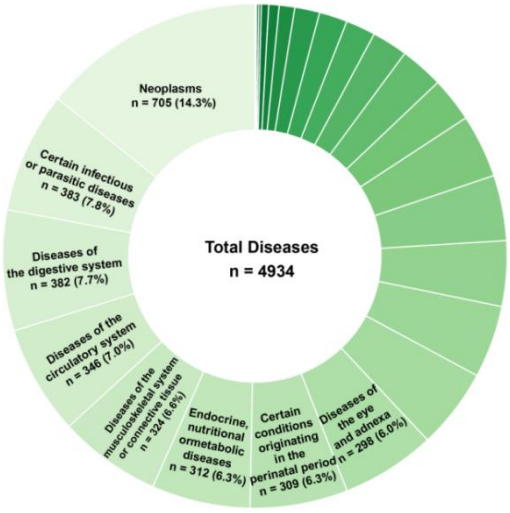
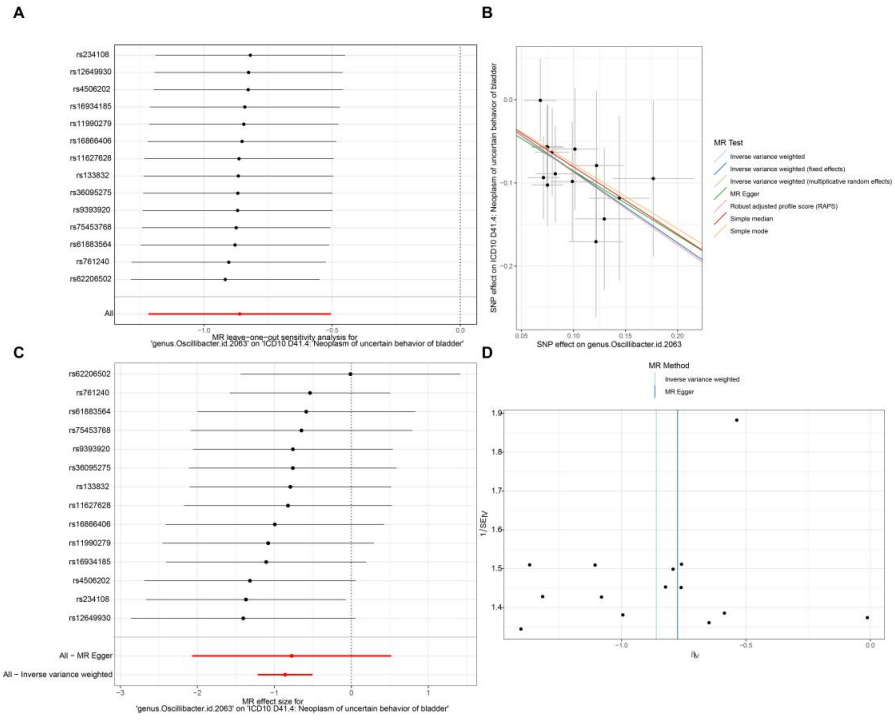
Supplementary Fig. S1. Distribution of the 4,934 disease GWAS outcomes across disease systems.



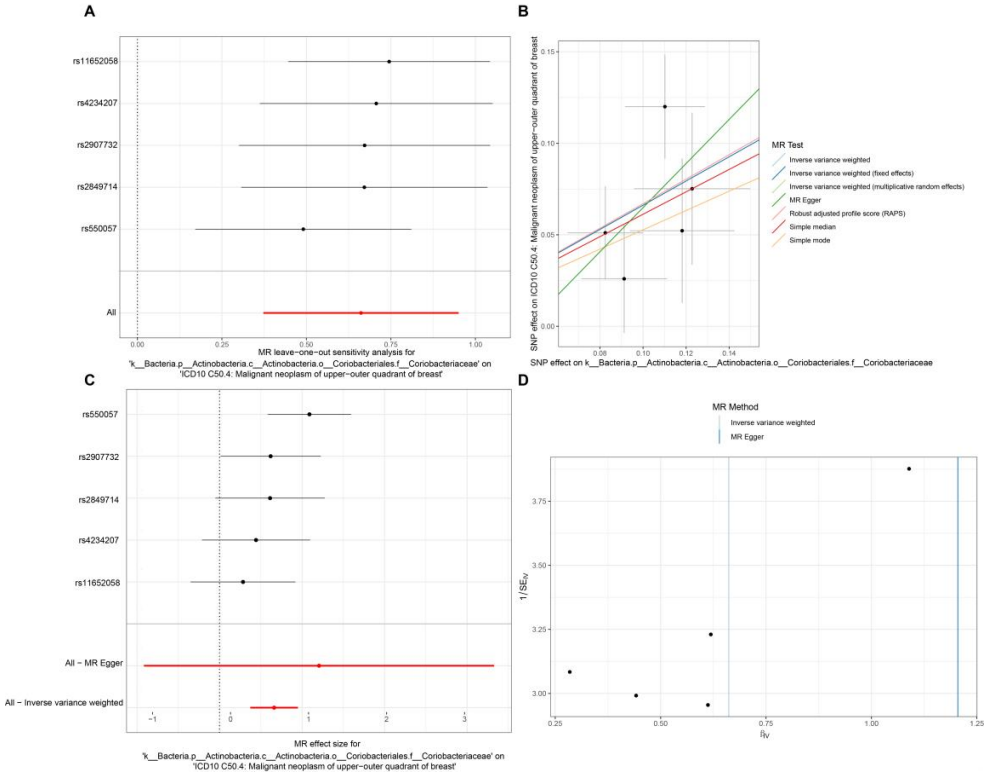
Panel descriptions for Supplementary Figs. S2 – S24. (A) Forest plots showing individual SNP estimates and combined MR estimates. (B) Scatter plots showing SNP – exposure and SNP – outcome associations, with fitted lines representing estimates from complementary MR methods. (C) Leave-one-out analyses showing MR estimates after sequentially excluding each SNP. (D) Funnel plots showing the distribution of individual SNP estimates.

(1) Neoplasms

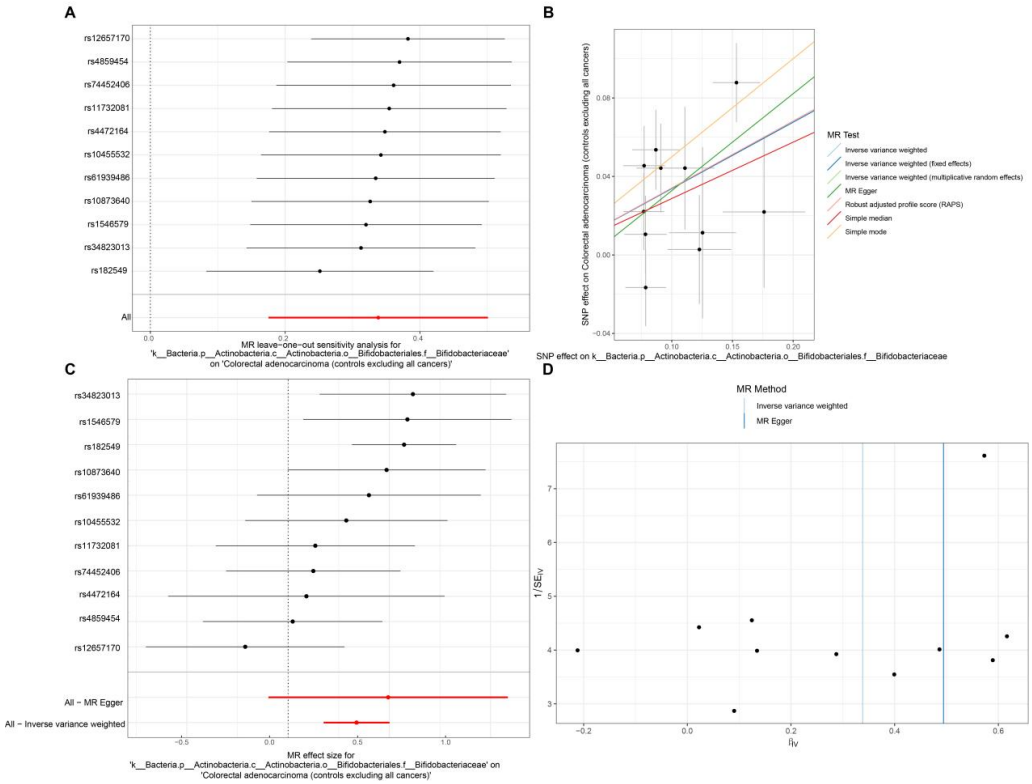
Supplementary Fig. S2. MR sensitivity analyses for the association between Oscillibacter and bladder neoplasm of uncertain behavior.



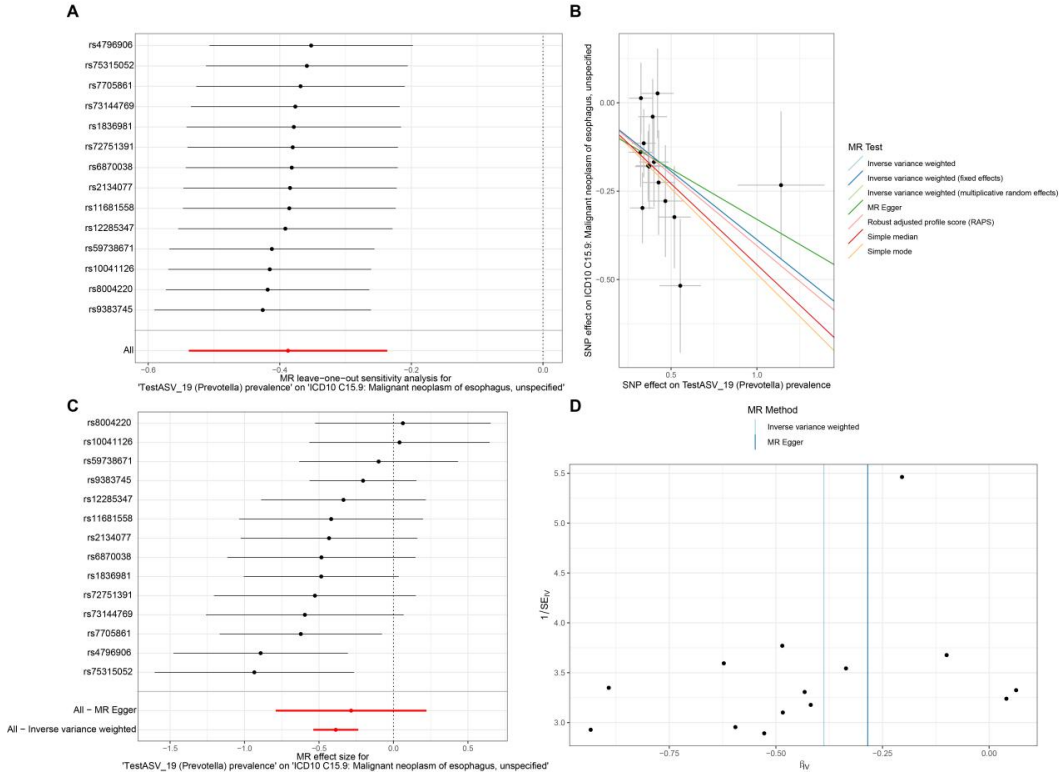
Supplementary Fig. S3. MR sensitivity analyses for associations of Coriobacteriales- and Coriobacteriaceae-related traits with breast cancer of the upper-outer quadrant.



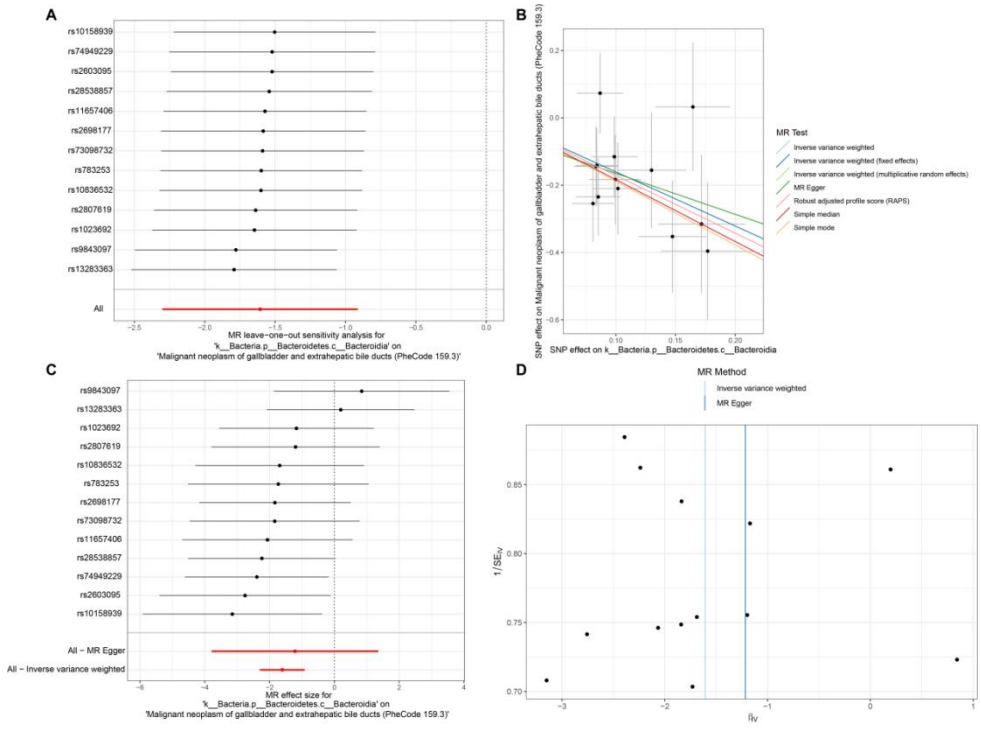
Supplementary Fig. S4. MR sensitivity analyses for associations of Bifidobacteriales- and Bifidobacteriaceae-related traits with colorectal adenocarcinoma.



Supplementary Fig. S5. MR sensitivity analyses for the association between the prevalence of the Prevotella-associated ASV TestASV_19 and esophageal cancer.

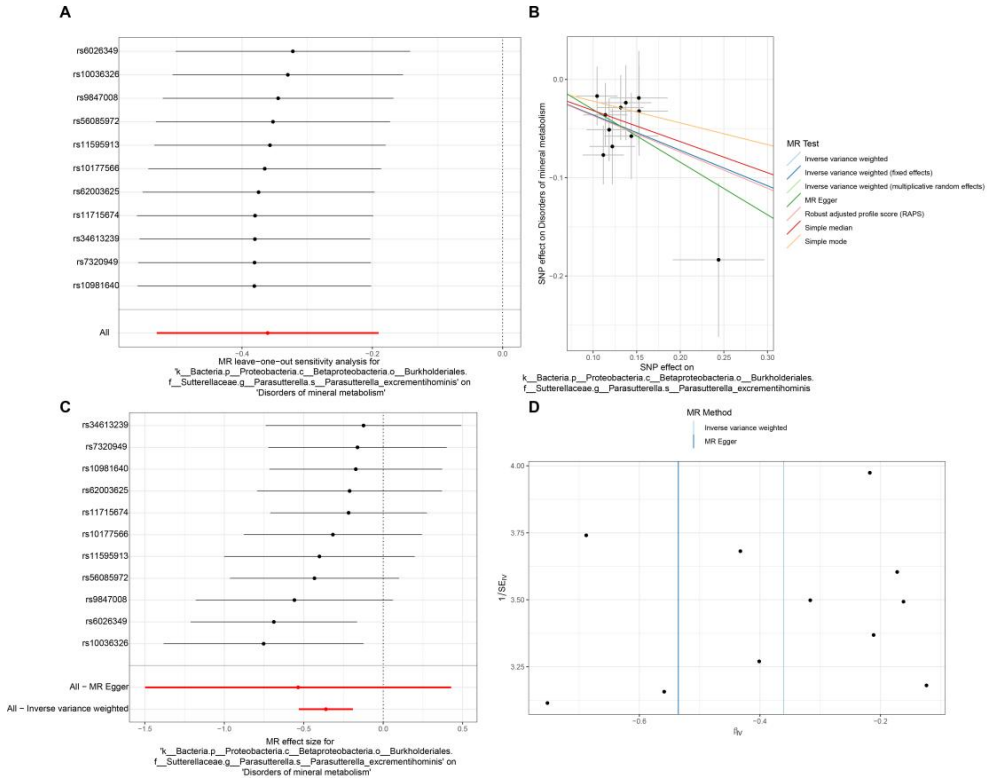


Supplementary Fig. S6. MR sensitivity analyses for associations of Bacteroidetes-, Bacteroidia-, and Bacteroidales-related traits with gallbladder and extrahepatic bile duct cancer.

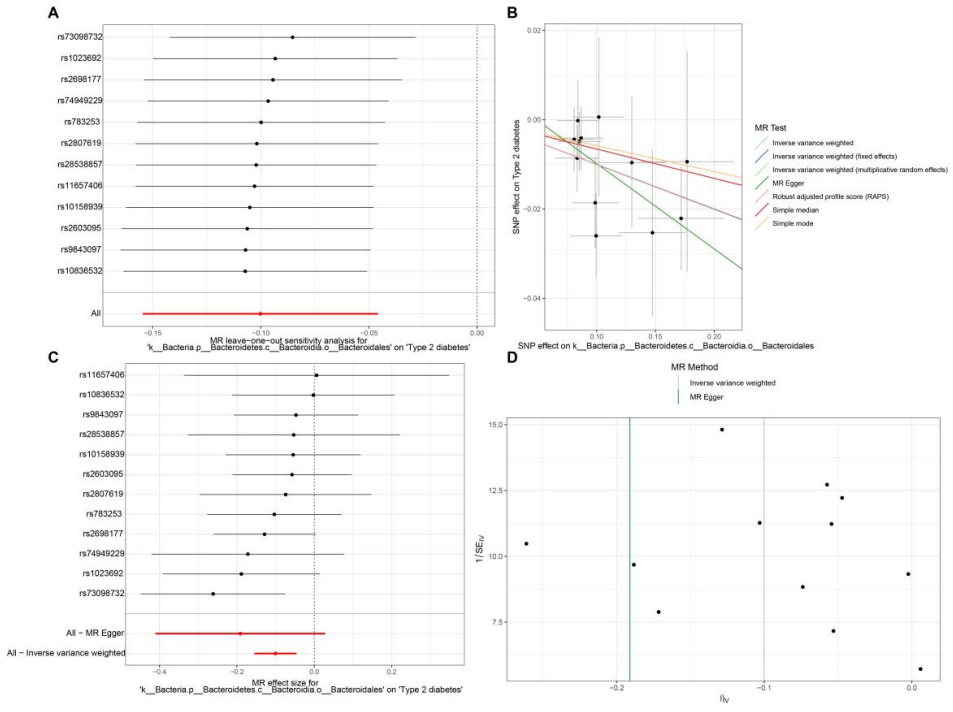


(2) Endocrine, nutritional or metabolic diseases

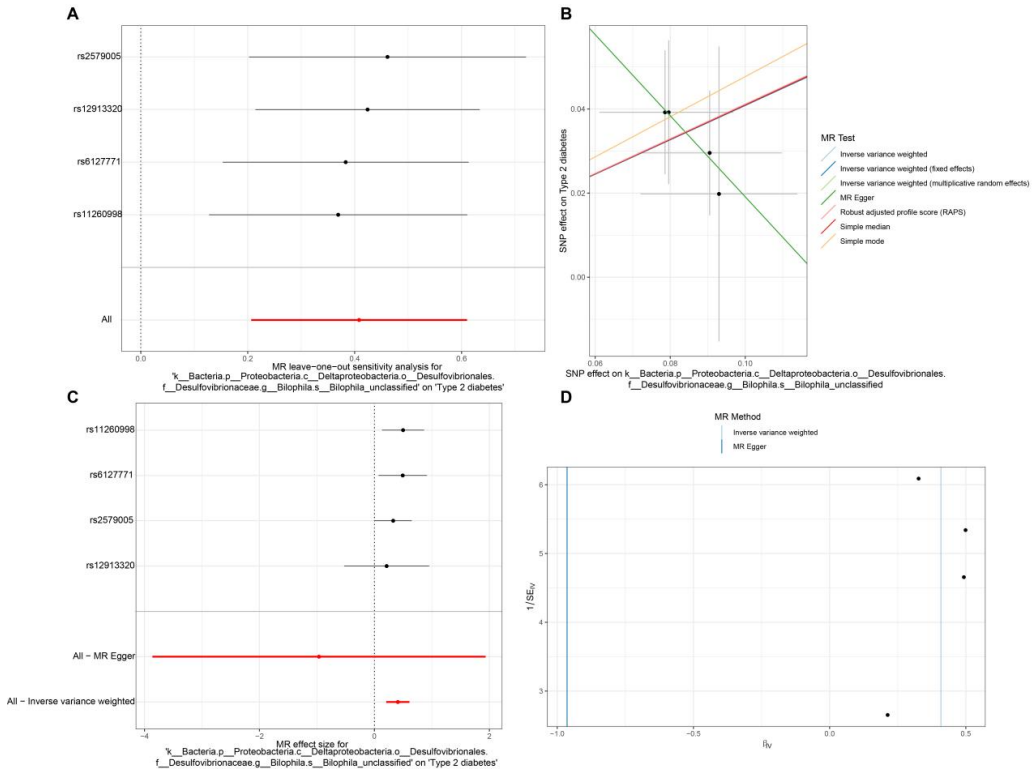
Supplementary Fig. S7. MR sensitivity analyses for associations of Burkholderiales-, Sutterellaceae-, and Parasutterella-related traits with disorders of mineral metabolism.



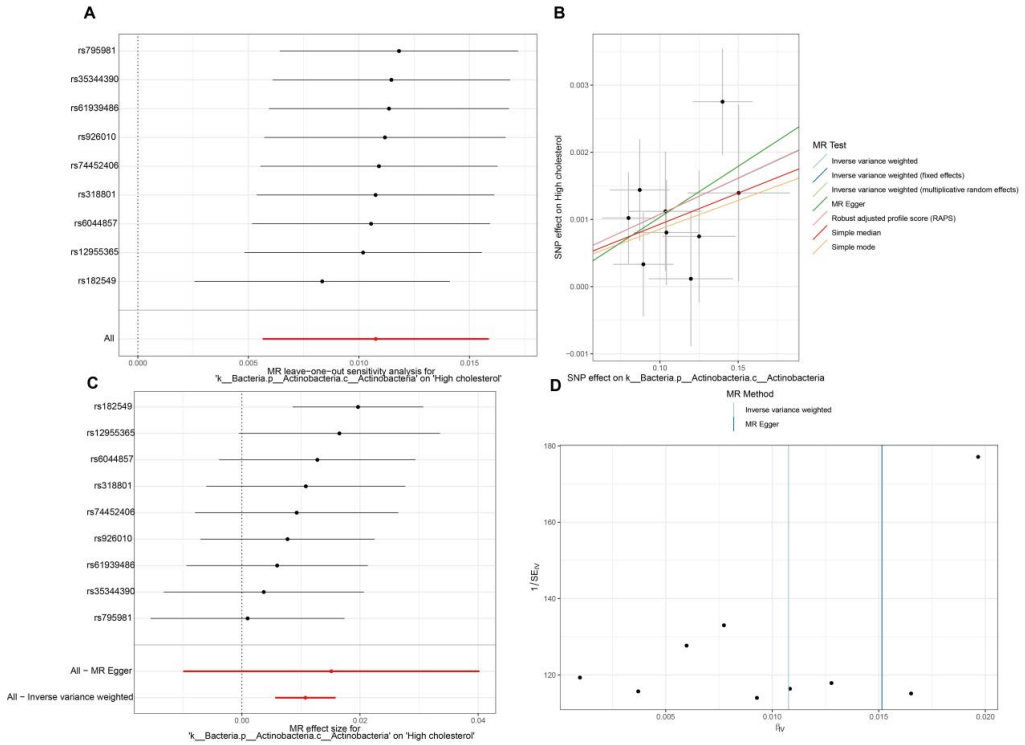
Supplementary Fig. S8. MR sensitivity analyses for associations of Bacteroidetes-, Bacteroidia-, and Bacteroidales-related traits with type 2 diabetes.



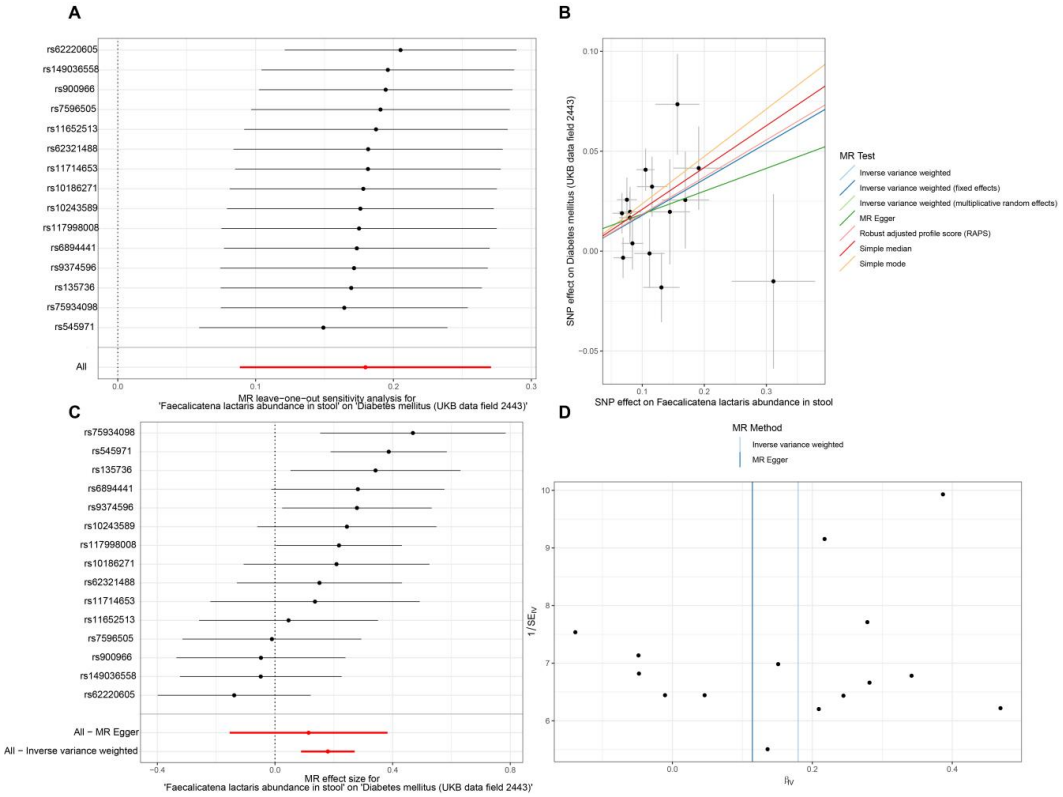
Supplementary Fig. S9. MR sensitivity analyses for associations of Deltaproteobacteria-, Desulfovibrionales-, Desulfovibrionaceae-, and Bilophila-related traits with type 2 diabetes.



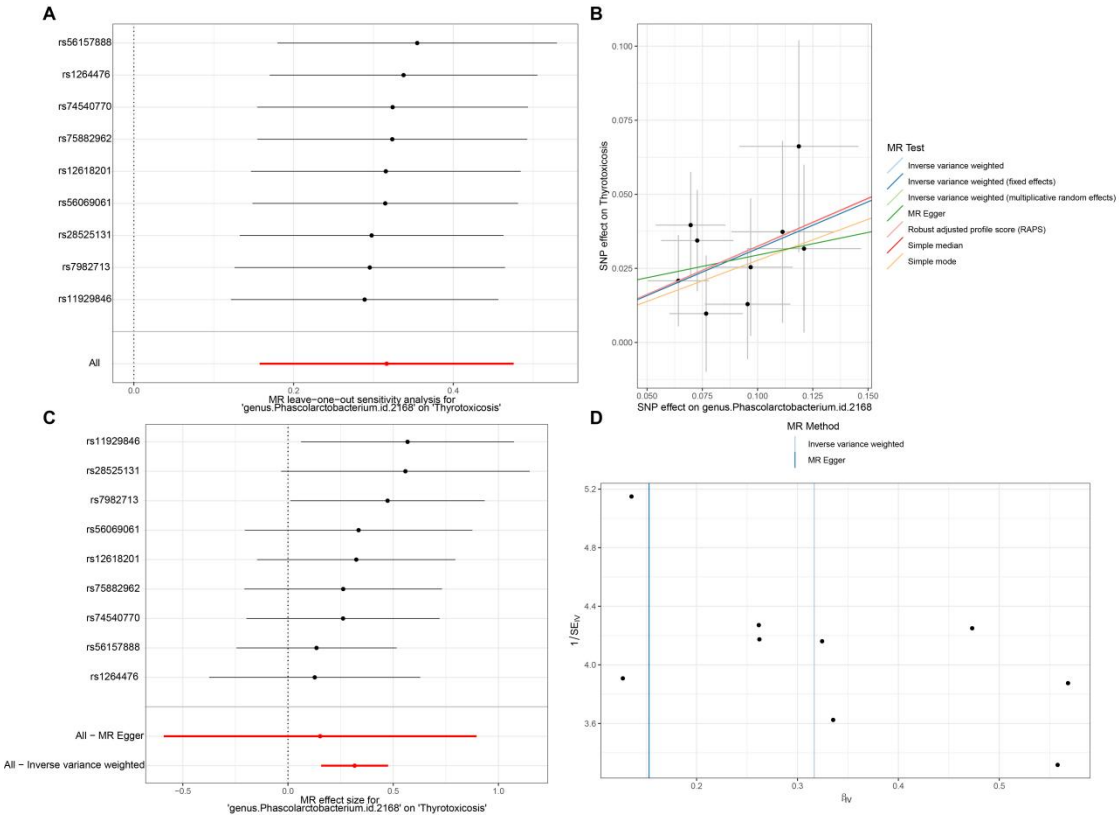
Supplementary Fig. S10. MR sensitivity analyses for the association between Actinobacteria and high cholesterol.



Supplementary Fig. S11. MR sensitivity analyses for the association between Faecalicatena lactaris and diabetes mellitus.

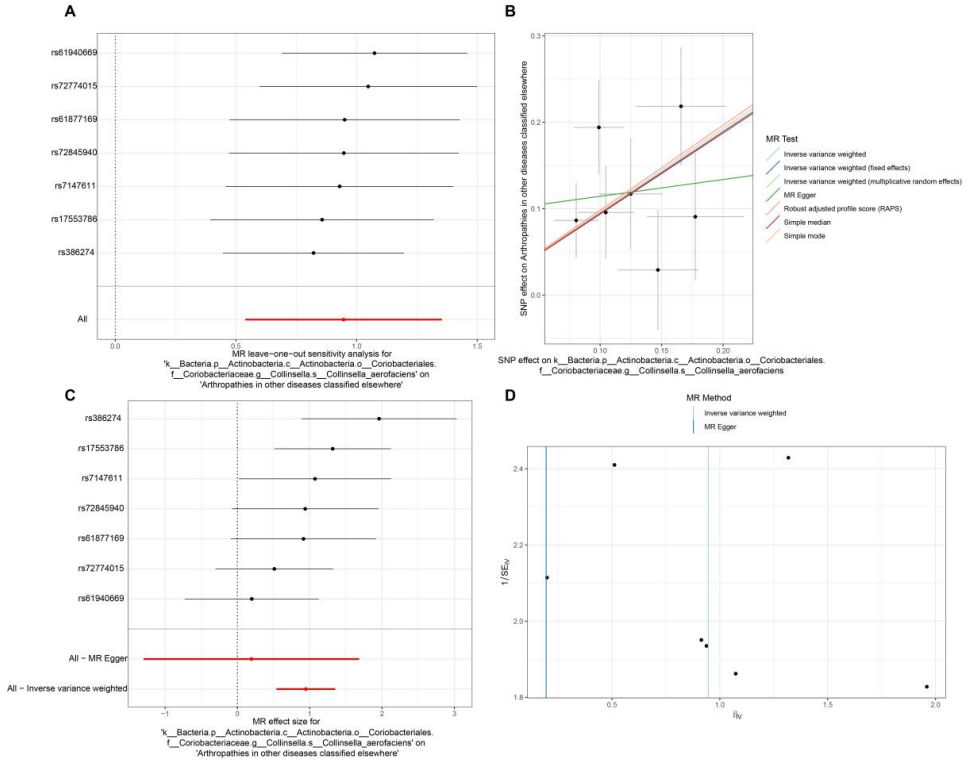


Supplementary Fig. S12. MR sensitivity analyses for the association between Phascolarctobacterium and thyrotoxicosis.

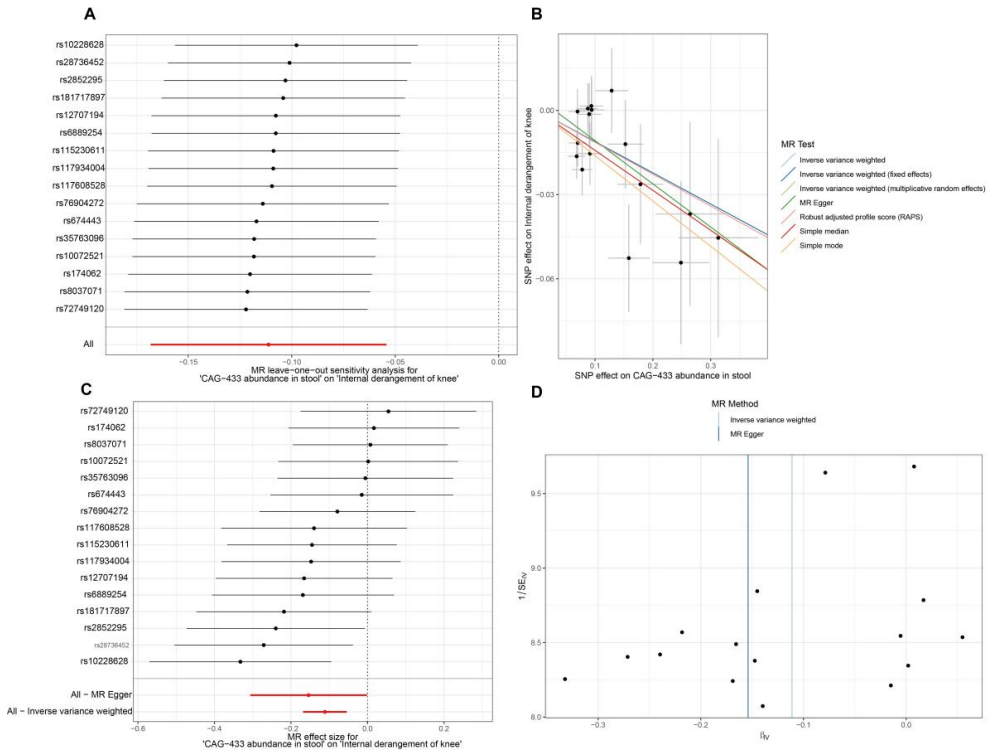


(3) Diseases of the musculoskeletal system or connective tissue

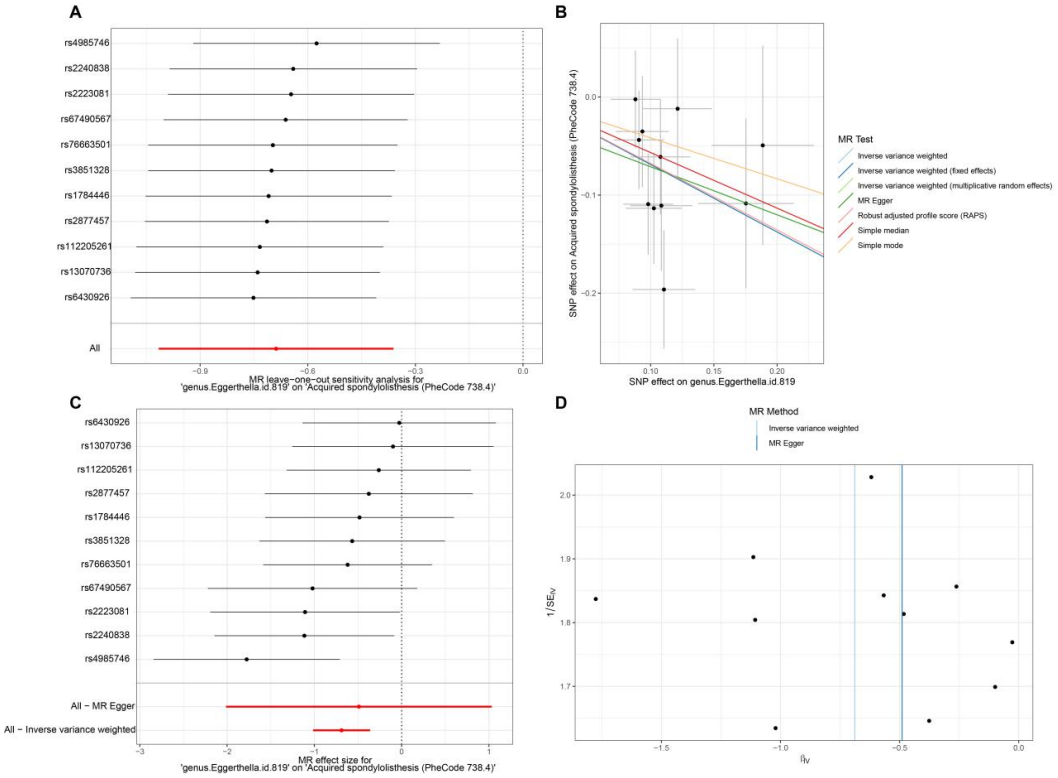
Supplementary Fig. S13. MR sensitivity analyses for associations of Coriobacteriaceae, Collinsella, and Collinsella aerofaciens with arthropathies in other diseases.



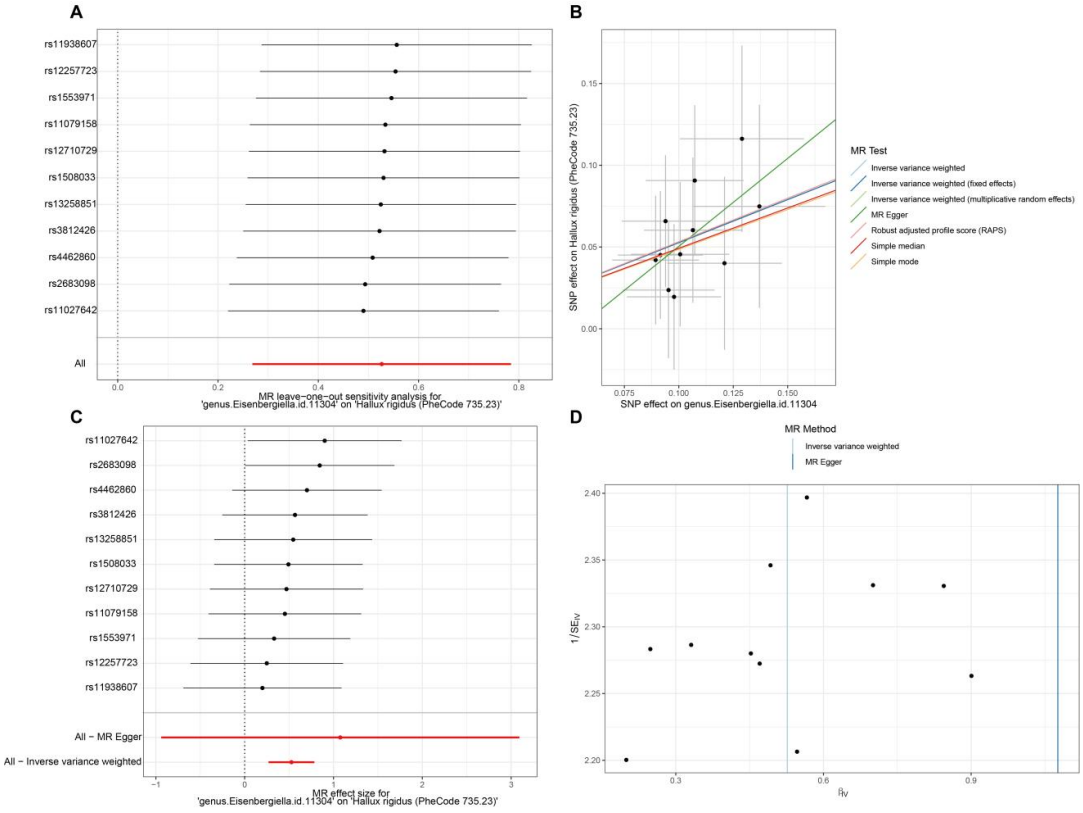
Supplementary Fig. S14. MR sensitivity analyses for the association between CAG-433 and internal derangement of the knee.



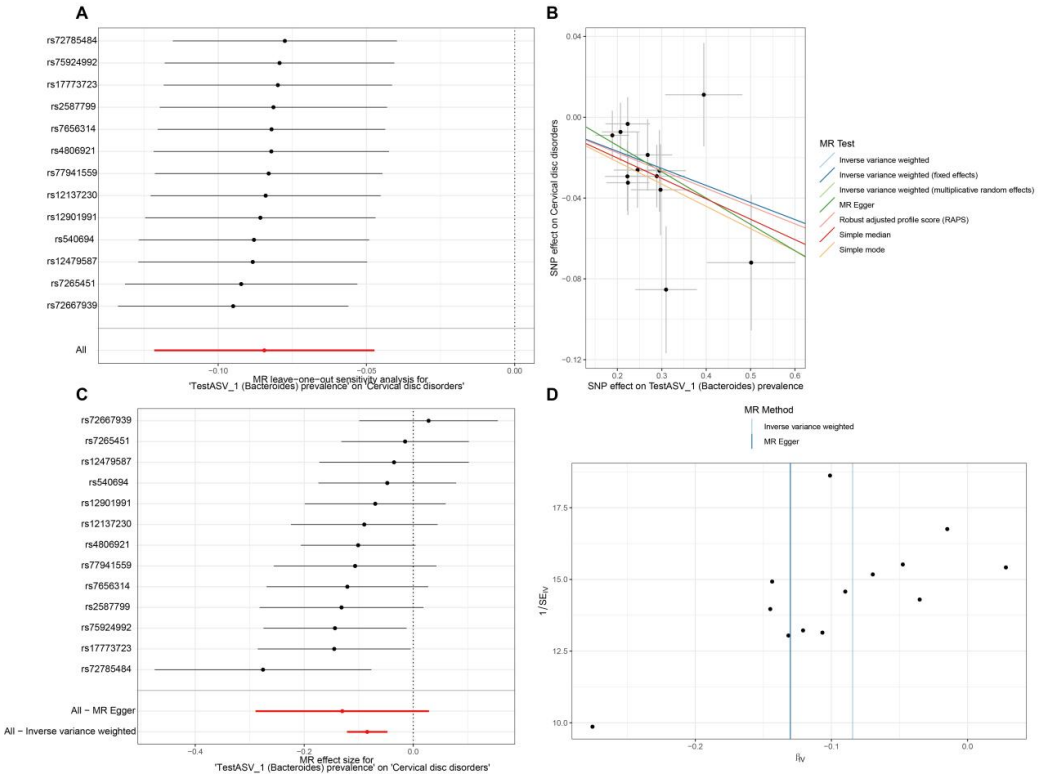
Supplementary Fig. S15. MR sensitivity analyses for the association between Eggerthella and acquired spondylolisthesis.



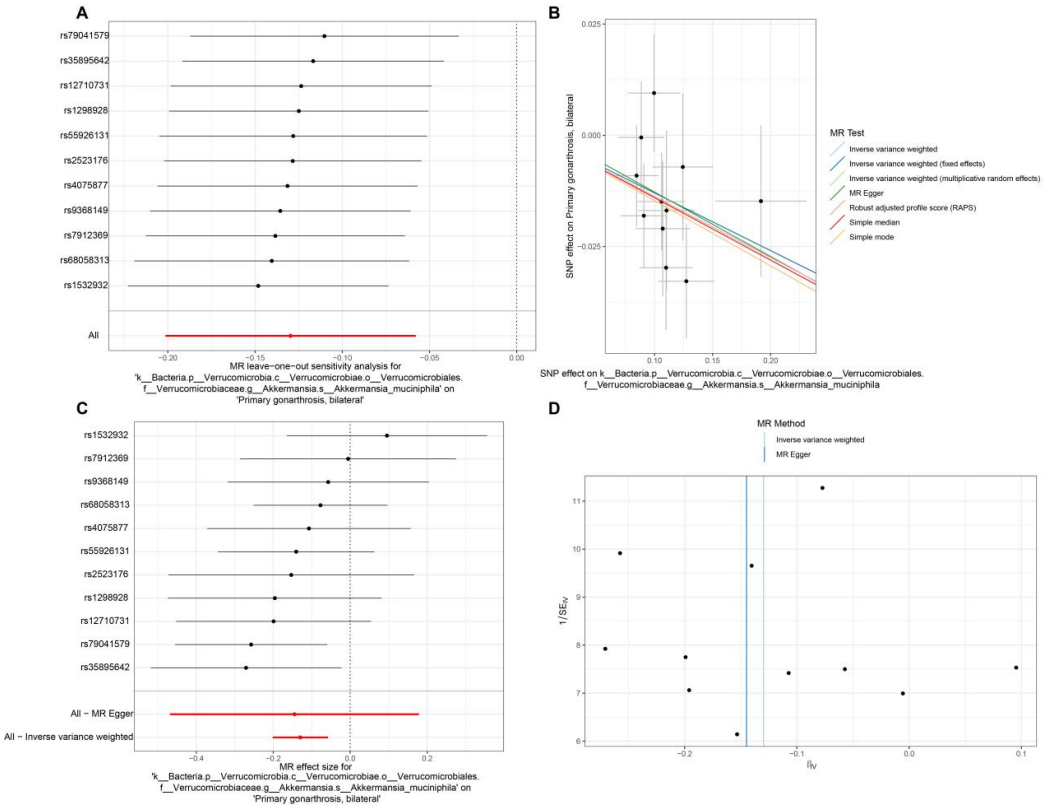
Supplementary Fig. S16. MR sensitivity analyses for the association between Eisenbergiella and hallux rigidus.



Supplementary Fig. S17. MR sensitivity analyses for the association between Bacteroides and cervical disc disorders.

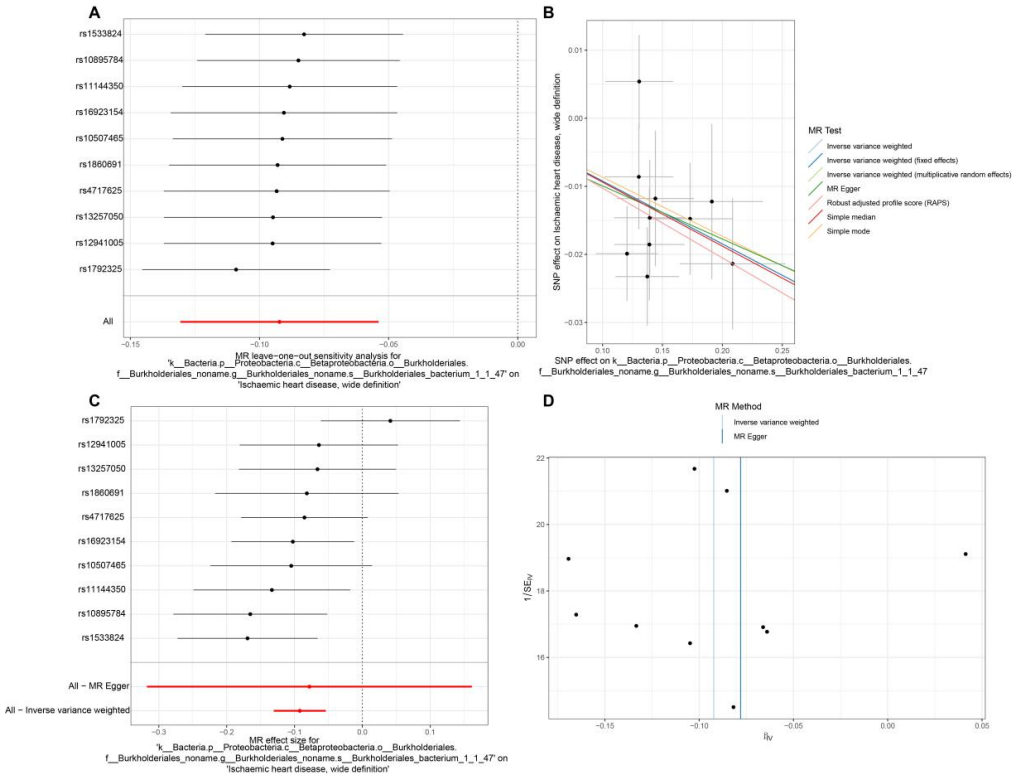


Supplementary Fig. S18. MR sensitivity analyses for associations of Verrucomicrobiaceae, Akkermansia, and Akkermansia muciniphila with bilateral primary gonarthrosis.

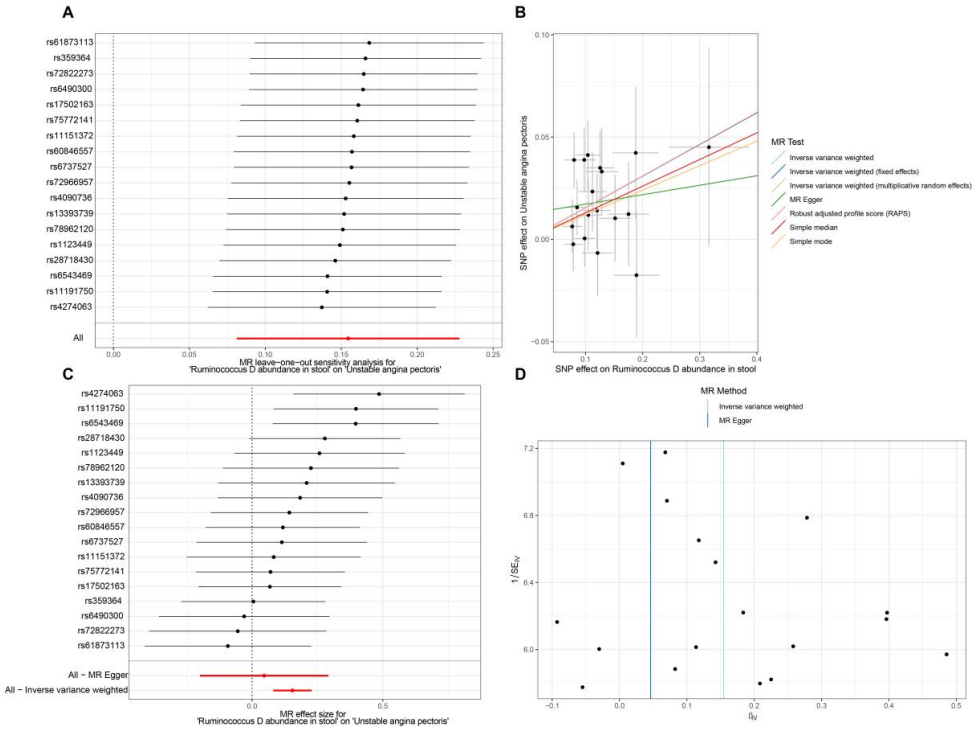


(4) Diseases of the circulatory system

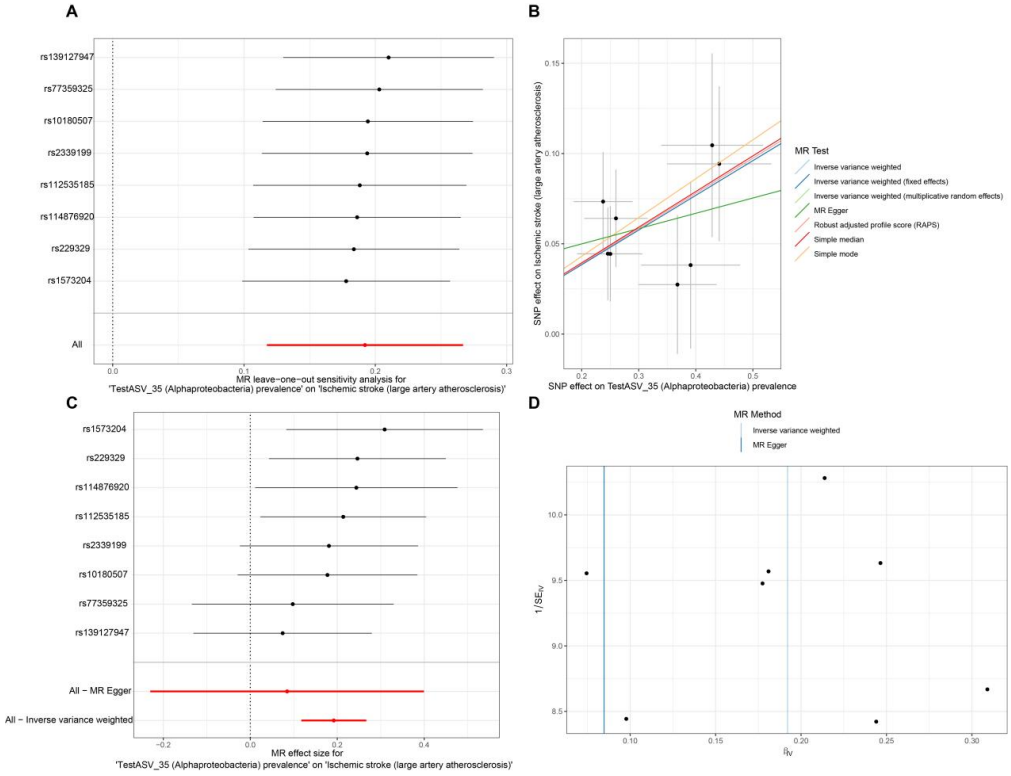
Supplementary Fig. S19. MR sensitivity analyses for associations of Burkholderiales noname and Burkholderiales bacterium 1_1_47 with ischaemic heart disease.



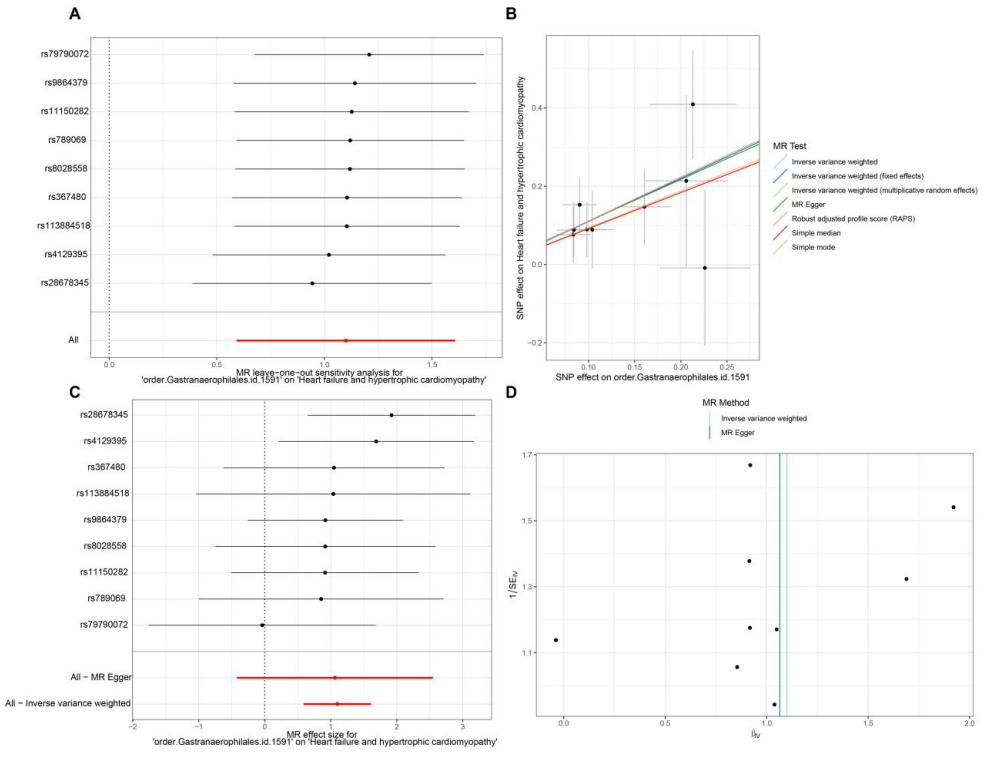
Supplementary Fig. S20. MR sensitivity analyses for the association between Ruminococcus D and unstable angina pectoris.



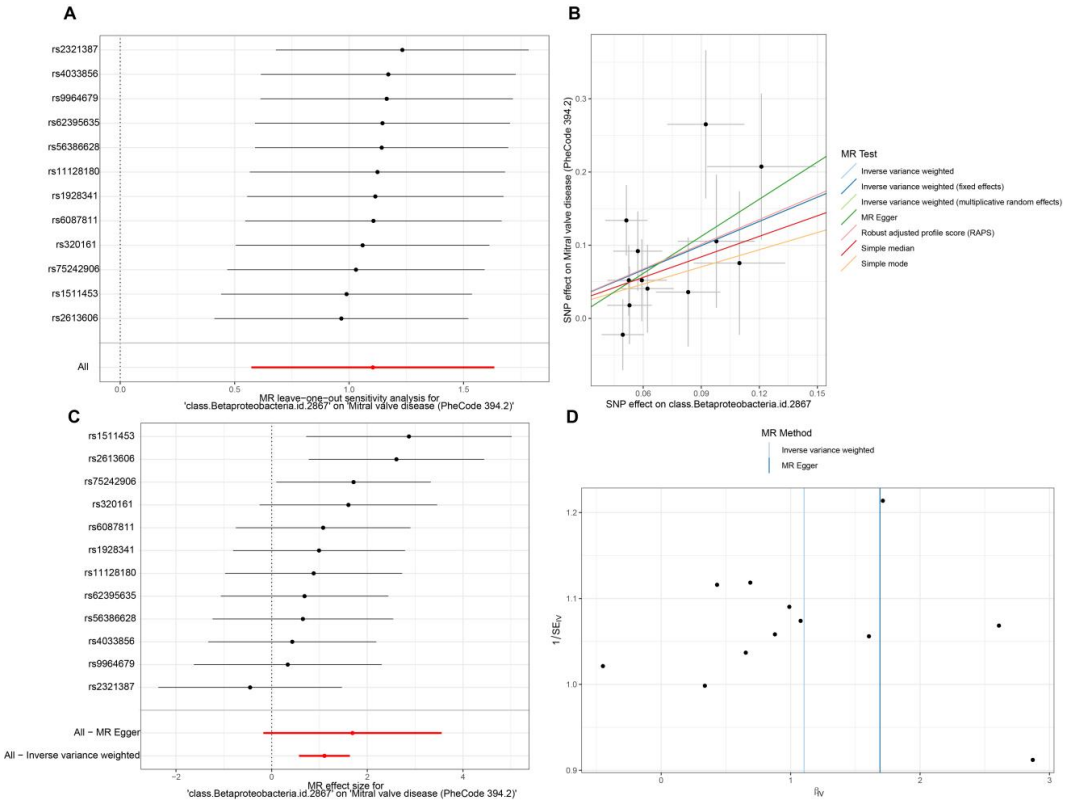
Supplementary Fig. S21. MR sensitivity analyses for the association between Acidaminococcaceae and ischaemic stroke due to large artery atherosclerosis.



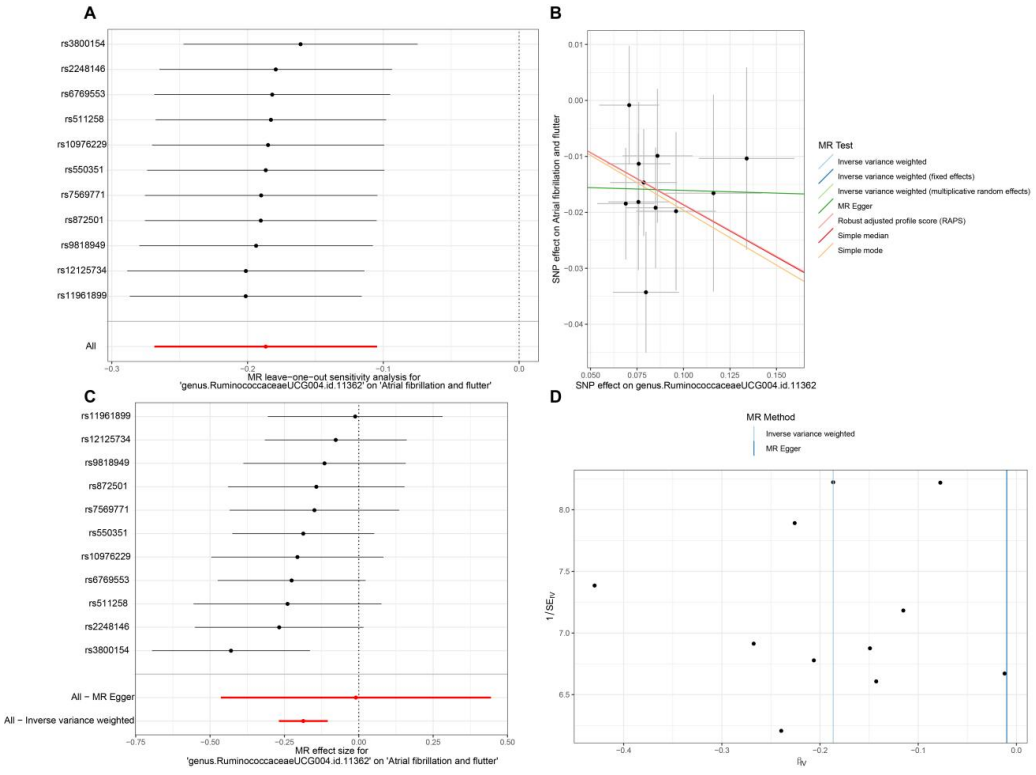
Supplementary Fig. S22. MR sensitivity analyses for the association between Gastranaerophilales and the disease phenotype "Heart failure and hypertrophic cardiomyopathy".



Supplementary Fig. S23. MR sensitivity analyses for associations of Betaproteobacteria- and Burkholderiales-related traits with mitral valve disease.

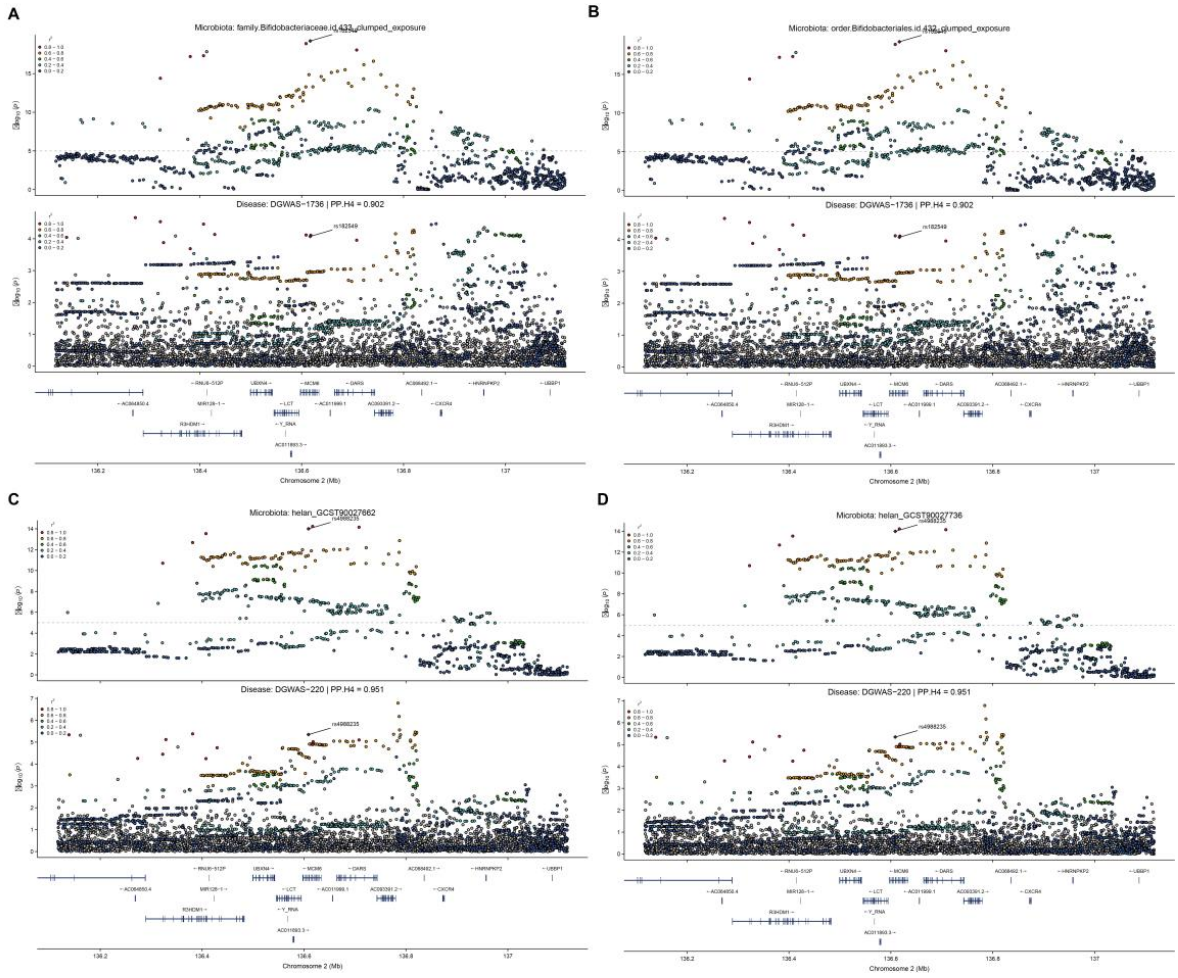


Supplementary Fig. S24. MR sensitivity analyses for the association between Ruminococcaceae UCG004 and atrial fibrillation and flutter.



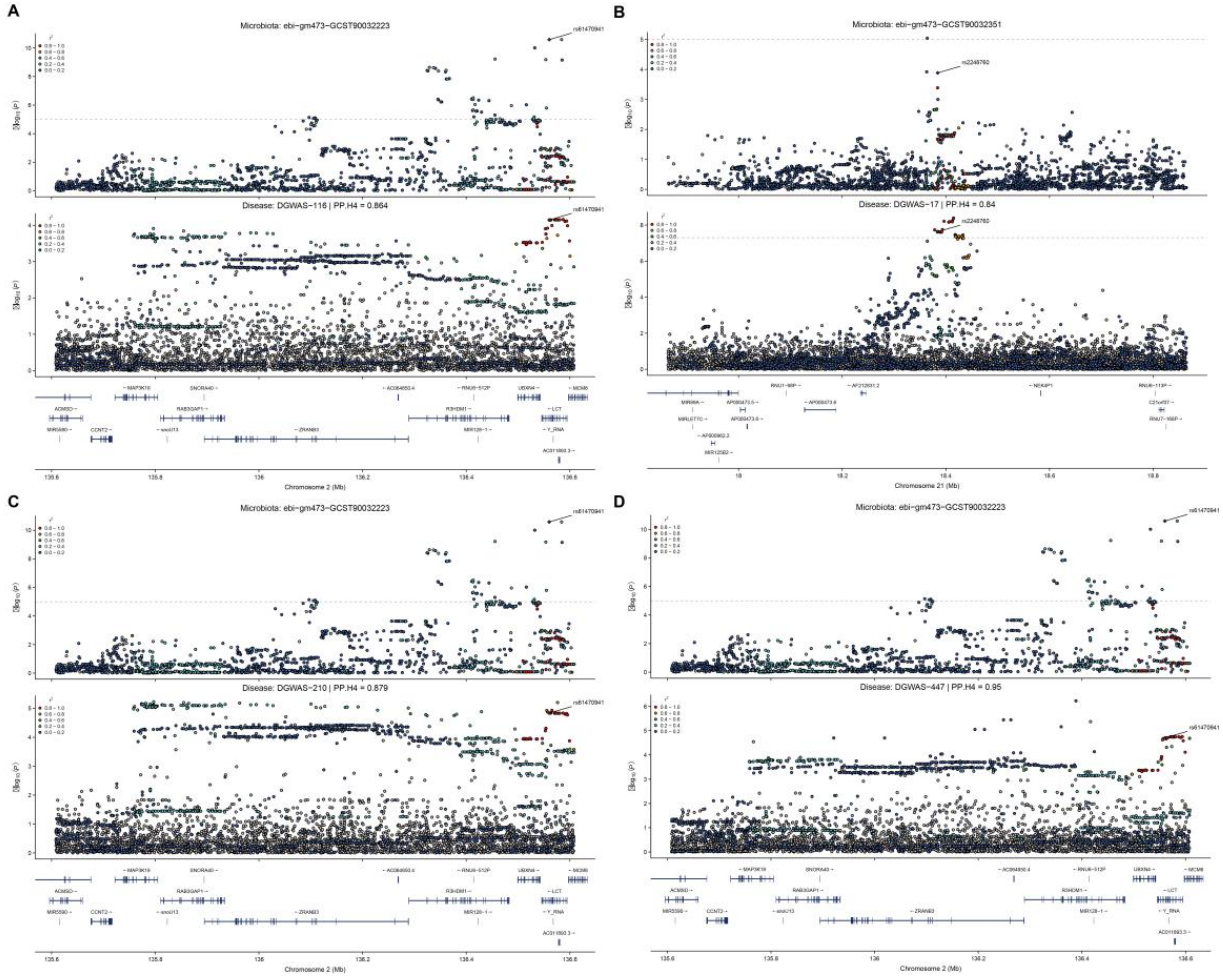
Plot descriptions for Supplementary Figs. S25–S28. In each panel, the upper and lower plots show regional GWAS associations for the gut microbial trait and disease outcome, respectively. The x-axis indicates genomic position (Mb, GRCh37/hg19), and the y-axis indicates −log10(P). Gene annotations are displayed below the association plots. Point colours indicate linkage disequilibrium (r^2) with the LD reference SNP used in each panel; points without available LD information are shown in grey. PP.H4 denotes the posterior probability that the two traits share a causal variant within the analysed region.

Supplementary Fig. S25. Regional colocalization plots for selected gut microbial trait–neoplasm associations.



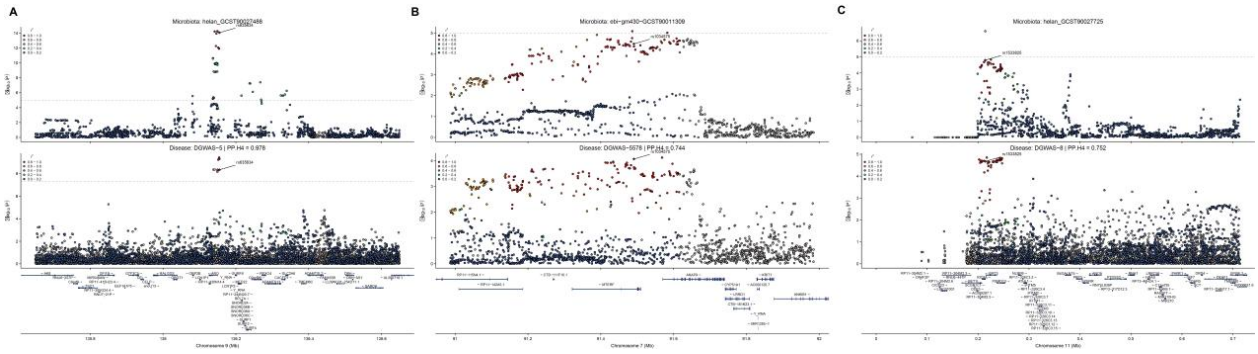
(A) Bifidobacteriaceae and benign neoplasm of the transverse colon (lead SNP: rs182549; PP.H4 = 0.902). (B) Bifidobacteriales and benign neoplasm of the transverse colon (lead SNP: rs182549; PP.H4 = 0.902). (C) Bifidobacteriaceae and colorectal adenocarcinoma (lead SNP: rs4988235; PP.H4 = 0.951). (D) Bifidobacteriales and colorectal adenocarcinoma (lead SNP: rs4988235; PP.H4 = 0.951).

Supplementary Fig. S26. Regional colocalization plots for selected gut microbial trait − musculoskeletal disease associations.



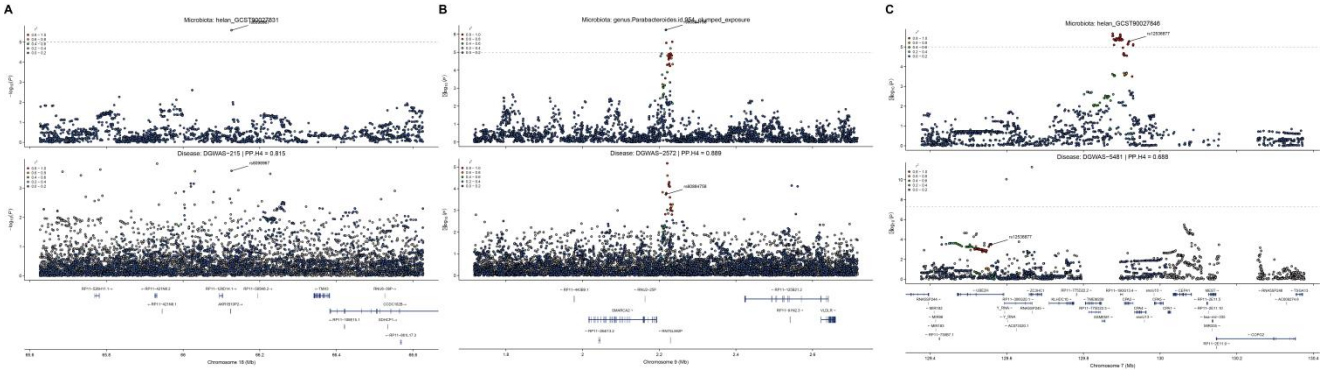
(A) Bifidobacterium breve and other joint disorders (lead SNP: rs61470941; PP.H4 = 0.864). (B) Eisenbergiella sp900066775 and gonarthrosis (lead SNP: rs2248760; PP.H4 = 0.840). (C) Bifidobacterium breve and internal derangement of knee (lead SNP: rs61470941; PP.H4 = 0.879). (D) Bifidobacterium breve and polyarthrosis (lead SNP: rs61470941; PP.H4 = 0.950)

Supplementary Fig. S27. Regional colocalization plots for selected gut microbial trait − circulatory disease associations.



(A) The lactose and galactose degradation I pathway and atrial fibrillation and flutter (lead SNP: rs635634; PP.H4 = 0.978). (B) Acidaminococcaceae and ischaemic stroke due to large artery atherosclerosis (lead SNP: rs1034575; PP.H4 = 0.744). (C) An unclassified genus within the order Burkholderiales and ischaemic heart disease (wide definition) (lead SNP: rs1533825; PP.H4 = 0.752).

Supplementary Fig. S28. Regional colocalization plots for selected gut microbial trait associations with endocrine, metabolic, and neuropsychiatric diseases.



(A) Bacteroides nordii and thyrotoxicosis with toxic multinodular goitre (lead SNP: rs8098967; PP.H4 = 0.815). (B) Parabacteroides and emotional disorders and disorders of social functioning with onset specific to childhood (lead SNP: rs60884758; PP.H4 = 0.889). (C) Dorea formicigenerans and type 2 diabetes (lead SNP: rs12536877; PP.H4 = 0.688).