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ORIGINAL RESEARCH

Causal Relationship Between Sleep Characteristics and Alopecia Areata and Other Non-Scarring Alopecia: A Two-Sample Bidirectional Mendelian Randomization Analysis

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Background: Previous studies have indicated an association between alopecia and sleep characteristics, but the causality is not clear. This study aimed to investigate the potential causal relationship between four sleep traits (morningness, sleep duration, insomnia, daytime napping) and four subtypes of alopecia (alopecia areata, androgenic alopecia, scarring, and other non-scarring alopecia).

Methods: A bidirectional mendelian randomization (MR) analysis based on genome-wide association studies (GWAS) data was employed to examine the causal relationship between alopecia and sleep characteristics. Sample sizes ranged from 209 to 452,633 participants for different traits. Various analytical approaches, including Inverse Variance Weighted (IVW), Weighted Median, MR-Egger and Weighted Mode were employed. Instrumental variables were selected based on conventional significance thresholds ($P < 5 \times 10^{-8}$ for sleep traits) and structured criteria for alopecia. A Bonferroni correction was applied to account for multiple testing. Sensitivity analyses, including Cochran's Q, leave-one-out, and MR pleiotropy residual sum and outlier (MR-PRESSO) methods, were subsequently conducted to affirm the robustness of the findings.

Results: IVW method suggested causal associations between genetically predicted insomnia and a higher risk of alopecia areata (OR (95% CI) = 3.88 (1.5–10.04), P = 0.01), genetically predicted alopecia areata and morningness (OR (95% CI) = 1.0102 (1.0005–-1.0201), P = 0.04), as well as genetically predicted non-scarring alopecia and reduced sleep duration (OR (95% CI) = 0.9881 (0.9767–0.9997), P = 0.04). However, these associations did not survive multiple testing correction. Cochran's Q test revealed heterogeneity in the analysis between scarring alopecia and daytime nap (Q = 39.29, P = 0.01), indicating potential variability in the genetic effects across different SNPs. Based on MR-PRESSO and leave-one-out analyses, outliers were removed, revealing no evidence of horizontal pleiotropy in this study.

Conclusion: This MR study suggests potential bidirectional causal associations between alopecia and sleep characteristics. However, the findings should be interpreted cautiously due to multiple testing considerations. Future work should investigate mechanisms and generalize findings across populations.

Keywords: alopecia, insomnia, sleep, Mendelian randomization, causal relationship, GWAS, circadian rhythm, autoimmunity

Introduction

Alopecia, a condition characterized by partial or complete hair loss,[1] has garnered significant attention due to its impact on individuals' psychological well-being and quality of life. The diverse manifestations of alopecia encompass various types, such as alopecia areata, androgenetic alopecia, scarring alopecia and non-scarring alopecia [corresponding to ICD-10 code L65, including L65.0 (telogen effluvium), L65.1 (anagen effluvium), L65.2 (alopecia mucinosa), L65.8 (other specified non-scarring hair loss), L65.9 (unspecified non-scarring hair loss)], each with its unique epidemiological

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patterns and clinical features.[2] Alopecia areata is an autoimmune disorder most commonly causing patchy hair loss,[3,4] while androgenetic alopecia, also known as pattern hair loss, predominantly affects men but also occurs in women and is mediated by genetic and hormonal factors.[5] Scarring alopecia refers to the destruction of hair follicles, leading to permanent hair loss and scarring of the scalp.[6,7] Non-scarring alopecia, on the other hand, involves the loss of hair without damaging the hair follicles, allowing for the potential regrowth of hair.[8] Given the detrimental impact of alopecia on an individual's quality of life, it is imperative to delve into the underlying unfavorable factors and devise tailored prevention strategies.

Sleep, a vital physiological process, encompasses several characteristics that can significantly impact an individual's overall health. These include chronotype (eg, morning or evening person), sleep duration, and specific sleep disorders such as insomnia, all of which have been implicated in various health outcomes.[9] Previous observational studies have explored the association between sleep characteristics and alopecia. Bewley et al have indicated that about 28.1% of patients with alopecia reported sleep problems.[10] Furthermore, it is reported that patients and animal models with androgenic alopecia treated with finasteride may have side effects of sleep during treatment.[11] However, such studies are inherently limited by potential confounding factors, reverse causation, and the inability to establish a definitive causal direction. Previous research has demonstrated associations between sleep disturbances and various autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and psoriasis.[12] Sleep disturbances are closely linked to the pathogenesis of autoimmune diseases. In rheumatoid arthritis, poor sleep exacerbates joint inflammation by increasing TNF-α secretion;[13] in systemic lupus erythematosus, sleep fragmentation correlates with disease activity and autoantibody levels;[14] in psoriasis, insomnia is associated with more severe skin lesions and higher levels of pro-inflammatory cytokines.[15] Sleep disturbances may affect alopecia via two key pathways: (1) Hypothalamic-pituitary-adrenal (HPA) axis activation, leading to elevated cortisol levels that disrupt hair follicle cycling; (2) Imbalance of pro-inflammatory (IL-6, TNF-α) and anti-inflammatory cytokines, breaking the immune privilege of hair follicles and triggering autoimmune alopecia.[16] Given that alopecia areata shares genetic and inflammatory characteristics with other autoimmune disorders, understanding the relationship between sleep and alopecia may provide insights into shared pathophysiological mechanisms. Furthermore, the bidirectional nature of this relationship warrants investigation using methods that can establish causality rather than mere association.

Mendelian randomization (MR) is a technique that leverages genetic variants as instrumental variables to mimic the effects of exposure on an outcome, thus minimizing the impact of confounding and reverse causation.[17] This overcomes the limitations of observational studies, which cannot distinguish between correlation and causality in the sleep-alopecia relationship. For example, MR has been used to confirm that genetic predisposition to insomnia increases the risk of ovarian cancer, highlighting its value in disentangling causal relationships.[18] The two-sample bidirectional MR approach allows for the assessment of causality in both directions by analyzing data from two independent samples, further enhancing the robustness of the findings.[19]

Therefore, this study aimed to employ a two-sample bidirectional MR analysis to investigate the causal relationship between sleep characteristics and alopecia. This study would help to understand the complex interplay between sleep and alopecia, with the potential to inform future research and clinical practice.

Materials and Methods

Study Design

In this study, genetic instrumental variables (IVs) were meticulously selected in the form of single nucleotide polymorphisms (SNPs) from genome-wide association studies (GWAS), ensuring rigorous adherence to the three cornerstone assumptions of MR:[20] (1) the chosen IVs exhibit a robust association with the exposure under study; (2) IVs are unconnected to any confounding variables; (3) the influence of IVs on the outcome is strictly mediated through the exposure, excluding any direct or alternative pathway effects.

In the forward MR study, the exposure factors were sleep characteristics (including morningness, daytime nap, insomnia and sleep duration), and the outcome were four types of alopecia, including alopecia areata, androgenic alopecia, scarring alopecia and non-scarring alopecia. The reverse MR study was the opposite (Figure 1). In addition,

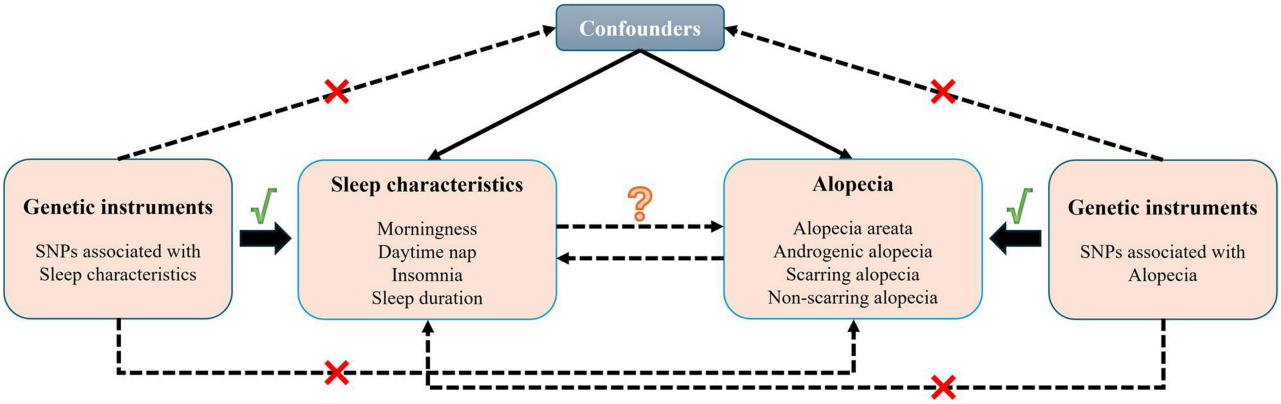

Figure 1 Diagram of three stringent assumptions of the present MR study. Genetic instruments (pink rounded rectangle): Single nucleotide polymorphisms (SNPs) associated with sleep characteristics or alopecia, serving as instrumental variables in Mendelian randomization. Sleep characteristics (blue rounded rectangle): Includes morningness, daytime nap, insomnia, and sleep duration, representing exposure/outcome variables related to sleep. Alopecia (blue rounded rectangle): Includes alopecia areata, androgenic alopecia, scarring alopecia, and non - scarring alopecia, representing exposure/outcome variables related to hair loss. Confounders (gray rectangle): Factors that may simultaneously affect sleep characteristics and alopecia; dashed lines with red "×" indicate that Mendelian randomization blocks the confounding effect. Solid black arrows (with green checkmarks): Indicate the direct effect of genetic instruments on sleep characteristics or alopecia. Dashed black arrows (with Orange "?"): Represent the potential bidirectional causal relationship between sleep characteristics and alopecia to be investigated.
Abbreviations: MR, Mendelian randomization; SNPs, single nucleotide polymorphisms.

this study was reported according to the "Strengthening the Reporting of Observational studies in Epidemiology using Mendelian Randomization" checklist.[21]

Data Source

The summary data of alopecia were derived from the FINNGen consortium, which has aggregated GWAS results for various diseases, encompassing the genomic and electronic health record data of over 100,000 Finnish participants.[22,23] Non-scarring alopecia in this study refers to hair loss disorders without permanent follicle damage, corresponding to ICD-10 code L65, including: L65.0 (Telogen effluvium), L65.1 (Anagen effluvium), L65.2 (Alopecia mucinosa), L65.8 (Other specified nonscarring hair loss), and L65.9 (Nonscarring hair loss, unspecified). This classification is consistent with the FinnGen database definition (GWAS ID: finn-b-L12_HAIRLOSSNONSCAR). The summary data of morningness were obtained from the analyses by Jones et al[24] which leveraged genome-wide data from 697,828 UK Biobank (UKB) and 23andMe participants identifies 351 genetic loci linked to morningness. The UKB is a large prospective study encompassing over 500,000 UK residents aged 40–69, residing within 25 miles of a study center, invited to participate from 2006−2010.[25] Among the participants in Jones's study, the self-report binary phenotype of chronotype-morning individuals, comprising 252,287 cases and 150,908 controls, was selected as the summary data for this study. Specifically, participants categorized as evening-types (definitely or more evening than morning) were coded 0 (controls), while morning-types (definitely or more morning than evening) were coded 1 (cases). "Don't know" or "No answer" responses were recorded as missing. Furthermore, the summary data of daytime nap with 452,633 cases were obtained from a study reported by Jones et al,[26] which conducted a GWAS of 8 sleep traits using accelerometer data from UKB participants, revealing 47 genetic associations. In addition, the summary data of insomnia with 386,533 cases were derived from the genome-wide analysis by Jansen et al,[27] which used a large genetic association sample (n = 1,331,010) from UKB (n = 386,533) and 23andMe (n = 944,477) cohorts to identify 202 loci and 956 genes associated with insomnia, revealing neurobiological pathways, tissue and cell types involved. Lastly, the summary data of sleep duration were derived from a genome-wide association study reported by Dashti et al,[28] which identified 78 loci associated with self-reported sleep duration in 446,118 adults of European ancestry from the UKB. The specific information is exhibited in the Table S1. This study utilized publicly available GWAS summary statistics. As per Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects, research using publicly available data with existing ethical approval is exempt from additional institutional review board approval. All original studies included in the GWAS datasets obtained appropriate ethical approval and participant consent.

Instrument Variables Selection

Firstly, in the forward MR analysis, SNPs significantly associated with sleep characteristics at a genome-wide level were screened with a threshold of $P < 5 * 10^{-8}$. For the reverse MR analysis with alopecia as the exposure, the threshold for scarring alopecia was set at $P < 5 * 10^{-5}$, while for the other three alopecia types, it was $P < 5 * 10^{-6}$. This differential threshold was implemented due to the lower genetic signal strength and smaller sample size for scarring alopecia (n=209 cases), which necessitated a more lenient threshold to obtain sufficient genetic instruments while maintaining statistical power. Given that different types of alopecia may have distinct genetic underpinnings and clinical characteristics, setting different thresholds can better capture these variations.[29] Secondly, SNPs with a minor allele frequency (MAF) > 0.01 were selected.[30] Subsequently, linkage disequilibrium (LD) among SNPs was removed based on the criteria of $R^2 < 0.001$ and a window size of 10,000kb.[31] When the selected IV was absent from the summary data of the outcome, a SNP with high LD ($R^2 > 0.8$) to the original IV from the same European ancestry population was identified as a proxy SNP for substitution.[20] Lastly, the F-statistic for each SNP was computed to evaluate its strength and mitigate potential weak instrument bias in the relationship between IVs and exposure factors. The formula $F = R^2 * (N-2) / (1-R^2)$ was applied, with R^2 signifying the fraction of exposure variation accounted for by the SNP in the IV. An F-statistic > 10 was deemed necessary.[32]

Statistical Analysis

This analysis primarily leveraged the inverse variance weighted (IVW) method to assess causality between exposure and outcome risk, estimating odds ratio (OR) with 95% confidence interval (95% CI).[33] IVW evaluates the weighted average effect, weighting each SNP by its inverse variance.[34] To ensure robustness, additional checks were implemented using the MR-Egger, weighted median, and weighted mode approaches, thereby bolstering the reliability of the findings. The MR-Egger method specifically addresses potential intercepts, providing precise causal estimates amidst pleiotropic biases.[35] Meanwhile, the weighted median approach assumes that half of the IVs remain valid, enabling an in-depth analysis of the causal relationship between exposure and outcome.[36] All analyses in this study were conducted using the R version 4.0.5 along with the "Two-sample MR" package. Visual representations were created through scatter plots, funnel plots, and forest plots. Scatter plots illustrate the relationship between the effects of IVs on both exposure and outcome, funnel plots identify potential biases, and forest plots display the effect estimates of SNPs and their consistency.[21]

Sensitivity Analysis

Sensitivity analysis was implemented to identify potential pleiotropic effects in the MR study. Heterogeneity among IVs was evaluated using Cochran's Q test and $P > 0.05$ indicates low heterogeneity, suggesting random variation in estimates across IVs with minimal impact on IVW outcomes.[37] Furthermore, MR-Egger regression method was utilized to probe for horizontal pleiotropy and an intercept term approaching zero or statistical insignificance indicates no pleiotropy.[38] Furthermore, Outliers in MR-PRESSO were defined as SNPs with a P-value <0.05 in the outlier test, indicating potential pleiotropic effects. For SNPs missing in the outcome GWAS, proxies were selected based on linkage disequilibrium (LD $r^2 > 0.8$).[39] Lastly, the leave-one-out analysis was applied to verify the robustness and consistency of the results.[34] A total of 32 bidirectional MR tests were performed (4 sleep traits × 4 alopecia subtypes × 2 directions). For MR-PRESSO analysis, the "global P-value" was used to assess horizontal pleiotropy: a global P<0.05 indicated significant pleiotropy caused by outliers. The "RAW P-value" and "Outlier-corrected P-value" in MR-PRESSO represent causal effect P-values before and after outlier removal, respectively. Due to the exploratory nature of this study and the use of sensitivity analyses (Cochran's Q, leave-one-out, MR-Egger) to validate results, we did not apply Bonferroni or FDR correction, but we note that marginal significant results (P=0.01–0.04) should be interpreted cautiously.

Results

Selection of IVs

In the forward MR analysis with sleep characteristics being the exposure factors, 124, 107, 13, and 131 distinct SNPs respectively in relation to morningness, daytime nap, insomnia, and sleep duration were identified and selected as IVs.

After calculation, the average F-statistic values for the IVs of these four sleep characteristics were 46, 46, 41, and 37, respectively, with minimum values of 29, 29, 30, and 30, and maximum values of 169, 217, 95, and 221, respectively. The F-statistics of SNPs all exceeded the threshold of 10, indicating that weak instrument bias was less likely to occur. During MR analysis with four types of alopecia being the outcomes, among SNPs related to morningness, 5 were absent with proxy SNPs identified for all, and 4 palindromic SNPs were excluded. For daytime nap SNPs, 11 had no matches with 6 finding proxies, and 3 palindromic SNPs were excluded. For sleep duration SNPs, 53 lacked matches with 17 finding proxies, and 3 palindromic SNPs were excluded. The detailed information is exhibited in Table S2.

In the reverse MR analysis with alopecia being the exposure factors, 17, 5, 24 and 5 independent SNPs respectively associated with alopecia areata, androgenic alopecia, scarring alopecia and non-scarring alopecia were identified and selected as IVs. The average F-statistic values for the IVs of these four types of alopecia were 24, 23, 18, 23, with minimum values of 21, 22, 17 and 21, and maximum values of 58, 23, 22 and 24, respectively. While the F-statistics for all SNPs exceeded the conventional threshold of 10, the average F-statistic for scarring alopecia (F=18) was relatively low, indicating a potential risk of weak instrument bias. During the MR analysis with morningness, daytime nap, insomnia, and sleep duration as outcomes, 5, 4, 9, and 5 alopecia areata SNPs; 1, 1, 2, and 1 androgenic alopecia SNPs; 1, 3, 4, and 1 scarring alopecia SNPs; and 2, 2, 2, and 2 non-scarring alopecia SNPs, respectively, lacked matching information. No proxy SNPs were identified for any of the aforementioned missing SNPs. The detailed information is exhibited in Table S3.

Causal Effect of Sleep Characteristics on Alopecia

In the forward MR analysis (Table 1), the IVW method indicated that the genetically predicted insomnia had a nominally significant causal effect on alopecia areata (OR (95% CI) = 3.88 (1.5–10.04), P = 0.01), indicating that insomnia is linked

Table 1 MR Results of Causal Effect of Sleep Characteristics on Alopecia

Outcome	Exposure	Methods	N. SNPs	OR (95% CI)	P
Alopecia areata	Morningness	IVW	120	0.81 (0.59–1.1)	0.17
		MR-Egger	120	0.92 (0.35–2.41)	0.87
		Weighted median	120	0.75 (0.47–1.2)	0.23
		Weighted mode	120	0.77 (0.26–2.24)	0.63
	Daytime nap	IVW	99	1.6 (0.46–5.55)	0.46
		MR-Egger	99	0.19 (0–17.47)	0.47
		Weighted median	99	0.68 (0.11–4.37)	0.68
		Weighted mode	99	0.52 (0.01–20.32)	0.72
	Insomnia	IVW	12	3.88 (1.5–10.04)	0.01
		MR-Egger	12	0.02 (0–73.8)	0.37
		Weighted median	12	3.94 (1.11–14.02)	0.03
		Weighted mode	12	5.38 (0.7–41.33)	0.13
	Sleep duration	IVW	92	0.4 (0.15–1.03)	0.06
		MR-Egger	92	1.31 (0.03–56.59)	0.89
		Weighted median	92	0.59 (0.15–2.28)	0.45
		Weighted mode	92	0.46 (0.07–2.82)	0.4
Androgenic alopecia	Morningness	IVW	120	0.68 (0.38–1.2)	0.18
		MR-Egger	120	0.41 (0.07–2.41)	0.33
		Weighted median	120	0.51 (0.21–1.21)	0.12
		Weighted mode	120	0.45 (0.07–3.01)	0.41
	Daytime nap	IVW	99	0.63 (0.06–6.5)	0.7
		MR-Egger	99	140.52 (0.03–659,118.2)	0.25
		Weighted median	99	1.68 (0.05–55.59)	0.77
		Weighted mode	99	5.62 (0–34,685.09)	0.7

(*Continued*)

Table 1 (Continued).

Outcome	Exposure	Methods	N. SNPs	OR (95% CI)	P
	Insomnia	IVW	13	1.76 (0.37–8.26)	0.48
		MR-Egger	13	2.09 (0.03–151.1)	0.74
		Weighted median	13	2.04 (0.23–17.66)	0.52
		Weighted mode	13	2.21 (0.15–32.97)	0.58
	Sleep duration	IVW	89	1.32 (0.24–7.36)	0.75
		MR-Egger	89	8793.87 (1.27–60,993,594.22)	0.05
		Weighted median	89	2.09 (0.17–25.81)	0.56
		Weighted mode	89	9.34 (0.11–788.04)	0.33
Scarring alopecia	Morningness	IVW	120	0.89 (0.49–1.6)	0.69
		MR-Egger	120	2.94 (0.48–18.13)	0.25
		Weighted median	120	1.03 (0.43–2.45)	0.95
		Weighted mode	120	3.51 (0.48–25.7)	0.22
	Daytime nap	IVW	99	0.58 (0.05–6.33)	0.66
		MR-Egger	99	26.26 (0–147,945.15)	0.46
		Weighted median	99	2.81 (0.08–94.03)	0.56
		Weighted mode	99	10.05 (0.01–7639.43)	0.5
	Insomnia	IVW	13	0.47 (0.07–3.1)	0.43
		MR-Egger	13	4.49 (0.02–847.03)	0.59
		Weighted median	13	0.87 (0.09–8.56)	0.9
		Weighted mode	13	2.67 (0.13–54.62)	0.54
	Sleep duration	IVW	92	1.38 (0.26–7.25)	0.7
		MR-Egger	92	3.21 (0–2196.87)	0.73
		Weighted median	92	1.6 (0.12–21.11)	0.72
		Weighted mode	92	1.57 (0.04–56.02)	0.8
Nonscarring alopecia	Morningness	IVW	120	0.85 (0.49–1.49)	0.57
		MR-Egger	120	0.3 (0.05–1.7)	0.18
		Weighted median	120	0.57 (0.25–1.31)	0.18
		Weighted mode	120	0.37 (0.06–2.35)	0.3
	Daytime nap	IVW	99	0.27 (0.03–2.67)	0.26
		MR-Egger	99	0.02 (0–98.01)	0.38
		Weighted median	99	0.64 (0.02–18)	0.79
		Weighted mode	99	1.78 (0–1063.16)	0.86
	Insomnia	IVW	13	1.29 (0.28–5.94)	0.74
		MR-Egger	13	4.88 (0.07–329.46)	0.48
		Weighted median	13	2.02 (0.25–16.09)	0.51
		Weighted mode	13	3.19 (0.2–49.98)	0.42
	Sleep duration	IVW	92	0.94 (0.19–4.61)	0.94
		MR-Egger	92	0.68 (0–352.72)	0.91
		Weighted median	92	0.72 (0.06–8.59)	0.79
		Weighted mode	92	0.35 (0.01–9.28)	0.53

Abbreviations: MR, mendelian randomization; MR-PRESSO, MR pleiotropy residual sum and outlier; N. SNPs, number of SNPs used in MR; IVW, inverse variance weighted; CI, confidence interval; OR, odds ratio.

to a higher risk of alopecia areata. The result of weighted median (OR (95% CI) = 3.94 (1.11–14.02), P = 0.03) concurred with this finding. In addition, no genetic relationship was observed between the remaining sleep characteristics and alopecia in the forward MR analysis. The scatter plot offer intuitive visualizations of the SNP-specific effect sizes on insomnia and alopecia areata after excluding the outliers according to leave-one-out analyses (Figure 2A). The forest plot illustrate the individual SNP effect estimates along with their coherence after excluding the outliers according to leave-one-out analyses (Figure 2B).

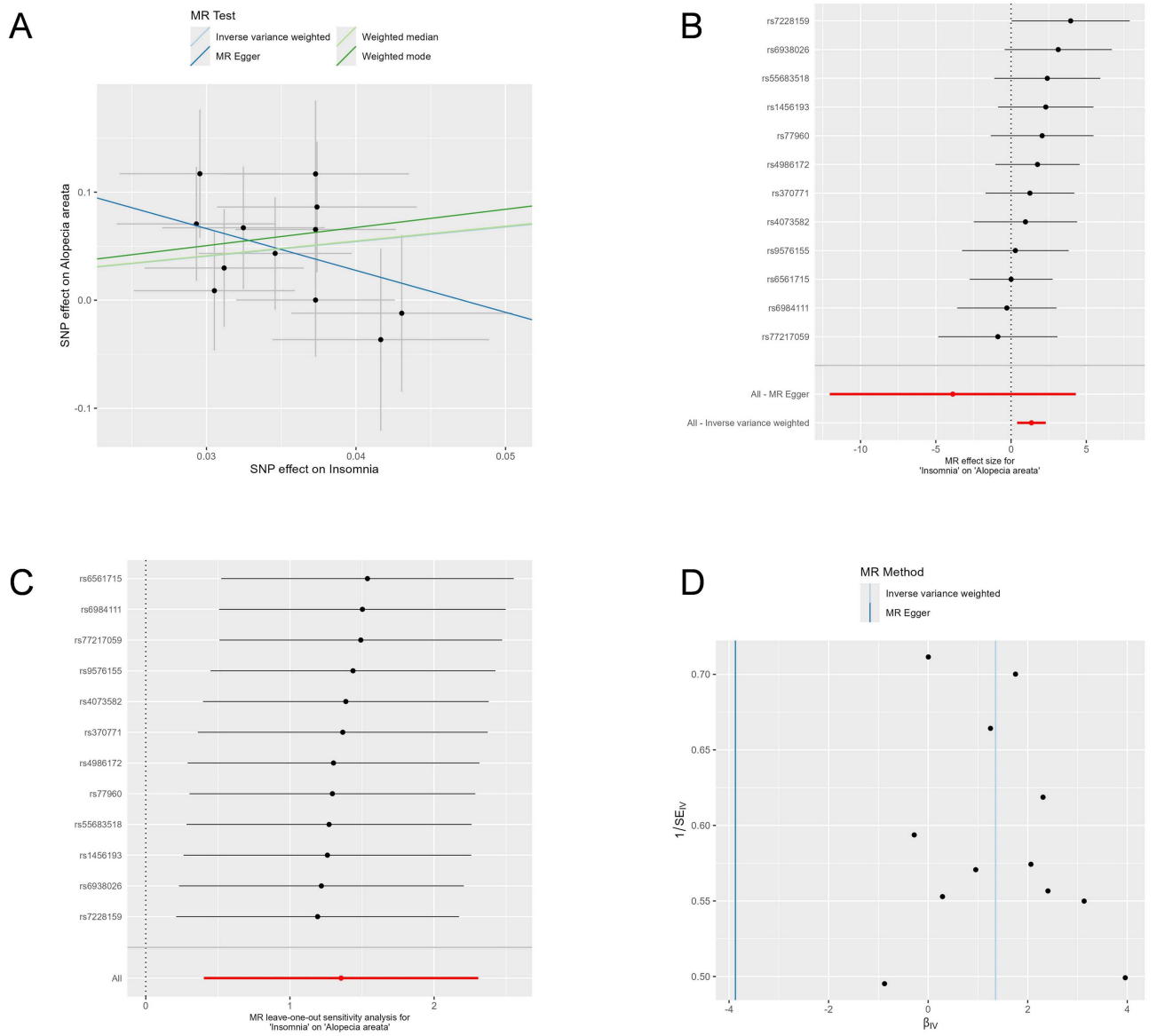

Figure 2 The scatter plot (**A**), forest plot (**B**), leave-one-out plot (**C**) and funnel plot (**D**) for analysis of causal effect of insomnia on alopecia areata after excluding outliers. (**A**) (Scatter plot): X - axis represents the SNP - specific effect on insomnia; Y - axis represents the SNP - specific effect on alopecia areata. Different lines correspond to different MR methods: inverse variance weighted (blue), MR - Egger (gray), weighted median (green), weighted mode (light green). (**B**) (Forest plot): Displays the MR - Egger (red line) and inverse variance weighted (dark red line) estimates of the causal effect of insomnia on alopecia areata, along with the effect size of each instrumental SNP (black lines). (**C**) (Leave - one - out plot): Shows the effect estimate when each SNP is omitted one at a time, with the red line representing the overall effect without omitting any SNP. (**D**) (Funnel plot): X - axis represents the causal effect estimate (β IV); Y - axis represents the inverse of the standard error (1/SE). Points represent individual SNPs, and lines correspond to inverse variance weighted (blue) and MR - Egger (light blue) methods, used to assess publication bias or pleiotropy.
Abbreviations: MR, Mendelian randomization; SNP, single nucleotide polymorphism.

In terms of sensitivity analysis, Cochran's Q test did not find strong evidence of heterogeneity for most associations (Table S4). Furthermore, the MR-Egger regression analysis did not detect significant horizontal pleiotropy for most associations, although a marginal association was observed for sleep duration on androgenic alopecia (P = 0.05) (Table S4). The MR-PRESSO test provided further confirmation, finding no significant outliers across all analyses (Table S5).

It is important to note that for the analysis of daytime nap on androgenic alopecia, the MR-Egger method yielded a biologically implausible OR (140.52, 95% CI: 0.03–659,118.2, P=0.25), as shown in our primary results (Table 1). This instability is attributed to the sparse genetic instruments available for this analysis (only 3 valid SNPs), leading to potential model overfitting. Thus, this specific result should not be interpreted as a valid causal effect.

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Additionally, the leave-one-out analysis did not identify any single SNP that disproportionately influenced the overall causal estimates, and the funnel plots showed symmetrical distribution, suggesting that the significant associations were not driven by individual pleiotropic variants (representative plots in Figures 2C-D).

Causal Effect of Alopecia on Sleep Characteristics

In the reverse MR analysis (Table 2), the IVW method indicated that the genetically predicted alopecia areata had a nominally significant causal effect on morningness (OR (95% CI) = 1.0102 (1.0005–1.0201), P = 0.04), indicating that individuals

Table 2 MR Results of Causal Effect of Alopecia on Sleep Characteristics

Outcome	Exposure	Methods	N. SNPs	OR (95% CI)	P
Morningness	Alopecia areata	IVW	12	1.0102 (1.0005–1.0201)	0.04
		MR-Egger	12	1.0137 (0.9956–1.0321)	0.17
		Weighted median	12	1.0119 (0.9988–1.0251)	0.07
		Weighted mode	12	1.0117 (0.9949–1.0288)	0.2
	Androgenic alopecia	IVW	4	0.997 (0.9836–1.0105)	0.66
		MR-Egger	4	1.0074 (0.9818–1.0336)	0.63
		Weighted median	4	0.9942 (0.9776–1.011)	0.49
		Weighted mode	4	0.9899 (0.9688–1.0114)	0.42
	Scarring alopecia	IVW	23	1.0008 (0.9947–1.0069)	0.79
		MR-Egger	23	0.9931 (0.979–1.0073)	0.35
		Weighted median	23	0.9984 (0.9904–1.0065)	0.7
		Weighted mode	23	0.9954 (0.9859–1.005)	0.35
	Nonscarring alopecia	IVW	3	1.0069 (0.986–1.0283)	0.52
		MR-Egger	3	0.9857 (0.9406–1.033)	0.66
		Weighted median	3	1.0062 (0.9852–1.0276)	0.57
		Weighted mode	3	1.0079 (0.9841–1.0323)	0.59
Daytime nap	Alopecia areata	IVW	11	0.9993 (0.9964–1.0021)	0.62
		MR-Egger	11	0.9979 (0.9924–1.0035)	0.48
		Weighted median	11	0.9993 (0.9954–1.0031)	0.71
		Weighted mode	11	0.9987 (0.9943–1.0032)	0.59
	Androgenic alopecia	IVW	4	0.9997 (0.9944–1.0049)	0.9
		MR-Egger	4	1.0063 (0.9996–1.0129)	0.21
		Weighted median	4	0.999 (0.9939–1.0041)	0.7
		Weighted mode	4	0.997 (0.9899–1.0041)	0.46
	Scarring alopecia	IVW	21	0.9999 (0.998–1.0019)	0.94
		MR-Egger	21	0.9981 (0.9935–1.0027)	0.43
		Weighted median	21	1 (0.9978–1.0023)	1
		Weighted mode	21	1.0004 (0.9979–1.0028)	0.77
	Nonscarring alopecia	IVW	3	0.9996 (0.9946–1.0046)	0.88
		MR-Egger	3	1.0046 (0.9934–1.016)	0.57
		Weighted median	3	0.9992 (0.994–1.0045)	0.77
		Weighted mode	3	0.9986 (0.9932–1.0041)	0.67
Insomnia	Alopecia areata	IVW	8	1.0034 (0.9895–1.0175)	0.63
		MR-Egger	8	0.9881 (0.9621–1.0148)	0.41
		Weighted median	8	1.003 (0.9861–1.0203)	0.73
		Weighted mode	8	1.0002 (0.9748–1.0263)	0.99
	Androgenic alopecia	IVW	3	0.9927 (0.9745–1.0112)	0.44
		MR-Egger	3	1.0164 (0.9806–1.0535)	0.54
		Weighted median	3	0.9929 (0.9731–1.013)	0.48
		Weighted mode	3	0.988 (0.9666–1.0098)	0.39

(*Continued*)

Table 2 (Continued).

Outcome	Exposure	Methods	N. SNPs	OR (95% CI)	P
	Scarring alopecia	IVW	20	1.0037 (0.9977–1.0098)	0.22
		MR-Egger	20	1.0076 (0.9934–1.0221)	0.31
		Weighted median	20	1.008 (0.9993–1.0167)	0.07
		Weighted mode	20	1.0084 (0.9979–1.0191)	0.13
	Nonscarring alopecia	IVW	3	0.9978 (0.9783–1.0178)	0.83
		MR-Egger	3	0.9747 (0.9317–1.0198)	0.47
		Weighted median	3	0.9983 (0.9761–1.0209)	0.88
		Weighted mode	3	1.0041 (0.9809–1.0279)	0.76
Sleep duration	Alopecia areata	IVW	12	0.9998 (0.9949–1.0047)	0.93
		MR-Egger	12	1.0004 (0.9914–1.0095)	0.94
		Weighted median	12	0.998 (0.9916–1.0045)	0.55
		Weighted mode	12	0.9957 (0.9869–1.0046)	0.36
	Androgenic alopecia	IVW	4	0.9967 (0.9901–1.0034)	0.33
		MR-Egger	4	0.9908 (0.9786–1.0031)	0.28
		Weighted median	4	0.9987 (0.9901–1.0073)	0.76
		Weighted mode	4	0.9996 (0.991–1.0083)	0.94
	Scarring alopecia	IVW	23	0.9988 (0.9956–1.0021)	0.47
		MR-Egger	23	0.9982 (0.9904–1.0061)	0.66
		Weighted median	23	0.9984 (0.9945–1.0022)	0.41
		Weighted mode	23	0.9979 (0.9934–1.0025)	0.39
	Nonscarring alopecia	IVW	3	0.9881 (0.9767–0.9997)	0.04
		MR-Egger	3	0.9834 (0.9496–1.0185)	0.52
		Weighted median	3	0.9867 (0.9754–0.9981)	0.02
		Weighted mode	3	0.9863 (0.9757–0.9969)	0.13

Abbreviations: MR, mendelian randomization; MR-PRESSO, MR pleiotropy residual sum and outlier; N. SNPs, number of SNPs used in MR; IVW, inverse variance weighted; CI, confidence interval; OR, odds ratio.

genetically predisposed to alopecia areata are slightly more likely to exhibit a morning chronotype. Similarly, the genetically predicted non-scarring alopecia had a causal effect on sleep duration (OR (95% CI) = 0.9881 (0.9767–0.9997), P = 0.04), indicating that non-scarring alopecia may contribute to a reduction in sleep time. In addition, no genetic relationship was observed between the remaining alopecia and sleep characteristics in the reverse MR analysis. Scatter plots offer intuitive visualizations of the SNP-specific effect sizes on alopecia and sleep characteristics (Figures 3A and 4A). Forest plots illustrate the individual SNP effect estimates along with their coherence (Figures 3B and 4B).

Cochran's Q test revealed significant heterogeneity in the analysis of causal effect of scarring alopecia on daytime nap (Q = 39.29, P = 0.01) (Table S6). This indicates that the individual SNP effects were inconsistent, making the IVW estimate for this association unreliable. Given that the primary methodology employed, IVW, is grounded in random effects, it inherently possesses the capability to accommodate a moderate level of heterogeneity. The results of the MR-Egger regression indicated that no horizontal pleiotropy was present in the analysis (Table S6). For the analysis of scarring alopecia on daytime nap, MR-PRESSO identified rs12203592 as an outlier (global test P=0.008, Table S7), which was subsequently removed. After outlier removal, the causal association remained non-significant (IVW OR=0.998, 95% CI: 0.995–1.001, P=0.23, Table S7), consistent with the pre-removal result. In addition, the leave-one-out analysis revealed no anomalous SNPs capable of influencing the causal estimation outcomes (Figures 3C and 4C). The funnel plots confirmed the unbiased nature of the results (Figures 3D and 4D).

Discussion

The present bidirectional two-sample MR study presents novel insights into the potential causal relationship between sleep characteristics and alopecia types. The primary positive findings suggest a significant causal association between

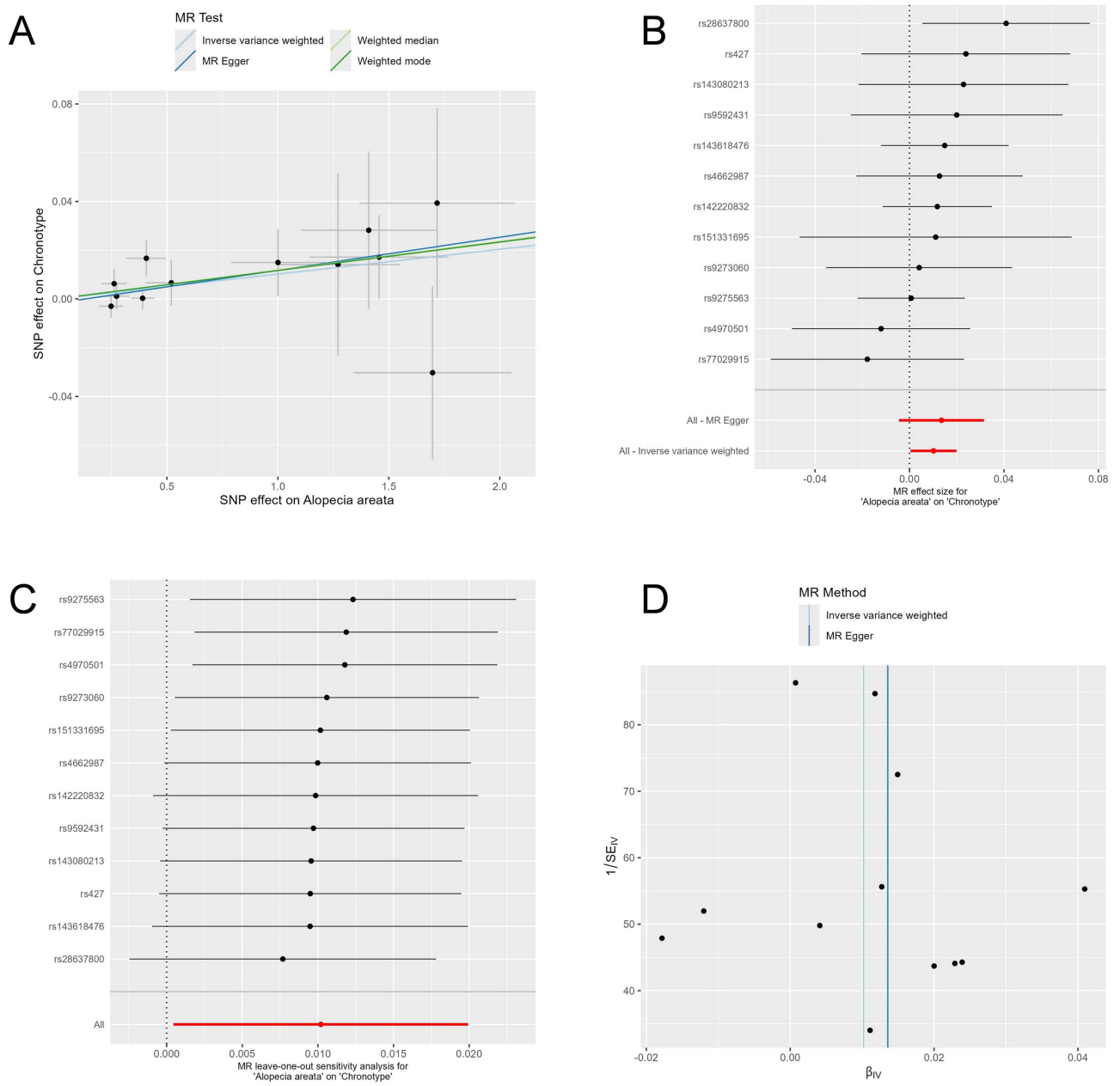

Figure 3 The scatter plot (**A**), forest plot (**B**), leave-one-out plot (**C**) and funnel plot (**D**) for analysis of causal effect of alopecia areata on morningness. Seem to Figure 2.
Abbreviations: MR, Mendelian randomization; SNP, single nucleotide polymorphism.

insomnia and alopecia areata, alopecia areata and morningness, as well as between non-scarring alopecia and sleep duration, advancing the understanding of their interconnections beyond mere associations.

Alopecia areata is an autoimmune disorder characterized by the sudden appearance of one or more circular patches of hair loss on the scalp, often without any visible signs of inflammation or scarring.[1] The exact cause of alopecia areata remains unclear, but it is believed to involve a malfunction of the immune system, which mistakenly attacks hair follicles, causing hair to fall out.[4] Furthermore, alopecia areata could be associated with other autoimmune disorders and be manifested due to inflammation and infectious conditions.[40] The identified causal association between genetically predicted insomnia and alopecia areata aligns with previous observational research. A cross-sectional study evaluated the sleep quality of alopecia areata patients, revealing impaired sleep quality and higher daytime sleepiness, particularly among those with anxiety or depression, highlighting the importance of addressing sleep and psychiatric comorbidities in

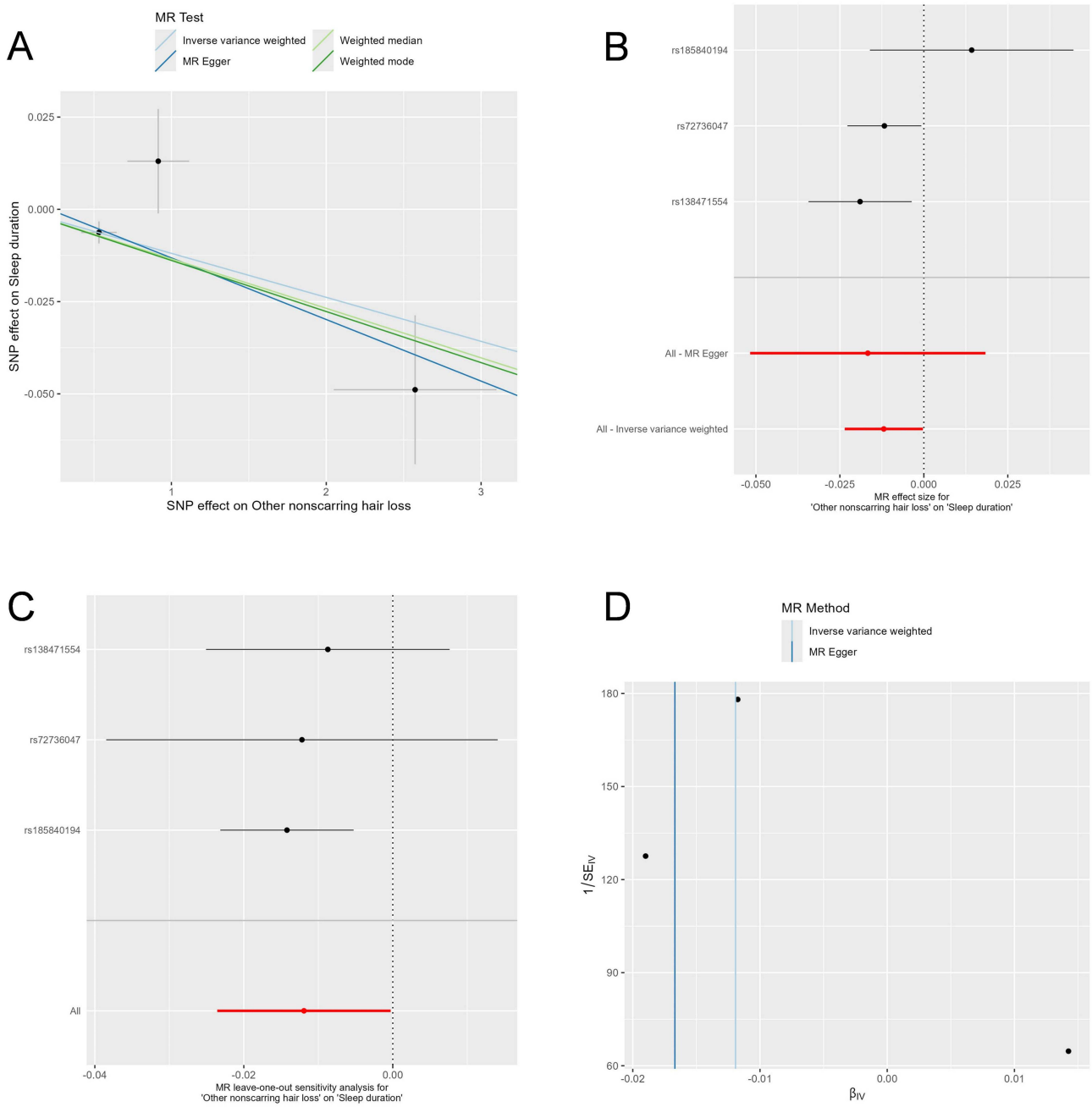

Figure 4 The scatter plot (**A**), forest plot (**B**), leave-one-out plot (**C**) and funnel plot (**D**) for analysis of causal effect of non-scarring alopecia on sleep duration. Seem to Figure 2.
Abbreviations: MR, Mendelian randomization; SNP, single nucleotide polymorphism.

alopecia areata clinical management.[41] A Korean population–based retrospective cohort study found that sleep disorders significantly increase the risk of alopecia areata, particularly in younger individuals, and are also associated with other comorbid diseases.[42] A population-based cohort study in Taiwan also found that sleep disorders, including obstructive sleep apnea and non-apnea insomnia, increase the risk of alopecia areata in patients, with hazard ratios of 4.70, 3.89, and 4.77, respectively.[43] It is speculated by previous studies that the causal relationship between insomnia and alopecia areata may involve hormonal, immune pathways and clock genes. Firstly, insomnia, characterized by difficulty initiating or maintaining sleep, has been suggested to disrupt normal circadian rhythms and hormonal balances, particularly stress hormones like cortisol, which can impact hair growth cycles.[41] Secondly, there is accumulating evidence that underscores

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a potential association between sleep disorders and autoimmune diseases, notably systemic lupus erythematosus and rheumatoid arthritis.[44] Given the fact that alopecia areata exhibits genetic and inflammatory characteristics analogous to those observed in other systemic autoimmune disorders, it is plausible to hypothesize that insomnia may influence alopecia areata through immune pathways.[43] Furthermore, sleep disturbances impact skin functions, causing dryness and itching. Circadian rhythm, governed by clock genes, regulates Aquaporin 3, essential for skin hydration. Disrupted rhythms hinder Aquaporin 3, affecting skin moisturization, which might be related to the aggravation of alopecia areata due to sleep disturbances.[45] Above all, future research needs to delve deeper into the biological mechanisms of the causal relationship between insomnia and alopecia areata. Clinically, the correlation between them emphasizes the importance of comprehensively assessing and managing sleep disorders in patients with alopecia areata. Our results suggest that the association between insomnia and alopecia areata may be mediated by immune pathways, a hypothesis that requires future two-step MR or mediation analysis integrating proteomic data (eg, cytokine levels) to be directly tested.

On the other hand, the present study also indicated that genetically predicted alopecia areata is nominally associated with morningness. Although we observed a statistically significant effect of alopecia areata on morningness (OR=1.0102, 95% CI: 1.0005–1.0201, P=0.04), the effect size is minimal (ΔOR=0.01). This indicates that alopecia areata has little practical impact on sleep chronotype, and the statistical significance may be driven by large sample size rather than clinical relevance. Residual confounding (eg, stress affecting both alopecia areata and sleep) cannot be fully excluded even with MR design. This association may reflect residual confounding that MR cannot fully eliminate, such as stress affecting both conditions. It is hypothesized that the underlying cause may likewise be intertwined with immune pathways. Alopecia areata, being an autoimmune disorder, is characterized by elevated levels of cytokines in patients' serum, and notably, these cytokines hold a pivotal role in the regulation of sleep, which might indicates the potential connection between alopecia areata and an early waking tendency.[43] Furthermore, this study also demonstrated that nonscarring alopecia might reduce the sleep duration. It is supposed that progressive hair loss, particularly in its early stages or when perceived as a cosmetic concern, can significantly impact an individual's psychological well-being, leading to stress and anxiety. Chronic stress is known to activate the immune system, promoting inflammation and disrupting sleep patterns. Inflammatory cytokines, released during stress responses, have been shown to affect sleep architecture, reducing sleep efficiency and total sleep time.[46] In summary, the results underscore the potential role of emotional distress and sleep hygiene in alopecia management.

This study utilized MR analysis, a robust approach to investigate causality, minimizes confounding and reverse causation biases. The stringent quality control measures, including assessment of weak instrument bias and horizontal pleiotropy, strengthen the credibility of the findings. However, there are some limitations should be noted. Firstly, our study involved 32 independent tests. After applying a Bonferroni correction, the nominal associations we initially observed no longer met the threshold for statistical significance, suggesting that these findings should be interpreted with caution as they could be false positives. Secondly, our power analysis indicated that the study was underpowered for detecting small to moderate effects for several associations, particularly in the reverse direction and for alopecia subtypes with low case counts. This low statistical power might have led to false-negative results (Table S8). Thirdly, the genetic data for all alopecia outcomes were sourced from the FinnGen consortium, which is limited to individuals of European ancestry. Therefore, our findings may not be generalizable to other populations. Fourthly, we observed a risk of weak instrument bias, particularly for scarring alopecia, where the average F-statistic was borderline (F=18). This could potentially lead to biased effect estimates. Fifthly, some sleep characteristic data were derived from self-reports, which are susceptible to recall bias. Future studies using objectively measured sleep data from accelerometers could help validate our findings. Sixthly, in the analysis of daytime napping on androgenetic alopecia, the MR-Egger method yielded an extremely unstable and implausible OR (140.52) with a very wide confidence interval. This suggests model instability, likely due to a sparse number of instruments, rendering this specific result unreliable. Finally, the biological plausibility of some findings, such as alopecia areata causing a slight tendency for morningness, is tenuous. Residual confounding, such as underlying stress influencing both conditions, cannot be entirely ruled out even with the MR design.

Conclusion

In conclusion, this MR study provides suggestive evidence for a bi-directional causal relationship between alopecia and sleep characteristics. However, these findings did not withstand rigorous correction for multiple testing, highlighting the need for cautious interpretation. Specifically, nominal associations were observed between insomnia and alopecia areata, as well as between alopecia areata and morningness. Future research should aim to replicate these findings in larger, more ethnically diverse cohorts to confirm these potential causal links and elucidate the underlying biological mechanisms.

Data Sharing Statement

All data generated or analyzed during this study are included in this article and supplementary information files.

Ethics Approval and Consent to Participate

This study was based on publicly available summary statistics from GWAS (UK Biobank and FinnGen). These databases have obtained ethical approval and informed consent from participants. According to the Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University IRB policy and Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (China, 2023), analyses using only publicly available, de-identified data are exempt from additional ethical review. All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Yanqi Li, Yuge Wang, Yankun Zhang, Wanchao Wang and Hongmei Ai declare that they have no competing interests.

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