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ORIGINAL RESEARCH

Causal Link of Distinct Mental Disorders with Androgenetic Alopecia and Alopecia Areata: A Bidirectional Two-Sample Mendelian Randomization Study

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Background: The concern that mental states affect the hair-loss has been growing, but the causal evidence is still limited. We aimed to investigate whether and in which direction there is a causal link of distinct mental disorders with androgenetic alopecia (AGA) and alopecia areata (AA) in European population.

Methods: We performed a bidirectional two-sample Mendelian randomization (MR) study to test their causality using summary statistics. The datasets of major depression disorder, anxiety disorder, panic attack, distress, and bipolar disorder were all accessed through the IEU OpenGWAS project. The datasets employed for AGA and AA analysis were sourced from the FinnGen release 10 databases, including 219,469 (220 AGA cases and 219,249 controls) and 394,872 (767 AA cases and 394,105 controls) participants, respectively. We utilized five extensively employed MR techniques to explore the bidirectional causal associations, including inverse variance weighted (IVW), weighted median, MR-Egger, weighted mode, and penalised weighted median.

Results: Based on the IVW method, a bidirectional causal association was revealed whereby major depression disorder is associated with an increased risk of AA (OR: 1.59; 95% CI: 1.16–2.17) and vice versa (OR: 1.02; 95% CI: 1.00–1.03). Notably, the statistical power of MR estimates was both <80%. No association of any genetically predicted mental disorders with AGA was found. Sensitivity analyses substantiated the robustness and reliability of our findings.

Conclusion: Our findings showed a bidirectional causal association between major depression disorder and AA, supporting the importance of therapies aimed at handling mental states for the prevention or treatment of AA rather than AGA.

Keywords: major depression disorder, androgenetic alopecia, alopecia areata, Mendelian randomization

Introduction

Alopecia represents a prevalent and challenging condition with multifaceted physical and mental implications, such as anxiety, depression, and emotional disorders,[1–3] which directly impact self-image, personal identity, and quality of life.[4,5] Androgenetic alopecia (AGA) and alopecia areata (AA) account for the majority of non-scarring alopecia.[6] The most common form of AGA involves representative receding of the forehead hairline in men and thinning the hair between the forehead and the apex of the scalp. The forehead hairline remains unchanged in women.[1,7,8] AA is a chronic follic-specific autoimmune disease characterized by patchy alopecia that can progress to diffuse or complete loss of scalp and body hair.[9] The prevalence of alopecia was also raised with age, and the impact of non-scarring alopecia on patients' lives was often underestimated.[1] Alopecia is associated with an increased risk of metabolic syndrome, cardiovascular disease, diabetes, and hypertension.[10–14]

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Numerous factors interact to promote the development of non-scarring alopecia, including genetic predisposition, endocrine factors, and mental implications.[15,16] Previous studies have suggested that mental disorders are linked with alopecia. A meta-analysis of 4 cross-sectional studies and 4 case–control studies including 6,010 patients with AA and 20,961 control individuals showed that AA has a positive association with anxiety and depression.[17] Moreover, existing Mendelian randomization (MR) has unveiled that AA can exert a risk effect on major depression disorder and anxiety.[18] Although AGA is primarily driven by genetic and androgen sensitivity, psychological stress might modulate disease severity through neuroendocrine and inflammatory pathways.[19–22] Testosterone and dihydrotestosterone modulate the neuroendocrine response to stress and are inversely related to depression rates.[23] A meta-analysis of 41 studies with 7995 patients found a significant association of AGA with moderate impairment of both health-related quality of life and emotions, but no association was found with depressive symptoms.[5] Besides, the latest MR study provided some clues that AGA may precipitate the development of depression.[24] However, evidence for causal associations between AA and other mental health states is insufficient, and it is unclear whether mental disorders have a causal impact on AGA. It is difficult to design studies on whether mental disorders play an etiologic role in the onset and progression of non-scarring alopecia at this stage, and some studies to explain the pathophysiological mechanisms remain speculative. To address the issues, we hypothesize that certain mental disorders may causally influence AA and AGA.

MR, leveraging the genetic variants as instrumental variables (IVs), has been widely used to address causal inference of exposure on outcomes. Genetic variants are randomly allocated at fertilization and not affected by factors later in life, thus the MR design can notably mitigate the residual confounding and preclude reverse causality. Compared with randomized controlled trials, MR design can reduce resource intensity and avoid long-term follow-up.[25] Therefore, to examine whether mental diseases (depression, anxiety, panic, distress, and bipolar disorder) are causally related to the pathogenesis of non-scarring alopecia as well as the causal effect of non-scarring alopecia on mental diseases, we executed a two-sample bidirectional MR using publicly available summary statistics from several large-scale genome-wide association studies (GWASs).

Materials and Methods

Study Design

We obtained all data and materials from public databases. Summary statistics from several large-scale GWASs regarding 5 mental disorders and 2 non-scarring alopecia were all obtained from European descent. The bidirectional two-sample MR design was utilized to examine the bidirectional association of mental diseases (depression, anxiety, panic, distress, and bipolar disorder) on non-scarring alopecia (AGA and AA). The forward MR analyses investigated the causal relationship between mental disorders and non-scarring alopecia. In contrast, the reverse MR analyses explored the causality with non-scarring alopecia and mental diseases (Figure 1). We reported this study according to the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR).[26] All the original studies were approved by their respective institutional review boards, and informed consent was provided by all participants. Due to the publicly available summary statistics used, no additional ethical approval was required.

Data Sources

The sources of summary statistics for mental disorders and non-scarring alopecia included in our work were placed in Supplementary Table S1. The definitions of all traits and corresponding details, such as recruitment criteria of population and quality control of genetic data, were directly referenced from the original reports without any changes. The datasets of major depression disorder (ieu-b-102), anxiety disorder (ukb-d-20544_15), panic attack (ukb-d-20544_6), distress (ukb-d-20499), and bipolar disorder (ieu-b-5110) were all accessed through the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/).

GWAS summary statistics for AGA and AA were sourced from the FinnGen Biobank study (Release 10), including 219,469 (220 AGA cases and 219,249 controls) and 394,872 (767 AA cases and 394,105 controls) participants, respectively (https://www.finngen.fi/en). The International Classification of Diseases (ICD) codes for AGA were L64 and 7040A; ICD codes for AA were L63, 7040B, 7040C, and 70400. Crucially, for both forward and reverse MR, to avoid bias and ensure a low type 1 error rate, we chose datasets of mental disorder and non-scarring alopecia with no overlap samples.

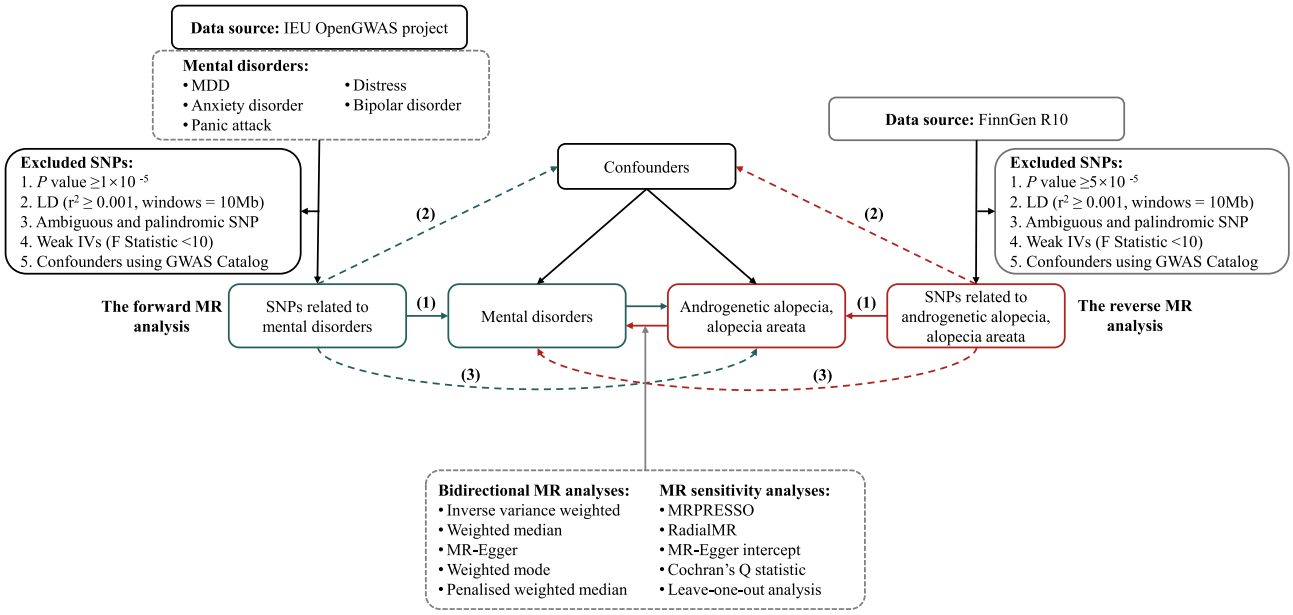

Figure 1 The design of a bidirectional two-sample MR study examining the causal association of mental disorders (depression, anxiety, panic, distress, and bipolar disorder) with AGA and AA. The causal effect of mental disorders on non-scarring alopecia was depicted in blue, while the reverse association was illustrated in red. To serve as an instrumental variable, three assumptions must be met: (1) Relevance. (2) Independence. (3) Exclusion.
Abbreviation: AA, alopecia areata; AGA, androgenetic alopecia; LD, linkage disequilibrium; MDD, major depression disorder; MR, Mendelian randomization.

Genetic IVs Selection

The genetic variant used in the MR design must fulfill three essential assumptions: (1) The genetic variant is robustly linked with the exposure (relevance); (2) The genetic variant is independent of any confounders (independence); (3) The genetic variant does not affect the outcome, except possibly via the exposure-outcome pathway (exclusion restriction).[25]

Single nucleotide polymorphisms (SNPs) were utilized as IVs. In the forward MR study, due to the limited number of SNPs of mental disorders, a more lenient significance level ($P < 1\times10^{-5}$) was set.[18] In the reverse MR study, considering the limited GWAS dataset of AGA and AA, SNPs with the threshold of $P < 5\times10^{-5}$ were obtained. SNPs were clumped at a stringent linkage disequilibrium (LD) threshold (window=10 Mb; $r^2 = 0.001$).[18] *F* statistics were calculated using the formula of β^2/se^2 for all SNPs involved; SNPs with *F* statistics <10 were removed to lessen weak instrument bias.[18,27,28] We screened the GWAS Catalog database (https://www.ebi.ac.uk/gwas/downloads/summary-statistics) to exclude SNPs ($P < 1\times10^{-5}$) associated with confounders (such as, autoimmune diseases and atopic diseases) that could potentially affect the AA.[29] When certain SNPs were not included in the outcome datasets, appropriate proxies in strong LD with $r^2 \geq 0.8$ were utilized.

Two-Sample Bidirectional MR

We utilized five MR methods to explore the causal associations between mental disorders and non-scarring alopecia, including inverse variance weighted (IVW),[30] weighted median,[31] MR-Egger,[32] weighted mode,[33] and penalised weighted median.[34] Results are presented as the odds ratio (OR) with 95% confidence interval (CI). The fixed-effects IVW method was the predominant analysis, which is a robust MR method under the assumption of valid IVs and balanced pleiotropy.[35] If heterogeneity exists, IVW with the outliers correction was used as the primary result.[35]

Sensitivity analyses were performed with the MR pleiotropy residual sum and outlier method (MR-PRESSO),[36] RadialMR method,[37] MR-Egger intercept, Cochran's Q statistic, and leave-one-out analysis. MR-PRESSO was employed to detect potential horizontal pleiotropy and heterogeneity and to correct the estimated causal effect by identifying and removing outlier SNPs.[36] RadialMR was also utilized to identify and remove outliers. We generally look for estimates that do not indicate bias from horizontal pleiotropy (MR-PRESSO global $P > 0.05$, also MR-Egger intercept $P > 0.05$).

We utilized Cochran's Q test to assess IV heterogeneity, with a *P*-value >0.05 indicating no heterogeneity. Leave-one-out analyses were conducted to evaluate the potential impact of each variant on the estimates.[36] Moreover, the visualization of scatter, forest, and funnel plots was also depicted.

Statistical Analysis

When we included the vast number of risk factors and outcomes, the significance would be penalized.[38] Notably, the findings should be interpreted cautiously, not based solely on a *P*-value threshold. To achieve more potentially important findings, we consider the expansive range of risk factors and outcomes a study strength, rather than constructing a "suggestive significance threshold". Therefore, associations with $P < 0.05$ were considered as significant. The statistical power of the MR estimates was calculated using the online tool (https://sb452.shinyapps.io/power/).[39] All analyses were conducted using R software, version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). TwoSampleMR, MRPRESSO, and RadialMR R packages were adopted for the MR analyses.

Results

Genetic Instruments

After the removal of ambiguous, palindromic, unavailable SNPs and potential confounding, each outcome finally had different IVs for inclusion. None of the SNP had F-statistics <10, and the minimum F-statistic for all SNPs included in two-sample bidirectional MR was 16.52, indicating that the possibility for weak IV bias is minimal (Supplementary Table S2-S6).

In the forward MR analysis, for the AGA and AA outcome, 204, 30, 28, 51, and 197 SNPs were extracted from GWAS data for major depression disorder, anxiety disorder, panic attacks, distress, and bipolar disorder, respectively. Reversely, to explore the causal association of AGA with mental disorders, 27 to 30 SNPs were chosen as the IVs from the corresponding GWAS datasets. For AA exposure, 9 to 15 SNPs were extracted (Supplementary Table S2).

Causal Effects of Mental Disorders on Non-Scarring Alopecia

In the forward MR analysis, no association between any genetically predicted mental disorders and AGA was found (Supplementary Figure S1). The weighted median, MR Egger, weighted mode, penalised weighted median, and MR-PRESSO method did not alter the findings from IVW. Outliers identified by the IVW Radial MR method were depicted in the Radial plot (Supplementary Figure S2). After the outlier correction, we still observed no associations between mental disorders and AGA (Supplementary Figure S3).

Besides, genetically predicted major depression disorder was positively associated with the risk of AA (OR: 1.59; 95% CI: 1.16–2.17; *P*=0.0042). In contrast, we uncovered no evidence that a higher genetic predisposition to panic attacks (OR: 1.74; 95% CI: 0.02–123.76; *P*=0.800), anxiety disorder (OR: 0.47; 95% CI: 0.03–7.80; *P*=0.596), distress (OR: 0.83; 95% CI: 0.17–4.03; *P*=0.814), and bipolar disorder (OR: 0.99; 95% CI: 0.85–1.15; *P*=0.906) was associated with AA. Additionally, other multiple analyses yielded similar estimates to IVW, indicating the robustness of our results (Figure 2). After eliminating additional outliers and potential confounders, genetically predicted major depression disorder was still associated with the risk of AA (OR: 1.55; 95% CI: 1.12–2.14; *P*=0.0083) (Supplementary Figure S4–S5).

No horizontal pleiotropy was shown in the MR-PRESSO method in all non-scarring alopecia analyses (all Global *P* value >0.05) (Supplementary Table S7). Except for the effect of bipolar disorder on AGA (*P* for intercept = 0.044), none of the MR-Egger intercepts deviated from 0 for other mental disorders included, indicating no horizontal pleiotropy (*P* for intercept >0.05). No heterogeneity among the IVs was detected by the Cochran's Q test (Supplementary Table S8). Additional visualizations of scatter plots, funnel plots, forest plots, and leave-one-out plots can be found in supplementary materials (Supplementary Figure S6–S21).

Causal Effects of Non-Scarring Alopecia on Mental Disorders

For the reverse MR analysis, we found no significant association between AGA and the risk of mental disorders (Supplementary Figure S22). Besides, genetically predicted AA was positively associated with the risk of major depression disorder (OR: 1.02; 95% CI: 1.00–1.03; *P*=0.0078). For the association of AA with major depression disorder,

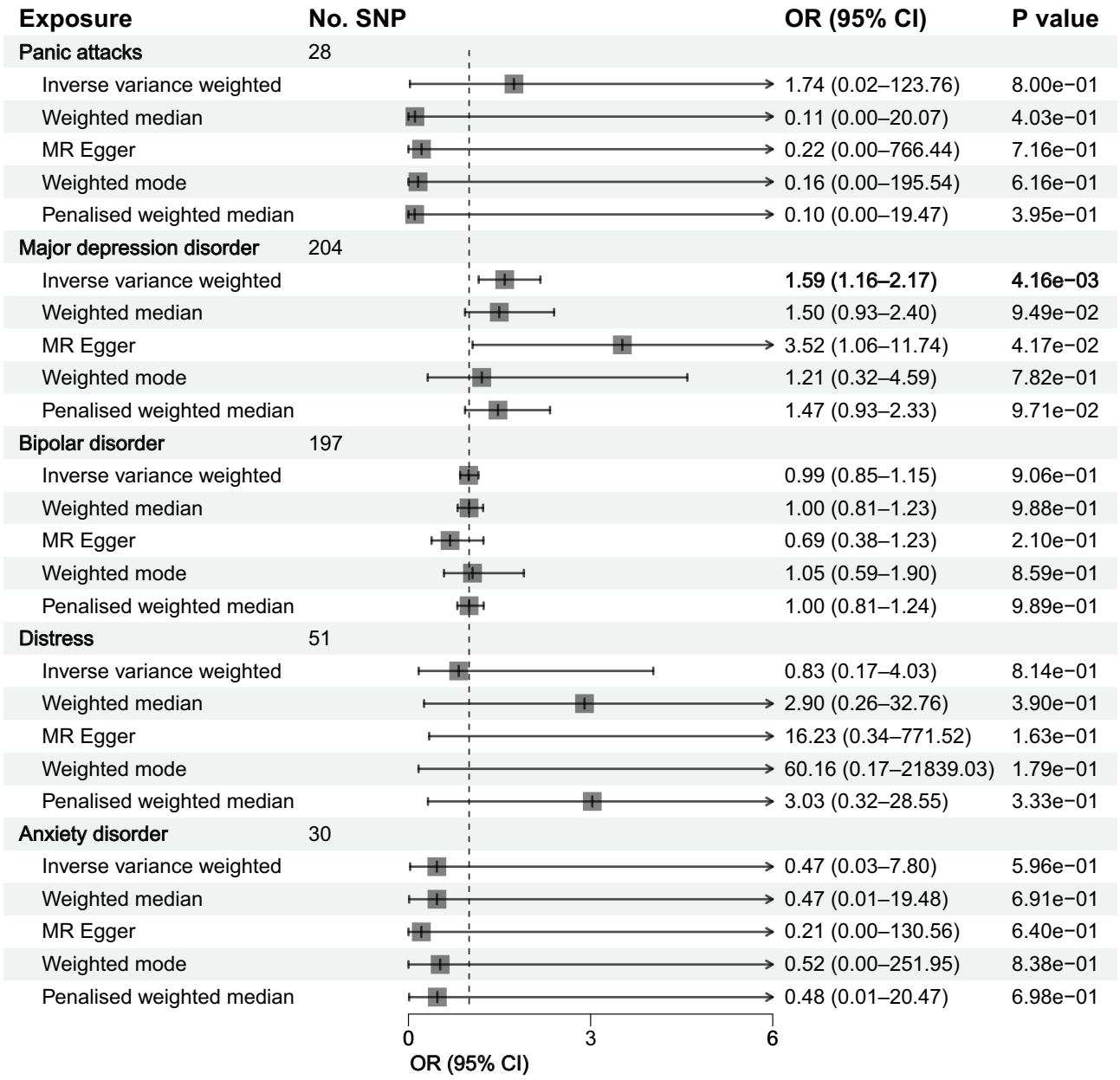

Figure 2 Association between genetically predicted mental disorders and alopecia areata.

little evidence of directional pleiotropy and heterogeneity among the individual SNP effects was found (Supplementary Table S7–S9). However, no evidence showed that a higher genetic predisposition to AA was linked to other mental disorders (Figure 3). After removing outliers, genetically predicted AA was still associated with the risk of major depression disorder (OR: 1.01; 95% CI: 1.00–1.02; P=0.0351) (Supplementary Figure S23).

Furthermore, the sensitivity analysis also substantiated the robustness and reliability of our findings. More detailed information on additional analyses can be found in the supplementary materials (Supplementary Figure S24–S32). In summary, bidirectional causality was observed between major depression disorder and AA. Notably, the statistical power of MR estimates may be insufficient (Supplementary Table S10).

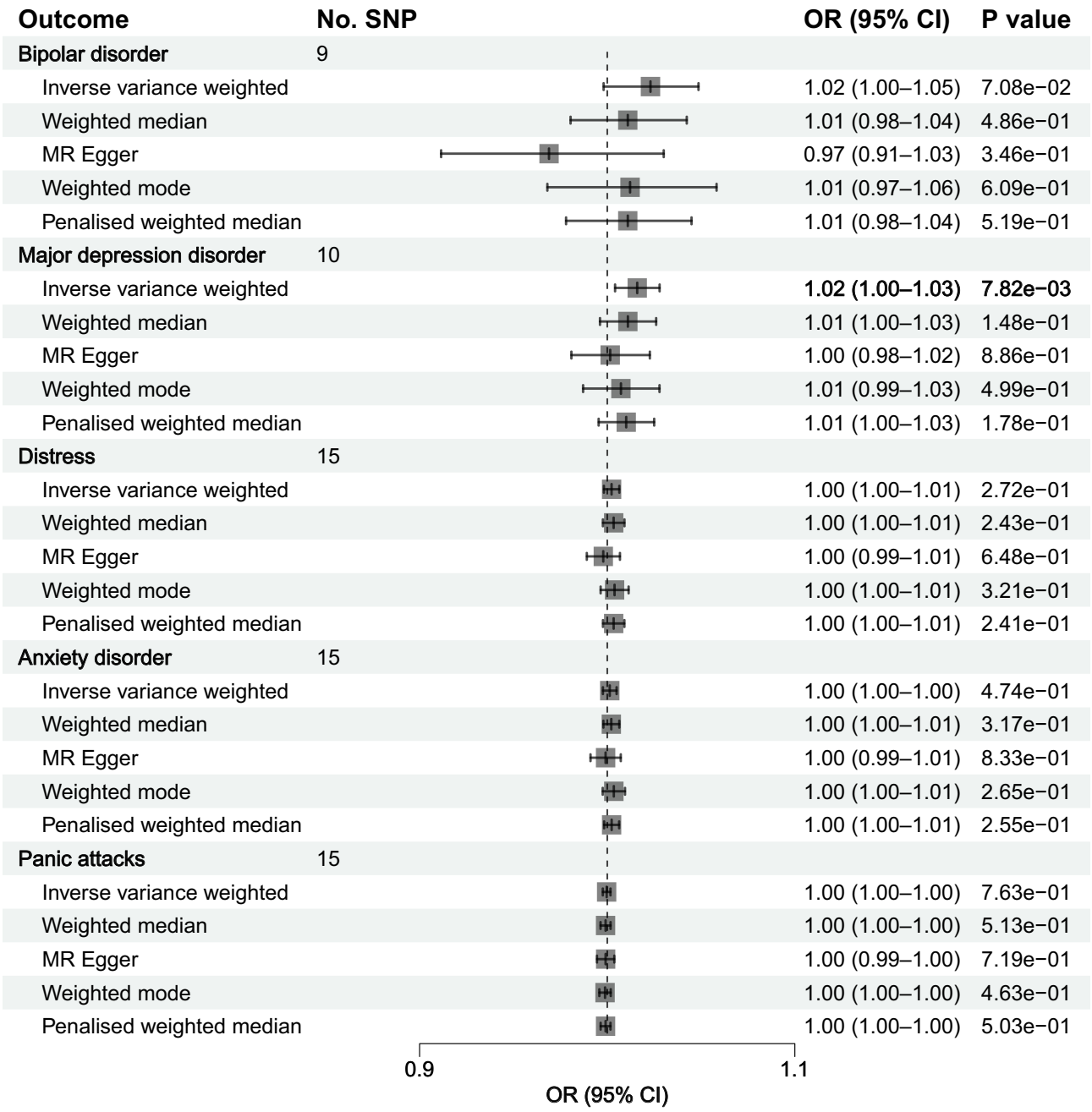

Figure 3 Forest plots for the associations of genetic susceptibility to alopecia areata with different Mendelian randomizations of mental disorders.

Discussion

We performed comprehensive bidirectional MR analyses to dissect the causal influence of mental disorders on the risk of non-scarring alopecia using summary statistics from large-scale GWASs. A bidirectional causal association of major depression disorder but not any other mental disorders with AA might exist. No association between any genetically predicted mental disorders and AGA was observed. These findings provide additional insights into non-scarring alopecia development, fostering the development of innovative strategies for non-scarring alopecia prevention and treatment.

Previous meta-analyses have shown a robust association of depression and anxiety with AA, though the causal effect and its direction are vague. A meta-analysis including 37 articles (29 on depression and 26 on anxiety) showed that 7% to 17% of patients with AA had depressive or anxiety disorders.[40] Another meta-analysis has consistently demonstrated

a positive association of AA with anxiety (pooled OR, 2.50) and depression (pooled OR, 2.71).[17] Our findings untangled an increase in AA risk by approximately 59% for each doubling odds increase in major depression disorder; while in the reverse direction, there was an increase in major depression disorder risk by approximately 2% for each doubling odds increase in AA, which is marginal and possibly clinically insignificant. Besides, no association was found between anxiety and AA in the current study. Nevertheless, an earlier MR study using datasets from FinnGen release 9 databases, genome-wide meta-analysis, and Anxiety Neuro Genetics Study Consortium unveiled the association of AA with major depression disorder and anxiety.[18] Compared with the current study, a similar effect magnitude but a different significance (*P*-value) in the association of AA with depression was found, while an inconsistent estimate in the association of AA with anxiety was observed. The discrepancies in results across MR studies may be due to the limited number of IVs and weak statistical power (<80%) (Supplementary Table S10). More GWAS datasets of mental disorders and non-scarring alopecia would be needed in the future to conduct two-sample MR studies, and the estimates from these analyses were then meta-analyzed further to increase the statistical power and reliability of the results. For individuals, those negative mental states may also be worsened in diverse social interactions. Accordingly, providing timely and suitable mental counseling is important. By identifying the potential mental burdens faced by AA patients and even general populations, clinicians can propose much-needed aid and interventions to handle their emotional well-being.

No evidence of a causal association between any genetically predicted mental disorders and AGA was found, which was inconsistent with a recent MR study. The reported MR has indicated that AGA may precipitate the development of depression, with a marginal increase in risk (IVW OR = 1.015).[24] Notably, in the above-mentioned MR study, the AGA (ukb-a-301) and depression (ebi-a-GCST90038650)[41] dataset were both derived from the UK Biobank study, which may introduce a false-positive rate, leading to unreliable conclusions. As the threshold for SNP selection ($P < 1\times10^{-5}$) is relatively loose, the possibility of weak instrument bias might also be caused. On the other hand, due to the missing report of statistical power in the MR study, interpretations should be made cautiously.

Potential physiologic mechanisms linking depression to AA may involve shared genetic factors and immune pathways. One significant genetic factor is the GRM8 gene, which encodes a protein involved in glutamatergic synapses. This gene shows significant associations with both conditions, as dysregulation of glutamatergic synapses can affect neuronal communication and has been linked to psychiatric disorders as well as hair loss.[18] On the other hand, depression exhibits dual features of immunosuppression and activation (eg, elevated IL-6, TNFα, CRP),[42] while AA is characterized by Th1/IFN-γ-dominated autoimmunity.[43] The etiology of AA is thought to involve immune events that lead to exposure of hair follicle autoantigens, with both Th1 and Th2 pathways implicated in the pathogenesis of AA.[43,44] Shared genetic and inflammatory pathways thus likely underlie their comorbidity.

Admittedly, some likely limitations are inevitable: First, study datasets are derived from European populations, and the generalization of results may be restricted. Future studies will incorporate diverse ancestral populations to validate these findings and disentangle genetic/environmental contributions to the depression–alopecia relationship. Second, to obtain more IVs of mental disorders and non-scarring alopecia and to increase the statistical power, a looser significant threshold was set, which may introduce some concerns. However, pleiotropy and heterogeneity among the individual SNP effects were not detected by the MR-PRESSO and MR-Egger regression intercepts method. In addition, a more liberal *P*-value threshold would likely bias the results toward the null.[45] Third, the association of mental disorders with non-scarring alopecia was not corrected by the Bonferroni method, so the findings should be interpreted with caution. Clinical research is also required to validate this finding further.

Conclusion

Our finding provided hints for a bidirectional causal association between major depression disorder and AA instead of AGA, which may partly explain the underlying mechanism of hair loss and offer clues in future prevention and intervention strategies. Mechanistic studies and prospective studies with individual-level data will be warranted to improve understanding of this link.

Abbreviations

AGA, androgenetic alopecia; AA, alopecia areata; MR, Mendelian randomization; IV, instrumental variable; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; LD, linkage disequilibrium; IVW, inverse variance weighted; MR-PRESSO, MR pleiotropy residual sum and outlier method.

Data Sharing Statement

All the original GWAS files are available for download from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/) and the FinnGen project (https://risteys.finngen.fi/).

Ethics Statement

According to Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Beings adopted by the National Science and Technology Ethics Committee of the People's Republic of China, ethical review can be exempted because the data used in this study do not cause any harm to human beings, do not involve any sensitive personal information or commercial interests, and the databases selected are open and legal.

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Disclosure

The authors declare that they have no competing interests.

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