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# Causal relationship between gut microbes and cardiovascular protein expression

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Evidence supports associations between gut microbiota and cardiovascular protein levels in plasma. However, it is unclear whether these associations reflect a causal relationship. To reveal the causal relationship between gut microbiota and cardiovascular protein levels in plasma, we estimated their causal effects using two-sample Mendelian randomization (MR) analysis. Sensitivity analysis was also performed to assess the robustness of our results. Genome-wide association study (GWAS) of microbiomes in the MiBioGen study included 211 bacterial taxa (18,473 individuals), and GWAS of 90 cardiovascular proteins included 30,931 individuals. There were 196 bacterial taxa from five levels available for analysis. The following 14 causal relationships were identified: phylum Euryarchaeota and carbohydrate antigen 125 ( $\beta$  = 0.289), order Bacillales and CSF-1 ( $\beta$  = -0.211), genus *Dorea* and HSP-27 ( $\beta$  = 0.465), phylum *Actinobacteria* and IL-8 ( $\beta$  = 0.274), order Enterobacteriales and KIM-1 ( $\beta$  = -0.499), class Actinobacteria, genus Bifidobacterium, phylum Actinobacteria and LEP ( $\beta$  = -0.219,  $\beta$  = -0.201, and  $\beta$  = -0.221), genus *Methanobrevibacter* and NT-proBNP ( $\beta$  = 0.371), family Peptostreptococcaceae and SRC ( $\beta$  = 0.191), order Verrucomicrobiales, phylum Verrucomicrobia and TNF-R2 ( $\beta$  = 0.251 and  $\beta$  = 0.233), family Veillonellaceae and t-PA ( $\beta$  = 0.271), and class *Erysipelotrichia* and VEGF-D ( $\beta$  = 0.390). Sensitivity analysis showed no evidence of pleiotropy or heterogeneity. The results of the reverse MR analysis showed no reverse causality for any of the 13 gut microbes and 11 cardiovascular proteins. Mendelian randomization estimates provide strong evidence for a causal effect of gut microbiota-mediated alterations on cardiovascular protein expression.

#### KEYWORDS

gut microbes, cardiovascular proteins, Mendelian randomization, causal effect, genome-wide association study

## Introduction

Gut microbiota is a dynamic and complex ecological community of microorganisms that inhabit the human gut (O'Hara and Shanahan, 2006). Twin-based heritability estimates and macrogenome-wide association studies have challenged the conventional view of the gut microbiota as a purely environmental factor (Blekhman et al., 2015; Turpin et al., 2016; Liu et al., 2021). Gut microbiota affects immunity, neurology, psychiatric traits, metabolism, and even circulation of the body (Gilbert et al., 2018). Many disease states have been associated with changes in faecal microbiota, including cardiovascular disease (Brown and Hazen, 2015). Indeed, specific gut microbiota-dependent metabolites affect host metabolism and cardiovascular disease. For example, phenylacetyl glutamine promotes adverse cardiovascular phenotypes in the host by interacting with multiple adrenergic receptors (Nemet et al., 2020). Additionally, it has been suggested that gut microbiota directly influence plasma levels of proinflammatory factors including some cardiovascular proteins. For example, Lee et al. found that enterotoxigenic Bacteroides fragilis-secreted toxin induces IL-8 secretion from intestinal epithelial cells via the E-Cadherin/β-Catenin/NF-κB pathway (Lee et al., 2022). Engevik et al. found that F. nucleatum produces outer membrane vesicles that activate Toll-like receptor 4 to drive extracellular signal-regulated kinase, NFκB, and proinflammatory cytokine expression (Engevik et al., 2021). Pallikkuth et al. studied rhesus monkeys as non-human primates, and found that highly abundant archaea and amoebae in aged animals had a direct correlation with plasma biomarkers of inflammation and immune activation, such as interleukin (IL)-6, IL-8, and TNF (Pallikkuth et al., 2021). However, most studies have examined only a few gut microbes and cardiovascular proteins. No comprehensive or systematic randomized controlled trials have been conducted on the causal relationship between gut microbes and cardiovascular protein expression in humans.

Typically, the gold standard to infer causality is a randomized controlled trial (RCT). Considering the difficulty in implementing RCTs, Mendelian randomization (MR) takes full advantage of this method. It is an epidemiological method that strengthens chance inferences by genetic variation as an instrumental variable for exposure (Burgess and Thompson, 2015). Because parental alleles are randomly assigned to offspring during meiosis in accordance with Mendel's second law, the method minimizes the interference of important confounding factors such as the natural environment and socioeconomic level. The use of genetic variation as a valid instrumental variable in MR analysis relies on three core assumptions. First, genetic variation must be strongly correlated to exposure factors (association assumption). Second, genetic variation cannot be directly correlated to outcomes (exclusion restriction assumption). Third, genetic variation cannot be correlated to any possible confounding factors (independence assumption) (Emdin et al., 2017). To date, genetic studies have shown that host genetic variation affects the composition of the gut microbiota (Sanna et al., 2019). Therefore, in the present study, we performed two-sample MR analysis to fully explore whether gut microbiota abundance has a causal effect on cardiovascular protein levels and to identify specific pathogenic bacterial taxa.

### Material and methods

#### Gut microbial samples

Sample summary statistics employed GWAS meta-analysis of the gut microbiome in the MiBioGen study, the largest cohort, multi-ethnic, genome-wide gut microbiome meta-analysis to date. The meta-analysis included 18,340 individuals from 22 cohorts consisting of adults or adolescents and two cohorts consisting of children. There were four multiple ancestry samples. Single ancestry samples included 16 European cohorts, one Middle Eastern cohort, one East Asian cohort, one US Hispanic/Latin cohort, and one African American cohort. The microbial composition was analysed by targeting three different variable regions of the 16S rRNA gene: V1–V2 (n=3,716), V3–V4 (n=4,211), and V4 (n=10,413). A total of 211 taxa were included in this study (131 genuses, 35 families, 20 orders, 16 phyla, and nine classes) (Kurilshikov et al., 2021).

#### Cardiovascular protein samples

Cardiovascular protein phenotypes were obtained from a recent genomic analysis of 90 cardiovascular proteins in 30,931 individuals. The study included 15 cohorts (13 discovery datasets and two replication datasets). The analysis identified 451 protein quantitative trait loci associated with the plasma levels of 85 proteins ( $P < 5 \times 10^{-8}$ ) (Folkersen et al., 2020).

#### Genetic instrument selection

Bacterial taxa were analysed at five levels (phylum, class, order, family, and genus). A unique taxonomic unit was defined as a feature. Considering that a gene cis region only constitutes a small proportion of the genome, we relaxed the conventional genome-wide significance P-value threshold for instrument selection to  $P<1\times10^{-5}$  (Sanna et al., 2019). We implemented a series of additional quality control steps to select eligible instrumental variables (IVs). First, SNPs with allelic inconsistencies between the exposure and result samples (i.e.,

A/G vs. A/C) were excluded. Second, palindromic A/T or G/C alleles were excluded to avoid distortions in strand orientation or allelic coding. Third, SNPs within each bacterial taxonomic unit were clustered together and only independent SNPs were retained. The linkage disequilibrium (LD) threshold for clustering was set to r2< 0.01 and the size of the clustering window was set to 500 kb. A total of 1,000 Genome Project sequencing data (phase 3) were used to estimate LD. Fourth, horizontal pleiotropy effects, i.e., confounding effects caused by other diseases, may violate the second hypothesis in the MR analysis (SNPs are not associated with outcomes). Once horizontal pleiotropic effects were found, this instrumental variable was deleted. The MR-Egger regression test and MR-PRESSO test were applied to detect potential horizontal pleiotropy and to eliminate the effect of pleiotropy by removing outliers (Verbanck et al., 2018). Additionally, genomic coordinates for all correlation analyses were based on Ensembl GRCh37 reference during the coordination process (Yates et al., 2020), which removed ambiguous and duplicate SNPs. For markers without SNP information, SNP conversion was performed using the ieugwasr package for chr:pos (radius set to 0).

#### Mendelian randomization analysis

We performed MR analyses to investigate the causal relationships between gut microbiota and 90 cardiovascular proteins. The causal relationship between each pair of bacterial taxa and plasma metrics was examined using four MR methods: the inverse variance weighted (IVW) test (Burgess et al., 2013), weighted median estimator (WME) (Bowden et al., 2016), MR-Egger regression (Bowden et al., 2015), and MR-PRESSO (Verbanck et al., 2018). Each of the four statistical methods has its own model assumptions that are explained in detail in each study (Burgess et al., 2013; Bowden et al., 2015; Bowden et al., 2016; Verbanck et al., 2018). The IVW method is slightly stronger than the other methods under certain conditions (Bowden et al., 2016). Therefore, we performed MR estimation using IVW as the main method. To account for multiple testing, we implemented a Bonferroni-corrected allowed type I error rate ( $\alpha$ ) of 0.05/n (the effective number of independent bacterial taxa at the taxonomic level): phylum P =  $5.56 \times 10^{-3}$  (0.05/9), class  $P = 3.33 \times 10^{-3}$  (0.05/15), order  $P=2.50\times 10^{-3}(0.05/20)$ , family  $P=1.56\times10^{-3}$  (0.0 5/32), and genus  $P=4.20\times10^{-4}$  (0.05/119). To assess the robustness of significant results, we performed several sensitivity analyses. The Cochrane Q test for IVW and MR-Egger regression was used to test for potential heterogeneity. Moreover, leave-one-out analyses were performed to determine whether the causal signal was driven by a single SNP.

Additionally, to assess the strength of the selected SNPs, the Fstatistic was calculated for each bacterial taxonomic unit using the following equation:

$$F = \frac{R^2(n-1-k)}{(1-R^2)k}$$

where  $R^2$  is the fraction of exposed variance explained by IVs, k is the number of IVs, and n is the sample size. F-statistic  $\geq 10$  indicates no strong evidence of weak instrument bias. IVs with an F-statistic of less than 10 were considered weak IVs and excluded (Pierce et al., 2011). Because the minor allele frequency was not provided for SNPs in gut microbes, we estimated the  $R^2$  values directly using the get\_r\_from\_pn function of the TwoSampleMR package. Additionally, we performed reverse MR analysis to explore the reverse causality of cardiovascular proteins. MR analysis was performed in R (version 4.1.3) (http://www.r-project.org ) using the TwoSampleMR package (Hemani et al., 2018).

#### Results

In the microbiome samples, we excluded three unknown families and 12 unknown genuses. Additionally, we found duplicate data for class Verrucomicrobiae and order Verrucomicrobiales, but fortunately, this did not affect the results. We therefore chose to retain the order Verrucomicrobiales with lower species relationships. Thus, nine phyla, 15 classes, 20 orders, 32 families, and 131 genuses bacterial taxa were included in the subsequent MR analysis. MR analyses by the IVW test are summarized in Supplementary Tables 1-3. We found 14 causal relationships between 13 bacterial characteristics and 11 cardiovascular protein indicators, including phylum Euryarchaeota and carbohydrate antigen 125 (CA-125) (P =  $1.26 \times 10^{-3}$ ), order *Bacillales* and colony-stimulating factor (CSF-1) (P =  $5.07 \times 10^{-4}$ ), genus *Dorea* and heat shock protein 27 (HSP-27) (P =  $6.28 \times 10^{-5}$ ), phylum Actinobacteria and interleukin-8 (IL-8) (P =  $2.30 \times 10^{-3}$ ), order *Enterobacteriales* and kidney injury molecule-1 (KIM-1) (P =  $2.04 \times 10^{-3}$ ), class Actinobacteria, genus Bifidobacterium, and the phylum Actinobacteria and leptin (LEP)  $(P = 1.79 \times 10^{-3}, P = 4.14 \times 10^{-4}, and P = 3.49 \times 10^{-3}, respectively),$ genus Methanobrevibacter and N-terminal pro-brain natriuretic peptide (NT-proBNP) (P =  $3.75 \times 10-4$ ), family Peptostreptococcaceae and proto-oncogene tyrosine-protein kinase Src (SRC) (P =  $5.49 \times 10^{-4}$ ), order Verrucomicrobiales and phylum Verrucomicrobia, and tumor necrosis factor receptor 2 (TNF-R2) (P =  $1.88 \times 10^{-3}$  and P =  $3.98 \times 10^{-3}$ , respectively), family Veillonellaceae and tissue plasminogen activator (t-PA) (P =  $9.84 \times$ 10<sup>-5</sup>), and class *Erysipelotrichia* and vascular endothelial growth factor D (VEGF-D) ( $P = 3.07 \times 10^{-3}$ ). Among them, nine bacterial traits were positively correlated to IL-8, CA-125, TNF-R2, VEGF-

D, SRC, t-PA, HSP-27, and NT-proBNP with regression coefficients ranging from 0.19 to 0.47. Five bacterial traits were negatively and causally correlated to LEP, CSF-1, and KIM-1 with regression coefficients ranging from -0.50 to -0.20. Notably, the

causal effects of phylum and class *Actinobacteria* on LEP, and phylum and order *Verrucomicrobia* on TNF-R2 were consistent in direction (Figure 1). Scatter plots of the 14 causal IVW, WME, and MR-Egger are shown in Figure 2. The F-statistics for all IVs were

Variable     Beta     Lower 95%CI     P       Prylum     Actinobacteria      I.e.     P       VW     0.274     0.184     0.363     2.28-02       WME     0.157     0.043     0.363     2.28-02       MR-Fager     -0.044     -0.061     0.011     3.77e-01       MR-Egger     -0.026     -0.145     3.48e-03     •       VWW     -0.221     -0.286     -0.145     3.48e-03     •       VWME     -0.021     -0.0361     0.08e-02     •     •       VWME     0.022     -0.286     0.108-02     •     •       VWME     0.326     0.229     0.199     0.378     1.08e-03     •       VWME     0.323     0.152     0.514     3.88e-03     •     •       VWME     0.233     0.152     0.514     3.88e-03     •     •       VWME     0.233     0.152     0.514     3.28e-02     •     •       VWME     0.233     0.162							
Phylum     Accinobacteria      IL-8       VWME     0.157     0.043     0.271     1.88-01       MR-Egger     -0.340     -0.661     0.011     3.77-01       MR-PRESSO     0.274     0.184     0.363     2.26e-02     •       MR-PRESSO     0.221     -0.288     -0.145     3.49e-03     •       WME     -0.221     -0.280     -0.145     3.49e-03     •       MR-Egger     -0.621     -0.388     -0.160     1.08e-02     •       Phylum     Euryarchacta      CA-125     •     •     •       VWM     0.289     0.199     0.378     1.28e-03     •     •       VME     0.233     0.161     0.378     2.33e-02     •     •       VWM     0.233     0.162     0.314     3.88e-02     •     •       VWME     0.233     0.166     0.201     1.88e-02     •     •       VWME     0.219     -0.200     0.144     3.89e-03     •	Variable	Beta L	ower 95%CI U	pper 95%Cl	P		
IVW   0.274   0.184   0.363   2.38-0-03     MR=Egger   0.340   -0.691   0.011   3.77-01     MR=Egger   0.274   0.184   0.363   2.38-02     Phytum   Actinobacteria    LEP     VW   -0.287   -0.388   -0.167   3.49e-03     MR=Egger   -0.621   -0.388   -0.107   1.35e-01     MR=PRESSO   -0.221   -0.218   -0.010   1.86e-03     VWE   0.228   0.199   0.378   1.28e-03     WR=Represso   0.228   0.199   0.378   2.33e-02     Phytum   Vurgarchaeta    TWF-R2   •     VWW   0.233   0.152   0.341   3.38-02   •     Phytum   Veruconicotai    TWF-R2   •   •     VWM   0.233   0.152   0.343   3.8e-03   •     VME   0.233   0.164   0.260   1.58e-02   •     VMM   -0.219   -0.266   0.173   3.25e-03   •     VME   0.225 </td <td>Phylum</td> <td>Actinobacteria</td> <td></td> <td>IL-8</td> <td></td> <td></td> <td></td>	Phylum	Actinobacteria		IL-8			
WME   0.157   0.043   0.271   1.68-01     MR-Egger   -0.340   -0.081   0.011   3.77e-01     MWE   0.221   -0.286   -0.145   3.49e-03     WME   -0.221   -0.286   -0.145   3.49e-03     WME   -0.221   -0.286   -0.167   4.33e-03     MR-Egger   -0.621   -0.386   -0.177   1.56e-03     VWME   0.222   0.427   1.28e-03   •     MR-Egger   0.280   0.199   0.378   1.28e-03   •     VVME   0.280   0.199   0.378   1.28e-03   •     VME   0.232   0.143   0.385   1.38e-01   •     MR-PRESSO   0.280   0.199   0.378   1.38e-03   •     VME   0.233   0.143   0.343   3.88e-03   •     VME   0.233   0.143   0.342   7.76e-01   •     VMME   -0.218   -0.206   -0.149   1.79e-03   •     VMME   -0.255   -0.347   -0.163   5.48e-01   •	IVW	0.274	0.184	0.363	2.30e-03		•
MR-RPESSO MR-PRESSO Phylum Actinobacteria Phylum Actinobacteria Phylum Actinobacteria Phylum Actinobacteria Phylum Euryarchaeota MR-Egger - 0.221 - 0.226 - 0.145 3 43e-03 MR-Egger - 0.221 - 0.281 - 0.160 1.08e-02 Phylum Euryarchaeota MR-PRESSO - 0.221 - 0.281 - 0.160 1.08e-02 Phylum Euryarchaeota MR-Egger 0.267 - 0.164 0.738 5.58e-01 MR-PRESSO 0.268 0.199 0.378 1.26e-03 MR-Egger 0.267 - 0.164 0.738 5.58e-01 MR-PRESSO 0.228 0.199 0.378 1.26e-03 MR-Egger - 0.261 - 1.064 0.542 7.78e-01 MR-PRESSO 0.239 0.1143 0.335 1.26e-02 MR-Egger - 0.261 - 1.064 0.542 7.78e-01 MR-PRESSO 0.233 0.162 0.314 3.88e-03 MR-Egger - 0.261 - 1.064 0.542 7.78e-01 MR-PRESSO 0.233 0.169 0.200 - 0.149 1.79e-03 MR-Egger - 0.261 - 1.064 0.542 7.78e-01 MR-PRESSO 0.233 0.169 0.200 - 0.149 1.79e-03 MR-Egger - 0.261 - 1.064 0.542 7.78e-01 MR-PRESSO 0.233 0.169 0.200 - 0.149 1.79e-03 MR-Egger - 0.265 - 0.347 - 0.163 5.48e-03 MR-Egger - 0.169 - 0.378 0.039 4.54e-01 MR-PRESSO 0.230 0.0269 0.521 3.07e-03 WME 0.323 0.169 0.477 3.55e-02 MR-Egger - 0.169 - 0.378 0.039 4.54e-01 VWW 0.300 0.259 0.521 3.07e-03 WME 0.323 0.169 0.477 3.55e-02 MR-Egger - 0.114 - 0.265 0.457 1.307e-03 WME 0.323 0.169 0.477 3.55e-02 MR-Egger - 0.114 - 0.261 0.377 2.04e-03 MR-Egger - 0.114 - 0.271 - 0.150 5.07e-04 WME 0.224 0.122 1.19e-02 MR-Egger - 0.114 - 0.665 0.437 8.70e-01 WME - 0.239 0.254 0.122 1.19e-02 MR-Egger - 0.114 - 0.665 0.437 8.70e-01 WME 0.225 0.129 0.326 2.11e-02 MR-Egger - 0.114 0.072 0.221 1.9e-02 MR-Egger - 0.114 0.072 0.221 1.9e-02 MR-Egger - 0.114 0.013 0.246 5.49e-01 WME 0.199 0.013 0.242 3.15e-01 MR-PRESSO 0.251 0.124 0.023 1.87e-01 MR-PRESSO 0.251 0.124 0.023 1.87e-01 MR-PRESSO 0.251 0.124 0.278 2.65e-03 Family Vetioneliaceae FMR-PRESSO 0.251 0.144 1.41e-04 MR-PRESSO 0.251 0.147 0.121 5.0e-02 MR-Egger - 0.188 0.082 0.341 1.27e-01 MR-PRESSO 0.251 0.147 0.121 7.2e-04 MR-Egger - 0.182 0.022 0.331 1.77e-02 MR-Egger - 0.182 0.022 0.331 1.77e-02 MR-Egger - 0.182 0.023 0.552 0.28e-05 MR-Egger - 0.162 0.034	WME	0.157	0.043	0.271	1.68e-01		1 <b>0</b> 1
MR-PRESSO 0.274 0.184 0.363 2.26-02 ● IVW -0.221 -0.286 0.187 4.33e-03 ● MR-Egger -0.621 -0.386 -0.187 4.33e-03 ● MR-PRESSO -0.221 -0.0386 -0.307 1.05e-01 ● Phylum Euryarchaeota - CA-125 IVW 0.289 0.199 0.378 1.26e-03 ● MR-PRESSO 0.267 -0.164 0.738 5.56e-01 ● MR-PRESSO 0.268 0.0199 0.378 1.26e-03 ● Phylum Verrucomicrobia TNF-R2 IVW 0.239 0.143 0.355 1.36e-02 ● Phylum Verrucomicrobia LEP Phylum Verrucomicrobia LEP IVW 0.219 -0.280 0.149 1.38e-02 ● MR-Egger -0.261 -1.064 0.542 7.78e-01 ● MR-PRESSO 0.233 0.186 0.240 1.88e-02 ● MR-Egger -0.219 -0.286 0.149 1.79e-03 ● VWE 0.229 0.413 0.385 1.36e-02 ● MR-Egger -0.219 -0.280 -0.149 1.79e-03 ● VWE 0.2219 -0.286 0.521 3.07e-03 ● VWE 0.2219 -0.286 0.521 3.07e-03 ● VWE 0.2219 -0.286 0.521 3.07e-03 ● VWME 0.2219 -0.286 0.521 3.07e-03 ● VWME 0.221 0.268 0.521 3.07e-03 ● VWME 0.221 0.268 0.521 3.07e-03 ● VWME 0.203 0.258 0.521 3.07e-03 ● VWME 0.203 0.268 0.521 3.07e-03 ● VMME 0.203 0.268 0.521 3.07e-04 ● VMME 0.203 0.268 0.521 3.07e-04 ● VMME 0.203 0.264 0.022 1.19e-02 ● VMME 0.203 0.264 0.221 1.19e-02 ● VMME 0.203 0.264 0.221 1.19e-02 ● VMME 0.221 0.203 0.244 0.221 1.19e-02 ● VMME 0.221 0.271 0.232 1.38e-03 ● VMME 0.141 0.070 0.322 1.38e-03 ● VMME 0.149 0.070 0.322 1.38e-03 ● VMME 0.140 0.070 0.221 1.39e-01 ● VMME 0.140 0.071 0.232 1.38e-03 ● VMME 0.141 0.070 0.232 1.38e-03 ● VMME 0.148 0.070 0.221 1.92e-01 ● VMME 0.148 0.070 0.221 0.366 5.49e-04 ● VMME 0.148 0.070 0.221 0.368 0.510 0.26 VMME 0.148 0.070 0.221 0.368 0.510 0.20 VMME 0.148 0.070 0.221 0.368 0.540-01 ● VMME 0.148 0.070 0.221 0.368 0.540-02 ● VMME 0.148 0.070 0.221 0.368 0.582 0.280-05 ● VMME 0.148 0.070 0.221 0.368 0.580	MR-Egger	-0.340	-0.691	0.011	3.77e-01		1
Phylum Acinobacteria LEP IVW -0.221 -0.296 -0.145 3.49e-03 WME -0.287 -0.388 -0.187 4.33e-03 MR-Egger -0.221 -0.281 -0.160 1.08e-02 Phylum Euryarchaeota CA-125 VW 0.289 0.199 0.378 1.28e-03 WME 0.326 0.225 0.427 1.28e-03 WME 0.328 0.268 0.199 0.378 2.38e-02 Phylum Veruconicobia TNF-R2 VW 0.233 0.152 0.314 3.88e-03 WME 0.230 0.143 0.385 1.28e-02 WME 0.233 0.152 0.314 3.88e-03 WME 0.230 0.143 0.385 1.28e-02 MR-Egger -0.261 -1.064 0.788 1.28e-03 WME 0.233 0.152 0.314 3.88e-03 WME 0.223 0.143 0.385 1.28e-02 Class Actinobacteria LEP VW 0-210 -0.206 -0.173 1.58e-02 MR-RESSO -0.211 -0.276 0.378 3.23e-03 Class Erysipelotrichia LEP VW 0-210 -0.266 -0.173 3.23e-03 Class Erysipelotrichia CSF-1 VW 0-211 -0.271 -0.159 5.07e-04 WME 0.323 0.169 0.477 3.52e-03 WME 0.324 0.129 0.326 1.014 WME -0.203 -0.284 0.521 4.15e-02 WME 0.224 0.271 -0.150 5.07e-04 WME 0.224 0.271 -0.150 5.07e-04 WME 0.224 0.271 -0.150 5.07e-04 WME 0.224 0.271 -0.132 1.19e-02 WME 0.148 0.072 0.224 1.88e-03 WME 0.148 0.072 0.224 0.270 WME 0.148 0.072 0.224 0.270 WME 0.149 0.032 2.18e-03 WME 0.148 0.072 0.224 0.270 WME 0.149 0.032 2.18e-03 WME 0.148 0.072 0.224 0.270 WME 0.149 0.0465 0.437 1.020 WME 0.149 0.046 0.324 1.17e-01 WME 0.149 0.046 0.324 0.170 WME 0.149 0.046 0.324 0.170 WME 0.149 0.046 0.349 0.522 0.28e-05 WME 0.0471 0.220 0.331 1.77e-01 WME 0.048 0.034 0.522 0.28e-05 WME 0.0440 0.025 0.538-0.24 WME 0.0465 0.349 0.522 0.28e-05 WME 0.0465 0.349 0.522 0.28e-05 WME 0.0465 0.349 0.522 0.28e-05 WME 0.0465 0.349 0.552 0.75e-04 WME 0.0465 0.34	MR-PRESSO	0.274	0.184	0.363	2.26e-02		•
IVW   -0.221   -0.296   -0.145 3.49e-03     MR-Egger   -0.621   -0.386   -0.307 1.05e-01     MR-PRESSO   -0.221   -0.281   -0.160 1.08e-02     Phylum   Euryarchaeota    CA-125     VW   0.289   0.199   0.378 1.28e-03     WME   0.326   0.225   0.427 1.28e-03     MR-Egger   0.287   -0.164   0.738 5.59e-01     MR-PRESSO   0.289   0.143   0.335 1.22e-02     Phylum   Verucomicrobia    TNF-R2     IVW   0.233   0.152   0.314 3.98e-03     WME   0.233   0.168   0.280 1.58e-02     IVW   -0.219   -0.266   -0.149 1.79e-03     WRE   -0.255   -0.347   -0.149 1.79e-03     WME   -0.268   0.521 3.07e-03   •     WME   0.3230   0.258   0.521 3.07e-03   •     WME   0.3230   0.258   0.521 3.07e-03   •     WME   0.3230   0.258   0.521 4.156-02   •     VMR   0.330   0.258	Phylum	Actinobacteria		LEP			
WME   -0.287   -0.388   -0.187 4.33e-03   •     MR-Egger   -0.621   -0.936   -0.307 1.05e-01   •     MR-PRESSO   -0.221   -0.281   -0.100 1.08e-02   •     VWW   0.289   0.199   0.378 1.28e-03   •     VME   0.326   0.225 0.427 1.28e-03   •     MR-FEGSO   0.289   0.199   0.378 2.33e-02   •     Phylum   Verucomicrobia	IVW	-0.221	-0.296	-0.145	3.49e-03	•	
MR-R-PRESSO -0.021 -0.036 -0.307 1.08e-01	WME	-0.287	-0.388	-0.187	4.33e-03		
Michress0   -0.221   -0.281   -0.100   1.08-02   •     IVW   0.289   0.199   0.378   1.28e-03   •     MR   0.326   0.225   0.427   1.28e-03   •     MR   0.326   0.225   0.427   1.28e-03   •     MR   0.289   0.199   0.378   2.33e-02   •     Phylum   Verucomicrobia	MR-Egger	-0.621	-0.936	-0.307	1.05e-01		
Tytum   CA   TALE     IVW   0.289   0.199   0.378   1.28e-03     WTE   0.326   0.225   0.427   1.28e-03     MR-Egger   0.287   -0.164   0.378   5.39e-01     MR-FRESSO   0.289   0.199   0.378   1.28e-03     MW   Veruconicrobia	Phylum	-0.221 Eurvarobaeota	-0.281	-0.160	1.08e-02		
MAE   0.226   0.227   0.427   1.28e-03     MR-ERESSO   0.289   0.199   0.378   2.38e-02     Phylum   Verrucomicrobia		0 289	0 199	0 378	1 26e-03		
MR-Egger   0.287   -0.164   0.738   5.58e-01     MR-PRESSO   0.289   0.199   0.378   2.33e-02     IVW   0.233   0.152   0.117-R2     IVW   0.239   0.143   0.356   1.26e-02     MR-Egger   -0.261   -1.064   0.542   7.76e-01     MR-Egger   -0.261   -1.064   0.242   7.76e-01     MR-Egger   -0.261   -0.163   6.46e-03   •     VWW   -0.219   -0.200   -0.141   1.79e-03   •     VME   -0.255   -0.347   -0.163   6.46e-03   •     MR-Egger   -0.169   -0.378   0.039   4.54e-01   •     MR-Egger   -0.169   0.376   0.376-03   •   •     VWME   0.323   0.169   0.473   3.55e-02   •     MR-Egger   1.375   0.906   1.844   6.08e-02   •   •     VME   -0.211   -0.271   -0.121   1.9e-02   •   •     VMME   -0.211   -0.271   -0.121	WME	0.326	0.225	0.070	1 28e-03		
MR-PRESSO   0.289   0.199   0.378   2.33e-02     Phylum   Verrucomicrobia    TNF-R2   9     WME   0.233   0.143   0.335   1.26e-03     WME   0.239   0.143   0.335   1.26e-02     MR-Egger   -0.261   -1.064   0.542   7.76e-01     MR-PRESSO   0.233   0.186   0.280   1.58e-02     Class   Actinobacteria    LEP   -     WWE   -0.255   -0.347   -0.183   5.64e-03     MR-PRESSO   -0.219   -0.266   -0.173   3.23e-03   -     MR-PRESSO   -0.230   0.258   0.521   3.07e-03   -     WME   0.323   0.169   0.477   3.55e-02   -     MR-PRESSO   0.390   0.258   0.521   4.15e-02   -     Order   Bacillales    CSF-1   -   -     IVW   -0.211   -0.271   -0.132   2.04e-03   -     Order   Enterobacteriales    TNF-R2   - <td< td=""><td>MR-Egger</td><td>0.287</td><td>-0.164</td><td>0.738</td><td>5.59e-01</td><td>-</td><td></td></td<>	MR-Egger	0.287	-0.164	0.738	5.59e-01	-	
Phylum     Verrucomicrobia      TNF-R2       IVW     0.233     0.152     0.314     3.98e-03       MR-Egger     -0.261     -1.064     0.542     7.76e-01       MR-PRESSO     0.233     0.166     0.200     1.58e-02       Class     Actinobacteria      LEP       VWW     -0.219     -0.200     -0.143     5.64e-03       MR-Egger     -0.169     -0.377     0.039     4.54e-01       MR-Egger     -0.169     -0.378     0.039     4.54e-01       MR-Egger     -0.169     -0.378     0.039     4.54e-01       MR-Egger     1.375     0.006     1.844     6.08e-02     •       VME     0.323     0.169     0.473     3.55e-02     •       MR-Egger     1.375     0.006     1.844     6.08e-02     •       VME     0.233     0.169     0.473     8.70e-01     •       Order     Bacillates      CSF-1     •     •       IVW     -0.	MR-PRESSO	0.289	0.199	0.378	2.33e-02		•
IVW   0.233   0.152   0.141   9.98-03     WME   0.239   0.143   0.335   1.28-02     MR-Egger   -0.261   -1.064   0.262   7.76e-01     MR-PRESSO   0.233   0.186   0.280   1.58e-02     IVW   -0.219   -0.290   -0.149   1.79e-03     WME   -0.255   -0.347   -0.163   5.64e-01     MR-Egger   -0.169   -0.378   0.039   5.64e-01     MR-Egger   -0.169   -0.378   0.039   5.64e-01     MR-Egger   -0.169   -0.378   0.039   5.64e-01     MR-Egger   -0.169   -0.378   0.309   6.251   3.07e-03     WME   0.323   0.169   0.477   3.55e-02   0.767     MR-Egger   0.137   0.0258   0.521   4.15e-02   0.767     VWW   -0.211   -0.271   -0.150   5.07e-04   0     VME   -0.223   -0.224   1.18e-02   0   0     Order   Enterobacteriales    CSF-1   0.224	Phylum	Verrucomicrobia		TNF-R2			
WME   0.239   0.143   0.335   1.26e-02     MR-Egger   -0.261   -1.064   0.542   7.76e-01     MR-PRESSO   0.233   0.188   0.280   1.58e-02     Class   Actinobacteria    LEP     IVW   -0.219   -0.270   -0.143   1.79e-03     WME   -0.255   -0.347   -0.163   5.64e-03   -     MR-Egger   -0.219   -0.266   -0.173   3.28e-03   -     Class   Erysipelotrichia    VEGF-D   -   -     IVW   0.323   0.169   0.477   3.55e-02   -   -     VME   0.323   0.169   0.437   3.56e-02   -   -     VME   0.323   0.258   0.521   4.15e-02   -   -     VME   0.201   -0.271   -0.150   5.07e-04   -   -     VME   0.228   0.122   1.9e-02   -   -   -   -     VME   0.228   0.129   0.326   2.11e-02   -   - <td< td=""><td>IVW</td><td>0.233</td><td>0.152</td><td>0.314</td><td>3.98e-03</td><td></td><td>•</td></td<>	IVW	0.233	0.152	0.314	3.98e-03		•
MR-Egger   -0.261   -1.064   0.542   7.76e-01     MR-PRESSO   0.233   0.186   0.280   1.58e-02     IVW   -0.219   -0.290   -0.149   1.79e-03     WME   -0.255   -0.347   -0.163   5.64e-03     MR-Egger   -0.169   -0.378   0.039   4.54e-01     MR-Egger   -0.169   -0.378   0.39   4.54e-01     INW   0.390   0.258   0.521   3.77e-03   •     INW   0.390   0.258   0.521   3.77e-03   •     INW   0.390   0.258   0.521   4.15e-02   •     INW   -0.203   -0.284   -0.122   1.19e-02   •     INW   -0.201   -0.271   -0.150   5.07e-04   •     INMR-Egger   -0.114   -0.661   -0.337   2.04e-03   •     INW   -0.201   -0.261   -0.337   2.04e-03   •     INW   0.225   0.170   0.332   1.88e-03   •     INW   0.2261   0.170   0.332	WME	0.239	0.143	0.335	1.26e-02		•
MR-PRESSO   0.233   0.186   0.280   1.58e-02     Class   Actinobacteria    LEP     WWE   -0.255   -0.347   -0.163   5.64e-03     MR-Egger   -0.169   -0.378   0.039   4.54e-01     MR-PRESSO   -0.219   -0.266   -0.173   3.22e-03     Class   Erysipelotichia    VEGF-D     IVW   0.390   0.258   0.521   1.15e-02     MR-Egger   1.375   0.906   1.844   6.08e-02      MR-PRESSO   0.390   0.258   0.521   4.15e-02      VME   0.201   -0.271   -0.125   1.15e-02      VME   0.2028   0.521   4.15e-02       VME   -0.203   -0.271   -0.123   1.16e-02      VME   -0.211   -0.271   -0.123   1.9e-02      VME   0.228   0.129   0.326   2.11e-02      VW   0.211   -0.271   0.202   2.41e-03	MR-Egger	-0.261	-1.064	0.542	7.76e-01	• • •	
Class Actinobacteria LEP IVW -0.219 -0.290 -0.149 1.79e-03 WME -0.255 -0.347 -0.163 5.64e-03 MR-Egger -0.169 -0.378 0.039 4.54e-01 MR-PRESSO -0.219 -0.266 -0.173 3.23e-03 Class Erysipelotrichia VEGF-D IVW 0.390 0.258 0.521 3.07e-03 WME 0.323 0.169 0.477 3.55e-02 MR-Egger 1.375 0.906 1.844 6.08e-02 MR-Egger 0.390 0.258 0.521 4.15e-02 Order Bacillales CSF-1 IVW -0.211 -0.271 -0.150 5.07e-04 WME 0.223 -0.284 -0.122 1.19e-02 MR-Egger -0.114 -0.665 -0.437 8.70e-01 Order Enterobacteriales KIM-1 IVW 0.499 -0.661 -0.337 2.04e-03 Order Verucomicrobiales TNF-R2 IVW 0.251 0.170 0.332 1.88e-03 MR-Egger 0.114 -0.266 5.49e-04 WME 0.228 0.129 0.328 2.11e-02 MR-PRESSO 0.251 0.224 0.278 2.65e-03 Family Peptostreptococaceae SRC IVW 0.191 0.136 0.246 5.49e-04 WME 0.146 0.072 0.221 5.06e-02 MR-PRESSO 0.251 0.224 0.278 2.65e-03 Family Velitoneliaceae FRC IVW 0.271 0.202 0.314 1.27e-01 MR-PRESSO 0.191 0.146 0.230 2.11e-02 MR-Egger 0.198 0.022 3.11 -0.2 MR-Egger 0.232 0.092 0.373 1.97e-01 Family Velitoneliaceae L-FA IVW 0.271 0.202 0.341 9.84e-05 WME 0.146 0.072 0.221 5.06e-02 MR-Egger 0.232 0.092 0.373 1.97e-01 MR-PRESSO 0.271 0.202 0.341 9.84e-05 WME 0.198 0.103 0.292 3.63e-02 MR-Egger 0.232 0.092 0.373 1.97e-01 MR-PRESSO 0.271 0.226 0.129 0.333 1.17e-02 Genus Bifldobacterium LEP IVW 0.0271 0.202 0.341 9.84e-05 WME 0.0465 0.349 0.582 6.28e-05 MR-Egger 0.013 -0.147 0.121 9.27e-01 MR-PRESSO 0.271 0.216 0.333 1.17e-02 MR-Egger 0.013 -0.147 0.121 9.27e-01 MR-PRESSO 0.201 -0.258 -0.144 4.14e-04 WME 0.0465 0.349 0.582 6.28e-05 WME 0.0465 0.349 0.582 6.28e-05 WME 0.0465 0.349 0.582 6.28e-05 WME 0.0465 0.369 0.562 1.71e-02 Genus Methanobrevbacter NT-pro BNP VW 0.0371 0.237 0.505 5.53e-03 MR-Egger 0.532 0.002 0.44 8.88e-01 -15	MR-PRESSO	0.233	0.186	0.280	1.58e-02		•
IVW   -0.219   -0.290   -0.149   1.796-03     MR-Egger   -0.265   -0.378   0.039   4.54e-01     MR-PRESSO   -0.219   -0.266   -0.173   3.23e-03     Other State   0.339   0.258   0.521   3.07e-03     WME   0.323   0.169   0.477   3.55e-02     MR-Egger   1.375   0.906   1.844   6.08e-02     MR-Egger   1.375   0.906   1.844   6.08e-02     MR-Egger   1.375   0.906   1.844   6.08e-02     MR-Egger   0.114   -0.251   4.15e-02   •     Order   Bacillales    CSF-1   •     IVW   -0.211   -0.271   -0.150   5.07e-04   •     VME   -0.203   -0.284   -0.122   1.19e-02   •     MR-Egger   -0.114   -0.661   -0.337   2.04e-03   •     VW   0.221   0.170   0.332   1.88e-03   •     VME   0.222   0.170   0.332   1.88e-03   • <t< td=""><td>Class</td><td>Actinobacteria</td><td></td><td>LEP</td><td></td><td></td><td></td></t<>	Class	Actinobacteria		LEP			
WME   -0.255   -0.347   -0.163   5.64e-03     MR-Egger   -0.169   -0.378   0.394   4.54e-01     MR-PRESSO   -0.219   -0.266   -0.173   3.23e-03     Class   Erysipelotrichia    VEGF-D     WWE   0.323   0.169   0.477   3.55e-02     MR-Egger   1.375   0.906   1.844   6.08e-02     MR-Egger   0.330   0.258   0.521   4.15e-02   •     Order   Bacillales    CSF-1   •   •     VWW   -0.211   -0.271   -0.150   5.07e-04   •     WME   -0.203   -0.122   1.19e-02   •     MR-Egger   -0.114   -0.665   0.437   8.70e-01   •     Order   Enterobacteriales    KM-1   •   •     VW   -0.221   0.170   0.332   1.88e-03   •     VME   0.228   0.129   0.326   2.11e-02   •     MR-PRESO   0.251   0.274   2.56e-03   •   •	IVW	-0.219	-0.290	-0.149	1.79e-03	•	
MR-Egger 0.169 -0.378 0.039 4.54e-01 MR-PRESSO 0.219 -0.266 -0.073 3.23e-03 Class Erysipelotrichia VEGF-D IVW 0.330 0.258 0.521 3.07e-03 MR-Egger 1.375 0.906 1.844 6.08e-02 MR-Egger 1.375 0.906 1.844 6.08e-02 MR-PRESSO 0.300 0.258 0.521 4.15e-02 Order Bacillales CSF-1 IVW 0.0211 -0.271 -0.150 5.07e-04 WME 0.203 -0.284 -0.122 1.19e-02 MR-Egger -0.114 -0.666 0.437 8.70e-01 Order Enterobacteriales TNF-R2 IVW 0.049 -0.661 -0.37 2.04e-03 Order Verrucomicrobiales TNF-R2 IVW 0.251 0.170 0.322 1.88e-03 WME 0.228 0.129 0.326 2.11e-02 MR-Egger 0.175 -0.481 0.832 8.15e-01 MR-PRESSO 0.251 0.224 0.278 2.65e-03 Family Peptostreptococcaese SRC IVW 0.191 0.136 0.246 5.49e-04 WME 0.146 0.072 0.221 5.06e-02 MR-PRESSO 0.251 0.224 1.278 2.65e-03 Family Veillonellacese t-PA WME 0.146 0.072 0.221 5.06e-02 MR-PRESSO 0.191 0.146 0.236 2.11e-03 Family Veillonellacese t-PA WME 0.198 0.103 0.292 3.63e-02 MR-Egger 0.232 0.092 0.373 1.97e-01 MR-PRESSO 0.271 0.202 0.341 9.84e-05 WME 0.198 0.103 0.292 3.63e-02 MR-Egger 0.038 0.0271 0.203 0.279 0.373 1.97e-01 MR-PRESSO 0.0271 0.210 0.333 1.97e-02 Genus Bifidobacterium LEP IVW 0.021 0.256 -0.144 4.14e-04 MR-Egger 0.013 0.147 0.121 9.27e-01 MR-PRESSO 0.0271 0.220 0.373 1.97e-01 MR-PRESSO 0.0271 0.223 0.089 0.373 1.97e-01 MR-PRESSO 0.0271 0.226 3-0.149 1.19e-02 Genus Bifidobacterium LEP IVW 0.465 0.349 0.682 6.28e-05 WME 0.440 0.283 0.597 5.038-03 MR-Egger 0.013 0.147 0.121 9.27e-01 MR-PRESSO 0.0201 -0.256 -0.144 4.14e-04 MR-Egger 0.013 0.147 0.121 9.27e-01 MR-PRESSO 0.0201 -0.256 0.149 1.19e-02 Genus Methanobrevibacter NT-PRD IVW 0.465 0.349 0.582 6.28e-05 WME 0.440 0.283 0.597 5.038-03 WME 0.371 0.267 0.475 3.75e-04 WME 0.371 0.267 0.475 3.75e-	WME	-0.255	-0.347	-0.163	5.64e-03	•	
MR-PRESSO   -0.219   -0.266   -0.173   3.232-03   •     IVW   0.390   0.258   0.521   3.07e-03   •     WME   0.323   0.169   0.477   3.55e-02   •     MR-Egger   1.375   0.906   1.844   6.08e-02   •     MR-PRESSO   0.390   0.258   0.521   4.15e-02   •     Order   Bacillales    CSF-1   •   •     IVW   -0.211   -0.271   -0.150   5.07e-04   •     VME   -0.203   -0.284   -0.122   1.19e-02   •     Order   Enterobacteriales    KIM-1   •   •     IVW   -0.499   -0.661   -0.337   2.04e-03   •     Order   Verucomicrobiales    TNF-R2   •   •     IVW   0.251   0.170   0.332   1.88e-03   •     WME   0.228   0.129   0.326   2.11e-02   •     MR-PRESSO   0.251   0.222   5.06e-01   •     W	MR-Egger	-0.169	-0.378	0.039	4.54e-01		-1
Class Eryspeotrenia VEGF-D IVW 0.390 0.258 0.521 3.07e-03 WME 0.323 0.169 0.477 3.55e-02 WR-Egger 1.375 0.906 1.844 6.08e-02 Order Bacillales CSF-1 IVW -0.211 -0.271 -0.150 5.07e-04 WME 0.223 0.284 -0.122 1.19e-02 MR-Egger -0.114 -0.665 0.437 8.70e-01 Order Enterobacteriales KIM-1 IVW -0.499 -0.661 -0.337 2.04e-03 Order Verrucomicrobiales TNF-R2 IVW 0.251 0.170 0.332 1.88e-03 WME 0.228 0.129 0.326 2.11e-02 MR-Egger 0.175 -0.481 0.832 8.15e-01 MR-PRESSO 0.251 0.224 0.278 2.65e-03 Family Peptostreptococcaeee SRC IVW 0.191 0.136 0.246 5.49e-04 WME 0.146 0.072 0.221 5.06e-02 MR-Egger 0.198 0.082 0.314 1.27e-01 MR-PRESSO 0.191 0.146 0.232 8.35e-03 Family Veillonellaceae t-PA IVW 0.271 0.202 0.341 9.84e-05 WME 0.198 0.103 0.292 3.63e-02 MR-Egger 0.232 0.092 0.373 1.97e-01 Family Veillonellaceae t-PA IVW 0.271 0.202 0.341 9.84e-05 WME 0.198 0.103 0.292 3.63e-02 MR-Egger 0.232 0.092 0.373 1.97e-01 MR-PRESSO 0.271 0.210 0.333 1.17e-02 Genus Bifidobacterium LEP IVW 0-0.201 -0.258 -0.144 4.14e-04 WME 0.013 0.292 0.373 1.97e-01 MR-PRESSO 0.271 0.210 0.333 1.17e-02 Genus Dorea KPC- Genus Dorea KPC- IVW 0-0.201 -0.258 -0.144 4.14e-04 WME 0.013 0.522 2.628e-05 WME 0.013 0.522 0.020 MR-Egger 0.332 0.092 0.373 1.97e-01 WME 0.0465 0.349 0.562 6.28e-05 WME 0.0465 0.349 0.562 6.28e-05 WME 0.440 0.283 0.567 5.03e-03 WME 0.446 0.267 0.475 3.75e-04 WME 0.446 0.267 0.475 3.75e-04 WME 0.371 0.237 0.505 5.53e-03 WME 0.371 0.237 0.505 5.53e-03	MR-PRESSO	-0.219	-0.266	-0.173	3.23e-03	•	
NW   0.236   0.245   0.021   5.07e-03     MR-Egger   1.375   0.906   1.844   6.08e-02     MR-FESSO   0.390   0.258   0.521   4.15e-02     Order   Bacillales    CSF-1     IVW   -0.211   -0.271   -0.150   5.07e-04     WME   -0.203   -0.284   -0.122   1.19e-02     MR-Egger   -0.114   -0.665   0.437   8.70e-01     Order   Enterobacteriales    TNF-R2     IVW   -0.499   -0.661   -0.337   2.04e-03     Order   Verrucomicrobiales    TNF-R2     IVW   0.221   0.170   0.332   1.88e-03     WME   0.228   0.129   0.326   2.11e-03     MR-Egger   0.191   0.136   0.246   5.49e-04     WME   0.191   0.136   0.246   5.49e-04     WME   0.191   0.146   0.232   0.362-02     MR-Egger   0.191   0.146   0.232   0.363e-02     MR-PRESSO		Erysipelotrichia	0.259	VEGF-D	2 070-02		
MR-Egger   0.325   0.109   0.417   3.36   0.2     MR-Egger   1.375   0.906   1.844   6.08e-02     MR-PRESSO   0.390   0.258   0.521   4.15e-02     Order   Bacillales    CSF-1     IVW   -0.203   -0.284   -0.122   1.19e-02     MR-Egger   -0.114   -0.665   0.437   8.70e-01     Order   Enterobacteriales    KIM-1     IVW   -0.499   -0.661   -0.337   2.04e-03     Order   Verrucomicrobiales    TNF-R2     IVW   0.251   0.170   0.332   1.88e-03     WME   0.228   0.129   0.326   2.11e-02     MR-Fgger   0.175   -0.481   0.832   8.15e-01     MR-PRESSO   0.251   0.224   0.278   2.65e-03     Family   Peptostreptoccccaceae    SRC     IVW   0.146   0.072   0.211   6.246     MR-PRESSO   0.191   0.146   0.236   2.11e-03     Fam		0.390	0.258	0.521	3.550=02		
MR = PRESSO   0.300   0.258   0.511   4.156-02     Order   Bacillales    CSF-1     IVW   -0.211   -0.271   -0.150   5.07e-04     WME   -0.203   -0.284   -0.122   1.19e-02     MR-Egger   -0.114   -0.665   0.437   8.70e-01     Order   Enterobacteriales    KIM-1     IVW   -0.499   -0.661   -0.337   2.04e-03     Order   Verucomicrobiales    TNF-FR2     IVW   0.251   0.170   0.332   1.88e-03     WME   0.228   0.129   0.326   2.11e-02     MR-Egger   0.175   -0.481   0.832   8.15e-01     MR-PRESSO   0.251   0.224   0.278   2.65e-03     Family   Peptostreptoccccaceae    SRC      IVW   0.191   0.146   0.072   0.221   5.06e-02      MR-Egger   0.198   0.082   0.314   1.27e-01      MR-Egger   0.193   0.221   5.06	MR-Egger	1.375	0.105	1 844	6.08e-02		
Order     Bacillales      CSF-1       IVW     -0.211     -0.271     -0.150     5.07e-04       WME     -0.203     -0.284     -0.122     1.19e-02       MR-Egger     -0.114     -0.665     0.437     8.70e-01       Order     Enterobacteriales      KIM-1       IVW     -0.499     -0.661     -0.337     2.04e-03       Order     Verrucomicrobiales      TNF-R2       IVW     0.251     0.170     0.332     1.88e-03       WME     0.228     0.129     0.326     2.11e-02       MR-Egger     0.175     -0.481     0.832     8.15e-01       MR-PRESSO     0.251     0.224     0.278     2.65e-03       Family     Peptostreptococcaceae      SRC       IVW     0.191     0.136     0.246     5.49e-04       MR-Egger     0.198     0.062     0.314     1.27e-01       MR-Egger     0.198     0.022     0.333     1.17e-01     MC	MR-PRESSO	0.390	0.258	0.521	4 15e-02		101
IVW   -0.211   -0.271   -0.150   5.07e-04     WME   -0.203   -0.284   -0.122   1.19e-02     MR-Egger   -0.114   -0.665   0.437   8.70e-01     Order   Enterobacteriales    KIM-1     IVW   -0.499   -0.661   -0.337   2.04e-03     Order   Verrucomicrobiales    TNF-R2     IVW   0.221   0.170   0.332   1.88e-03     WME   0.228   0.129   0.326   2.11e-02     MR-Egger   0.175   -0.481   0.832   8.15e-01     MR-PRESSO   0.251   0.224   0.278   2.65e-03     IVW   0.191   0.136   0.246   5.49e-04     WME   0.198   0.062   0.314   1.27e-01     MR-Fgger   0.198   0.022   0.341   9.7e-01     Family   Veillonellaceae    t-PA     IVW   0.271   0.202   0.331   1.7e-01     MR-Egger   0.282   0.092   3.63e-02   MR-Egger     MR-Egger	Order	Bacillales		CSF-1			
WME   -0.203   -0.284   -0.122   1.19e-02     MR-Egger   -0.114   -0.665   0.437   8.70e-01     Order   Enterobacteriales    KIM-1     IVW   -0.499   -0.661   -0.337   2.04e-03     Order   Verrucomicrobiales    TNF-R2     IVW   0.221   0.170   0.332   1.88e-03     WME   0.228   0.129   0.326   2.11e-02     MR-Egger   0.175   -0.481   0.832   8.15e-01     MR-Egger   0.121   0.224   0.278   2.65e-03     Family   Peptostreptococcaceae    SRC     IVW   0.191   0.136   0.246   5.49e-04     WME   0.146   0.072   0.221   5.06e-02     MR-Egger   0.198   0.082   0.314   1.27e-01     MR-PRESSO   0.191   0.146   0.236   2.11e-03     Family   Velilonellaceae    t-PA   VW   0.271   0.202   0.313   1.7e-01     MR-Egger   0.232   <	IVW	-0.211	-0.271	-0.150	5.07e-04	•	
MR-Egger   -0.114   -0.665   0.437   8.70e-01     Order   Enterobacteriales    KIM-1     IVW   -0.499   -0.661   -0.337   2.04e-03     Order   Verrucomicrobiales    TNF-R2     IVW   0.251   0.170   0.332   1.88e-03     WME   0.228   0.129   0.326   2.11e-02     MR-Egger   0.175   -0.481   0.832   8.15e-01     MR-PRESSO   0.251   0.224   0.278   2.65e-03     Family   Peptostreptococcaceae    SRC     IVW   0.191   0.136   0.246   5.49e-04     WME   0.198   0.020   0.314   1.27e-01     MR-Egger   0.198   0.022   0.314   1.27e-01     MR-Egger   0.232   0.092   0.373   1.97e-01     MR-Egger   0.232   0.092   0.373   1.97e-01     MR-Egger   0.232   0.092   0.373   1.97e-01     MR-Egger   0.232   0.021   0.258   -0.144   4.14e-04	WME	-0.203	-0.284	-0.122	1.19e-02	•	
Order     Enterobacteriales      KIM-1       IVW     -0.499     -0.661     -0.337     2.04e-03       Order     Verrucomicrobiales      TNF-R2       IVW     0.251     0.170     0.332     1.88e-03       WME     0.228     0.129     0.326     2.11e-02       MR-Egger     0.175     -0.481     0.832     8.15e-01       MR-PRESSO     0.251     0.224     0.278     2.65e-03       Family     Peptostreptococcaceae      SRC       IVW     0.191     0.136     0.246     5.49e-04       WME     0.146     0.072     0.221     5.06e-02       IWR-Egger     0.198     0.082     0.314     1.27e-01       MR-Egger     0.198     0.082     0.314     1.27e-01       IWW     0.271     0.202     0.341     9.84e-05       WME     0.198     0.103     0.292     3.63e-02       MR-Egger     0.232     0.092     0.333     1.17e-01       MR-	MR-Egger	-0 114	-0.665	0 437	8.70e-01		
IVW   -0.499   -0.661   -0.337   2.04e-03     Order   Verucomicrobiales    TNF-R2     IVW   0.2261   0.170   0.332   1.88e-03     WME   0.228   0.129   0.326   2.11e-02     MR-Egger   0.175   -0.481   0.832   8.15e-01     MR-PRESSO   0.251   0.224   0.278   2.65e-03     Family   Peptostreptococcaceae    SRC     IVW   0.191   0.136   0.246   5.49e-04     MR-Egger   0.198   0.082   0.314   1.27e-01     MR-PRESSO   0.191   0.146   0.276   2.11e-03   •     Family   Veillonellaceae    t-PA   •   •     IVW   0.271   0.202   0.341   9.84e-05   •     WME   0.198   0.103   0.292   3.63e-02   •     MR-Egger   0.232   0.092   0.333   1.97e-01   •     MR-Egger   0.232   0.092   0.333   1.97e-01   •     MR-PRESSO			-0.005	0.457		· · · · · · · · · · · · · · · · · · ·	
Order     Verrucomicrobiales      TNF-R2       IVW     0.251     0.170     0.332     1.88e-03       WME     0.228     0.129     0.326     2.11e-02       MR-Egger     0.175     -0.481     0.832     8.15e-01       MR-PRESSO     0.251     0.224     0.278     2.65e-03       Family     Peptostreptococcaceae      SRC       IVW     0.191     0.136     0.246     5.49e-04       WME     0.146     0.072     0.221     5.06e-02       MR-Egger     0.198     0.082     0.314     1.27e-01       MR-PRESSO     0.191     0.146     0.238     2.11e-03       Family     Veillonellaceae      t-PA       I/W     0.271     0.202     0.341     9.84e-05       WME     0.198     0.103     0.292     3.63e-02       WR-Fgger     0.232     0.092     0.373     1.97e-01       I/W     0.210     -0.258     -0.144     4.14e-04     WME	Order	Enterobacteriales	-0.005	KIM-1			
IVW   0.251   0.170   0.332   1.88e-03     WME   0.228   0.129   0.326   2.11e-02     MR-Egger   0.175   -0.481   0.832   8.15e-01     MR-PRESSO   0.251   0.224   0.278   2.65e-03     Family   Peptostreptococcaceae    SRC     IVW   0.191   0.136   0.246   5.49e-04     WME   0.146   0.072   0.21   5.06e-02     MR-Egger   0.198   0.082   0.314   1.27e-01     MR-PRESSO   0.191   0.146   0.236   2.11e-03     Family   Veillonellaceae    t-PA     I/W   0.271   0.202   0.341   9.84e-05     WME   0.198   0.103   0.292   3.63e-02     MR-Egger   0.232   0.092   0.373   1.97e-01     MR-FRESSO   0.271   0.210   0.333   1.77e-02     WME   -0.256   -0.332   -0.144   4.14e-04   WME     WME   -0.256   -0.332   -0.149   1.92e-01   <	Order IVW	Enterobacteriales -0.499	-0.665  -0.661	KIM-1 -0.337	2.04e-03	H <b>O</b> -1	
WME   0.228   0.129   0.326   2.11e-02     MR-Egger   0.175   -0.481   0.832   8.15e-01     MR-PRESSO   0.251   0.224   0.278   2.65e-03     Family   Peptostreptococcaceae    SRC     IVW   0.191   0.136   0.246   5.49e-04     WME   0.146   0.072   0.221   5.06e-02     MR-Egger   0.198   0.082   0.314   1.27e-01     MR-PRESSO   0.191   0.146   0.236   2.11e-03     Family   Veillonellaceae    t-PA     IVW   0.271   0.202   0.341   9.8e-02     WME   0.198   0.103   0.292   3.63e-02     MR-Egger   0.232   0.092   0.373   1.97e-01     MR-Egger   0.232   0.092   0.373   1.97e-01     MR-Egger   0.201   -0.258   -0.144   4.14e-04     WME   -0.201   -0.253   -0.149   1.19e-02     Genus   Dorea    HSP-27   MR-Egger   -0.162	Order IVW Order	Enterobacteriales -0.499 Verrucomicrobiales	-0.663  -0.661 	KIM-1 -0.337 TNF-R2	2.04e-03	H	
MR-PRESSO   0.251   0.224   0.278   2.65e-03     Family   Peptostreptococcaceae    SRC     IVW   0.191   0.136   0.246   5.49e-04     WME   0.146   0.072   0.221   5.06e-02     MR-Egger   0.198   0.082   0.314   1.27e-01     MR-FRESSO   0.191   0.146   0.236   2.11e-03     Family   Veillonellaceae    1-PA     IVW   0.271   0.202   0.341   9.86e-02     MR-Egger   0.232   0.092   0.373   1.97e-01     MR-Egger   0.201   -0.258   -0.144   4.14e-04   •     WME   -0.201   -0.258   -0.144   4.14e-04   •     MR-Fgger   -0.013   -0.147   0.121   9.27e-01   •     MR-Fgger   -0.021   -0.253 <td>Order IVW Order IVW</td> <td>Enterobacteriales -0.499 Verrucomicrobiales 0.251</td> <td>-0.661  0.170</td> <td>KIM-1 -0.337 TNF-R2 0.332</td> <td>2.04e-03 1.88e-03</td> <td><b>⊢●</b>1</td> <td>•</td>	Order IVW Order IVW	Enterobacteriales -0.499 Verrucomicrobiales 0.251	-0.661  0.170	KIM-1 -0.337 TNF-R2 0.332	2.04e-03 1.88e-03	<b>⊢●</b> 1	•
MR-FRESSO   0.251   0.224   0.274   0.28-03     IVW   0.191   0.136   0.246   5.49e-04     IVW   0.191   0.136   0.246   5.49e-04     WME   0.146   0.072   0.221   5.06e-02     MR-Egger   0.198   0.082   0.314   1.27e-01     MR-PRESSO   0.191   0.146   0.236   2.11e-03     Family   Veillonellaceae    t-PA     IVW   0.271   0.202   0.341   9.84e-05     WME   0.198   0.103   0.292   3.63e-02     MR-Egger   0.232   0.092   0.373   1.97e-01     MR-Egger   0.232   0.092   0.333   1.17e-02     Genus   Bifidobacterium    LEP   IVW   -0.201   -0.258     IVW   -0.201   -0.258   -0.144   4.14e-04   IVM   IVME   0.322   0.149   1.19e-02   IVMR     Genus   Dorea    HSP-27   IVW   0.465   0.349   0.582   6.28e-05   IVMR	Order IVW Order IVW WME	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.228 0.127	-0.661  0.170 0.129	KIM-1 -0.337 TNF-R2 0.332 0.326	2.04e-03 1.88e-03 2.11e-02	F <b>O</b> -1	
NW   0.191   0.136   0.246   5.49e-04     WME   0.146   0.072   0.221   5.06e-02     MR-FRESSO   0.191   0.146   0.236   2.11e-03     Family   Veillonellaceae    t-PA     IVW   0.271   0.202   0.341   9.84e-05     WME   0.198   0.103   0.292   3.63e-02     MR-FRESSO   0.271   0.210   0.333   1.17e-02     Genus   Bifidobacterium    LEP     IVW   -0.201   -0.258   -0.144   4.14e-04     WME   -0.201   -0.253   -0.141   7.12e-01     MR-Egger   -0.013   -0.147   0.121   9.27e-01     MR-RESSO   -0.201   -0.253   -0.141   7.12e-04     MR-PRESSO   -0.201   -0.253   -0.149   1.19e-02     Genus   Dorea    HSP-27      IVW   0.465   0.349   0.582   6.28e-05   •     MR-Egger   -0.162   -0.654   0.311   7.74e-01   •	Order IVW Order IVW WME MR-Egger	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.228 0.175	-0.661  0.170 0.129 -0.481	KIM-1 -0.337 TNF-R2 0.332 0.326 0.832	2.04e-03 1.88e-03 2.11e-02 8.15e-01	F <b>•</b> -	
NM   0.134   0.135   0.245   0.566-02     MR-Egger   0.198   0.082   0.314   1.27e-01     MR-PRESSO   0.191   0.146   0.232   5.066-02     MR-PRESSO   0.191   0.146   0.236   2.11e-03     Family   Veillonellaceae    t-PA     IVW   0.271   0.202   0.341   9.84e-05     WME   0.198   0.103   0.292   3.63e-02     MR-Fgger   0.232   0.092   0.373   1.97e-01     MR-PRESSO   0.271   0.210   0.333   1.17e-02     Genus   Bifdobacterium    LEP     IVW   -0.256   -0.332   -0.181   7.12e-04     MR-Egger   -0.013   -0.147   0.121   9.27e-01     MR-PRESSO   -0.201   -0.253   -0.149   1.19e-02   0     Genus   Dorea    HSP-27   IVW   0.465   0.331   7.74e-01   0     MR-Egger   -0.162   -0.654   0.331   7.74e-01   0   0   0	Order IVW Order IVW WME MR-Egger MR-PRESSO	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.228 0.175 0.251	-0.661  0.170 0.129 -0.481 0.224	KIM-1 -0.337 TNF-R2 0.332 0.326 0.832 0.278	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03	·••	
MR-Egger 0.198 0.092 0.314 1.27e-01   MR-PRESSO 0.191 0.146 0.236 2.11e-03   Family Veillonellaceae  t-PA   IVW 0.271 0.202 0.341 9.84e-05   WME 0.198 0.103 0.292 9.63e-02   MR-Egger 0.232 0.092 0.373 1.97e-01   MR-PRESSO 0.271 0.210 0.333 1.17e-02   Genus Bifidobacterium  LEP   I/W -0.201 -0.256 -0.144 4.14e-04   WME -0.256 -0.332 -0.181 7.12e-04   MR-PRESSO -0.013 -0.147 0.121 9.27e-01   MR-PRESSO -0.201 -0.253 -0.181 7.12e-04   MR-PRESSO -0.201 -0.253 -0.149 1.19e-02   Genus Dorea  HSP-27   I/W 0.465 0.349 0.582 6.28e-05   WME 0.440 0.283 0.597 5.03e-03   MR-Egger -0.162 -0.654 0.331 7.74e-01   MR-PRESSO 0.465 0.369 0.562 1.71e-02   Genus	Order IVW Order IVW WME MR-Egger MR-PRESSO Family Family	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.228 0.175 0.251 Peptostreptococcaceae 0.191	-0.661 	KIM-1 -0.337 TNF-R2 0.332 0.326 0.832 0.278 SRC 0.246	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03	•• •	
MR-PRESSO   0.191   0.146   0.236   2.11e-03     Family   Veillonellaceae    t-PA     IVW   0.271   0.202   0.341   9.84e-05     WME   0.198   0.103   0.292   3.63e-02     MR-Egger   0.232   0.092   0.373   1.97e-01     MR-PRESSO   0.271   0.210   0.333   1.17e-02     Genus   Bifidobacterium    LEP   Image: Comparison of the second of the	Order IVW Order IVW WME MR-Egger MR-PRESSO Family IVW WMF	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.228 0.175 0.251 Peptostreptococcaceae 0.191 0.146	-0.661  0.170 0.129 -0.481 0.224  0.136 0.072	KIM-1 -0.337 TNF-R2 0.332 0.326 0.832 0.278 SRC 0.246 0.221	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02	•••	•
Family     Veillonellaceae      t-PA       IVW     0.271     0.202     0.341     9.84e-05       WME     0.198     0.103     0.292     3.63e-02       MR-Egger     0.232     0.092     0.373     1.97e-01       MR-PRESSO     0.271     0.210     0.333     1.17e-02       Genus     Bifidobacterium      LEP       IVW     -0.201     -0.258     -0.141     4.14e-04       WME     -0.256     -0.332     -0.181     7.12e-04       MR-Egger     -0.013     -0.147     0.121     9.27e-01       MR-Egger     -0.013     -0.147     0.121     9.27e-01       MR-Egger     -0.013     -0.147     0.121     9.27e-01       MR-Egger     -0.201     -0.253     -0.149     1.9e-02     0       Genus     Dorea      HSP-27     -     0       WME     0.440     0.283     0.597     5.03e-03     -       MR-PRESSO     0.465     0.369 <t< td=""><td>Order       IVW       Order       IVW       MR-Egger       MR-PRESSO       Family       IVW       WME       MR-Egger</td><td>Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.228 0.175 0.251 Peptostreptococcaceae 0.191 0.146 0.198</td><td>-0.005  -0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082</td><td>KIM-1 -0.337 TNF-R2 0.332 0.326 0.832 0.278 SRC 0.246 0.221 0.314</td><td>2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01</td><td></td><td>• • •</td></t<>	Order       IVW       Order       IVW       MR-Egger       MR-PRESSO       Family       IVW       WME       MR-Egger	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.228 0.175 0.251 Peptostreptococcaceae 0.191 0.146 0.198	-0.005  -0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082	KIM-1 -0.337 TNF-R2 0.332 0.326 0.832 0.278 SRC 0.246 0.221 0.314	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01		• • •
IVW 0.271 0.202 0.341 9.84e-05   WME 0.198 0.103 0.292 3.63e-02   MR-Egger 0.232 0.092 0.373 1.97e-01   MR-PRESSO 0.271 0.210 0.333 1.17e-02   Genus Bifidobacterium  LEP   IVW -0.201 -0.258 -0.144 4.14e-04   WME -0.256 -0.332 -0.181 7.12e-04   MR-Egger -0.013 -0.147 0.121 9.27e-01   MR-PRESSO -0.201 -0.253 -0.149 1.19e-02   Genus Dorea  HSP-27   IVW 0.465 0.349 0.582 6.28e-05   WME 0.440 0.283 0.597 5.03e-03   MR-Egger -0.162 -0.654 0.311 7.74e-01   MR-PRESSO 0.465 0.369 0.562 1.71e-02   Genus Methanobrevibacter  NT-pro_BNP   IVW 0.371 0.237 0.505 5.58e-03   MR-Egger 0.532 0.202 1.044 4.88e-01	Order       IVW       Order       IVW       WME       MR-PRESSO       Family       IVW       WME       MR-PRESSO       MR-PRESSO       MR-PRESSO	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.228 0.175 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191	-0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146	KIM-1 -0.337 TNF-R2 0.332 0.326 0.832 0.278 SRC 0.246 0.221 0.314 0.236	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03		•
WME   0.198   0.103   0.292   3.63e-02     MR-Egger   0.232   0.092   0.373   1.97e-01     MR-PRESSO   0.271   0.210   0.333   1.17e-02     Genus   Blifdobacterium    LEP     IVW   -0.201   -0.258   -0.144   4.14e-04     MR-Egger   -0.013   -0.147   0.121   9.27e-01     MR-PRESSO   -0.201   -0.253   -0.149   1.19e-02     Genus   Dorea    HSP-27     IVW   0.465   0.349   0.582   6.28e-05     WME   0.440   0.283   0.597   5.03e-03     MR-Egger   -0.162   -0.654   0.311   7.74e-01     MR-PRESSO   0.465   0.369   0.562   1.71e-02     Genus   Methanobrevibacter    NT-pro_BNP   •     VW   0.371   0.267   0.475   3.75e-04   •     MR-Egger   0.532   0.202   1.044   4.88e-01   •	Order IVW Order IVW WME MR-Egger MR-PRESSO Family IVW WME MR-Egger MR-PRESSO Family	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.228 0.175 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae	-0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146 	KIM-1 -0.337 TNF-R2 0.332 0.326 0.832 0.278 SRC 0.246 0.221 0.314 0.236 t-PA	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03		
MR-Egger   0.232   0.092   0.373   1.97e-01     MR-PRESSO   0.271   0.210   0.333   1.17e-02     Genus   Bifdobacterium    LEP     IVW   -0.201   -0.258   -0.144   4.14e-04     WME   -0.256   -0.332   -0.181   7.12e-04     MR-PRESSO   -0.013   -0.147   0.121   9.27e-01     MR-PRESSO   -0.201   -0.253   -0.149   1.19e-02     Genus   Dorea    HSP-27     IVW   0.465   0.349   0.582   6.28e-05     WME   0.440   0.283   0.597   5.03e-03     MR-Egger   -0.162   -0.654   0.311   7.74e-01     MR-PRESSO   0.465   0.369   0.562   1.71e-02     Genus   Methanobrevibacter    NT-pro_BNP   MWE     IVW   0.371   0.267   0.475   3.75e-04   •     WME   0.371   0.237   0.505   5.53e-03   •     MR-Egger   0.532   0.020   1.044 <td< td=""><td>Order IVW Order IVW WME MR-Egger MR-PRESSO IVW WME MR-Egger MR-PRESSO Family IVW</td><td>Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271</td><td>-0.661  0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.202</td><td>KIM-1 -0.337 TNF-R2 0.332 0.326 0.832 0.278 SRC 0.246 0.221 0.314 0.236 t-PA 0.341</td><td>2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05</td><td>• </td><td></td></td<>	Order IVW Order IVW WME MR-Egger MR-PRESSO IVW WME MR-Egger MR-PRESSO Family IVW	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271	-0.661  0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.202	KIM-1 -0.337 TNF-R2 0.332 0.326 0.832 0.278 SRC 0.246 0.221 0.314 0.236 t-PA 0.341	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05	• 	
MR-PRESSO     0.271     0.210     0.333     1.17e-02       Genus     Bifidobacterium      LEP       I/W     -0.201     -0.258     -0.144     4.14e-04       WME     -0.256     -0.332     -0.181     7.12e-04       MR-Egger     -0.013     -0.147     0.121     9.27e-01       MR-PRESSO     -0.201     -0.253     -0.149     1.19e-02       Genus     Dorea      HSP-27       I/W     0.465     0.349     0.582     6.28e-05       WME     0.440     0.283     0.597     5.03e-03       MR-Egger     -0.162     -0.654     0.331     7.74e-01       MR-PRESSO     0.465     0.369     0.562     1.71e-02       Genus     Methanobrevibacter      NT-pro_BNP     VME       I/W     0.371     0.267     0.475     3.75e-04     •       WME     0.371     0.237     0.505     5.53e-03     •       MR-Egger     0.532     0.202     1.044	Order       IVW       Order       IVW       WME       MR-PRESSO       Family       IVW       WME       MR-PRESSO       Family       IVW       WME       MR-PRESSO       Family       VWWE	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198	-0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.202 0.103	KIM-1 -0.337 TNF-R2 0.326 0.326 0.246 0.241 0.314 0.236 t-PA 0.341 0.341 0.242	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02	• 	
Genus     Bifidobacterium      LEP       IVW     -0.201     -0.258     -0.144     4.14e-04       WME     -0.256     -0.322     -0.181     7.12e-04       MR-Egger     -0.013     -0.147     0.121     9.27e-01       MR-PRESSO     -0.201     -0.253     -0.149     1.19e-02       Genus     Dorea      HSP-27       I/W     0.465     0.349     0.582     6.28e-05       WME     0.440     0.283     0.597     5.03e-03       MR-PRESSO     0.465     0.369     0.562     1.71e-02       Genus     Methanobrevibacter      NT-pro_BNP       I/W     0.371     0.267     0.475     3.75e-04       WME     0.371     0.237     0.505     5.53e-03     -       MR-Egger     0.532     0.020     1.044     4.88e-01     -	Order       IVW       Order       IVW       WME       MR-PRESSO       Family       IVW       WME       MR-PRESSO       Family       IVW       WME       MR-PRESSO       Family       VME       MR-PRESSO       Family       VWWE       MR-PRESSO       Family       VWWE       MR-Egger	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.228 0.175 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.271	-0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.202 0.103 0.092	KIM-1 -0.337 TNF-R2 0.332 0.326 0.832 0.278 SRC 0.246 0.221 0.314 0.236 t-PA 0.341 0.242 0.341	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01		• • • • • •
IVW   -0.201   -0.258   -0.144   4.14e-04     WME   -0.256   -0.332   -0.181   7.12e-04     WR-Egger   -0.013   -0.147   0.121   9.27e-01     MR-PRESSO   -0.201   -0.253   -0.149   1.19e-02     Genus   Dorea    HSP-27     IVW   0.465   0.349   0.582   6.28e-05     WME   0.440   0.283   0.597   5.03e-03     MR-Egger   -0.162   -0.654   0.331   7.74e-01     MR-PRESSO   0.465   0.369   0.562   1.71e-02     Genus   Methanobrevibacter    NT-pro_BNP     IVW   0.371   0.237   0.505   5.53e-03     MR-Egger   0.532   0.020   1.044   4.88e-01	Order       IVW       Order       IVW       WME       MR-PRESSO       Family       IVW       WME       MR-PRESSO       Family       IVW       WME       MR-PRESSO       Family       IVW       MR-Bgger       MR-PRESSO	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.228 0.175 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271	-0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.202 0.103 0.092 0.210	KIM-1 -0.337 TNF-R2 0.332 0.332 0.278 SRC 0.246 0.221 0.314 0.236 t-PA 0.341 0.292 0.373 0.333	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.66e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02		
WME   -0.256   -0.332   -0.181   7.12e-04     MR-Egger   -0.013   -0.147   0.121   9.27e-01     MR-PRESSO   -0.201   -0.253   -0.149   1.19e-02     Genus   Dorea    HSP-27     IVW   0.465   0.349   0.582   6.28e-05     WME   0.440   0.283   0.597   5.03e-03     MR-Egger   -0.162   -0.654   0.331   7.74e-01     MR-PRESSO   0.465   0.369   0.562   1.71e-02     Genus   Methanobrevibacter    NT-pro_BNP     IVW   0.371   0.267   0.475   3.75e-04     WME   0.371   0.237   0.505   5.53e-03     MR-Egger   0.532   0.020   1.044   4.88e-01	Order IVW Order IVW WME MR-Egger MR-PRESSO Family IVW WME MR-Egger MR-PRESSO Family IVW WME MR-RESSO Genus	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.254 0.175 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271 Bifidobacterium	-0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.202 0.103 0.092 0.210 	KIM-1 -0.337 TNF-R2 0.332 0.332 0.278 SRC 0.246 0.221 0.314 0.236 t-PA 0.341 0.292 0.373 0.333 LEP	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02		
MR-Egger   -0.013   -0.147   0.121   9.27e-01     MR-PRESSO   -0.201   -0.253   -0.149   1.19e-02     Genus   Dorea    HSP-27     IVW   0.465   0.349   0.582   6.28e-05     WME   0.440   0.283   0.597   5.03e-03     MR-Egger   -0.162   -0.654   0.311   7.74e-01     MR-PRESSO   0.465   0.369   0.562   1.71e-02     Genus   Methanobrevibacter    NT-pro_BNP     IVW   0.371   0.267   0.475   3.75e-04     WME   0.371   0.237   0.505   5.53e-03     MR-Egger   0.532   0.020   1.044   4.88e-01	Order IVW Order IVW WME MR-Egger MR-PRESSO Family IVW WME MR-RESSO Family IVW WME MR-PRESSO Genus IVW	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271 Bifidobacterium -0.201	-0.661  0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.202 0.103 0.092 0.210  -0.258	KIM-1 KIM-1 -0.337 TNF-R2 0.326 0.322 0.278 SRC 0.246 0.221 0.314 0.236 t-PA 0.341 0.292 0.373 0.333 LEP -0.144	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02 4.14e-04	•	
MR-PRESSO     -0.201     -0.233     -0.149     1.19e-02     •       IVW     Dorea      HSP-27     • </td <td>Order       IVW       Order       IVW       WME       MR-PRESSO       Family       IVW       WME       MR-PRESSO       Family       VWWE       MR-PRESSO       Family       VW       WME       MR-PRESSO       Family       IVW       WME       MR-PRESSO       Genus       IVW       WME</td> <td>Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271 Bifidobacterium -0.201 -0.256</td> <td>-0.352 -0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.202 0.103 0.092 0.210  -0.258 -0.332</td> <td>KIM-1 -0.337 TNF-R2 0.322 0.326 0.832 0.278 SRC 0.246 0.241 0.314 0.236 t-PA 0.314 0.236 t-PA 0.341 0.292 0.373 0.333 LEP -0.144 -0.181</td> <td>2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02 4.14e-04 7.12e-04</td> <td>•</td> <td></td>	Order       IVW       Order       IVW       WME       MR-PRESSO       Family       IVW       WME       MR-PRESSO       Family       VWWE       MR-PRESSO       Family       VW       WME       MR-PRESSO       Family       IVW       WME       MR-PRESSO       Genus       IVW       WME	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271 Bifidobacterium -0.201 -0.256	-0.352 -0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.202 0.103 0.092 0.210  -0.258 -0.332	KIM-1 -0.337 TNF-R2 0.322 0.326 0.832 0.278 SRC 0.246 0.241 0.314 0.236 t-PA 0.314 0.236 t-PA 0.341 0.292 0.373 0.333 LEP -0.144 -0.181	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02 4.14e-04 7.12e-04	•	
Series     Dolea     Hor Z1       IVW     0.465     0.349     0.582     6.28e-05       WME     0.440     0.283     0.597     5.03e-03       MR-Egger     -0.162     -0.654     0.331     7.74e-01       MR-PRESSO     0.465     0.369     0.562     1.71e-02       Genus     Methanobrevibacter      NT-pro_BNP       IVW     0.371     0.267     0.475     3.75e-04       WME     0.371     0.237     0.505     5.53e-03       IR-Egger     0.532     0.020     1.044     4.88e-01	Order       IVW       Order       IVW       WRE       MR-PRESSO       Family       IVW       WME       MR-PRESSO       Family       IVW       WME       MR-PRESSO       Family       IVW       WME       MR-Egger       MR-PRESSO       Genus       IVW       WME       MR-Egger       MR-PRESSO       Genus       IVW       WME       MR-Egger       MR-Egger	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271 Bifidobacterium -0.201 -0.256 -0.013	-0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.082 0.146  0.202 0.103 0.092 0.210  -0.258 -0.332 -0.147	KIM-1 -0.337 TNF-R2 0.322 0.322 0.322 0.322 0.332 0.278 SRC 0.221 0.314 0.221 0.314 0.236 t-PA 0.314 0.292 0.373 0.333 0.333 0.333	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02 4.14e-04 7.12e-04 9.27e-01		
WME     0.400     0.545     0.502     0.503       MR-Egger     -0.162     -0.654     0.331     7.74e-01       MR-PRESSO     0.465     0.369     0.562     1.71e-02       Genus     Methanobrevibacter      NT-pro_BNP       IVW     0.371     0.267     0.475     3.75e-04       WME     0.371     0.237     0.505     5.53e-03       MR-Egger     0.532     0.020     1.044     4.88e-01	Order IVW Order IVW WME MR-Egger IVW WME MR-Egger MR-PRESSO Family IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.25 0.251 0.251 0.251 0.251 0.251 0.251 0.175 0.251 0.191 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271 Bifidobacterium -0.201 -0.256 -0.013 -0.201	-0.000  -0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.202 0.103 0.092 0.210  -0.258 -0.332 -0.147 -0.253	KIM-1 -0.337 TNF-R2 0.332 0.332 0.278 SRC 0.246 0.221 0.314 0.226 0.241 0.314 0.292 0.373 0.333 LEP -0.144 0.121 0.121	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 9.84e-05 3.63e-02 4.14e-04 7.12e-04 4.14e-04 7.12e-04 1.19e-02		
MR-Egger     -0.162     -0.654     0.331     7.74e-01       MR-PRESSO     0.465     0.369     0.562     1.71e-02       Genus     Methanobrevibacter      NT-pro_BNP       IVW     0.371     0.267     0.475     3.75e-04       WME     0.371     0.237     0.505     5.53e-03       MR-Egger     0.532     0.020     1.044     4.88e-01	Order IVW Order IVW WME MR-Egger MR-PRESSO Family IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 0.251 0.251 0.251 0.251 0.251 0.251 0.175 0.251 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271 Bifidobacterium -0.201 0.256 -0.013 -0.201 Dorea 0.465	-0.0661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.202 0.103 0.092 0.210  -0.258 -0.332 -0.147 -0.253 -0.147	KIM-1 -0.337 TNF-R2 0.332 0.332 0.278 SRC 0.246 0.221 0.314 0.226 t-PA 0.341 0.292 0.373 0.333 LEP -0.144 -0.181 0.129	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02 4.14e-04 7.12e-04 9.27e-01 1.19e-02 6.29e-05 6.29e-		
MR-PRESSO     0.465     0.369     0.562     1.71e-02       Genus     Methanobrevibacter      NT-pro_BNP       IVW     0.371     0.267     0.475     3.75e-04       WME     0.371     0.237     0.505     5.53e-03       MR-Egger     0.532     0.020     1.044     4.88e-01	Order IVW Order IVW WME MR-Egger MR-PRESSO Family IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW VME MR-PRESSO Genus IVW VME MR-PRESSO Genus IVW VME MR-PRESSO Genus IVW VME MR-PRESSO Genus IVW VME MR-PRESSO Genus IVW VME MR-PRESSO Genus IVW VME MR-PRESSO Genus IVW VME MR-PRESSO Genus IVW	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271 Bifidobacterium -0.201 -0.201 0.013 -0.201 Dorea 0.465 0.440	-0.333  -0.661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.202 0.103 0.092 0.210  -0.258 -0.332 -0.147 -0.253  0.349 0.283	KIM-1 -0.337 TNF-R2 0.332 0.332 0.278 SRC 0.246 0.221 0.314 0.236 t-PA 0.341 0.292 0.373 0.333 LEP -0.144 -0.121 -0.124 HSP-27 0.582 0.582	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02 4.14e-04 7.12e-04 9.27e-01 1.19e-02 6.28e-05 5.03e-03	•	
Genus     Methanobrevibacter      NT-pro_BNP       IVW     0.371     0.267     0.475     3.75e-04       WME     0.371     0.237     0.505     5.53e-03       MR-Egger     0.532     0.020     1.044     4.88e-01	Order IVW Order IVW WME MR-Egger MR-PRESSO Family IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW MR-Egger MR-PRESSO Genus IVW MR-Egger MR-PRESSO Genus IVW MR-Egger MR-PRESSO Genus IVW MR-Egger MR-PRESSO Genus IVW MR-Egger MR-PRESSO Genus IVW MR-Egger MR-PRESSO Genus IVW MR-Egger MR-PRESSO Genus IVW MR-Egger MR-PRESSO Genus IVW MR-Egger MR-PRESSO Genus IVW	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271 Bifidobacterium -0.201 -0.256 -0.013 -0.201 Dorea 0.465 0.440 -0.162	-0.333  -0.661  0.129 -0.481 0.224  0.481 0.224  0.82 0.146  0.202 0.103 0.092 0.210  -0.258 -0.332 -0.147 -0.253 -0.349 0.283 -0.654	KIM-1 -0.337 TNF-R2 0.332 0.332 0.278 SRC 0.246 0.241 0.314 0.236 1-PA 0.341 0.292 0.373 0.333 LEP -0.144 -0.181 0.121 -0.149 HSP-27 0.582 0.597 0.331	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02 4.14e-04 7.12e-04 9.27e-01 1.19e-02 6.28e-05 5.03e-03 7.74e-01	•	
IVW     0.371     0.267     0.475     3.75e-04       WME     0.371     0.237     0.505     5.53e-03       MR-Egger     0.532     0.020     1.044     4.88e-01	Order IVW Order IVW WME MR-Egger MR-PRESSO Family IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO IVW WME MR-Egger MR-PRESSO	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.228 0.175 0.251 0.251 0.251 0.251 0.175 0.175 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271 Bifidobacterium -0.201 -0.256 -0.013 -0.201 Dorea 0.465 0.440 -0.162 0.465	-0.3661  0.170 0.129 -0.481 0.224  0.136 0.072 0.082 0.146  0.082 0.146  -0.258 -0.332 -0.147 -0.258 -0.332 -0.147  0.349 0.283 -0.654 0.369	KIM-1 KIM-1 -0.337 TNF-R2 0.332 0.332 0.278 SRC 0.246 0.221 0.314 0.236 t-PA 0.341 0.292 0.373 0.333 LEP -0.144 -0.141 0.121 -0.149 HSP-27 0.5597 0.331 0.5597 0.331 0.5597 0.331 0.5597 0.331 0.5597 0.331 0.5597 0.331 0.5597 0.331 0.5597 0.331 0.5597 0.55	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02 4.14e-04 7.12e-04 9.27e-01 1.19e-02 6.28e-05 5.03e-03 7.74e-01 1.71e-02	•	
WME     0.371     0.237     0.505     5.53e=03       MR-Egger     0.532     0.020     1.044     4.88e=01	Order IVW Order IVW WME MR-Egger MR-PRESSO Family IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.25 0.251 0.251 0.251 0.251 0.251 0.251 0.251 0.251 0.191 0.191 0.198 0.232 0.271 0.198 0.232 0.271 Bifidobacterium -0.201 0.271 0.201 0.201 0.201 0.26 -0.013 -0.201 0.074 0.465 0.440 -0.162 0.465 0.445	-0.000 	KIM-1 -0.337 TNF-R2 0.332 0.332 0.278 SRC 0.246 0.221 0.314 0.226 t-PA 0.341 0.292 0.373 0.333 LEP -0.144 -0.181 0.121 -0.149 HSP-27 0.5597 0.331 0.5597 0.331	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 9.84e-05 3.63e-02 4.14e-04 7.12e-04 4.14e-04 7.12e-04 9.27e-01 1.19e-02 6.28e-05 5.03e-03 7.74e-01 1.71e-02	•	
MR-Egger 0.532 0.020 1.044 4.88e-01	Order IVW Order IVW WME MR-Egger MR-PRESSO Family IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW MR-Egger MR-PRESSO Genus IVW MR-PRESSO Genus IVW	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 0.251 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271 Bifidobacterium -0.201 0.256 -0.013 -0.256 0.440 -0.162 0.465 Methanobrevibacter 0.371	-0.000 	KIM-1 -0.337 TNF-R2 0.332 0.332 0.278 SRC 0.246 0.221 0.314 0.226 t-PA 0.341 0.292 0.373 0.333 LEP -0.144 -0.181 0.129 HSP-27 0.582 0.582 0.582 0.582 0.582	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02 4.14e-04 7.12e-04 9.27e-01 1.19e-02 6.28e-05 5.03e-03 7.74e-01 1.71e-02 3.75e-04	•	
-15 0 15	Order IVW Order IVW WME MR-Egger MR-PRESSO Family IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus IVW WME MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWW MR-PRESSO Genus VWM MR-PRESSO Genus MR-PRESSO MR-PRESSO MR-PRESSO MR-P	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 0.251 Peptostreptococcaceae 0.191 0.146 0.198 0.191 Veillonellaceae 0.271 0.198 0.232 0.271 Bifidobacterium -0.201 -0.256 -0.013 -0.201 Dorea 0.465 0.440 -0.162 0.371 0.371	-0.335 	KIM-1 -0.337 TNF-R2 0.332 0.332 0.278 SRC 0.246 0.221 0.314 0.236 t-PA 0.341 0.292 0.373 0.333 LEP -0.144 -0.181 0.121 -0.149 HSP-27 0.582 0.597 0.331 0.562 T-pro_BNP 0.475 0.505	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02 4.14e-04 7.12e-04 9.27e-01 1.19e-02 6.28e-05 5.03e-03 7.74e-04 1.77e-04 5.53e-03	•	
	Order IVW Order IVW WME MR-Egger MR-PRESSO Family IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-Egger MR-PRESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW WME MR-RESSO Genus IVW MR-RESSO Genus IVW MR-RESSO Genus IVW MR-RESSO MR-RESSO Genus IVW MR-RESSO MR-RES	Enterobacteriales -0.499 Verrucomicrobiales 0.251 0.251 0.251 Peptostreptococcaceae 0.251 0.191 0.191 0.198 0.198 0.198 0.232 0.271 0.198 0.232 0.271 Bifidobacterium -0.201 -0.256 -0.013 -0.201 Dorea 0.465 0.440 -0.162 0.445 Methanobrevibacter 0.371 0.371 0.331	-0.332 -0.661  0.129 -0.481 0.224  0.222 0.136 0.072 0.082 0.146  0.202 0.103 0.092 0.210  -0.258 -0.332 -0.147 -0.253 -0.349 0.283 -0.654 0.369 N 0.267 0.237 0.020	KIM-1 -0.337 TNF-R2 0.332 0.332 0.278 SRC 0.246 0.221 0.314 0.236 t-PA 0.341 0.292 0.373 0.333 LEP -0.144 -0.181 0.212 -0.144 -0.181 0.121 -0.149 HSP-27 0.582 0.597 0.331 T-pro_BNP 0.3562 T-pro_BNP	2.04e-03 1.88e-03 2.11e-02 8.15e-01 2.65e-03 5.49e-04 5.06e-02 1.27e-01 2.11e-03 9.84e-05 3.63e-02 1.97e-01 1.17e-02 4.14e-04 7.12e-04 9.27e-01 1.19e-02 6.28e-05 5.03e-03 3.75e-04 5.53e-03 4.88e-01	•	

FIGURE 1

Forest plot of causal relationships estimated for 13 microbiota and 11 cardiovascular proteins using four MR methods. IVW, inverse variance weighted; WME, weighted median estimator; MR-Egger, MR-Egger regression; MR-PRESSO, MR-PRESSO test; MR, Mendelian randomization.



Mendelian randomization estimation using multiple SNPs. Light blue, green, and dark blue lines represent the association between microbiota (exposure) and cardiovascular proteins (outcome) estimated by the IVW method, weighted median estimator, and MR-Egger regression, respectively. Vertical and horizontal black lines around each point show the 95% confidence interval for each polymorphism exposure association and polymorphism outcome association, respectively. SNP, single nucleotide polymorphism.

greater than 10, indicating no evidence of weak instrument bias (Supplementary Table 4). The MR-Presso test and MR-Egger regression test did not show a horizontal multidirectional effect (p>0.05), whereas the statistics for the IVW test and MR-Egger regression showed no evidence of heterogeneity among the identified outcomes (P>0.05) (Table 1). Additionally, the leave-one-out sensitivity analysis showed that no single SNP significantly affected the causal association (Supplementary Figure 1). The reverse MR analysis showed no common SNPs for cardiovascular proteins (P< 1 × 10<sup>-5</sup>) and the identified bacterial features. Therefore, we did not find the presence of reverse causality.

# Discussion

In this study, we performed MR analyses to assess the potential causal relationship between gut microbiota and 90 cardiovascular proteins. Using multi-cohort GWAS statistics of the gut microbiome and cardiovascular proteins, we identified 13 bacterial signatures that were causally associated with 11 cardiovascular proteins. Phylum *Euryarchaeota* has a high incidence and diversity in two body sites, the gut and oral cavity, as shown by Cai et al. Phylum *Euryarchaeota*, as an archaea may produce cancer-related metabolites that contribute to the human tumour microenvironment and carcinogenesis.

TABLE 1 Sensitive analysis of identified bacterial taxa with cardiovascular proteins.

Bacterial taxa (exposure)	cardiovascular proteins (outcome)	No. of SNP	Pleiotropy					Heterogeneity		
			MR-PRESSO Global P-value	Egger intercept	intercept's se	MR- egger P- value	IVW test's Q	IVW test P- value	MR Egger's Q	MR-egger P-value
Phylum Actinobacteria	IL-8	7	0.401	0.039	0.022	0.131	6.770	0.343	3.523	0.620
Phylum Actinobacteria	LEP	7	0.726	0.025	0.019	0.247	3.850	0.697	2.133	0.831
Phylum Euryarchaeota	CA-125	6	0.191	0.000	0.068	0.997	8.735	0.120	8.735	0.068
Phylum Verrucomicrobia	TNF-R2	4	0.829	0.034	0.054	0.599	1.014	0.798	0.632	0.729
Class Actinobacteria	LEP	7	0.875	-0.004	0.016	0.810	2.619	0.855	2.554	0.768
Class Erysipelotrichia	VEGF-D	5	0.324	-0.060	0.028	0.119	5.831	0.212	1.157	0.763
Order Bacillales	CSF-1	3	NA	-0.013	0.074	0.889	1.205	0.547	1.169	0.280
Order Enterobacteriales	KIM-1	2	NA	NA	NA	NA	1.189	0.276	NA	NA
Order Verrucomicrobiales	TNF-R2	4	0.957	0.005	0.047	0.918	0.337	0.953	0.323	0.851
Family Peptostreptococcaceae	SRC	10	0.797	-0.001	0.009	0.947	5.922	0.748	5.917	0.656
Family Veillonellaceae	t-PA	5	0.579	0.004	0.012	0.768	3.131	0.536	3.026	0.388
Genus Bifidobacterium	LEP	6	0.546	-0.021	0.013	0.197	4.182	0.523	1.796	0.773
Genus Dorea	HSP-27	4	0.651	0.041	0.031	0.320	2.079	0.556	0.362	0.834
Genus Methanobrevibacter	NT-pro_BNP	3	NA	-0.022	0.070	0.802	0.341	0.843	0.238	0.626

IL-8, Interleukin-8.

LEP, Leptin.

CA-125, Carbohydrate antigen 125.

TNF-R2, Tumor necrosis factor receptor 2.

VEGF-D, Vascular endothelial growth factor D.

CSF-1, Macrophage-colony stimulating factor.

KIM-1, Kidney injury molecular1.

SRC, Proto-oncogene tyrosine-protein kinase Src.

t-PA, Tissue plasminogen activator.

HSP-27, Heat shock protein 27.

NT-pro\_BNP, N-terminal pro-brain natriuretic peptide.

NA, Not Applicable.

No. of SNP, Number of SNPs.

This is consistent with our findings of a positive correlation between phylum Euryarchaeota and CA-125 (Cai et al., 2022). CSF-1 stimulates macrophage colonization and granulocyte function, and lowers blood cholesterol (Hume and MacDonald, 2012). He et al. found that order Bacillales lowers cholesterol (He et al., 2021). Unfortunately, this contradicts our results. Heat shock protein 27 (Hsp27), also known as heat shock protein beta-1 (HSPB1), is encoded by the HSPB1 gene. It has a molecular chaperone activity, contributes to heat resistance, inhibits apoptosis, and regulates cell development and differentiation (Van Montfort et al., 2001). Qiu et al. found that, after concurrent chemoradiotherapy of patients with nonsmall cell lung cancer, patients in the long-term progression-free survival group had increased faecal genus Dorea abundance (Qiu et al., 2022). Interestingly, we also found a positive causal relationship between genus *Dorea* and HSP-27 ( $\beta = 0.465$ ). In a randomized controlled trial on the diet of patients with irritable bowel syndrome, serum proinflammatory IL-6 and IL-8 levels, and faecal abundance of actinomycetes, bifidobacteria, and E. faecalis were significantly lower in patients on the low-FODMAP diet (Hustoft et al., 2017). Coincidentally, Feng et al. reduced bacterial load with shenling-bai-zhu-san, which reduced bacterial abundance including Actinobacteria and inhibited interleukin (IL)-1β, IL-6, tumour necrosis factor-a, and IL-8 (Feng et al., 2020). In accordance with our results, a decrease in IL-8 may be partly caused by reduced abundance of phylum Actinobacteria. Many studies have reported that increased order Enterobacteriales may allow endotoxins to continuously enter circulation through an impaired intestinal barrier function, inducing a systemic inflammatory response to worsen the condition of patients with chronic kidney disease (Wu et al., 2021; Liu et al., 2022). Similarly, our study suggested that order Enterobacteriales was negatively correlated to plasma KIM-1 levels. Significantly elevated plasma levels of KIM-1 usually indicate early kidney injury. During this period, KIM-1 may be involved in early injury and repair of renal tubular epithelial cells and renal interstitial fibrosis through adhesion, clearance of apoptotic cells, and the immune response (Ichimura et al., 2012). Additionally, we found that phylum and class Actinobacteria was negatively correlated to LEP, a hormone produced mainly by adipocytes and intestinal epithelial cells in the small intestines, which regulates the energy balance by suppressing appetite and reducing fat storage in adipocytes (Machleidt and Lehnert, 2011). This is consistent with the findings of Yin et al. and Marques et al. who found that lysine restriction increases appetite by increasing the abundance of Actinobacteria, Saccharibacteria, and Synergistetes (Yin et al., 2017). Similarly, Marques et al. found lower levels of Actinobacteria spp. and Prevotella, but higher levels of Bifidobacterium and Lactobacillus in the intestinal flora of a high-fat-diet-induced obese rat model

(Marques et al., 2016). These possible intermediates are caused by a decrease of LEP in plasma through Actinobacteria and Bifidobacterium. NT-proBNP is a hormone with an inactive Nterminal of 76 amino acids, which is cleaved from the molecule to release brain natriuretic peptide (Bhalla et al., 2004). Infusion of BNP at pathophysiological concentrations into hypertensive patients results in a progressive decrease in the left ventricular end-diastolic volume and left ventricular end-systolic volume as well as a reduction in cardiac preload (Atisha et al., 2004). Ly et al. found significant reductions in five bacterial species in the gut microbiota profile of early-onset preeclampsia women, including genus Methanobrevibacter (Lv et al., 2019). Thus, we hypothesized that plasma NT-proBNP decreases with the decrease in faecal genus Methanobrevibacter, which contributes to elevated blood pressure in patients. Jia et al. found an increase in the abundance of four bacteria, Lactobacillus, Actinomyces, Peptostreptococcaceae, and Alloscardovia, in the intestinal microbiota of intrahepatic cholangiocarcinoma patients (Jia et al., 2020). Furthermore, Liu et al. found that autocrine osteopontin promotes hepatic progenitor cell expansion and migration by binding to av integrins and activating SRC activity to reduce membrane Ecalmodulin and increase free cytoplasmic β-linked proteins. Moreover, this pathway plays a key role in the oncogenic transformation of hepatic progenitor cells (Liu et al., 2015). In combination with these previous studies, our findings led us to the hypothesis that the role of family Peptostreptococcaceae in the progression of tumours, including hepatocellular carcinoma, may be mediated through activation of SRC protein kinase, causing activation of downstream pathways. Tumour necrosis factor receptor 2 (TNFR2), also known as tumour necrosis factor receptor superfamily member 1B (TNFRSF1B) and CD120b, is one of two membrane receptors that bind tumour necrosis factor- $\alpha$  (TNF $\alpha$ ) (Schall et al., 1990). In a study of the effect of intermittent fasting (IF) on diabetic retinopathy, Beli et al. found that the intestinal tract of IF mice had a reduction in both Bacteroidetes and Verrucomicrobia bacteria and that IF decreased retinal TNF- $\alpha$  expression compared with mice fed ad libitum (Beli et al., 2018). Therefore, understanding whether phylum and order Verrucomicrobia are also involved in reductions of TNF-α and its membrane receptor TNF-R2 may provide another novel insight into the causal relationship between Verrucomicrobia and TNF-R2. Sickle cell disease (SCD) is an inherited blood disorder that causes intravascular haemolysis, and slow blood flow can cause microthrombosis resulting in organ damage. In 14 healthy controls and 14 SCD subjects, severe ecological dysregulation was observed in SCD patients with many flora being abundant, including the family Veillonellaceae (Brim et al., 2021). t-PA is a protein involved in thrombus breakdown. It is a serine protease that catalyses conversion of fibrinogen to fibrinolytic enzymes, the main enzyme responsible for clot breakdown (Wardlaw et al., 2012). In agreement with our results, an increase in family *Veillonellaceae* positively led to an increase in plasma t-PA. Pindjakova et al. found that, compared with mice fed a hypercholesterolemic and proatherogenic diet, low-fat diet (Paigen diet)-fed mice, *Gammaproteobacteria*, *Delataproteobacteria*, and *Erysipelotrichia* were more abundant in obese mice fed a dietary, high-fat obesogenic, but non-inflammatory diet (Pindjakova et al., 2017). Unfortunately, we did not find any correlation between class *Erysipelotrichia* and VEGF-D for the time reported. We screened 11 plasma cardiovascular proteins and found 14 causal relationships between gut microbiota and these proteins.

In fact, in addition to the effect of gut microbiota on cardiovascular disease, we found that gut microbiota influences markers for tumour progression, endocrine metabolism, and renal organism on the basis of previous studies. However, it is undeniable that our study has certain shortcomings. Due to the limitations of data from gut microbes studies, the bacterial taxa mentioned in this article were only analysed at the genus and above level and not at the level of more specific species or strains. Our sample sizes of gut microbiota and cardiovascular proteins were not very large compared with some MR analyses with different aims. Moreover, the number of SNPs representative of each microbiota was relatively small. Further large-scale RCT clinical trials and studies of biological mechanisms are needed.

Overall, we comprehensively assessed the potential causal relationship between gut microbiota and cardiovascular protein expression. Combined with other studies, we partially confirmed our conclusions. Therefore, this study may provide new insights into microbially mediated alterations in cardiovascular protein levels.

#### Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

# **Ethics statement**

Studies involving human participants were reviewed and approved, and all studies were approved by their respective institutional review boards. No new data were collected and no new institutional review boards' approval was required.

# Author contributions

All authors contributed to the work presented in this paper. Conceptualisation, WZ and ZW. Resources, visualisation, and analysis, SZ, FZ and JD. writing—original draft preparation, WZ and SZ. writing—editing, ZW. supervision, ZW. project administration, WZ and ZW. funding acquisition, FZ and ZW. All authors approved the submitted version.

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# **Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/ fcimb.2022.1048519/full#supplementary-material

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