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Review Article

Risk of Schizophrenia in Patients with Psoriasis: A Systematic Review and Meta-Analysis

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Background. Several studies have shown that psoriasis patients have a higher prevalence rate of schizophrenia, but none has thoroughly examined this association across different ages and genders. Thus, our systematic review and meta-analysis aims to combine all available evidence and evaluate the risk of schizophrenia in psoriasis patients. *Methods*. Two independent investigators extracted published studies from PubMed, Embase, Medline, and Web of Science databases from inception until May 2023 and screened 160 articles for eligibility. We included 8 studies in this meta-analysis. A random-effects model was employed to estimate the pooled odds ratio (OR) and 95% confidence interval (CI) for schizophrenia in patients with psoriasis. The study protocol is registered with PROSPERO, number CRD42023428576. *Results*. A total of eight studies with 889,747,79 participants met the eligibility criteria. The pooled OR of psoriasis in patients with schizophrenia versus subjects without schizophrenia was 1.66 (95% CI: [1.20, 2.29]) with a significant level of heterogeneity ($I^2 = 97\%$). Specifically, the OR for psoriasis in children with schizophrenia was 12.90 (95% CI: [1.97, 84.64]), with an I^2 combined value of 98% and psoriasis in adults with schizophrenia 2.57 (95% CI: [1.44, 4.58]), with an I^2 combined value of 61.3%. The combined OR for all age groups was 5.27 (95% CI: [3.02, 9.19]). Additionally, we found that the OR value for psoriasis in females with schizophrenia was 1.74 (95% CI: [1.74, 2.11]), with an I^2 combined value of 59%. For male patients, the OR value was 1.58 (95% CI: [1.25, 2.01]), with an I^2 combined value of 77%. *Conclusions*. Our study shows an increased risk of schizophrenia in people with psoriasis. We demonstrated a significantly increased risk of schizophrenia among children with psoriasis and found that females with psoriasis were more likely to have schizophrenia than men with psoriasis under the same conditions.

1. Introduction

Psoriasis is a chronic inflammatory skin condition characterized by the pruritic, scaly patches that frequently occur on the skin, nails, and joints [1–4]. It is a quite burdensome disease, affecting about 2-3% general population globally [5–8]. Although psoriasis is not life-threatening, it can have a significant impact on quality of life, leading to physical discomfort, social stigmatization, and psychological distress [8, 9]. Previous studies have suggested that psoriasis may be associated with an increased risk of psychiatric disorders, including depression, anxiety, bipolar disorder, and schizophrenia [10, 11].

Schizophrenia is a severe mental illness that affects approximately 1% of the population [12] and is characterized by a range of symptoms, including delusions, hallucinations, disordered thinking, and social withdrawal [13]. The illness usually begins in late adolescence or early adulthood which is known to have a complex etiology, involving genetic, environmental, and neurodevelopmental factors [12].

The cooccurrence of psoriasis and schizophrenia has been associated with significant comorbidity, resulting in a reduced quality of life and increased healthcare utilization [14–16]. Multiple studies have shown that patients with schizophrenia have an increased risk of developing psoriasis compared to healthy persons [17–20]. Similarly, cross-sectional studies have revealed increased rates and prevalence ratios of schizophrenia in patients with psoriasis compared to those without psoriasis [21, 22]. However,

a case-control study reported a similar prevalence of schizophrenia in psoriasis groups [14]. Additionally, a retrospective cohort study did not find a significant correlation between schizophrenia and psoriasis [23]. Given these conflicting conclusions, the overlap and association between psoriasis and schizophrenia urgently remain to be clarified. Therefore, the objective of this meta-analysis is to evaluate the risk of schizophrenia in patients with psoriasis by summarizing all available evidence.

To explore the association between psoriasis and schizophrenia within the children population, we conducted subgroup analyses. These analyses involved separating studies that included children from those that focused on adult populations. This allowed us to evaluate the association in different age groups and provide a more comprehensive understanding of the relationship in the children context.

2. Methods

2.1. Search Strategy. This meta-analysis was conducted following the Meta-Analysis of Observational Studies in Epidemiology guidelines [24] as described in Figure 1. This flow diagram is based on PRISMA. In our search process, we employed a set of key search terms, including "schizophrenia," "psoriasis," "adults," and "children," among others. Additionally, we utilized MeSH (Medical Subject Headings) to explore medical synonyms associated with these keywords. These keywords were used in various combinations during searches. A study protocol was developed prior to the search process. Two independent investigators, Peixin Zhu and Qi He, conducted a comprehensive search for relevant studies indexed in the following databases: PubMed, Embase, Medline, and Web of Science, from inception until May 2023.

2.2. Inclusion Criteria. Articles were screened according to the following inclusion criteria: (1) a control group with nonpsoriasis disease, (2) patients with psoriasis diagnosed by dermatologists according to standardized diagnostic criteria, (3) patients with schizophrenia diagnosed by DSM-III, DSM-IV, and ICD-10 standards or other widely accepted diagnostic criteria, and (4) studies reporting the risk or prevalence of schizophrenia in patients with psoriasis. Articles were excluded if they were (1) animal studies, (2) reviews, meta-analyses, editorials, and meeting summaries, and (3) studies reporting on comorbidity with other psychiatric or dermatologic disorders without separate data on schizophrenia.

In the selected studies, control groups served as the reference, consisting of individuals without a psoriasis diagnosis.

Dermatologist diagnoses of psoriasis were determined through a rigorous and standardized process. The dermatologist's diagnosis needs to include clinical assessment and standardized diagnostic criteria, as well as medical records and history. A dermatologist's diagnosis of psoriasis should be based on the following guidelines: Chinese Guidelines for Psoriasis Treatment (2018, concise version), Chinese Biologics Diagnosis and Treatment Guidelines (2021), American Academy of Dermatology-National Psoriasis Foundation Guidelines (2019), European Guidelines (Part 1, 2019, Part 2, 2020), British Guidelines (2020), Asian Guidelines for the Local Treatment of Moderate to Severe Plaque Psoriasis (2018), and American Academy of Dermatology-National Psoriasis Foundation Guidelines (2021).

Children were defined as individuals under the age of 18 years. This age threshold aligns with established definitions of the pediatric population in clinical and medical practice. It is consistent with widely accepted age categorizations for pediatric research.

After a preliminary screening of titles and abstracts, two investigators independently assessed the data sources and outcome measures of eligible studies. All included studies were reviewed by a third investigator to ensure that they met the inclusion criteria. Disagreements were resolved through discussion among all study authors to address inconsistencies in study eligibility. The quality of the included studies was appraised using the Newcastle-Ottawa quality assessment scale [25].

2.3. Data Extraction. To ensure accuracy, two investigators independently performed data extraction, sorting out information such as the first author's name, year of study, country or region where the study was conducted, study design, year of publication, number of participants, subjects, schizophrenia and skin disease diagnosis, and confounder adjustment. Any discrepancies found in the case record forms were resolved by referring back to the original articles.

2.4. Statistical Analysis. Statistical analyses were performed using Review Manager 5.4.1 software from the Cochrane Collaboration (London, United Kingdom). A random-effects model was employed due to differences in study design and populations, which can lead to high likelihood of study variance. Heterogeneity was assessed using the Review Manager software and supplemented with the I^2 statistic. The I^2 value of 0–50% indicates low heterogeneity, 51–75% indicates moderate heterogeneity, and 76–100% indicates high heterogeneity [26].

To assess the possibility of publication bias, a bias funnel plot was used. Odds ratios (ORs) were computed from the extracted data with 95% confidence intervals. The center of the diamond represents the pooled odds ratio, while the lateral tips of the diamond represent its 95% confidence interval.

3. Results

3.1. Search Results. After a thorough screening process, we excluded review articles, commentaries, editorials, case reports, correspondence, animal studies, and interventional studies, as shown in Figure 1. Six articles were excluded as they reported the risk of psoriasis in patients with schizophrenia. Therefore, we included eight studies in the meta-analysis [14–16, 21, 22, 27–29]. The literature review and

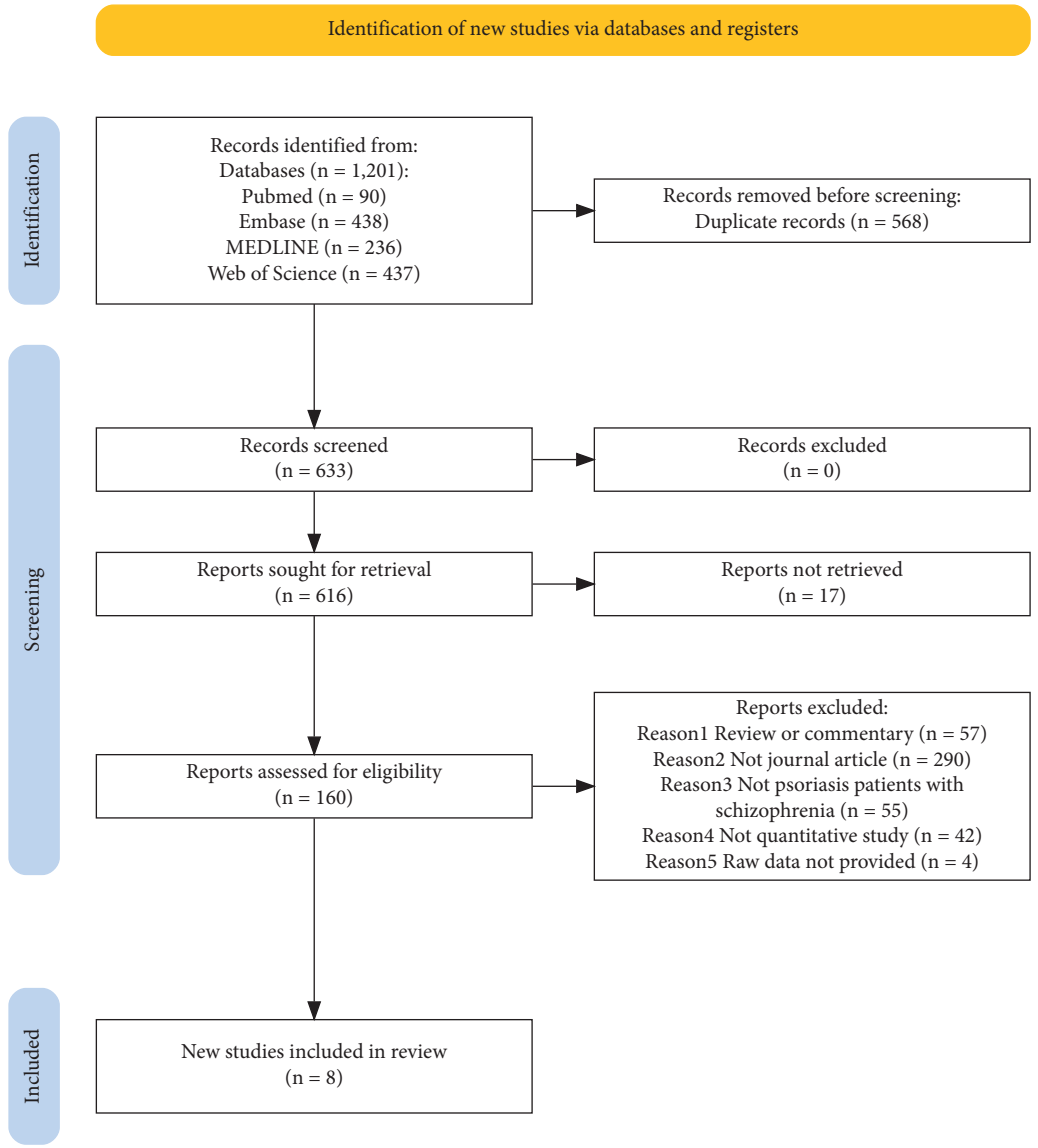

Figure 1: Summary search process based on PRISMA.

selection process are summarized in Figure 1. The main characteristics and Newcastle-Ottawa Scores of the included studies are presented in Table 1.

3.2. Outcome. Meta-analysis was performed on 8 studies with a total of 889,747,79 participants (88,497,134 controls/264,899 cases) to investigate the association between psoriasis and schizophrenia. The pooled odds ratio (OR) was 1.66 (95% CI: [1.20, 2.29]), indicating a significant positive association between the two conditions in the overall population. (Figure 2) Heterogeneity was high ($I^2 = 97\%$).

In our study, we investigated the association between psoriasis and schizophrenia in a diverse population comprising both children and adults. The control groups included 14,962,797 children and 73,590,070 adults. Among the adult controls, 51,243,604 were females, and 36,534,717 were males. 5,428 individuals were children (under the age of eighteen), and 259,471 were adults among those diagnosed with psoriasis. In the adult cases, 102,825 were females, and 114,623 were males.

Subgroup analyses were conducted based on age and gender. For children, the OR was 12.90 (95% CI: [1.97, 84.64]), while for adults, the OR was 2.57 (95% CI: [1.44, 4.58]), with an I^2 of 61.3% (Figure 3). The combined OR for all age groups was 5.27 (95% CI: [3.02, 9.19]). There appears to be a stronger association between psoriasis and schizophrenia in children compared to adults. For female patients, the OR was 1.74 (95% CI: [1.74, 2.11]) with an I^2 of 59% (Figure 4), while for male patients, the OR was 1.58 (95% CI: [1.25, 2.01]) with an I^2 of 77% (Figure 5). These results suggest a slightly stronger association between psoriasis and schizophrenia in female patients compared to male patients.

Table 1: Main characteristics of the 8 included studies (2010–2019), based on the Newcastle-Ottawa quality assessment scale.

References; year of publication	Country	Study design	Sample	Diagnosis time/age/ duration of psoriasis	Subject	Confounder adjustment	Quality assessment (Newcastle-Ottawa Score)
Ahn et al. [27]; 2019	Korea	Cross-sectional study	182,127 (42,641 diagnosis/139,486 comparison) including 21,899 children (<18)	Not mentioned	Diagnosis: patients with psoriasis were identified from the Korean National Health Insurance Research Database in 2015 Comparison: sex and age-matched comparisons without psoriasis were randomly selected from the same database	Age, gender	Selection: 3 comparability: 1 outcome: 3
Kara et al. [16]; 2019	Turkey	Case-control study	108 (54 cases/54 controls) including 215 children (<18)	Diagnosis duration of psoriasis: at least 3 months	Cases: patients with psoriasis were identified from the University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital Dermatology Department Controls: sex and age-matched controls without psoriasis were randomly selected from the same department	Age, gender, and comorbidities	Selection: 3 comparability: 2 outcome: 3
Leisner et al. [29]; 2019	Denmark	Case-control study	154,715 (13,675 cases/ 141,040 controls) including 76,980 female adults; 78,400 male adults; and 7,297 children (<18)	Diagnosis age of psoriasis: 0–19; 20–39; 40–59; 60–79; ≥80	Cases: patients with psoriasis identified from all Danish hospitals between 1900 and 1995 Controls: sex and age-matched controls without psoriasis were randomly selected from the same hospital	Age, gender, birth year, age at first psoriasis diagnosis, education, and comorbidities	Selection: 3 comparability: 2 outcome: 3
Raikhy et al. [22]; 2017	India	Case-control study	1,089 (89 cases/1,000 controls)	Not mentioned	Cases: patients with psoriasis identified from Psychiatry Department of NIMS Medical College Controls: sex and age-matched controls without psoriasis were randomly selected from the same department	Age, gender, marital status, religion, education, and occupation	Selection: 3 comparability: 2 outcome: 3

Table 1: Continued.

References; year of publication	Country	Study design	Sample	Diagnosis time/age/ duration of psoriasis	Subject	Confounder adjustment	Quality assessment (Newcastle-Ottawa Score)
Tu et al. [21]; 2017	Taiwan	Cross-sectional study	778,123 (10,796 diagnosis/767,327 comparison) including 403,565 female adults; 379,532 male adults	Diagnosis time: with psoriasis during the period from January 1, 1997 to December 31, 2010	Diagnosis: patients with psoriasis identified from Taiwan's National Health Insurance Research Database Comparison: sex and age-matched comparisons without psoriasis were randomly selected from the same database	Age, gender, comorbidities, and duration	Selection: 3 comparability: 1 outcome: 3
Patel et al. [28]; 2019	USA	Case-control study	87,053,095 (188,089 cases/86,865,066 controls) including 53,907,819 female adults; 38,341,356 male adults; and 15,004,737 children (<18)	Diagnosis duration of psoriasis: 5–10 years >10 years	Cases: patients with psoriasis identified from the National Inpatient Sample of all US hospitalizations between 2002 and 2012 Controls: sex and age-matched controls without psoriasis were randomly selected from the same sample	Age, gender, and race	Selection: 3 comparability: 2 outcome: 3
Parisi et al. [15]; 2017	U.K.	Cohort-comparison study	933,880 (56,961 patients/ 876,919 comparison)	Not mentioned	Cohort: patients with psoriasis identified from the Clinical Practice Research Datalink linked to Hospital Episode Statistics and the Office for National Statistics mortality records in England between 1998 and 2014 Comparison: sex and age-matched controls without psoriasis were randomly selected from the same cohort	Age, sex, and general practice	Selection: 3 comparability: 1 outcome: 3

Table 1: Continued.

References; year of publication	Country	Study design	Sample	Diagnosis time/age/ duration of psoriasis	Subject	Confounder adjustment	Quality assessment (Newcastle-Ottawa Score)
Schmitt and Ford [14]; 2010	Germany	Case-control study	6294 (3,147 cases/3,147 controls) including 3,528 female adults; 6,377 male adults	Not mentioned	Cases: patients with psoriasis identified from an interdisciplinary administrative healthcare database Controls: sex and age-matched controls without psoriasis were randomly selected from the same cohort	Age, sex, personal income, and comorbidities	Selection: 3 comparability: 2 outcome: 3

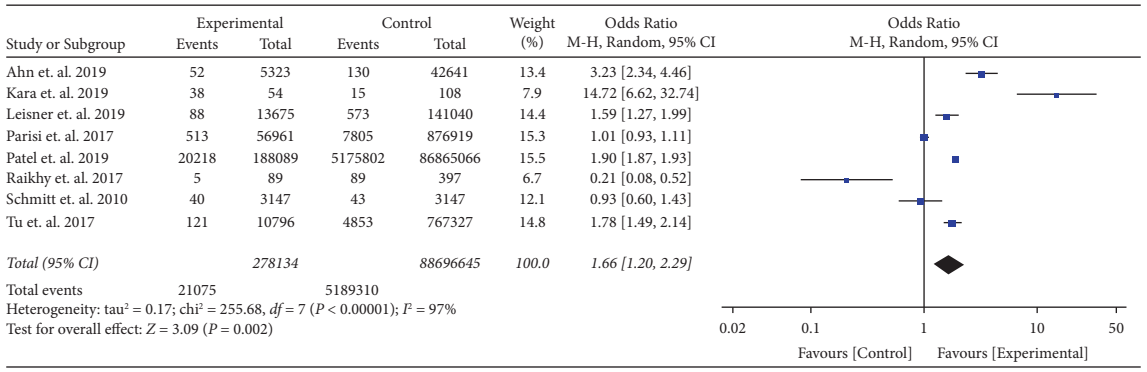

Figure 2: Forest plot of odds ratio and 95% CIs for schizophrenia in patients with psoriasis.

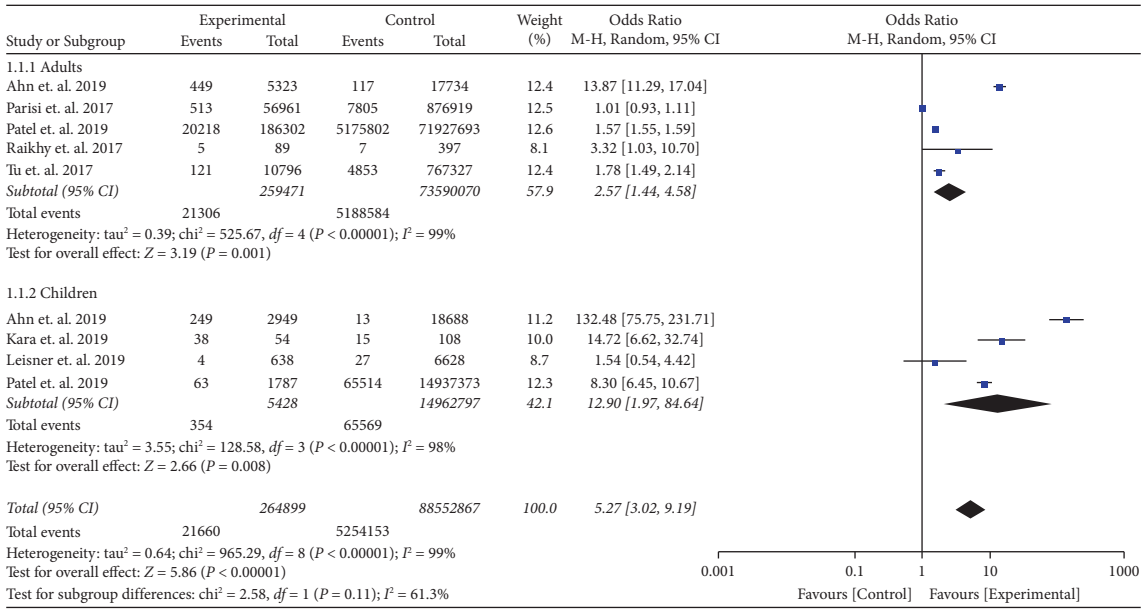

Figure 3: Forest plot of odds ratio and 95% CIs for schizophrenia in adults and children with psoriasis.

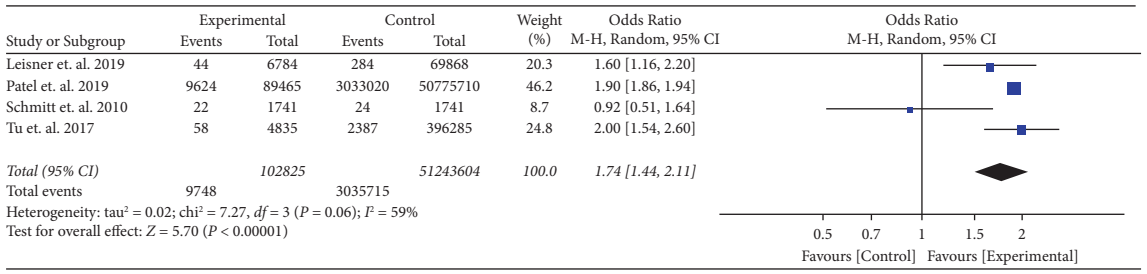

Figure 4: Forest plot of odds ratio and 95% CIs for schizophrenia in female adults with psoriasis.

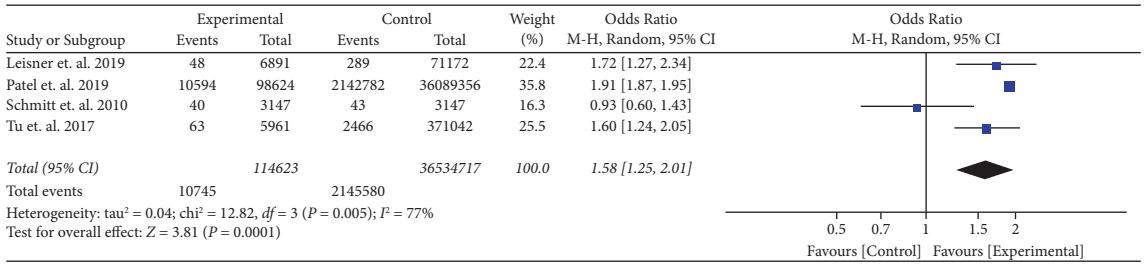

Figure 5: Forest plot of odds ratio and 95% CIs for schizophrenia in male adults with psoriasis.

Overall, our findings provide evidence for a positive association between psoriasis and schizophrenia, and further studies are needed to explore the underlying mechanisms and potential clinical implications of this association.

4. Discussion

These findings highlight the variability of the association between schizophrenia and psoriasis across different age groups and between genders. The observed differences in odds ratios indicate the need for further investigation into the underlying mechanisms and potential factors that may contribute to this relationship.

The pathogenesis of this comorbidity is not unclear but there are some suggested mechanisms which may include genetic factors, immunologic mechanisms, biochemical pathways, and similar embryological origins [30].

The immune system plays a key role in both psoriasis and schizophrenia involving immune dysregulation, and a dysregulated immune response has been implicated in their pathogenesis [4]. Understanding the relationship between psoriasis and schizophrenia may provide insight into the shared mechanisms underlying these disorders and potential therapeutic targets.

An implicated gene *PSORS1* located on neighbouring region of chromosomes 6p21.3 and 6p22.1 has been respectively suspected in major locus for psoriasis and schizophrenia. Furthermore, located on chromosome 6p21.36p22.1, immune-related genes such as heparin cofactor II (*HCII*) may indicate the mutual immunologic pathology in schizophrenia and psoriasis [18]. A previous study investigated the crucial chromosome 6 where 5 single nucleotide polymorphism (SNP) variants on the human leukocyte antigen (*HLA*) gene. Through a regulatory effect, the 5 SNPs may make contribution to the etiology of schizophrenia and psoriasis. Moreover, the HLA gene suggests a common role of calcium signaling in schizophrenia and psoriasis [31]. The endoplasmic reticulum plays an important role in the transportation of calcium ion in cells. A report therefore provided some level of validation of the potential role of calcium signaling in the etiology of schizophrenia and psoriasis [31].

Immune mechanisms implicate shared underlying etiology that psoriasis is a chronic immune-mediated inflammatory disorder with T helper 17 (Th17) cells and proinflammatory cytokines such as tumor necrosis factor (TNF)-α playing the dominant role for its pathogenesis. According to the mild encephalitis hypothesis, which is supported by immunologic, cerebrospinal fluid and imaging studies, inflammation of the central nervous system (CNS) may play a pivotal role in the development of schizophrenia in a significant subgroup of patients. Microglia is active by Th 17 cells in the CNS, which leads to local production of TNF-α and strongly implies its key players in neuroinflammation [32]. Moreover, the dopamine which increased in schizophrenia further increases Th17 signaling and is combined with psoriasis [30]. By resetting systemic regulatory T cells control of immune signaling, methotrexate is considered to improve autoimmune disorders including psoriasis. A recent research shows that low-dose methotrexate has potential antipsychotic effects in patients with schizophrenia which indicates the theory of T-cell involvement in schizophrenia [33]. Methotrexate's similar action in the CNS and efficacy in schizophrenia support a shared immune pathogenesis for both conditions.

There are multiple strengths to this systematic review and meta-analysis, including comprehensively combined evidences and large number of international studies with more than 8,000,000 patients and involved controls. Primary studies included were also of high quality as reflected by the high Newcastle-Ottawa Scores.

In this analysis, the major limitation is the statistical heterogeneity that was moderate to high. Differences between relative study designs may have affected statistical heterogeneity. The analysis encountered limitations primarily related to the high degree of statistical heterogeneity, which can be attributed to differences in study designs among the included studies. Particularly, cross-sectional studies showed relatively high I^2 value, possibly due to their susceptibility to bias and scattered results. Another limitation was the use of diagnostic codes in electronic medical record databases, which may have affected the validity of the preliminary findings due to low sensitivity and specificity. Since most of the included literature did not give a clear time of diagnosis, further studies on the time of diagnosis could not be carried out. Furthermore, the lack of complete information on medication use in our study prevented a comprehensive assessment of the potential confounding effect of medications on the association between schizophrenia and psoriasis.

5. Conclusions

The meta-analysis results suggest that the association between schizophrenia and psoriasis varies across age groups and between genders, highlighting the need for further research to explore the underlying mechanisms and potential factors influencing this relationship.

Future research should focus on elucidating the biological, genetic, and environmental factors that could influence the association between schizophrenia and psoriasis. Additionally, exploring the impact of treatment modalities, lifestyle factors, and psychosocial variables may provide valuable insights into the complex interplay between these two conditions. A better understanding of these factors could lead to the development of targeted interventions and personalized treatment approaches for individuals with comorbid schizophrenia and psoriasis.

Data Availability

The data that support the findings of this study are available upon reasonable request to the corresponding author.

Conflicts of Interest

All authors declare no conflicts of interest relating to any aspect of this study.

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Supplementary Materials

Figure S1: Funnel plot of schizophrenia in patients with psoriasis. Figure S2: Funnel plot of schizophrenia in adults and children with psoriasis. Figure S3: Funnel plot of schizophrenia in female adults with psoriasis. Figure S4: Funnel plot of schizophrenia in male adults with psoriasis. (*Supplementary Materials*)

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