
<i>Gemmiger formicilis</i>	UniRef90_A0A1T4Y4W1	1.038142638	0.251722107	4.124161554	3.72088E-05	0.007154714	0.049837698

Supplementary Text

We also did the same analysis on those species identified by anpan gene association model with the continuous outcome to observe successive within-species functional variations in aging, and similar functions were identified (sFig8b). But there was one intriguing phenomenon. *Bacteroides uniformis*, which was widely acknowledged as a probiotic and played a crucial role in a variety of diseases¹⁻⁵ showed two distinct enriched functions. Interestingly, it enriched the GO term of Maintenance of CRISPR repeat elements and defense response to virus while aging suggesting that CRISPR-based microbial immunity⁶ prevented it from HGT to stabilize its genome. This genomic stabilization likely ensures the preservation of its beneficial properties, offering a potential application for the development of probiotics for the elderly population.



Supplementary Fig1. The plot depicts the results of a Gene Set Enrichment Analysis (GSEA) for different species across various Gene Ontology (GO) terms related to aging. The x-axis represents the GO terms, while the size of each circle corresponds to the number of associated genes in the UniRef90 gene family (with smaller circles indicating fewer than 16 genes, medium circles indicating 16–40 genes, and larger circles indicating over 40 genes). The color gradient represents normalized enrichment scores (NES), where blue indicates depletion during aging and red indicates enrichment during aging. Symbols indicate statistical significance: # represents $FDR < 0.05$ and * represents $FDR < 0.1$, with Benjamini-Hochberg correction applied for multiple testing.

Reference

1. Hao, Z., *et al.* Positive mood-related gut microbiota in a long-term closed environment: a multiomics study based on the "Lunar Palace 365" experiment. *Microbiome* **11**, 88 (2023).
2. Nie, Q., *et al.* Gut symbionts alleviate MASH through a secondary bile acid biosynthetic pathway. *Cell* **187**, 2717–2734 e2733 (2024).
3. Cheng, M., *et al.* Stage-specific roles of microbial dysbiosis and metabolic disorders in rheumatoid arthritis. *Annals of the Rheumatic Diseases* **81**, 1669–1677 (2022).
4. Romani-Perez, M., *et al.* *Bacteroides uniformis* CECT 7771 requires adaptive immunity to improve glucose tolerance but not to prevent body weight gain in diet-induced obese

- mice. *Microbiome* **12**, 103 (2024).
5. Lopez-Almela, I., *et al.* Bacteroides uniformis combined with fiber amplifies metabolic and immune benefits in obese mice. *Gut Microbes* **13**, 1-20 (2021).
 6. Gasiunas, G., Sinkunas, T. & Siksnys, V. Molecular mechanisms of CRISPR-mediated microbial immunity. *Cell Mol Life Sci* **71**, 449-465 (2014).