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| --- | --- | --- | --- | --- | --- | --- |
|  | **IBS ⟶ DEP** | **DEP ⟶ IBS** | **IBS ⟶ DED** | **DED ⟶ IBS** | **DED ⟶ DEP** | **DEP ⟶ DED** |
| **GWAS**  **COJO**  **SAIGE** | A graph of a graph  Description automatically generated with medium confidence | A graph of a graph of a person  Description automatically generated with medium confidence | A graph of a line graph  Description automatically generated with medium confidence | A graph of a graph of a graph  Description automatically generated with medium confidence | A graph with lines and numbers  Description automatically generated | A graph with lines and numbers  Description automatically generated |
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Figure 2. Scatter plot of the Mendelian randomization (MR) analysis: one-sample Mendelian randomization (OSMR). GWAS: genome-wide association study; COJO: conditional and joint association analysis; IBS, inflammatory bowel disease; DEP, depression; DED, dry eye disease. \* SAIGE was only applied in the IBS to DEP, DEP to IBS, IBS to DED, and DED to IBS groups due to the low case‒control ratio.

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| **GWAS**  **SAIGE**  **COJO** | **IBS ⟶ DEP** | **DEP ⟶ IBS** | **IBS ⟶ DED** | **DED ⟶ IBS** | **DED ⟶ DEP** | **DEP ⟶ DED** |
|  | A graph of a graph  Description automatically generated with medium confidence | A graph of a graph  Description automatically generated with medium confidence | A graph of a graph  Description automatically generated with medium confidence | A graph of a graph of a graph  Description automatically generated with medium confidence | A graph with lines and numbers  Description automatically generated | A graph of lines and dots  Description automatically generated |
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Figure 3. Scatter plot of the Mendelian randomization (MR) analysis: two-sample Mendelian randomization (TSMR). GWAS: genome-wide association study; COJO: conditional and joint association analysis; IBS, inflammatory bowel disease; DEP, depression; DED, dry eye disease. \* SAIGE was only applied in the IBS to DEP, DEP to IBS, IBS to DED, and DED to IBS groups due to the low case‒control ratio.

A screenshot of a graph

Description automatically generated

**GWAS**

**COJO**

**SAIGE**

**DEP ⟶ DED**

**DED ⟶ DEP**

**DED ⟶ IBS**

**DEP ⟶ IBS**

**IBS ⟶ DED**

**IBS ⟶ DEP**

Figure 4. Effect size (beta) of leave-one-out (LOO) approach for heterogeneity analysis of one-sample Mendelian randomization (OSMR) using the inverse-variance weighted (IVW) method. LOO omits instrumental single-nucleotide polymorphisms (SNPs) one by one to explore whether the MR estimates were disproportionately influenced by certain SNPs. GWAS: genome-wide association study; COJO: conditional and joint association analysis; IBS, inflammatory bowel disease; DEP, depression; DED, dry eye disease. \* SAIGE was only applied in the IBS to DEP, DEP to IBS, IBS to DED, and DED to IBS groups due to the low case‒control ratio.

A screenshot of a graph

Description automatically generated

**GWAS**

**COJO**

**SAIGE**

**IBS ⟶ DEP**

**IBS ⟶ DED**

**DEP ⟶ IBS**

**DED ⟶ IBS**

**DED ⟶ DEP**

**DEP ⟶ DED**

Figure 5. Effect size (beta) of leave-one-out (LOO) approach for heterogeneity analysis of two-sample Mendelian randomization (TSMR) using the inverse-variance weighted (IVW) method. LOO omits instrumental single-nucleotide polymorphisms (SNPs) one by one to explore whether the MR estimates were disproportionately influenced by certain SNPs. GWAS: genome-wide association study; COJO: conditional and joint association analysis; IBS, inflammatory bowel disease; DEP, depression; DED, dry eye disease. \* SAIGE was only applied in the IBS to DEP, DEP to IBS, IBS to DED, and DED to IBS groups due to the low case‒control ratio.