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ORIGINAL ARTICLE

Gut Microbiota, Disorders of Gut-Brain Interaction and Psychiatric Disorders: a Mendelian Randomization Study

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SUMMARY

Background: **Observational studies suggest that there are associations among gut microbiota, disorders of gut–brain interaction (DGBIs) and psychiatric disorders. Therefore, the aim of this study was to use Mendelian randomization (MR) to systematically identify the causality of the associations among the abundances of several gut microbiota and the risk of developing DGBIs and psychiatric disorders.**

Methods: **Genetic data associated with gut microbiota, DGBIs, and psychiatric disorders were obtained from large-scale genome-wide association studies (GWASs). Inverse-variance weighting, MR-Egger, and weighted median methods were used to examine causal associations. The sensitivity analyses were conducted via the MR-Egger intercept test, Cochran's Q test, MR-pleiotropy residual sum and outlier (MR-PRESSO) test, leave-one-out analysis, and funnel plots. Reverse-MR analysis was performed to evaluate the possibility of reverse causation. Finally, we used MR mediation analysis to explore potential mediators of the causal associations among the abundances of gut microbiota and the risk of developing DGBIs and psychiatric disorders.**

Results: **Our MR analysis revealed 44 causal relationships between the abundances of several gut microbiota and the risk of developing DGBIs and 66 causal relationships between the abundances of several gut microbiota and the risk of developing psychiatric disorders. In addition, in the reverse-MR analysis, 15 causal relationships between the risk of developing DGBIs and the abundances of several gut microbiota and 47 causal relationships between the risk of developing psychiatric disorders and the abundances of several gut microbiota were explored. Our results showed that the abundances of some microbiota and their child taxa might be closely associated with the risk of developing certain diseases. Moreover, we observed one causal relationship between the risk of developing DGBIs and the risk of developing psychiatric disorders and 7 causal relationships between the risk of developing psychiatric disorders and the risk of developing DGBIs. Compared with the causal effect of the risk of developing DGBIs on the risk of developing psychiatric disorders, the risk of developing psychiatric disorders was more likely to causally influence the risk of developing DGBIs. Further sensitivity analyses reinforced the robustness of these results.**

Conclusions: **Our results indicate potential genetic predispositions linking gut microbiota, DGBIs, and psychiatric disorders. This information may be useful for providing new insights into the underlying pathophysiological modulators and treatment strategies for bidirectional dysregulation of brain-gut interactions.**

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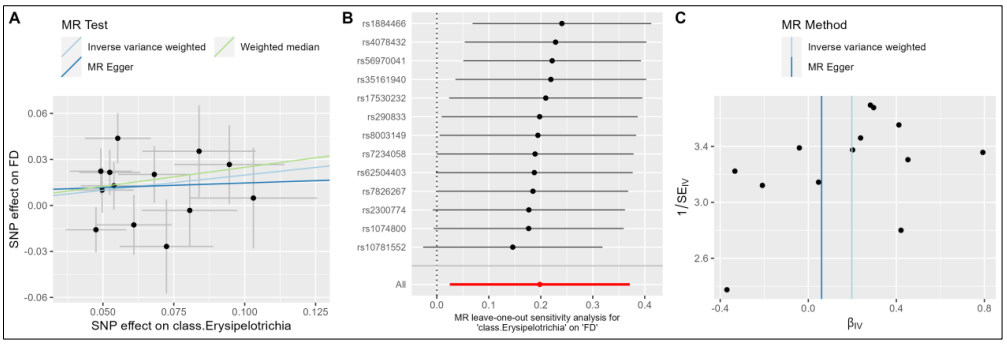
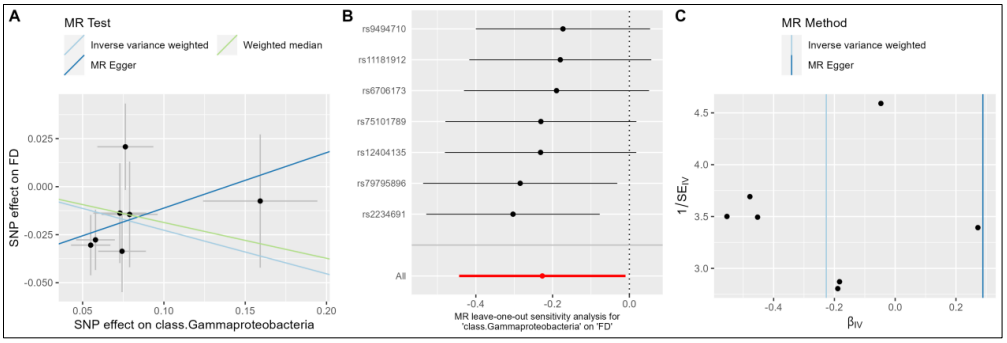
Supplementary Data

Figure S1. Scatter plots (A), leave-one-out plots (B) and funnel plots (C) of positive MR results for the causal effects of the abundances of several gut microbiota on the risk of developing DGBIs.

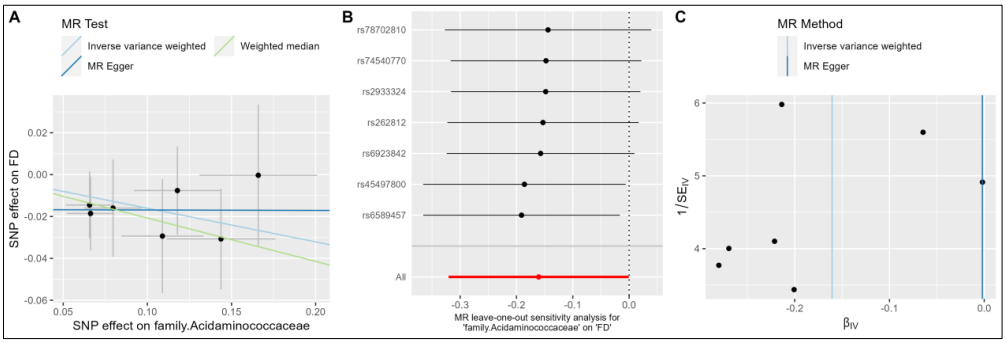
Exposure: class.Erysipelotrichia; Outcome: FD



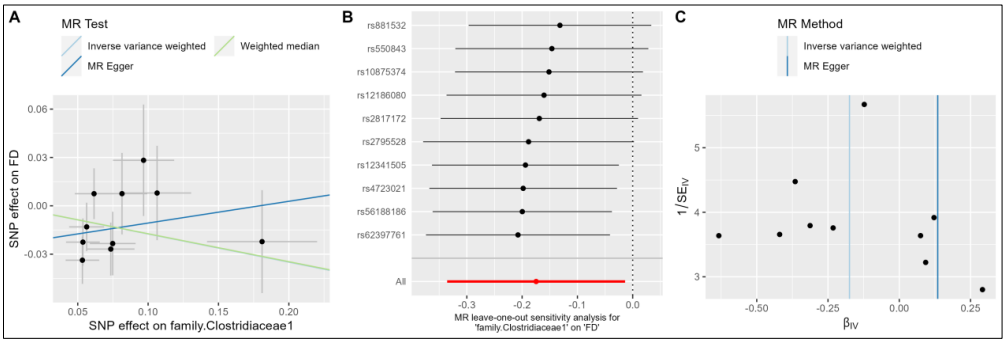
Exposure: class.Gammaproteobacteria; Outcome: FD



Exposure: family.Acidaminococcaceae; Outcome: FD



Exposure: family.Clostridiaceae1; Outcome: FD



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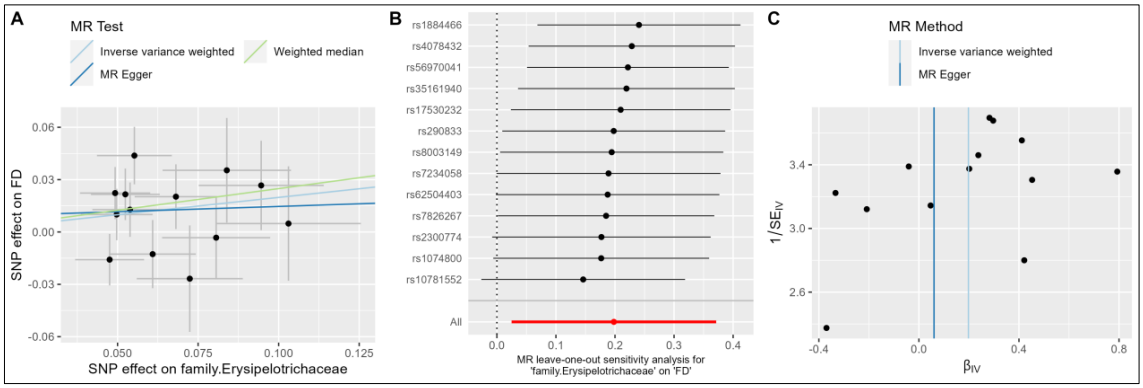
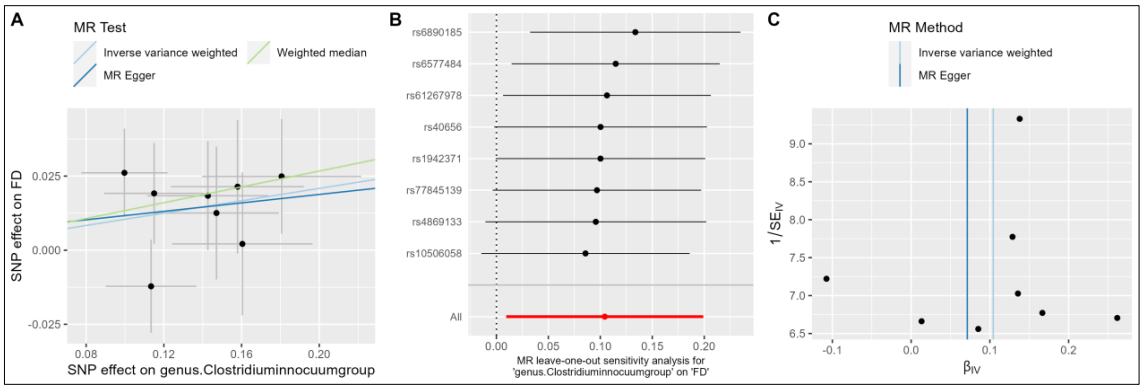
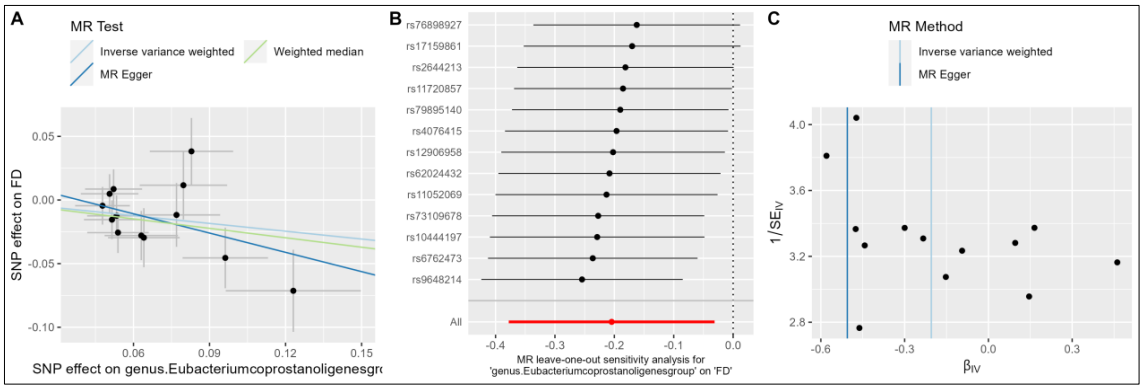


Exposure: genus.Clostridiuminnocuumgroup; Outcome: FD



Exposure: genus.Eubacteriumcoprostanoligenesgroup; Outcome: FD



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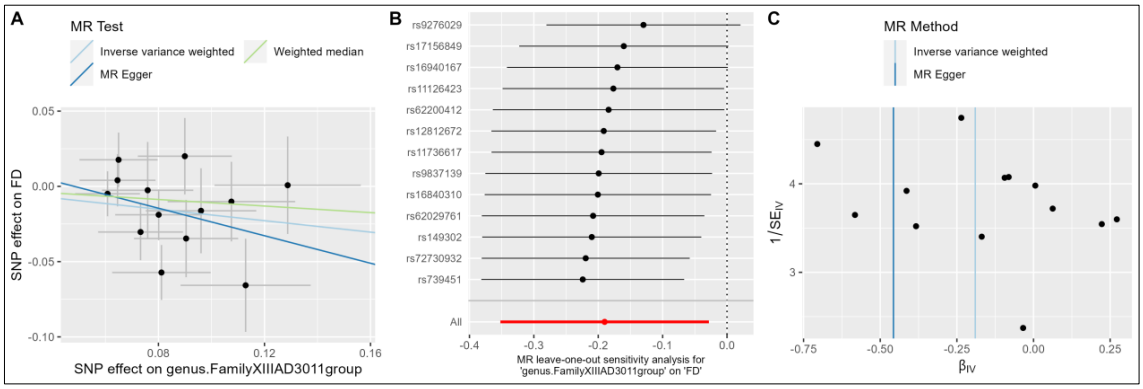

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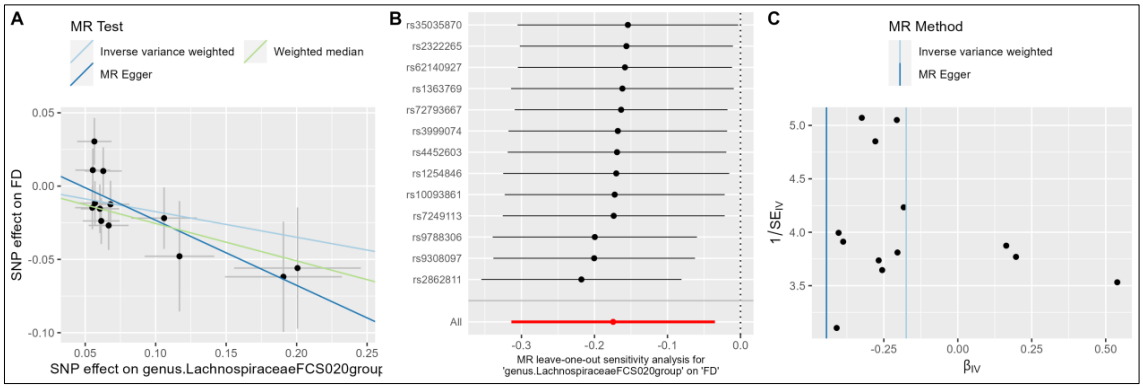

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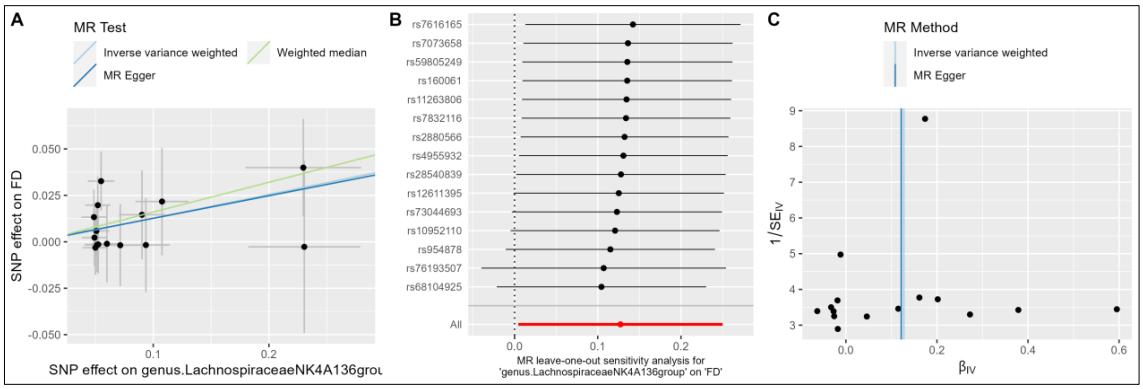
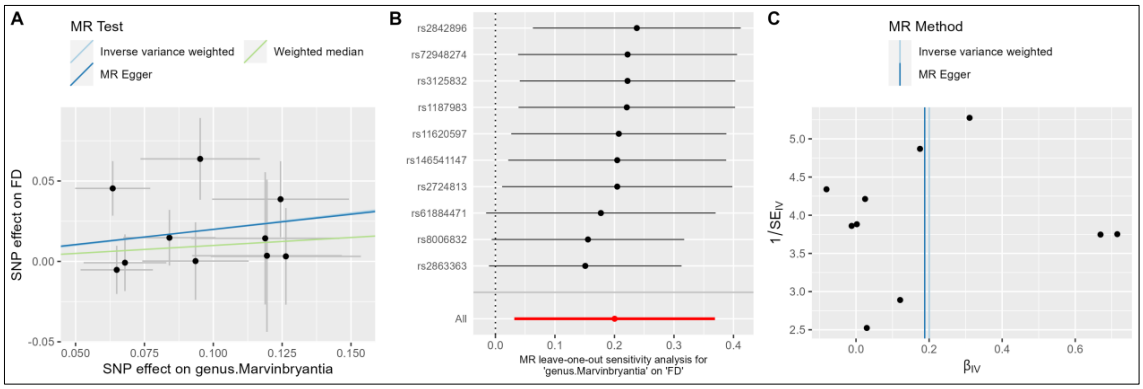
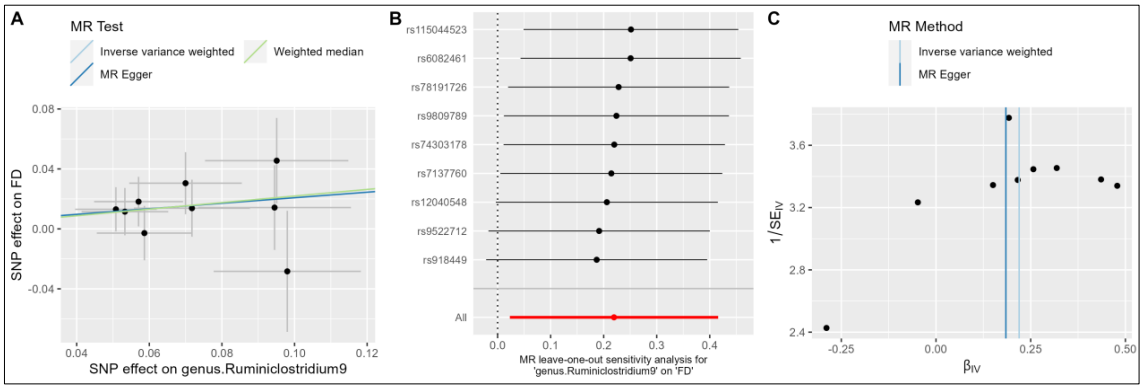


Exposure: genus.Marvinbryantia; Outcome: FD



Exposure: genus.Ruminiclostridium9; Outcome: FD



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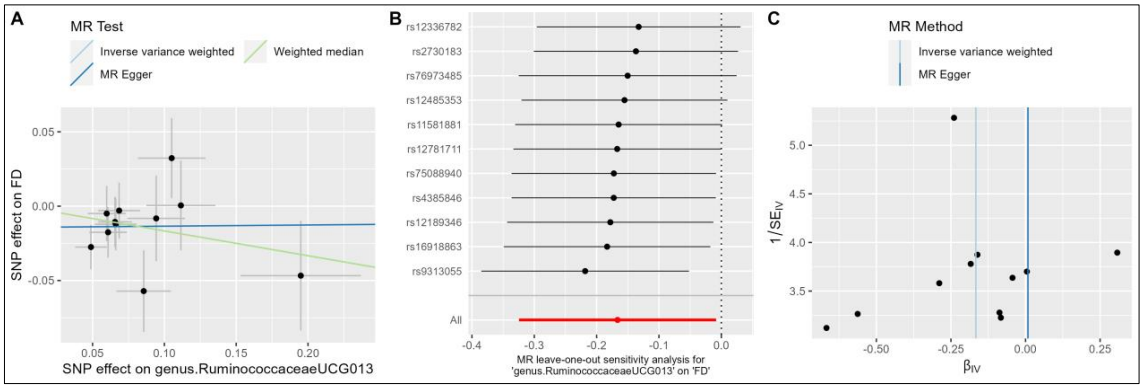
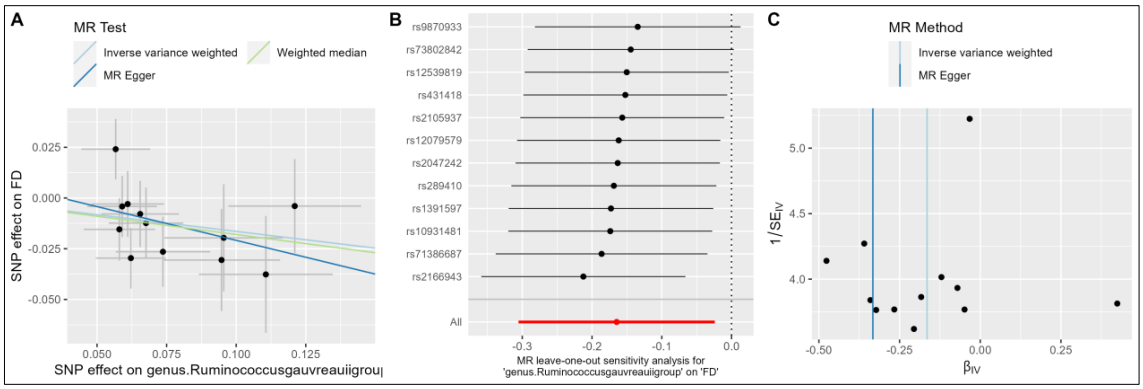
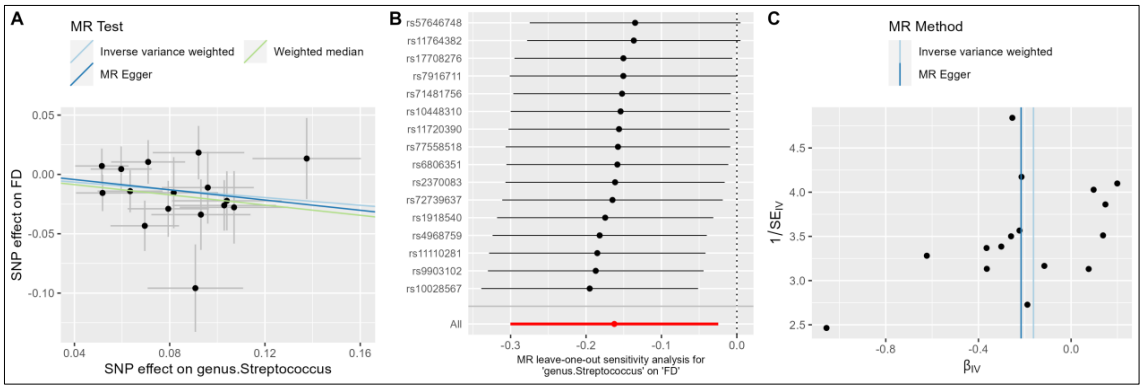


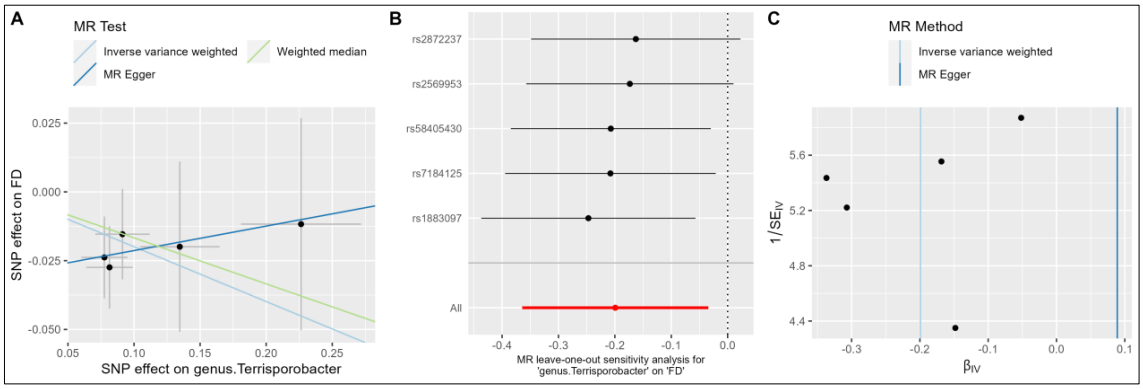
Exposure: genus.Ruminococcusgauvreauiigroup; Outcome: FD



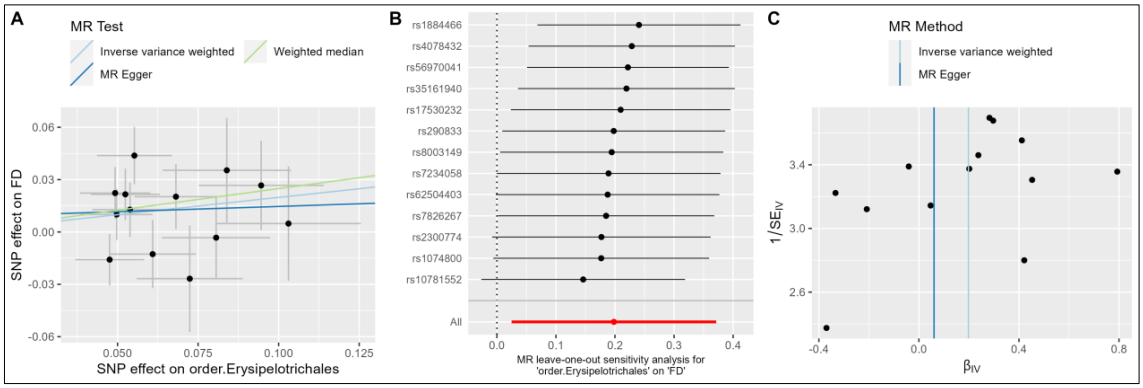
Exposure: genus.Streptococcus; Outcome: FD



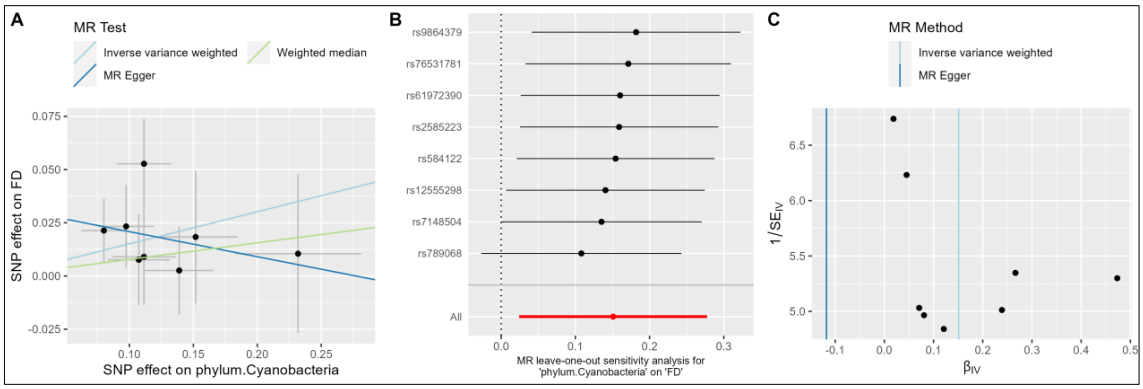
Exposure: genus.Terrisporobacter; Outcome: FD



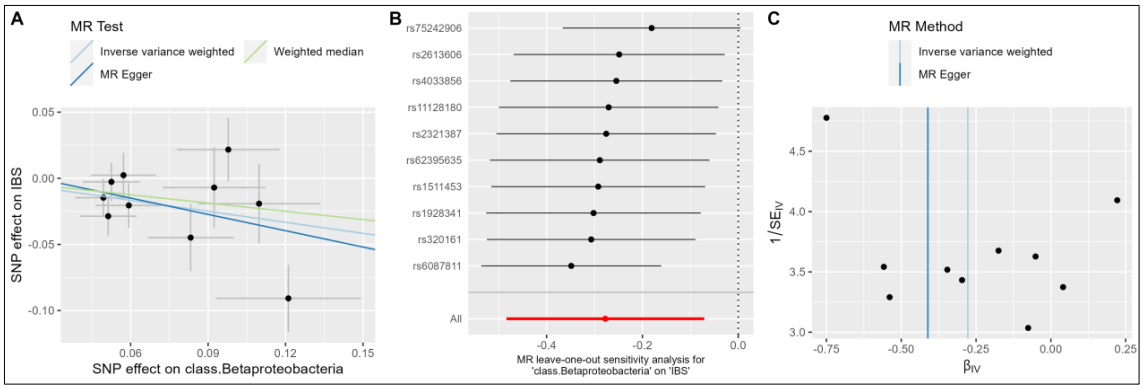
Exposure: order.Erysipelotrichales; Outcome: FD



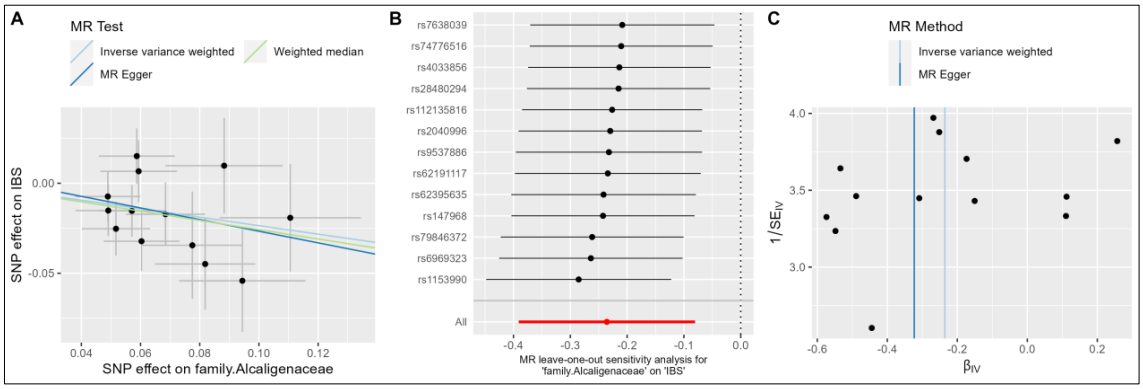
Exposure: phylum.Cyanobacteria; Outcome: FD



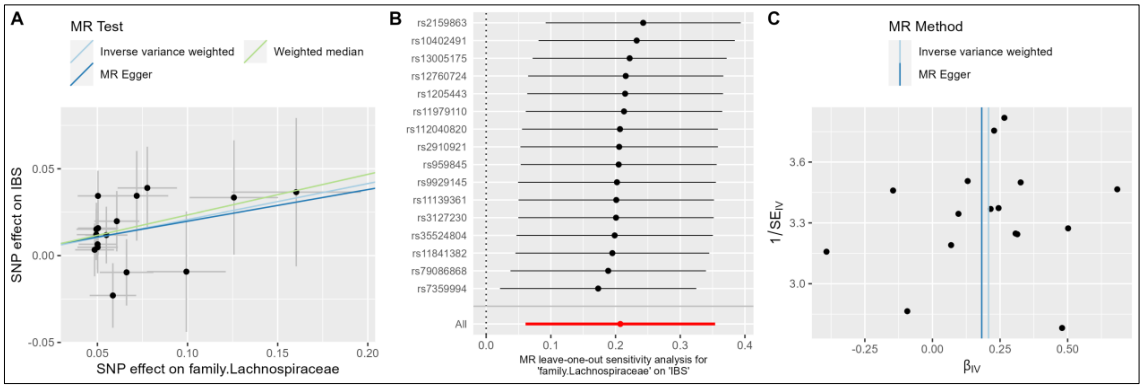
Exposure: class.Betaproteobacteria; Outcome: IBS



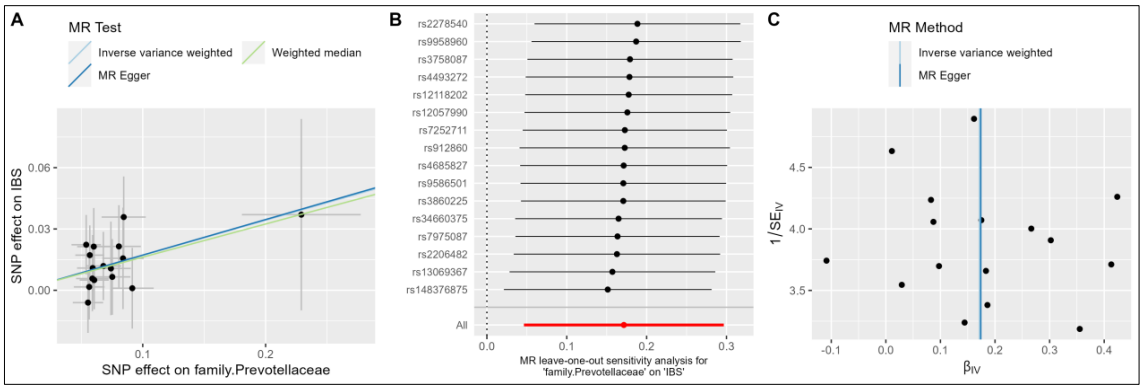
Exposure: family.Alcaligenaceae; Outcome: IBS



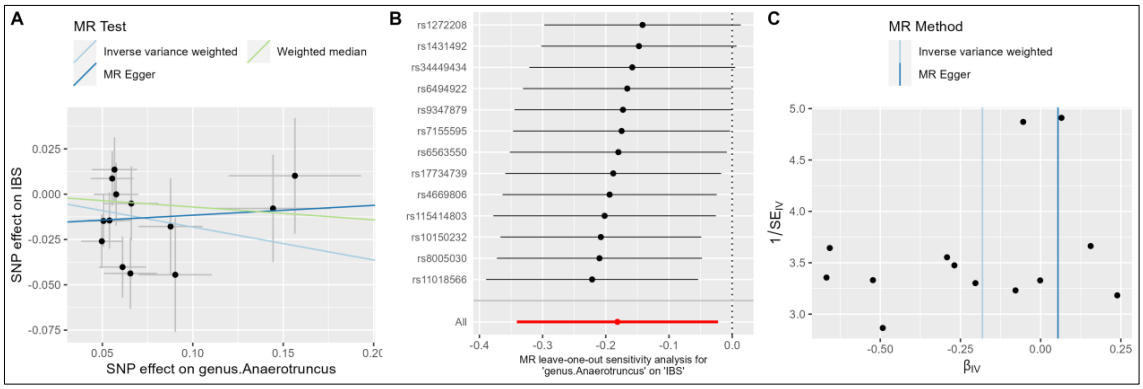
Exposure: family.Lachnospiraceae; Outcome: IBS



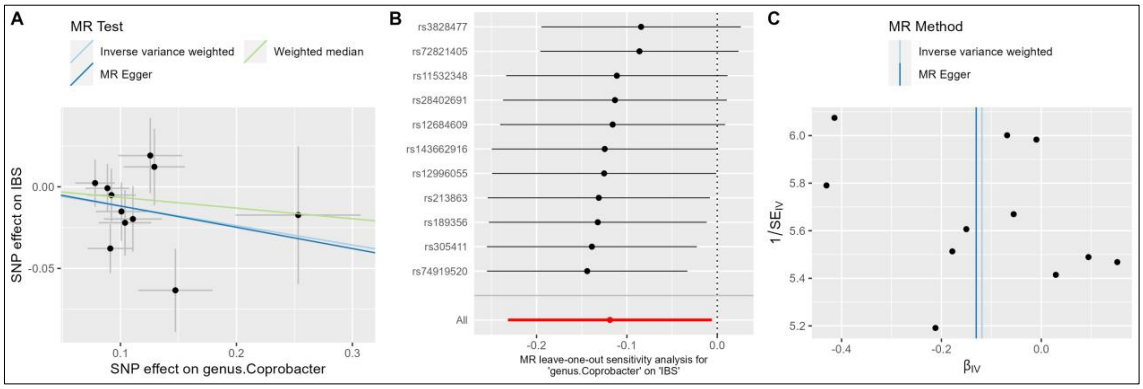
Exposure: family.Prevotellaceae; Outcome: IBS



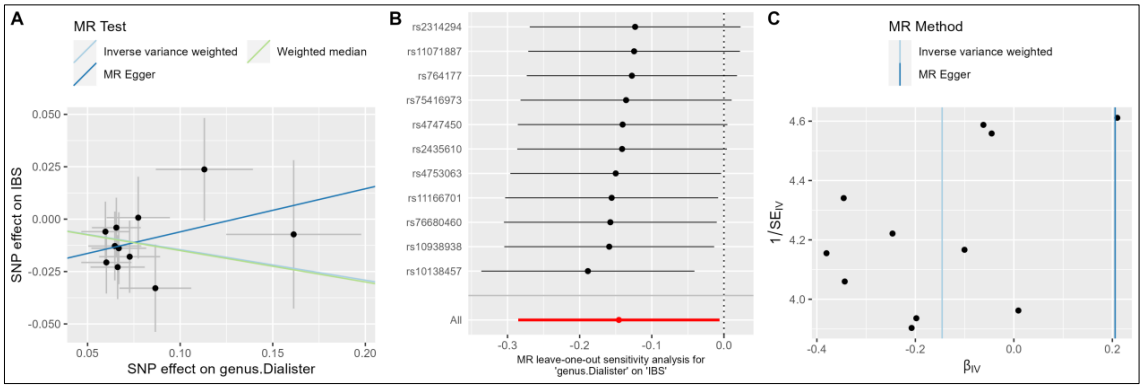
Exposure: genus.Anaerotruncus; Outcome: IBS



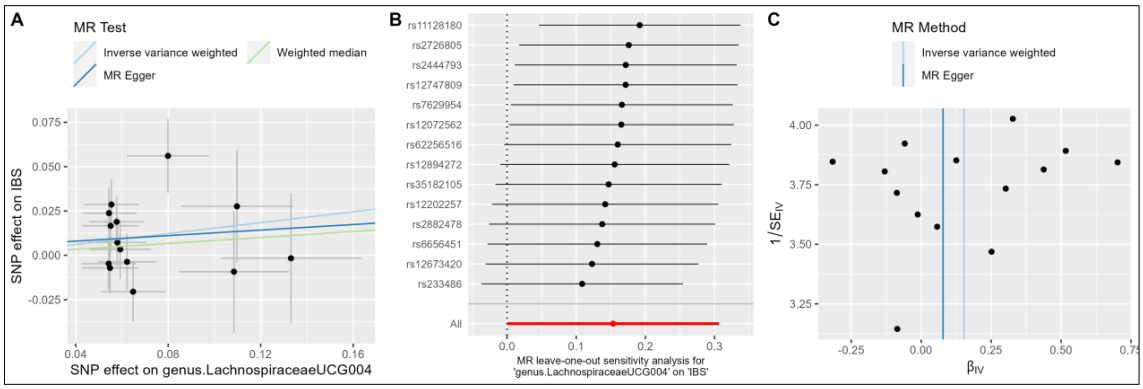
Exposure: genus.Coprobacter; Outcome: IBS



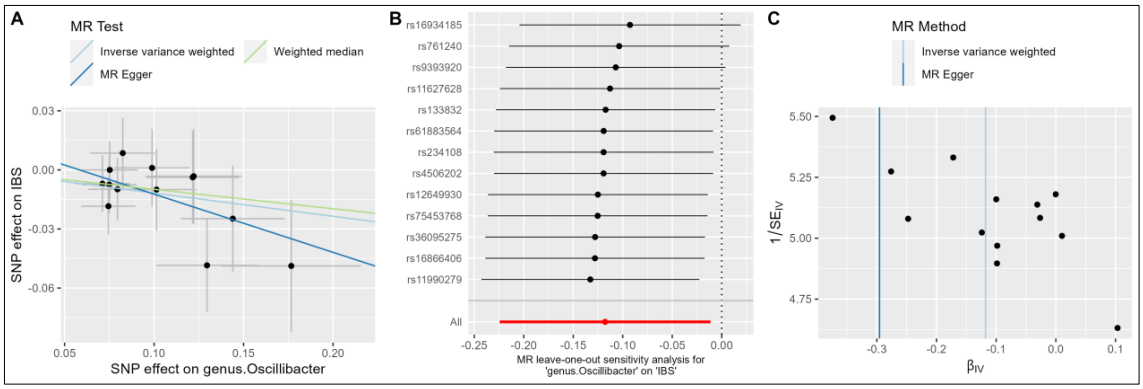
Exposure: genus.Dialister; Outcome: IBS



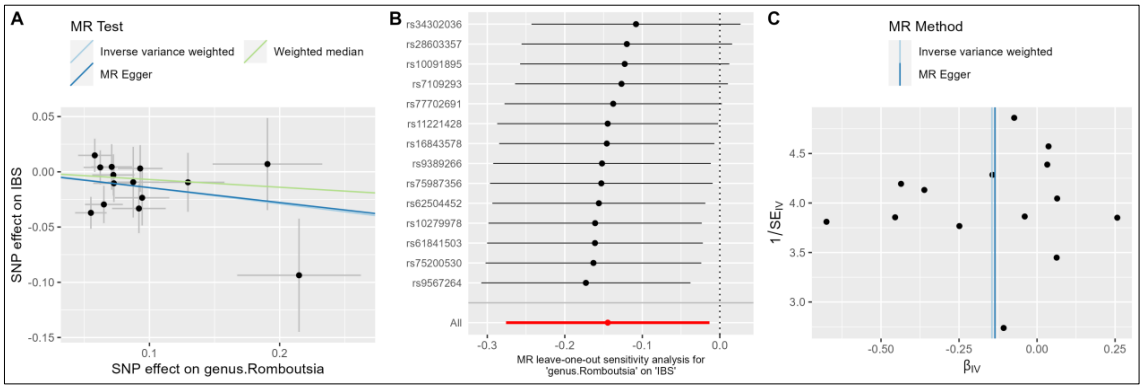
Exposure: genus.LachnospiraceaeUCG004; Outcome: IBS



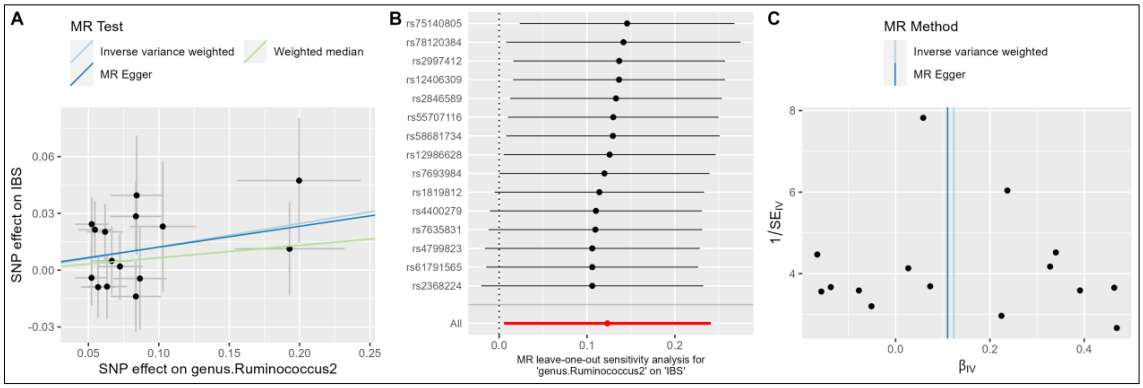
Exposure: genus.Oscillibacter; Outcome: IBS



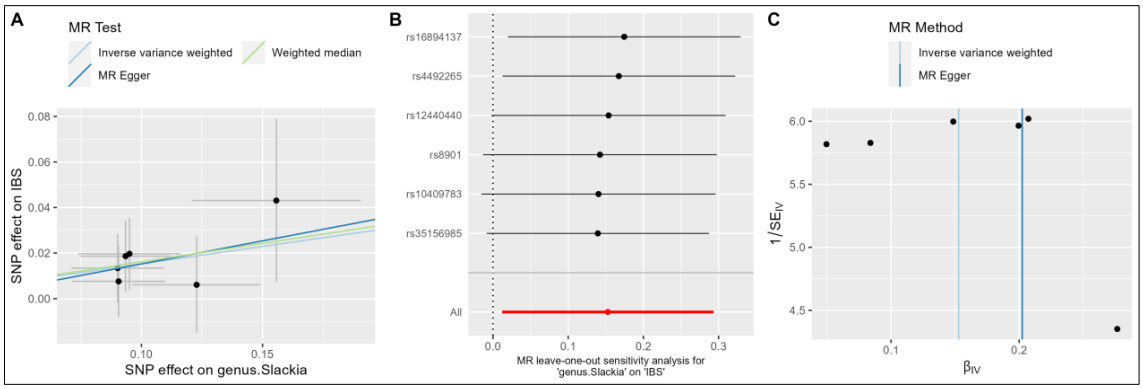
Exposure: genus.Romboutsia; Outcome: IBS



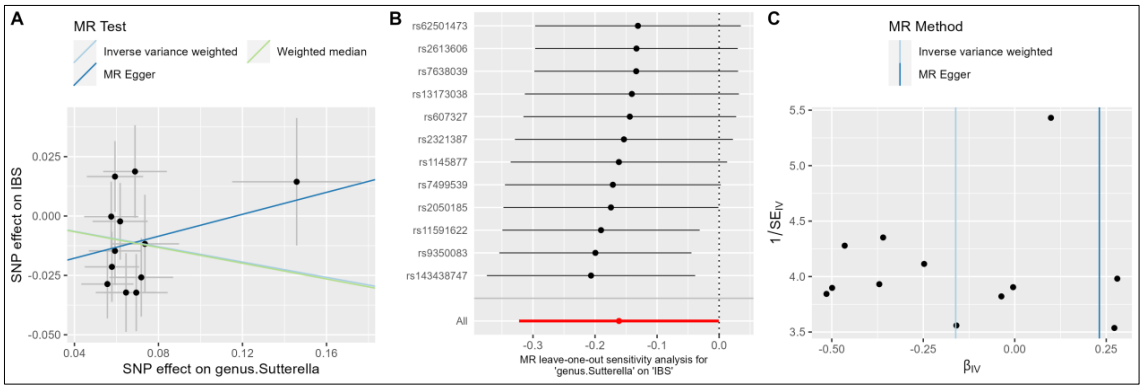
Exposure: genus.Ruminococcus2; Outcome: IBS



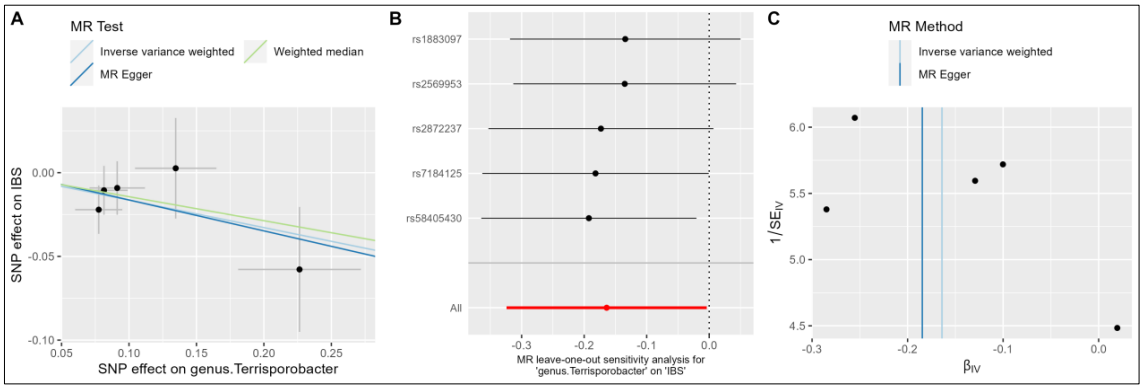
Exposure: genus.Slackia; Outcome: IBS



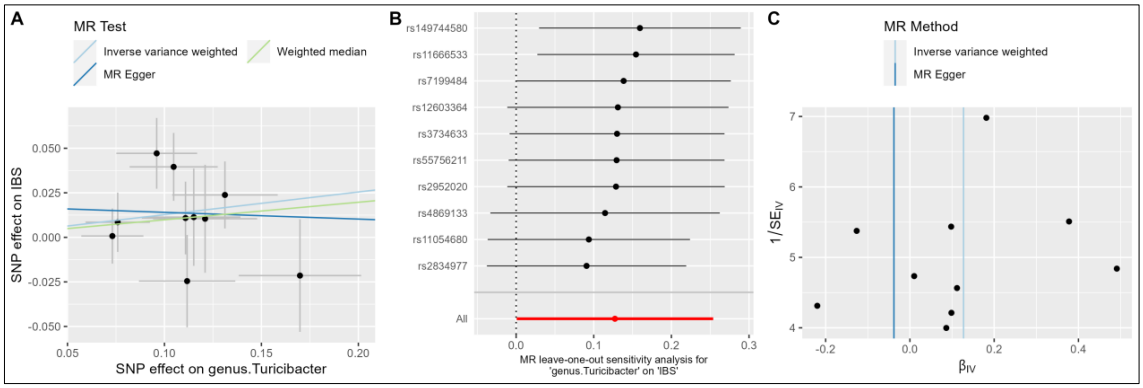
Exposure: genus.Sutterella; Outcome: IBS



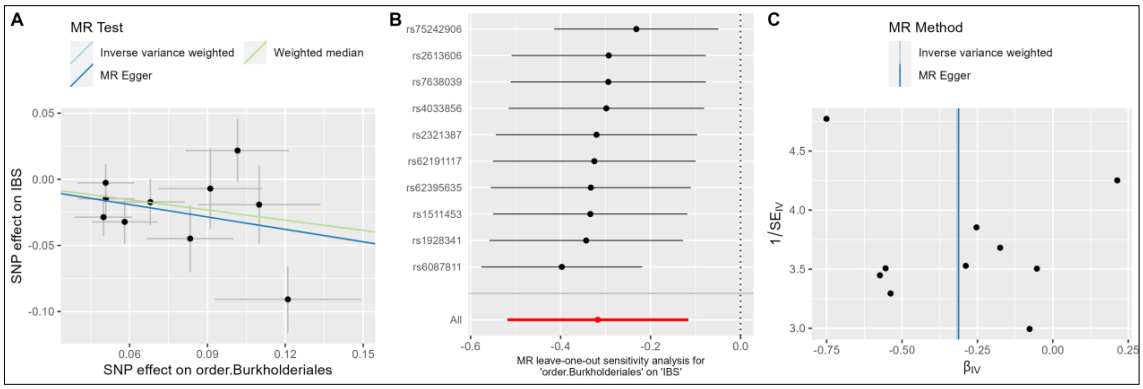
Exposure: genus.Terrisporobacter; Outcome: IBS



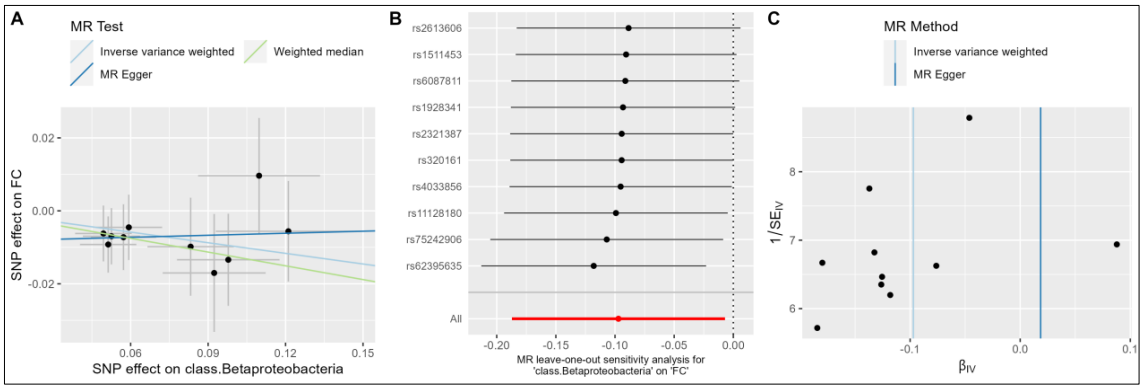
Exposure: genus.Turicibacter; Outcome: IBS



Exposure: order.Burkholderiales; Outcome: IBS



Exposure: class.Betaproteobacteria; Outcome: FC



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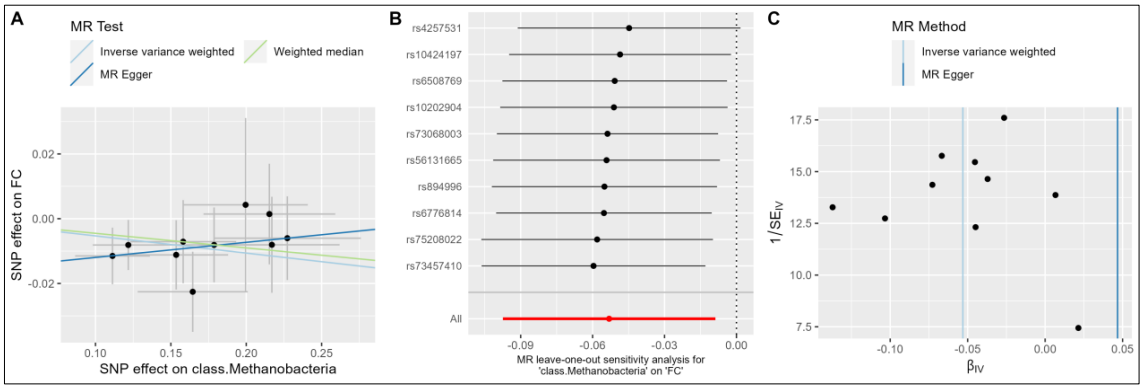

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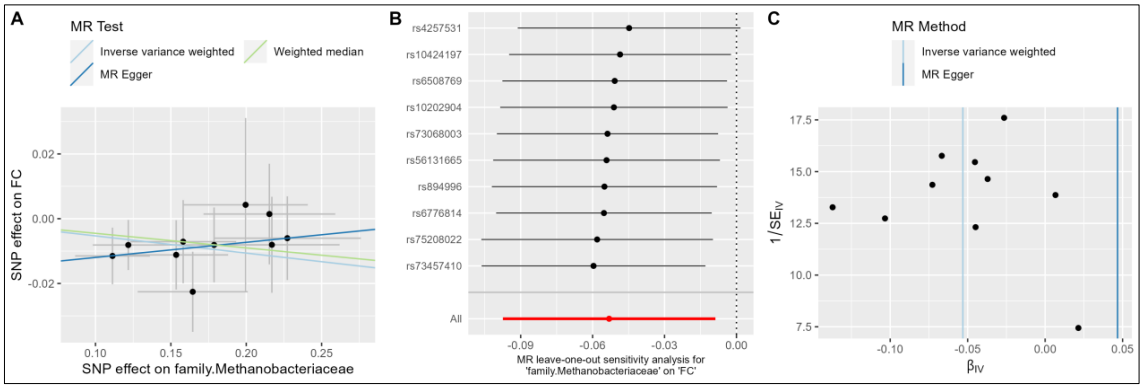
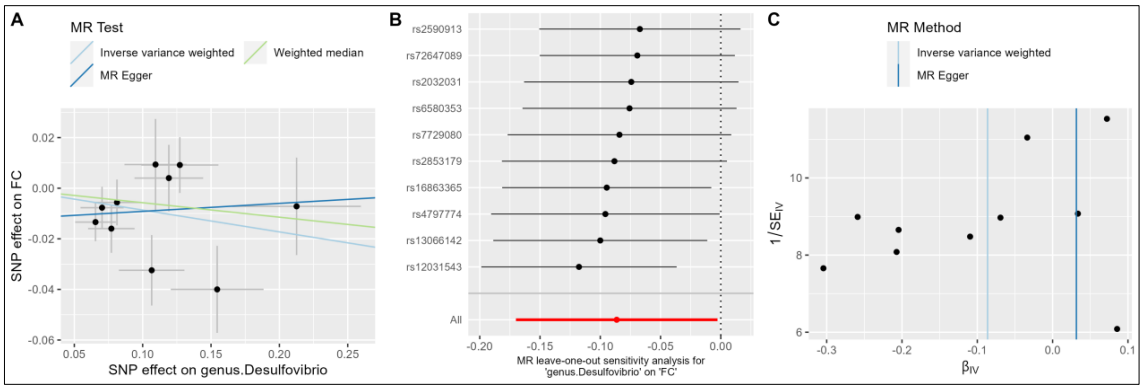


Exposure: genus.Desulfovibrio; Outcome: FC



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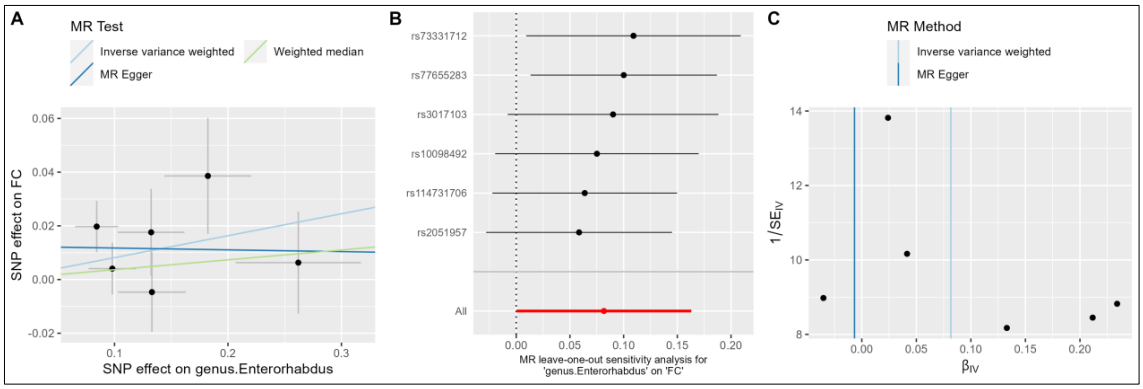
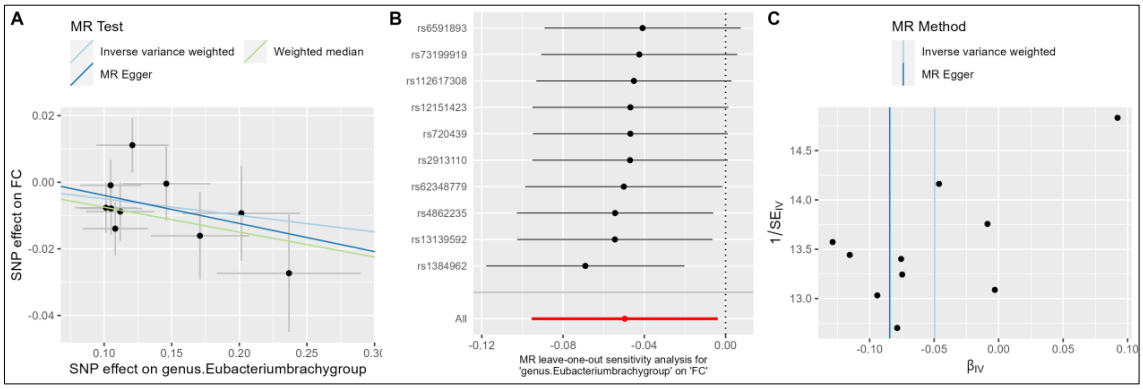
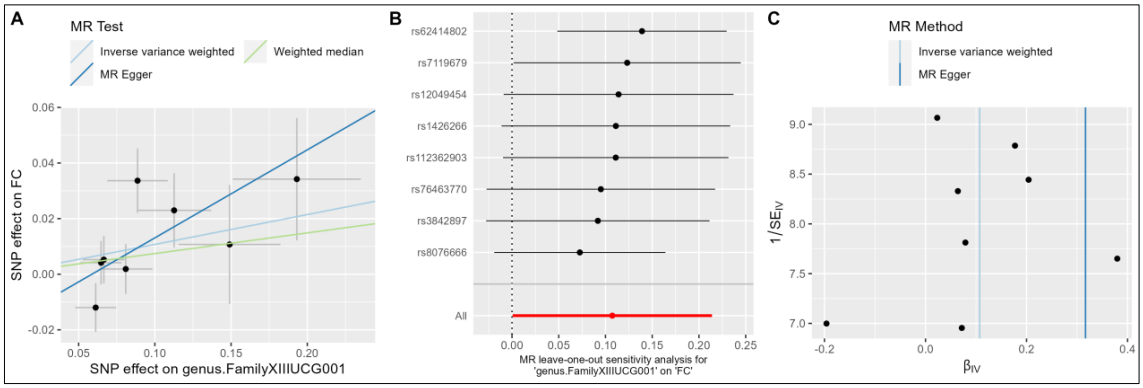


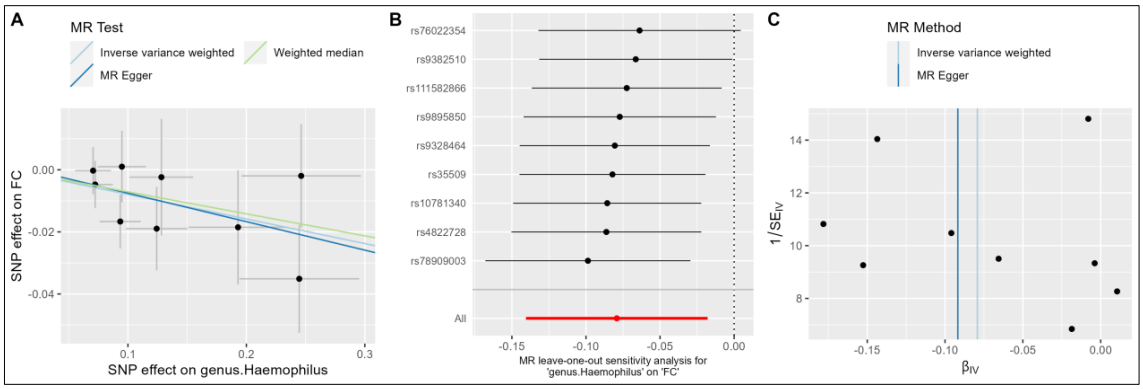
Exposure: genus.Eubacteriumbrachygroup; Outcome: FC



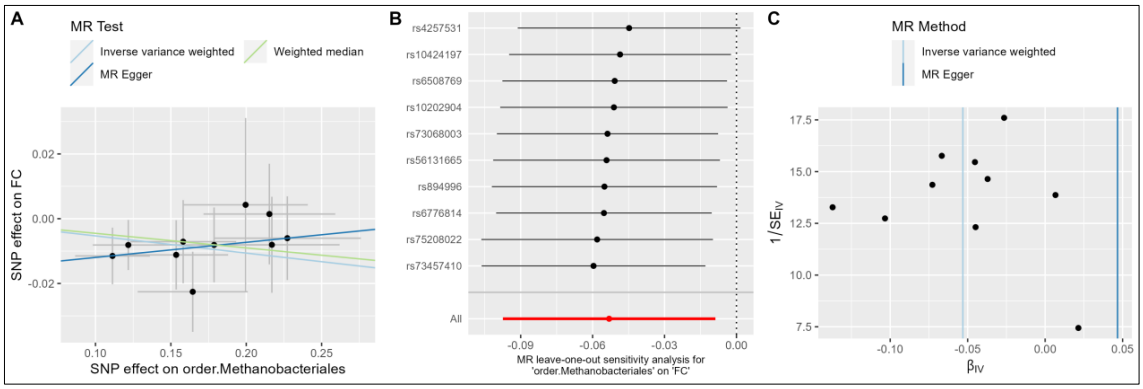
Exposure: genus.FamilyXIIIUCG001; Outcome: FC



Exposure: genus.Haemophilus; Outcome: FC



Exposure: order.Methanobacteriales; Outcome: FC



Exposure: phylum.Firmicutes; Outcome: FC

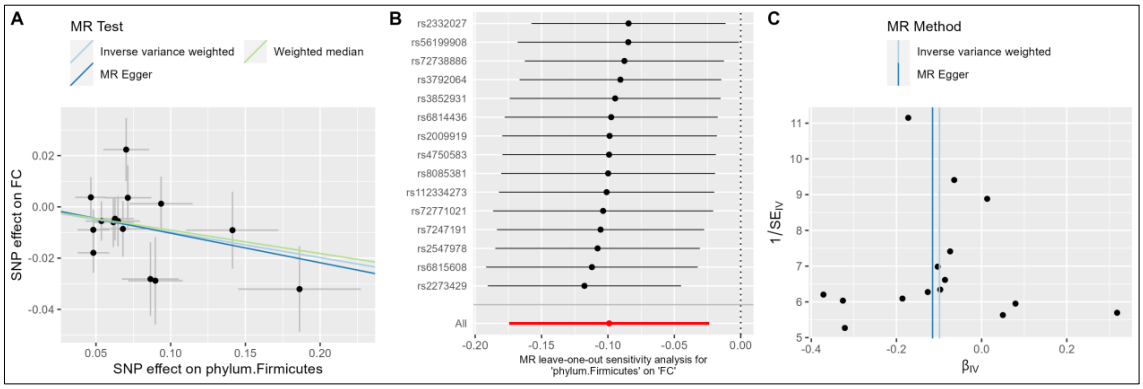
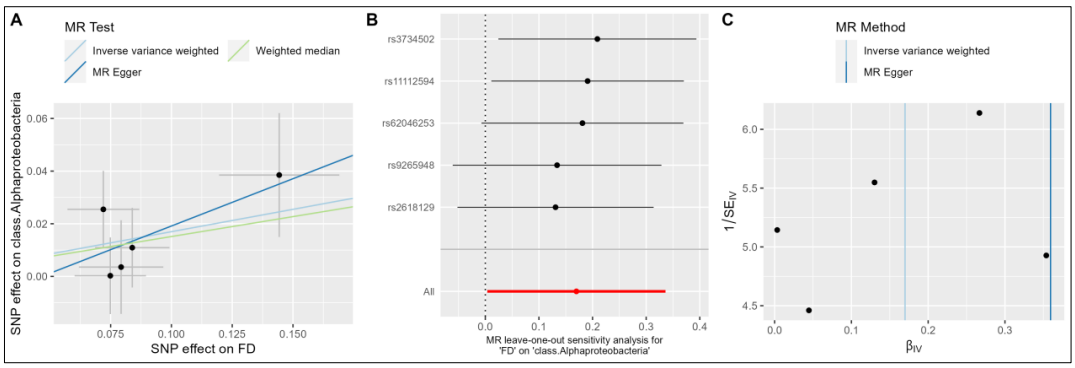
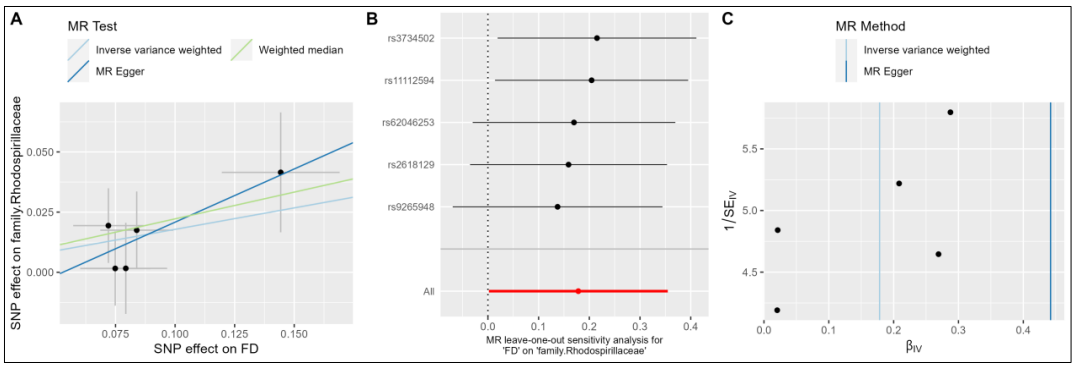


Figure S2. Scatter plots (A), leave-one-out plot (B) and funnel plot (C) of positive MR results for the causal effects of the risk of developing DGBIs on the abundances of several gut microbiota.

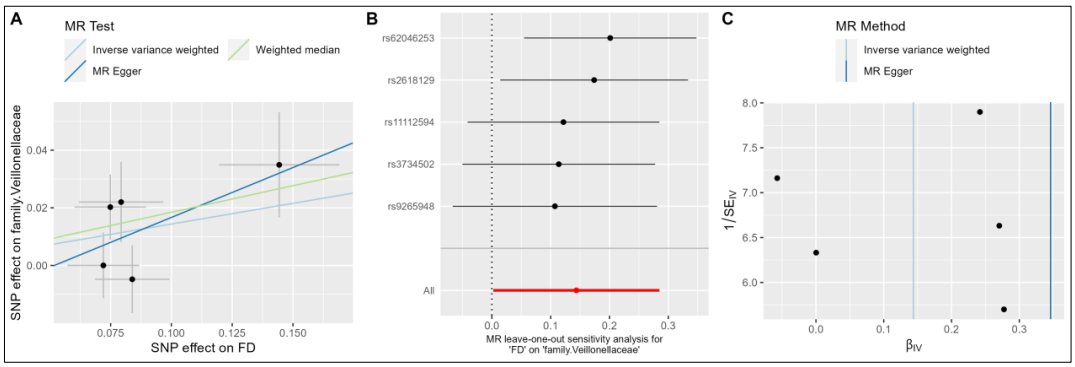
Exposure: FD; Outcome: class.Alphaproteobacteria



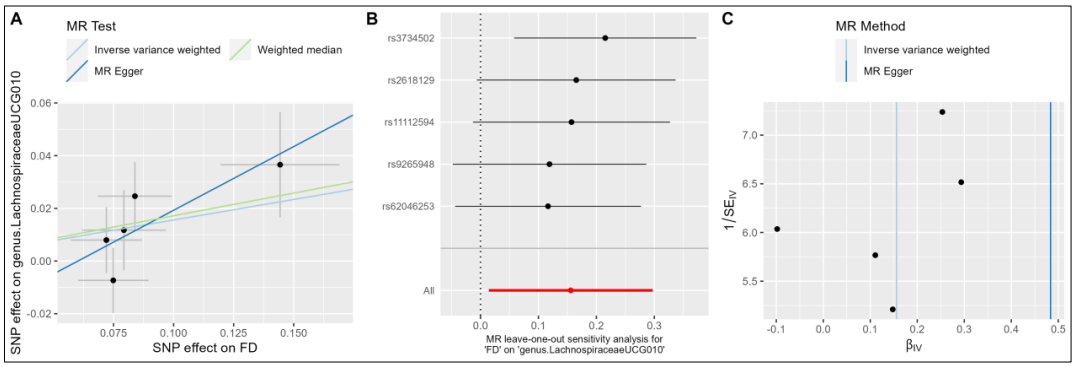
Exposure: FD; Outcome: family.Rhodospirillaceae



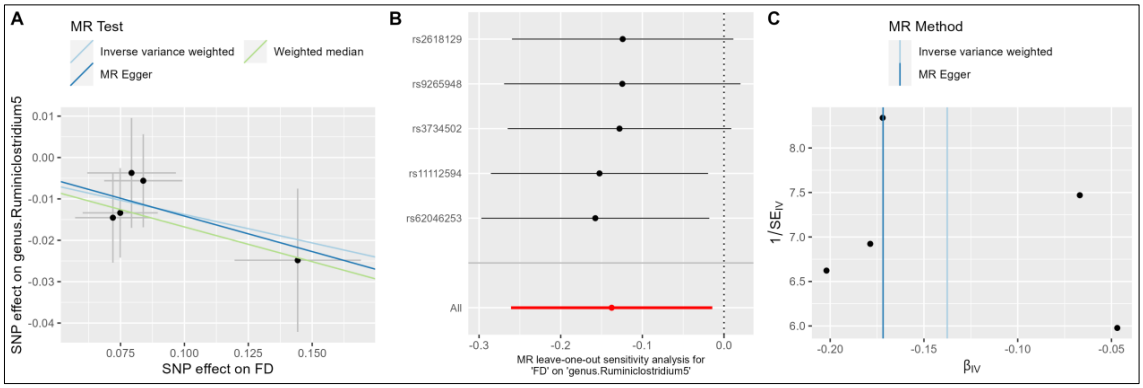
Exposure: FD; Outcome: family.Veillonellaceae



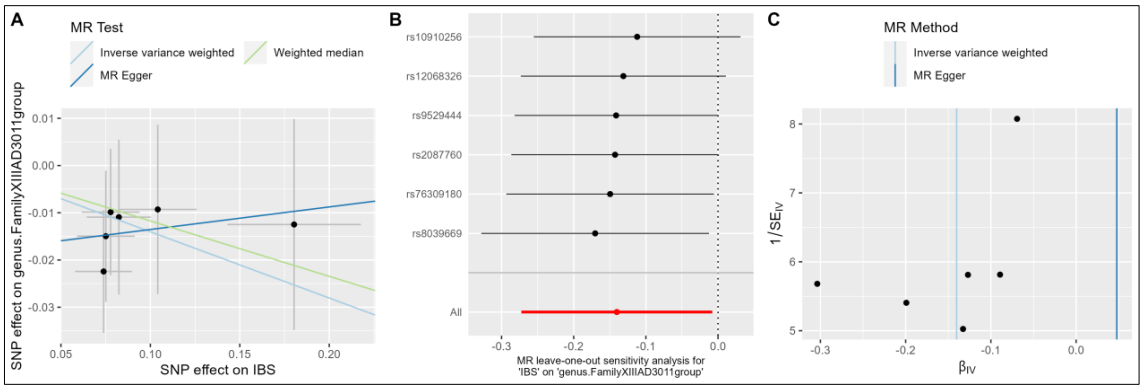
Exposure: FD; Outcome: genus.LachnospiraceaeUCG010



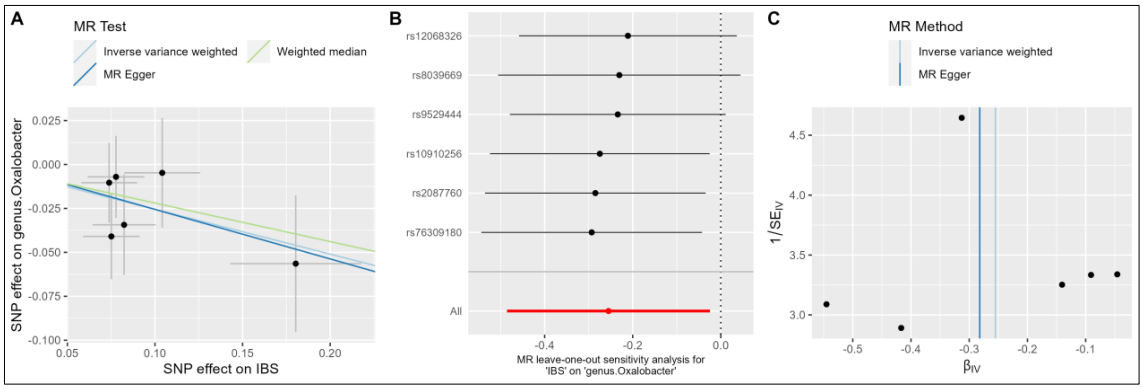
Exposure: FD; Outcome: genus.Ruminiclostridium5



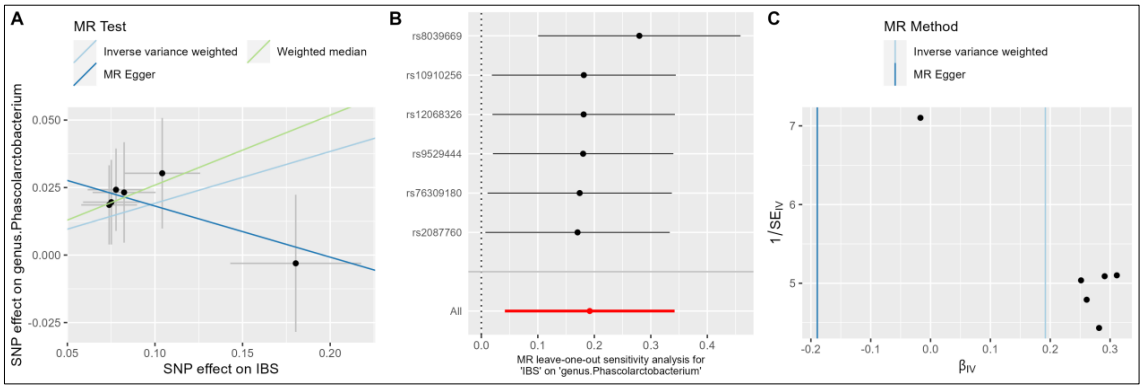
Exposure: IBS; Outcome: genus.FamilyXIIIAD3011group



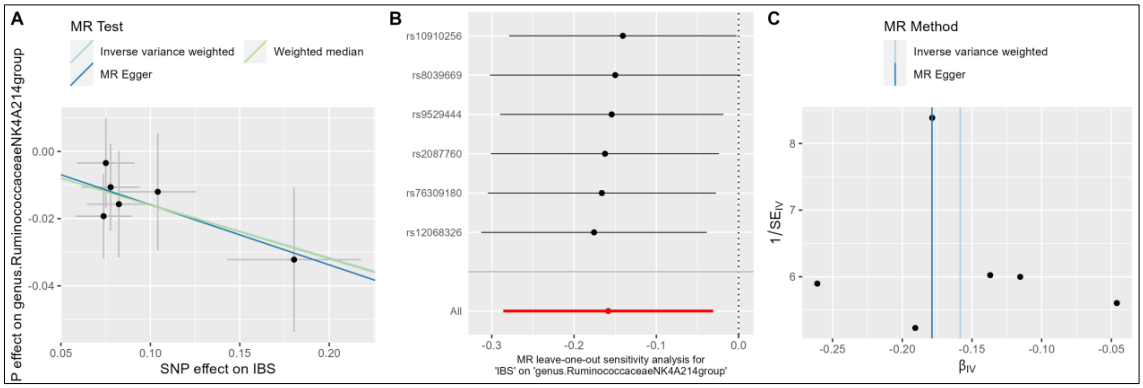
Exposure: IBS; Outcome: genus.Oxalobacter



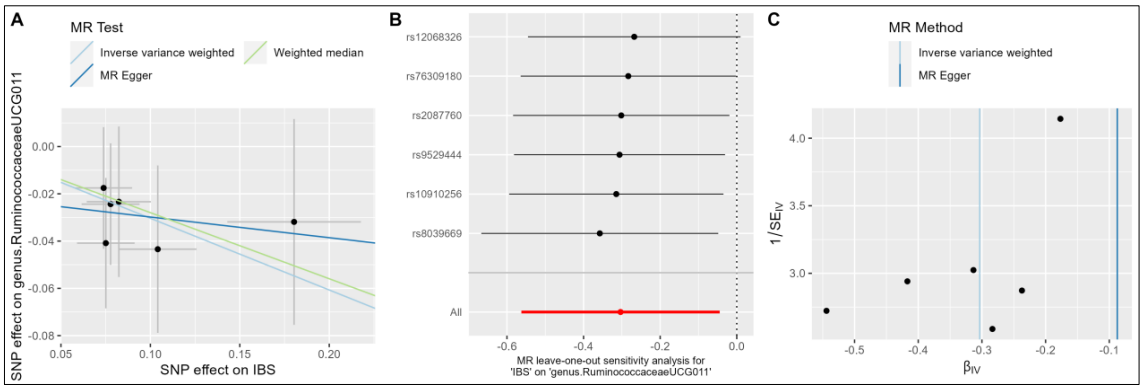
Exposure: IBS; Outcome: genus.Phascolarctobacterium



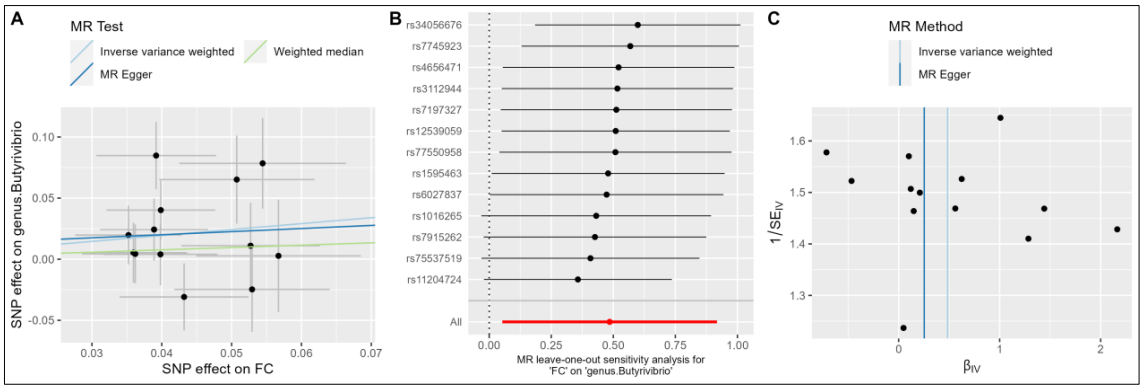
Exposure: IBS; Outcome: genus.RuminococcaceaeNK4A214group



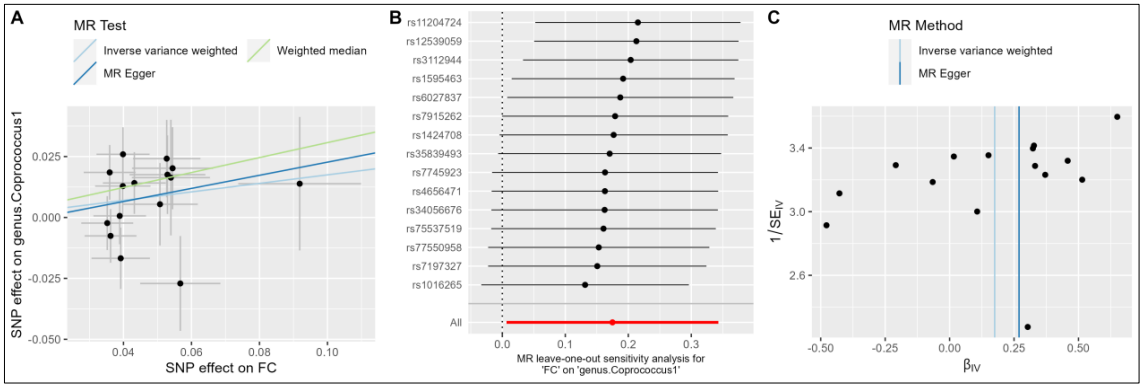
Exposure: IBS; Outcome: genus.RuminococcaceaeUCG011



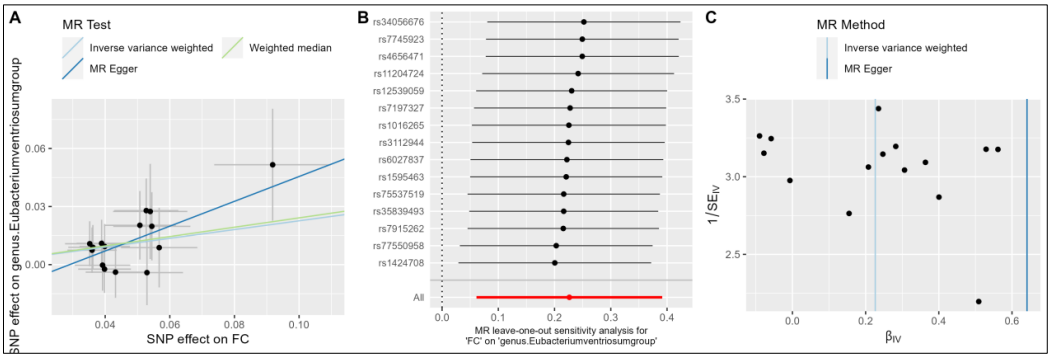
Exposure: FC; Outcome: genus.Butyrivibrio



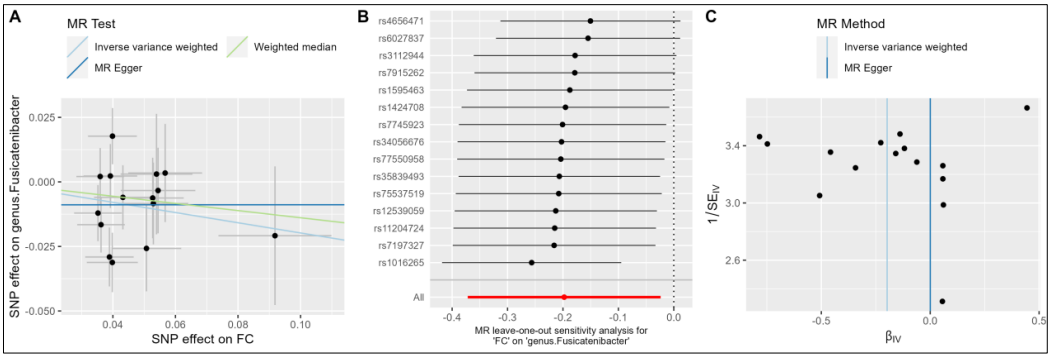
Exposure: FC; Outcome: genus.Coprococcus1



Exposure: FC; Outcome: genus.Eubacteriumventriosumgroup



Exposure: FC; Outcome: genus.Fusicatenibacter



Exposure: FC; Outcome: genus.Ruminococcus2

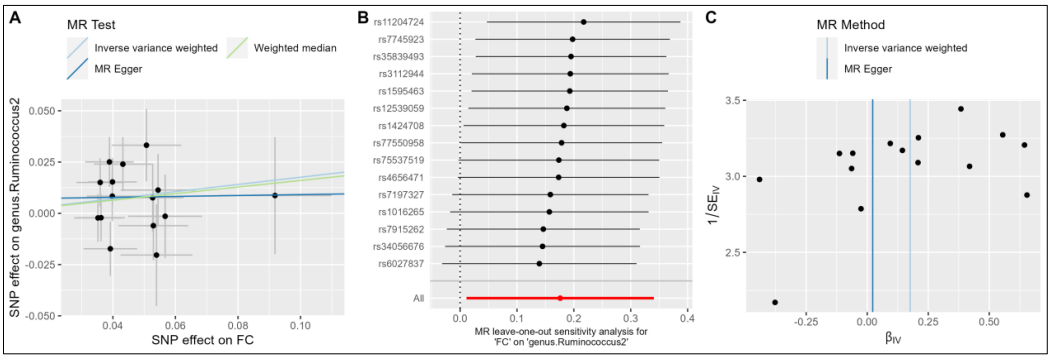
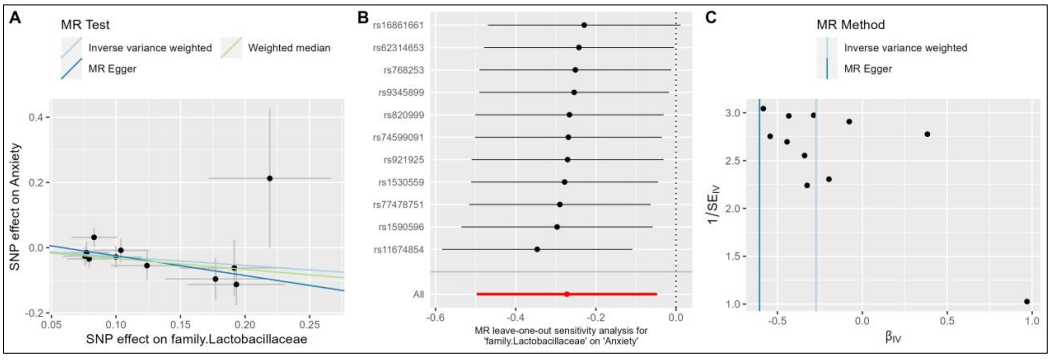
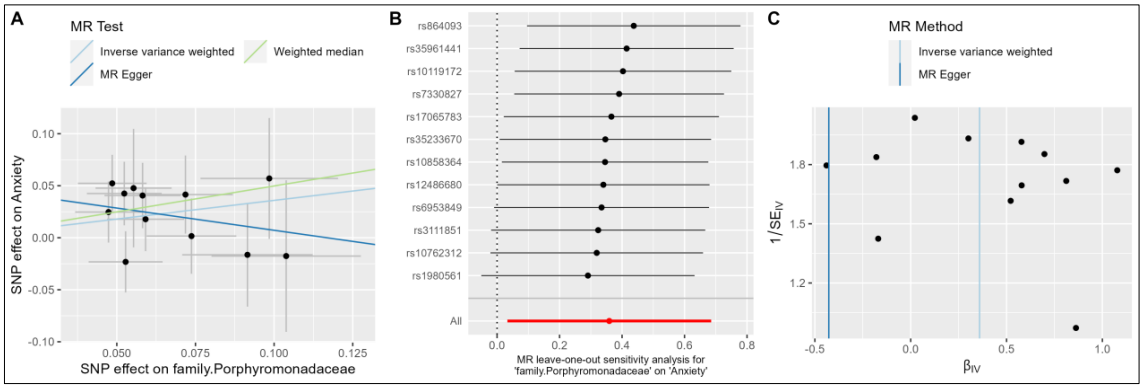


Figure S3. Scatter plots (A), leave-one-out plot (B) and funnel plot (C) of positive MR results for the causal effects of the abundances of several gut microbiota on the risk of developing psychiatric disorders.

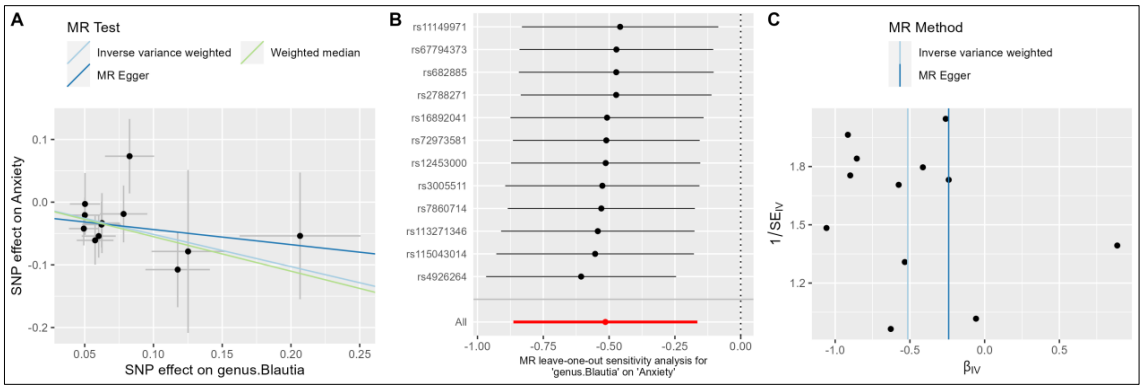
Exposure: family.Lactobacillaceae; Outcome: Anxiety



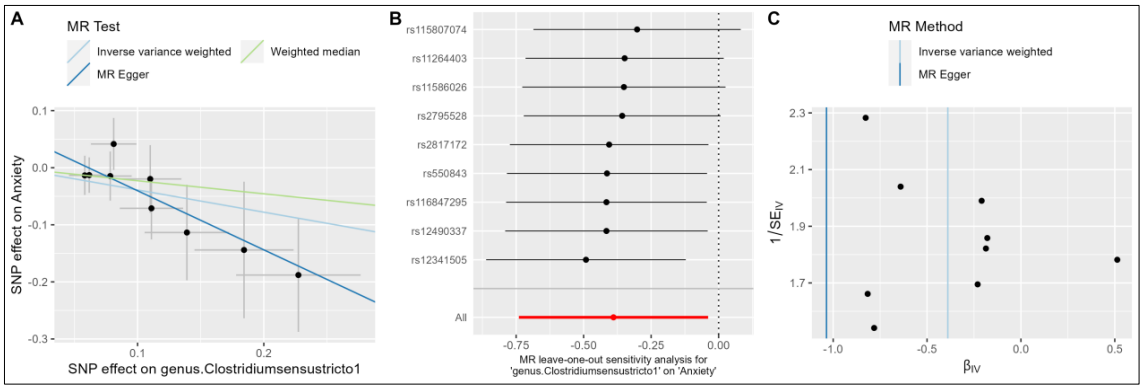
Exposure: family.Porphyromonadaceae; Outcome: Anxiety



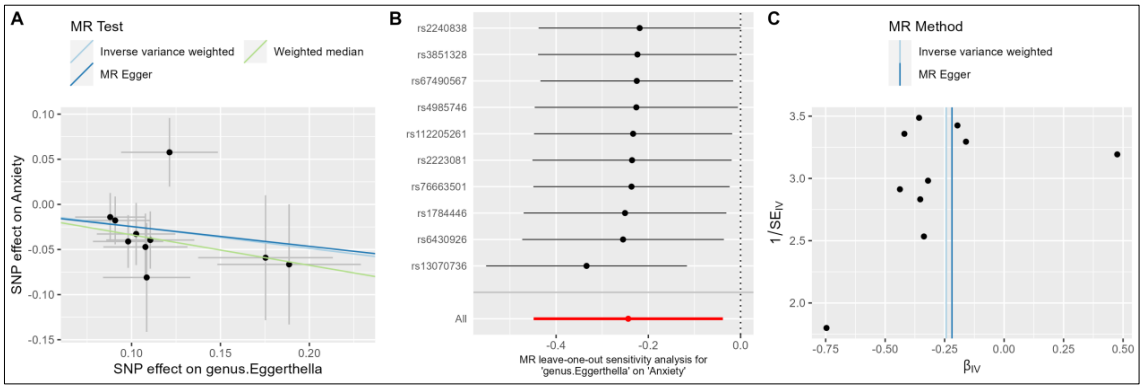
Exposure: genus.Blautia; Outcome: Anxiety



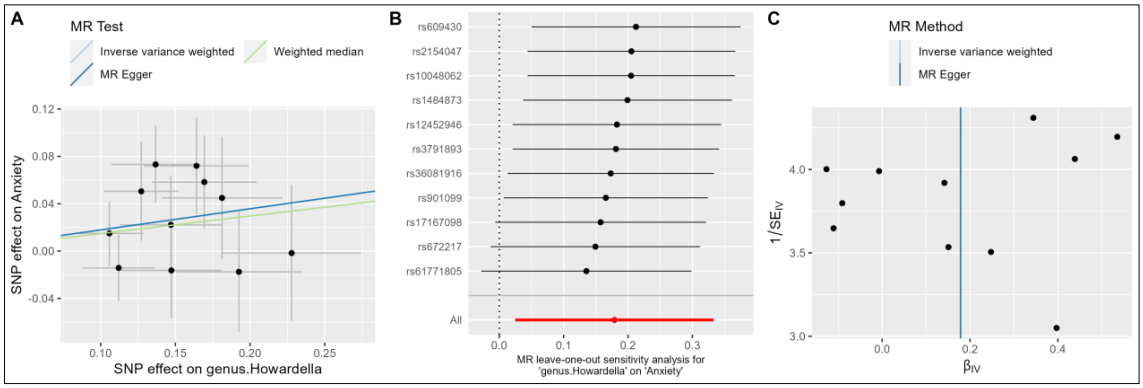
Exposure: genus.Clostridiumsensustricto1; Outcome: Anxiety



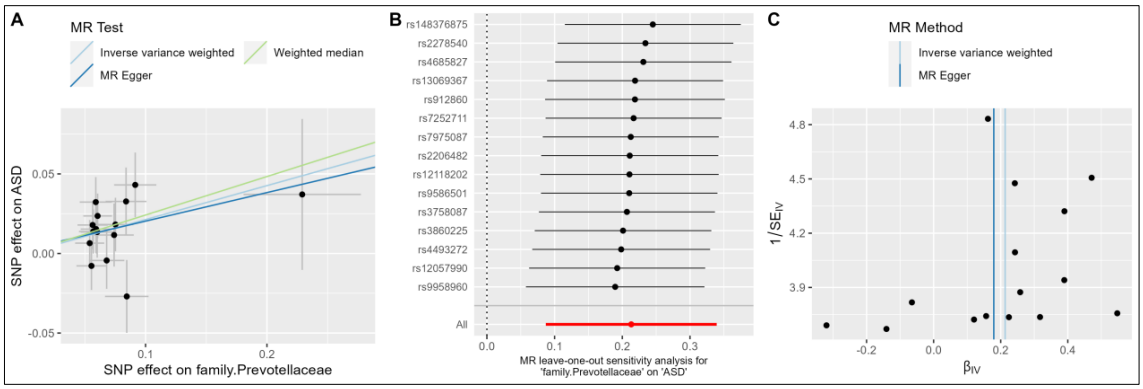
Exposure: genus.Eggerthella; Outcome: Anxiety



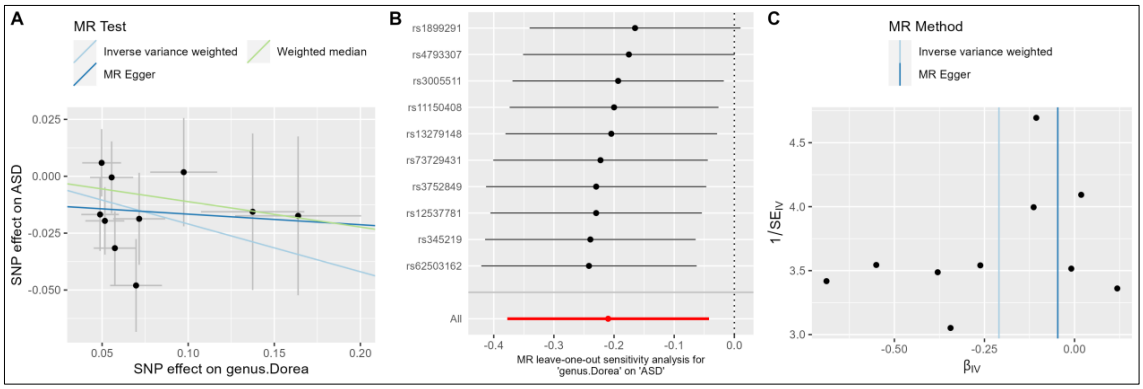
Exposure: genus.Howardella; Outcome: Anxiety



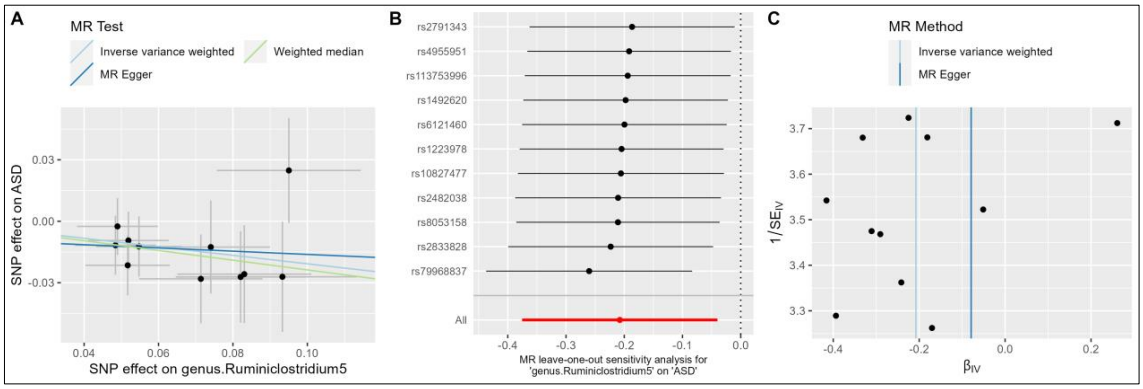
Exposure: family.Prevotellaceae; Outcome: ASD



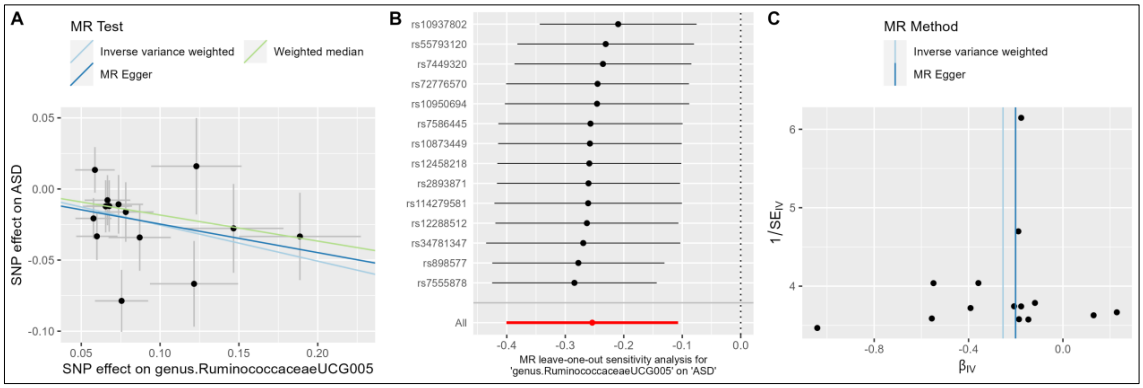
Exposure: genus.Dorea; Outcome: ASD



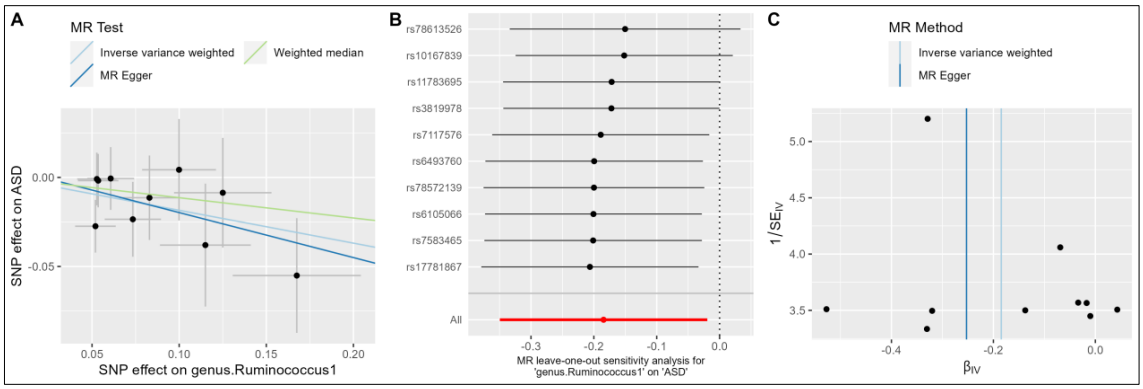
Exposure: genus.Ruminiclostridium5; Outcome: ASD



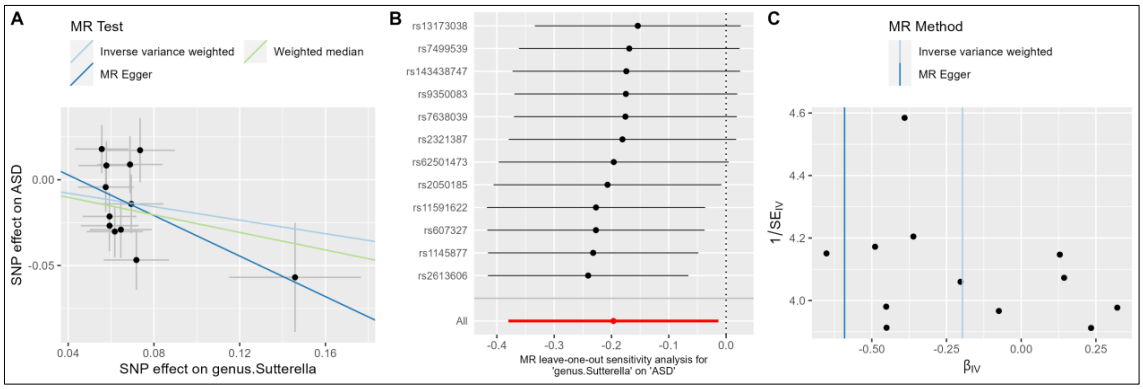
Exposure: genus.RuminococcaceaeUCG005; Outcome: ASD



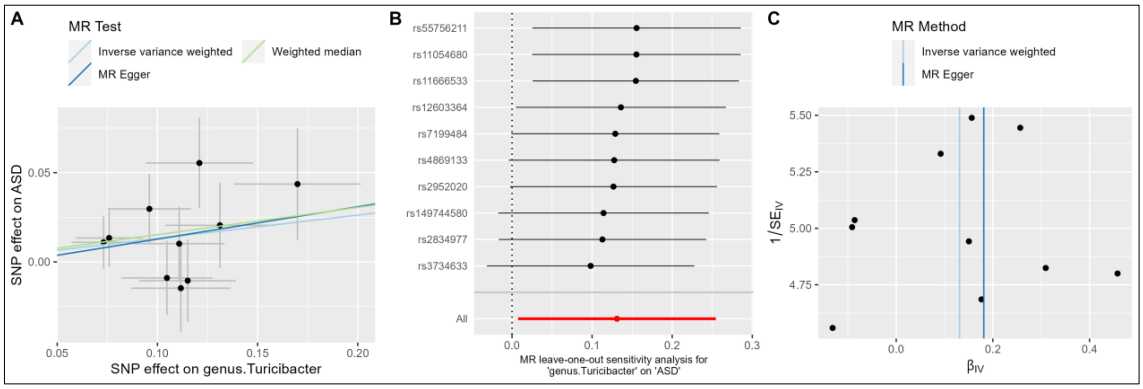
Exposure: genus.Ruminococcus1; Outcome: ASD



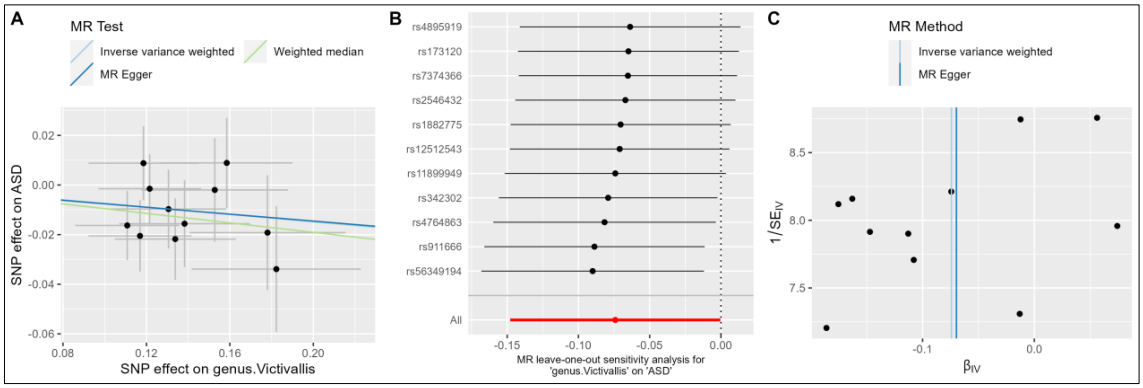
Exposure: genus.Sutterella; Outcome: ASD



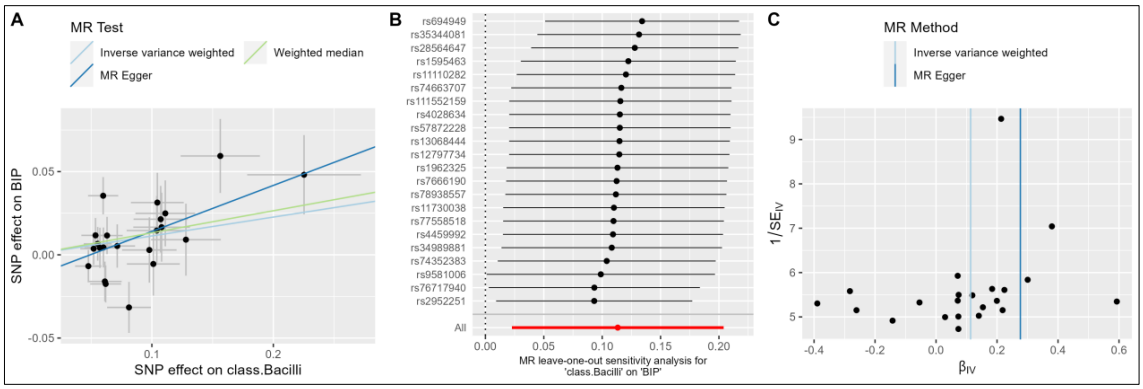
Exposure: genus.Turicibacter; Outcome: ASD



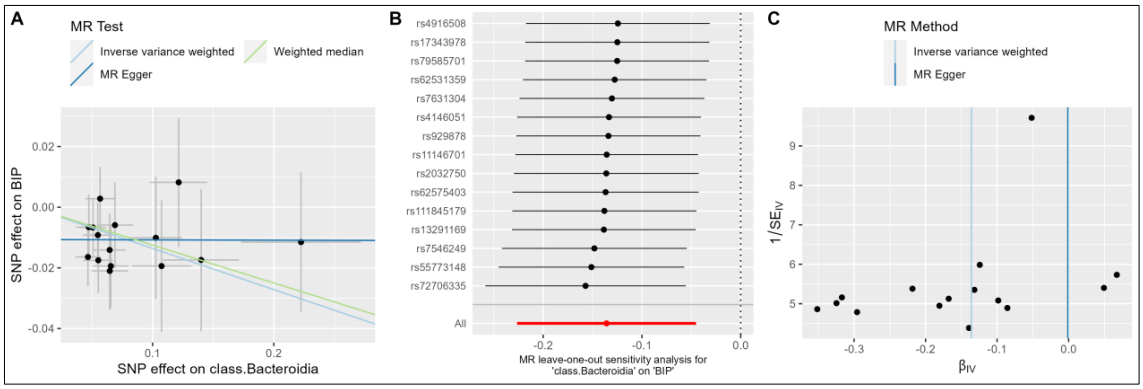
Exposure: genus.Victivallis; Outcome: ASD



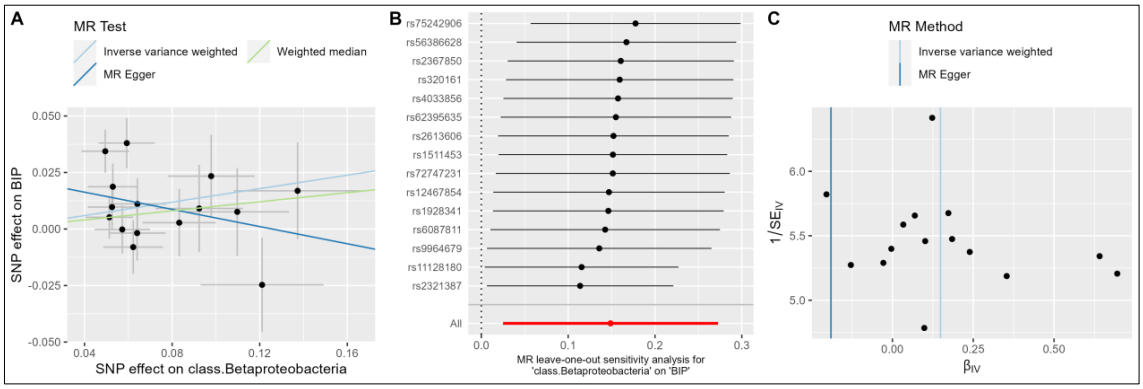
Exposure: class.Bacilli; Outcome: BIP



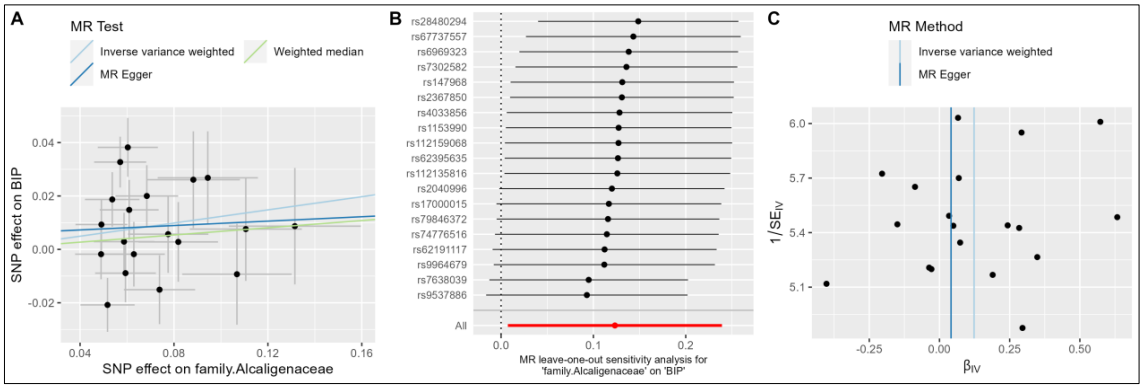
Exposure: class.Bacteroidia; Outcome: BIP



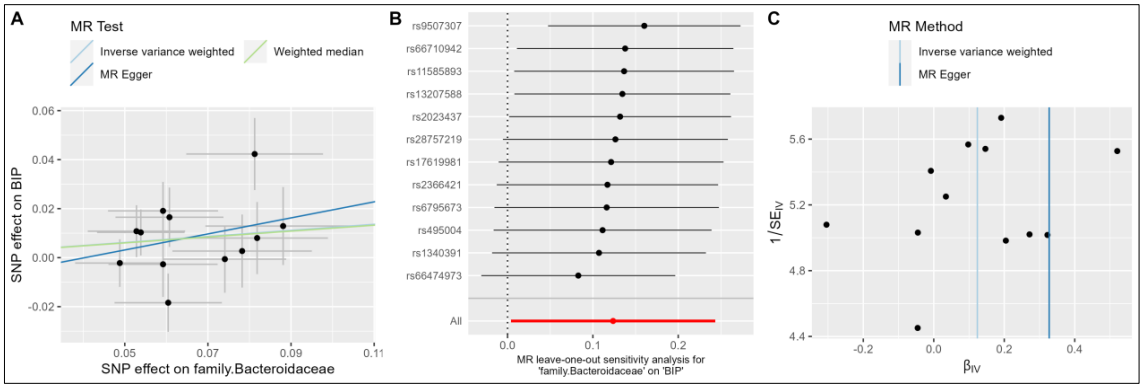
Exposure: class.Betaproteobacteria; Outcome: BIP



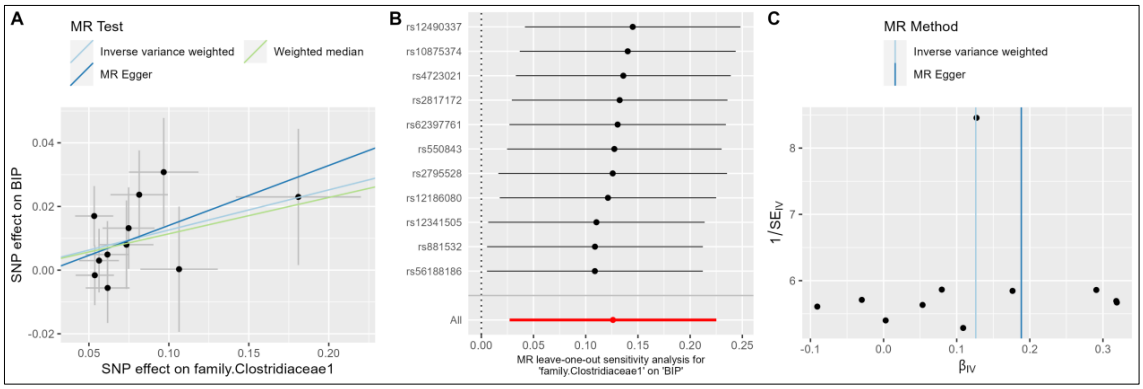
Exposure: family.Alcaligenaceae; Outcome: BIP



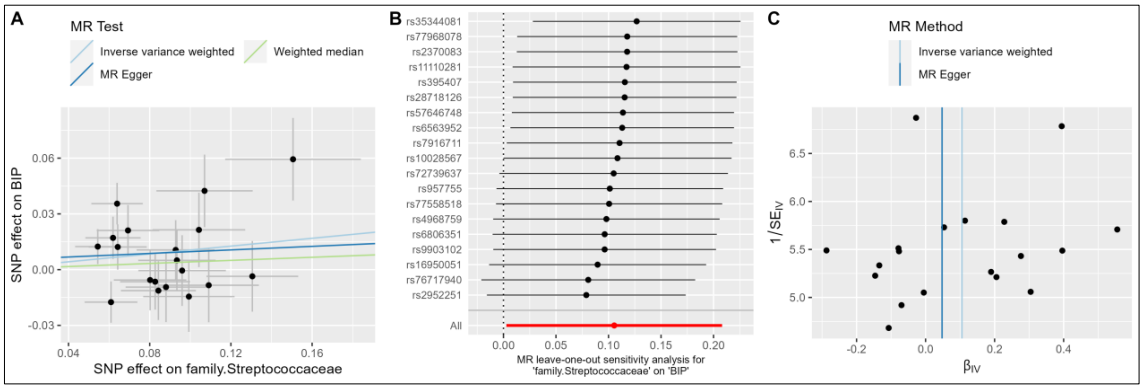
Exposure: family.Bacteroidaceae; Outcome: BIP



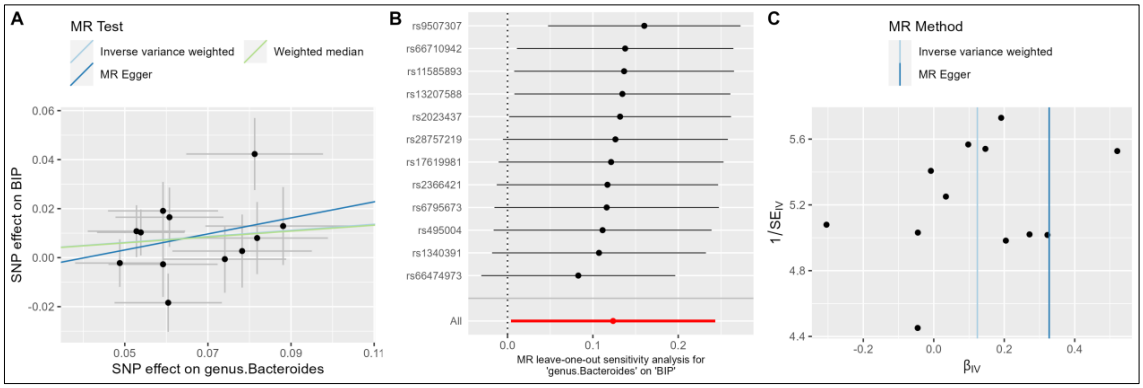
Exposure: family.Clostridiaceae1; Outcome: BIP



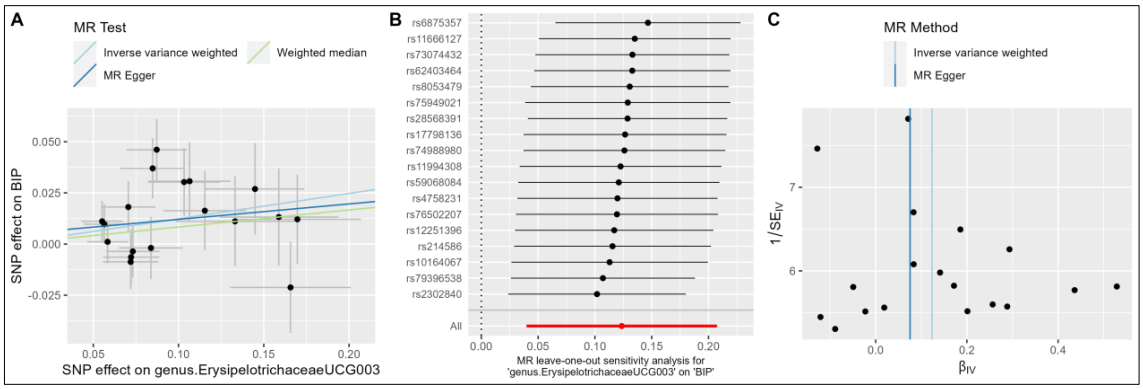
Exposure: family.Streptococcaceae; Outcome: BIP



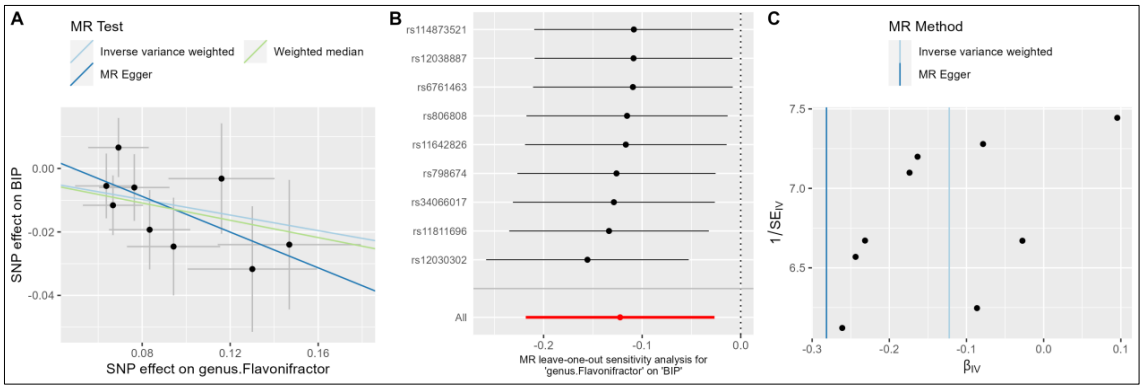
Exposure: genus.Bacteroides; Outcome: BIP



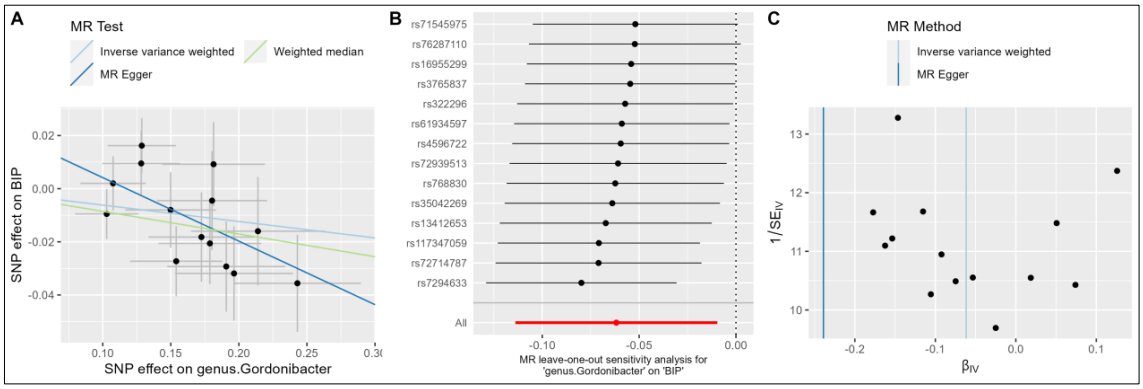
Exposure: genus.ErysipelotrichaceaeUCG003; Outcome: BIP



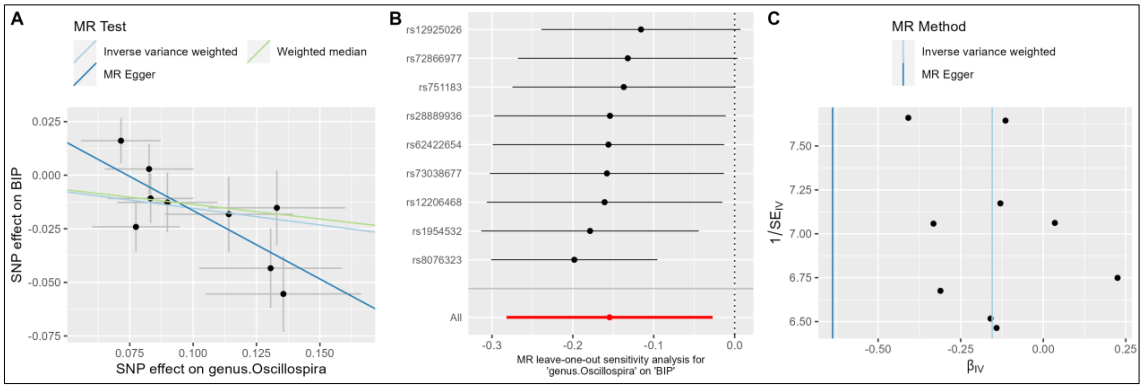
Exposure: genus.Flavonifractor; Outcome: BIP



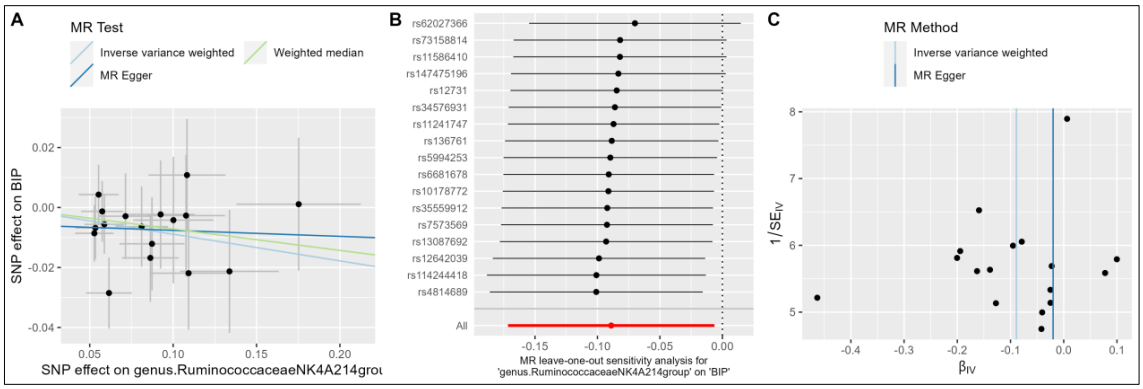
Exposure: genus.Gordonibacter; Outcome: BIP



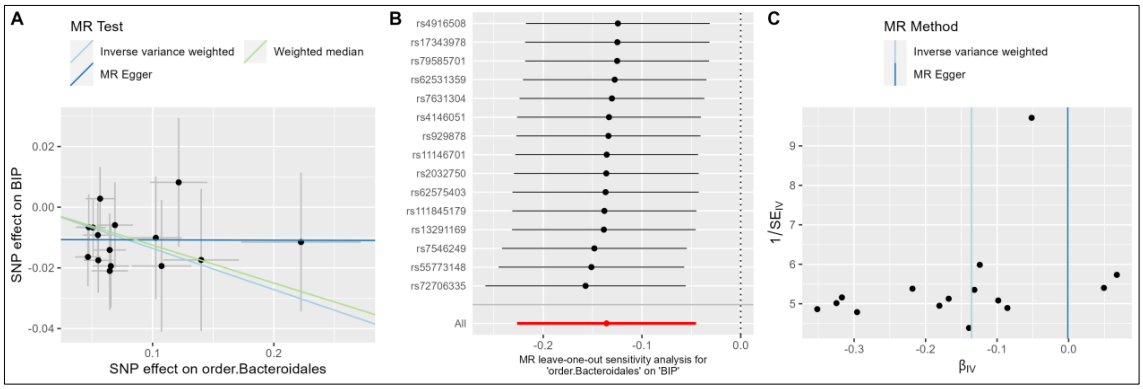
Exposure: genus.Oscillospira; Outcome: BIP



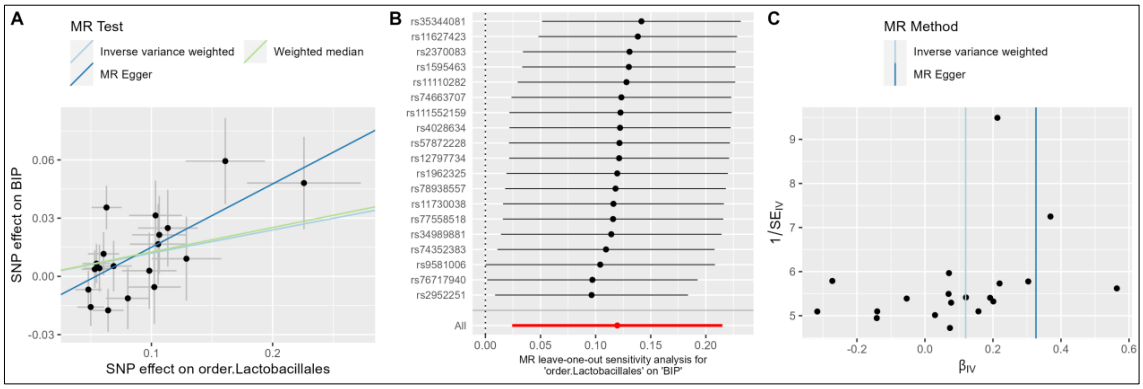
Exposure: genus.RuminococcaceaeNK4A214group; Outcome: BIP



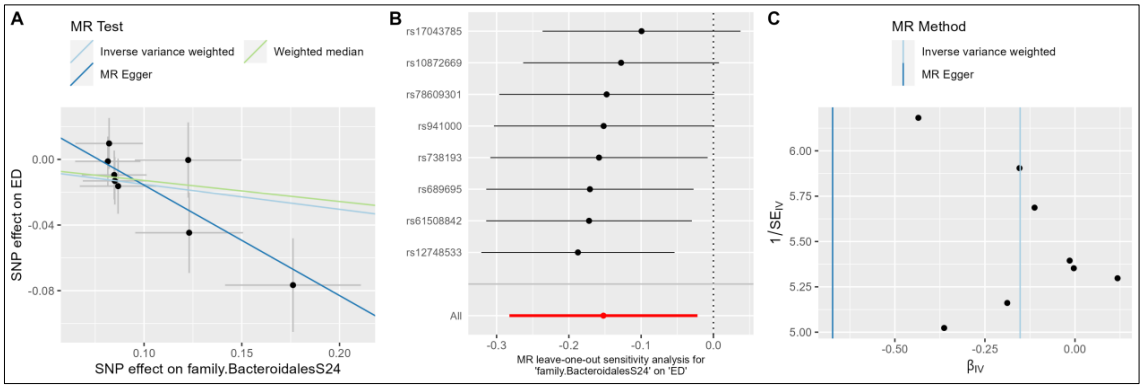
Exposure: order.Bacteroidales; Outcome: BIP



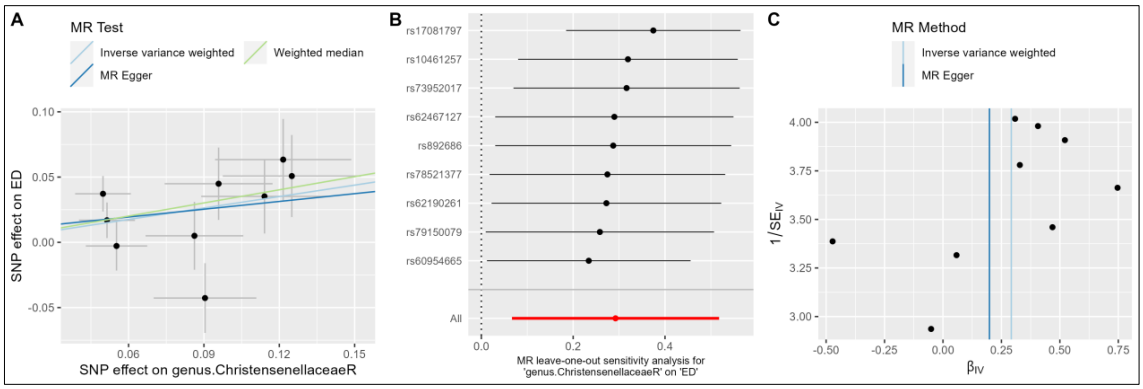
Exposure: order.Lactobacillales; Outcome: BIP



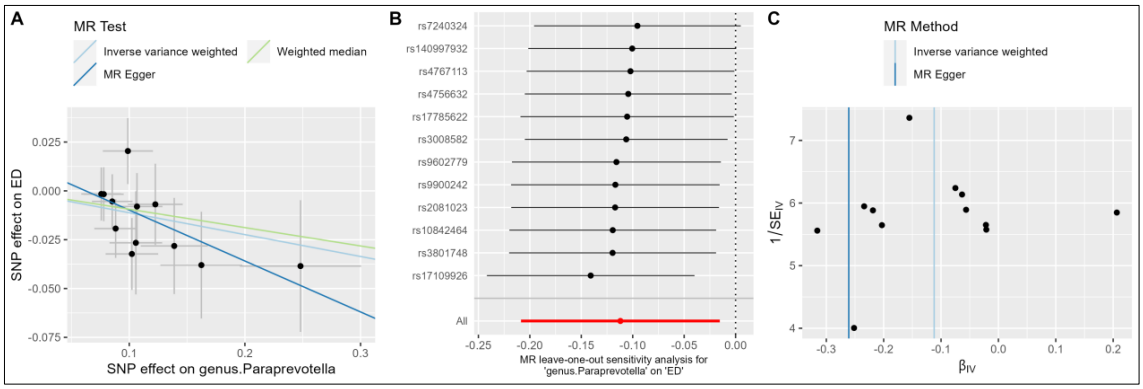
Exposure: family.BacteroidalesS24.7group; Outcome: ED



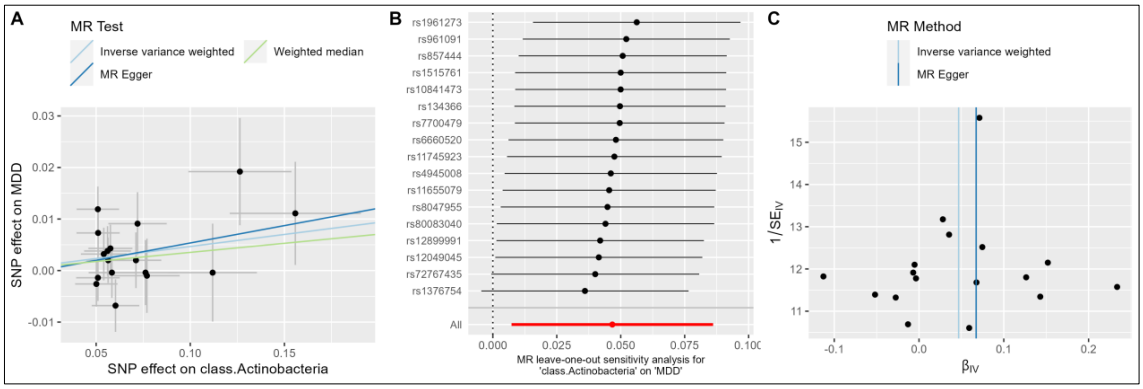
Exposure: genus.ChristensenellaceaeR.7group; Outcome: ED



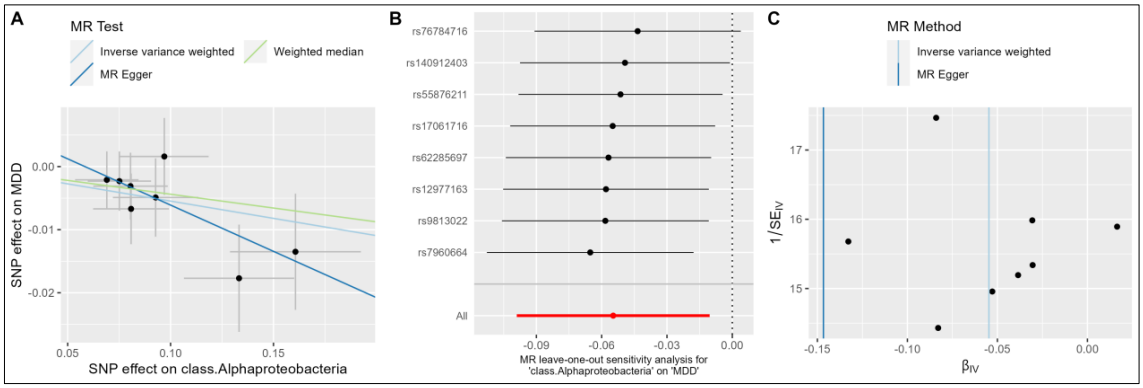
Exposure: genus.Paraprevotella; Outcome: ED



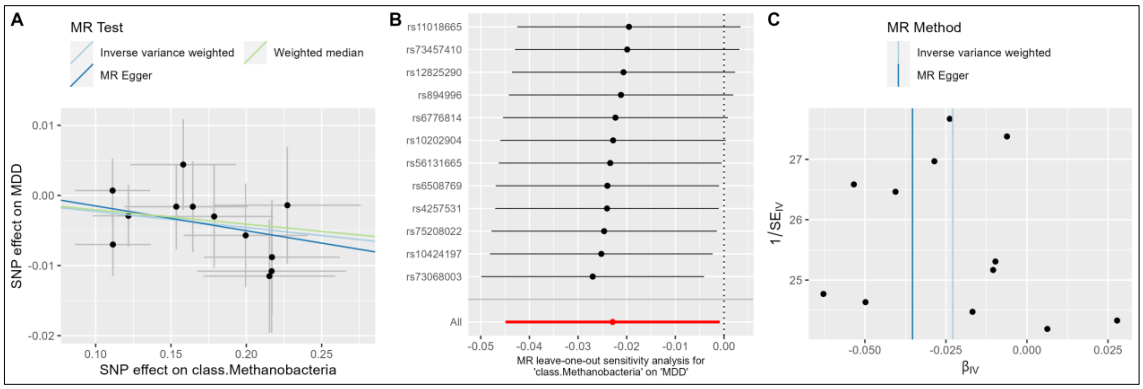
Exposure: class.Actinobacteria; Outcome: MDD



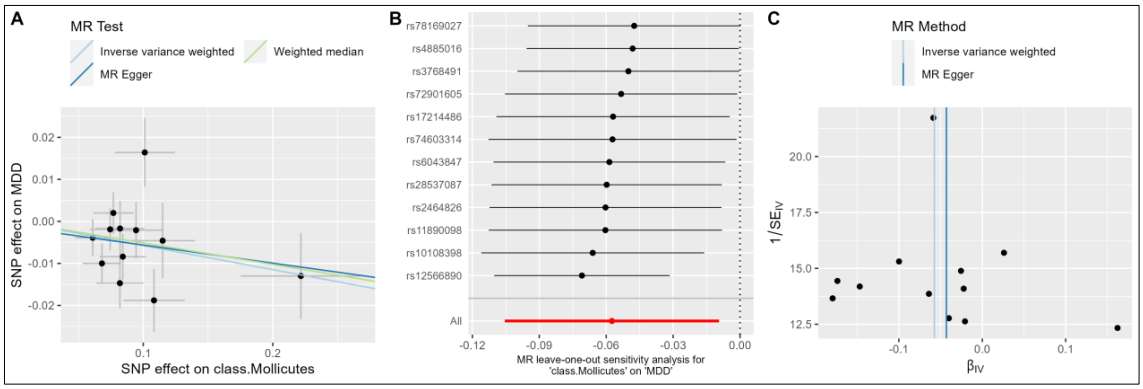
Exposure: class.Alphaproteobacteria; Outcome: MDD



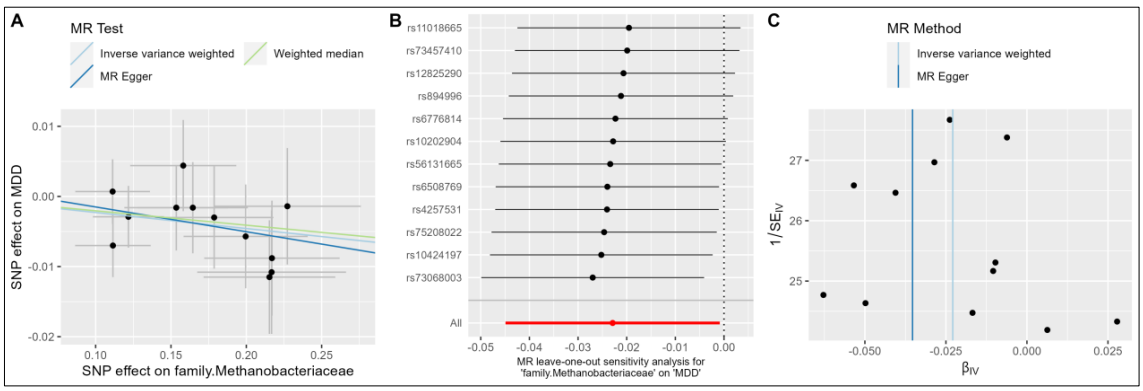
Exposure: class.Methanobacteria; Outcome: MDD



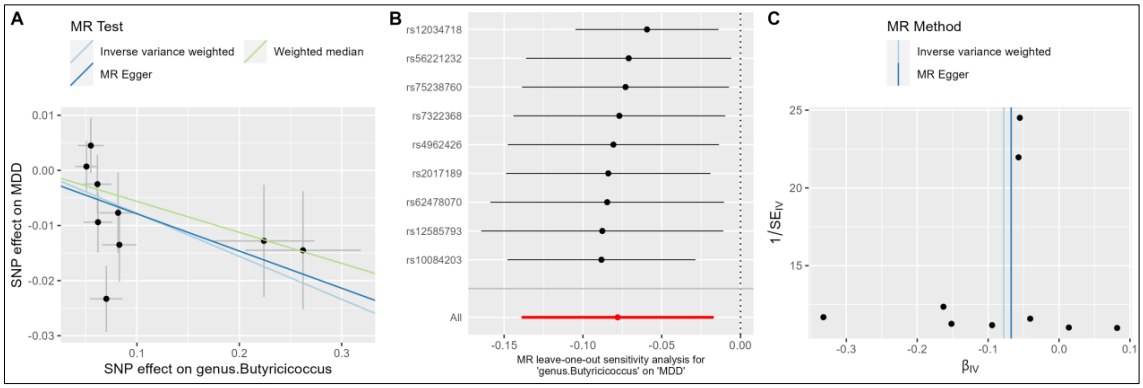
Exposure: class.Mollicutes; Outcome: MDD



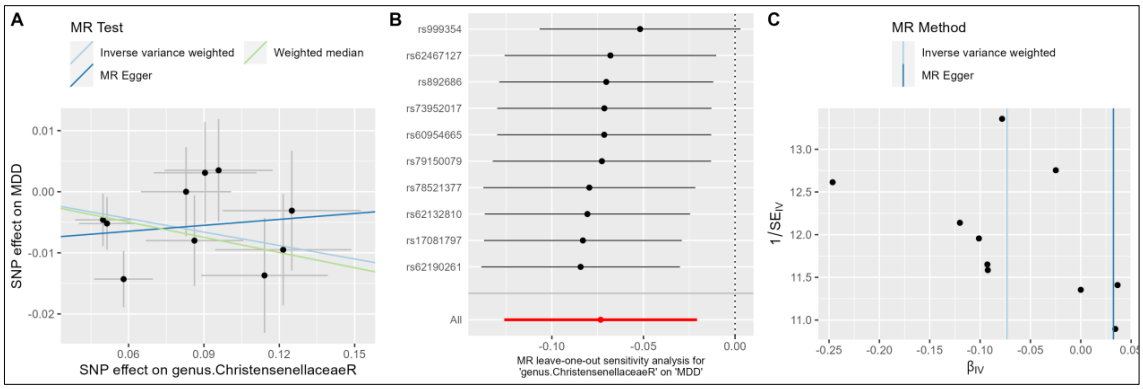
Exposure: family.Methanobacteriaceae; Outcome: MDD



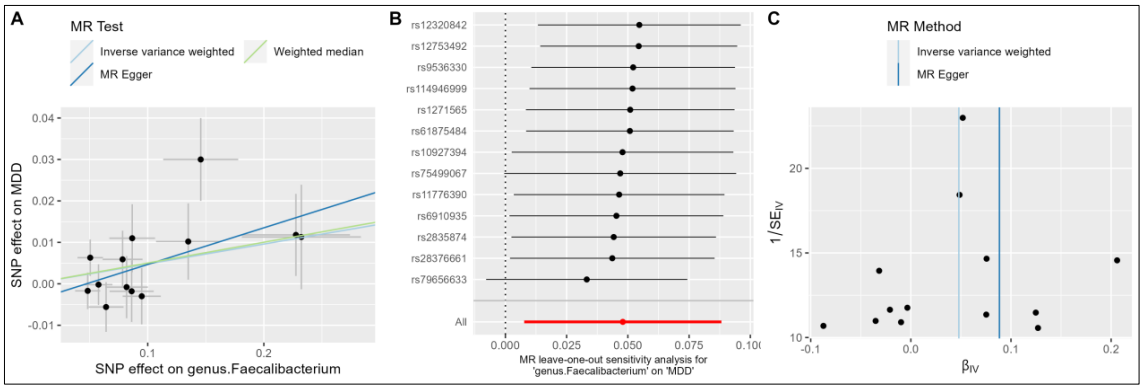
Exposure: genus.Butyricicoccus; Outcome: MDD



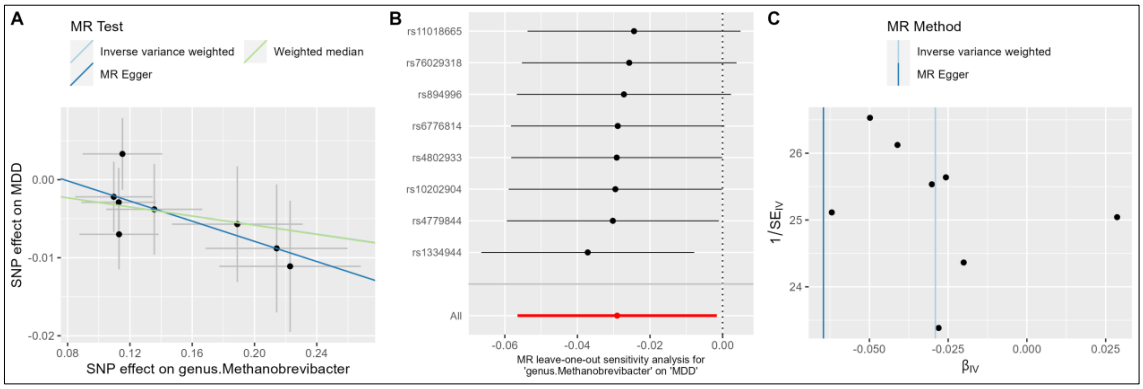
Exposure: genus.ChristensenellaceaeR.7group; Outcome: MDD



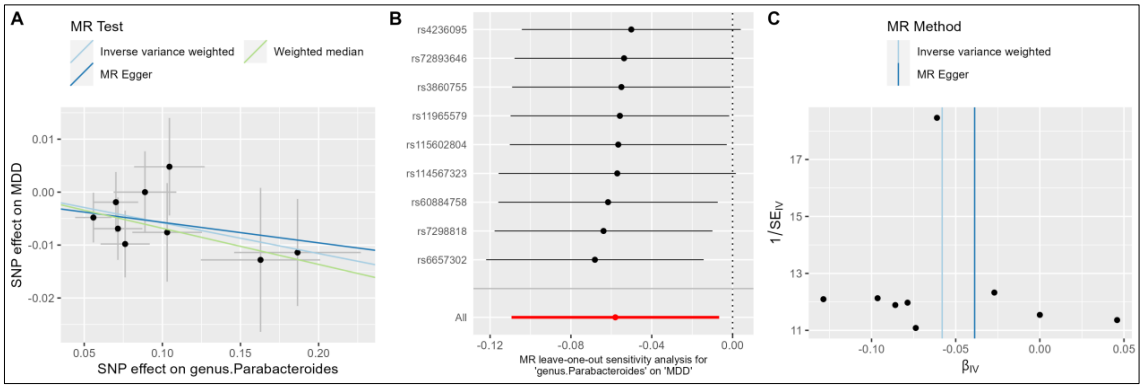
Exposure: genus.Faecalibacterium; Outcome: MDD



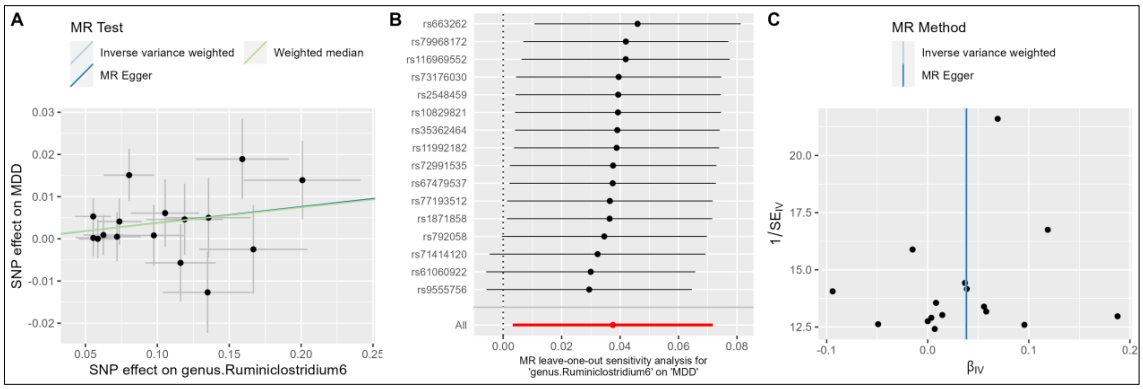
Exposure: genus.Methanobrevibacter; Outcome: MDD



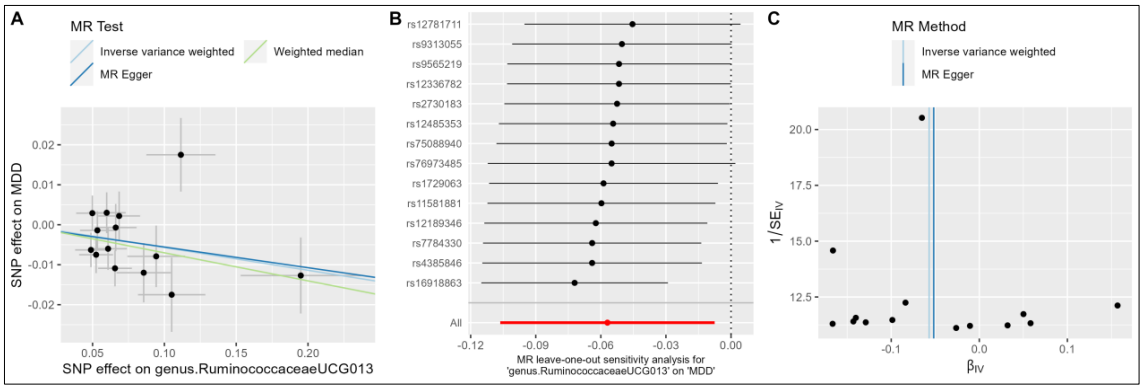
Exposure: genus.Parabacteroides; Outcome: MDD



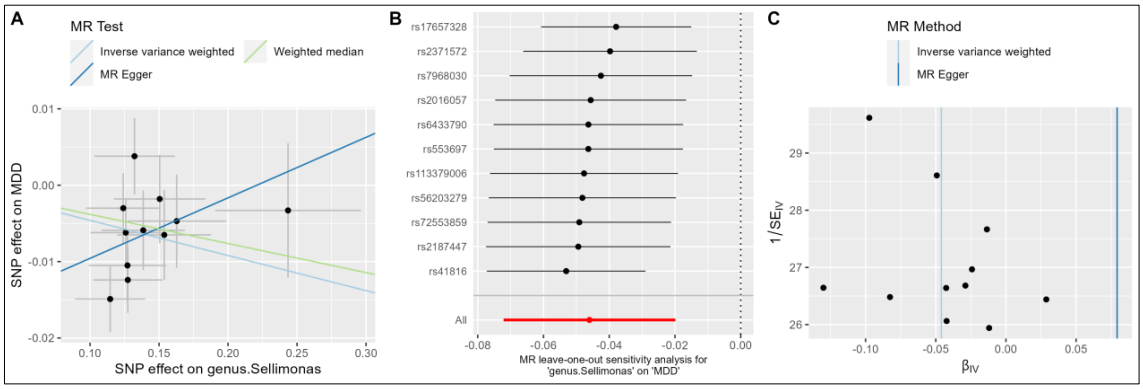
Exposure: genus.Ruminiclostridium6; Outcome: MDD



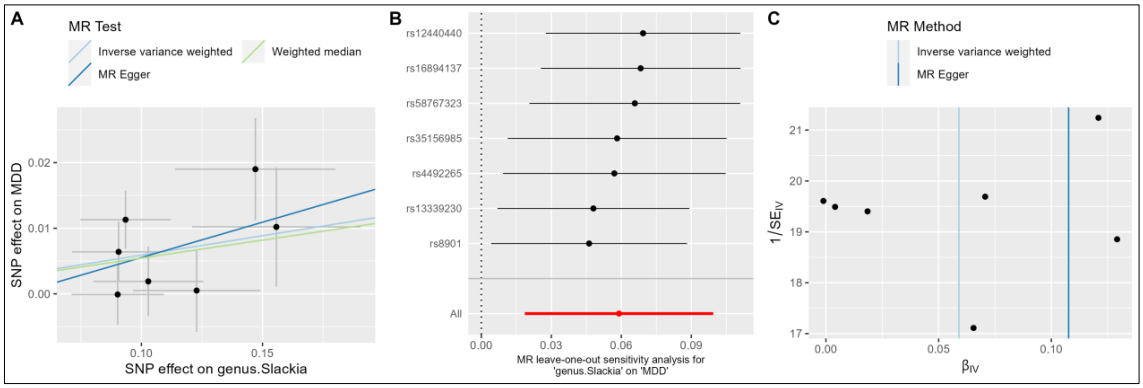
Exposure: genus.RuminococcaceaeUCG013; Outcome: MDD



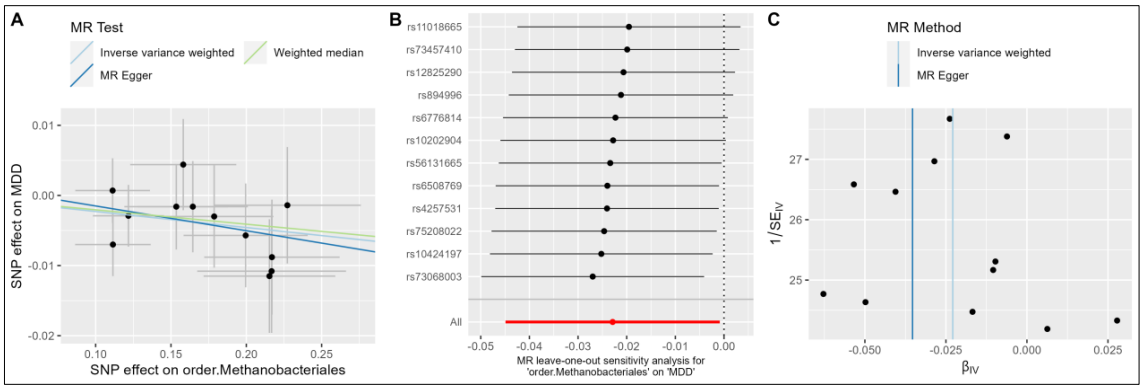
Exposure: genus.Sellimonas; Outcome: MDD



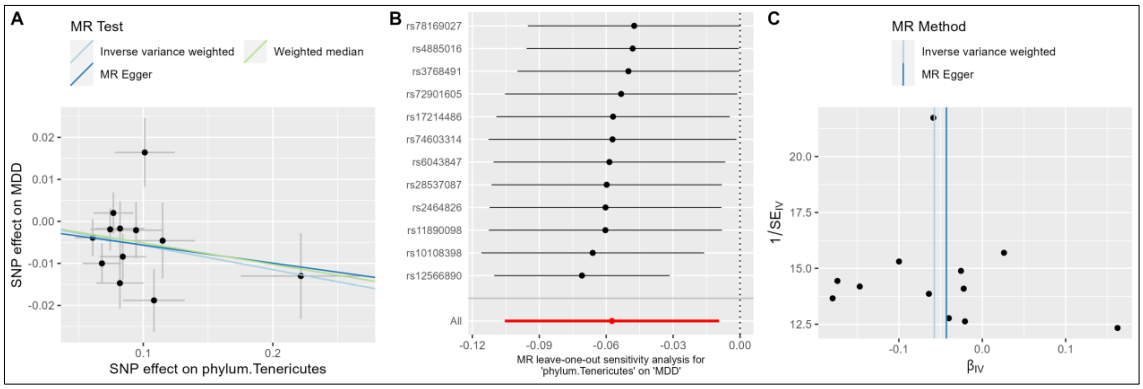
Exposure: genus.Slackia; Outcome: MDD



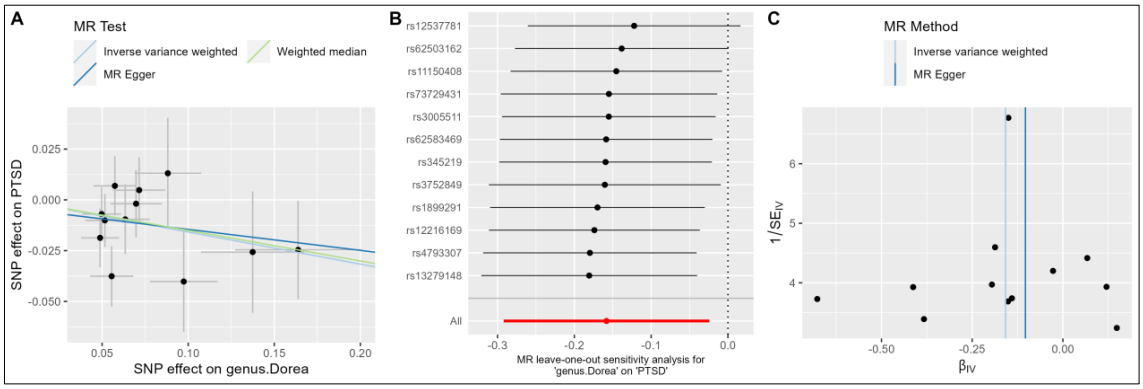
Exposure: order.Methanobacteriales; Outcome: MDD



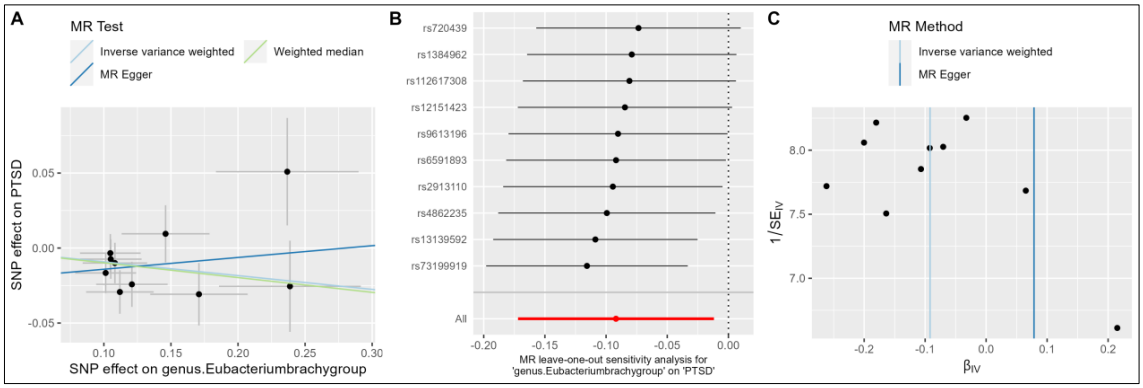
Exposure: phylum.Tenericutes; Outcome: MDD



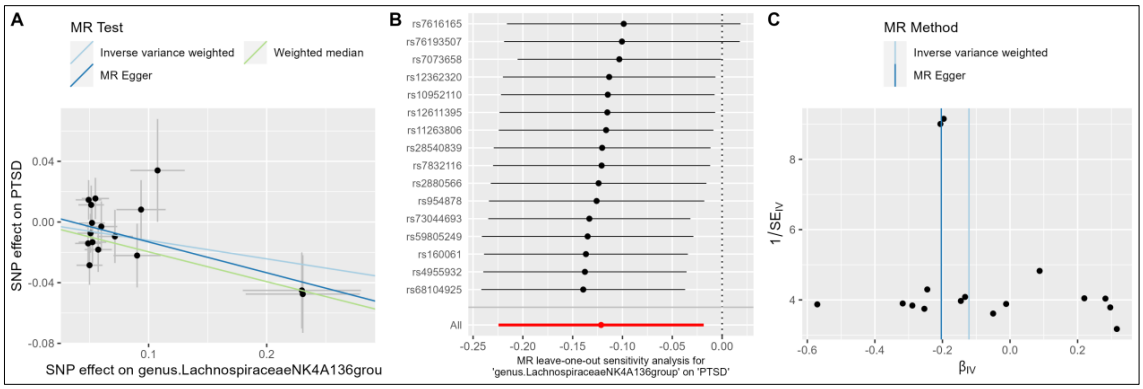
Exposure: genus.Dorea; Outcome: PTSD



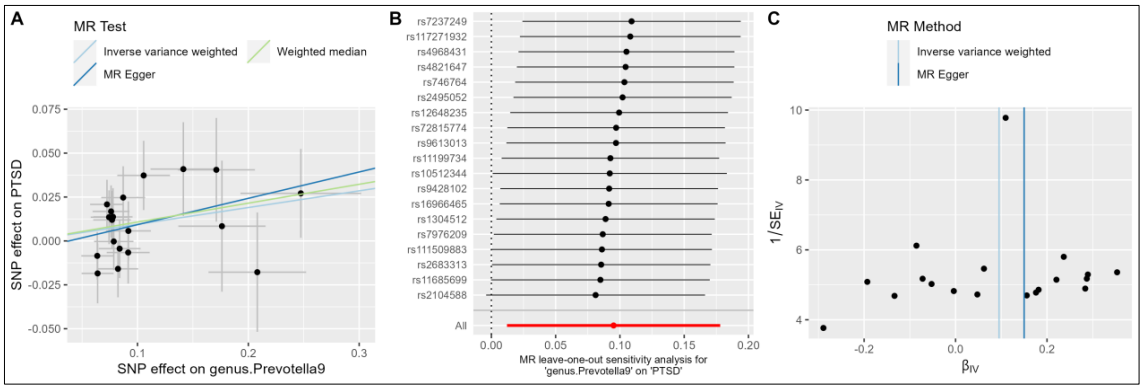
Exposure: genus.Eubacteriumbrachygroup; Outcome: PTSD



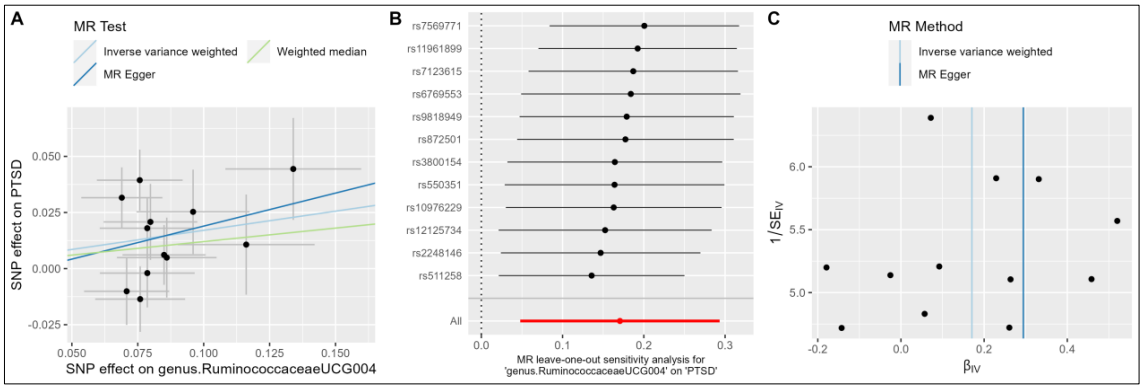
Exposure: genus.LachnospiraceaeNK4A136group; Outcome: PTSD



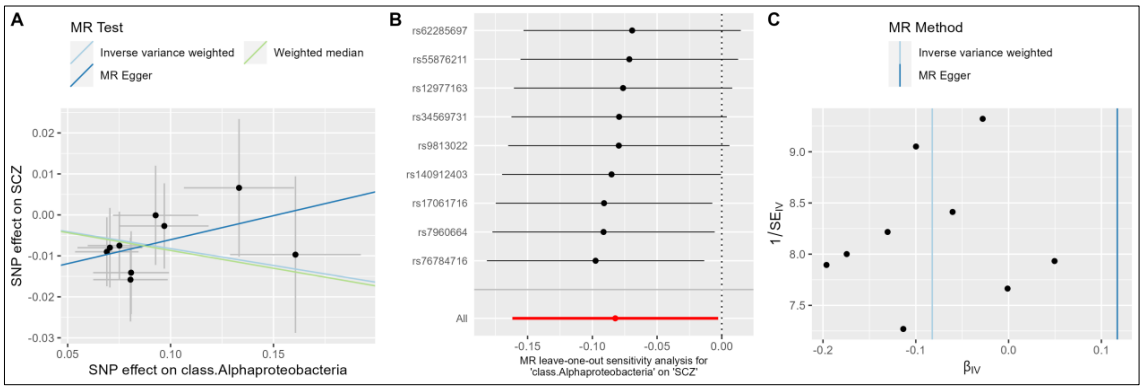
Exposure: genus.Prevotella9; Outcome: PTSD



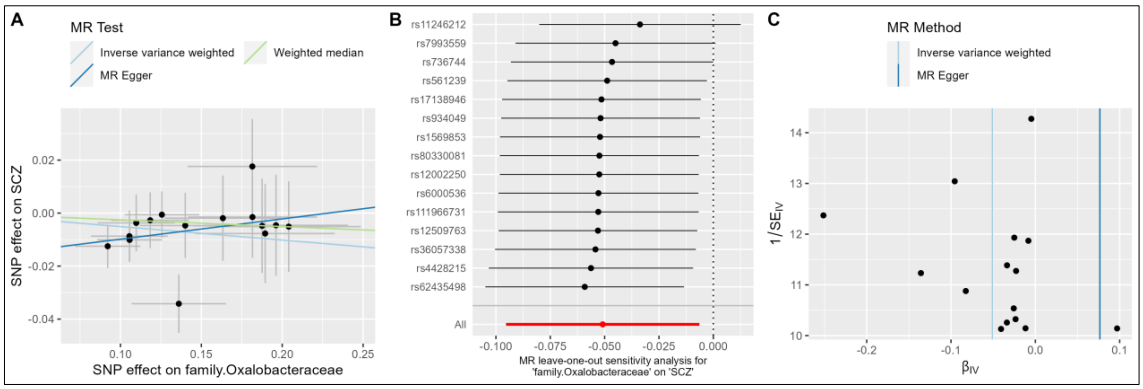
Exposure: genus.RuminococcaceaeUCG004; Outcome: PTSD



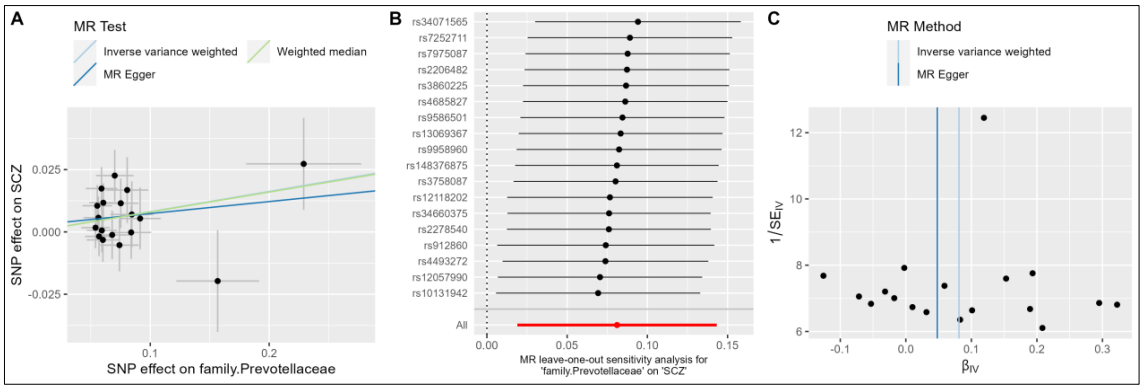
Exposure: class.Alphaproteobacteria; Outcome: SCZ



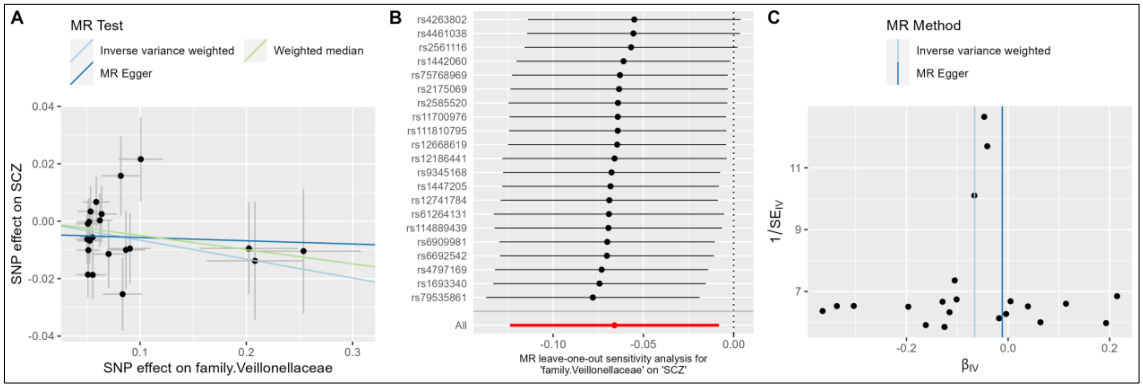
Exposure: family.Oxalobacteraceae; Outcome: SCZ



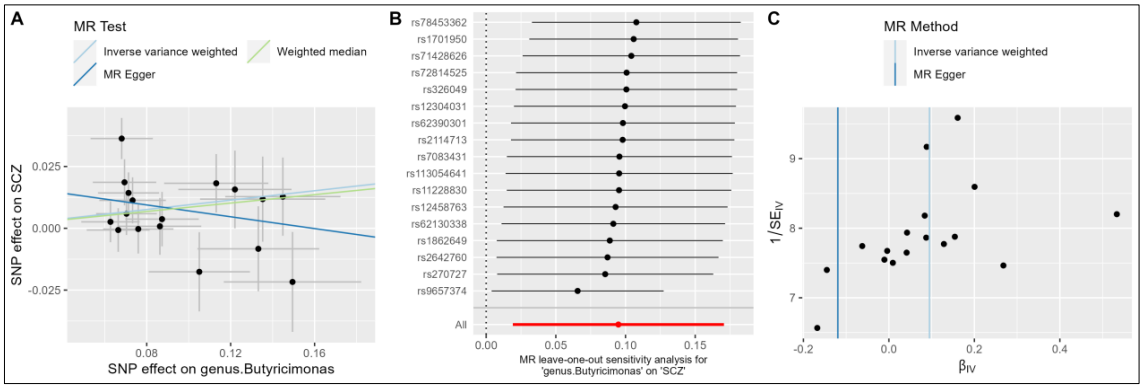
Exposure: family.Prevotellaceae; Outcome: SCZ



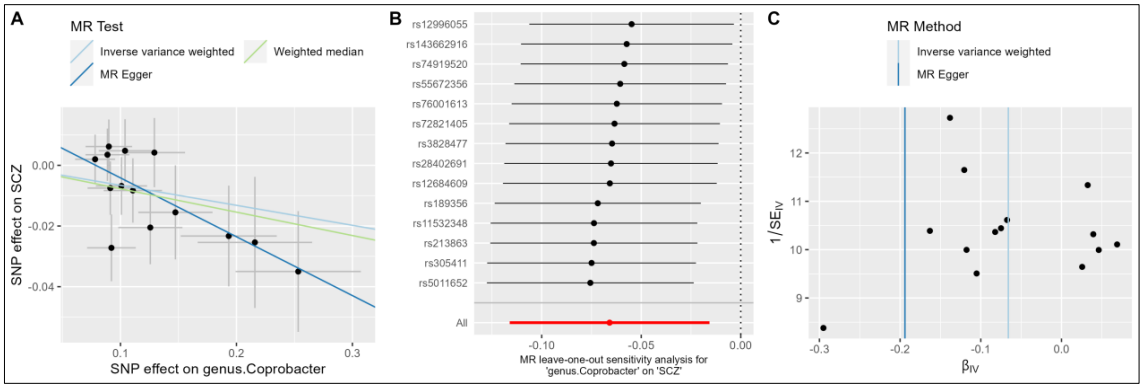
Exposure: family.Veillonellaceae; Outcome: SCZ



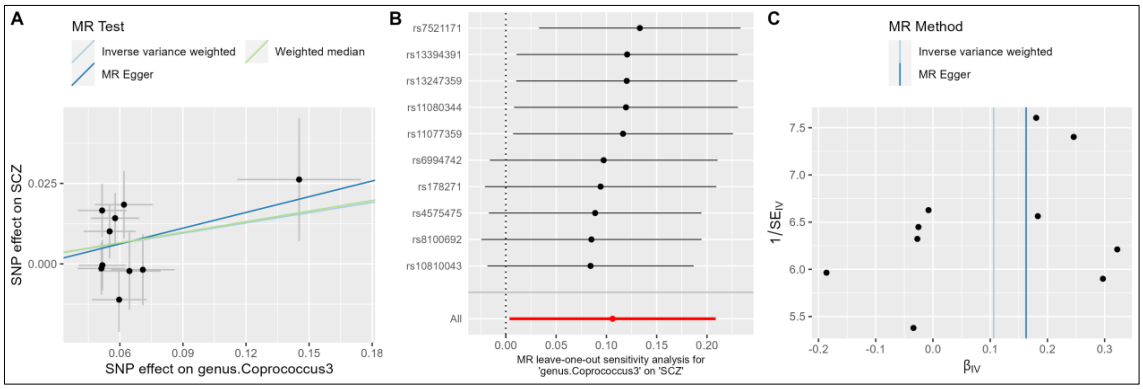
Exposure: genus.Butyricimonas; Outcome: SCZ



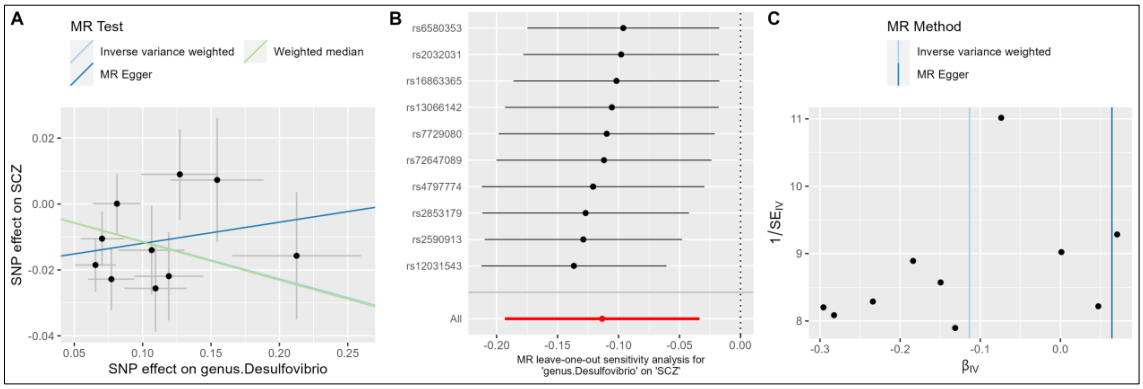
Exposure: genus.Coprobacter; Outcome: SCZ



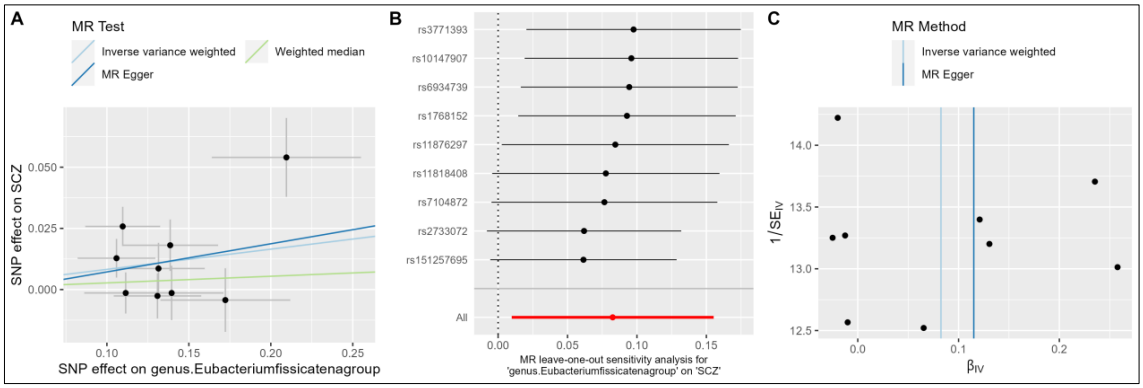
Exposure: genus.Coprococcus3; Outcome: SCZ



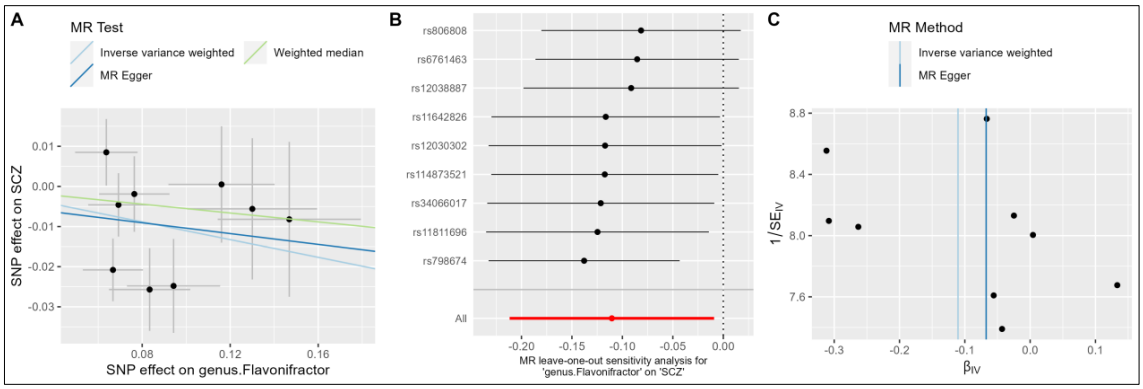
Exposure: genus.Desulfovibrio; Outcome: SCZ



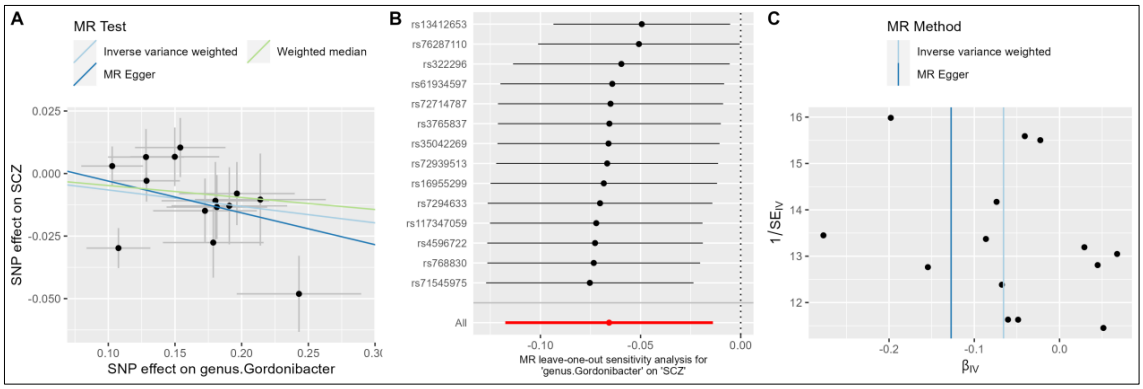
Exposure: genus.Eubacteriumfissicatenagroup; Outcome: SCZ



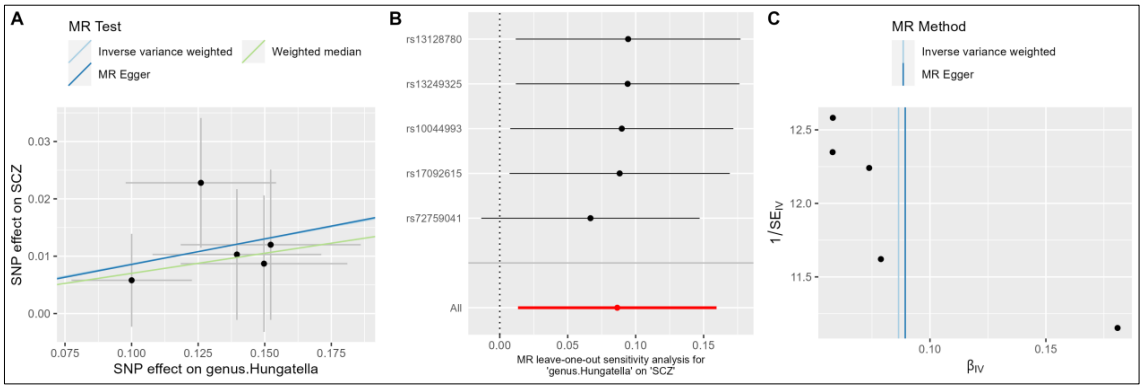
Exposure: genus.Flavonifractor; Outcome: SCZ



Exposure: genus.Gordonibacter; Outcome: SCZ



Exposure: genus.Hungatella; Outcome: SCZ



Exposure: genus.Subdoligranulum; Outcome: SCZ

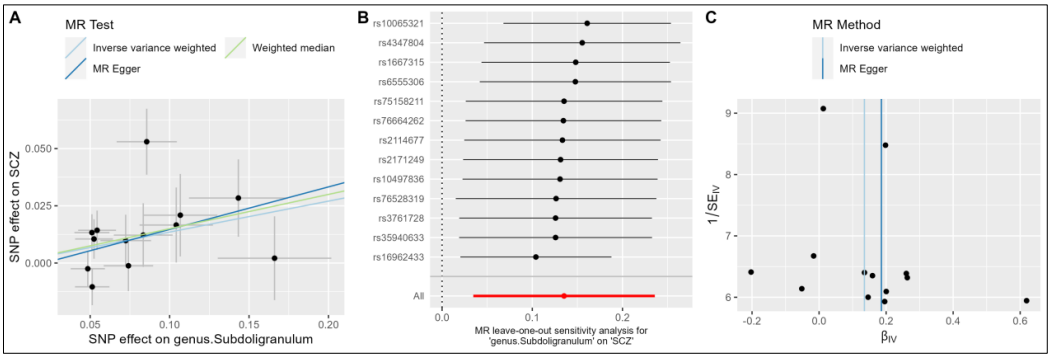
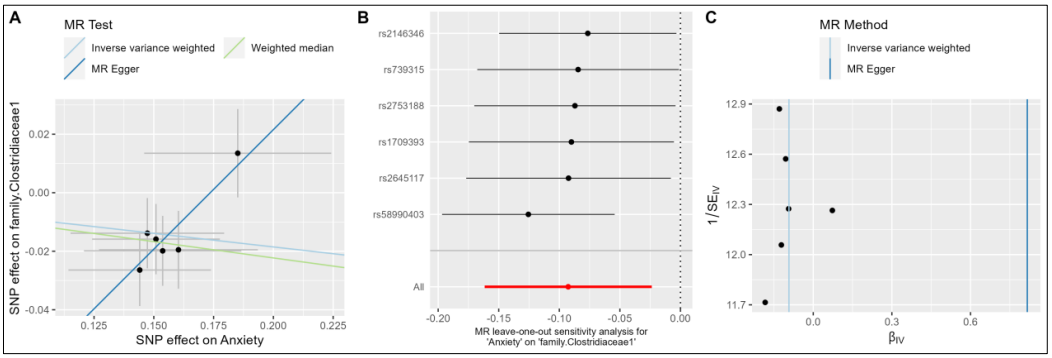
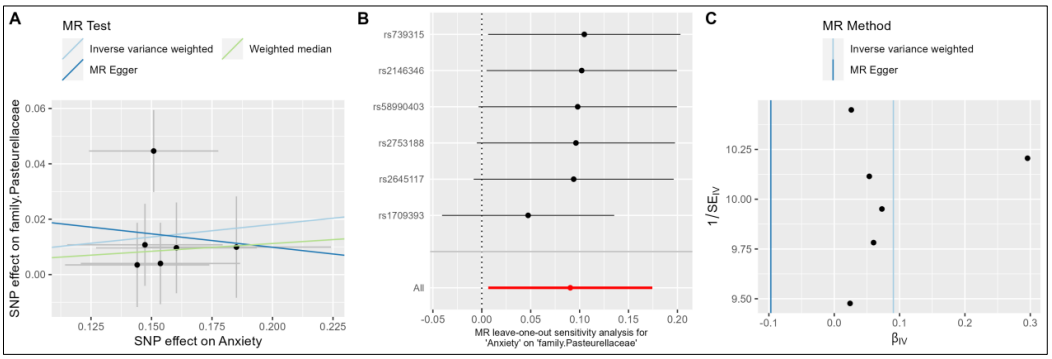


Figure S4. Scatter plots (A), leave-one-out plot (B) and funnel plot (C) of positive MR results for the causal effects of the risk of developing psychiatric disorders on the abundances of several gut microbiota.

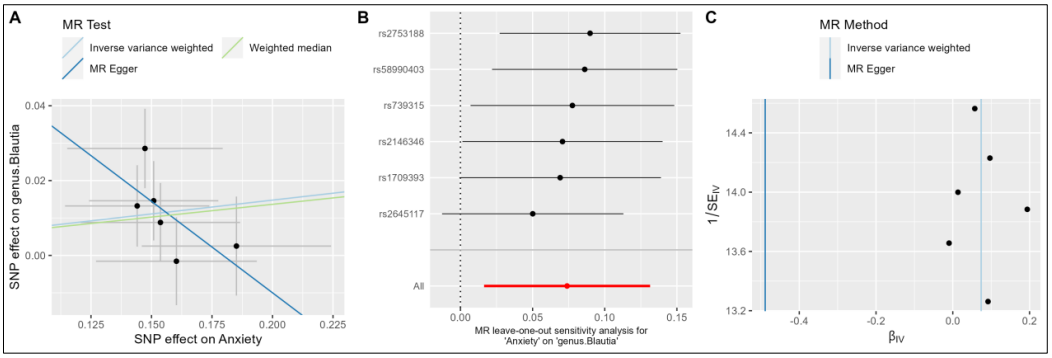
Exposure: Anxiety; Outcome: family.Clostridiaceae1



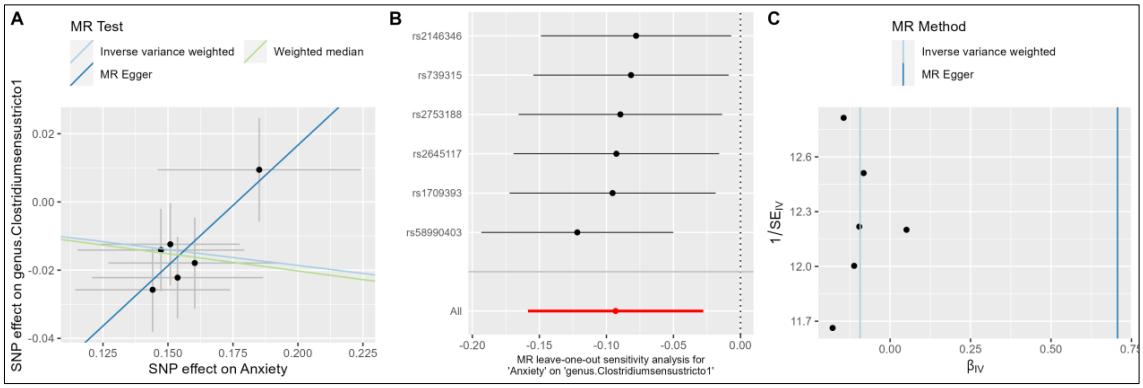
Exposure: Anxiety; Outcome: family.Pasteurellaceae



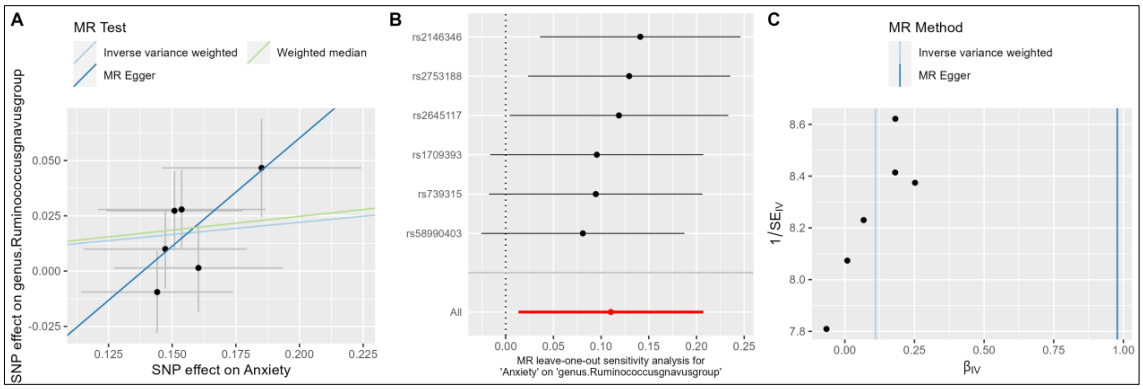
Exposure: Anxiety; Outcome: genus.Blautia



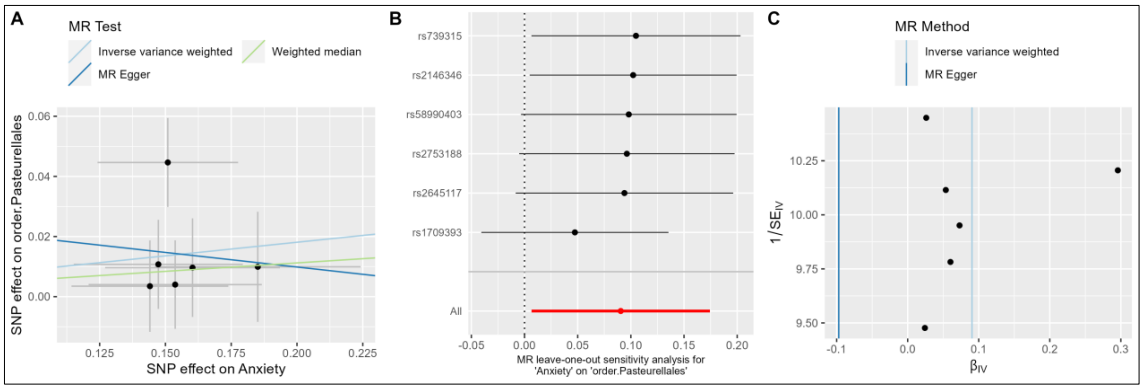
Exposure: Anxiety; Outcome: genus.Clostridiumsensustricto1



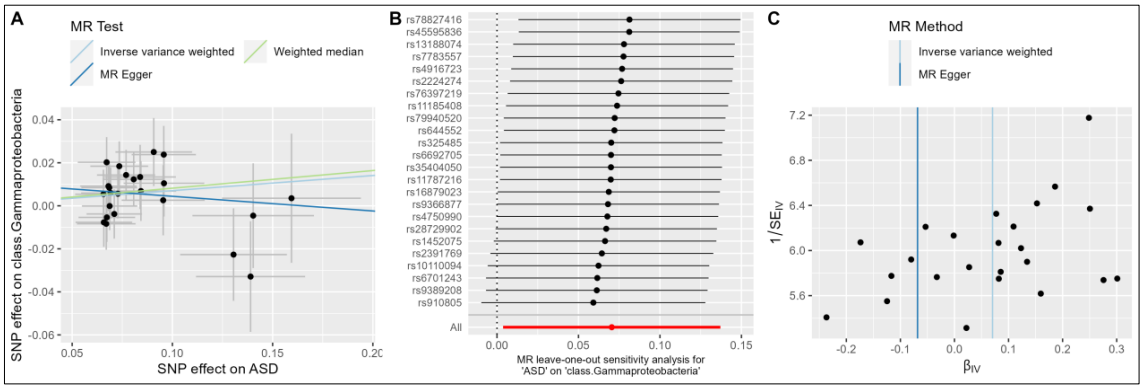
Exposure: Anxiety; Outcome: genus.Ruminococcusgnavusgroup



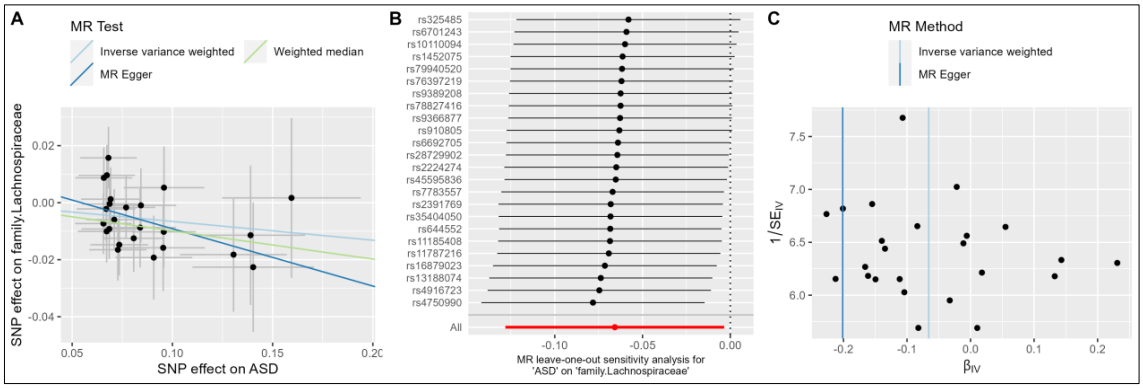
Exposure: Anxiety; Outcome: order.Pasteurellales



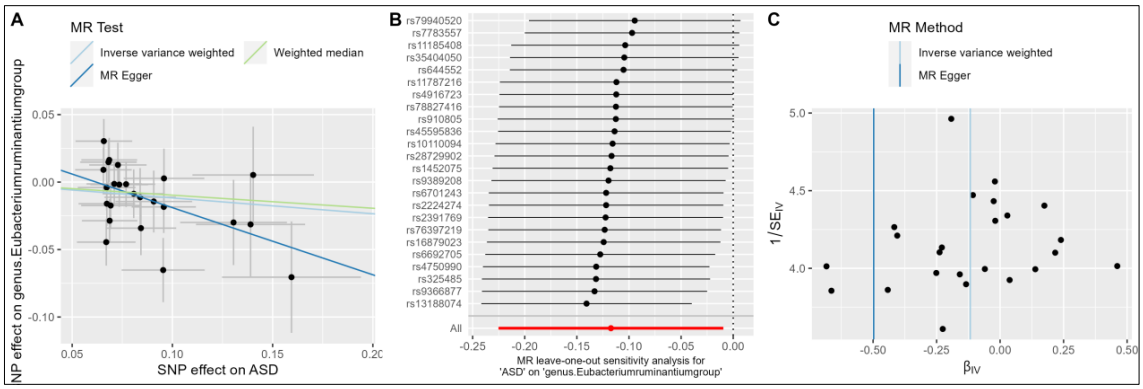
Exposure: ASD; Outcome: class.Gammaproteobacteria



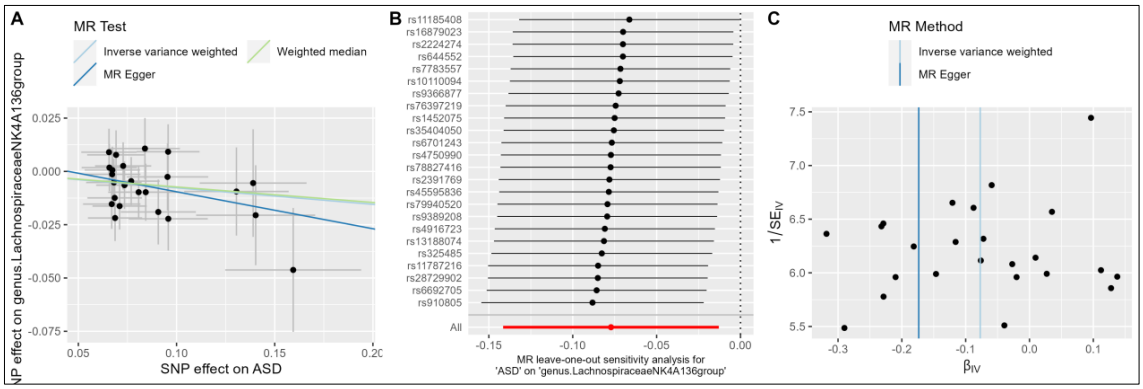
Exposure: ASD; Outcome: family.Lachnospiraceae



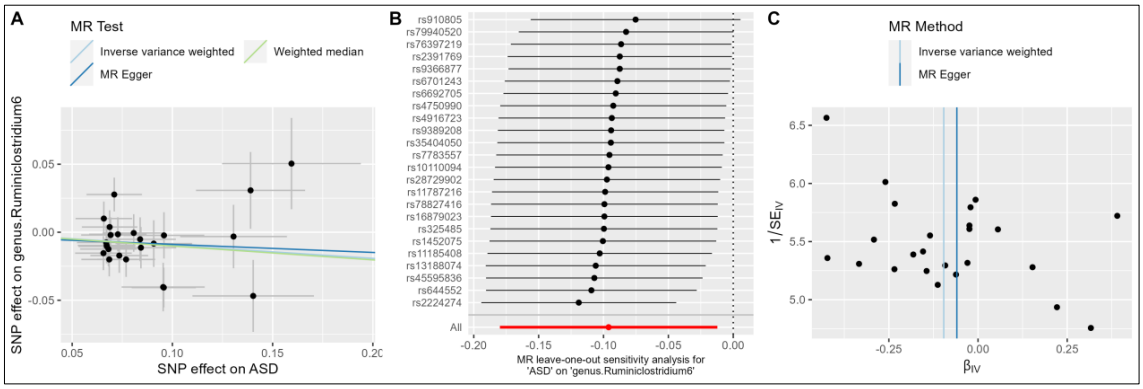
Exposure: ASD; Outcome: genus.Eubacteriumruminantiumgroup



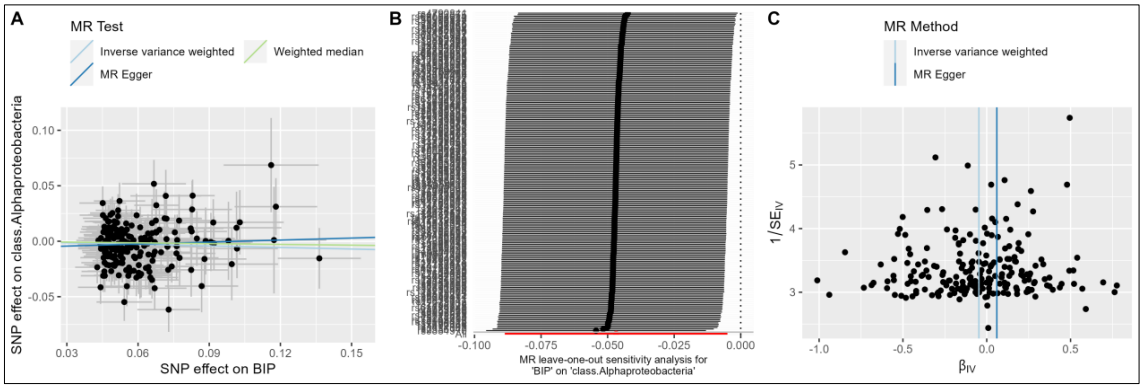
Exposure: ASD; Outcome: genus.LachnospiraceaeNK4A136group



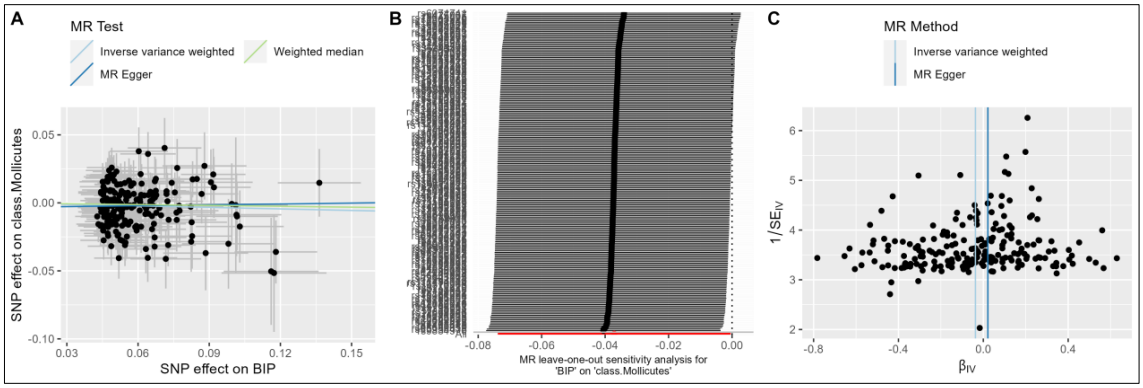
Exposure: ASD; Outcome: genus.Ruminiclostridium6



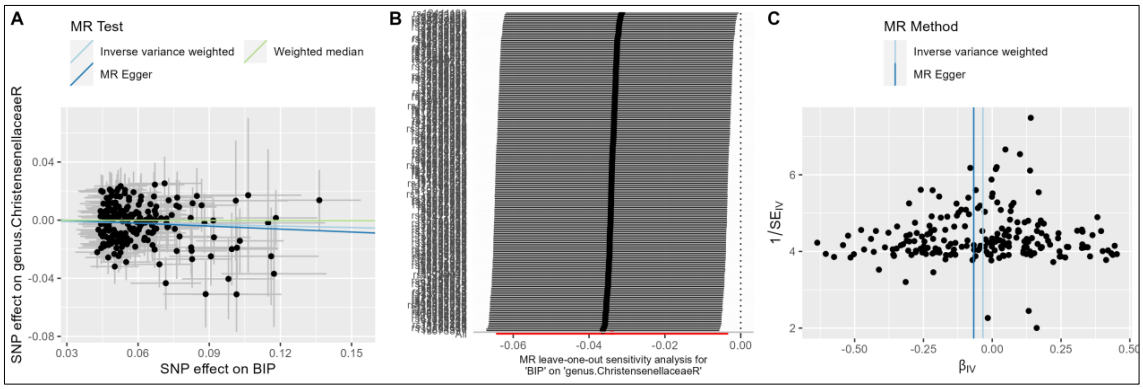
Exposure: BIP; Outcome: class.Alphaproteobacteria



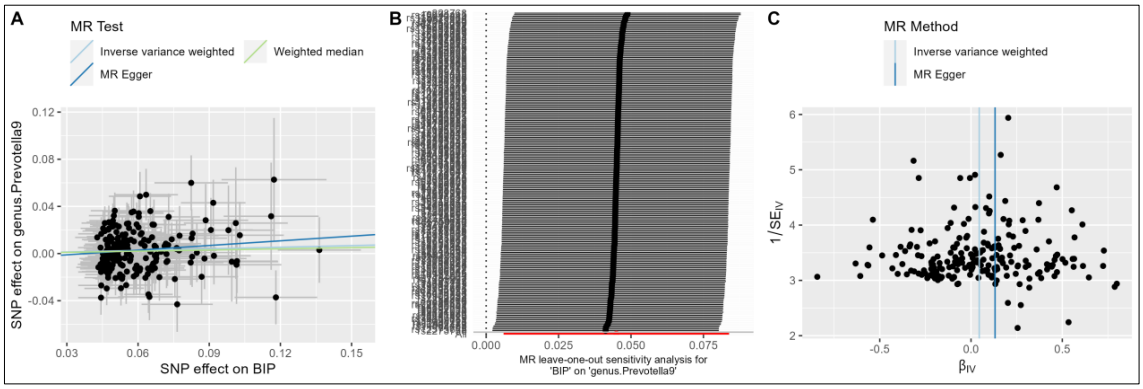
Exposure: BIP; Outcome: class.Mollicutes



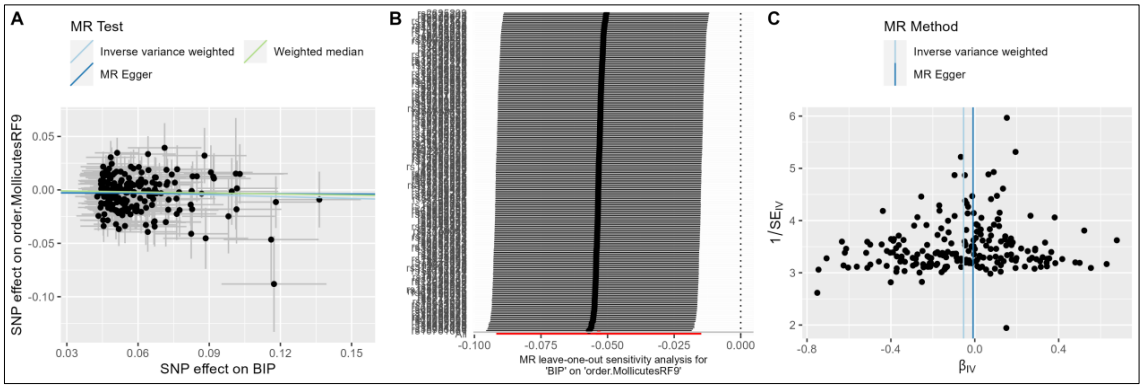
Exposure: BIP; Outcome: genus.ChristensenellaceaeR.7group



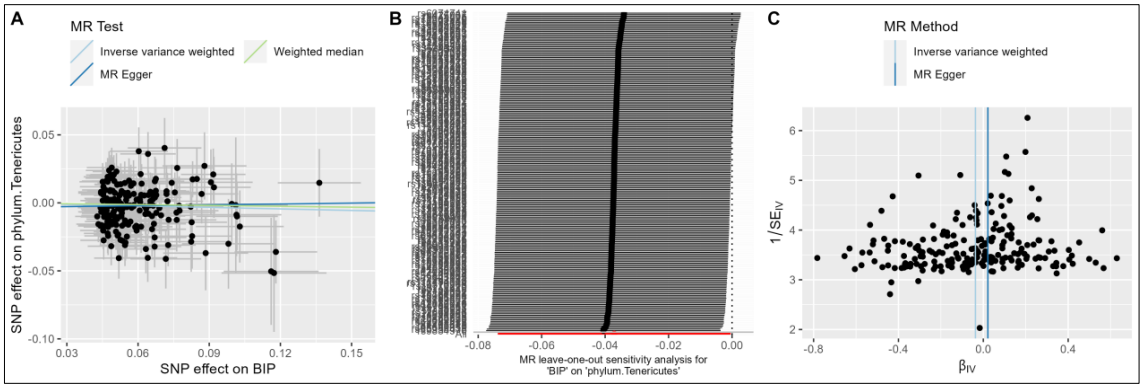
Exposure: BIP; Outcome: genus.Prevotella9



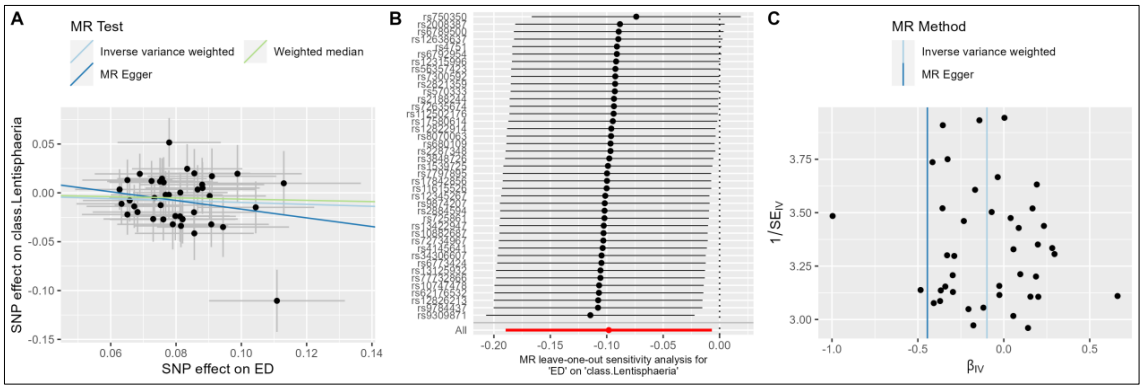
Exposure: BIP; Outcome: order.MollicutesRF9



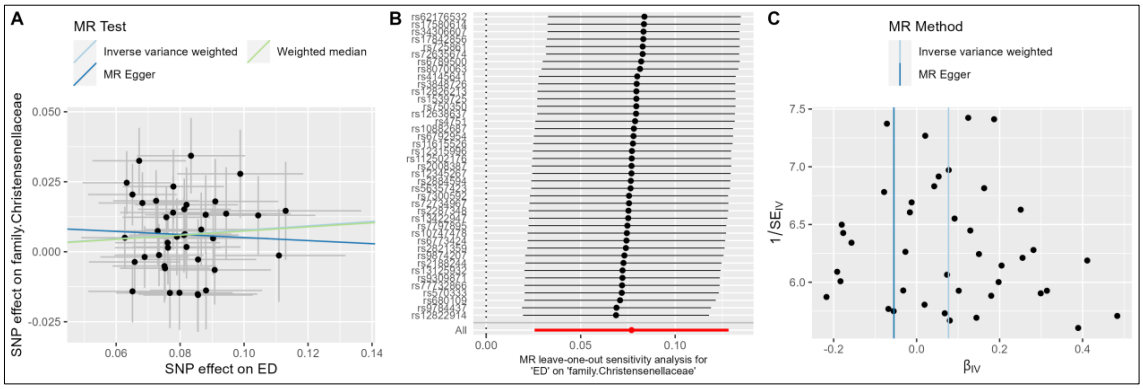
Exposure: BIP; Outcome: phylum.Tenericutes



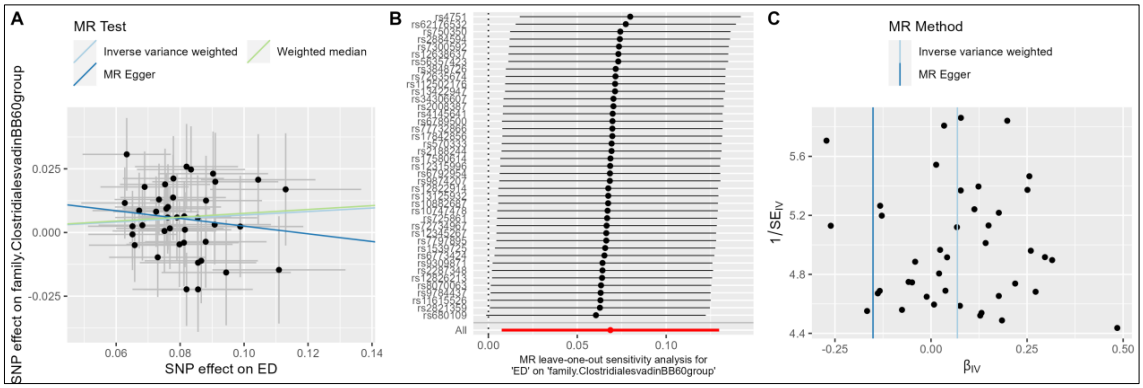
Exposure: ED; Outcome: class.Lentisphaeria



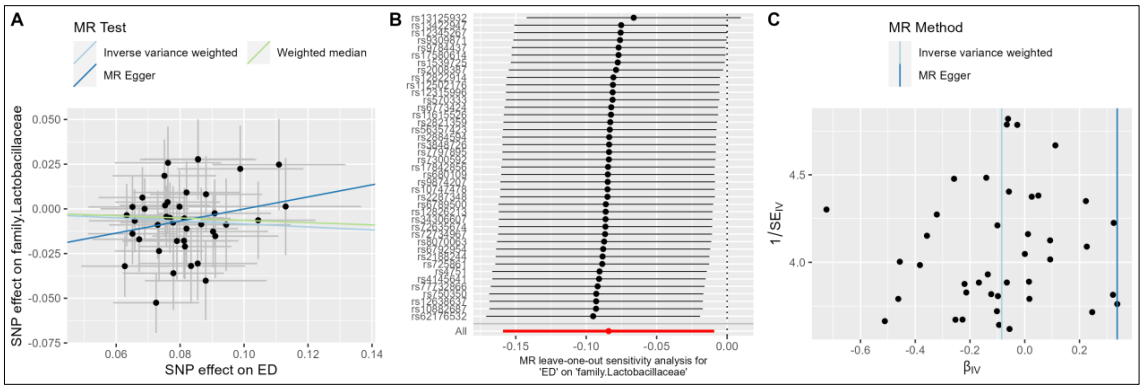
Exposure: ED; Outcome: family.Christensenellaceae



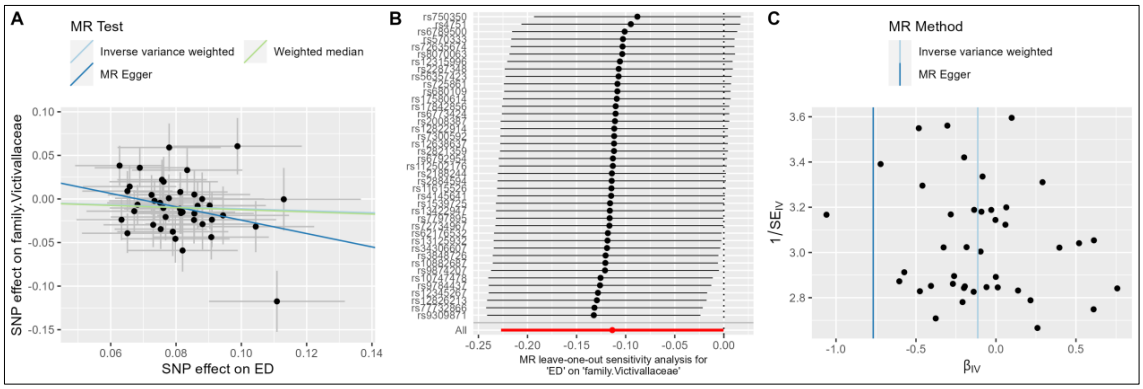
Exposure: ED; Outcome: family.ClostridialesvadinBB60group



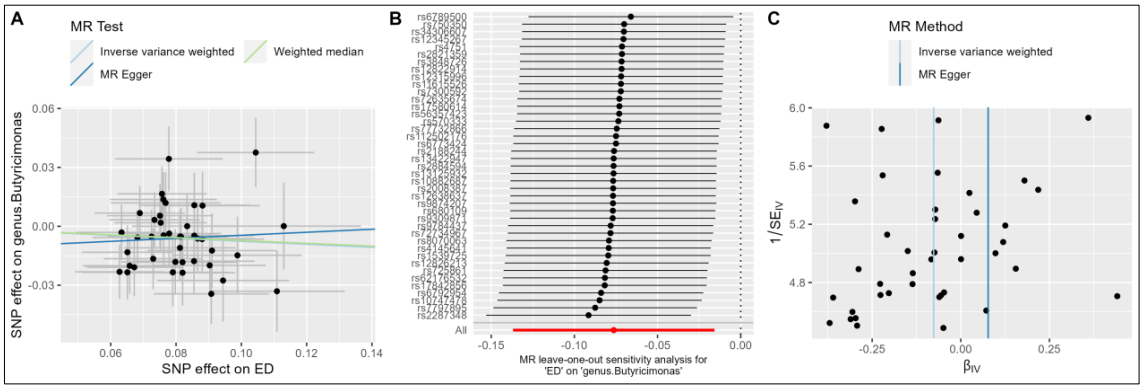
Exposure: ED; Outcome: family.Lactobacillaceae



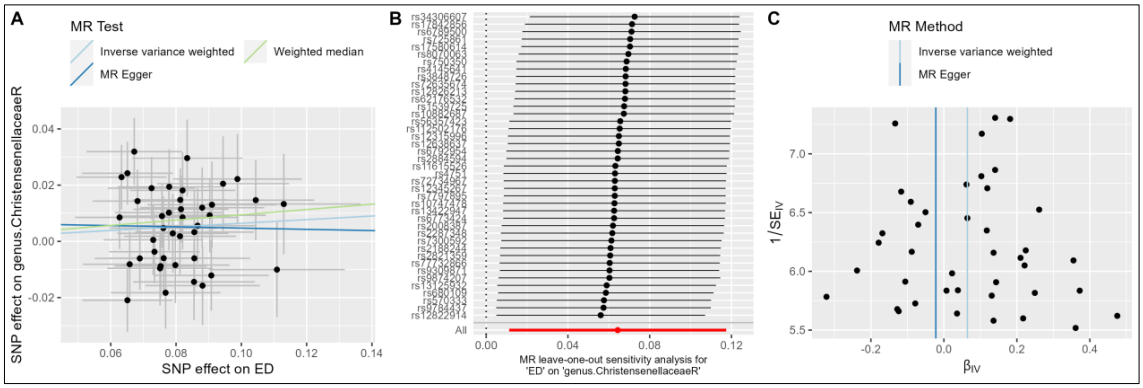
Exposure: ED; Outcome: family.Victivallaceae



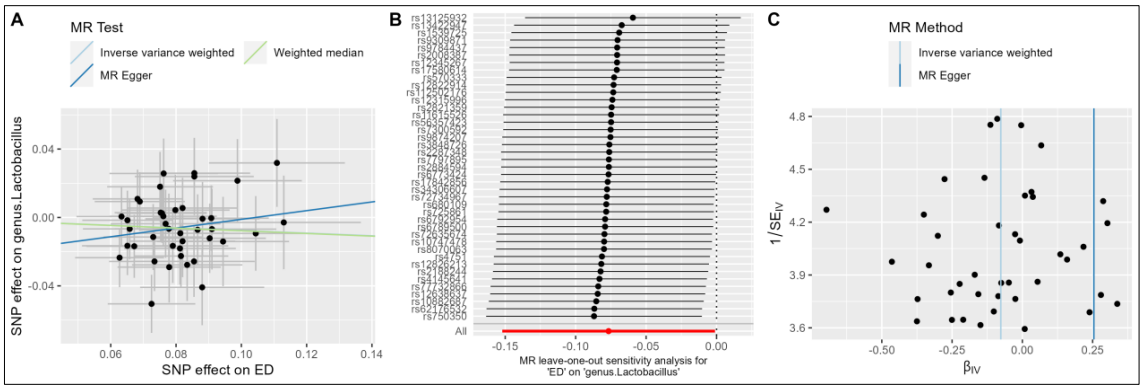
Exposure: ED; Outcome: genus.Butyricimonas



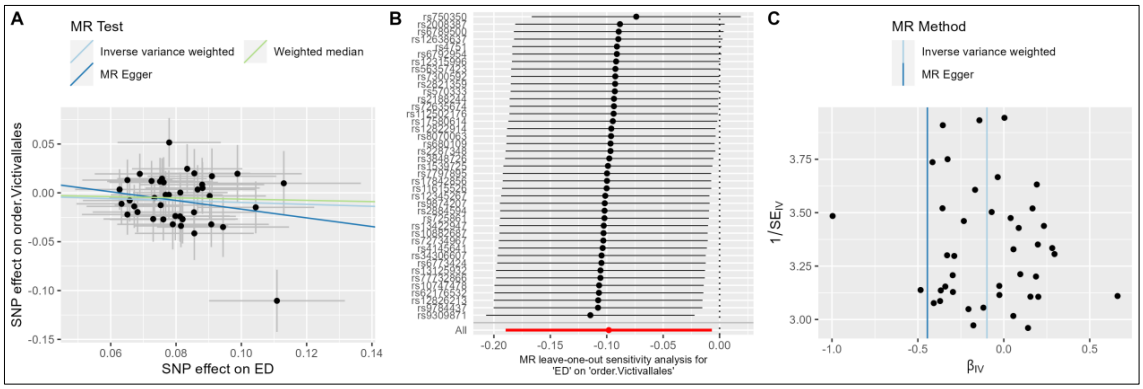
Exposure: ED; Outcome: genus.ChristensenellaceaeR.7group



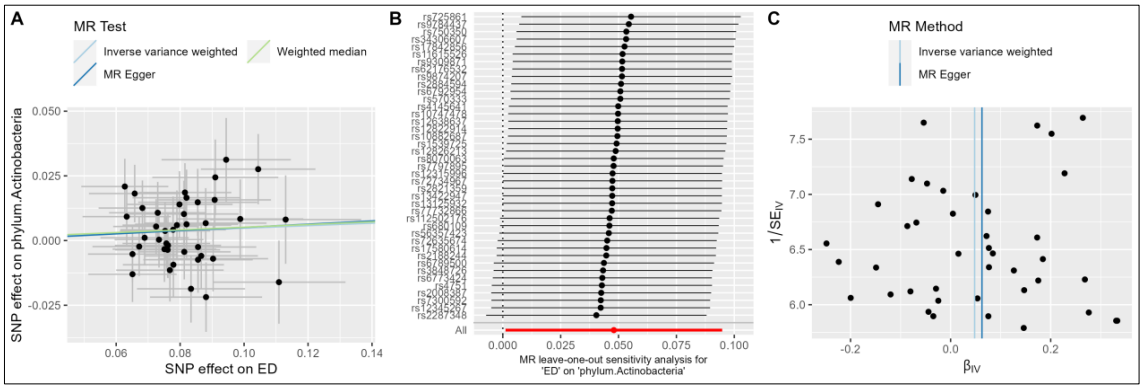
Exposure: ED; Outcome: genus.Lactobacillus



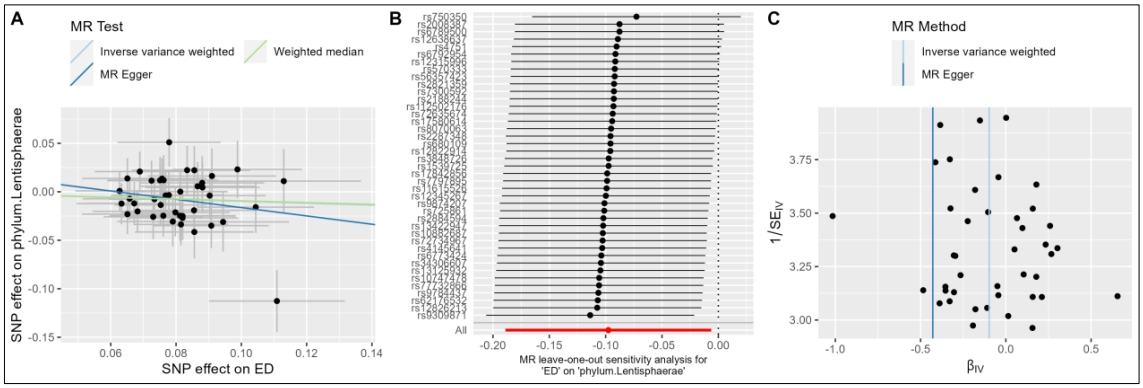
Exposure: ED; Outcome: order.Victivallales



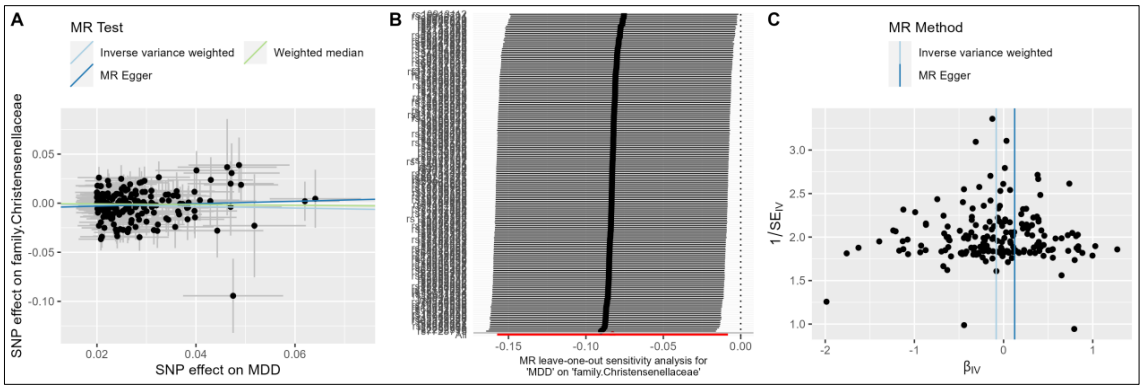
Exposure: ED; Outcome: phylum.Actinobacteria



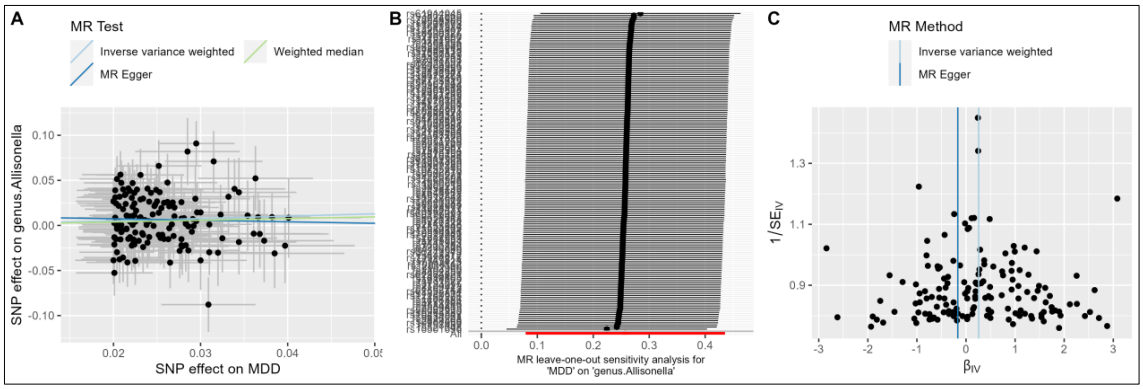
Exposure: ED; Outcome: phylum.Lentisphaerae



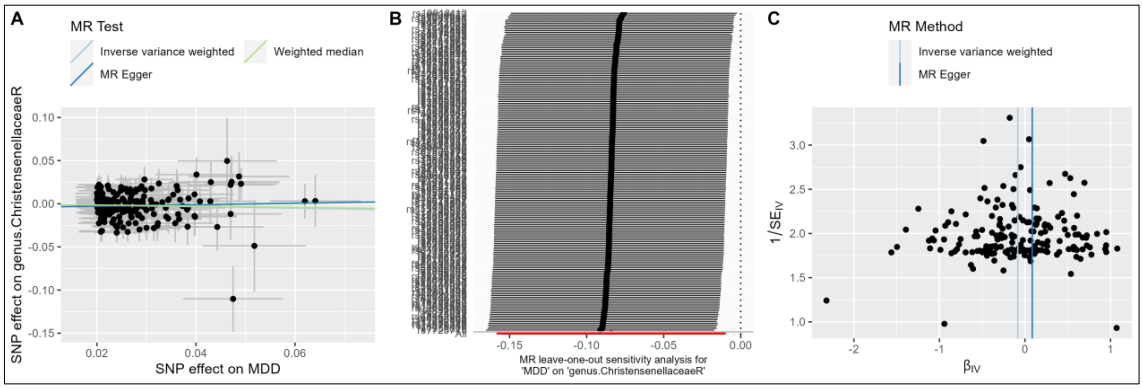
Exposure: MDD; Outcome: family.Christensenellaceae



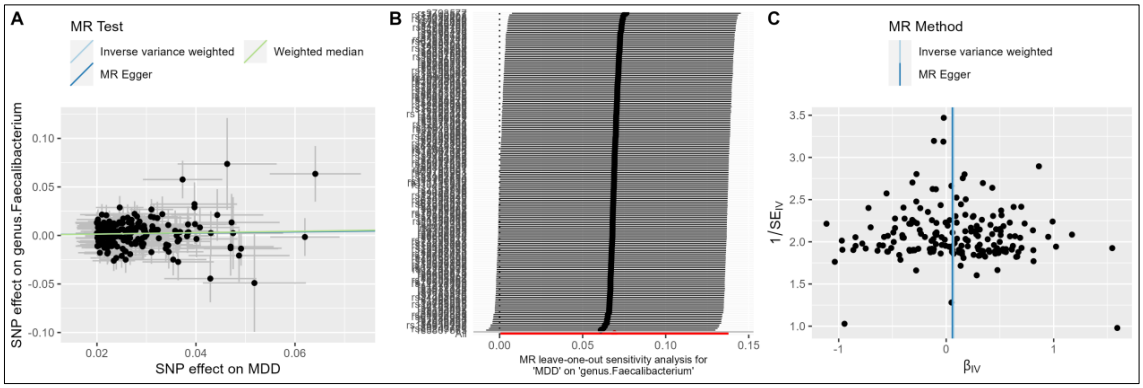
Exposure: MDD; Outcome: genus.Allisonella



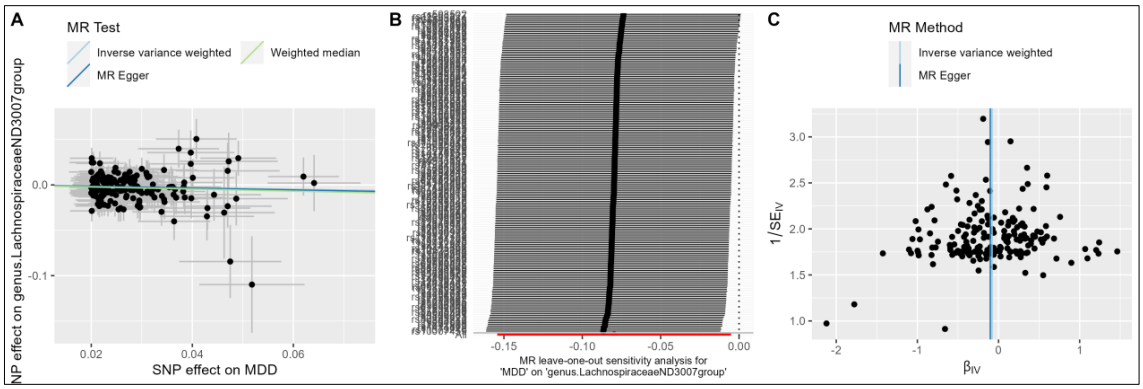
Exposure: MDD; Outcome: genus.ChristensenellaceaeR.7group



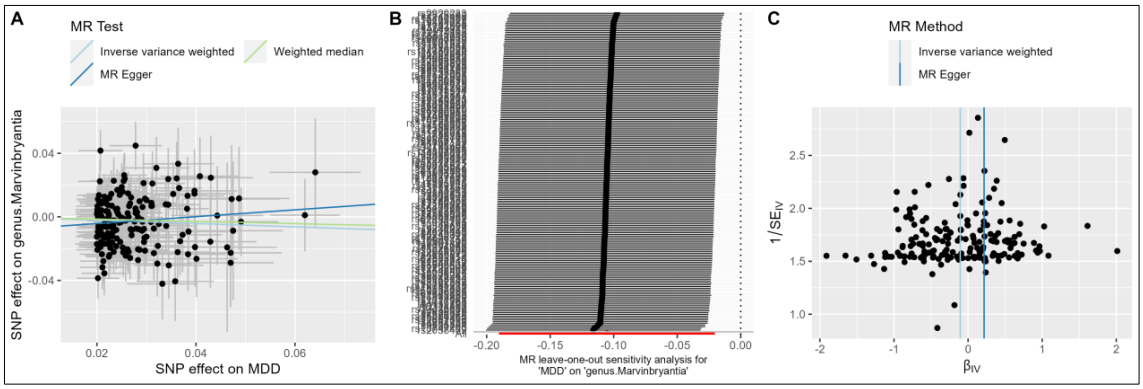
Exposure: MDD; Outcome: genus.Faecalibacterium



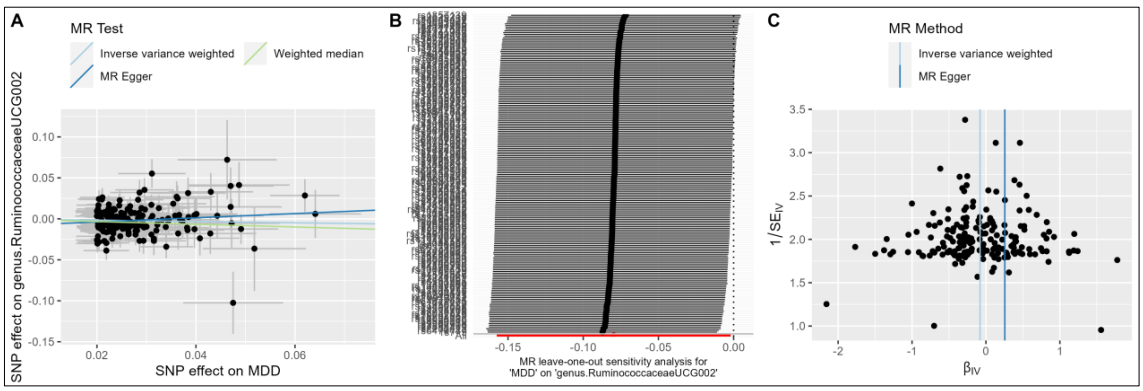
Exposure: MDD; Outcome: genus.LachnospiraceaeND3007group



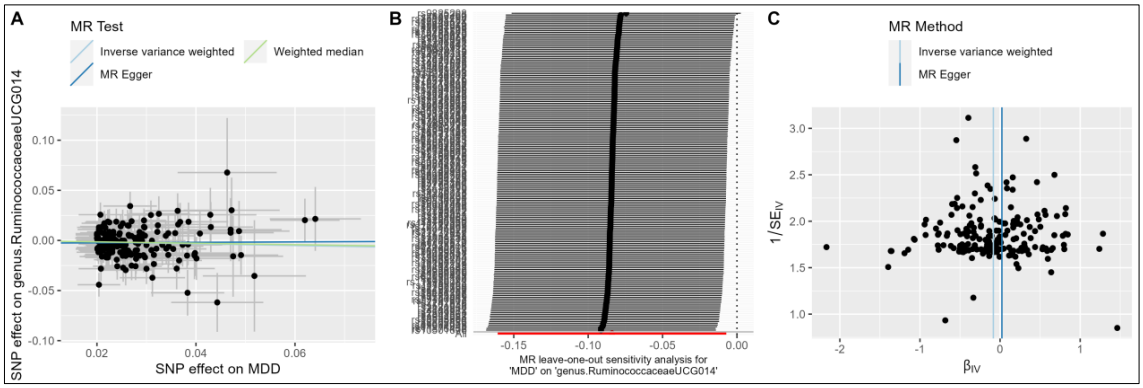
Exposure: MDD; Outcome: genus.Marvinbryantia



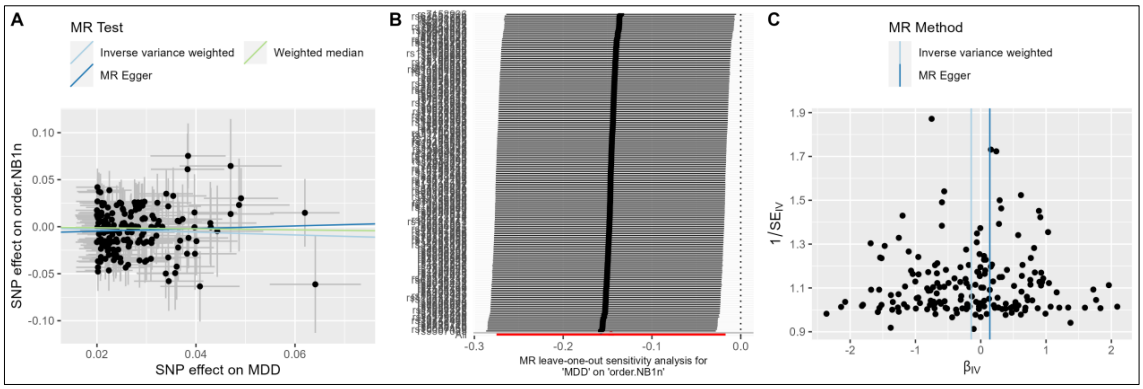
Exposure: MDD; Outcome: genus.RuminococcaceaeUCG002



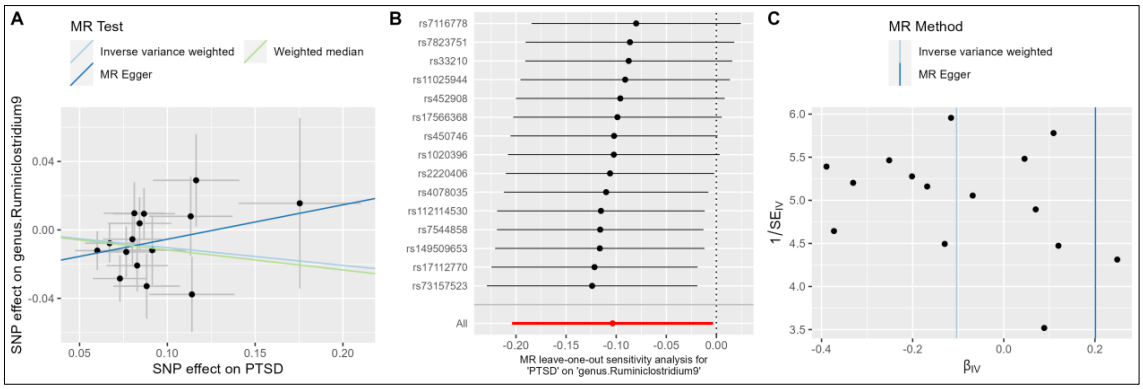
Exposure: MDD; Outcome: genus.RuminococcaceaeUCG014



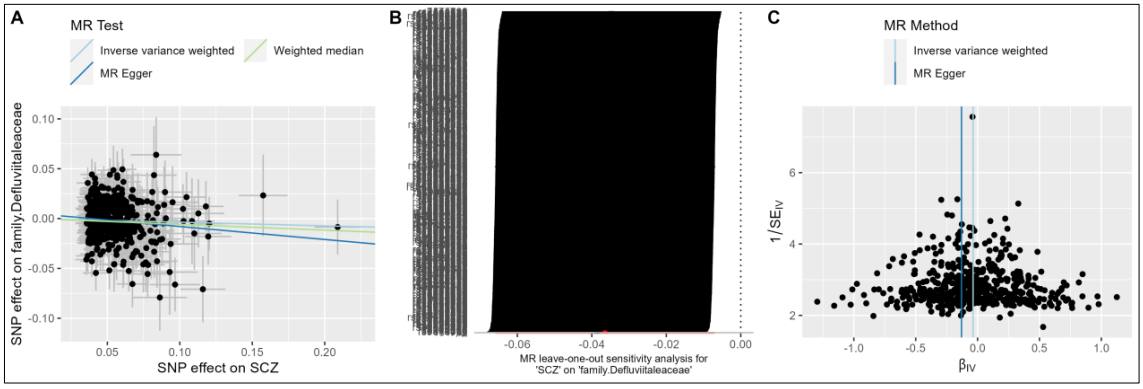
Exposure: MDD; Outcome: order.NB1n



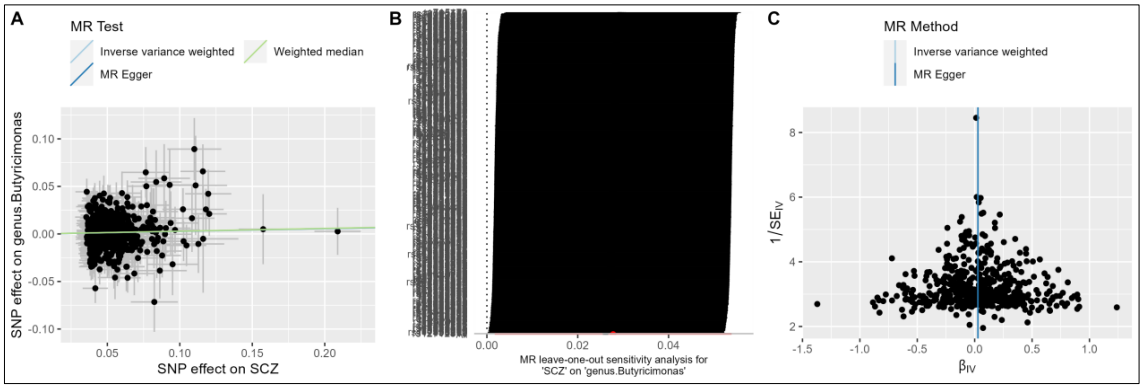
Exposure: PTSD; Outcome: genus.Ruminiclostridium9



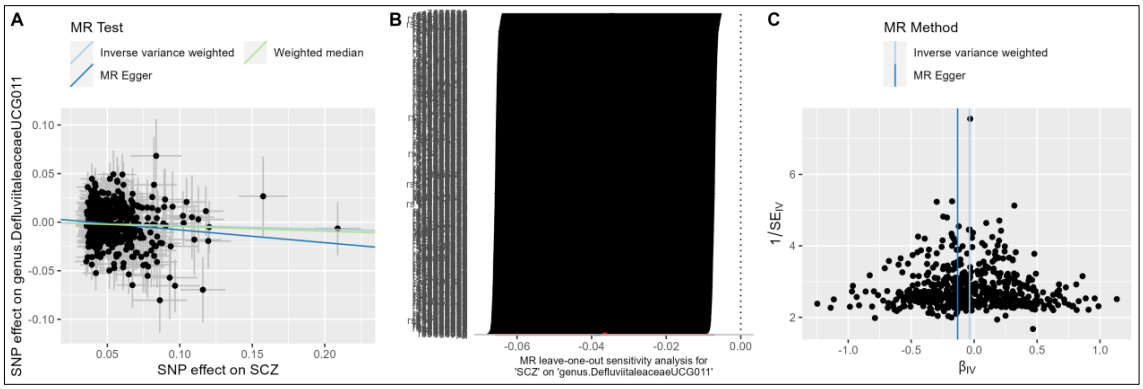
Exposure: SCZ; Outcome: family.Defluviitaleaceae



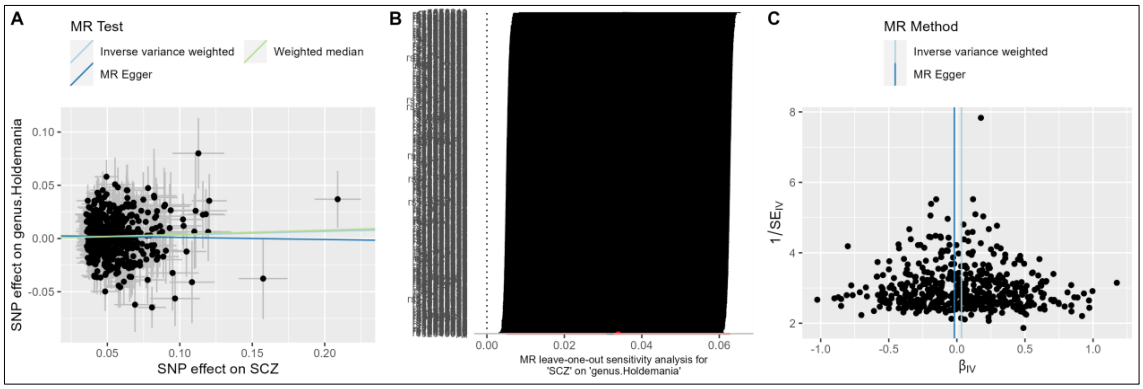
Exposure: SCZ; Outcome: genus.Butyricimonas



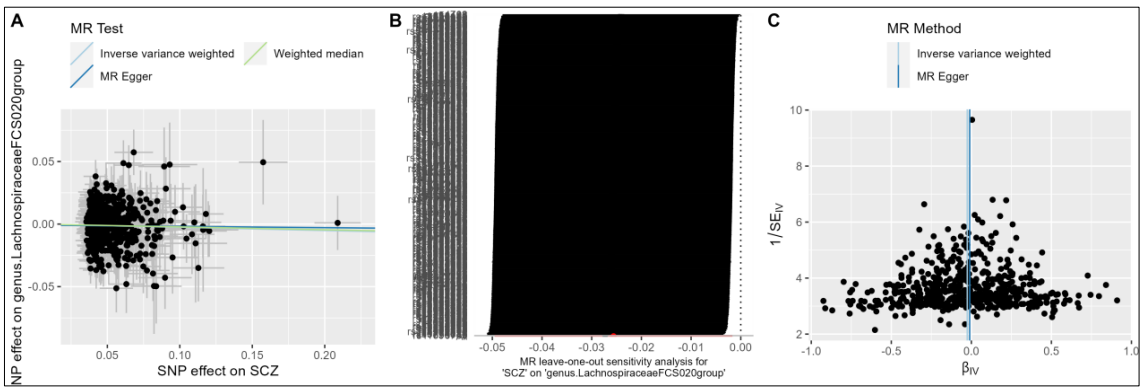
Exposure: SCZ; Outcome: genus.DefluviitaleaceaeUCG011



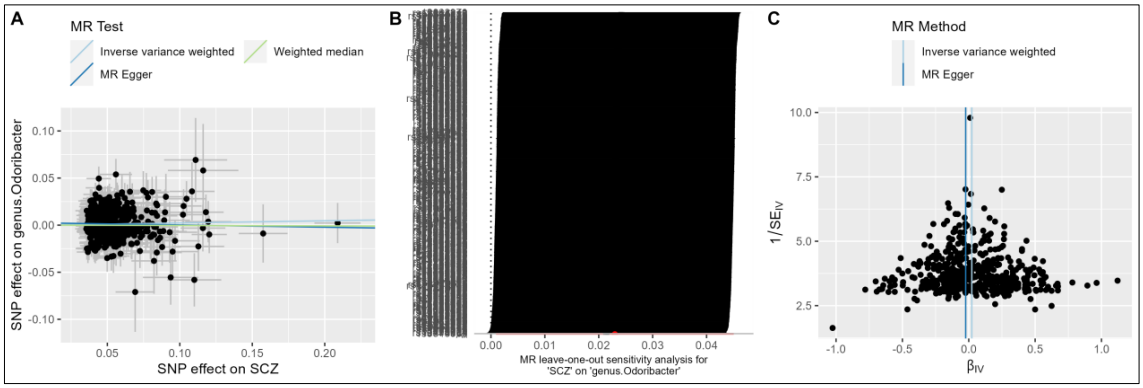
Exposure: SCZ; Outcome: genus.Holdemania



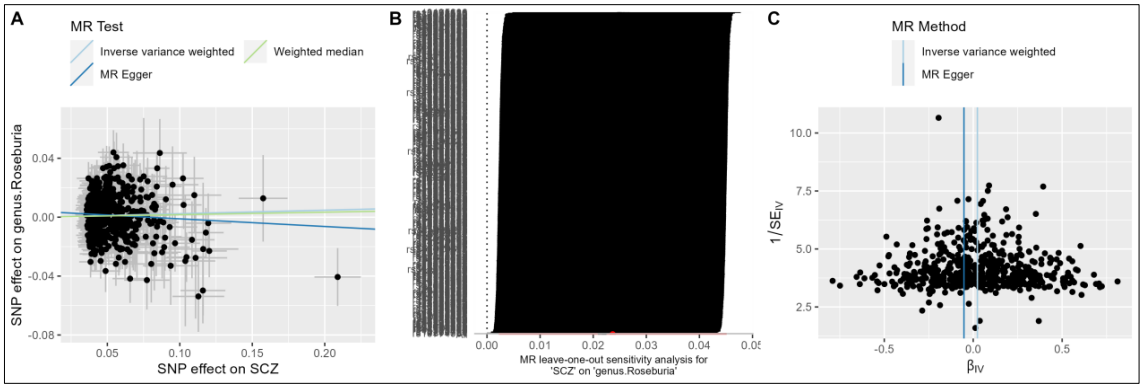
Exposure: SCZ; Outcome: genus.LachnospiraceaeFCS020group



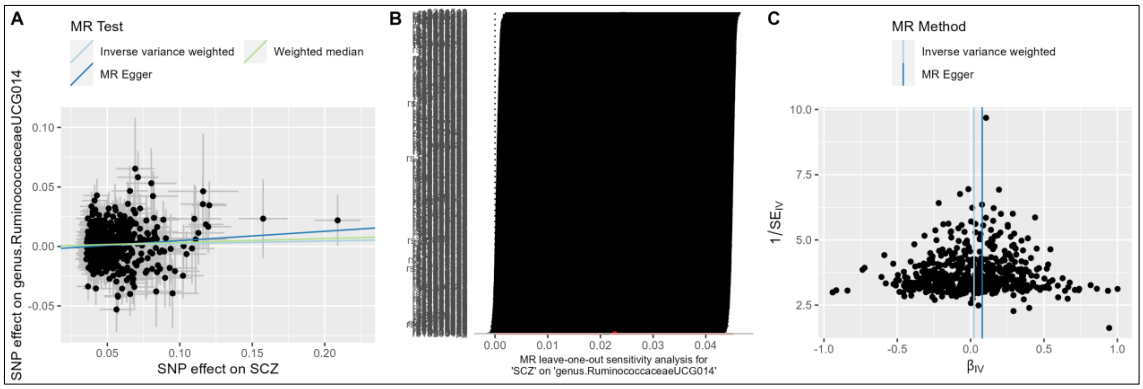
Exposure: SCZ; Outcome: genus.Odoribacter



Exposure: SCZ; Outcome: genus.Roseburia



Exposure: SCZ; Outcome: genus.RuminococcaceaeUCG014



Exposure: SCZ; Outcome: genus.Turicibacter

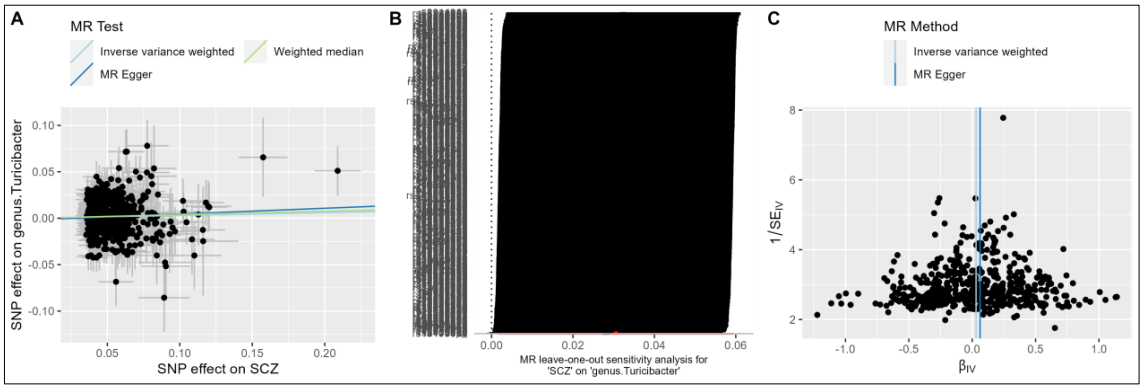


Figure S5. Scatter plots (A), leave-one-out plot (B) and funnel plot (C) of positive MR results for the causal effects of the risk of developing DGBIs on the risk of developing psychiatric disorders.

Exposure: FC; Outcome: MDD

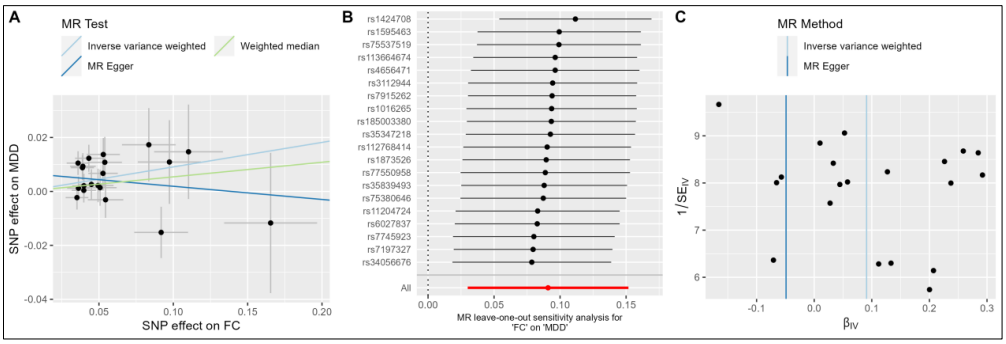
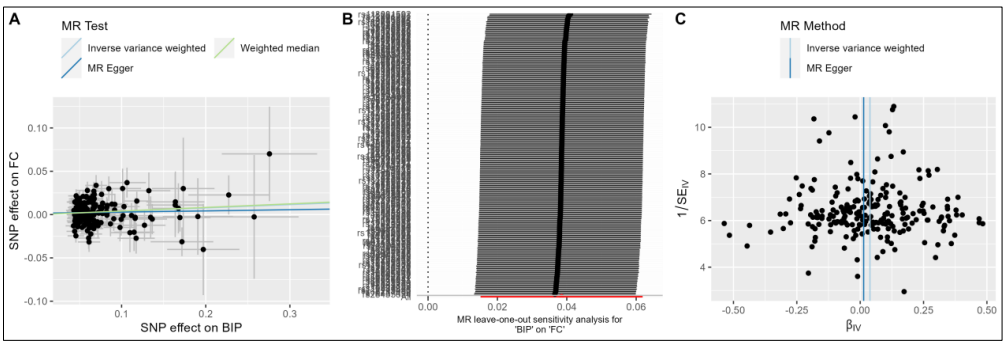
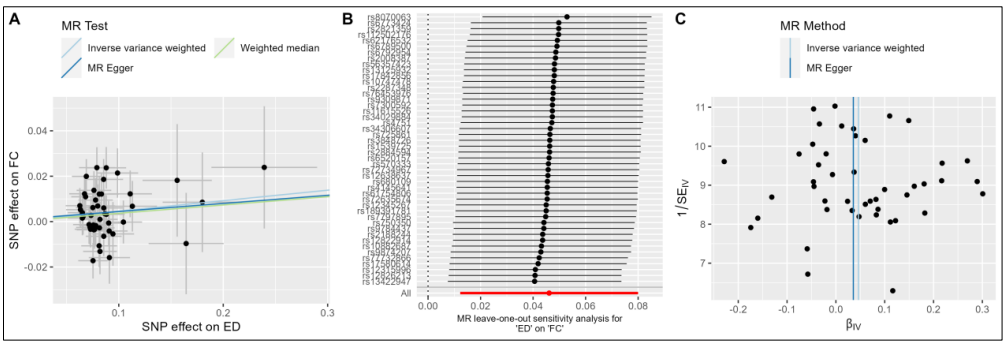


Figure S6. Scatter plots (A), leave-one-out plot (B) and funnel plot (C) of positive MR results for the causal effects of the risk of developing psychiatric disorders on the risk of developing DGBIs.

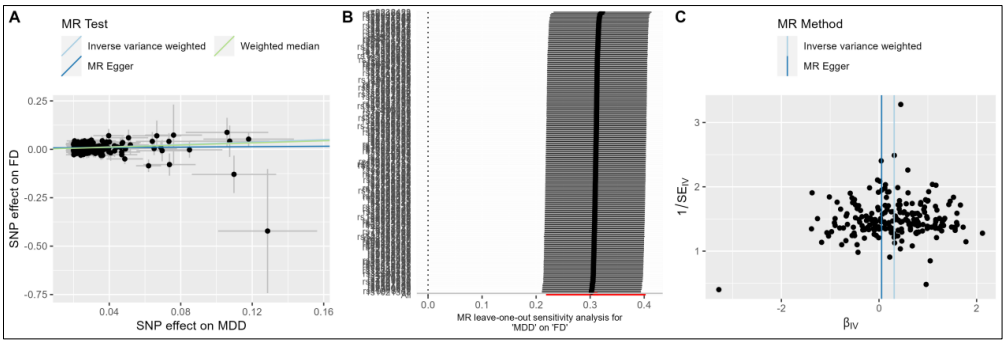
Exposure: BIP; Outcome: FC



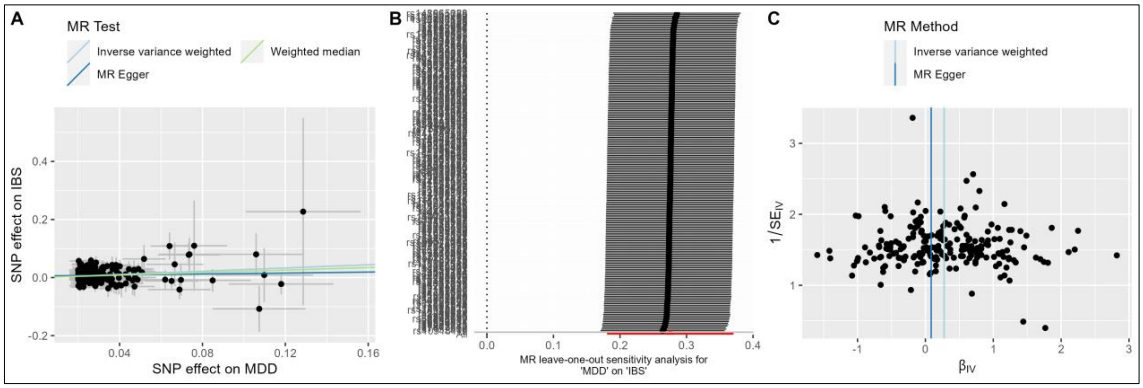
Exposure: ED; Outcome: FC



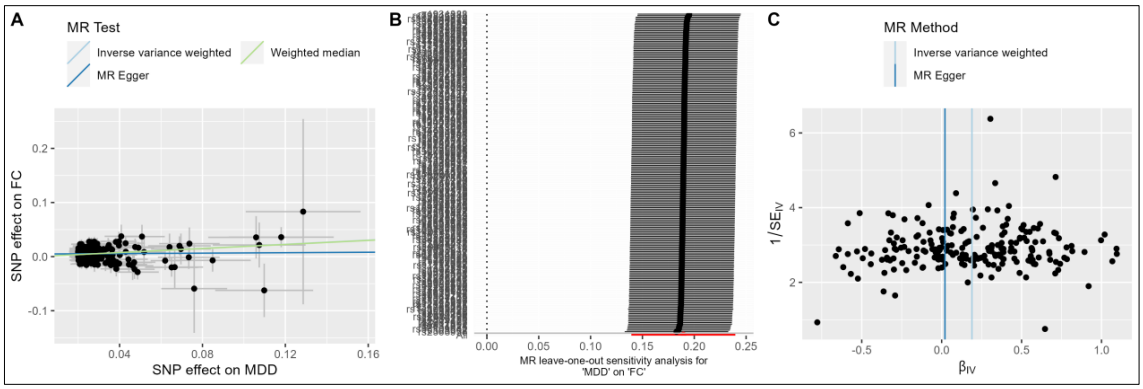
Exposure: MDD; Outcome: FD



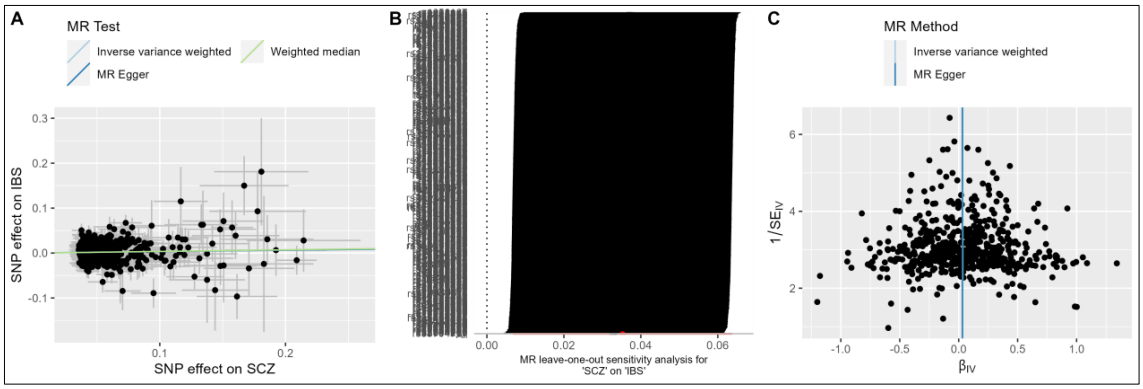
Exposure: MDD; Outcome: IBS



Exposure: MDD; Outcome: FC



Exposure: SCZ; Outcome: IBS



Exposure: SCZ; Outcome: FC