# Result

A bidirectional, two-sample MR analysis was used to investigate the causative link between MDD levels and the risk of migraine and its subtypes. Our MR findings demonstrated a link between genetic vulnerability to MDD and an elevated risk of migraine and its subtypes; however, a link between migraine risk and MDD levels could not be established.

## Causal effects of MDD on AN

### Selection of instrumental variables

The publicly accessible MDD GWAS dataset was retrieved using the R programming language. We included 50 SNPs that were both substantially (p < 5E-08) linked with exposure (MDD) and independent (r2 < 0.001 and KB > 10,000). Some SNPs not detected in the result dataset were eliminated when utilizing these SNPs to correlate with the concluding GWAS dataset. One SNP was lost in the three MDD-migraine, MDD-MA, and MDD-MO analysis groups (rs35469634). After that, we removed two palindromic SNPs with intermediate allele frequencies from all three investigations (rs2876520 and rs4730387). It is worth noting that the OR direction of the MR-Egger transformation was inconsistent with other approaches when assessing MDD and MO; thus, we decreased P 10E-09 and repeated the MR study. Finally, 47 SNPs were identified as IVs in the MDD versus migraine and MA analysis (Supplementary Table 1), and 27 SNPs were identified as IVs in the MDD versus MO analysis (Supplementary Table S1). All F-statistics for the instrumental variables utilized in the final analysis were more extensive than 10 (MDD-Migraine and MDD-MA: mean value of 30–78, range of 39; MDD-MO: mean value of 34–78, range of 44). It was suggested that these are robust IVs and satisfy the strong correlation assumption of MR.

### Two-sample Mendelian randomization analysis

IVW was used as the primary method of analysis, which revealed a causal relationship between genetic susceptibility to MDD and increased risk of AN (OR:1.520, 95% CI:1.190-1.950, p<0.001). Secondary analysis methods included MR-Egger OR: 1.722, 95% CI:0.437-6.785, p<0.442), weighted median (OR, 1.474, 95% CI:1.122-1.936,p = 0.004), weighted mode (OR, 1.371, 95% CI:0.738-2.546,p = 0.325). The resulting OR values were all greater than 1 after transforming the relative risk ratios (Figures 2, ​,33s).

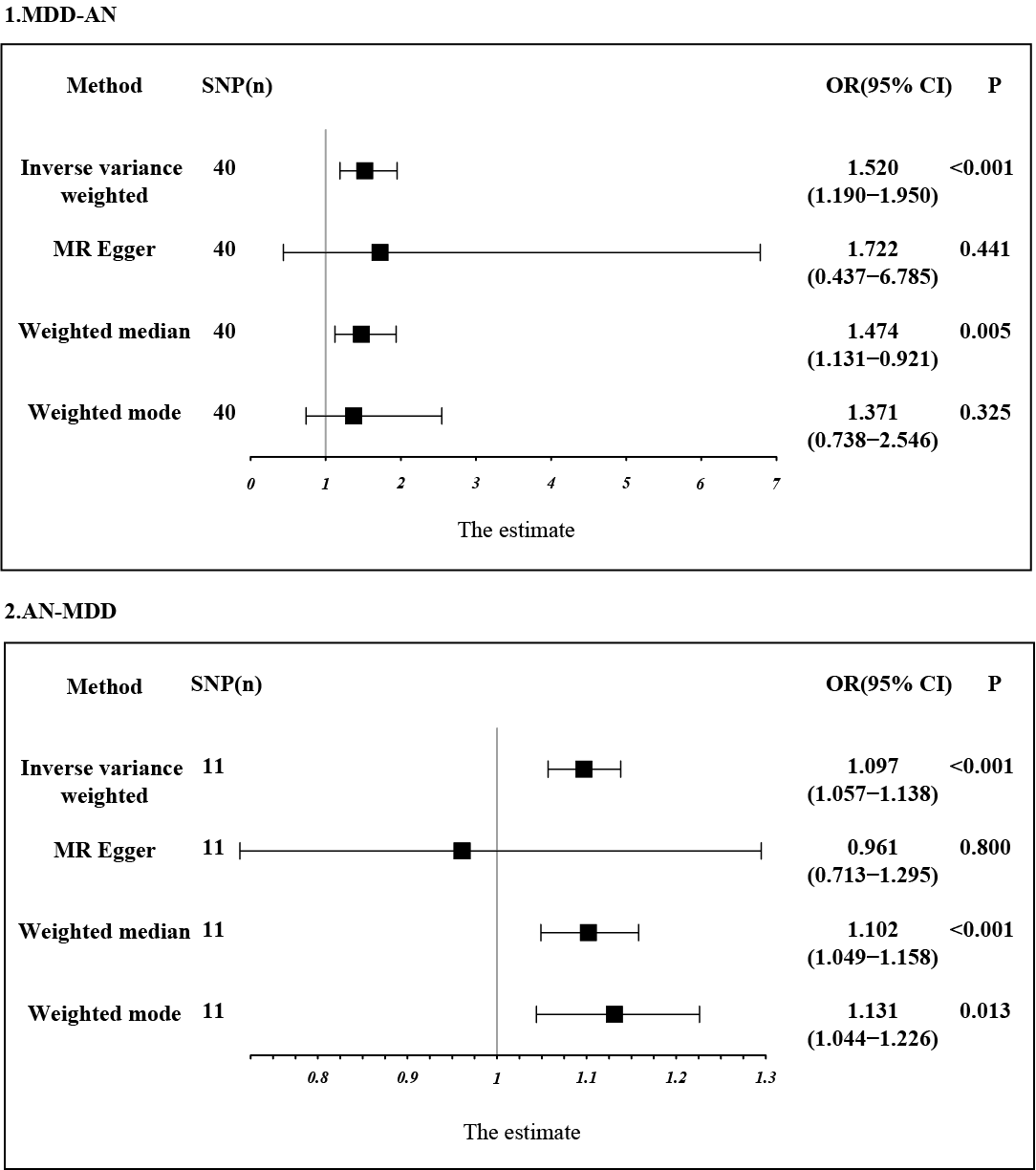


Fig2 Estimation of the causal relationship between MDD and migraine (MA and MO) using different MR methods. An OR value greater than 1 suggests that the exposure indicator is a risk factor while the opposite is a protective factor.

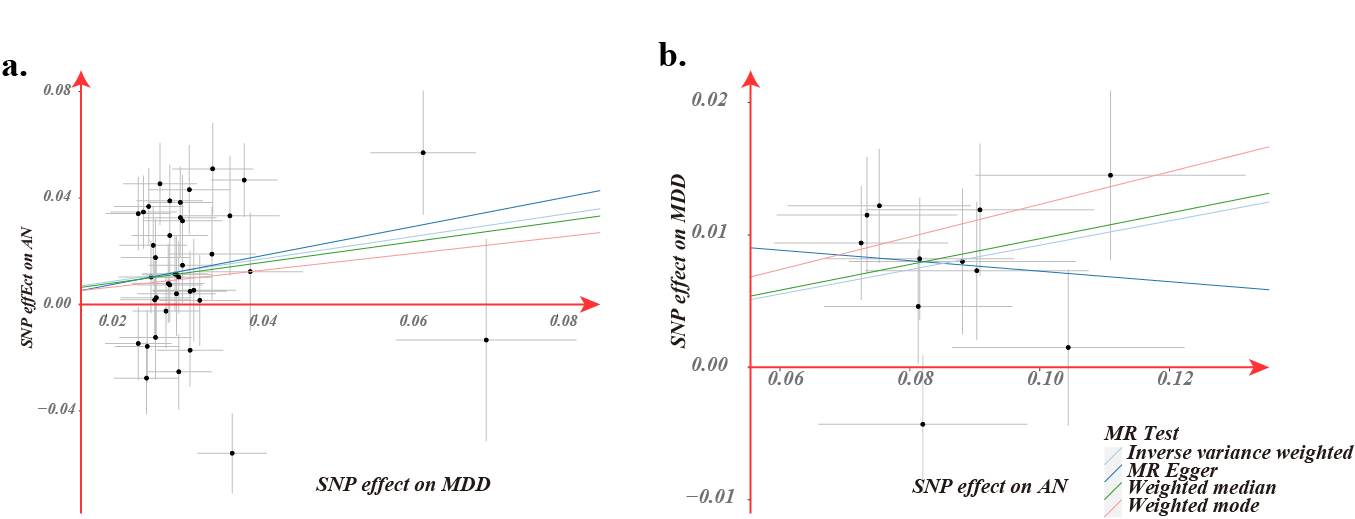


Fig3 Scatter plot of genetic correlation between MDD and migraine by different MR analysis methods.

### Sensitivity analysis and visualization

MR-Egger regression and IVW analysis were used to detect heterogeneity. MR-Egger regression (MDD-Migraine: Cochran’s Q = 52.376) and IVW (Cochran’s Q = 52.967, p = 0.223) indicated that there was no heterogeneity in the study. Funnel plots for the visualization of heterogeneity are shown in Supplementary Figure S1. The MR-Egger intercept did not show horizontal pleiotropy (Egger intercept, 0.013, p = 0.480). The MR-PRESSO test found no outliers, and the global test showed no pleiotropy (global test: MDD-Migraine: p = 0.269; MDD-MA: p = 0.471; MDD-MO: p = 0.725). We used the leave-one-out method to eliminate SNPs one at a time to determine whether the causal association was due to a single IV, and the final results demonstrated that the TSMR analysis results were robust (Figure 4). Forest plots for MR analyses of the relationship between MDD and migraine (both MA and MO) (Supplementary Figure S2).

## Reverse TSMR analysis