ORIGINAL REPORT

Plasma Metabolomic and Proteomic Profiling of the Mechanisms Underlying the Cumulative Impact of Co-occurring Psychiatric Disorders on Atopic Dermatitis

Peizhi DENG[1], Yiyi YUYANG[1], Jinron ZENG[1*] and Jianyun LU[1,2*]
[1]*Department of Dermatology, The Third Xiangya Hospital, Central South University, Tongzipo Road, Changsha, Hunan 410008, China, and* [2]*Medical Ozone Research Center, The Third Xiangya Hospital, Central South University, Tongzipo Road, Changsha, Hunan, 410008, China*

Atopic dermatitis (AD) has been linked to psychiatric disorders, but the cumulative contribution of psychiatric multimorbidity to incident AD remains unclear. We integrated genome-wide association study summary statistics with UK Biobank cohort, metabolomic and proteomic data to evaluate genetic relationships, longitudinal associations and putative biological intermediates. High-definition likelihood and bidirectional GSMR assessed shared genetic architecture and directionality. Cox models, multimorbidity counts, weighted composite scores and stratified analyses assessed incident AD, including effect modification by serum vitamin D. Plasma metabolomic and proteomic data were examined using mediation analysis and proteome-wide Mendelian randomization. Genetic liability to 5 psychiatric traits was associated with higher AD risk, whereas reverse AD-to-psychiatric effects were not supported. Psychiatric disorders were prospectively associated with incident AD, with higher risk among participants with co-occurring disorders and higher weighted psychiatric burden. Vitamin D status modified these associations although causality cannot be inferred. A branched-chain amino acid metabolic pattern showed statistically significant but modest mediation (1.04%). Proteomic analyses prioritized HLA-DRA, MMP12, TNFRSF14, and VCAM1 as nonspecific inflammatory proteins associated with AD risk in psychiatric populations. Psychiatric multimorbidity marks a sustained elevation in AD risk, potentially through overlapping inflammatory and metabolic pathways.

Key words: Psychiatric multimorbidity; Atopic dermatitis; Metabolomics; Plasma proteomic; UK Biobank.

Submitted Nov 14, 2025. Accepted after revision Jun 29, 2026

Published Aug 4, 2026.
DOI: 10.2340/actadv.v106.adv-2025-0181

Acta Derm Venereol 2026; 106: adv-2025-0181.

Corr: Jinron Zeng, Department of Dermatology, The Third Xiangya Hospital, Central South University, Changsha, China and Jianyun Lu, Department of Dermatology, The Third Xiangya Hospital, Central South University, Changsha, China. Emails: dpz19981011@163.com; xiaoyun3@csu.edu.cn

SIGNIFICANCE

While atopic dermatitis (AD) has been linked to individual psychiatric disorders, the cumulative contribution of psychiatric multimorbidity to incident AD has been insufficiently characterized. This study shows that psychiatric disorder-related traits, especially co-occurring conditions and higher weighted psychiatric burden, are associated with increased long-term AD risk. Serum vitamin D modified these associations, but the finding should not be interpreted as proof that supplementation prevents AD. Metabolomic mediation was statistically significant but modest, and the prioritized plasma proteins likely reflect shared inflammatory activity rather than AD-specific biomarkers.

Psychiatric disorders occupy a prominent share of the global disease landscape, accounting for 17.2% of total years lived with disability worldwide in 2021. Among them, depression and anxiety disorder stand out – not only for their disabling nature but also for their tendency to co-occur with each other (1, 2). Beyond psychological suffering, individuals with psychiatric disorders often contend with physical comorbidities, particularly skin diseases such as atopic dermatitis (AD), which are far more common in this population than in the general public (3). The brain and the skin are tightly linked by neuro-immunological pathways. Studies have shown that psychiatric disorders disrupt this balance, enhancing sympathetic nervous system activity while dampening parasympathetic tone – an imbalance that can ignite inflammatory cascades in the skin (4–6). The result is a chronic, proinflammatory cutaneous state, which may erode the skin's barrier function and set the stage for AD (7).

Although the concept of the brain–skin axis is well established, most longitudinal studies and many Mendelian randomization (MR) analyses have emphasized the direction from AD to later depression, anxiety disorder or other psychiatric outcomes (3, 8). Recent genetic studies have begun to evaluate the reverse direction and suggest that liability to selected neuropsychiatric disorders may also contribute to AD or eczema risk, although the effect sizes are generally modest and phenotype-specific (9). What remains insufficiently defined is the long-term dermatological consequence of cumulative psychiatric burden within the same individual. This gap is clinically important

because psychiatric conditions rarely occur in isolation; they cluster through shared genetic, neurobiological, behavioural and inflammatory pathways (10). Failing to account for psychiatric multimorbidity may therefore underestimate the combined burden relevant to AD risk stratification. A weighted composite score offers a more nuanced way to quantify the cumulative psychiatric load that may contribute to AD susceptibility. In addition, psychiatric conditions often have a biological footprint marked by proinflammatory cytokines, innate immune activation, metabolic disturbance and altered neuroendocrine signalling. These shared mechanisms raise the possibility that circulating biomarkers may help explain, but not fully determine, the association between psychiatric burden and AD (11–13).

In this study, we first applied High-Definition Likelihood (HDL) (14) and bidirectional Generalized Summary Data-Based Mendelian Randomization (GSMR) (15, 16) to quantify the genetic correlations and causal relationships between each psychiatric disorder and AD. We then leveraged the UK Biobank data to perform multivariable Cox proportional hazards regression, estimating the associations of single psychiatric disorder, co-occurring psychiatric disorder status and the weighted composite psychiatric disorder score with incident AD. A series of sensitivity analyses assessed the robustness of these findings, and subgroup stratification identified priority populations for AD risk management among psychiatric patients. Finally, we investigated plasma metabolomic and proteomic biomarkers as potential mediators of the link between psychiatric disorders and AD.

MATERIALS AND METHODS

Data on genetic correlation and bidirectional causal inference

Summary-level genetic data for AD and 7 psychiatric disorder-related traits were selected from the largest publicly available European-ancestry GWAS datasets with compatible phenotype definitions and no sample overlap with UK Biobank whenever possible (Table SI). The AD GWAS was obtained from Release 12 of FinnGen (31,245 cases and 432,874 controls), which provided the largest accessible European AD endpoint with case-control ascertainment suitable for the present analyses. For psychiatric traits, we preferentially used large-scale case-enriched consortia or population resources, including PGC- or IEU-derived datasets when available, rather than relying exclusively on FinnGen. For detailed information on GWAS source, phenotype definition and quality-control procedures, please refer to the respective data source websites and GWAS publications (Table SI). We first applied the HDL method to evaluate shared genetic heritability and genetic correlation between psychiatric traits and AD (14). Independent SNPs were selected using a p-value threshold of $p<1 \times 10^{-5}$ and linkage disequilibrium (LD) cutoff of $r^2<0.05$. To explore potential causal relationships, bidirectional GSMR analysis was subsequently conducted (15, 16). A more stringent genome-wide significance threshold ($p<5 \times 10^{-8}$) was not used because it would have left too few instruments for several psychiatric traits. A p threshold of 0.01 was applied for HEIDI-outlier filtering in both single- and multi-SNP analyses to remove variants with strong evidence of horizontal pleiotropy.

UK Biobank cohort

The UK Biobank is a large-scale, population-based cohort. Further methodological details have been published previously (17). Briefly, over 500,000 individuals aged 37-73 years were recruited between 2006 and 2010 at 22 assessment centres across the UK, where they completed touchscreen surveys, underwent physical examinations and contributed biological specimens. For the current analysis, individuals were excluded if they had withdrawn from the cohort, had prevalent AD/eczema at baseline or had missing values or selected "prefer not to answer"/"do not know" responses for variables required to define exposure, outcome, follow-up time or core covariates. These key variables included age, sex, ethnicity, Townsend deprivation index, body mass index, smoking status, alcohol drinking status, education, employment, vitamin D, triglycerides, $PM_{2.5}$ exposure, asthma, allergic rhinitis and psychiatric disorder-related traits. For genetic and PRS analyses, we used UK Biobank genotype data after central sample-level quality control and additionally restricted analyses to participants of European genetic ancestry with complete genotype information, excluding individuals flagged for sex discordance, excess heterozygosity or missingness, close relatedness or missing genotype data. Criteria for inclusion and exclusion are outlined in Fig. S1. Ethical approval for the UK Biobank was obtained from the North West Multicenter Research Ethics Committee (11/NW/0382), and all participants gave written informed consent. The data in this research were available with permission via application number 224336.

Ascertainment of clinical diagnosis

The diagnosis of disease was primarily confirmed through clinical data from hospital admission records and primary care, with some input from self-reported information on whether the individual had been diagnosed by a doctor. Additional cases were identified from supplementary sources. This cohort included 8 psychiatric disorder-related traits, AD

and AD-related atopic comorbidities (asthma and allergic rhinitis). Diagnoses were ascertained using ICD-10 codes and questionnaire data: F32-F33 for depression, F40-F41 for anxiety disorders, F20 for schizophrenia, F31 for bipolar disorder (BD), F50 for eating disorder (ED), F42 for obsessive-compulsive disorders (OCD), L20 for AD, J45 for asthma, J30 for allergic rhinitis, data-Field 1200 for sleeplessness/insomnia and data-Field 20127 for neuroticism score (Table SII). We did not use ICD-10 codes for allergic or irritant contact dermatitis (L23-L25) to define AD. Because UK Biobank and prior epidemiological work often capture AD under eczema-related self-report terms, participants with recorded AD or self-reported eczema were classified under the broader AD/eczema outcome (18). Adult-onset AD could not be perfectly separated from chronic eczema phenotypes in this data source; therefore, participants with baseline AD/eczema were excluded and analyses focused on incident recorded AD/eczema during follow-up. Neuroticism scores were dichotomized at the median, with individuals scoring above the median classified as neuroticism and those at or below the median classified as non-neurotic. UK Biobank health records included self-reported information, primary care data, hospital admission data and death certificates. All diagnoses were validated through nurse-led verbal interviews and corroborated by primary care and inpatient data.

Additionally, we studied the status of 2 common psychiatric disorders – depression and anxiety based on questionnaire assessments. Depression was assessed using the Recent Depressive Symptoms-4 (RDS-4), a categorical measure evaluating 4 core depressive symptoms (19), with total scores ranging from 4 to 16. Anxiety severity was evaluated using the Generalized Anxiety Disorder-7 (GAD-7) scale (20), which captures 7 key anxiety-related symptoms, yielding scores between 0 and 21. Detailed descriptions of the RDS-4 and GAD-7 measures have been reported in prior publications (19, 21).

Covariates

Baseline covariates were selected primarily according to a recent study and supplemented with factors known to affect AD onset and progression, including vitamin D levels and air pollution (22). The details of covariates are shown in Appendix S1. Model 1 included sex, age, ethnicity and Townsend deprivation index. Model 2 accounted for model 1 plus body mass index, employment status, education level, smoking status, alcohol drinker status, triglycerides, Vitamin D, $PM_{2.5}$, history of asthma and allergic rhinitis and 7 psychiatric disorders at baseline.

Polygenic risk score calculation

To assess whether genetic susceptibility to AD modified the association between psychiatric disorder-related traits and long-term AD risk, we computed an AD polygenic risk score (PRS) in UK Biobank. PRSice-2 was applied after variant-level quality control, including removal of ambiguous variants and filtering by imputation quality, minor allele frequency and LD clumping. The best-fit PRS was selected by PRSice-2 according to model R2 across the tested *p*-value thresholds and then used as the genetic susceptibility variable in interaction analyses. Information regarding PRS calculation, clumping and analysis is included in the Appendix S1.

NMR metabolomics

Between June 2019 and April 2020, baseline plasma samples (collected 2006–2010) were analysed using Nightingale Health's high-throughput NMR spectroscopic platform to obtain absolute quantification of 168 metabolic biomarkers. Most of the biomarkers fall into lipid subclasses (apolipoproteins, cholesterol esters, fatty acids) (23). Details on sample handling, spectral acquisition and quality-control procedures are available on the UK Biobank website. A complete list of metabolites and their biochemical classifications appears in Table SIII.

Plasma proteomic profiling

The UKB-PPP cohort contributed plasma specimens from 54,219 participants. These were analyzed using the Olink Explore 3072 platform, which quantified 2,941 proteins across 8 predefined panels covering cardiometabolic, inflammatory, neurological and oncological domains (each with 2 panels). Whole blood was collected into 9 mL EDTA tubes and separated into 850 µL portions to isolate plasma, buffy coat and red blood cells. Plasma fractions were stored at −80 °C and transported on dry ice to Olink's laboratory in Sweden. Raw protein measurements were converted to Normalized Protein eXpression (NPX) values. Detailed methods for sample selection, quality control and NPX generation have been described elsewhere. A complete list of proteins and their respective panels is available in Table SIV.

Statistical analysis

Associations between individual psychiatric disorder-related traits and AD risk.

Descriptive analyses were conducted for individuals with and without incident AD. Continuous variables were summarized as means and standard deviations (SD), while categorical variables were presented as percentages. Group comparisons for continuous variables were performed using the Kruskal–Wallis

test, and categorical variables were assessed using χ^2 tests. The cumulative incidence of AD was estimated via the Kaplan–Meier method, and differences between individuals with and without psychiatric disorder-related traits were tested using the log-rank test. Cox proportional hazards models were applied to investigate associations between 8 psychiatric disorder-related traits, a composite score and AD risk, using follow-up duration as the underlying time scale. Individuals without psychiatric disorder-related traits served as the reference population, with all models adjusted for relevant covariates. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Because insomnia and neuroticism represent psychiatric-related traits rather than clinician-coded psychiatric diagnoses, we use "psychiatric disorder-related traits" when referring to the full exposure set and reserve "psychiatric disorders" for clinician-coded diagnoses. Additionally, restricted cubic spline (RCS) regression was used to assess the dose-response relationships of RDS-4 and GAD-7 scores with AD risk (24). For spline modelling, we applied Akaike information criteria to select 4 knots placed at the 5th, 35th, 65th and 95th percentiles. The proportional hazards assumption was evaluated using Schoenfeld residuals, with no evidence of violation detected.

Replication analyses of associations

We conducted several sensitivity analyses to assess the robustness of our findings: 1) to address the potential influence of pre-existing psychiatric multimorbidities on AD risk, we carried out secondary analyses adjusting for additional psychiatric disorders; 2) to evaluate the long-term association between psychiatric disorders and AD, individuals diagnosed with AD within the first 3 years of follow-up were excluded in a separate analysis; 3) to reduce potential selection bias due to missing information, we applied multiple imputation with 10 datasets generated to account for incomplete data (25); and 4) to control for unmeasured confounding, we implemented propensity score matching (PSM) to construct a matched cohort and replicated the main analysis. Details of the PSM procedure have been described in the Appendix S1.

Additive effects of co-occurring psychiatric disorder status on AD

Given that individuals with 2 or more psychiatric disorders frequently exhibit comorbid chronic conditions and may therefore have further impaired skin health, we evaluated the influence of multiple co-occurring psychiatric disorders on AD using 3 complementary approaches. First, participants were grouped by the number of psychiatric disorders, with those free of any diagnosis serving as the reference category; we then estimated AD risk among individuals with 1, 2 and 3 or more disorders. Second, in recognition of the high comorbidity between depression and anxiety disorder, we set participants without either condition as the referent and compared AD risk in those with anxiety disorder alone, depression alone and both disorders. To further capture the varying influence of different psychiatric disorders on AD susceptibility, we constructed a weighted composite score reflecting cumulative psychiatric burden. This score was calculated by summing the 7 psychiatric disorders, each weighted by their multivariable-adjusted risk estimates from the primary analysis. The formula used was sum of β-weighted psychiatric disorders × (7/total β coefficients). This composite score, representing 7 disorders, ranged from 0 to 1.191. Based on the distribution, participants were stratified into 3 categories: low, moderate and high burden. To explore potential dose–response relationships, RCS regression was applied to assess the association between the weighted score and AD risk. Additionally, we evaluated effect modification by including interaction terms for covariates and conducted stratified analyses for variables with significant interactions.

Mediating effects of plasma metabolome

Given the complex interconversion of metabolites within the circulatory system, analysing individual metabolomic markers separately may fail to capture the underlying interrelationships among them. Grouping plasma metabolites into broader metabolic patterns can enhance the ability to identify profiles linked to the association between psychiatric disorders and AD. Accordingly, we employed 2 complementary strategies to investigate how psychiatric disorders relate to plasma metabolomic profiles and AD risk. Detailed information regarding the mediation approach can be found in the Appendix S1.

Association between psychiatric disorder-related proteins and AD

To examine the relationship between psychiatric disorder-related proteins and AD, we conducted a 3-step association framework. In the first step, logistic regression models were used with adjustment for relevant covariates to identify proteins associated with 7 psychiatric disorders. In the second step, we applied Cox proportional hazards models to assess the link between psychiatric disorder-related circulating proteins and AD incidence. The third step involved proteome-wide Mendelian randomization (MR) to validate the associations observed in step 2. Proteins were considered putative modulators of AD

only if consistent associations were observed across both steps 2 and 3.

Protein instruments for MR were obtained from the UKB-PPP GWAS (26,). Independent SNPs (cis-pQTLs) significantly associated with plasma protein levels ($p<5 \times 10^{-8}$) and located within 1 Mb of the encoding gene were selected. Independence among SNPs was ensured using the 1000 Genomes European reference panel, applying linkage disequilibrium filtering with $r^2<0.001$ within a 10,000-kb clumping window. For proteins with only one valid instrument, we applied the Wald ratio method; for those with multiple instruments, the inverse variance-weighted MR (MR-IVW) method was used (27). Additional MR sensitivity methods such as MR-Egger and weighted median were not applied as primary analyses because most cis-pQTL instrument sets contained very few independent variants, which would make these estimators unstable. Therefore, proteomic findings were interpreted as genetically supported potential candidate associations that required concordance with observational protein–AD associations, rather than as definitive proof of AD-specific causality. Effect estimates were reported as odds ratios (ORs) per SD increase in protein levels. All statistical tests were 2-sided, adjusted for multiple comparisons using the Benjamini–Hochberg procedure, and significance was defined as FDR<0.05.

PPI and pathway enrichment analysis. PPI networks were generated using the STRING database (https://string-db.org/) to illustrate connections among plasma proteins associated with AD. To investigate the biological mechanisms linking AD-related proteins to psychiatric disorders, we performed pathway enrichment analyses based on Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG). These analyses were used to identify major biological processes and signalling pathways. GO terms were categorized into 3 domains: Biological Process, Cellular Component and Molecular Function.

RESULTS

Genetic correlation and bidirectional causal inference

We performed HDL to assess shared heritability between psychiatric disorder-related traits and AD. SNP-based heritability was acceptable for the 7 psychiatric traits and AD (Table SV). HDL analysis revealed significant genetic correlations between 5 psychiatric traits and AD ($p<0.05$). Next, we conducted bidirectional GSMR to infer the direction of association between 7 psychiatric traits and AD. In the forward analysis, genetic liability to each psychiatric trait was used as the exposure and AD as the outcome. Higher genetic liability to depression (OR=1.45, 95% CI: 1.11–1.88, $p=0.006$), anxiety disorder (OR=1.15, 95% CI: 1.11–1.20, $p=0.009$), schizophrenia (OR=1.06, 95% CI: 1.01–1.11, $p=0.0118$), bipolar disorder (OR=1.03, 95% CI: 1.01–1.05, $p=0.0013$), and sleeplessness/insomnia (OR=1.13, 95% CI: 1.09–1.18, $p=0.006$) was associated with increased AD risk, whereas ED and OCD did not show significant forward effects. In the reverse direction, genetic liability to AD was not significantly associated with any psychiatric trait (all $p>0.05$; Table SVI).

Relationships of each psychiatric disorder and its status with AD risk

Among the 502,140 UK Biobank participants, we excluded 3,328 participants with missing data and 10,781 participants who had a diagnosis of AD at baseline, resulting in a final sample of 488,031 AD-free participants included in the discovery phase (Fig. S1). In this prospective study, we identified 7,695 participants who developed AD, with a median follow-up time of 13.18 years (IQR: 12.81–14.34 years) in the UKB cohort. Baseline characteristics are summarized in **Table I**. As illustrated in Fig. S2, individuals with psychiatric disorders exhibited a significantly higher cumulative incidence of AD compared to those without, with all log-rank test p-values <0.05. When compared with participants free of psychiatric diagnoses, those with a single disorder showed a markedly elevated risk of AD, even after adjusting for major covariates (**Fig. 1**A; Table SVII). Among all disorders, ED was associated with the highest AD incidence (HR=2.20, 95% CI: [1.47, 3.28], $p<0.001$), followed by OCD (HR=1.99, [1.24, 3.20], $p=0.005$), schizophrenia (HR=1.56, [1.02, 2.41], $p=0.041$), and anxiety disorder (HR=1.51, [1.37, 1.67], $p<0.001$). These associations remained robust after full adjustment (Fig. 1A; Table SVII), were consistent across stratified subgroups (Fig. S4) and were only slightly attenuated after extensive sensitivity testing (Tables SVIII–SXI). As shown in Table SXII, multivariable-adjusted models revealed a positive association between both RDS-4 and GAD-7 scores and increased AD risk. A dose-dependent relationship was also evident, with higher RDS-4 scores corresponding to greater AD risk, confirmed by a significant non-linear trend (Fig. S3, p for nonlinear = 0.003).

Associations between co-occurring psychiatric disorder status and AD risks

Compared with individuals without psychiatric disorders, those with one or more diagnoses had a significantly elevated risk of developing AD after adjusting for covariates (**Fig. 2**). Specifically, the risk was 1.17 times higher among individuals with a single psychiatric disorder (95% CI: 1.10–1.24, $p<0.001$), 1.48 times higher for those with 2 disorders (95% CI: 1.32–1.66, $p<0.001$), and 1.77 times higher among those with

Table I. Baseline characteristics of participants categorized by AD and Non-AD among UK biobank populations

Characteristic	Level	Non-AD (*N*=480,336)	AD (*N*=7,695)	*p*-value
Age, years		56.52 (8.09)	57.75 (7.88)	<0.001
Female sex		261,249 (54.4)	4,065 (52.8)	0.007
Townsend deprivation index		−1.30 (3.09)	−1.12 (3.13)	<0.001
Body mass index, kg/m^2		27.42 (4.79)	28.01 (5.26)	<0.001
Ethnicity	Others	43,758 (9.1)	719 (9.3)	0.492
	White	436,578 (90.9)	6,976 (90.7)	
Smoking status	Never	262,522 (54.9)	3,821 (49.9)	<0.001
	Previous	165,375 (34.6)	2,933 (38.3)	
	Current	50,615 (10.6)	909 (11.9)	
Alcohol drinker status	Never	21,301 (4.4)	364 (4.7)	<0.001
	Previous	17,173 (3.6)	345 (4.5)	
	Current	441,281 (92.0)	6,970 (90.8)	
Employment status	Retired/Others	200,080 (42.0)	3,744 (49.2)	<0.001
	Employed	275,798 (58.0)	3,859 (50.8)	
Education level	Others	235,741 (60.4)	3,660 (61.2)	0.213
	University/college or above	154,416 (39.6)	2,318 (38.8)	
Obesity grades	Lean	158,171 (32.9)	2,317 (30.1)	<0.001
	Non-lean	322,165 (67.1)	5,378 (69.9)	
Triglycerides, mmol/L		1.75 (1.03)	1.79 (1.07)	<0.001
Vitamin D, nmol/L		48.67 (21.10)	47.47 (21.16)	<0.001
$PM_{2.5}$, μg/m^3		9.99 (1.06)	10.09 (1.08)	<0.001
Asthma		54,991 (11.4)	1,600 (20.8)	<0.001
Allergic rhinitis		40,846 (8.5)	1,011 (13.1)	<0.001
Neuroticism score		4.11 (3.26)	4.46 (3.37)	<0.001
Depression		41,644 (8.7)	930 (12.1)	<0.001
Anxiety disorder		17,962 (3.7)	419 (5.4)	<0.001
Schizophrenia		845 (0.2)	21 (0.3)	0.062
Bipolar disorder		1,638 (0.3)	37 (0.5)	0.047
Eating disorder		772 (0.2)	24 (0.3)	0.002
Obsessive-compulsive disorders		563 (0.1)	17 (0.2)	0.014
Sleeplessness / insomnia		134,965 (28.1)	2,468 (32.1)	<0.001
Weighted composite score		0.06 (0.11)	0.08 (0.13)	<0.001

Note: Continuous variables were presented as mean (SD). Categorical variables were presented as number (percentage).

3 or more psychiatric conditions (95% CI: 1.40–2.25, p<0.001) (Fig. 1B; Table SXIII). Notably, individuals with both depression and anxiety exhibited the highest risk of AD, exceeding the risk associated with either condition alone (depression: HR=1.46, 95% CI: 1.35–1.57; anxiety disorder: HR=1.45, 95% CI: 1.28–1.65; joint depression and anxiety disorder: HR=1.76, 95% CI: 1.52–2.04) (Fig. 1B; Table SXIV). Furthermore, there was strong evidence of a nonlinear positive association between the weighted composite psychiatric disorder score and AD risk (p=0.019), with a steadily increasing risk observed across the full spectrum of the score and a more pronounced effect at higher scores (Fig. S5). Consistent findings emerged when stratifying by score tertiles: participants in the moderate and high-score groups showed 1.18-fold (95% CI: 1.11–1.24, p<0.001) and 1.58-fold (95% CI: 1.48–1.68, p<0.001) increases in AD risk, respectively (Table SXV). In subgroup analyses, vitamin D demonstrated a significant interaction with the weighted composite score (p<0.05), with individuals exposed to psychiatric disorders showing higher AD risk under lower vitamin D levels (Tables SXVI and SXVII).

The mediating effect of plasma metabolomic markers

Fig. 3 presents the overall analytical strategy. The associations between the weighted composite psychiatric disorder score and 168 plasma metabolomic

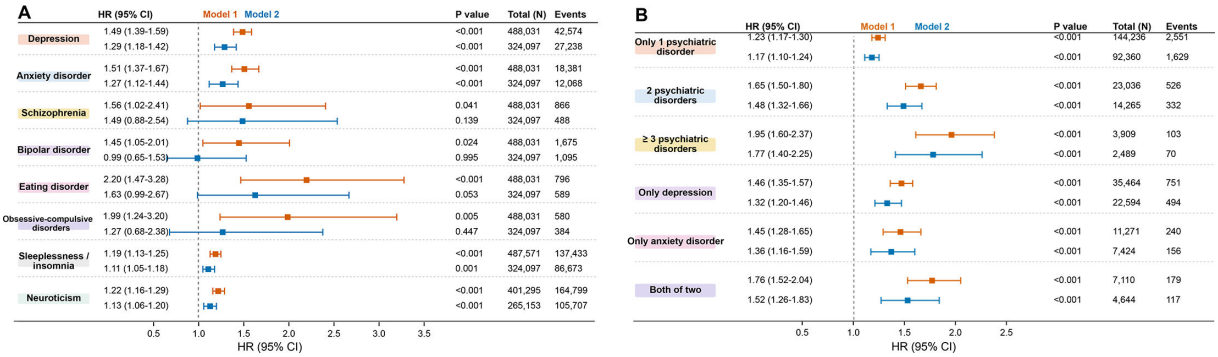

Fig. 1. Prospective associations of psychiatric disorder and incidence of atopic dermatitis. (A). Each psychiatric disorder-related trait on the risk of atopic dermatitis; (B). co-occurring status on the risk of atopic dermatitis. Note: CI, confidence interval; HR, hazard ratio.

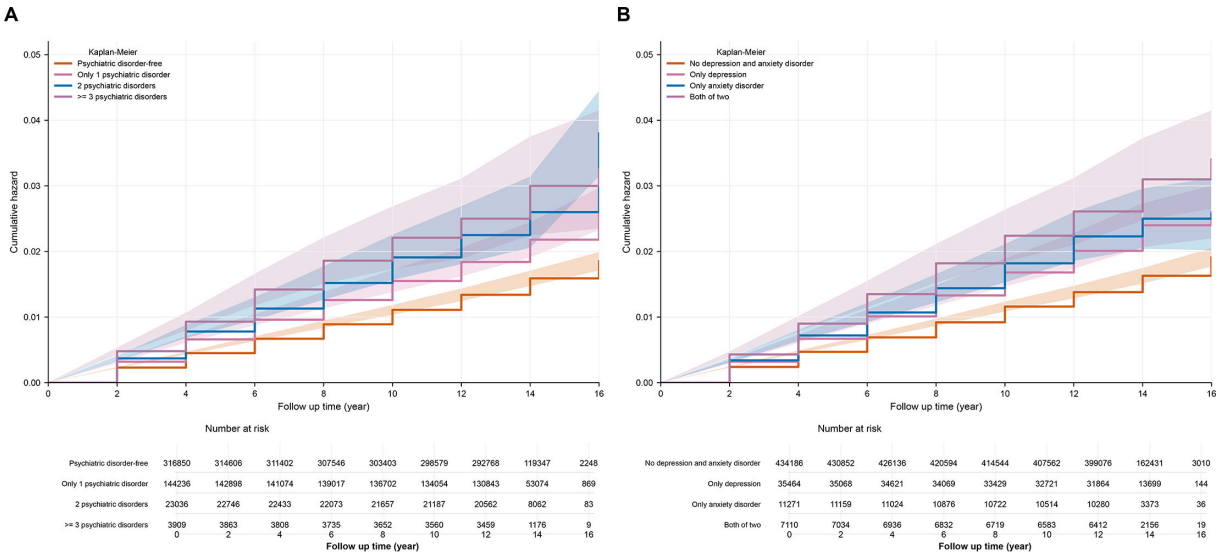

Fig. 2. Cumulative hazards of atopic dermatitis in participants with co-occurring psychiatric disorders at baseline in the UK Biobank populations. (A). Compared with individuals without psychiatric disorders, AD risks increased along with the number of co-occurring psychiatric disorder. (B). Joint association of depression and anxiety disorder on the cumulative hazards of atopic dermatitis.

markers are summarized in **Fig. 4**A and Table SXVIII. After applying FDR correction, the score was positively correlated with 17 metabolites and inversely associated with 28. In total, 60 markers were significantly linked to AD incidence at FDR<0.05 (Fig. 4B; Table SXIX). In mediation analysis, 9 individual metabolites demonstrated significant indirect effects between psychiatric burden and AD risk (PFDR-value <0.05). Among lipid-related metabolites, small LDL particles, fatty acids, amino acids, glycolysis-related compounds and ketone bodies were statistically significant mediators, although the estimated mediated proportions were small (Fig. 4C; Table SXX). To further explore the metabolic structure, all 168 markers were subjected to principal component analysis (PCA), yielding 7 components with eigenvalues >2 (TableXXI). Based on interpretability and variance explained, 6 principal components (PCs) were retained, accounting for 87.87% of the total variation in NMR-derived metabolites. These selected PCs and their primary characteristics are detailed in Table SXXII. Of these, only PC5-characterized by branched-chain amino acids (BCAAs) showed a statistically significant but quantitatively modest mediating effect on the psychiatric disorder–AD association, accounting for 1.04% of the indirect pathway (Table SXXIII).

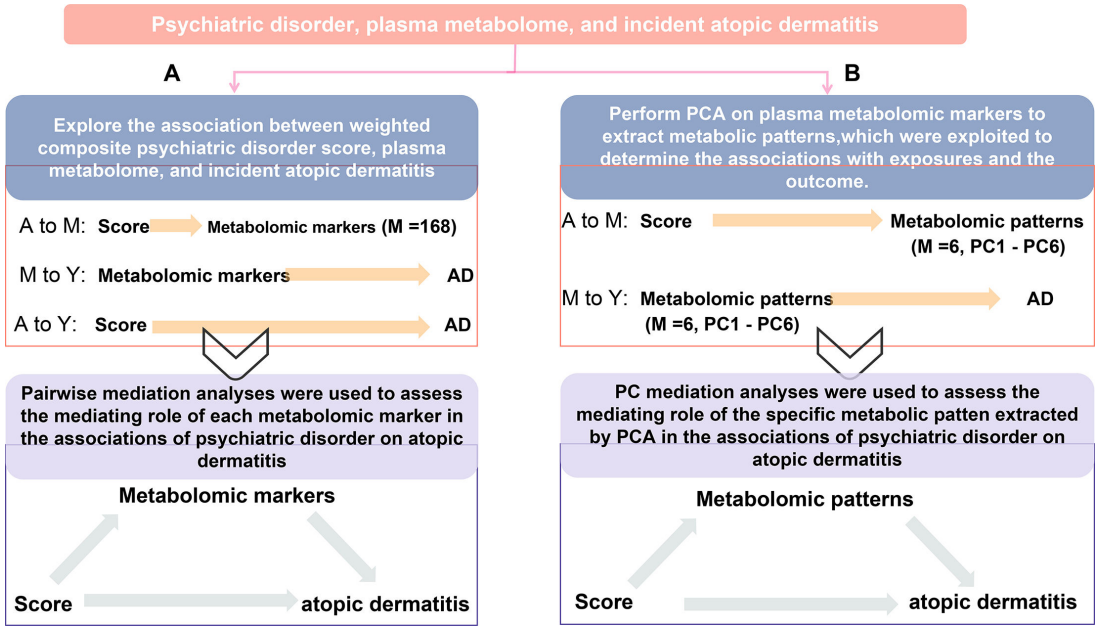

Fig. 3. Flow chart for the analytic strategy of psychiatric disorder, plasma metabolomic markers and atopic dermatitis: (A). analysed each plasma metabolomic marker separately and (B). clustered the plasma metabolomic markers into different metabolic patterns for further analysis.

Psychiatric disorder-related proteins and the risk of AD

Following FDR correction, we identified 173 to 1,797 significant associations between proteins and 7 psychiatric disorders, as well as the weighted composite score, involving a total of 2,211 distinct proteins (**Fig. 5**A; Table SXXIV). We next evaluated the proportion of proteins significantly linked to each disorder. Cardiometabolic-related proteins showed the highest proportions in ED (36.5%) and BD (28.2%), while inflammation-related proteins were more prominent in schizophrenia (32.9%) and anxiety disorder (27.9%) (Fig. 5B). In addition, we examined cross-disorder protein overlap and identified 4 proteins commonly associated with each psychiatric condition, including CCER2, FLT3, IFI30 and RARRES2 (Fig. 5C; Table SXXIV).

To gain further insight into biological pathways associated with AD in individuals with psychiatric conditions, we focused on proteins shared across all 7 psychiatric disorders. These shared proteins may provide clues to molecular pathways linking psychiatric burden with inflammatory skin disease, but they should not be interpreted as AD-specific markers. We identified 1,385 significant associations between 7 psychiatric disorder-related proteins and AD following FDR correction, involving a total of 377 unique proteins (Table SXXV). Proteome-wide MR supported genetically predicted associations between 4 proteins and AD, with consistent effect directions in IVW or Wald ratio analyses (Table SXXVI).

PPI network and biological function of validated AD related proteins

The PPI network among MR-prioritized proteins comprised 9 nodes and 14 edges for AD (PPI enrichment p=0.002, Fig. S6). Next, we examined the biological pathways involved in these AD-related proteins. GO enrichment revealed that AD-associated proteins were clustered in the positive regulation of immune system process and T cell activation (Fig. S7A-C and Table SXXVII). KEGG analysis further linked proteins set to the cell adhesion molecules and

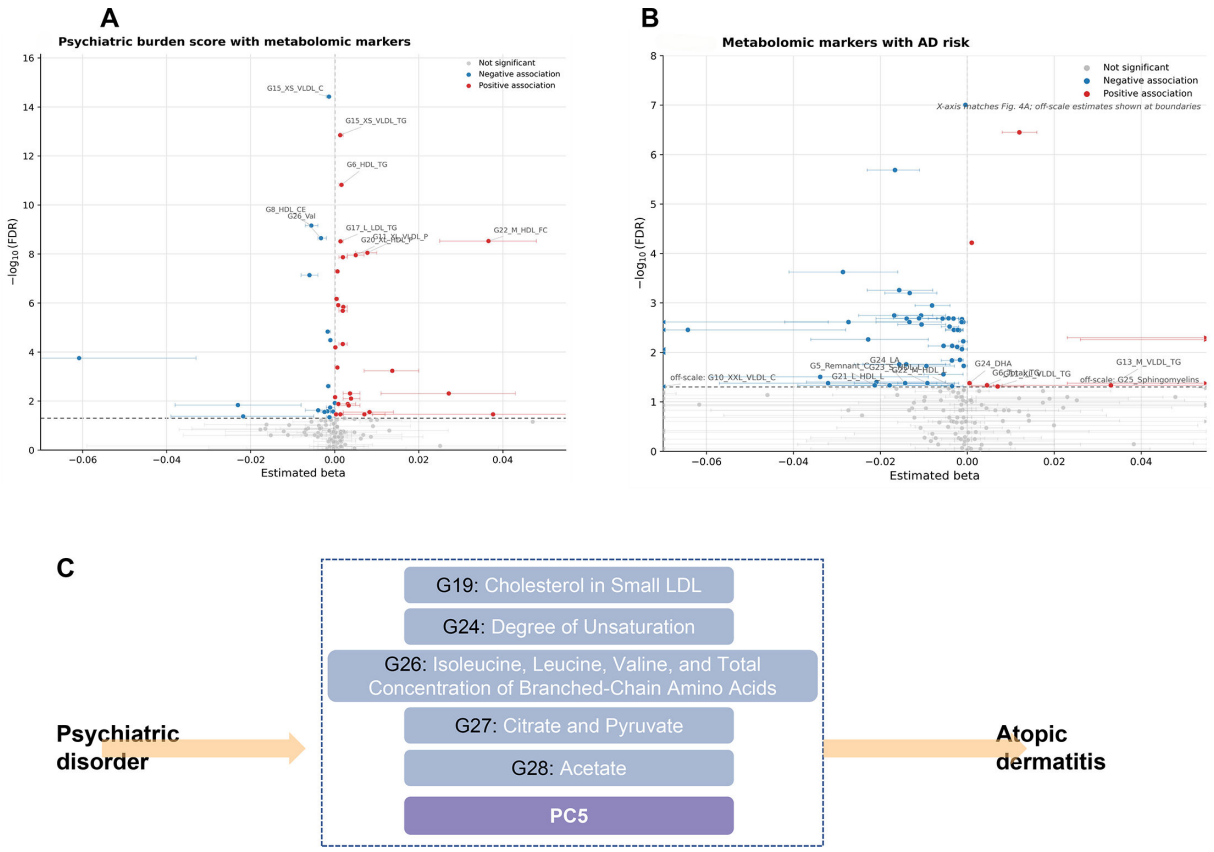

Fig. 4. Associations of weighted composite psychiatric disorder score with metabolomic markers, and metabolomic markers with incident atopic dermatitis. (A) Regression coefficients for associations between weighted composite psychiatric disorder score and metabolomic markers. (B) Regression coefficients for associations between metabolomic markers and incident atopic dermatitis. Horizontal error bars in panels A and B indicate 95% confidence intervals. In panel B, the estimated beta axis was truncated to improve visualization of significant findings; off-scale markers are denoted at the plot boundary. (C) Mediation analyses showed that 9 metabolic markers significantly and partially mediated the prospective association between composite psychiatric disorder scores and atopic dermatitis incidence while controlling for covariates and multiple comparisons. All regression models were adjusted for age, sex, Townsend deprivation index, ethnicity, BMI, smoking status, alcohol drinking status, triglycerides, vitamin D level, PM2.5 level, history of asthma and history of allergic rhinitis.

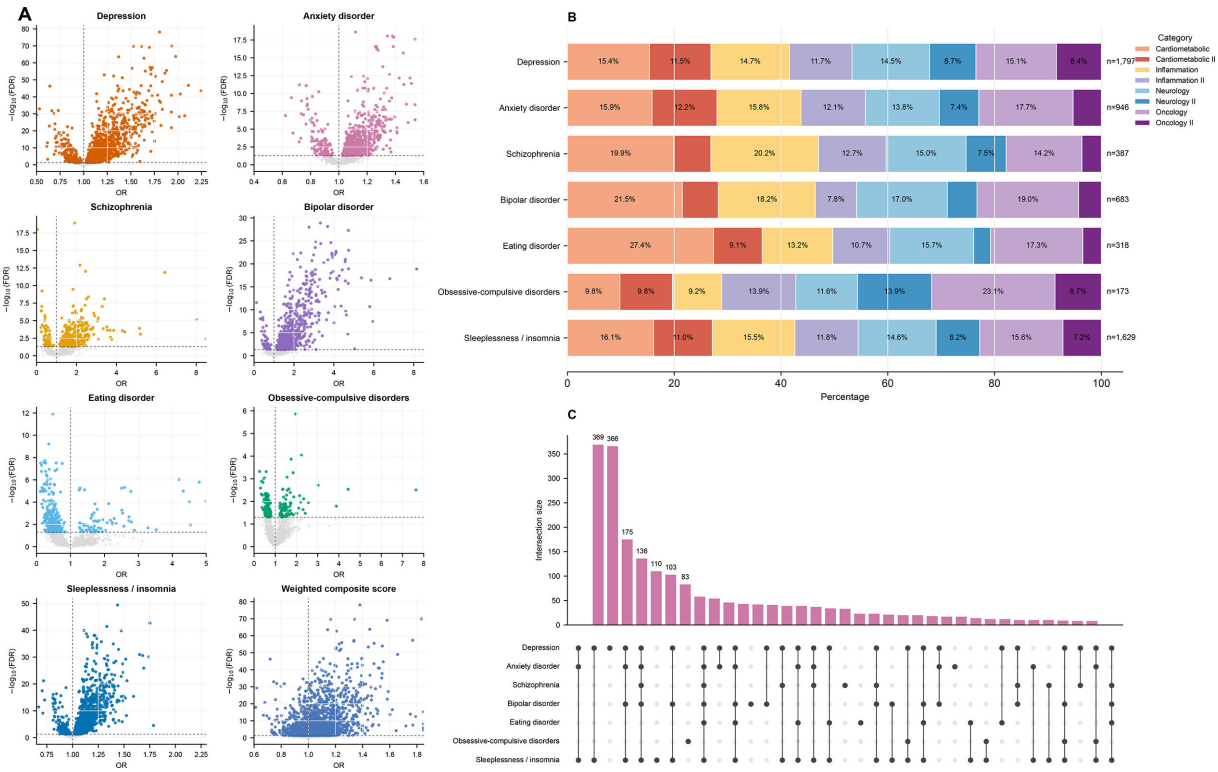

Fig. 5. Relationship between psychiatric disorder and plasma proteins. (A). Logistic regression model was used to examine the association between protein levels and psychiatric disorder-related trait. Analyses were adjusted for age, sex, Townsend deprivation index, ethnicity, BMI, smoking status, alcohol drinking status, triglycerides, vitamin D level, $PM_{2.5}$ level, history of asthma and allergic rhinitis. The *p*-values shown are 2-sided and adjusted for multiple comparisons. The coloured dots above the line indicate that the protein was significantly associated with the disease (FDR<0.05). The vertical line represents a dividing line with an odds ratio of 1, and the point to the right of the line indicates that the higher level of this protein increased the risk of disease. (B). Stacked bars show the proportion of each category of proteins significantly associated with psychiatric disorder-related trait, including 7 categories. (C). UpSet plot visualizes the enrichment overlap of 2,923 proteins across 7 psychiatric disorders. Set Size (left panel): Horizontal bars show the total number of proteins significantly enriched in each individual disorder. Disorders with longer bars (e.g., depression) have more associated proteins. Matrix Layout (bottom panel): Each column of dots corresponds to a particular combination of disorders. A filled dot marks inclusion of that disorder in the combination, while a hollow dot marks exclusion. The count above each bar equals the number of proteins common to that exact set of disorders.

antigen processing and presentation (Fig. S7D and Table SXXVII).

DISCUSSION

Leveraging a large-scale post-GWAS framework with 13-year prospective follow-up in the UK Biobank cohort, we found that individuals with psychiatric disorder-related traits had an increased incidence of AD/eczema. These associations remained directionally consistent across sensitivity and supplementary analyses. From the perspective of psychiatric multimorbidity, joint depression and anxiety disorder, a higher count of concurrent psychiatric diagnoses and an elevated weighted composite psychiatric disorder score were each associated with higher AD risk. Integrative metabolomic and proteomic profiling identified modest metabolic mediation and prioritized 4 inflammation- and adhesion-related proteins as candidate markers of AD risk in psychiatric populations, implicating overlapping inflammatory and metabolic dysregulation rather than a single AD-specific pathway.

Although numerous studies have examined the association between AD and psychiatric conditions (22, 28, 29), fewer have focused on whether psychiatric vulnerability precedes incident AD. Prior intergenerational studies suggest that maternal anxiety or depression during pregnancy may increase offspring AD risk (9, 30). Recent MR analyses have also evaluated the reverse direction, reporting genetic evidence that selected psychiatric liabilities, including bipolar disorder or major depressive disorder, may increase AD or eczema risk, although estimates vary by phenotype and are generally modest (8, 31, 32). Our study extends this work by evaluating multiple psychiatric disorder-related traits in a large prospective cohort and by examining cumulative psychiatric burden rather than isolated diagnoses alone. Based on clinically coded and questionnaire-derived psychiatric traits, our findings demonstrate that psychiatric burden is associated with increased AD risk, with HRs ranging from 1.19 to 2.20 in minimally adjusted analyses.

Multiple psychiatric disorders share common genetic underpinnings, leading to widespread multimorbidity across conditions (10, 33). However, population-based longitudinal evidence on psychiatric multimorbidity and incident AD remains limited, and observed associations may be influenced by genetic susceptibility, systemic inflammation, behaviour and healthcare contact. Our findings support a cumulative association: joint depression and anxiety disorder and an increasing number of psychiatric disorders were both linked to elevated AD risk. Given the disproportionate influence of psychiatric multimorbidity on AD incidence, categorical classification may underestimate disease burden and bias risk estimates. To address this, we developed a weighted composite score that reflects individual-level psychiatric health load (34). This score was nonlinearly associated with AD risk, which rose markedly when the score exceeded 0.7, suggesting a potential threshold for clinical risk stratification. These findings also support the value of future multivariate GWASs of AD-related psychiatric disorders, which may enhance the discovery of shared genetic architecture and downstream biological pathways relevant to psychiatric-dermatologic multimorbidity.

Stratified analyses also revealed significant interactions between vitamin D levels and psychiatric burden on AD risk. Higher vitamin D levels were associated with attenuation of risk, but this finding should be interpreted as effect modification rather than evidence that vitamin D supplementation prevents AD. Seasonal variation, supplementation behaviour, outdoor activity, diet and reverse causation may influence serum vitamin D levels, and prior MR evidence has even suggested that AD may lead to higher vitamin D levels rather than the reverse (35). Mechanistically, activated vitamin D3 metabolites may protect against DNA damage and oxidative stress, promote keratinocyte differentiation, exert anti-inflammatory and anti-fibrotic effects, and upregulate barrier proteins such as filaggrin and keratins (36, 37).

Our study offers preliminary mechanistic insight into the link between psychiatric disorders and AD. While the lipidomic characteristics involved in this association remain poorly defined, we employed 2 complementary approaches to investigate the potential mediating role of 168 plasma metabolomic markers in the connection between psychiatric conditions and AD. We first analysed each metabolite individually and found that amino acids, small LDL particles, glycolysis-related metabolites and fatty acids may play more prominent roles. Next, we clustered metabolites into distinct metabolic patterns and identified a BCAA-dominant component as a statistically detectable, but quantitatively modest, mediator of the psychiatric burden-AD association. Elevated BCAAs and glycolysis-related metabolites have been linked to systemic insulin resistance and metabolic syndrome, both of which are associated with low-grade chronic inflammation (38, 39). Metabolic dysregulation is common in individuals with psychiatric disorders, and this combined metabolic-inflammatory stress may contribute to AD susceptibility (12, 40). However, the mediated proportion for the BCAA-related component was only 1.04%, and the individual metabolite mediation estimates were also small. These findings should therefore be considered exploratory signals rather than evidence that the metabolic pathway is the dominant mechanism. Additional mechanisms, including immune cell activation, sleep disturbance, scratching behaviour, autonomic imbalance, and neuroendocrine dysregulation, are likely involved (7, 40).

Furthermore, our findings highlight the value of integrating targeted plasma proteomics with large-scale population cohorts to explore the complex mechanisms underlying AD development in individuals with psychiatric disorders. We identified 4 psychiatric disorder-associated proteins involved in immune-inflammatory responses, cell adhesion and antigen processing and presentation. TNFRSF14 and HLA-DRA are inflammation-related proteins that may contribute to AD-related pathways by promoting immune activation, keratinocyte stress responses and Th2-skewed inflammation (41–43). MMP12, a macrophage elastase, may aggravate epidermal barrier damage by promoting extracellular matrix degradation and disturbing stratum corneum remodeling (44–46). VCAM1 is a vascular adhesion molecule linked to systemic inflammation and metabolic state, and it has been observed in inflammatory skin lesions (47, 48). Importantly, these proteins are not specific to AD and may reflect a broader inflammatory burden in psychiatric populations. Their value in the present study is therefore hypothesis-generating: they may help prioritize shared inflammatory and barrier-related pathways for future mechanistic and clinical validation, rather than serving as definitive AD-specific biomarkers.

This study possesses several key strengths. First, it utilizes a large-scale prospective cohort of over 500,000 participants and comprehensively evaluates the associations between individual psychiatric disorder-related traits, psychiatric multimorbidity and a weighted composite psychiatric score with long-term AD risk over extended follow-up. Given the increased risk of AD among individuals with psychiatric burden, early identification of psychiatric symptoms may assist dermatologists and other clinicians in recognizing vulnerable individuals who may benefit from closer skin monitoring and integrated care. Second, we investigated potential effect modification by PRS and environmental/biological factors, including age and serum vitamin D

levels. Higher vitamin D levels appeared to attenuate the adverse association between psychiatric burden and AD risk, although causal interpretation remains limited. Third, we linked weighted psychiatric burden with plasma metabolomic profiles in relation to AD risk. We identified metabolic features with modest mediating effects and accounted for complex interdependencies among biomarkers by classifying them into metabolic patterns. The consistency across 2 analytic approaches strengthens internal coherence while preserving the exploratory interpretation.

Finally, given the limited proteomic research on AD within psychiatric populations, we addressed this gap by applying one of the most comprehensive proteomic platforms to date. Longitudinal profiling of psychiatric disorder-associated proteins enabled novel insights into the proteomic pathways potentially contributing to AD susceptibility.

We acknowledge several limitations. First, AD/eczema ascertainment relied on linked health records and self-reported eczema, which may introduce misclassification, particularly for adult-onset AD vs chronic eczema phenotypes. We used ICD-10 L20 and eczema-related self-report terms and did not use contact dermatitis codes, but UK Biobank cannot fully distinguish adult-onset AD from all other eczematous disorders. Second, psychiatric disorders – particularly depression and anxiety disorder – may exhibit subclinical or asymptomatic presentations, potentially leading to underestimation of their true epidemiological burden. Neuroticism and insomnia are psychiatric-related traits rather than clinical diagnoses, and their inclusion was intended to capture broader psychiatric vulnerability; results for clinician-coded disorders should therefore be interpreted separately from trait-based analyses. Third, residual confounding remains possible. In particular, patients with psychiatric disorders may have more frequent healthcare contact, increasing the opportunity for AD diagnosis. We attempted to reduce bias through multivariable adjustment, delayed-entry sensitivity analyses excluding AD diagnosed within the first 3 years, multiple imputation and propensity score matching, but direct adjustment for consultation frequency was not available. Fourth, vitamin D analyses were observational and may be affected by season, supplementation behaviour, outdoor activity, diet and reverse causation; they should not be interpreted as evidence that supplementation prevents AD. Fifth, metabolomic markers were measured from nonfasting plasma samples, and the mediation effects were statistically significant but biologically modest. Sixth, Olink technology offers broad proteomic coverage but remains restricted to predefined panels and does not provide unbiased detection of all proteins or post-translational modifications. The prioritized proteins are not AD-specific and may reflect general inflammatory burden. Finally, although we controlled the false discovery rate across high-dimensional analyses, the multiple testing burden was substantial, and the predominantly White European ancestry of participants may limit generalizability to more diverse populations.

In summary, psychiatric disorder-related traits were associated with increased incident AD/eczema risk, particularly among individuals with ED and OCD in minimally adjusted analyses and among those with co-occurring psychiatric conditions or higher weighted psychiatric burden. Higher serum vitamin D levels modified these associations, but the finding should be viewed as hypothesis-generating rather than as proof of a preventive supplementation effect. Metabolomic analyses identified BCAAs, fatty acids and glycolysis-related metabolites as exploratory and quantitatively modest mediators. Proteomic analyses prioritized HLA-DRA, MMP12, TNFRSF14, and VCAM1 as non-specific inflammatory and adhesion-related proteins that may help guide future studies of shared psychiatric–dermatologic pathways.

ACKNOWLEDGEMENTS

The authors would like to thank all the staff and study participants involved in this study or contributed to the UK Biobank.

Protocol registration number: Not applicable.

Funding sources: This work was supported by grants from the Hunan Provincial Health Commission Health Research Key Poject (No. 20256627), the National Science Foundation of China (No. 82273506, No. 82574011), the science and technology innovation Program of Hunan Province (No. 2024RC3064), the Wisdom Accumulation and Talent Cultivation Project of the Third Xiangya Hospital of Central South University (No. YX202214), Tibet Autonomous Region Science and Technology Project (No. XZ202402ZY0002), and Hunan Provincial Natural Science Foundation of China (2026JJ80021). The funder had no role in study design, data collection, analysis, reporting, or the decision to submit for publication.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics committee: This study was conducted using the UK Biobank Resource and was ethically approved by the NHS North West Multi-centre Research Ethics Committee (reference: 11/NW/0382). All participants provided written informed consent.

Disclosure: Nothing to disclose.

The authors have no conflicts of interest to declare.

REFERENCES

1. Collaborators GAMD. The epidemiology and burden of ten mental disorders in countries of the Association of Southeast Asian Nations (ASEAN), 1990-2021: findings from the Global Burden of Disease Study 2021. Lancet Public Health 2025; 10: e480–e491.
2. Cosci F, Fava GA. When anxiety and depression coexist: the role of differential diagnosis using clinimetric criteria.

Psychother Psychosom 2021; 90: 308–317. https://doi.org/10.1159/000517518
3. Xu X, Li S, Chen Y, Deng X, Li J, Xiong D, et al. Association between allergic diseases and mental health conditions: an umbrella review. J Allergy Clin Immunol 2025; 155: 701–713. https://doi.org/10.1016/j.jaci.2024.10.030
4. Biazus Soares G, Mahmoud O, Yosipovitch G, Mochizuki H. The mind-skin connection: a narrative review exploring the link between inflammatory skin diseases and psychological stress. J Eur Acad Dermatol Venereol 2024; 38: 821–834. https://doi.org/10.1111/jdv.19813
5. Slominski AT, Zmijewski MA, Zbytek B, Tobin DJ, Theoharides TC, Rivier J. Key role of CRF in the skin stress response system. Endocr Rev 2013; 34: 827–884. https://doi.org/10.1210/er.2012-1092
6. Slominski RM, Raman C, Jetten AM, Slominski AT. Neuro-immuno-endocrinology of the skin: how environment regulates body homeostasis. Nat Rev Endocrinol 2025; 21: 495–509. https://doi.org/10.1038/s41574-025-01107-x
7. Zhang H, Wang M, Zhao X, Wang Y, Chen X, Su J. Role of stress in skin diseases: a neuroendocrine-immune interaction view. Brain Behav Immun 2024; 116: 286–302. https://doi.org/10.1016/j.bbi.2023.12.005
8. Wu Z, Wu C, Chen X, Qian Q, Yao Z. Bidirectional relationship between atopic dermatitis and psychiatric comorbidities in individuals of European ancestry: a Mendelian randomization study. Acta Derm Venereol 2025; 105: adv43133. https://doi.org/10.2340/actadv.v105.43133
9. Wu JY, Wang YS, Hao YH, Duan CC, Xu Y, Zhou FY, et al. Antenatal depressive and anxiety symptoms in early pregnancy and offspring allergic diseases during toddlerhood. World J Pediatr 2025; 21: 478–488. https://doi.org/10.1007/s12519-025-00911-9
10. Romero C, Werme J, Jansen PR, Gelernter J, Stein MB, Levey D, et al. Exploring the genetic overlap between twelve psychiatric disorders. Nat Genet 2022; 54: 1795–1802. https://doi.org/10.1038/s41588-022-01245-2
11. Zeng Y, Chourpiliadis C, Hammar N, Seitz C, Valdimarsdóttir UA, Fang F, et al. Inflammatory biomarkers and risk of psychiatric disorders. JAMA Psychiatry 2024; 81: 1118–1129. https://doi.org/10.1001/jamapsychiatry.2024.2185
12. You H, Liang Y. Atopic dermatitis: the relationship between immune mediators and skin lipid barrier. Clin Rev Allergy Immunol 2025; 68: 49. https://doi.org/10.1007/s12016-025-09057-y
13. Guo X, Feng Y, Ji X, Jia N, Maimaiti A, Lai J, et al. Shared genetic architecture and bidirectional clinical risks within the psycho-metabolic nexus. EBioMedicine 2025; 111: 105530. https://doi.org/10.1016/j.ebiom.2024.105530
14. Ning Z, Pawitan Y, Shen X. High-definition likelihood inference of genetic correlations across human complex traits. Nat Genet 2020; 52: 859–864. https://doi.org/10.1038/s41588-020-0653-y
15. Zhu Z, Zheng Z, Zhang F, Wu Y, Trzaskowski M, Maier R, et al. Causal associations between risk factors and common diseases inferred from GWAS summary data. Nat Commun 2018; 9: 224. https://doi.org/10.1038/s41467-017-02317-2
16. Clarke L, Zheng-Bradley X, Smith R, Kulesha E, Xiao C, Toneva I, et al. The 1000 Genomes Project: data management and community access. Nat Methods 2012; 9: 459–462. https://doi.org/10.1038/nmeth.1974
17. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015; 12: e1001779. https://doi.org/10.1371/journal.pmed.1001779
18. Deng P, Tang S, Zeng J, Lu J. Inflammatory and genetic mechanisms mediate the association between frailty and incident atopic dermatitis in middle-aged and elderly adults. Mech Ageing Dev 2026; 230: 112148. https://doi.org/10.1016/j.mad.2025.112148
19. Johns S, Lea-Carnall C, Shryane N, Maharani A. Depression, brain structure and socioeconomic status: A UK Biobank study. J Affect Disord 2025; 368: 295–303. https://doi.org/10.1016/j.jad.2024.09.102
20. Singla DR, Silver RK, Vigod SN, Schoueri-Mychasiw N, Kim JJ, La Porte LM, et al. Task-sharing and telemedicine delivery of psychotherapy to treat perinatal depression: a pragmatic, noninferiority randomized trial. Nat Med 2025; 31: 1214–1224. https://doi.org/10.1038/s41591-024-03482-w
21. Dutt RK, Hannon K, Easley TO, Griffis JC, Zhang W, Bijsterbosch JD. Mental health in the UK Biobank: A roadmap to self-report measures and neuroimaging correlates. Hum Brain Mapp 2022; 43: 816–832. https://doi.org/10.1002/hbm.25690
22. Wan J, Wang S, Shin DB, Syed MN, Abuabara K, Lemeshow AR, et al. Neuropsychiatric disorders in adults with atopic dermatitis: A population-based cohort study. J Eur Acad Dermatol Venereol 2024; 38: 543–548. https://doi.org/10.1111/jdv.19518
23. Julkunen H, Cichońska A, Tiainen M, Koskela H, Nybo K, Mäkelä V, et al. Atlas of plasma NMR biomarkers for health and disease in 118,461 individuals from the UK Biobank. Nat Commun 2023; 14: 604. https://doi.org/10.1038/s41467-023-36231-7
24. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med 2010; 29: 1037–1057. https://doi.org/10.1002/sim.3841
25. Nguyen CD, Carlin JB, Lee KJ. Practical strategies for handling breakdown of multiple imputation procedures. Emerg Themes Epidemiol 2021; 18: 5. https://doi.org/10.1186/s12982-021-00095-3
26. Eldjarn GH, Ferkingstad E, Lund SH, Helgason H, Magnusson OT, Gunnarsdottir K, et al. Large-scale plasma proteomics comparisons through genetics and disease associations. Nature 2023; 622: 348–358. https://doi.org/10.1038/s41586-023-06563-x
27. Zhao J, Stewart ID, Baird D, Mason D, Wright J, Zheng J, et al. Causal effects of maternal circulating amino acids on offspring birthweight: a Mendelian randomisation study. EBioMedicine 2023; 88: 104441. https://doi.org/10.1016/j.ebiom.2023.104441
28. Minhas S, Chandan JS, Knibb R, Diwakar L, Adderley N. Association between atopic disorders and mental ill health: a UK-based retrospective cohort study. BMJ Open 2025; 15: e089181. https://doi.org/10.1136/bmjopen-2024-089181
29. Mann C, Wollenberg A, Ständer S, Staubach P, Thaçi D, Zirpel H. Risk of developing sleep disorders and psychologic comorbidity in children with inflammatory skin diseases—A population-based study. J Am Acad Dermatol 2025; 92: 1261–1268. https://doi.org/10.1016/j.jaad.2025.02.001
30. Zhou J, Wu P, Cai W, Lu J, Guo Y, Teng Y, et al. The impact of maternal anxiety during pregnancy on children's eczema and allergic rhinitis: The Ma'anshan birth cohort study. J Psychosom Res 2024; 181: 111621. https://doi.org/10.1016/j.jpsychores.2024.111621
31. Mo N, Yang Y, Wang W, Zhou P, Liu F, Zhang Y, et al. Causal associations between psoriasis, eczema, urticaria, and mental illness: a bidirectional Mendelian randomization study of the European population. Medicine 2024; 103: e38586. https://doi.org/10.1097/MD.0000000000038586
32. Antonatos C, Pontikas A, Akritidis A, Mitsoudi D, Georgiou S, Stratigos AJ, et al. A genome-wide pleiotropy study between atopic dermatitis and neuropsychiatric disorders. Hum Genomics 2025; 19: 86. https://doi.org/10.1186/s40246-025-00801-1
33. Momen NC, Plana-Ripoll O, Agerbo E, Benros ME, Børglum AD, Christensen MK, et al. Association between mental disorders and subsequent medical conditions. N Engl J Med 2020; 382: 1721–1731. https://doi.org/10.1056/NEJMoa1915784
34. Xiong Y, Xia Y, Zhang X, Jiang B, Zhang Z, Xie C, et al. Joint exposure to multiple air pollutants, genetic risk and incident psoriasis: a large-scale prospective cohort study. Br J Dermatol 2025; 192: 420–429. https://doi.org/10.1093/bjd/ljae391
35. Drodge DR, Budu-Aggrey A, Paternoster L. Causal analysis shows evidence of atopic dermatitis leading to an increase in

vitamin D levels. J Invest Dermatol 2021; 141: 1339–1341. https://doi.org/10.1016/j.jid.2020.09.013
36. Chu DK, Koplin JJ, Ahmed T, Islam N, Chang CL, Lowe AJ. How to prevent atopic dermatitis (eczema) in 2024: theory and evidence. J Allergy Clin Immunol Pract 2024; 12: 1695–1704. https://doi.org/10.1016/j.jaip.2024.04.048
37. Slominski AT, Kim TK, Janjetovic Z, Slominski RM, Li W, Jetten AM, et al. Biological effects of CYP11A1-derived vitamin D and lumisterol metabolites in the skin. J Invest Dermatol 2024; 144: 2145–2161. https://doi.org/10.1016/j.jid.2024.04.022
38. Morrow MR, Batchuluun B, Wu J, Ahmadi E, Leroux JM, Mohammadi-Shemirani P, et al. Inhibition of ATP-citrate lyase improves NASH, liver fibrosis, and dyslipidemia. Cell Metab 2022; 34: 919–936. https://doi.org/10.1016/j.cmet.2022.05.004
39. Yu D, Richardson NE, Green CL, Spicer AB, Murphy ME, Flores V, et al. The adverse metabolic effects of branched-chain amino acids are mediated by isoleucine and valine. Cell Metab 2021; 33: 905–922. https://doi.org/10.1016/j.cmet.2021.03.025
40. Cameron S, Donnelly A, Broderick C, Arichi T, Bartsch U, Dazzan P, et al. Mind and skin: exploring the links between inflammation, sleep disturbance and neurocognitive function in patients with atopic dermatitis. Allergy 2024; 79: 26–36. https://doi.org/10.1111/all.15818
41. Dworzak MN, Fröschl G, Printz D, Fleischer C, Pötschger U, Fritsch G, et al. Skin-associated lymphocytes in the peripheral blood of patients with atopic dermatitis: signs of subset expansion and stimulation. J Allergy Clin Immunol 1999; 103: 901–906. https://doi.org/10.1016/s0091-6749(99)70436-7
42. Herro R, Antunes RDS, Aguilera AR, Tamada K, Croft M. The tumor necrosis factor superfamily molecule LIGHT promotes keratinocyte activity and skin fibrosis. J Invest Dermatol 2015; 135: 2109–2118. https://doi.org/10.1038/jid.2015.110
43. Hyun YS, Jo HA, Lee YH, Kim SM, Baek IC, Sohn HJ, et al. Comprehensive analysis of CD4+ T cell responses to CMV pp65 antigen restricted by single HLA-DR, -DQ, and -DP allotype within an individual. Front Immunol 2020; 11: 602014. https://doi.org/10.3389/fimmu.2020.602014
44. Cook-Mills JM, Emmerson LN. Epithelial barrier regulation, antigen sampling, and food allergy. J Allergy Clin Immunol 2022; 150: 493–502. https://doi.org/10.1016/j.jaci.2022.06.018
45. Dorjay Tamang JS, Banerjee S, Baidya SK, Das S, Ghosh B, Jha T, et al. An overview of matrix metalloproteinase-12 in multiple disease conditions, potential selective inhibitors, and drug designing strategies. Eur J Med Chem 2025; 283: 117154. https://doi.org/10.1016/j.ejmech.2024.117154
46. Pereira da Fonseca A, Traidl S, Gutzmer R, Schaper-Gerhardt K, Werfel T, Mommert S. Histamine and Th2 cytokines independently and synergistically upregulate MMP12 expression in human M2 macrophages. Front Immunol 2024; 15: 1429009. https://doi.org/10.3389/fimmu.2024.1429009
47. Machoń NJ, Zdanowska N, Klimek-Trojan P, Owczarczyk-Saczonek A. Vascular cell adhesion molecule 1 and E-selectin as potential cardiovascular risk biomarkers in psoriasis. Int J Mol Sci 2025; 26: 26. https://doi.org/10.3390/ijms26020792
48. Marinović Kulišić S, Takahashi M, Himelreich Perić M, Mužić Radović V, Jurakić Tončić R. Immunohistochemical analysis of adhesion molecules E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 in inflammatory lesions of atopic dermatitis. Life 2023; 13: 13. https://doi.org/10.3390/life13040933