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Article

Mental disorders and the risk of atopic dermatitis: A two-sample mendelian randomization study

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Abstract: Background: Growing evidence suggests that mental disorders are associated with an increased risk of atopic dermatitis (AD). But until now, the causal association between them has been unclear. We conducted a Mendelian randomization study to determine the bidirectional causal association between atopic dermatitis and mental disorders. Simultaneously, the correlation between biomechanics and atopic dermatitis (AD) has been analyzed. **Objective:** This two-sample Mendelian randomization (MR) study aims to assess the causal relationship between mental disorders and the incidence of atopic dermatitis (AD). **Methods:** Single nucleotide polymorphisms (SNPs) associated with severe depression, generalized anxiety disorder, sleep disorders, schizophrenia, and AD were selected from the genome-wide association study (GWAS) databases. Causal effects between exposure and outcomes were analyzed using methods such as inverse-variance weighted (IVW), weighted median (WM), and MR-Egger, with results primarily assessed by the *P*-values, odds ratios (ORs), and 95% confidence intervals (CIs) from the IVW method. Sensitivity analyses were conducted using IVW, MR-Egger, and MR-PRESSO methods. **Results:** The findings indicate a positive causal effect of severe depression on the risk of developing AD, with the IVW method yielding an OR of 1.177 (95% CI 1.083–1.280, $P < 0.001$) and the WM method showing an OR of 1.182 (95% CI 1.061–1.317, $P < 0.001$). Heterogeneity tests using the IVW method's Cochran Q test resulted in a *P*-value of 0.132 and an I^2 of 19.34%. Pleiotropy tests with MR-PRESSO showed a *P*-value of 0.193, and the MR-Egger regression intercept yielded a *P*-value of 0.009, indicating the presence of heterogeneity or pleiotropy. No causal relationships were found between generalized anxiety disorder (OR = 1.024, 95% CI 0.996–1.052, $P > 0.05$), sleep disorders (OR = 0.970, 95% CI 0.928–1.014, $P > 0.05$), or schizophrenia (OR = 1.006, 95% CI 0.983–1.029, $P > 0.05$) and the incidence of AD. **Conclusion:** Major depressive disorder exhibits a unidirectional causal influence on Alzheimer's disease development risk. It is recommended that patients with severe depression undergo enhanced screening and prevention for AD to mitigate the risk of developing this condition. Biomechanics plays a significant role in the onset and progression of atopic dermatitis (AD).

Keywords: atopic dermatitis; mental disorders; mendelian randomization; causal effect; biomechanical

1. Introduction

Mental disorders encompass a range of conditions that affect human mental and emotional states, often resulting from disturbances in brain function due to physiological, psychological, and social factors. These disorders can manifest as impairments in cognition, affect, behavior, and volition to varying degrees, affecting approximately 18% of the global population [1]. This statistic highlights the widespread nature of mental health issues, emphasizing the need for increased

awareness and resources dedicated to understanding and treating these conditions. Mental disorders can range from mild anxiety to severe conditions such as schizophrenia, illustrating the diverse spectrum of mental health challenges faced by individuals around the world. Atopic dermatitis (AD) is a prevalent inflammatory skin condition marked by recurring eczema-like rashes and intense itching. This chronic condition often begins in childhood but can persist into adulthood, affecting individuals at various life stages. The physical manifestations of AD, including red, inflamed patches of skin, can lead to discomfort and pain, significantly impacting the quality of life of those affected. The intense itching associated with AD can disrupt daily activities and lead to sleep disturbances, further complicating the mental health of patients. AD is also recognized as an immune-mediated psychosomatic disorder, with extensive research indicating a strong association between AD and various mental disorders such as low self-esteem, anxiety, depression, sleep disorders, and schizophrenia [2]. This connection underscores the importance of a holistic approach to treatment, where both physical and mental health are addressed concurrently. Patients with AD may experience a cycle where their skin condition exacerbates their mental health issues, which in turn can worsen their skin symptoms, creating a challenging situation to manage. This condition impacts individuals across all age groups and ethnicities, placing considerable social and psychological strains on both patients and their families. The impact of AD extends beyond the individual, often affecting family dynamics and relationships. Families may experience stress as they navigate the challenges of managing a chronic condition, leading to increased caregiver burden and emotional strain. Furthermore, societal perceptions of visible skin conditions can lead to stigma, isolation, and discrimination, further exacerbating the psychological toll on patients. AD is also one of the primary dermatological causes of psychological stress [3]. The visible nature of the lesions can lead to self-consciousness and social withdrawal, as individuals may avoid situations where their skin is exposed. This avoidance can hinder social interactions and opportunities, leading to feelings of loneliness and depression. Epidemiological studies, both cross-sectional and longitudinal [4], indicate that the prevalence of AD diagnosed and persisting for more than one year in adults is approximately 1.2% in Asia and 17.1% in Europe, while in children, the rates are about 0.96% in Asia and 22.6% in Europe. These statistics reveal significant regional differences in the prevalence of AD, which may be influenced by environmental factors, genetics, and lifestyle choices. Understanding these variations is crucial for creating tailored interventions and public health initiatives that aim at reducing the incidence and impact of this condition. Due to the visible location of lesions on exposed parts of the body, atopic dermatitis (AD) often causes significant distress in the lives and social interactions of sufferers, leading to psychological responses such as low self-esteem and anxiety. This distress can manifest in various ways, including avoidance of social situations, reluctance to participate in physical activities, and a general decline in overall mental well-being. The interplay between physical symptoms and psychological health highlights the need for integrated care approaches that consider the full spectrum of a patient's experience. Additionally, the recurrent nature of AD exacerbates the psychological burden on patients. A study concerning U.S. adults with AD [5] showed that compared to non-AD individuals, patients with AD had higher average scores on the Anxiety

(HADS-A) (7.7 vs. 5.6) and Depression (HADS-D) (6.0 vs. 4.3) subscales of the Hospital Anxiety and Depression Scale. Moreover, the incidence of abnormal scores (≥ 11) was higher in AD patients for HADS-A (28.6% vs. 1.5%) and HADS-D (13.5% vs. 9.0%). In multivariate linear and logistic regression models adjusted for sociodemographic factors, AD was associated with higher average scores for HADS-A and HADS-D (7.7 and 6.0, respectively) and correlated with abnormal HADS-A odds ratios [(OR) 2.19, 95% confidence interval (CI) 1.65–2.91] and elevated HADS-D scores (OR 1.50, 95% CI 1.04–2.17), with all groups showing significance ($P \leq 0.03$). Furthermore, analyses have found that [6] compared to individuals without AD, patients with AD have significantly increased odds of suicidal ideation and attempted suicide. This analysis included 15 studies encompassing 4,770,767 participants, with 310,681 AD patients (52.7% female) and 4,460,086 controls (50.9% female). In this analysis, patients with atopic dermatitis (AD) exhibited a 44% higher likelihood of experiencing suicidal ideation (OR 1.44, 95% CI 1.25–1.65) and a 36% higher likelihood of attempted suicide (OR 1.36, 95% CI 1.09–1.70) compared to those without AD. Although numerous studies have confirmed a correlation between AD and mental disorders, the specific pathophysiological mechanisms linking the two remain unclear, and studies that infer causality between their risks are relatively scarce.

Mendelian randomization (MR) is a widely used research method for assessing the causal effects between exposure factors and diseases. This method is based on the principles of Mendelian inheritance, utilizing an epidemiological study design and data analysis [7]. The fundamental idea behind Mendelian Randomization (MR) studies is to utilize genetic variants, particularly single nucleotide polymorphisms (SNPs), that are robustly linked to an exposure as instrumental variables (IVs). By employing MR regression, which is a form of single linear regression analysis, the objective is to investigate the causal link between the exposure and the resulting outcome. In this study, our goal is to unravel the intricate causal connections between mental disorders and the likelihood of developing Alzheimer's Disease (AD) through the application of MR [8].

2. Methods and subjects

2.1. Study design

This study employs a Two-Sample Mendelian Randomization (TSMR) approach to assess the causal relationship between mental disorders and atopic dermatitis (AD), with the exposure being mental disorders including severe depression, generalized anxiety disorder, sleep disorders, and schizophrenia, and the outcome being AD. MR analysis requires instrumental variables (IVs) to satisfy three core assumptions. The criteria for including instrumental variables (IVs) in this study are as follows: (1) Relevance Assumption: All IVs are significantly associated with the exposure diseases at the genome-wide level ($P < 5 \times 10^{-8}$). (2) Independence Assumption: The included IVs show no linkage disequilibrium, with a kb = 10,000 and $r^2 < 0.001$. (3) Exclusion Restriction Assumption: There are no genome-wide significant associations between the IVs and the outcome ($P < 5 \times 10^{-5}$). Since all genetic data are sourced from publicly available databases or publicly accessible publications, this study does not require ethical approval or patient informed consent.

2.2. Data sources

The genetic data used are derived from publicly available and legally accessible genome-wide association study (GWAS) databases. The exposure in this study primarily includes the following four disorders: severe depression, generalized anxiety disorder, sleep disorders, and schizophrenia. The data for severe depression and schizophrenia are sourced from the UK Biobank, while data for generalized anxiety disorder and sleep disorders are obtained from the FinnGen database. The data for atopic dermatitis (AD) come from https://www.ebi.ac.uk/gwas/studies/GCST90244787. For detailed basic information on the data, refer to **Table 1**.

Table 1. Basic information of exposure and outcome.

Exposure/Outcome	Year	Ethnicity	Sample Size	Number of SNPs	PMID	GWAS ID/URL
Severe Depression	2019	European	500,199	\	30,718,901	ieu-b-102
Generalized Anxiety Disorder	2021	European	200,273	16,380,388	\	Finn-b-F5_GAD
Sleep Disorders	2021	European	216,700	16,380,458	\	Finn-b-SLEEP
Schizophrenia	2022	European	127,906	\	35,396,580	ieu-b-5102
Atopic Dermatitis	2023	European	864,982		37,794,016	https://www.ebi.ac.uk/gwas/studies/GCST90244787

2.3. Selection of instrumental variables

To ensure the robustness and efficacy of the instrumental variables (IVs) included, the following steps were undertaken: Firstly, we set the parameters to $P < 5 \times 10^{-8}$, linkage disequilibrium $r^2 < 0.001$, and a window size of kb = 10,000. If the number of SNPs that meet these criteria is less than three, we relax the threshold to $P < 5 \times 10^{-6}$. The strength of the instrumental variables is assessed using the *F*-statistic, where an *F*-value > 10 indicates a strong instrumental variable, which will be included in the MR analysis. The formula for calculating the *F*-value is: $F = \beta 2/SE2$, where β is the effect size of the allele, and SE is the standard error of the allele effect size [9,10]. SNPs that meet the above criteria are used as instrumental variables for the MR analysis.

2.4. MR analysis methods

The inverse-variance weighted method (IVW) is the primary analytical approach used in this study [11], with MR-Egger and the weighted median (WM) methods serving as supplementary approaches [12,13]. These three methods are currently the most recognized and commonly used in MR analyses.

2.5. Sensitivity analysis

Sensitivity analysis primarily includes heterogeneity and pleiotropy tests to ensure the reliability and stability of the MR analysis results. The MR-Egger intercept method, MR pleiotropy residual sum and outlier test (MR-PRESSO) are employed to detect the presence of horizontal pleiotropy and identify outliers [13–15]; Heterogeneity is assessed by examining the symmetry of scatter distribution on either side of the IVW line in funnel plots; “Leave-one-out” sensitivity analysis is used to

verify the impact of individual SNPs on the causal relationship between exposure and outcome [16]; Cochran's Q statistic is utilized to evaluate the presence of potential violations of Mendelian assumptions with instrumental variables; if $P < 0.05$,this indicates heterogeneity, prompting the use of a random effects model under IVW to further validate and assess result consistency [15]; The Wald ratio method estimates the causal effect of exposure on outcomes using individual IVs [17].

2.6. Statistical analysis

This study conducts two-sample Mendelian randomization analyses using the R language (Version 4.3.1 Windows x64) and the TwoSampleMR package (Version 0.5.8), with outlier detection performed by the MR-PRESSO package (Version 1.0). All analysis results are presented as odds ratios (OR) and their 95% confidence intervals (CI), with $P < 0.05$ indicating statistical significance.

3. Results

3.1. The causal effect of severe depression on AD

With severe depression as the exposure, instrumental variables for MR analysis are selected based on criteria of $P < 5 \times 10^{-8}$, $R^2 < 0.001$, kb = 10,000, and F-value > 10. After MR-PRESSO testing, rs1367635 and rs754287 are identified as outliers and excluded, resulting in 45 SNPs being included in the final analysis. MR analysis results indicate a positive causal relationship between severe depression and atopic dermatitis (AD). The inverse-variance weighted (IVW) method shows an odds ratio (OR) of 1.177 with a 95% confidence interval (CI) of 1.083–1.280 ($P < 0.001$), and the weighted median (WM) method displays an OR of 1.182 with a 95% CI of 1.061–1.317 ($P < 0.001$). **Figure 1** presents the causal effects of severe depression on AD using three analytical methods. The forest plot for the IVW method also supports a positive causal relationship between severe depression and AD, as shown in **Figure 2**. Results from Cochran's Q tests for both the IVW and MR-Egger methods, as presented in **Table 2**, indicate no heterogeneity. The MR-Egger intercept test reveals horizontal pleiotropy exists, and the MR-PRESSO Global test also indicated horizontal pleiotropy. Leave-one-out analysis demonstrates that the causal relationship between severe depression and AD is not driven by any single SNP, as illustrated in **Figure 3**. The symmetry of scatter distribution on either side of the IVW line in the funnel plot, shown in **Figure 4**, also suggests no bias in the results.

Table 2. Sensitivity analysis for exposures of instrumental variables in GWAS for AD.

	Horizontal Pleiotropy				**Heterogeneity**	
Exposure	**MR-Egger Intercept Test**	***P*-value**	**MR-PRESSO Global Test**	***P*-value**	**Cochran *Q* Heterogeneity Test**	***P*-value**
Severe Depression	0.009	0.193	56.923	0.148	54.554	0.132
Generalized Anxiety Disorder	0.008	0.238	7.613	0.725	5.508	0.702
Sleep Disorders	−0.002	0.751	27.735	0.409	25.042	0.404
Schizophrenia	0.002	0.555	212.038	< 0.001	209.323	< 0.001

Note: The results of the Cochran Q heterogeneity test are reported for the IVW method.

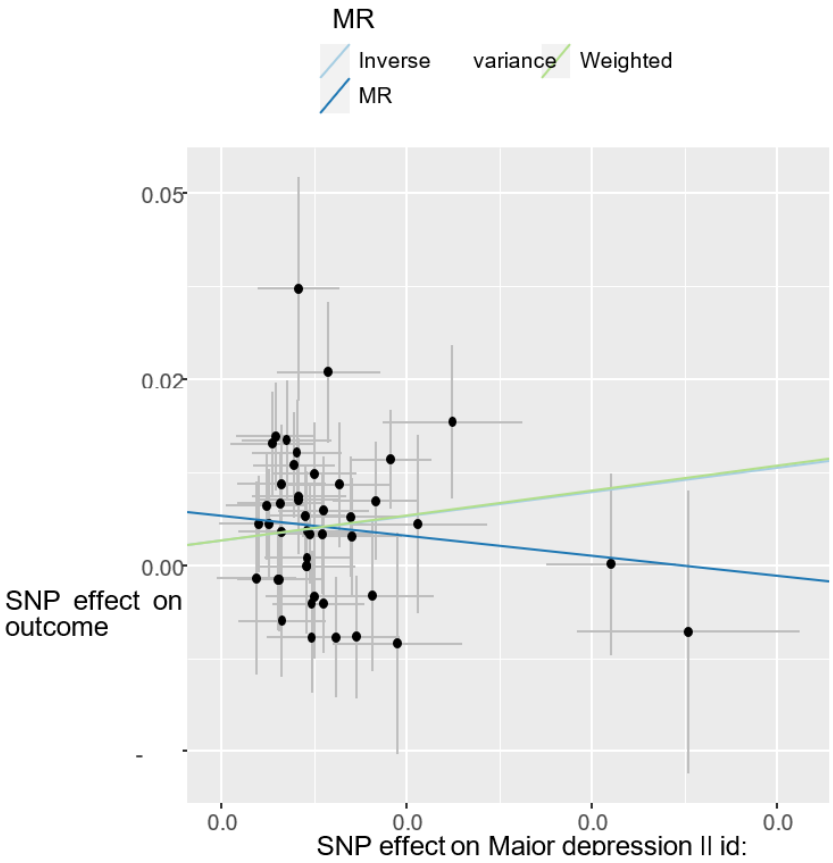

Figure 1. MR scatterplot of the causal effect of major depressive disorder on AD risk.

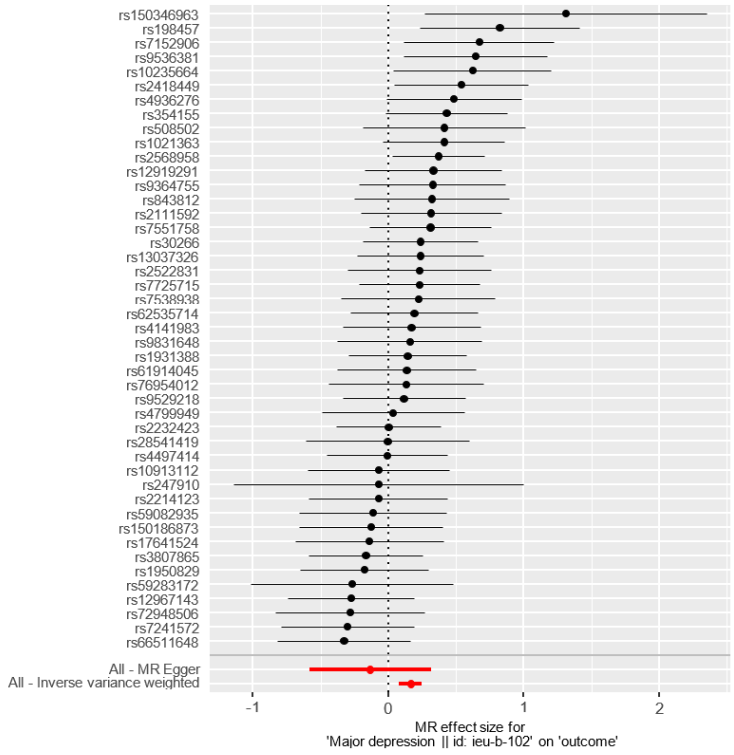

Figure 2. MR scatterplot of the causal effect of major depressive disorder on AD risk.

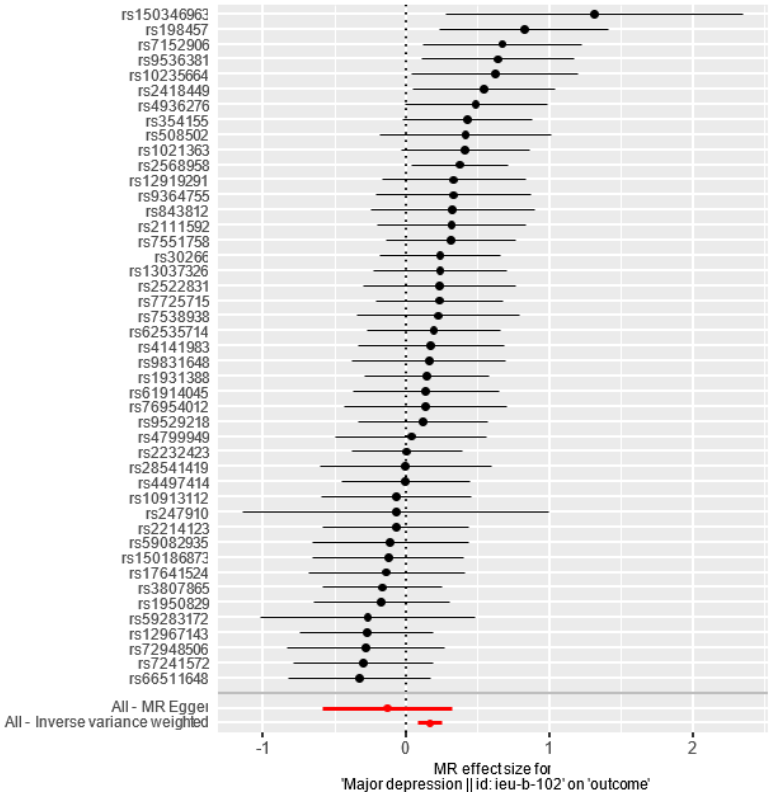

Figure 3. Result of leave-one-out sensitivity analysis.

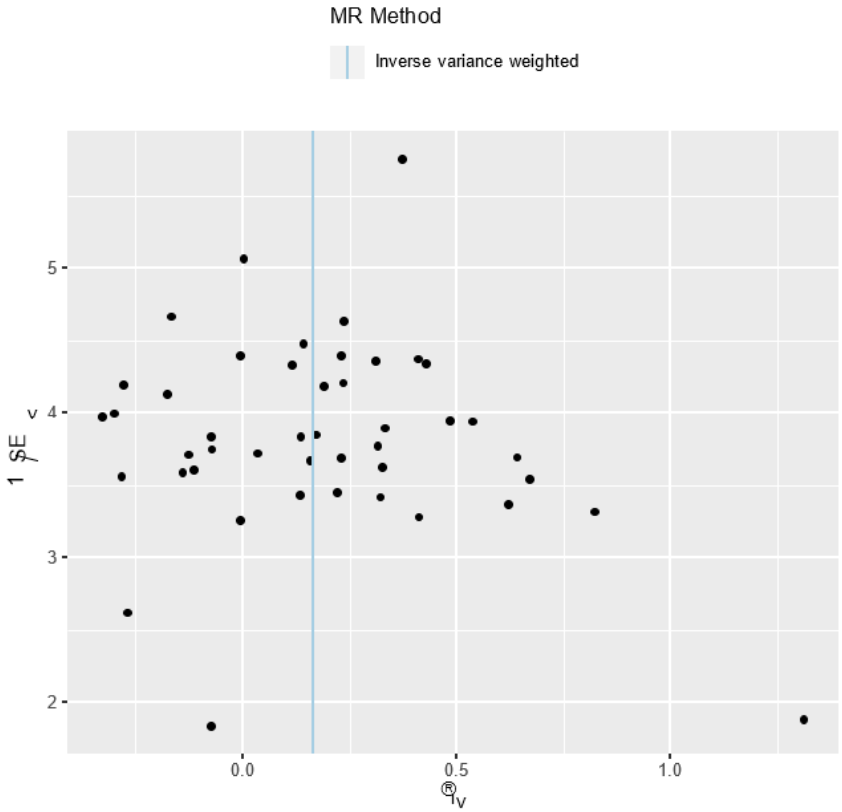

Figure 4. Funnel plot showing overall heterogeneity in the impact of major depressive disorder on the risk of AD.

3.2. The causal relationship between generalized anxiety disorder and AD

With generalized anxiety disorder as the exposure, instrumental variables were selected under the criterion of $P < 5 \times 10^{-6}$ to meet the strong relevance assumption. After excluding linkage disequilibrium and palindromic sequences, no outliers were detected by the MR-PRESSO method, ultimately including 9 SNPs. MR analysis reveals no causal relationship between generalized anxiety disorder and AD. The IVW method yields an OR of 1.024 with a 95% CI of 0.996–1.052 ($P > 0.05$), the WM method shows an OR of 1.019 with a 95% CI of 0.985–1.055 ($P > 0.05$), and the MR-Egger method presents an OR of 1.005 with a 95% CI of 0.966–1.046 ($P > 0.05$).

3.3. The causal relationship between sleep disorders and AD

Using sleep disorders as the exposure factor, instrumental variables (IVs) for MR analysis were selected based on the criteria of $P < 5 \times 10^{-6}$, $R^2 < 0.001$, kb = 10,000, and F-value > 10. No outliers were detected by the MR-PRESSO method, and ultimately 25 SNPs were included. MR analysis indicates that there is no causal relationship between sleep disorders and AD. The IVW method reports an OR of 0.970 with a 95% CI of 0.928–1.014 ($P > 0.05$); the WM method shows an OR of 0.987 with a 95% CI of 0.923–1.054 ($P > 0.05$); and the MR-Egger method presents an OR of 0.986 with a 95% CI of 0.885–1.098 ($P > 0.05$).

3.4. The causal relationship between schizophrenia and AD

With schizophrenia as the exposure, instrumental variables were selected under the strong relevance assumption with a criterion of $P < 5 \times 10^{-8}$. After excluding linkage disequilibrium and removing palindromic sequences, MR-PRESSO testing identified rs113264400 as an outlier, which was then excluded, ultimately incorporating 147 SNPs. MR analysis shows that there is no causal relationship between schizophrenia and AD. The IVW method yields an OR of 1.006 with a 95% CI of 0.983–1.029 ($P > 0.05$); the WM method reports an OR of 1.024 with a 95% CI of 0.994–1.055 ($P > 0.05$); and the MR-Egger method indicates an OR of 0.979 with a 95% CI of 0.983–1.073 ($P > 0.05$).

4. Discussion

This study utilized Mendelian randomization (MR) methods to analyze the impact of four psychiatric characteristics—major depressive disorder, generalized anxiety disorder, sleep disorders, and schizophrenia—on the risk of atopic dermatitis (AD). The results indicate a positive causal effect of major depressive disorder on the risk of AD. The inverse-variance weighted (IVW) method yielded an odds ratio (OR) of 1.177 with a 95% confidence interval (CI) of 1.083–1.280 ($P < 0.001$), and the weighted median (WM) method showed an OR of 1.182 with a 95% CI of 1.061–1.317 ($P < 0.001$). The findings from the MR analysis suggest that genetic variations point to AD being a risk factor associated with major depressive disorder, indicating an increased risk of AD in patients with severe depression. No causal relationships have been found between generalized anxiety disorder, sleep disorders, schizophrenia, and the risk of AD. A study on the potential mechanisms linking atopic dermatitis (AD) with major depressive disorder (MDD) revealed, through extensive literature data

mining, that AD regulates MDD via 18 upstream factors. These include seven cytokines (TNF, IL33, NPPB, CRH, IL6, IL4, AGER), seven small molecules (acetylcholine, ROS, catecholamines, vitamin D3, Mg^{2+}, ascorbic acid, ATP), and inflammatory cells and related factors (serotonin receptors, inflammatory cytokines, cytokines). Mega-analysis identified significant expression changes in four genes (BMP7, USP46, AR, ISG15) in AD, which are conducive to the development of MDD. Pathway Enrichment Analysis (PEA) supports the functional linkage between AD and potential associated genes (CRH, NPPB, and BMP7) with MDD. This study's findings align with those of Yang et al. [18], confirming that major depressive disorder is associated with the incidence of AD ($P < 0.05$). Extensive research indicates that individuals with AD are at an increased risk of severe depression, yet studies focusing on the incidence of AD among patients with severe depression are sparse. This scenario suggests that healthcare professionals should pay more attention to the dermatological health of patients suffering from severe depression. This research establishes a causal link between AD and severe depression from a genetic standpoint, providing new evidence for enhanced screening and prevention of AD in patients with clinical mental disorders. Atopic dermatitis (AD) is a psychosomatic disorder, with symptoms of depression and anxiety being particularly common among those affected. In a cross-sectional study investigating the relationship between AD and psychological factors [19], a questionnaire was administered to 135,950 adult participants. Using self-reported data and the validated psychiatric assessment tool, the Mini International Neuropsychiatric Interview (M.I.N.I.), a total of 56,896 participants were included (average age 55.8 years, 39.7% male). The results indicated a positive correlation between AD and self-reported depression, social phobia, attention deficit hyperactivity disorder, and eating disorders among the participants. Current research tends to focus on the psychiatric conditions of patients with AD but lacks attention to skin diseases in patients with mental disorders. Research in the field of psychoneuroimmunology has established that primary stress mediators, such as cortisol, adrenocorticotropic hormone (ACTH), and the activation of the hypothalamic-pituitary-adrenal (HPA) axis via corticotropin-releasing hormone (CRH), are capable of triggering diverse immune responses within the skin. Skin cells themselves have the ability to produce these hormones and actively contribute to skin inflammation. Consequently, the localized skin CRH-proopiomelanocortin (POMC)-ACTH-corticosteroid axis plays a pivotal role in responses induced by stress. Moreover, keratinocytes and fibroblasts synthesize signaling peptides that are typically associated with the hypothalamus and pituitary gland, and they express receptors (including CRH receptors and peptides that degrade POMC along with melanocortin receptors). This enables them to respond to CRH by activating the POMC gene, ultimately leading to the secretion of adrenocorticotropic hormone and corticosteroids. Furthermore, keratinocytes express receptors for various neurotransmitters (like adrenaline, noradrenaline, dopamine, histamine, and acetylcholine), neurotrophic factors, and neuropeptides (such as substance P and nerve growth factor), all of which are crucial in connecting the mechanisms of psychoneuroimmunology [20]. This study has certain limitations. Firstly, the data is predominantly from European populations, and caution is required when extrapolating these findings to patients of other ethnicities, necessitating further exploration with larger sample sizes and genome-wide association studies. Secondly, despite multiple

sensitivity analyses, the assessment of horizontal pleiotropy remains limited. Although Mendelian Randomization (MR) studies are recognized for their ability to mitigate confounding factors, some potential and unknown confounders cannot be completely eliminated, leading to potential discrepancies between the study conclusions and actual clinical observations. Additionally, due to the lack of more detailed information in the GWAS datasets, this study could not perform stratified analyses based on different characteristics, such as age, gender, or severity of the disease.

The biomechanical alterations in AD have significant implications for the disease process and its management.

1) Impact on Skin Barrier Function

The compromised skin barrier in AD not only allows for excessive water loss but also makes the skin more susceptible to external insults. This condition significantly undermines the skin's natural defenses, leading to a cycle of irritation and discomfort. As the barrier weakens, it becomes increasingly difficult for the skin to retain moisture, which can result in dryness and flakiness. This increased permeability can promote the entry of allergens, irritants, and pathogens into the skin, exacerbating inflammation and skin damage [21].

2) Role in Itching and Scratching Behavior

Itching is a hallmark symptom of AD, and scratching behavior is a common response. The biomechanical alterations in AD skin, such as reduced elasticity and increased fragility, can exacerbate itching and promote scratching. This persistent itch often leads to a compulsion to scratch, which can provide temporary relief but ultimately results in more significant damage to the skin. Over time, this behavior can create a cycle where the skin becomes increasingly sensitive and reactive. This scratching behavior can further damage the skin barrier, leading to a vicious cycle of itching, scratching, and skin damage [22,23]. Moreover, the inflammation associated with atopic dermatitis can heighten the sensation of itch, making it even more challenging for individuals to resist the urge to scratch. As the skin barrier weakens, it becomes more susceptible to irritants and allergens, which can trigger additional flare-ups of itching and discomfort. Understanding this cycle is crucial for developing effective treatment strategies aimed at breaking the cycle and promoting healing in affected individuals.

3) Implications for Treatment

Understanding the biomechanical aspects of AD can inform the development of new treatment strategies. By analyzing how the skin's structure and function are altered in atopic dermatitis, researchers can identify specific targets for intervention. For example [24], topical emollients and moisturizers can help restore skin hydration and barrier function, reducing TEWL and improving skin elasticity. These products work by forming a protective layer on the skin, which not only prevents moisture loss but also helps to soothe irritation and reduce the frequency of flare-ups. Additionally, novel therapies targeting the skin's extracellular matrix and collagen fibers may hold promise for improving skin strength and reducing fragility in AD patients [25]. Such treatments could enhance the skin's resilience, making it less prone to damage from environmental factors and reducing the overall severity of symptoms. By focusing on these biomechanical elements, healthcare providers can better tailor treatment plans to meet the needs of individuals suffering from atopic dermatitis, ultimately improving

their quality of life.

Biomechanics, the study of the mechanical properties and behaviors of biological systems, has emerged as a critical factor in AD pathogenesis and treatment. Itch-induced scratching, a common symptom in AD patients, exacerbates skin inflammation and perpetuates the disease cycle. Understanding these mechanical interactions is essential for developing effective interventions. Itch-induced scratching, a common symptom in AD patients, exacerbates skin inflammation and perpetuates the disease cycle. Mechanical stimuli from scratching promote the secretion of inflammatory cytokines like TSLP from skin cells, enhancing AD inflammation and forming a "scratch-itch cycle." This cycle not only contributes to the persistence of symptoms but also complicates the overall management of the condition. Additionally, scratching directly disrupts the skin barrier, facilitating the infiltration of bacteria and allergens into the skin tissue, further aggravating inflammation. This breach in the skin's protective layer can lead to secondary infections, compounding the challenges faced by patients. It is worth noting that there is a close interplay between acute inflammation-induced oxidative stress and mechanical scratching in atopic dermatitis (AD): intense scratching exacerbates oxidative stress, which in turn triggers acute inflammation. Conversely, inflammation mediated by oxidative stress sensitizes cells to mechanical stimuli, thereby intensifying the inflammatory response when scratching occurs [26]. This intricate relationship highlights the importance of addressing both mechanical and inflammatory aspects of atopic dermatitis to break the cycle and promote healing.

In response to the role of biomechanics in AD, researchers have developed novel treatment approaches. For instance, the Bionic Engineering and Biomechanics Institute (BEBC) at Xi'an Jiaotong University, in collaboration with the Department of Dermatology at the Second Affiliated Hospital of Xi'an Jiaotong University, has created a multifunctional hydrogel skin dressing through interdisciplinary efforts in mechanics, materials science, and dermatology, achieving mechano-chemical synergistic treatment of AD for the first time. This dressing, loaded with polydopamine nanoparticles for reactive oxygen species (ROS) scavenging and liposome-encapsulated FAK inhibitors, demonstrated significant improvements in scratching behavior, skin inflammation, and barrier function in AD mouse models.

Beyond biomechanics-based treatments, the development of novel drugs has also provided new options for AD management. Recently, the STAT6 pathway has gained recognition as a crucial therapeutic target for treating inflammatory diseases, including atopic dermatitis (AD), asthma, and chronic obstructive pulmonary disease. As a transcription factor essential for IL-4 and IL-13 cytokine signaling, STAT6 holds a central role in Th2-driven inflammatory responses. Johnson & Johnson has recently acquired rights to Kaken Pharmaceutical's STAT6 program, including lead candidate KP-723, which is expected to enter Phase I trials this year. Other companies, such as Sanofi, Nurix Therapeutics, and Recludix Pharma, are also actively exploring this area [27,28].

With a deepening understanding of AD pathogenesis, biomarkers are playing an increasingly important role in precision medicine for AD. Biomarkers can help predict disease onset and trajectories, informing tailored treatment strategies. For instance, biomarkers based on Th2 cytokines and chemokines are being developed for AD

diagnosis, severity assessment, prognosis prediction, and monitoring. Additionally, individualized treatments and research targeting different AD subtypes are underway, propelling the era of precision medicine for AD.

In the realm of immunological innovations for AD treatment, novel biologics and small molecule drugs have shown promising progress. For example, Siplizumab, China's first domestically produced class I new drug approved for AD, offers a new treatment option for patients with moderate-to-severe AD. Demonstrating long-term efficacy and good safety in Phase III clinical trials, Siplizumab rapidly controls itching, achieves potent treatment goals, and significantly improves itching and skin lesions in various body parts, including the head and face [29,30].

Although considerable advancements have been achieved in comprehending the biomechanics of atopic dermatitis (AD), numerous unanswered questions still persist. Therefore, future research endeavors should prioritize the investigation of the molecular mechanisms that underlie the biomechanical changes observed in AD skin. Additionally, studies investigating the efficacy of novel therapies targeting skin mechanics are warranted. Moreover, a collaborative effort across disciplines, including dermatologists, immunologists, biomechanical engineers, and other specialists, will be essential in deepening our understanding of atopic dermatitis (AD) and devising more efficacious treatment strategies.

5. Conclusion

In summary, this study utilized genetic data to conduct an MR analysis of mental disorders and AD and found a potential positive causal effect of major depressive disorder on AD in the European population. While this study provides some statistical evidence for a causal link between major depressive disorder and AD, there remains a discrepancy between this causal effect and real-world clinical scenarios. Therefore, further in-depth investigations and comprehensive analyses through large-scale prospective cohort studies are still required to more accurately understand the relationship between the two, providing a more reliable basis for future treatment and prevention strategies for major depressive disorder and AD. Additionally, atopic dermatitis is a complex skin condition with significant biomechanical implications. The compromised skin barrier, altered mechanical properties, and associated itching and scratching behavior all contribute to the disease process. By understanding the biomechanics of AD, we can gain insights into the disease pathogenesis and develop more targeted treatment strategies. As research in this field continues to evolve, we can expect to see improvements in the management and quality of life of AD patients.

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