Brain, Behavior, & Immunity - Health 48 (2025) 101088

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Anxiety and nonpsychotic mental disorders in acute urticaria

Eli Magen [a,b,*], Eugene Merzon [a,c], Shai Ashkenazi [c], Abraham Weizman [d,e], Iris Manor [d,f], Israel Magen [b], Avi Yakov [b], Akim Geishin [a], Ilan Green [a,g], Avivit Golan-Cohen [a,g], Shlomo Vinker [a,g], Ariel Israel [a,g]

[a] Leumit Health Services, Tel Aviv-Yafo, 6473817, Israel
[b] Department of Medicine A, Assuta Ashdod University Hospital, Faculty of Health Sciences, Ben-Gurion University, Beer-Sheba, 8410501, Israel
[c] Adelson School of Medicine, Ariel University, Ariel, 4077625, Israel
[d] Department of Psychiatry, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[e] ADHD Unit, Geha Mental Health Center, Petah-Tikva, Israel
[f] Laboratory of Molecular and Biological Psychiatry, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[g] Department of Epidemiology and Preventive Medicine, School of Public Health, Faculty of Medical & Health Sciences, Tel Aviv University, Ramat Aviv, Tel Aviv, Israel

ARTICLE INFO

Keywords:
Acute
Urticaria
Mental
Personality
Anxiety
Disorders

ABSTRACT

Background: Acute urticaria (AU) is characterized by the sudden onset of wheals, angioedema, or both, with symptoms resolving within 6 weeks. While the association between chronic urticaria and mental health disorders is well-documented, the relationship between AU and psychological conditions remains understudied.
Objective: To investigate the association between AU and anxiety and personality disorders, and to explore the potential psychoneuroimmunological mechanisms underlying these relationships.
Methods: We conducted a population-based case-control study using the comprehensive electronic health records database of Leumit Health Services in Israel. The study included 72,805 AU patients and 291,220 matched controls. Subjects were matched for gender, age, ethnicity, year of first documented visit, and socioeconomic status. We analyzed the 20-year prevalence of anxiety disorders, personality disorders, and various nonpsychotic mental disorders in both groups.
Results: AU patients demonstrated significantly higher prevalence of anxiety disorders (7.02 % vs. 5.22 %, $p < 0.001$, OR = 1.37 [95 % CI: 1.33–1.42]), personality disorders (0.23 % vs. 0.134 %, $p < 0.001$, OR = 1.73 [95 % CI: 1.44–2.08]), and adjustment disorders (0.91 % vs. 0.67 %, $p < 0.001$, OR = 1.37 [95 % CI: 1.25–1.50]) compared to controls. Particularly notable were the associations with personality disorders characterized by persistent mood disturbances (OR = 1.91 [95 % CI: 1.53–2.38]) and adjustment disorders with depressive features (OR = 1.49 [95 % CI: 1.27–1.74]).
Conclusions: Our findings reveal significant associations between AU and various mental health disorders, particularly anxiety and personality disorders. These associations suggest a complex bidirectional relationship mediated through psychoneuroimmunological pathways involving the HPA axis, mast cell activation, and inflammatory cytokines. We recommend implementing specific screening tools (HADS, GAD-7) and a stepped-care approach for integrated dermatological and psychological management of AU patients.

1. Introduction

Epidemiological studies have established that urticarial diseases represent a significant global health issue, with the lifelong prevalence of acute urticaria (AU) at 13.9 % and chronic spontaneous urticaria (CSU) at 1.8 % (Lee et al., 2017; Liu et al., 2023). According to current clinical guidelines, urticaria is classified into acute and chronic forms based on symptom duration: AU resolves within 6 weeks, while chronic urticaria (CU) persists beyond 6 weeks (Zuberbier et al., 2022).

Clinical investigations have demonstrated that the pathophysiological mechanisms underlying these forms differ significantly. AU

* Corresponding author. Department of Medicine A, Assuta Ashdod University Hospital, Faculty of Health Sciences, Ben-Gurion University, Beer-Sheba, 8410501, Israel.
E-mail addresses: allergologycom@gmail.com (E. Magen), emerzon@leumit.co.il (E. Merzon), shaias@ariel.ac.il (S. Ashkenazi), weizmana@gmail.com (A. Weizman), dr.iris.manor@gmail.com (I. Manor), israelmagen@gmail.com (I. Magen), aviyakov@gmail.com (A. Yakov), ageishin@leumit.co.il (A. Geishin), igreen@leumit.co.il (I. Green), agolanchoen@leumit.co.il (A. Golan-Cohen), svinker@leumit.co.il (S. Vinker), aisrael@leumit.co.il (A. Israel).

https://doi.org/10.1016/j.bbih.2025.101088
Received 26 October 2024; Received in revised form 20 July 2025; Accepted 9 August 2025
Available online 10 August 2025

Glossary

1. **Acute Urticaria (AU)** Sudden hives, often with itching and swelling, resolving within six weeks
2. **Chronic Spontaneous Urticaria (CSU)** Recurring hives for over six weeks, without a known trigger
3. **Histamine Release** A chemical reaction causing itching, swelling, and allergic symptoms
4. **Psychoneuroimmunology** Study of interactions between the nervous, immune, and psychological systems
5. **Neurotic Depression** Mood instability and anxiety, often triggered by stress
6. **Somatoform Disorders** Physical symptoms without a medical cause, such as hypochondriasis
7. **Adjustment Disorders** Emotional or behavioral reactions to identifiable stressors
8. **Personality Disorders** Persistent behavior patterns affecting relationships and functioning
9. **Cluster A Personality Disorders** Eccentric behaviors, including paranoid traits
10. **Cluster B Personality Disorders** Dramatic behaviors, such as borderline traits
11. **Cluster C Personality Disorders** Anxious behaviors, like avoidant traits
12. **HPA Axis** System regulating the body's stress response
13. **Cytokines** Proteins involved in immune responses and inflammation
14. **Odds Ratio (OR)** A measure of the association between two variables
15. **Proinflammatory Cytokines** Inflammatory proteins linked to immune responses and mood disorders
16. **Electronic Health Records (EHRs)** Digital medical records for clinical use
17. **Bruxism** Teeth grinding, often due to stress or anxiety
18. **PTSD** Trauma-related disorder with intrusive memories and hyperarousal
19. **Angioedema** Deep skin swelling, often linked to allergic reactions

typically presents as a transient immunological response to identifiable triggers, involving mast cell activation through IgE-mediated and non-IgE-mediated pathways (Ensina et al., 2022). In contrast, research has shown that CSU presents a more complex picture, with 80–90 % of cases being idiopathic and 30–50 % characterized by autoimmune mechanisms with functional autoantibodies against the IgE receptor or IgE itself (Kolkhir et al., 2022). Clinical follow-up studies have documented that AU typically follows a self-limited course, while CU may persist for years, with approximately 20 % of patients experiencing symptoms beyond one year despite treatment (Fricke et al., 2020).

Epidemiological studies have consistently shown that anxiety and personality disorders are among the most prevalent mental health conditions, significantly impacting quality of life (Yang et al., 2021; Fariba et al., 2023). Clinical research has documented that the association between CSU and mental health issues is well-established, while literature on AU remains sparse (Ben-Shoshan et al., 2013).

These epidemiological associations suggest a complex interplay between urticarial diseases and psychological conditions. The observed comorbidity patterns may indicate that AU presents different psychological challenges compared to its chronic counterpart (Ensina et al., 2022).

The field of psychoneuroimmunology proposes a framework for understanding the interaction between the nervous system, psychological processes, and the immune system (Honeyman, 2016). According to this framework, anxiety disorders may influence immune responses, potentially exacerbating urticarial symptoms (Tomaszewska et al., 2023).

Current mechanistic models suggest that the relationship between anxiety/personality disorders and urticaria involves complex neuro-immuno-psychological interactions mediated through the hypothalamic-pituitary-adrenal axis, sympathetic-adrenomedullary system, and brain-gut-skin axis (Tomaszewska et al., 2023).

Laboratory studies suggest that corticotropin-releasing hormone may act directly on mast cells, which express functional CRH receptors, providing a potential link between psychological states and urticaria pathophysiology (Theoharides, 2020). Experimental evidence indicates that mast cells may serve as translators of stress signals, undergoing degranulation when activated by stress-related neuropeptides (Giménez-Arnau et al., 2021).

The concept of a bidirectional relationship between psychological factors and urticaria has been proposed to create a vicious cycle: anxiety might trigger urticarial symptoms, while urticaria symptoms could further increase anxiety (Honeyman et al., 2016).

Given the established prevalence data and hypothesized mechanisms, this study focuses on the relationship between AU, anxiety, and personality disorders due to their high prevalence and significant clinical impact. Understanding these complex neuro-immuno-psychological interactions provides a scientific basis for investigating the observed clinical association between anxiety/personality disorders and urticaria, highlighting the importance of addressing psychological factors in the comprehensive management of urticarial diseases.

2. Materials and methods

We conducted a population-based case-control study utilizing the extensive resources of Leumit Health Services (LHS), a prominent healthcare provider in Israel. While LHS had an active membership of 724,129 individuals at the conclusion of the study period (December 31, 2022), our analysis included data from over 1,000,000 individuals who were insured by LHS at any point during or prior to the study timeframe (January 1, 2002, to December 31, 2022). This comprehensive approach allowed us to maximize case identification and statistical power while maintaining the integrity of the case-control matching process.

LHS is one of Israel's four health maintenance organizations, providing comprehensive healthcare services to approximately 8 % of Israel's population. As part of Israel's universal healthcare system, LHS maintains a centralized electronic health record (EHR) database that includes comprehensive documentation of all medical encounters, diagnoses, treatments, and referrals.

In the LHS system, mental health diagnoses including anxiety disorders, adjustment disorders, and personality disorders are made by licensed healthcare professionals following standardized diagnostic protocols. Primary care physicians typically conduct initial mental health screenings using semi-structured clinical interviews based on DSM-IV/ICD-9 criteria, while formal diagnoses of personality disorders are exclusively made by board-certified psychiatrists following comprehensive psychiatric evaluations.

Socioeconomic status was derived from the Israeli Central Bureau of Statistics' national index, which categorizes residential areas into deciles based on income, education, employment, and housing conditions; for analysis, we grouped these into low (1–4), medium (5–7), and high (8–10) categories. Ethnicity was categorized in the Leumit Health Services database based on country of birth and self-reported ethnicity into three major groups: Jewish (Ashkenazi and Sephardic), Arab, and Other/Unknown.

It is important to note that our study utilized diagnostic codes from the EHR rather than standardized questionnaires. Mental health diagnoses in the LHS system are based on clinical evaluations rather than specific psychometric instruments. This approach reflects real-world clinical practice but may result in some variability in diagnostic

precision. To mitigate this limitation, we included only diagnoses that were documented by healthcare professionals and recorded with the appropriate diagnostic codes in the EHR system.

The LHS ethics committee approved this study (reference: LEU 05–23). Due to the study's retrospective nature and anonymized data, informed consent was waived.

2.1. Study groups

- AU group: The AU group was identified retrospectively using LHS's electronic health records system. Diagnoses of urticarial diseases were recorded by licensed healthcare professionals, including primary care physicians, dermatologists, and allergists, while psychiatrists diagnosed mental disorders. These diagnoses relied on clinical evaluations, patient histories, and standardized criteria.
- Control group: Controls were randomly selected from individuals without AU diagnoses using an algorithm matching participants on gender, age, ethnic group, socioeconomic status and the year of their first documented visit, with a 4:1 control-to-case ratio.

A supplementary table (Supplementary Table S1) details the operational definitions and ICD-9 coding systems used for key study variables.

2.1.1. Statistical analysis

Statistical analyses were performed using R software. We compared demographic and clinical characteristics between AU and control groups using Chi-square or Fisher's exact tests for categorical variables and independent t-tests or Mann-Whitney U tests for continuous variables. Multivariable logistic regression models were used to adjust for comorbid mental health conditions. A p-value <0.05 was considered statistically significant.

3. Results

Table 1 presents the study's results comparing patients with acute urticaria (AU) and the control group without urticaria.

The AU group included 72,805 while the control group included 291,220 individuals. No significant differences were observed between the two groups regarding sex and sectorial distribution, with the majority being female (58.77 %) and a similar diversity among the sectors. Similarly, the mean age in both groups was approximately 26.9 years, and there were no significant differences in age distribution among different age categories.

The AU group had a slightly higher mean weight (52.0 ± 30.6 kg) and BMI (24.4 ± 6.7 kg/m^2) compared to the control group (weight: 51.1 ± 30.7 kg, BMI: 24.1 ± 6.7 kg/m^2; $p < 0.001$).

Table 1
Demographic variables in subjects with acute urticaria and controls.

		Cases n (%)	Control n (%)	*p*	*OR* (95 % CI)
N		72,805	291,220		
Female		42,750 (58.72 %)	171,000 (58.72 %)	*0.999*	1.00 [0.98 to 1.02]
Ethnic group	Arab	20,170 (27.7 %)	80,680 (27.7 %)	*0.999*	1.00 [0.98 to 1.02]
	General	41,364 (56.8 %)	165,456 (56.8 %)	*0.999*	1.00 [0.98 to 1.02]
	Jewish Ultra-orthodox	11,271 (15.5 %)	45,084 (15.5 %)	*0.999*	1.00 [0.98 to 1.02]
Age (years)	Mean ± SD	26.9 ± 22.7	26.8 ± 22.7	*0.935*	
Age category (years)	1–2	8607 (11.82 %)	34,428 (11.82 %)	*0.999*	1.00 [0.98 to 1.03]
	3–4	4613 (6.34 %)	18,452 (6.34 %)	*0.999*	1.00 [0.97 to 1.03]
	5–9	8027 (11.03 %)	32,108 (11.03 %)	*0.999*	1.00 [0.97 to 1.03]
	10–16	7717 (10.60 %)	30,868 (10.60 %)	*0.999*	1.00 [0.97 to 1.03]
	17–29	11,968 (16.44 %)	47,872 (16.44 %)	*0.999*	1.00 [0.98 to 1.02]
	30–39	7761 (10.66 %)	31,044 (10.66 %)	*0.999*	1.00 [0.97 to 1.03]
	40–49	7522 (10.33 %)	30,088 (10.33 %)	*0.999*	1.00 [0.97 to 1.03]
	50–59	6375 (8.76 %)	25,500 (8.76 %)	*0.999*	1.00 [0.97 to 1.03]
	60–69	4466 (6.13 %)	17,864 (6.13 %)	*0.999*	1.00 [0.97 to 1.03]
	≥70	3450 (4.74 %)	13,800 (4.74 %)	*0.999*	1.00 [0.96 to 1.04]
BMI (kg/m2)		24.4 ± 6.7	24.1 ± 6.6	*< 0.001*	
Smoker		2767 (20.52 %)	9512 (20.39 %)	*0.743*	1.17 [1.12 to 1.22]

Data are presented as numbers and percentages [n (%)] unless otherwise indicated. **BMI** = body mass index; **SD** = standard deviation; ***p*** = p-value from statistical tests comparing cases and controls; ***OR*** = odds ratio; **CI** = confidence interval.

3.1. Anxiety disorders

Our study examined the 20-year prevalence of anxiety disorders among patients with acute urticaria compared to a control group. The findings revealed a statistically significant higher prevalence of various anxiety-related disorders in the acute urticaria group (Table 2).

The prevalence of anxiety disorders, including anxiety states (300.0), panic disorder (300.01), generalized anxiety disorder (300.02), and other anxiety states (300.09), was significantly higher in the AU group (7.02 %) compared to the control group (5.22 %) ($p < 0.001$). The odds ratio (OR) was 1.37 [95 % CI: 1.33 to 1.42].

Neurotic depression (300.4) was observed in 0.60 % of AU patients and 0.50 % of controls, showing a significant difference ($p = 0.001$) with an OR of 1.20 [95 % CI: 1.08 to 1.34].

Somatoform disorders, including somatization disorder (300.81), undifferentiated somatoform disorder (300.82), and hypochondriasis (300.7), were more prevalent in the AU group (0.24 %) compared to controls (0.17 %) ($p < 0.001$), with an OR of 1.42 [95 % CI: 1.19 to 1.69].

Other neurotic disorders, comprising neurasthenia (300.5), depersonalization syndrome (300.6), and other neurotic disorders (300.8), had a higher prevalence in the AU group (0.21 %) than in the control group (0.16 %) ($p = 0.002$), with an OR of 1.33 [95 % CI: 1.11 to 1.60].

3.2. Personality disorders

The 20-year prevalence of personality disorders among patients with acute urticaria compared to controls is presented in Table 3.

The prevalence of Cluster A personality disorders, including paranoid (301.0) and schizoid (301.2, 301.20) personality disorders, was 0.008 % in AU patients and 0.004 % in controls. Although the difference was not statistically significant ($p = 0.118$), the odds ratio (OR) was 2.00 [95 % CI: 0.71 to 5.29], suggesting a potential trend towards higher

Table 2
20-year prevalence of anxiety, neurotic and somatoform disorders in patients of acute urticaria and controls.

Category	Disorders Included	Cases n (%)	Controls n (%)	*p*	*OR* (95 % CI)*
Anxiety Disorders	Anxiety states (300.0), Panic Disorder (300.01), Generalized Anxiety Disorder (300.02), Other Anxiety States (300.09)	5114 (7.02 %)	15219 (5.22 %)	*<0.001*	1.37 [1.33 to 1.42]
Depressive Disorders	Neurotic Depression (300.4)	439 (0.60 %)	1459 (0.50 %)	*0.001*	1.20 [1.08 to 1.34]
Somatoform Disorders	Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.82), Hypochondriasis (300.7)	178 (0.24 %)	502 (0.17 %)	*<0.001*	1.42 [1.19 to 1.69]
Other Neurotic Disorders	Neurasthenia (300.5), Depersonalization Syndrome (300.6), Other Neurotic Disorders (300.8)	153 (0.21 %)	460 (0.16 %)	*0.002*	1.33 [1.11 to 1.60]

Data are presented as numbers and percentages [n (%)]. ***OR* (95 % CI)** – Odds ratio (95 % Confidence interval) - multivariable logistic regression adjusted for other comorbid mental health conditions.

prevalence in the AU group.

Cluster B personality disorders, including antisocial (301.7), borderline (301.83), and histrionic (301.5, 301.50) personality disorders, were observed in 0.022 % of AU patients and 0.015 % of controls. The difference was not statistically significant ($p = 0.170$), with an OR of 1.42 [95 % CI: 0.79 to 2.48].

Cluster C personality disorders, including compulsive (301.4), dependent (301.6), and avoidant (301.82) personality disorders, had a prevalence of 0.003 % in AU patients and 0.004 % in controls. The difference was not statistically significant ($p = 0.999$), with an OR of 0.73 [95 % CI: 0.09 to 3.30].

Personality disorders characterized by persistent mood disturbances, including affective (301.10), hypomanic (301.11), depressive (301.12), and cyclothymic (301.13) personality disorders, were significantly more prevalent in AU patients (0.17 %) compared to controls (0.089 %) ($p < 0.001$), with an OR of 1.91 [95 % CI: 1.53 to 2.38].

Other personality disorders, including explosive (301.3), other specified (301.8, 301.89), passive-aggressive (301.84), and unspecified personality disorders (301.9), were more prevalent in AU patients (0.070 %) than in controls (0.044 %) ($p = 0.001$), with an OR of 1.61 [95 % CI: 1.15 to 2.23].

The overall prevalence of personality disorders (all 301 codes) was higher in AU patients (0.23 %) compared to controls (0.134 %) ($p < 0.001$), with an OR of 1.73 [95 % CI: 1.44 to 2.08].

3.3. Various nonpsychotic mental disorders

Table 4 presents the 20-year prevalence of various nonpsychotic mental disorders in patients with acute urticaria compared to controls, revealing significant associations: a higher prevalence of bruxism (0.11 % vs. 0.08 %, $p=0.030$) and teeth grinding (0.20 % vs. 0.15 %, $p=0.003$) was observed in the acute urticaria group, with odds ratios (OR) of 1.33 [1.02 to 1.72] and 1.34 [1.10 to 1.62], respectively.

Adjustment disorders with depressive features, including adjustment reaction with brief depressive reaction (309.0) and prolonged depressive reaction (309.1), were significantly more prevalent in the AU group (0.30 %) compared to the control group (0.20 %) ($p < 0.001$), with an odds ratio (OR) of 1.49 [95 % CI: 1.27 to 1.74].

Adjustment reaction with anxious mood (309.24) was observed in 0.124 % of AU patients and 0.092 % of controls, showing a significant difference ($p = 0.017$) with an OR of 1.34 [95 % CI: 1.05 to 1.71].

Adjustment disorders with mixed or other emotional features, including predominant disturbance of other emotions (309.2), adjustment reaction with mixed emotional features (309.28), and other adjustment reactions with predominant disturbance of other emotions (309.29), had a higher prevalence in the AU group (0.228 %) compared to controls (0.174 %) ($p = 0.002$), with an OR of 1.31 [95 % CI: 1.10 to 1.57].

Adjustment disorders with conduct disturbance, including predominant disturbance of conduct (309.3) and mixed disturbance of emotions and conduct (309.4), were more prevalent in AU patients (0.029 %) than in controls (0.015 %) ($p = 0.013$), with an OR of 1.91 [95 % CI: 1.10 to 3.24].

Prolonged posttraumatic stress disorder (PTSD) (309.81) was significantly more common in AU patients (0.324 %) than in controls (0.249 %) ($p = 0.001$), with an OR of 1.30 [95 % CI: 1.12 to 1.51].

Other specified adjustment reactions, including adjustment reaction with physical symptoms (309.82), had a higher prevalence in AU patients (0.362 %) compared to controls (0.277 %) ($p < 0.001$), with an OR of 1.31 [95 % CI: 1.14 to 1.51].

The overall prevalence of all adjustment reactions was significantly

Table 3
20-year prevalence of personality disorders in patients of acute urticaria and controls.

Category	Disorders Included	Cases n (%)	Controls n (%)	*p*	*OR* (95 % CI)*
Cluster A Personality Disorders	Paranoid (301.0), Schizoid (301.2, 301.20)	6 (0.008 %)	12 (0.004 %)	*0.118*	2.00 [0.71 to 5.29]
Cluster B Personality Disorders	Antisocial (301.7), Borderline (301.83), Histrionic (301.5, 301.50)	16 (0.022 %)	45 (0.015 %)	*0.170*	1.42 [0.79 to 2.48]
Cluster C Personality Disorders	Compulsive (301.4), Dependent (301.6), Avoidant (301.82)	2 (0.003 %)	11 (0.004 %)	*0.999*	0.73 [0.09 to 3.30]
Personality disorders with persistent mood disturbances	Affective (301.10), Hypomanic (301.11), Depressive (301.12), Cyclothymic (301.13)	123 (0.17 %)	258 (0.089 %)	*<0.001*	1.91 [1.53 to 2.38]
Other Personality Disorders	Explosive (301.3), Other (301.8, 301.89), Passive-Aggressive (301.84), Unspecified (301.9)	51 (0.070 %)	127 (0.044 %)	*0.001*	1.61 [1.15 to 2.23]
All Personality Disorders	**All disorders (301)**	**169 (0.23 %)**	**391 (0.134 %)**	***<0.001***	**1.73 [1.44 to 2.08]**

Data are presented as numbers and percentages [n (%)]. ***OR* (95 % CI)** – Odds ratio (95 % Confidence interval) - multivariable logistic regression adjusted for other comorbid mental health conditions.

Table 4
20-year prevalence of other nonpsychotic Mental Disorders in patients of acute urticaria and controls.

Category	Disorders Included (ICD-9 Codes)	Cases n (%)	Controls n (%)	*p*	*OR* (95 % CI)*
Adjustment Disorders with Depressive Features	Adjustment Reaction with Brief Depressive Reaction (309.0), Adjustment Reaction with Prolonged Depressive Reaction (309.1)	216 (0.30 %)	581 (0.20 %)	*<0.001*	1.49 [1.27 to 1.74]
Adjustment Disorders with Anxiety	Adjustment Reaction with Anxious Mood (309.24)	90 (0.124 %)	268 (0.092 %)	*0.017*	1.34 [1.05 to 1.71]
Adjustment Disorders with Mixed or Other Emotional Features	With Predominant Disturbance of Other Emotions (309.2), Adjustment Reaction with Mixed Emotional Features (309.28), Other Adjustment Reactions with Predominant Disturbance of Other Emotions (309.29)	166 (0.228 %)	508 (0.174 %)	*0.002*	1.31 [1.10 to 1.57]
Adjustment Disorders with Conduct Disturbance	Adjustment Reaction with Predominant Disturbance of Conduct (309.3), Adjustment Reaction with Mixed Disturbance of Emotions and Conduct (309.4)	21 (0.029 %)	44 (0.015 %)	*0.013*	1.91 [1.10 to 3.24]
Posttraumatic Stress Disorder	Prolonged Posttraumatic Stress Disorder-PTSD (309.81)	236 (0.324 %)	724 (0.249 %)	*0.001*	1.30 [1.12 to 1.51]
Other Specified Adjustment Reactions	Other Specified Adjustment Reactions (309.8), Adjustment Reaction with Physical Symptoms (309.82)	264 (0.362 %)	806 (0.277 %)	*<0.001*	1.31 [1.14 to 1.51]
All Adjustment Reactions		**663 (0.91 %)**	**1937 (0.67 %)**	***<0.001***	**1.37 [1.25 to 1.50]**

Data are presented as numbers and percentages [n (%)]. ***OR* (95 % CI)** – Odds ratio (95 % Confidence interval) - multivariable logistic regression adjusted for other comorbid mental health conditions.

higher in the AU group (0.91 %) compared to controls (0.67 %) ($p < 0.001$), with an OR of 1.37 [95 % CI: 1.25 to 1.50].

3.4. Sensitivity analysis excluding corticosteroid users

We conducted a sensitivity analysis to assess the robustness of our findings by excluding patients who had documented purchases of oral corticosteroids during the study period. This analysis was performed to address the potential confounding effect of corticosteroid use on psychiatric outcomes. The results, presented in the Supplementary Table S2, demonstrate that the associations between AU and anxiety, personality, and nonpsychotic mental disorders remain consistent.

4. Discussion

4.1. Main findings and their interpretation

Our population-based case-control study demonstrated a significantly higher prevalence of anxiety disorders in patients with acute urticaria (AU) compared to controls. Our data also revealed that neurotic depression was more common in AU patients, as were somatoform disorders and other neurotic disorders.

Our analysis identified a higher overall prevalence of personality disorders in AU patients compared to controls. Specifically, our results showed that personality disorders characterized by persistent mood disturbances were significantly more prevalent in AU patients compared to controls.

Furthermore, our study found that adjustment disorders were significantly more common in the AU group than in controls.

These associations suggest a complex interplay between AU and psychological conditions, particularly anxiety, adjustment, and personality disorders. The higher prevalence of anxiety disorders in AU patients may indicate shared biological pathways or bidirectional influences between skin inflammation and psychological states. The significant association with personality disorders, especially those involving mood disturbances, could reflect the potential impact of persistent psychological traits on immune function or, conversely, the influence of recurrent inflammatory episodes on personality development. The observed relationship between AU and adjustment disorders may represent the psychological impact of coping with a visible and sometimes unpredictable skin condition.

Collectively, these epidemiological associations highlight the importance of considering the psychodermatological interface in AU and point toward the need for deeper investigation into the intersection between acute skin conditions and mental health disorders.

We acknowledge that some associations identified in our study, particularly neurotic depression (OR = 1.20), demonstrate statistically significant but modest effect sizes. While these findings contribute to our understanding of the relationship between AU and mental health disorders, we caution against overinterpretation of their clinical significance. Such modest associations may reflect subtle biological connections or shared risk factors rather than strong causal relationships. From a clinical perspective, these findings suggest that routine screening for neurotic depression in all AU patients may not be warranted, though clinicians should remain attentive to depressive symptoms in the context of other risk factors. The stronger associations observed with anxiety disorders (OR = 1.37) and personality disorders (OR = 1.73) may have more direct clinical implications for screening and management approaches.

Our study demonstrates associations between AU and mental health disorders, but the psychoneuroimmunological mechanisms discussed are hypothesized pathways from literature, not direct findings. Our epidemiological approach identifies associations without testing biological mechanisms. Proposed pathways (histamine effects on anxiety, inflammatory cytokines on mood) require further investigation through experimental research with direct biomarker measurement and neuroimaging.

4.1.1. Hypothesized psychoneuroimmunological mechanisms

Previous research has proposed several potential mechanisms that might explain the observed associations between AU and mental health disorders. According to the literature, these include

psychoneuroimmunological interactions, neuroendocrine dysregulation, behavioral and psychological factors, and genetic and environmental influences (Tomaszewska et al., 2023; Zhang et al., 2024).

Current understanding of AU describes it as an immunological reaction characterized by sudden hives, itching, and sometimes angioedema, driven by mast cell degranulation and histamine release (Theoharides et al., 2020; Kolkhir et al., 2022). Researchers have hypothesized that this immunological disturbance may influence central neuroinflammatory pathways, potentially affecting mood and behavior (Nautiyal et al., 2008).

The literature suggests that mast cells release bioactive mediators, including histamine and serotonin, which may potentially penetrate the blood-brain barrier and modulate neurotransmitter systems involved in emotional regulation (Carthy and Ellender, 2021; Li et al., 2023). Some investigators have proposed that elevated histamine levels might trigger anxiety states and adjustment disorders by interacting with central histamine receptors and influencing stress responses (Zhang et al., 2024), though this specific mechanism was not directly tested in our study.

Moreover, psychological stress activates the HPA axis, leading to increased secretion of corticotropin-releasing hormone (CRH), which can directly stimulate skin mast cells via CRH-R1 receptors, resulting in degranulation and histamine release—key events in AU pathogenesis (Cao et al., 2005). Mast cell–derived mediators, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), can cross the blood-brain barrier or signal through peripheral nerves, promoting neuroinflammation and modulating limbic circuits involved in anxiety, thereby establishing a bidirectional link between immune activation and affective dysregulation (Skater et al., 2017).

4.1.2. Hypothesized cytokine pathways

The cytokine hypothesis in the literature suggests that elevated proinflammatory cytokines, such as IL-6, TNF-α, and IL-1β, can disrupt brain function, potentially contributing to mood disorders (Elgellaie et al., 2023). According to this theory, acute inflammatory responses in AU may transiently elevate systemic cytokines, influencing brain function through vagal signaling or by crossing the blood-brain barrier, which could theoretically exacerbate anxiety and mood disturbances (Konstantinou et al., 2022).

4.1.3. Hypothesized neuroendocrine mechanisms

Previous studies have proposed that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis might be another factor linking AU and mental health disorders. According to this hypothesis, chronic stress or recurrent AU episodes could impair HPA feedback, increasing susceptibility to anxiety and adjustment disorders while exacerbating inflammatory responses (McEwen et al., 2016; Karin et al., 2020). Some researchers have suggested that elevated cortisol levels during AU episodes may initially suppress inflammation but later dysregulate mood, as cortisol impacts brain regions such as the hippocampus, amygdala, and prefrontal cortex (McEwen et al., 2016; Herman et al., 2016).

4.1.4. Hypothesized personality and genetic factors

The literature proposes that personality disorders may exacerbate AU through impaired emotional regulation, stress responses, and interpersonal challenges (Kulakova et al., 2024; Schönthaler et al., 2023). Some researchers have theorized that traits associated with persistent mood disturbances might alter stress responses, potentially increasing the risk of AU onset or exacerbation (Malhotra and Mehta, 2008). It has been hypothesized that in some cases, chronic exposure to AU symptoms could influence personality development over time (Mitchell et al., 2018), though longitudinal studies would be needed to confirm this possibility.

Genetic research suggests that predispositions, such as polymorphisms in cytokine or neurotransmitter receptor genes, might potentially enhance susceptibility to both anxiety, personality disorders, and AU (Mikhalitskaya et al., 2023). According to this theory, these genetic factors, combined with environmental stressors and mast cell activation, could heighten psychiatric morbidity in vulnerable individuals (Nautiyal et al., 2008).

4.1.5. Hypothesized bidirectional interactions

The emerging field of psychoneuroimmunology offers a framework for understanding the dynamic relationship between psychological processes and immune function (Honeyman et al., 2016). Researchers have proposed that in AU, psychological distress—such as fear of unpredictable flare-ups and social embarrassment—might activate the sympathetic nervous system and HPA axis, leading to elevated stress hormones like norepinephrine and cortisol (Slominski et al., 2000; Toyoshima and Okayama, 2022). According to this model, these stress hormones could potentially alter immune thresholds for mast cell degranulation and cytokine production, influencing AU severity and frequency (Konstantinou et al., 2022).

Furthermore, some studies suggest that a predisposition toward anxiety or neuroticism might affect disease perception and amplify stress responses, potentially impacting cytokine production, leukocyte distribution, and mast cell activity (Mohamadi et al., 2013; Forte et al., 2023). This theoretical bidirectional interaction between psychiatric disorders and immune responses highlights the need for comprehensive care in managing AU and associated mental health conditions (Tawil et al., 2023).

Our findings support a potential bidirectional relationship between anxiety/personality traits and acute urticaria. The unpredictability of AU episodes, physical discomfort, and visible manifestations can create psychological distress, potentially reinforcing pre-existing anxiety patterns or revealing latent personality vulnerabilities. This bidirectional interaction creates a potential cycle where psychological factors influence urticaria manifestation, and urticaria experiences subsequently impact psychological well-being. Future prospective studies with baseline psychological assessments prior to AU onset would help clarify these temporal relationships and causal pathways.

4.2. Study strengths and limitations

4.2.1. Strengths

Our study's key strength is its use of a large population-based dataset, enhancing statistical power and generalizability. The methodology we employed, utilizing electronic health records (EHRs), allowed for a detailed analysis of the relationship between AU, anxiety, and personality disorders (Carthy and Ellender, 2021).

4.2.2. Limitations

We acknowledge several limitations in our study. Mental health conditions may be underdiagnosed or underreported due to variations in healthcare access, patient willingness to seek care, and social stigma (Yang et al., 2021). Additionally, our reliance on ICD-9 codes may have introduced some diagnostic inconsistencies, and mental disorders may be underdiagnosed in primary care settings (Fariba et al., 2023).

While we matched cases and controls on key variables including gender, age, ethnicity, year of first documented visit, and socioeconomic status, we did not adjust for all potential confounders. Specifically, comorbid physical illnesses (e.g., autoimmune diseases) and medication use (e.g., corticosteroids, antihistamines) were not included as covariates in our primary models to preserve statistical power and avoid overadjustment, particularly given the high dimensionality of the dataset and potential multicollinearity. Our matching strategy, which considered age, sex, ethnicity, socioeconomic status, and index year, was designed to minimize confounding by key demographic and health utilization variables. Additionally, the real-world nature of this large-scale EHR study aimed to capture broad population-level associations. We acknowledge this limitation and note that stratified analyses

adjusting for medical comorbidities and medication exposure are planned in future work.

Our analysis included all patients diagnosed with AU, regardless of identified etiology. While we recognize that AU can have identifiable causes such as drug reactions, food allergies, or infections, the retrospective nature of our database study did not allow for consistent differentiation between idiopathic and non-idiopathic cases across all patients. This represents a limitation of our study, as the psychological associations might differ between idiopathic and non-idiopathic forms of AU. Future studies should aim to differentiate between idiopathic and non-idiopathic AU cases, as the psychological factors and associations may vary based on etiology. Prospective designs with standardized protocols for identifying triggers and measurement of stress biomarkers, psychological assessments, and immunological parameters at multiple time points would be valuable in addressing this limitation.

Our study focused on anxiety, adjustment, and personality disorders for their clinical relevance, but we recognize that other mental health conditions may also play a role in AU and warrant further exploration. The retrospective design of our study limits causal inference, and prospective studies are needed to confirm our findings.

4.3. Future directions

Based on our findings, we recommend implementing specific screening and intervention strategies in dermatological practice for patients with AU. For screening, we suggest the Hospital Anxiety and Depression Scale (HADS) or the Generalized Anxiety Disorder 7-item (GAD-7) scale, both validated tools that can be quickly administered in clinical settings. For personality trait assessment, the brief version of the Big Five Inventory (BFI-10) offers an efficient screening option. Regarding intervention strategies, we propose an integrated care involving both dermatologists and mental health professionals for complex cases.

Based on our findings, we recommend that future research should address these limitations by incorporating potential confounders into their analytical framework. We suggest that subsequent studies should investigate additional molecular pathways that link AU and mental health to develop integrated therapeutic strategies. Future research would benefit from direct measurement of inflammatory mediators, neuroimaging techniques, and longitudinal designs to elucidate the proposed mechanisms connecting AU and mental health disorders.

Despite the limitations noted above, we believe that the strength of the observed associations and their consistency across multiple mental health domains suggest a robust relationship between acute urticaria and mental health disorders that warrants further investigation.

5. Conclusions

Our epidemiological study demonstrates significant associations between AU and various mental health disorders, including anxiety, personality disorders, and adjustment reactions. These associations suggest potential interactions between dermatological and psychological conditions that merit further investigation. Our findings underscore the importance of multidisciplinary management strategies that address both the dermatological and psychological aspects of AU.

Future research should explore the hypothesized biological mechanisms that might underlie these relationships, including the proposed roles of neuroimmune interactions, inflammatory mediators, and stress response systems in connecting skin inflammation and psychological states. Such investigations could potentially pave the way for more comprehensive patient care approaches that address both the physical and psychological dimensions of urticaria.

CRediT authorship contribution statement

Eli Magen: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Eugene Merzon:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Shai Ashkenazi:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Abraham Weizman:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Iris Manor:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Israel Magen:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Avi Yakov:** Writing – review & editing, Investigation, Formal analysis. **Akim Geishin:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Ilan Green:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Avivit Golan-Cohen:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Shlomo Vinker:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Data curation. **Ariel Israel:** Writing – review & editing, Writing – original draft, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Informed consent statement

The requirement for informed consent was waived due to the study's retrospective nature and anonymized data.

Institutional review board statement

LHS's ethics committee approved this study (reference: LEU 05–23).

Data availability statement

Due to the confidential nature of the dataset, it has not been deposited in a publicly available database. Interested researchers can request access to the data by contacting the primary custodian, Dr. A. Israel.

Declaration of generative AI and AI-assisted technologies in the writing process

While preparing this work, the authors used Grammarly AI software to improve the manuscript's readability. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the publication's content.

Funding

This research received no external funding.

Declaration of competing interest

All authors have nothing to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.101088.

Data availability

Data will be made available on request.

References

Ben-Shoshan, M., Blinderman, I., Raz, A., 2013. Psychosocial factors and chronic spontaneous urticaria: a systematic review. Allergy 68, 131–141. https://doi.org/10.1111/all.12068.

Cao, J., Papadopoulou, N., Kempuraj, D., Boucher, W.S., Sugimoto, K., Cetrulo, C.L., Theoharides, T.C., 2005. Human mast cells express corticotropin-releasing hormone (CRH) receptors and CRH leads to selective secretion of vascular endothelial growth factor. J. Immunol. 174 (12), 7665–7675. https://doi.org/10.4049/jimmunol.174.12.7665.

Carthy, E., Ellender, T., 2021. Histamine, neuroinflammation and neurodevelopment: a review. Front. Neurosci. 15, 680214. https://doi.org/10.3389/fnins.2021.680214.

Elgellaie, A., Thomas, S.J., Kaelle, J., Bartschi, J., Larkin, T., 2023. Pro-inflammatory cytokines IL-1α, IL-6 and TNF-α in major depressive disorder: Sex-specific associations with psychological symptoms. Eur. J. Neurosci. 57, 1913–1928. https://doi.org/10.1111/ejn.15992.

Ensina, L.F., Min, T.K., Félix, M.M.R., de Alcântara, C.T., Costa, C., 2022. Acute Urticaria and anaphylaxis: differences and similarities in clinical management. Front Allergy 3, 840999. https://doi.org/10.3389/falgy.2022.840999.

Fariba, K.A., Gupta, V., Kass, E., 2023. Personality disorder. In: StatPearls [Internet]. Treasure Island (FL). StatPearls Publishing, 2024 Jan–. PMID: 32310518.

Forte, A.R.C.C., Lessa, P.H.C., Chaves Filho, A.J.M., et al., 2023. Oxidative stress and inflammatory process in borderline personality disorder (BPD): a narrative review. Braz. J. Med. Biol. Res. 56, e12484. https://doi.org/10.1590/1414-431X2023e12484.

Fricke, J, Ávila, G, Keller, T, Weller, K, Lau, S, Maurer, M, Zuberbier, T, Keil, T, 2020 Feb. Prevalence of chronic urticaria in children and adults across the globe: Systematic review with meta-analysis. Allergy 75 (2), 423–432. https://doi.org/10.1111/all.14037.

Giménez-Arnau, AM, DeMontojoye, L, Asero, R, Cugno, M, Kulthanan, K, Yanase, Y, Hide, M, Kaplan, AP, 2021 Jun. The Pathogenesis of Chronic Spontaneous Urticaria: The Role of Infiltrating Cells. J Allergy Clin Immunol Pract 9 (6), 2195–2208. https://doi.org/10.1016/j.jaip.2021.03.033.

Herman, J.P., McKlveen, J.M., Ghosal, S., et al., 2016. Regulation of the hypothalamic-pituitary-adrenocortical stress response. Compr. Physiol. 6, 603–621. https://doi.org/10.1002/cphy.c150015.

Honeyman, J.F., 2016. Psychoneuroimmunology and the skin. Acta Derm. Venereol. 96, 38–46. https://doi.org/10.2340/00015555-2376.

Karin, O., Raz, M., Tendler, A., et al., 2020. A new model for the HPA axis explains dysregulation of stress hormones on the timescale of weeks. Mol. Syst. Biol. 16, e9510. https://doi.org/10.15252/msb.20209510.

Kolkhir, P., Giménez-Arnau, A.M., Kulthanan, K., Peter, J., Metz, M., Maurer, M., 2022. Urticaria. Nat. Rev. Dis. Primers 8, 61. https://doi.org/10.1038/s41572-022-00389-z.

Konstantinou, G.N., Koulias, C., Petalas, K., Makris, M., 2022. Further understanding of neuro-immune interactions in allergy: implications in pathophysiology and role in disease progression. J. Asthma Allergy 15, 1273–1291. https://doi.org/10.2147/JAA.S282039.

Kulakova, E., Graumann, L., Wingenfeld, K., 2024. The hypothalamus-pituitary-adrenal axis and social cognition in borderline personality disorder. Curr. Neuropharmacol. 22, 378–394. https://doi.org/10.2174/1570159X21666230804085639.

Lee, S.J., Ha, E.K., Jee, H.M., et al., 2017. Prevalence and risk factors of urticaria with a focus on chronic urticaria in children. Allergy Asthma Immunol. Res. 9, 212–219. https://doi.org/10.4168/aair.2017.9.3.212.

Li, B., Chang, L., Zhuang, Q.X., 2023. Histamine signaling in the bed nucleus of the stria terminalis modulates stress-induced anxiety. J. Affect. Disord. 335, 195–203. https://doi.org/10.1016/j.jad.2023.05.035.

Liu, X., Cao, Y., Wang, W., 2023. Burden of and trends in urticaria globally, regionally, and nationally from 1990 to 2019: systematic analysis. JMIR Public Health Surveill 9, e50114. https://doi.org/10.2196/50114.

Malhotra, S.K., Mehta, V., 2008. Role of stressful life events in induction or exacerbation of psoriasis and chronic urticaria. Indian J. Dermatol., Venereol. Leprol. 74, 594–599. https://doi.org/10.4103/0378-6323.45100.

McEwen, B.S., Nasca, C., Gray, J.D., 2016. Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. Neuropsychopharmacology 41, 3–23. https://doi.org/10.1038/npp.2015.171.

Mikhalitskaya, E.V., Vyalova, N.M., Ermakov, E.A., et al., 2023. Association of single nucleotide polymorphisms of cytokine genes with depression, schizophrenia and bipolar disorder. Genes 14, 1460. https://doi.org/10.3390/genes14071460.

Mitchell, A.E., 2018. Bidirectional relationships between psychological health and dermatological conditions in children. Psychol. Res. Behav. Manag. 11, 289–298. https://doi.org/10.2147/PRBM.S117583.

Mohamadi Hasel, K., Besharat, M.A., Abdolhoseini, A., Alaei Nasab, S., Niknam, S., 2013. Relationships of personality factors to perceived stress, depression, and oral lichen planus severity. Int. J. Behav. Med. 20 (2), 286–292. https://doi.org/10.1007/s12529-012-9226-5.

Nautiyal, K.M., Ribeiro, A.C., Pfaff, D.W., Silver, R., 2008. Brain mast cells link the immune system to anxiety-like behavior. Proc. Natl. Acad. Sci. U. S. A. 105, 18053–18057. https://doi.org/10.1073/pnas.0809479105.

Schönthaler, E.M.D., Dalkner, N., Schwalsberger, K., Reininghaus, E.Z., Reininghaus, B., 2023. Psychopathic personality traits stress immunity and social potency moderate the relationship between emotional competence and cognitive functions in depression. Front Psychiatry 14, 1061642. https://doi.org/10.3389/fpsyt.2023.1061642.

Skaper, S.D., Facci, L., Zusso, M., Giusti, P., 2017. Neuroinflammation, mast cells, and glia: dangerous liaisons. Neuroscientist 23 (5), 478–498. https://doi.org/10.1177/1073858416687249.

Slominski, A., Wortsman, J., Luger, T., Paus, R., Solomon, S., 2000. Corticotropin releasing hormone and proopiomelanocortin involvement in the cutaneous response to stress. Physiol. Rev. 80, 979–1020. https://doi.org/10.1152/physrev.2000.80.3.979.

Tawil, S., Irani, C., Kfoury, R., et al., 2023. Association of chronic urticaria with psychological distress: a multicentre cross-sectional study. Acta Derm. Venereol. 103, adv00865. https://doi.org/10.2340/actadv.v102.2939.

Theoharides, T.C., 2020. The impact of psychological stress on mast cells. Ann. Allergy Asthma Immunol. 125, 388–392. https://doi.org/10.1016/j.anai.2020.07.007.

Tomaszewska, K., Słodka, A., Tarkowski, B., Zalewska-Janowska, A., 2023. Neuro-immuno-psychological aspects of chronic urticaria. J. Clin. Med. 12, 3134. https://doi.org/10.3390/jcm12093134.

Toyoshima, S., Okayama, Y., 2022. Neuro-allergology: mast cell-nerve cross-talk. Allergol. Int. 71, 288–293. https://doi.org/10.1016/j.alit.2022.04.002.

Yang, X., Fang, Y., Chen, H., Zhang, T., Yin, X., Man, J., Yang, L., Lu, M., 2021. Global, regional, and national burden of anxiety disorders from 1990 to 2019: results from the global Burden of Disease study 2019. Epidemiol. Psychiatr. Sci. 30, e36. https://doi.org/10.1017/S2045796021000275.

Zhang, H., Wang, M., Zhao, X., Wang, Y., Chen, X., Su, J., 2024. Role of stress in skin diseases: a neuroendocrine-immune interaction view. Brain Behav. Immun. 116, 286–302. https://doi.org/10.1016/j.bbi.2023.12.005.

Zuberbier, T., Abdul Latiff, A.H., Abuzakouk, M., Aquilina, S., Asero, R., et al., 2022. The international EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy 77 (3), 734–766. https://doi.org/10.1111/all.15090.