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Assessing Causality Between Androgenetic Alopecia with Depression: A Bidirectional Mendelian Randomization Study

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Background: Androgenetic alopecia (AGA) is the most common form of alopecia globally, which exerts a negative impact on patients' self-esteem and overall quality of life. Previous observational studies have found a significant increase in the prevalence of depression in AGA patients, but the causal relationship remains to be elucidated.

Methods: In this study, we conducted a bidirectional Mendelian randomization (MR) using genome-wide association studies (GWAS) datasets. The available GWAS dataset of AGA was obtained from the Neale Lab consortium (n=154988). The dataset for depression was obtained from the ebi-a-GCST90038650 (n=484598). The main analysis method for determining the causal link between AGA and depression was inverse variance weighted (IVW). Subsequently, pleiotropy and heterogeneity tests were performed to determine the reliability of the results.

Results: Utilizing the IVW method, depression does not significantly contribute to the incidence of AGA (IVW odds ratio [OR] = 1.101, 95% confidence interval [CI] =0.890–1.362, P = 0.374). Conversely, the data suggested a statistically significant association where AGA may precipitate the development of depression, with a notable increase in risk (IVW OR = 1.015, 95% CI = 1.002–1.029, P = 0.020).

Conclusion: We are the first to use MR analysis to explore the causal relationship between AGA and depression, revealing an increased risk of depression in individuals with AGA.

Keywords: androgenetic alopecia, depression, Mendelian randomization, genome-wide association study

Introduction

Androgenic alopecia (AGA) is a common, hereditary condition characterized by the progressive miniaturization of hair follicles.[1] In males, AGA is typically manifested by a receding hairline on the forehead and temporal regions or thinning at the crown, while females with AGA exhibit diffuse thinning of hair, particularly in the central scalp area.[1,2] Epidemiological studies have established that the incidence of AGA correlates with age, gender, and ethnicity. By the age of 70, AGA affects at least 80% of men and 50% of women, with the incidence increases with age.[3,4] Genetic predisposition and androgen are pivotal in the etiology of AGA.[5] Emerging research have shown that additional factors such as inflammation, oxidative stress, neuroendocrine disruptions, angiogenesis, and lifestyle factors (including smoking) also play an important role in the pathophysiology of male AGA.[6,7] Through genome-wide association studies (GWAS), Hagenaars et al identified 287 independent genetic loci associated with severe male pattern hair loss, of which 247 were located on autosomes and 40 on X chromosomes.[8]

Depression is characterized by persistent melancholy, lack of interest or pleasure, and disruptions in sleep and physical functioning, which can diminish an individual's work capacity, potentially leading to disability, and significantly impacts the social and economic structures.[9,10] Research indicates a marked increase in the prevalence of depression

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among young adults over the past decade, particularly among female, which may correlate with heightened social demands and stress, hormonal fluctuations, and neurodevelopmental changes.[11]

Hair is a significant component of an individual's self-image, self-confidence, and social interactions.[12] Although alopecia is not life-threatening, it can adversely affect self-esteem and self-consciousness, consequently diminishing the quality of life for those affected.[13] Through meta-analysis, Hannah Frith et al found that AGA significantly decreases the mental health and life quality of male patients, and most of the studies proved that the impact was moderate.[14] Therefore, patients with AGA may experience feelings of depression, low self-esteem, and anxiety due to the increased severity of hair loss. These negative emotions may not only induce but also aggravate depressive symptoms. Conversely, the influence of hormonal changes and life stress events in depression patients may induce or exacerbate hair loss. Thus, a potential vicious cycle may exist between AGA and depression.

Mendelian Randomization (MR) is an epidemiological technique that utilizes GWAS data to identify eligible single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) for investigating the causality between exposure and outcome.[15,16] Unlike traditional observational studies, MR leverages the random assignment of genetic variations at the time of conception, thus minimizes the influence of biases and confounding factors to establishing causality.[17] Considering that the incidence of AGA and depression is increasingly affecting younger individuals, and there are similar pathogenesis contributing to these conditions, including genetic factors, hormones, immune dysregulation and stress,[7,18,19] while current observational research have not established a direct causal link between AGA and depression. Therefore, this study employs a two-sample MR analysis to explore the potential causal relationship between AGA and depression, which will help patients to establish effective psychological coping mechanisms. Furthermore, early intervention can also lead to the optimized allocation of medical resources, thereby elevating the overall standard of healthcare.

Materials and Methods

Research Design

This study was reviewed and approved by the Ethics Committee of Minhang Hospital, Fudan University. In this study, we employed a two-sample MR method to investigate the potential causal link between AGA and depression. To mitigate the impact of confounding factors, the MR analysis adhered to three fundamental assumptions: (1) SNPs significantly associated with AGA were selected as instrumental variables (IVs), in which we set the significance threshold of SNPs as $P < 1.0 \times 10^{-5}$ (Association hypothesis) due to the limited number of SNPs available for MR analysis at a lower threshold; (2) IVs were assumed to be independent of any known or unknown confounding factors (independence hypothesis); (3) IVs were hypothesized to influence the outcome solely through exposure risk factors, ruling out other causal pathways (exclusive hypothesis) (Figure 1).

Database Selection

The AGA dataset was sourced from the Neale Lab Consortium's "ukb-a-301" dataset for the European population (n = 154,988), including males and females, comprising 35,563 cases and 119,435 controls. Depression data were extracted from the "ebi-a-GCST90038650" dataset (n = 484,598), including 27,568 cases and 457,030 controls.

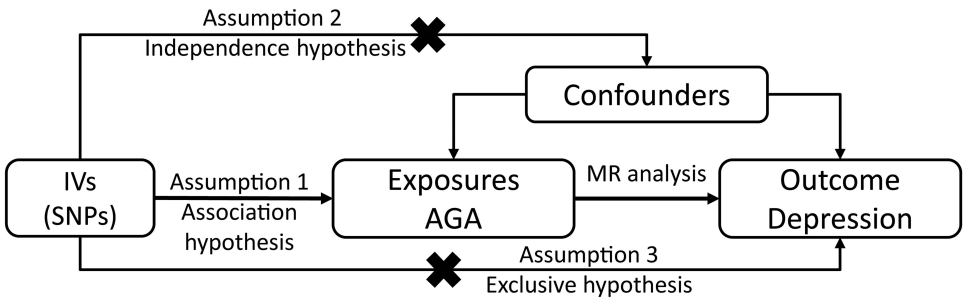

Figure 1 MR assumptions.
Abbreviations: AGA, androgenetic alopecia; IVs, instrumental variables; MR, Mendelian randomization; SNPs, single nucleotide polymorphisms.

Statistical Analysis

This study employed five distinct MR methods to ascertain the genetic correlation between AGA and depression: inverse variance weighted (IVW), MR-Egger regression, weighted median, and both simple and weighted mode methods. The IVW method, predicated on the validity of all SNPs as IVs, was regarded as yielding the most reliable estimates and was thus selected as the primary analytical approach. Subsequent to the primary analysis, a multivariable effect test and a heterogeneity test were conducted to assess the stability of the results. Statistical analysis of this study was performed using R (version 4.3.2) and TwoSampleMR software packages. $P < 0.05$ was considered statistically significant.

Results

The Causal Relationship Between AGA on Depression

The IVW analysis indicated that higher AGA genetic susceptibility may lead to the development of depression (odds ratio [OR] = 1.015, 95% confidence interval [CI] = 1.002–1.029, P = 0.020). Cochrane's Q test was conducted to assess data heterogeneity, yielding a non-significant result (P=0.884). Furthermore, the P value for the MR-Egger intercept was 0.389, suggesting the absence of horizontal pleiotropy (Table 1 and Figure 2).

The Causal Relationship Between Depression on AGA

The reverse-direction MR analysis showed that there was no significant correlation between the genetic susceptibility of depression and AGA (IVW OR = 1.101, 95% CI = 0.890–1.362, P = 0.374). Cochrane's Q test identified that there was no significant heterogeneity (P = 0.420) in the data. Additionally, the MR-Egger intercept revealed no significant evidence of directional pleiotropy in AGA (P = 0.569) (Table 2 and Figure 3).

Discussion

This study employed the MR method to investigate the genetic correlation between AGA and depression, uncovering a one-way causality where individuals with AGA are at an elevated risk of depression. Hair, being a crucial component of an individual's self-image, significantly influences emotions and social behavior. Surveys indicate that over 25% of male AGA patients find hair loss to be a source of frustration, and approximately 65% report experiencing mild to moderate emotional distress.[20] Patients with alopecia may endure a diminished sense of personal attractiveness, increased psychological burden, lowered self-esteem, anxiety about aging, and detrimental impacts on their social life.[21–23] However, these adverse psychological effects are often underestimated or overlooked by those who are not directly affected.

A questionnaire-based survey of 351 patients conducted by Tabolli et al revealed a significant increase in the prevalence of depression and anxiety in AGA patients, with female patients exhibiting more pronounced effects. This study included 237 male patients with a mean age of 31.53±10.57 and 114 female patients with a mean age of 44.13 ±16.93.[24] Through meta-analysis, Huang et al confirmed a significant correlation between AGA and substantial impairment in health-related quality of life and mood (pooled score, 29.22; 95% CI, 24.17–34.28, P<0.001).[25] In the study of 170 AGA patients in Shanghai, Moorthy et al discovered a marked negative impact of AGA on the quality of life for patients under 30 years old, those who were single, and with lower levels of education.[26]

Table 1 MR Results for the Relationship Between AGA on Depression

Exposures	Outcomes	No. of SNPs	Method	OR (95% CI)	P	Heterogeneity Test		Pleiotropy Test
						Cochrane's Q (I^2)	P	P Intercept
AGA	Depression	40	IVW	1.015 (1.002–1.029)	0.020	28.797	0.884	0.389
			MR Egger	1.029 (0.996–1.065)	0.098	28.038	0.882	
			Weighted median	1.018 (0.997–1.040)	0.094			
			Simple mode	1.021 (0.980–1.063)	0.331			
			Weighted mode	1.021 (0.993–1.049)	0.155			

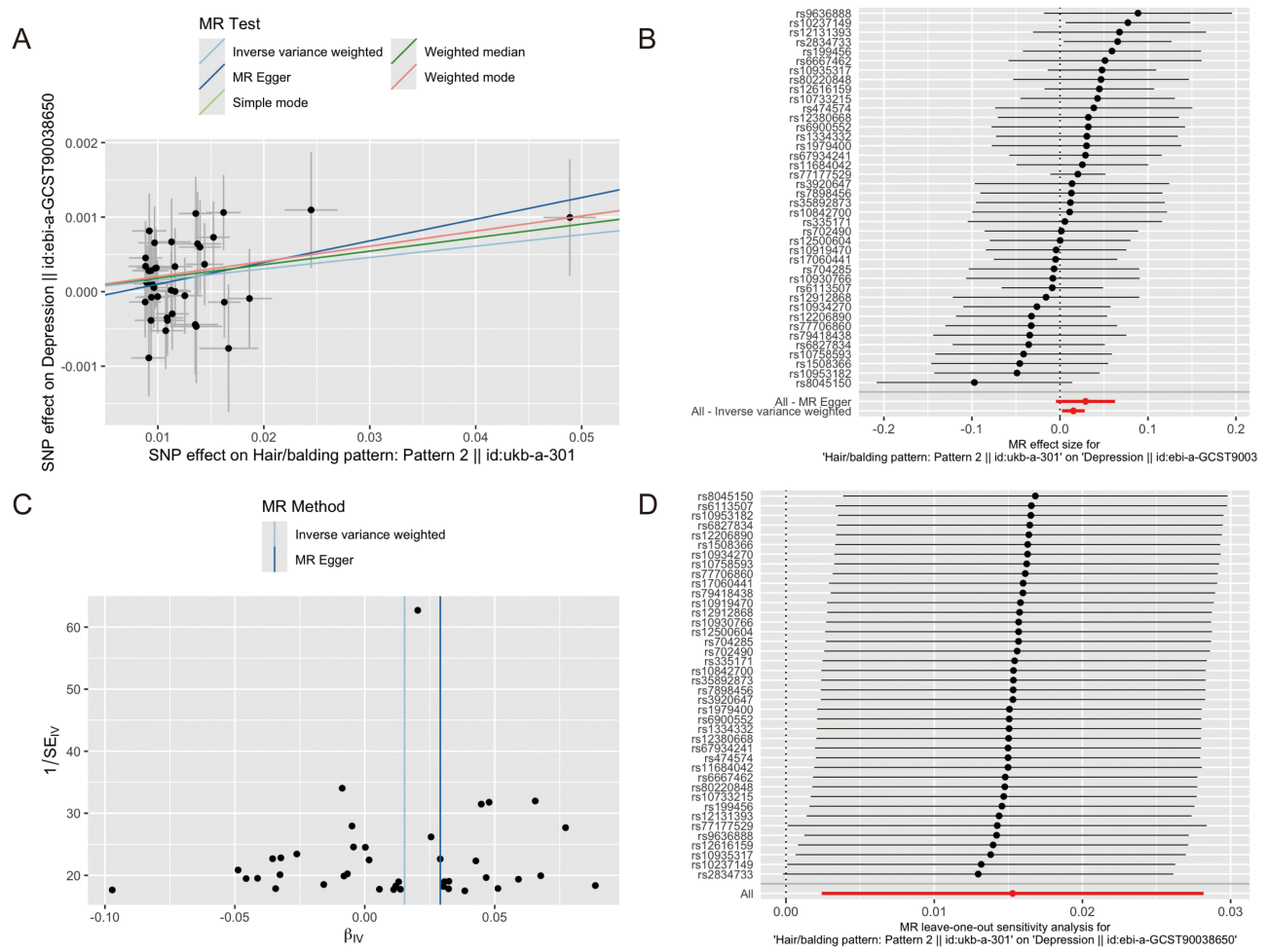

Figure 2 Causal effects of AGA on depression. (**A**) Scatter plot of AGA effect estimates on depression. (**B**) Forest plot summarizing AGA's overall impact on depression. (**C**) Funnel plot for bias assessment of the estimates. (**D**) Sensitivity analysis via "leave-one-out" plots.
Abbreviations: AGA, androgenetic alopecia; MR, Mendelian randomization.

Furthermore, the progressive nature of hair loss in AGA is linked to a decline in quality of life, which is associated with heightened anxiety, depression, social isolation, and diminished self-esteem.[21,27] It has been observed that even minor improvements in alopecia severity following topical minoxidil treatment can lead to enhanced satisfaction and an improved quality of life for patients.[28,29] Nilforoushzadeh et al assessed the psychosocial status of 35 male AGA patients pre- and post-hair transplantation using questionnaires, the findings indicated a significant reduction in loneliness, anxiety, and depression post-transplantation compared to pre-transplantation levels,[30] suggesting that clinical interventions can also yield psychological benefits. Given the potential for depression in AGA patients, the importance of early intervention and psychological assessment is paramount.

Table 2 MR Results for the Relationship Between Depression on AGA

Exposures	Outcomes	No. of SNPs	Method	OR (95% CI)	P	Heterogeneity Test		Pleiotropy Test
						Cochrane's Q (I^2)	P	P Intercept
Depression	AGA	41	IVW	1.101 (0.890–1.362)	0.374	41.157	0.420	0.569
			MR Egger	1.319 (0.687–2.534)	0.411	40.812	0.391	
			Weighted median	0.923 (0.683–1.248)	0.605			
			Simple mode	0.697 (0.332–1.463)	0.346			
			Weighted mode	0.703 (0.363–1.360)	0.301			

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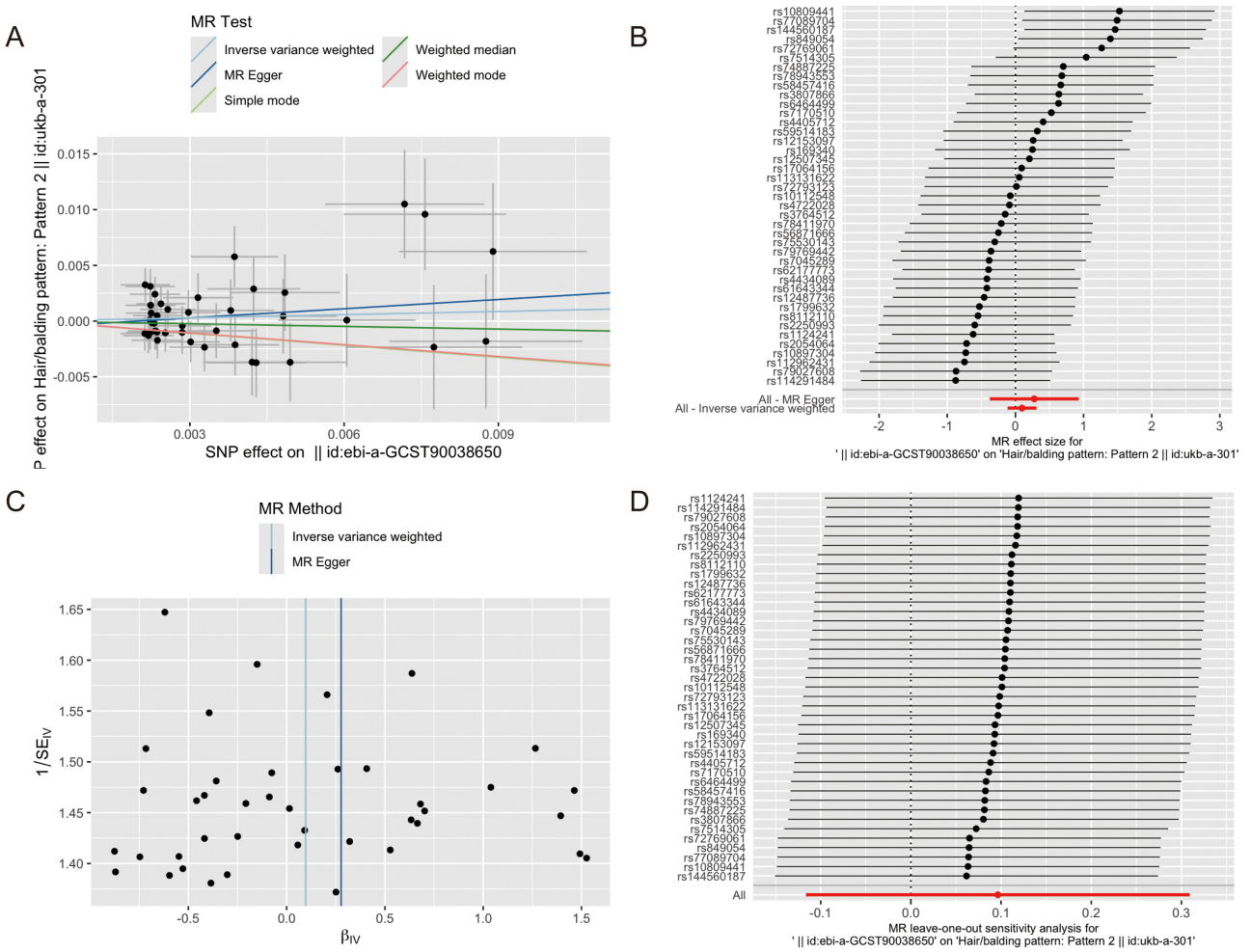

Figure 3 Causal effects of depression on AGA. (**A**) Scatter plot of depression effect estimates on AGA. (**B**) Forest plot summarizing depression's overall impact on AGA. (**C**) Funnel plot for bias assessment of the estimates. (**D**) Sensitivity analysis via "leave-one-out" plots.
Abbreviations: AGA, androgenetic alopecia; MR, Mendelian randomization.

While clinical observations suggest a potential association between depression and hair loss, the underlying mechanisms are multifaceted. Long-term diminished interests and psychological stress can lead to hormonal imbalances, such as increased levels of cortisol,[18] which may interfere with the hair growth cycle, potentially resulting in hair loss.[31] In fact, studies have demonstrated that individuals with AGA also exhibit significantly elevated levels of cortisol compared to control groups.[31–33] Furthermore, many antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs), may have side effects of hair loss.[34,35] Research indicates that bupropion carries the highest risk of hair loss, significantly surpassing that of six SSRIs (fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram, paroxetine) and three SNRIs (duloxetine, venlafaxine, desvenlafaxine).[34] However, our findings indicate that depression does not significantly contribute to the incidence of AGA (P = 0.374). We hypothesize that this may be partly due to depression potentially increasing the risk of other types of hair loss, such as telogen effluvium, or due to patients' heightened concern about pre-existing hair loss and the influence of antidepressants. Therefore, while depression may increase the risk of hair loss, it is not yet a singular cause of AGA.

However, there are still some limitations in this study. Firstly, the dataset of AGA patients was derived from a large-scale meta-analysis of GWAS focused on the European population. The selection bias of population may limit the generalizability of the findings to other ethnic groups, given the potential for genetic variations across different populations. Secondly, the GWAS data utilized in this study did not provide analyses stratified by specific variables such as gender, age, or disease duration, which constrains the capacity to explore the nuances of these factors within the

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study. Furthermore, while the MR analysis examined the causal relationship between AGA and depression, it did not delve into the underlying biological mechanisms that may mediate this relationship. Future research endeavors should aim to address these limitations to further elucidate the potential associations between AGA and depression.

In the contemporary context where aesthetic demands are on the rise, the mental health comorbidities of AGA patients are emerging as a significant concern for clinicians. Consequently, the focus should not be solely on traditional treatments aimed at ameliorating alopecia symptoms. There is a growing need for the early identification of potential psychological stressors and negative emotional responses, such as depression, anxiety, and anger, that AGA patients may encounter. At the initial visit of AGA patients, dermatologists should assess patients' perceptions of the extent of hair loss, their motivation for treatment, and their expectations. Concurrently, administering psychological questionnaires related to hair loss and evaluating patients' current quality of life can establish baseline data prior to treatment. During follow-up visits, re-assessing the patient's condition allows for the assessment of the effects of psychological interventions and the adjustment of treatment plans as needed. Briefly, in the treatment of AGA patients, dermatologists should strengthen the psychological interventions to promote disease rehabilitation.

Conclusion

In summary, our research provides evidence for a causal relationship between AGA and depression, indicating that individuals with AGA are at an elevated risk of depression. Therefore, providing timely and appropriate psychosocial support and intervention for these AGA individuals is of paramount importance.

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Disclosure

The authors report no conflicts of interest in this work.

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