Research Square

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Psychiatric Disorders and Risk of Psoriasis: Evidence From Cohort Analysis and Mendelian Randomization

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Abstract

Background:

Although psychiatric disorders have been linked to multiple chronic diseases, the association between psychiatric disorders and the risk of psoriasis, as well as the underlying biological mechanisms, remains insufficiently understood.

Methods:

This prospective cohort study included 336,349 participants from the UK Biobank. Psychiatric disorders—including depression, anxiety, stress-related disorders, substance misuse, psychotic disorders, and dementia—were identified using medical records and self-reported data. Genetic susceptibility to psoriasis was assessed using polygenic risk scores. Cox proportional hazards models were applied to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for sociodemographic characteristics, lifestyle factors, and medical history. Mediation analyses were conducted to evaluate accelerated biological aging as a potential pathway linking psychiatric disorders to psoriasis. Mendelian randomization analyses were further performed to explore potential causal relationships.

Results:

Psychiatric disorders were associated with a significantly increased risk of psoriasis (HR = 1.57, 95% CI: 1.45–1.71), with stress-related disorders showing the strongest association (HR = 2.06, 95% CI: 1.33–3.21). A significant synergistic effect was observed between psychiatric disorders and genetic susceptibility to psoriasis (HR = 3.85, 95% CI: 3.29–4.50). Accelerated biological aging partially mediated the association between psychiatric disorders and psoriasis risk.

Conclusions:

Psychiatric disorders are associated with an elevated risk of psoriasis, particularly among individuals with high genetic susceptibility. Accelerated biological aging may partially mediate this association, highlighting a potential biological pathway linking mental health and inflammatory skin diseases.

Introduction

Psoriasis is a chronic immune-mediated dermatosis characterized by well-demarcated erythematous plaques with silvery scaling, resulting from keratinocyte hyperproliferation and dermal inflammation[1,2]. Although its precise pathogenesis remains unclear, research indicates that genetic factors, environmental exposures, and chronic immune activation play a role in the emergence of the disease[3,4]. Around 2% to 3% of people worldwide suffer from psoriasis, creating a significant strain on public health[5], with incidence rates continuing to rise[6]. Identifying modifiable risk factors is therefore essential for prevention and early intervention.

Psychiatric disorders are severe conditions that can impair cognition and behavior, often resulting in long-lasting neurobiological changes[7]. Specifically, mood disorders are listed as one of the top ten global contributors to disease burden, with rising prevalence across populations [8,9]. In recent years, the influence of psychiatric conditions on public health has become more and more important.

Several studies have reported links between psoriasis and psychiatric disorders, especially depression and anxiety[10]. Cognitive impairment and dementia have also been found to occur more frequently in individuals with psoriasis[11].

Notably, psychiatric disorders may not only arise as psychological responses to psoriasis but could also act as potential risk factors. For example, a cohort study from France identified schizophrenia before the diagnosis of psoriasis[12]. However, findings across studies remain inconsistent. Some research has found no significant associations between mental disorders, including depression, anxiety, schizophrenia, and bipolar disorder, and the risk of psoriasis[13]. Overall, the evidence remains inconclusive, and there's a notable absence of extensive future-oriented research examining how clinically diagnosed psychiatric disorders influence future psoriasis risk. The biological mechanisms underlying this potential link are also poorly understood. Moreover, most existing evidence is derived from observational studies, which are inherently susceptible to residual confounding and reverse causation, highlighting the need for complementary genetic approaches, such as Mendelian randomization, to strengthen causal inference.

From a genetic perspective, early family-based studies revealed a clustering of psoriasis within families, suggesting a strong genetic component in disease susceptibility[14]. In addition, emerging research points to a close relationship between mental disorders, particularly depression, anxiety, and dementia, and accelerated biological aging[15,16]. Psoriasis has also been associated with markers of biological aging[17]. However, no studies to date have examined whether biological aging mediates the link between mental disorders and psoriasis risk.

To bridge these informational voids, a forward-looking cohort analysis was carried out, utilizing information from the UK Biobank to explore the links among diverse psychiatric conditions, genetic predisposition, and the ensuing likelihood of psoriasis. Our investigation extended to the possible intermediary function of biological aging in the noted correlations.

Methods

Data source

Between 2006 and 2010, the UK Biobank enlisted more than 500,000 individuals aged 40 to 69, gathering detailed data on lifestyle, health, and biochemical markers[18]. The research followed the STROBE guidelines for reporting observational studies. From the initial 502,128 participants, we excluded those with a baseline diagnosis of psoriasis (n = 11,051), individuals with incomplete genetic data (n = 15,963), and those who had missing or extreme data that could not be used for calculating biological aging (n = 138,765) (Figure S1). This left 336,349 participants for the final analysis. Participants were followed from enrollment until psoriasis diagnosis, death, loss to follow-up, or study end (July 6, 2023), whichever occurred first.

Assessment of psoriasis

Psoriasis diagnoses were primarily confirmed using hospital inpatient records from the Hospital Episode Statistics (England), Scottish Morbidity Records, and the Patient Episode Database for Wales. Additional cases were identified by linking self-reported data, primary care records, and death registries. The coding of diagnoses followed the International Classification of Diseases, 10th Revision (ICD-10), categorizing psoriasis under the "first occurrence" section (category ID: 1712). For full-scale details regarding psoriasis evaluation within the UK Biobank, access the UK Biobank's official site (https://www.biobank.c.k/).

Ascertainment of psychiatric disorders

All psychiatric disorders were identified using the ICD-10 codes (F00-F99). Relevant cases were determined through linkage with primary care data, hospital inpatient records, death registries, and self-reported data. Building on prior research[19,20], we specifically focused on six types of mental disorders: depression (F32-F33), anxiety (F40-F41), dementia (F00-F03), substance misuse (F10-F19), psychotic disorders (F20-F29), and stress-related disorders (F43).

Genetic Information

The UK Biobank research platform provides a standardized polygenic risk score (PRS), created through a meta-analysis of data from multiple genome-wide association studies (GWAS). Previous research has helped clarify the PRS methodology and the standard PRS sets used in GWAS data [21]. In brief, the UK Biobank uses standardized definitions for subgroups, diseases, and quantitative traits to ensure consistent PRS assessment. The PRS algorithm is based on meta-analysis of specific traits, utilizing the Bastion method to integrate data from diverse ancestral populations and related traits. A higher PRS indicates a greater genetic susceptibility to the disease. For psoriasis (Field ID: 26269), participants were categorized into low (quintile 1), medium (quintiles 2–4), and high (quintile 5) genetic risk groups based on PRS quintiles[22].

Covariates

Baseline sociodemographic and lifestyle data were collected via a touchscreen questionnaire. Sociodemographic variables included age (< 60 years vs ≥ 60 years), race (white vs non-white), sex, Townsend Deprivation Index (divided into five quintiles), household income (< £18,000, £18,000–30,999, £31,000–51,999, £52,000-100,000, or > £100,000) and education level (degree, professional qualification, or secondary school). Lifestyle factors included smoking status (never smoked, former smoker, or current smoker), alcohol consumption habit (never, former, or current drinker), BMI (< 25, 25-29.9, ≥ 30), activity level (low, medium, high), and self-reported history of chronic diseases (coronary artery disease, hypertension, diabetes). A "Missing" category was included for participants who were uncertain or declined to respond.

Phenotypic age and PhenoAgeAccel calculation

The evaluation of biological aging utilized the PhenoAge algorithm, which estimates all-cause mortality risk based on a Gompertz proportional hazards model incorporating age alongside nine clinical indicators: albumin, alkaline phosphatase, creatinine, C-reactive protein, glucose, average corpuscular volume, width of red blood cell distribution, count of white blood cells, and the percentage of lymphocytes. These biomarkers were identified through a Cox penalized regression model using data from the NHANES III cohort [23]. PhenoAge acceleration (PhenoAgeAccel), indicative of variations in biological aging concerning actual age, was determined by the leftover value from the regression of PhenoAge against chronological age[24]. To address skewed distributions of certain biomarkers, percentile-based winsorization was applied, adjusting values below the 1st percentile and above the 99th percentile to the corresponding cutoff points to minimize outlier influence [25]. All calculations were performed using the "BioAge" package in R.

Mendelian randomization analysis

To further strengthen causal inference regarding the association between psychiatric disorders and psoriasis, we performed two-sample Mendelian randomization analyses using summary-level genome-wide association study (GWAS) data. Genetic instruments for psychiatric disorders were obtained from previously published large-scale GWAS. Single-nucleotide polymorphisms (SNPs) associated with each exposure were initially selected at the genome-wide significance threshold ($P < 5 \times 10^{-8}$)[26]. For psychiatric traits with an insufficient number of genome-wide significant variants, supplementary analyses were conducted using less stringent thresholds ($P < 1 \times 10^{-6}$ and $P < 1 \times 10^{-5}$). To ensure the independence of instrumental variables, linkage disequilibrium clumping was performed using the European reference panel from the 1000 Genomes Project ($r^2 < 0.001$ within a 10,000 kb window). Instrument strength was assessed using the F statistic, with $F > 10$ considered indicative of sufficiently strong instruments[27].

Summary-level GWAS data for psoriasis were obtained from publicly available studies. Exposure and outcome datasets were harmonized to align effect alleles. Palindromic SNPs with ambiguous strand orientation were excluded, and only variants retained after harmonization were included in subsequent MR analyses.

The inverse variance weighted (IVW) method was used as the primary approach to estimate causal effects. Robustness was further assessed using MR-Egger regression, weighted median, weighted mode, and simple mode methods. Directional horizontal pleiotropy was evaluated using the MR-Egger intercept test, and heterogeneity among instrumental variables was assessed using Cochran's Q statistic. Scatter plots were generated to visualize SNP-specific associations and to illustrate the consistency of effect estimates across different MR methods. Detailed information on the GWAS datasets used for MR analyses, including sample size, ancestry, and original publications, is provided in Supplementary Table S9. All MR analyses were conducted in R using the TwoSampleMR package.

Statistical analysis

We conducted statistical tests for categorical and continuous variables, including χ^2 tests, the Wilcoxon–Mann–Whitney test, and Student's t-test. To explore the relationship between any psychiatric disorders, genetic risk, and psoriasis onset, we employed Cox proportional hazards models. Additionally, we used Cox regression to assess the independent effects of six specific psychiatric conditions (depression, anxiety, stress-related disorders, substance misuse, psychotic disorders, and dementia) on the likelihood of psoriasis development.

The analysis we conducted employed a trio of distinct model collections. During the analysis of psoriasis patients in Model 1, adjustments were made considering their age, gender, ethnicity, and educational background. The development of Model 2 was based on Model 1, incorporating additional modifications for variables like alcohol intake, smoking habits, TDI, BMI, and physical activity. In Model 3, we extended the analysis by incorporating additional adjustments for the history of chronic diseases, such as hypertension, diabetes, and cardiovascular conditions, on top of the variables from Model 2. We also examined potential interactions between any psychiatric disorders and genetic factors regarding the risk of psoriasis. For evaluating these interplays, an interaction variable (any psychiatric disorders × genetic risk) was incorporated into the Cox proportional hazards model, and likelihood ratio tests were employed to measure the interaction's impact. For evaluating the interaction, we computed three primary measures: a) the interaction's relative additional risk (RERI), b) the risk percentage ascribed to the interaction (AP), and c) the synergy index (SI). These metrics' 95% confidence intervals were derived using a bootstrap method[28].

To explore the underlying mechanisms further, we evaluated biological age acceleration as a potential mediator in the link between any psychiatric disorders and psoriasis onset. Mediation analysis followed a three-step process[29]: Step 1 examined the link between psychiatric disorders and psoriasis events; Step 2 assessed the relationship between psychiatric disorders and biological age acceleration; Step 3 investigated the link between biological age acceleration and psoriasis events. Upon confirmation of all three links, causal mediation analysis was performed using R's "mediation" package, incorporating 1000 bootstrap iterations. Through the amalgamation of the mediator and outcome models, and accounting for every covariate, we calculated the indirect, direct, and overall impacts, as well as the proportion of the effect mediated by each mediator.

In addition, Mendelian randomization analyses were conducted to strengthen causal inference regarding the association between psychiatric disorders and psoriasis, using genetic variants as instrumental variables. Detailed methods for the MR analyses are described in the Mendelian randomization analysis section.

Multiple sensitivity tests were conducted to evaluate the consistency of the main findings. Initially, to mitigate the risk of bias due to reverse causality, we omitted individuals diagnosed with psoriasis within two years following the baseline. Second, we excluded participants with missing data for all covariates. Third, participants with a chronic disease history

were omitted from our study. For assessing how baseline psychiatric disorders influence psoriasis risk, a two-tailed p-value below 0.05 was deemed to hold statistical significance. A p-value less than the Bonferroni correction (0.05/6 = 0.008) was deemed statistically significant for the six distinct psychiatric conditions: depression, anxiety, stress-related disorders, substance abuse, psychotic disorders, and dementia. Every analysis was performed utilizing the R software version 4.3.3.

Results

Baseline characteristics

A total of 336,297 participants were enrolled in the study, with a mean age of 56.7 years, and 53.6% were female (Table 1). At baseline, 54,580 participants were identified as having psychiatric disorders, including 20,857 with depression, 17,634 with anxiety, 798 with stress-related disorders, 20,746 with substance misuse, 1,154 with psychotic disorders, and 5,242 with dementia (Table S1). Individuals with psychiatric conditions, compared with those without, were older on average, more likely to be male, less likely to have attained a university degree, and had higher levels of socioeconomic deprivation. They were also more likely to be current smokers, have a higher BMI, engage in less physical activity, and show a greater prevalence of chronic conditions, including diabetes, hypertension, and cardiovascular disease.

Table 1
Baseline characteristics of participants with or without psychiatric disorders.

Characteristic	Overall (N = 336,297)	Without psychiatric disorders (N = 281,717)	With psychiatric disorders (N = 54,580)	*P* value
Age (years)	56.7 ± 8.0	56.4 ± 8.0	57.7 ± 8.1	< 0.001
Age group				< 0.001
60 and above	147,390 (43.8%)	120,081 (42.6%)	27,309 (50.0%)	
Under 60	188,959 (56.2%)	161,671 (57.4%)	27,288 (50.0%)	
Sex				0.025
Female	180,395 (53.6%)	151,352 (53.7%)	29,043 (53.2%)	
Male	155,954 (46.4%)	130,400 (46.3%)	25,554 (46.8%)	
Ethnicity				0.048
White	319,422 (95.0%)	267,480 (94.9%)	51,942 (95.1%)	
Other	16,927 (5.0%)	14,272 (5.1%)	2,655 (4.9%)	
Education				< 0.001
Degree	109,149 (32.5%)	96,230 (34.2%)	12,919 (23.7%)	
Professional qualification	17,509 (5.2%)	14,678 (5.2%)	2,831 (5.2%)	
Secondary school	149,552 (44.5%)	125,152 (44.4%)	24,400 (44.7%)	
Other	60,139 (17.9%)	45,692 (16.2%)	14,447 (26.5%)	
TDI				< 0.001
1	133,804 (39.8%)	116,172 (41.2%)	17,632 (32.3%)	
2	123,466 (36.7%)	104,298 (37.0%)	19,168 (35.1%)	
3	54,836 (16.3%)	43,670 (15.5%)	11,166 (20.5%)	
4	21,664 (6.4%)	15,781 (5.6%)	5,883 (10.8%)	
5	2,169 (0.6%)	1,499 (0.5%)	670 (1.2%)	
Missing	410 (0.1%)	332 (0.1%)	78 (0.1%)	

Note: BMI: body mass index; TDI: Townsend deprivation index.

Characteristic	Overall (N = 336,297)	Without psychiatric disorders (N = 281,717)	With psychiatric disorders (N = 54,580)	*P* value
Smoking status				< 0.001
Current	32,859 (9.8%)	18,585 (6.6%)	14,274 (26.1%)	
Previous	116,687 (34.7%)	97,792 (34.7%)	18,895 (34.6%)	
Never	185,204 (55.1%)	164,159 (58.3%)	21,045 (38.5%)	
Missing	1,599 (0.5%)	1,216 (0.4%)	383 (0.7%)	
Alcohol status				< 0.001
Current	310,760 (92.4%)	262,212 (93.1%)	48,548 (88.9%)	
Previous	11,097 (3.3%)	7,772 (2.8%)	3,325 (6.1%)	
Never	13,754 (4.1%)	11,282 (4.0%)	2,472 (4.5%)	
Missing	738 (0.2%)	486 (0.2%)	252 (0.5%)	
BMI				< 0.001
< 25.0	108,292 (32.2%)	93,080 (33.0%)	15,212 (27.9%)	
25.0-29.9	144,696 (43.0%)	121,973 (43.3%)	22,723 (41.6%)	
≥ 30	82,265 (24.5%)	65,901 (23.4%)	16,364 (30.0%)	
Missing	1,096 (0.3%)	798 (0.3%)	298 (0.5%)	
Physical activity				< 0.001
Low	46,512 (13.8%)	38,259 (13.6%)	8,253 (15.1%)	
Medium	132,922 (39.5%)	114,258 (40.6%)	18,664 (34.2%)	
High	82,068 (24.4%)	69,214 (24.6%)	12,854 (23.5%)	
Missing	74,847 (22.3%)	60,021 (21.3%)	14,826 (27.2%)	
Cardiovascular disease				< 0.001
Yes	17,944 (5.3%)	12,749 (4.5%)	5,195 (9.5%)	

Note: BMI: body mass index; TDI: Townsend deprivation index.

Characteristic	Overall (N = 336,297)	Without psychiatric disorders (N = 281,717)	With psychiatric disorders (N = 54,580)	*P* value
No	318,405 (94.7%)	269,003 (95.5%)	49,402 (90.5%)	
Hypertension				< 0.001
Yes	136,423 (40.6%)	105,800 (37.6%)	30,623 (56.1%)	
No	199,926 (59.4%)	175,952 (62.4%)	23,974 (43.9%)	
Diabetes				< 0.001
Yes	29,532 (8.8%)	20,857 (7.4%)	8,675 (15.9%)	
No	306,817 (91.2%)	260,895 (92.6%)	45,922 (84.1%)	
Albumin (g/dl)	45.3 ± 2.4	45.3 ± 2.4	45.0 ± 2.4	< 0.001
Lymphocyte (%)	29.0 ± 6.7	29.1 ± 6.6	28.6 ± 6.7	< 0.001
Mean cell volume (fl)	91.2 ± 3.8	91.1 ± 3.8	91.7 ± 4.0	< 0.001
Serum glucose (mg/dl)	5.0 ± 0.7	5.0 ± 0.7	5.1 ± 0.8	< 0.001
Red cell distribution width (%)	13.4 ± 0.7	13.4 ± 0.7	13.5 ± 0.7	< 0.001
Creatinine (mg/dl)	72.0 ± 13.4	72.1 ± 13.3	71.6 ± 13.5	< 0.001
C-reactive protein (mg/dl)	2.2 ± 2.6	2.1 ± 2.5	2.6 ± 2.9	< 0.001
Alkaline phosphatase (U/liter)	82.5 ± 20.8	81.9 ± 20.6	85.4 ± 21.6	< 0.001
White blood cell count (1000 cells/μl)	6.8 ± 1.5	6.7 ± 1.5	7.2 ± 1.7	< 0.001
Note: BMI: body mass index; TDI: Townsend deprivation index.				

Association between psychiatric disorders and the risk of psoriasis

In the fully adjusted model, psychiatric disorders are significantly linked with a 57% increased risk of psoriasis (95% CI: 1.45–1.71). Additionally, six specific psychiatric disorders at baseline were found to significantly increase the subsequent risk of psoriasis. Among them, stress-related disorders showed the strongest association with psoriasis, with a hazard ratio of 2.06 (95% CI: 1.33–3.21, p = 0.003). Furthermore, as the number and variety of psychiatric disorders increased, the risk of psoriasis also rose significantly (p < 0.001) (Table 2).

Table 2
Association between psychiatric disorders and the risk of psoriasis.

	Model1		Model2		Model3	
	HR (95%CI)	***P* value**	**HR (95%CI)**	***P* value**	**HR (95%CI)**	***P* value**
Any psychiatric disorder						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.93(1.79,2.09)	< 0.001	1.70(1.56,1.84)	< 0.001	1.57(1.45,1.71)	< 0.001
Depression						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.96(1.75,2.18)	< 0.001	1.75(1.57,1.95)	< 0.001	1.62(1.45,1.81)	< 0.001
Anxiety						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.77(1.57,2.00)	< 0.001	1.65(1.46,1.86)	< 0.001	1.53(1.35,1.73)	< 0.001
Stress-related disorders						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	2.62(1.69,4.07)	< 0.001	2.27(1.46,3.53)	< 0.001	2.06(1.33,3.21)	0.003
Substance misuse						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	2.06(1.86,2.30)	< 0.001	1.63(1.44,1.84)	< 0.001	1.51(1.33,1.70)	< 0.001
Psychotic						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	2.30(1.55,3.40)	< 0.001	1.93(1.30,2.86)	0.001	1.81(1.22,2.69)	0.003
Dementia						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.58(1.27,1.97)	< 0.001	1.54(1.24,1.92)	< 0.001	1.41(1.13,1.76)	0.002
Number of special psychiatric disorders at baseline						
0	Reference	Reference	Reference	Reference	Reference	Reference
1	1.78 (1.63, 1.95)	< 0.001	1.57 (1.43, 1.73)	< 0.001	1.48 (1.34, 1.62)	< 0.001
2	2.23 (1.92, 2.58)	< 0.001	1.95 (1.68, 2.26)	< 0.001	1.79 (1.54, 2.08)	< 0.001
3	2.90(2.23, 3.76)	< 0.001	2.35 (1.80 3.06)	< 0.001	2.08 (1.59, 2.71)	< 0.001

Notes: HR: hazard ratio; CI: confidence interval;

Model 1: adjusted for age, sex, education, and ethnicity.

Model 2: adjusted for age, sex, ethnicity, education, BMI, TDI, alcohol status, smoking status, and physical activity.

Model 3: adjusted for age, sex, ethnicity, education, BMI, TDI, alcohol status, smoking status, physical activity, hypertension, diabetes, and cardiovascular disease.

	Model1		Model2		Model3	
	HR (95%CI)	***P* value**	**HR (95%CI)**	***P* value**	**HR (95%CI)**	***P* value**
> 3	4.85 (2.81, 8.37)	< 0.001	3.86 (2.23, 6.68)	< 0.001	3.27 (1.89, 5.66)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	
Notes: HR: hazard ratio; CI: confidence interval;						
Model 1: adjusted for age, sex, education, and ethnicity.						
Model 2: adjusted for age, sex, ethnicity, education, BMI, TDI, alcohol status, smoking status, and physical activity.						
Model 3: adjusted for age, sex, ethnicity, education, BMI, TDI, alcohol status, smoking status, physical activity, hypertension, diabetes, and cardiovascular disease.						

Joint effects of psychiatric disorders and genetic susceptibility

Individuals with high genetic risk exhibited a significantly greater susceptibility to psoriasis compared with those at low genetic risk (HR = 2.23, 95% CI: 1.99–2.49) (Table S2). Further analysis revealed a synergistic effect between psychiatric disorders and genetic risk on psoriasis incidence (Fig. 1). Notably, participants with both high genetic risk and a psychiatric disorder demonstrated the highest risk of developing psoriasis (HR = 3.85, 95% CI: 3.29–4.50) compared to the reference group (low genetic risk and no psychiatric history). Subgroup analyses demonstrated that individuals with specific psychiatric conditions—including anxiety, depression, substance misuse, and dementia—also had elevated psoriasis risk when combined with high genetic predisposition (Fig. 2). Even after applying Bonferroni correction for multiple testing, the associations retained statistical significance (threshold: 0.008).

Moreover, significant links between genetic risk and psychiatric disorders were observed on both multiplicative (interaction p = 0.004) and additive scales. Additive interaction analysis yielded a RERI of 1.53 (95% CI: 0.81–2.25) and an AP of 40% (95% CI: 21%–59%), suggesting that a considerable proportion of the risk is attributable to the synergistic effect between the exposures (Table S5).

Subgroup and sensitivity analyses

In fully adjusted subgroup analyses, psychiatric disorders were significantly associated with elevated psoriasis risk in participants with a high genetic susceptibility (Table 3). The hazard ratios were 4.44 (95% CI: 3.56–5.53) for those under 60 years and 3.28 (95% CI: 2.62–4.10) for those aged 60 or older. Of particular interest, while depression, anxiety, substance misuse, and dementia history were significantly associated with increased psoriasis risk in high-genetic-risk males, psychotic disorders exhibited a distinct sex-specific pattern, with high-genetic-risk females showing significantly elevated risk (HR = 6.63, 95% CI: 2.94–14.96). Sex and age significantly modified the psychiatric disorder-psoriasis associations for both overall and six specific mental conditions (Tables S3-S4).

Table 3
Association between psychiatric disorders and the risk of psoriasis across different subgroups.

	Age				**Sex**			
	Under 60		**60 and above**		**Female**		**Male**	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Any psychiatric disorder								
Low PRS								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.53 (1.12, 2.1)	0.007	1.12 (0.81, 1.54)	0.496	1.35 (0.99, 1.83)	0.056	1.27 (0.92, 1.77)	0.148
Middle PRS								
No	1.42 (1.2, 1.68)	< 0.001	1.29 (1.09, 1.53)	0.003	1.30 (1.10, 1.53)	0.002	1.42 (1.19, 1.68)	< 0.001
Yes	2.30(1.88, 2.81)	< 0.001	1.69 (1.38, 2.06)	< 0.001	1.95 (1.60, 2.37)	< 0.001	2.00 (1.63, 2.46)	< 0.001
High PRS								
No	2.23 (1.86, 2.68)	< 0.001	1.77 (1.47, 2.14)	< 0.001	1.96 (1.63, 2.35)	< 0.001	2.05 (1.70, 2.48)	< 0.001
Yes	4.44 (3.56, 5.53)	< 0.001	3.28 (2.62, 4.10)	< 0.001	3.56 (2.85, 4.44)	< 0.001	4.16 (3.33, 5.20)	< 0.001
Depression								
Low PRS								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.75 (1.17, 2.62)	0.007	1.47 (0.94, 2.30)	0.095	1.42 (0.95, 2.13)	0.085	1.87 (1.19, 2.95)	0.006
Middle PRS								
No	1.46 (1.25, 1.71)	< 0.001	1.34 (1.15, 1.57)	< 0.001	1.32 (1.13, 1.53)	< 0.001	1.49 (1.27, 1.75)	< 0.001
Yes	2.28 (1.81, 2.89)	< 0.001	1.89 (1.47, 2.44)	< 0.001	2.10 (1.68, 2.62)	< 0.001	2.03 (1.54, 2.67)	< 0.001
High PRS								

Notes: HR: hazard ratio; CI: confidence interval;

Cox regression models were adjusted for age, sex, ethnicity, education, BMI, TDI, alcohol status, smoking status, physical activity, hypertension, diabetes, and cardiovascular disease.

	Age				Sex			
	Under 60		60 and above		Female		Male	
No	2.36 (2.00, 2.80)	< 0.001	2.01 (1.70, 2.39)	< 0.001	2.05 (1.73, 2.42)	< 0.001	2.34 (1.97, 2.78)	< 0.001
Yes	4.56 (3.50, 5.93)	< 0.001	3.32 (2.42, 4.55)	< 0.001	3.82 (2.93, 4.98)	< 0.001	4.20 (3.08, 5.72)	< 0.001
Anxiety								
Low PRS								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.68 (1.06, 2.66)	0.028	1.10 (0.65, 1.86)	0.717	1.50 (0.99, 2.27)	0.056	1.11 (0.59, 2.11)	0.737
Middle PRS								
No	1.43 (1.23, 1.67)	< 0.001	1.33 (1.14, 1.55)	< 0.001	1.33 (1.14, 1.55)	< 0.001	1.43 (1.23, 1.67)	< 0.001
Yes	2.52 (1.97, 3.22)	< 0.001	1.64 (1.24, 2.15)	< 0.001	2.05 (1.62, 2.60)	< 0.001	2.05 (1.53, 2.75)	< 0.001
High PRS								
No	2.38 (2.02, 2.81)	< 0.001	2.00 (1.69, 2.36)	< 0.001	2.09 (1.77, 2.47)	< 0.001	2.30 (1.94, 2.71)	< 0.001
Yes	4.31 (3.20, 5.81)	< 0.001	2.84 (2.01, 4.00)	< 0.001	3.57 (2.68, 4.75)	< 0.001	3.55 (2.47, 5.12)	< 0.001
Psychotic								
Low PRS								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	2.34 (0.58, 9.42)	0.233	1.63 (0.23, 11.61)	0.627	2.90 (0.72, 11.66)	0.134	1.24 (0.17, 8.88)	0.828
Middle PRS								
No	1.44 (1.25, 1.67)	< 0.001	1.35 (1.16, 1.56)	< 0.001	1.34 (1.16, 1.55)	< 0.001	1.45 (1.25, 1.68)	< 0.001
Yes	2.49 (1.27, 4.86)	0.008	0.46 (0.06, 3.27)	0.437	1.10 (0.35, 3.44)	0.868	2.25 (1.06, 4.79)	0.036

Notes: HR: hazard ratio; CI: confidence interval;

Cox regression models were adjusted for age, sex, ethnicity, education, BMI, TDI, alcohol status, smoking status, physical activity, hypertension, diabetes, and cardiovascular disease.

	Age				Sex			
	Under 60		60 and above		Female		Male	
High PRS								
No	2.4 (2.05, 2.81)	< 0.001	2.03 (1.72, 2.38)	< 0.001	2.12 (1.81, 2.48)	< 0.001	2.33 (1.98, 2.74)	< 0.001
Yes	6.24 (2.93, 13.29)	< 0.001	6.57 (2.70, 15.99)	< 0.001	6.63 (2.94, 14.96)	< 0.001	6.06 (2.68, 13.69)	< 0.001
Substance misuse								
Low PRS								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.05 (0.66, 1.67)	0.843	1.12 (0.69, 1.83)	0.643	0.93 (0.54, 1.62)	0.81	1.21 (0.78, 1.86)	0.390
Middle PRS								
No	1.39 (1.19, 1.63)	< 0.001	1.33 (1.14, 1.56)	< 0.001	1.29 (1.11, 1.50)	< 0.001	1.45 (1.23, 1.70)	< 0.001
Yes	2.04 (1.60, 2.60)	< 0.001	1.59 (1.21, 2.09)	< 0.001	1.86 (1.42, 2.43)	< 0.001	1.82 (1.42, 2.33)	< 0.001
High PRS								
No	2.23 (1.88, 2.63)	< 0.001	1.89 (1.6, 2.25)	< 0.001	2.00 (1.70, 2.36)	< 0.001	2.14 (1.79, 2.55)	< 0.001
Yes	4.35 (3.34, 5.67)	< 0.001	4.03 (3.01, 5.41)	< 0.001	3.72 (2.74, 5.05)	< 0.001	4.64 (3.58, 6.01)	< 0.001
Dementia								
Low PRS								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Yes	3.81 (1.22, 11.91)	0.022	0.94 (0.44, 2)	0.876	0.56 (0.14, 2.27)	0.419	1.88 (0.92, 3.81)	0.082
Middle PRS								
No	1.45 (1.25, 1.69)	< 0.001	1.32 (1.14, 1.54)	< 0.001	1.32 (1.14, 1.52)	< 0.001	1.47 (1.26, 1.71)	< 0.001
Yes	1.83 (0.75,	0.181	1.75 (1.24,	0.001	1.78 (1.13,	0.012	1.88 (1.22,	0.004

Notes: HR: hazard ratio; CI: confidence interval;

Cox regression models were adjusted for age, sex, ethnicity, education, BMI, TDI, alcohol status, smoking status, physical activity, hypertension, diabetes, and cardiovascular disease.

	Age				Sex			
	Under 60		60 and above		Female		Male	
	4.46)		2.46)		2.78)		2.90)	
High PRS								
No	2.41 (2.06, 2.83)	< 0.001	2.00 (1.69, 2.35)	< 0.001	2.10 (1.80, 2.46)	< 0.001	2.34 (1.98, 2.76)	< 0.001
Yes	6.70 (2.97, 15.11)	< 0.001	3.15 (2.05, 4.86)	< 0.001	2.66 (1.41, 5.02)	0.003	4.64 (2.89, 7.45)	< 0.001
Notes: HR: hazard ratio; CI: confidence interval;								
Cox regression models were adjusted for age, sex, ethnicity, education, BMI, TDI, alcohol status, smoking status, physical activity, hypertension, diabetes, and cardiovascular disease.								

Our sensitivity analyses employed multiple validation approaches to ensure the robustness of the results. Specifically, we confirmed three distinct validation scenarios: (1) removal of psoriasis cases with less than 2 years of follow-up, (2) removing participants with missing covariates, and (3) excluding individuals with chronic disease history. The results remained consistently significant across all these analytical scenarios, demonstrating the reliability of our primary findings.

PhenoAgeAccel as a Mediator in the Relationship Between Psychiatric Disorders and Psoriasis Risk

We next investigated whether PhenoAgeAccel mediates the effects of psychiatric disorders (both overall and six specific conditions) on psoriasis risk. Using a regression-based mediation approach, all effect estimates and mediation proportions were calculated through direct counterfactual imputation with bootstrap inference. Our analysis revealed that PhenoAge acceleration partially mediated the association between any psychiatric disorder and psoriasis risk, accounting for 2.64% of the total effect. Furthermore, PhenoAge acceleration also mediated portions of the associations between psoriasis and specific psychiatric conditions, including depression (2.71%), anxiety (1.40%), substance misuse (5.65%), stress-related disorders (2.51%), and psychotic disorders (5.19%) (Fig. 3). To further validate these mediation effects, we performed a series of sensitivity analyses, and the results consistently confirmed the stability and reliability of our primary findings (Figure S3).

Mendelian Randomization Analysis Results

In the two-sample Mendelian randomization analyses, genetically predicted psychiatric disorders showed heterogeneous associations with psoriasis risk (Fig. 4). Using the inverse variance weighted method as the primary analysis, genetically predicted depression was significantly associated with an increased risk of psoriasis (odds ratio [OR] = 1.50, 95% confidence interval [CI]: 1.27–1.76, P < 0.001), which remained significant after false discovery rate correction. Similarly, genetically predicted anxiety was associated with a higher risk of psoriasis (OR = 2.16, 95% CI: 1.24–3.77, P = 0.007) and retained statistical significance following FDR correction.

No significant associations with psoriasis risk were observed for genetically predicted stress-related disorders, substance use disorders, or psychotic disorders in the IVW analyses. Genetically predicted dementia showed a suggestive association with psoriasis risk (OR = 1.53, 95% CI: 0.99–2.36, P = 0.055) but did not remain significant after correction for multiple testing.

Sensitivity analyses using MR-Egger regression, weighted median, weighted mode, and simple mode methods yielded effect estimates that were directionally consistent with the IVW results, supporting the robustness of the primary findings despite some variation in effect magnitude (Table S10 and Figure S4).

Cochran's Q statistics indicated no substantial heterogeneity for most psychiatric disorders (Table S11). Moderate heterogeneity was observed in the dementia analysis; however, MR-Egger intercept tests showed no evidence of directional horizontal pleiotropy for depression, stress-related disorders, substance use disorders, or dementia (Table S12). For anxiety and psychotic disorders, the MR-Egger intercept suggested potential horizontal pleiotropy, and these results should be interpreted with caution.

Mendelian randomization scatter plots further illustrated SNP-level effect estimates across different MR methods, supporting consistency in the direction of the causal associations (Figure S4).

Discussion

Using data from the prospective UK Biobank cohort, this study systematically evaluated the association between psychiatric disorders and the risk of incident psoriasis. We found that, after adjusting for potential confounding factors, both overall mental disorders and six specific types of mental illnesses (such as depression, anxiety, psychotic disorders, stress-related disorders, substance abuse, and dementia) were associated with an increased risk of psoriasis. Notably, stress-related disorders showed the strongest association, with the risk reaching 2.06-fold higher. Furthermore, psychiatric disorders significantly interacted with genetic susceptibility with respect to psoriasis risk, and accelerated biological aging appeared to play a partial mediating role.

Prior studies have indicated that mental disorders may be linked to an increased risk of psoriasis. A longitudinal study, for instance, demonstrated a reciprocal relationship between depression and psoriasis[30]. Moreover, evidence from a large-scale population-based case-control study showed that individuals with schizophrenia had an increased likelihood of developing psoriasis, with an odds ratio of 1.21[31]. However, a Mendelian randomization analysis did not find significant associations between schizophrenia, bipolar disorder, major depression, or anxiety and psoriasis[32]. In the present study, Mendelian randomization analyses provided supportive evidence for potential causal effects of genetically predicted depression and anxiety on psoriasis risk, whereas associations observed for other psychiatric disorders in observational analyses may partly reflect residual confounding or shared risk factors.

In parallel, by leveraging large-scale prospective cohort data with comprehensive adjustment for potential confounders, our study quantified the risk of incident psoriasis across six major psychiatric disorders. This methodological approach provides robust epidemiological evidence supporting links between mental illness and psoriasis. Furthermore, we identified a potential synergistic effect between psychiatric disorders and high genetic risk. In addition, our findings suggest that accelerated biological aging may serve as a partial mediator in the association between mental disorders and psoriasis, offering new perspectives for future research on underlying mechanisms.

Following adjustment for potential confounders, individuals with psychiatric disorders were at a significantly higher risk of developing psoriasis (HR = 1.57). When analyzing the six specific mental disorders, patients with stress-related disorders, substance abuse, and depression showed a higher risk of psoriasis, consistent with findings from previous studies[33,34]. The observed association may be attributable to the impact of mental stress on the immune system. Stress enhances the migration of CLA + T cells and natural killer (NK) cells, promoting the accumulation of these immune cells in the skin, thereby exacerbating the inflammatory response in psoriasis[35,36]. Moreover, chronic mental stress may reduce the number of CD3+/CD25 + T cells and exacerbate skin damage through neurogenic mechanisms, such as the release of CGRP and VIP[37,38]. Mental stress may also affect the function of Langerhans cells, altering the immune microenvironment of the skin, which in turn promotes the onset and exacerbation of psoriasis[39].

Patients with dementia were observed to have a significantly higher risk of psoriasis, with a hazard ratio of 1.74. According to a recent meta-analysis, patients with psoriasis were at increased risk for developing both vascular and non-vascular forms of dementia, with risk ratios of 1.41 and 1.13, respectively, compared to non-psoriasis patients[11]. This phenomenon may be linked to the role of TNF-α in Alzheimer's disease. TNF-α, an important pro-inflammatory cytokine, can exacerbate the pathological processes of Aβ and tau, and this inflammatory mechanism may also be involved in the underlying mechanisms leading to psoriasis[40]. Studies have demonstrated that TNF inhibitors can enhance cognitive performance in Alzheimer's patients[41], suggesting that immune system regulation may play a significant role in the interaction between psoriasis and dementia. These findings suggest that mental disorders may exacerbate psoriasis through an overall immune system response. Future research should explore how mental disorders influence the immune system, neuroendocrine pathways, and other mechanisms in the development and progression of psoriasis. Additionally, understanding the interactions between mental health and the immune system could provide important insights for early prevention, intervention strategies, and personalized treatments for psoriasis.

In our subgroup analysis, we found that individuals under the age of 60 with mental disorders exhibited a significantly elevated risk of psoriasis. This suggests that younger individuals are more likely to suffer from both mental illness and psoriasis[42,43]. Specifically, the link between depression, anxiety, stress-related disorders, substance abuse, schizophrenia, and dementia with psoriasis appeared stronger in patients younger than 60 years. Among these psychiatric disorders, stress-related disorders were most strongly associated with an increased risk of psoriasis. Young individuals often face higher levels of life stress and psychological burdens. Chronic psychological stress and emotional fluctuations may activate the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) system, leading to an increase in stress-related hormones, including cortisol and adrenaline. This, in turn, can trigger chronic inflammation and immune system dysfunction, ultimately promoting the onset and exacerbation of psoriasis[44,45]. Furthermore, we found no substantial differences between genders regarding the association between psychiatric disorders and psoriasis. However, within specific mental disorders, the link between depression, anxiety, schizophrenia, and stress-related disorders with psoriasis was more pronounced in females than in males. Research from prospective cohort studies has indicated that depression is an independent risk factor for psoriasis among females in the U.S[46]. This phenomenon may be linked to the stronger immune system reactivity in females compared to males. Women's immune systems are typically more active, so when they have mental disorders, their immune responses may be more intense, thereby exacerbating the immune reaction in psoriasis[47,48].

We also found a synergistic effect between psychiatric disorders and genetic susceptibility. In the population with both high genetic risk and mental disorders, the risk of developing psoriasis was as high as 4.16 (95%CI: 3.33, 5.20), with a significant interaction (P = 0.004). This result suggests that the interaction between genetic susceptibility and mental disorders may jointly contribute to the onset of psoriasis through multiple mechanisms. Specifically, mental disorders may increase psoriasis-related inflammation by affecting immune system function or neuroendocrine pathways (such as activating the hypothalamic-pituitary-adrenal axis), while individuals with high genetic risk may exhibit stronger immune responses or higher immune susceptibility in this process, thereby significantly increasing the risk of psoriasis[49,50]. Finally, our study suggests that PhenoAgeAccel may mediate the relationship between psychiatric disorders and psoriasis. Mental disorders, particularly depression and anxiety, lead to chronic inflammation, which accelerates biological aging[51,52]. Research has shown that biological aging is linked to an increased risk of developing psoriasis[17]. The PhenoAge index reflects an individual's inflammatory status by assessing nine clinical biomarkers, and psoriasis is a disease primarily caused by chronic inflammation. Research has found that the progression of biological aging might be linked to elevated rates of depression and anxiety in middle-aged and older populations[15]. Biological aging is often accompanied by low-grade, chronic, systemic inflammation[53]. Therefore, mental disorders, by accelerating biological aging, may act as an indirect factor in the development of psoriasis. Overall, our findings indicate that psychiatric

disorders not only affect mental health but may also promote the onset of psoriasis by accelerating the biological aging process.

This research offers several advantages. Notably, it leverages data from the UK Biobank, featuring a substantial sample size and extended follow-up duration, thereby enhancing the statistical robustness of the findings. Second, this study explores the association between mental disorders, including six specific types of mental illness, and psoriasis, providing valuable evidence to inform personalized psoriasis prevention strategies. Third, the study suggests that biological aging may function as an intermediary factor linking mental health disorders with psoriasis development, indicating a potentially complex interaction between mental and skin health.

Despite these strengths, several limitations should be acknowledged. First, the study population was derived from a relatively narrow demographic, which may limit the generalizability of the findings to other age groups or populations with different cultural backgrounds. Second, although multiple covariates were adjusted for, the potential influence of residual confounding cannot be entirely excluded. Furthermore, while polygenic risk scores were used to assess genetic susceptibility, this approach may not fully capture the complexity of genetic architecture. In addition, incomplete and potentially inaccurate medication data in the UK Biobank precluded adjustment for medication use, which may have introduced residual confounding. Finally, although our analyses suggest that accelerated biological aging may represent a potential mechanistic pathway linking psychiatric disorders and psoriasis, the observed mediation effect was relatively modest, indicating that other mediating mechanisms remain to be identified.

Conclusion

This study demonstrates a clinically relevant association between psychiatric disorders and an increased risk of incident psoriasis, with stress-related disorders showing the strongest association. We further identified a synergistic interaction between mental disorders and genetic susceptibility, as well as a potential mediating role of accelerated biological aging. Collectively, these findings suggest that mental health may play an important role in psoriasis development and highlight the importance of incorporating mental health considerations into psoriasis prevention and management. Future studies are warranted to further elucidate the underlying biological mechanisms and genetic factors linking psychiatric disorders and psoriasis, thereby informing targeted prevention and intervention strategies.

Declarations

Author Contribution declaration

Rongqian Tian and Yu Huang contributed equally to this work. Rongqian Tian and Yu Huang designed the study, performed the data analyses, and drafted the manuscript. Rongqian Tian led the conceptualization of the study framework and coordinated the overall research process. Yu Huang contributed to the development of the research methodology and ensured its alignment with the study objectives. Ming Chen, Shuying Lai, Huanxin Liang, and Xiang Huang contributed to data acquisition and provided technical support. Lixia Lin and Jiating Wen assisted with data interpretation and manuscript revision. Jun Lyu contributed to data analysis and interpretation. Liehua Deng supervised the study, secured funding, and critically reviewed the manuscript. All authors reviewed and approved the final manuscript.

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Declaration of competing interests

The authors declare that they have no competing financial interests or personal relationships that could influence this research.

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Clinical trial number

Not applicable.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki.

The UK Biobank has obtained ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/03820). All participants provided written informed consent prior to data collection.

The present study involved secondary analysis of anonymized UK Biobank data.

Consent for publication

No identifiable images were used in this manuscript, so consent to publish

was not applicable.

Data availability

Data will be made available on request.

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Figures

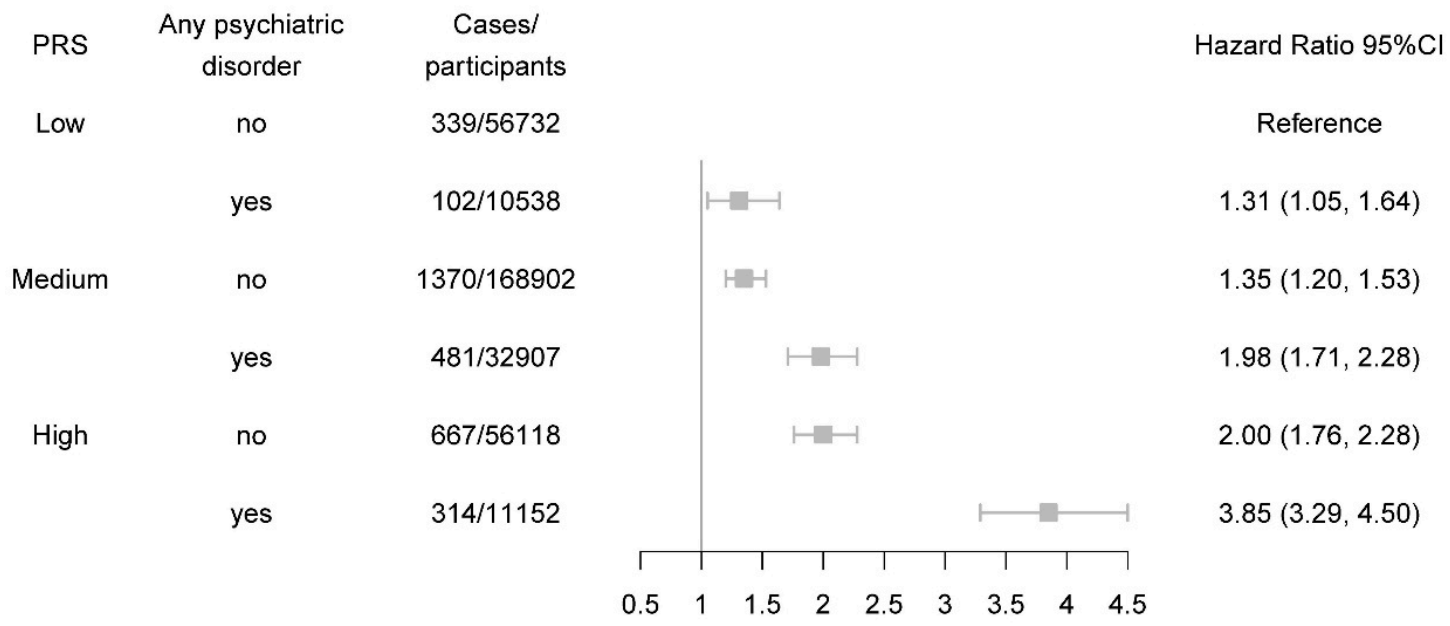


Figure 1

The risk of developing psoriasis was assessed according to psychiatric disorders and genetic susceptibility. Adjusted for age, sex, ethnicity, education, BMI, TDI, alcohol status, smoking status, physical activity, hypertension, diabetes, and cardiovascular disease.CI: confidence interval; PRS: polygenic risk score.

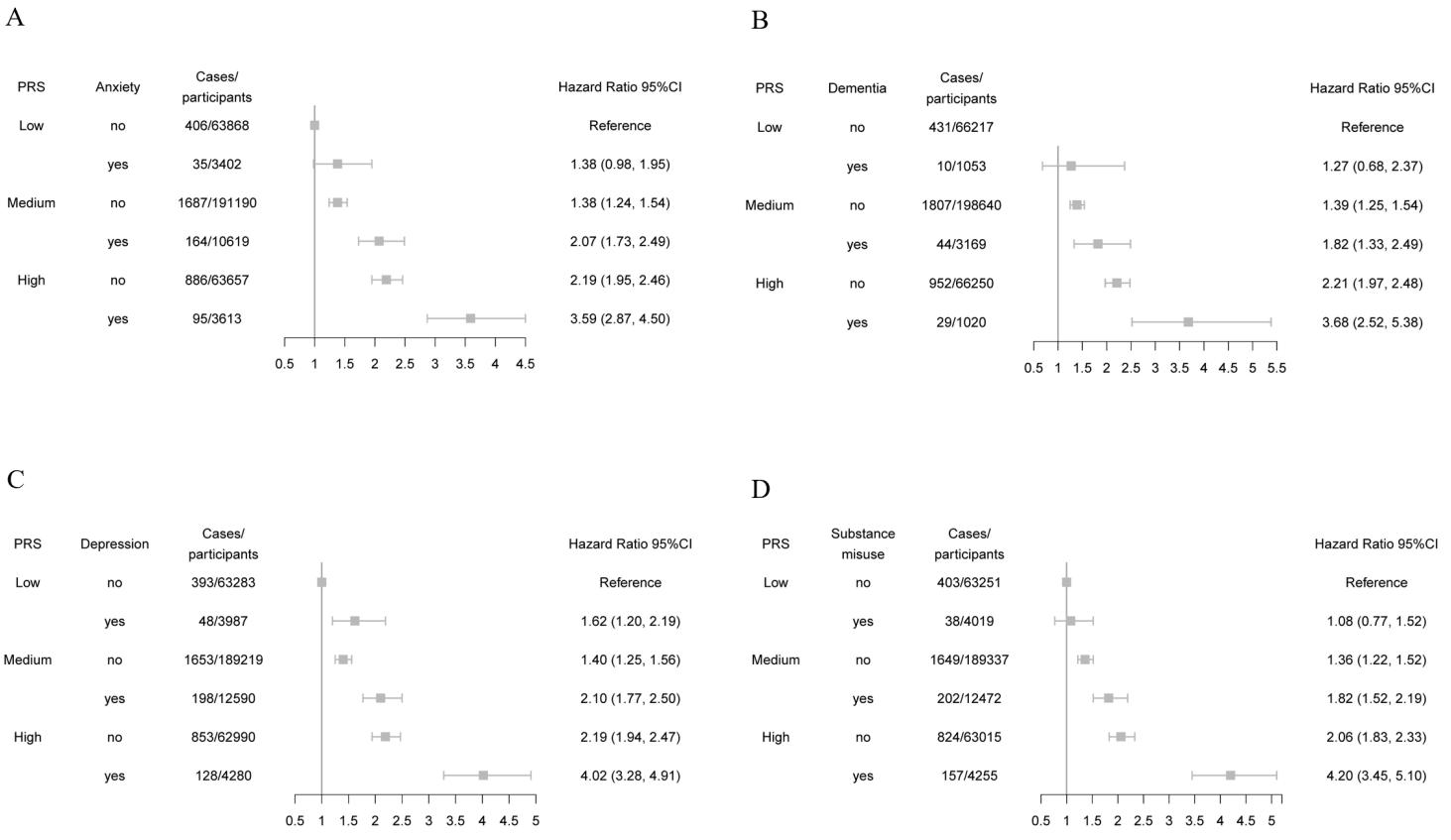


Figure 2

The risk of developing psoriasis was assessed according to 6 different psychiatric disorders and genetic susceptibility. Adjusted for age, sex, ethnicity, education, BMI, TDI, alcohol status, smoking status, physical activity, hypertension, diabetes, and cardiovascular disease.CI: confidence interval; PRS: polygenic risk score.

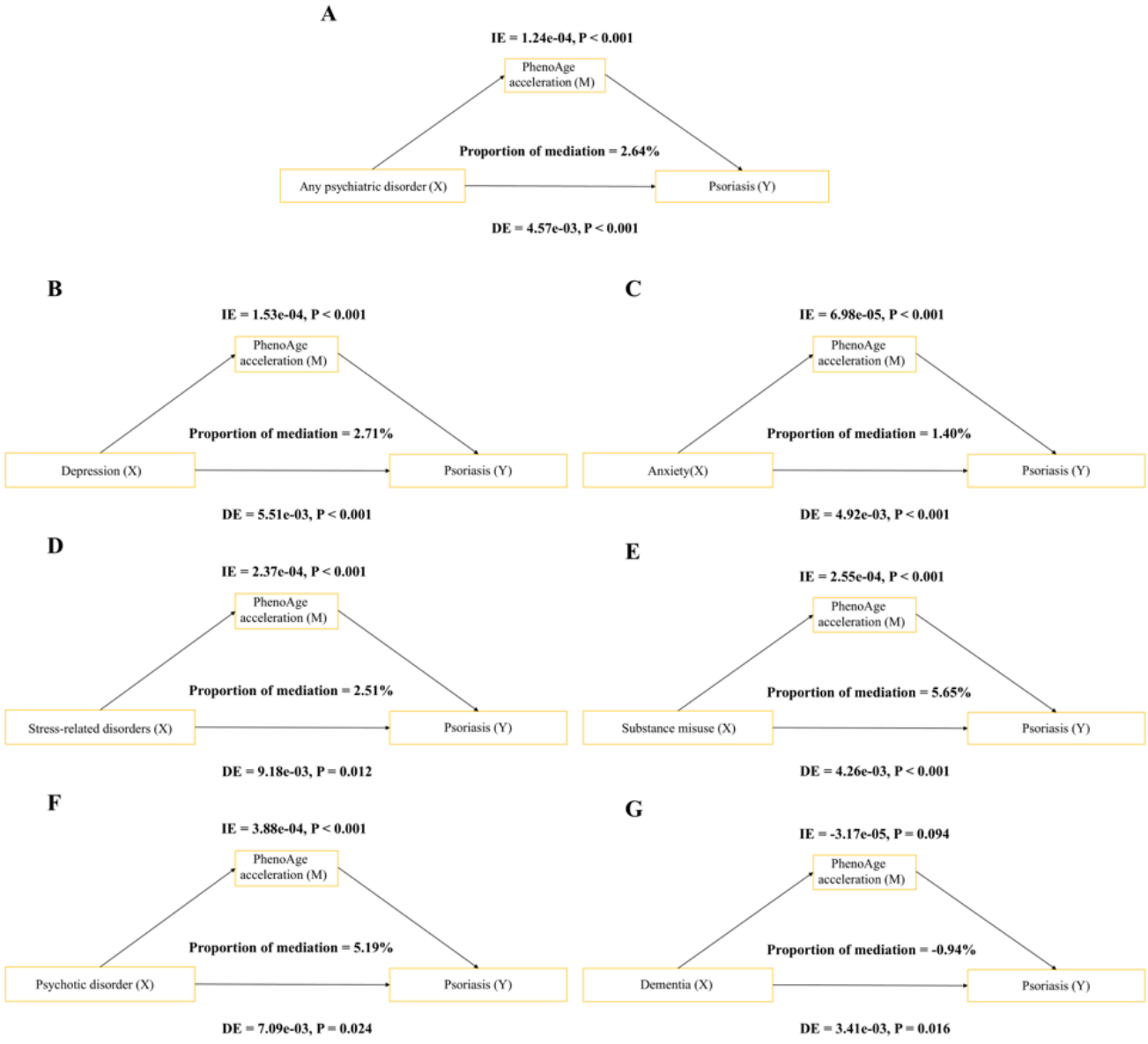


Figure 3

Mediation analysis of the relationship between psychiatric disorders and incident psoriasis, with PhenoAgeAccel as the mediator. Adjusted for age, sex, ethnicity, education, BMI, TDI, alcohol status, smoking status, physical activity, hypertension, diabetes, and cardiovascular disease. IE: indirect effect, DE: direct effect; CI: confidence interval.

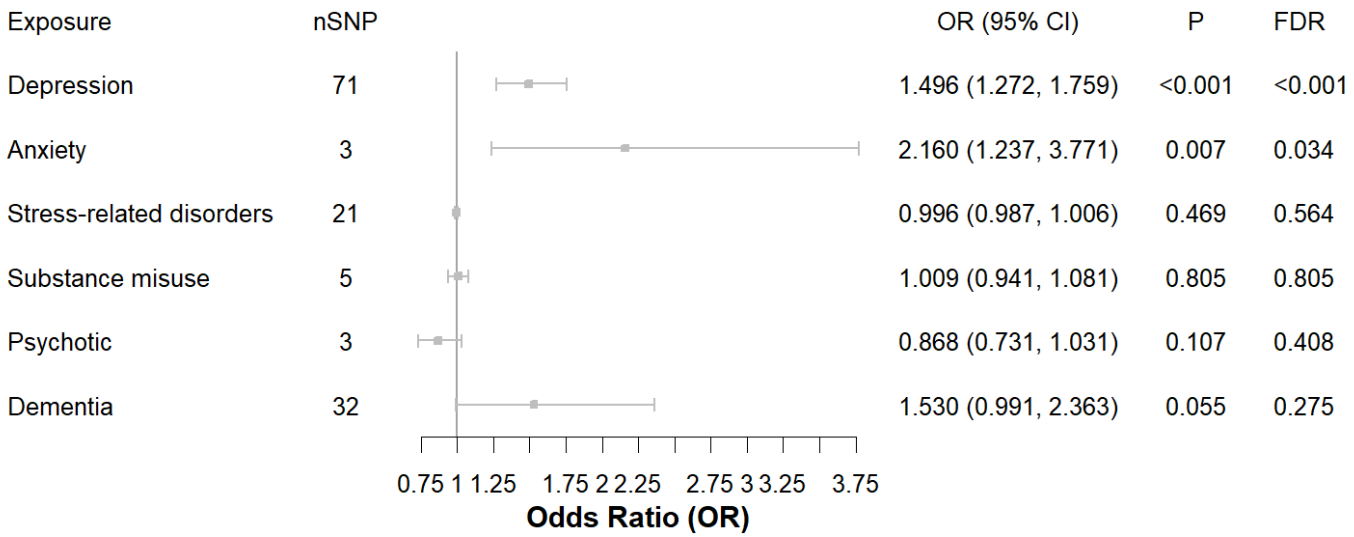


Figure 4

The results of forward two-sample Mendelian randomization analysis assessing the causal effects of psychiatric disorders on psoriasis risk. Points represent odds ratios (ORs) and horizontal lines indicate 95% confidence intervals (CIs). Depression and anxiety showed statistically significant associations with increased psoriasis risk after false discovery rate (FDR) correction, whereas dementia exhibited a suggestive association.

Supplementary Files

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