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**Chronic urticaria patients have a higher risk of psychiatric disorders: a
population-based study**

Short title: Psychiatric comorbidities of CU in Taiwan

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Keywords: anxiolytics; anti-depressant; psychiatric disorders; psychiatric drug; urticaria

Abstract

Background: The prevalences of psychiatric comorbidities in patients with chronic urticaria (CU) in a national population are largely unknown.

Methods: The data were sourced from the National Health Insurance Research Database (NHIRD) of Taiwan for 2011. Patients who had a primary/secondary ICD-9-CM diagnosis code of 708.1, 708.8, or 708.9 during the year with at least two outpatient visits and an antihistamine prescription were identified as the cases of CU. CU cases were classified into 3 disease severity groups according to their medication types. Psychiatric disorders were identified by the patients having 3 outpatient visits with the primary or secondary diagnosis of a given psychiatric disease. Psychiatric medication use was defined by having at least 4 outpatient visits with prescribing anxiolytics, antidepressants, or sleeping pills in the same year or previous year, respectively.

Results: Among the 167,132 CU patients diagnosed in 2011, 82.5% had mild CU, 17.0% had moderate CU, and 0.41% had severe CU. CU patients had higher prevalences of psychiatric disorders and psychiatric medication prescription than control groups in the general population. The relative risk (RR) of psychiatric disorders was 1.43 for mild, 1.50 for moderate, and 2.32 for severe CU patients compared to the

controls ($P<.0001$). For psychiatric medication prescription, the RR compared to the controls was 1.95 for mild, 2.70 for moderate, and 2.09 for severe CU patients ($P<.0001$).

Conclusions: CU patients had higher prevalences and risks of psychiatric disorders and psychiatric medication prescription than control groups in the general population.

What's already known about this topic?

- Previous studies have shown a high prevalence of psychiatric comorbidities in chronic spontaneous urticaria (CSU) patients, with the rates ranging from 35-60%.
- Anxiety, depression, and somatoform disorders have been reported as the most prevalent mental disorders in CSU patients.

What does this study add?

- CU patients had higher prevalences of psychiatric disorders and psychiatric medication use than control groups in the general population.
- The relative risk (RR) of psychiatric disorders was 1.43 for mild, 1.50 for moderate, and 2.32 for severe CU patients compared to the controls.
- The RR of psychiatric medication use was 1.95 for mild, 2.70 for moderate, and 2.09 for severe CU patients compared to the controls.
- Mental health evaluations and management are important elements in CU management.

Introduction

Chronic urticaria (CU) is characterized by the repeated occurrence of itchy wheals with or without angioedema for more than 6 weeks. It is further classified into chronic inducible urticaria (CindU) and chronic spontaneous urticaria (CSU) according to whether a specific trigger for urticaria symptoms and signs can be identified or not.¹⁻⁴ Previous studies have shown a high prevalence of psychiatric comorbidities in CSU patients, with the rates ranging from 35-60%.³⁻¹⁷ Anxiety, depression, and somatoform disorders have been reported to be the most prevalent mental disorders in CSU patients.⁵⁻¹⁶ We have also found that anxiety, dissociative, and somatoform disorders were the most prevalent psychiatric comorbidities, especially in cases of CU that persisted longer.³

In a systematic review of psychosocial factors and CSU, 30 eligible studies were mostly hospital-based studies that used questionnaires to assess psychological symptoms, rather than collecting medical records with the confirmed psychiatric diagnoses.¹⁴ Although a few recent population-based studies have investigated the association of psychiatric disorders and urticaria,^{3, 18} the relative risk of various psychiatric disorders and the usage of psychiatric medications among CU patients in a large population is largely unknown. In this study, therefore, we aimed to investigate

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the prevalence and relative risks of psychiatric disorders or psychiatric medication use among CU patients by CU severity level.

Methods

Data sources

The National Health Insurance (NHI) program in Taiwan was put into effect in March 1995, which covers more than 99% of the total population of Taiwan with a comprehensive benefits package (including preventive medicine, dental care services, outpatient and inpatient services, prescription drugs, and Chinese herbal remedies). The National Health Insurance Research Database (NHIRD) was established by the National Health Research Institute, in cooperation with the National Health Insurance Administration, with the aim of promoting research to address the current and emerging medical issues in Taiwan. The 2005 sample cohort files, which contain all the aforementioned claims records of a sample of 997,771 enrollees representative of the Taiwanese population in 2005, were used to identify a comparison cohort of the study cases.

Study population

Patients who had at least two outpatient visits with a primary or secondary ICD-9-CM diagnosis code of 708.1 (idiopathic urticaria), 708.8 (other specified urticaria), or 708.9 (urticaria unspecified), as well as an H1 anti-histamine prescription, were identified from NHIRD for the year of 2011 as the CU cases. The first outpatient visit in the year was defined as the index date. Patients who met either of the following two criteria were excluded. First, if the interval between the index date and the date of the last CU outpatient visit in 2011 was less than 6 weeks. Second, any patient who had at least two outpatient visits with a primary or secondary ICD-9-CM code of 287.0 (vasculitis and allergic purpura) within 3 months before or after the index date. The CU cases were further divided into mild, moderate, and severe groups according to their medication types based on the national guidelines of CU treatment in Taiwan.¹⁹ Briefly, patients receiving combination therapy with H1 or H2 antihistamines and one of the following third-line treatments (cyclosporine, azathioprine, cyclophosphamide, mycophenolic acid, omalizumab, methotrexate, or interferon) for at least 28 days were considered severe cases; patients not meeting the above criteria but receiving any 2 of the first-, second-, or third-line treatments for at least 14 days were considered moderate cases; and patients not meeting the above criteria but receiving only monotherapy with H1 antihistamines or combination therapies with 1st and 2nd generation H1 antihistamines

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or H2 antihistamines were considered mild cases. The case identification process is presented in Fig. 1. and After excluding the CU patients in the 2005 sample cohort files, a comparison cohort was established by matching the CU cases at a 4:1 ratio based on age, gender, urbanization level of residential areas.²⁰

Confidentiality assurances were addressed by abiding by the data regulations of the NHI Administration, and the study was approved by National Taiwan University Hospital Research Ethics Committee (201402045RINB).

Definition of measurements

Psychiatric disorders were defined as patients who had at least 3 outpatient visits with any of the following primary or secondary diagnosis in 2011: episodic mood disorders (ICD-9-CM code: 296); anxiety, dissociative, and somatoform disorders (ICD-9-CM code: 300); obsessive-compulsive personality disorder (ICD-9-CM code: 301.4); drug dependence (ICD-9-CM code: 304); nondependent abuse of drugs (ICD-9-CM code: 307.4); specific disorders of sleep of nonorganic origin (ICD-9-CM codes: 531.4, 531.5, 531.6); adjustment reaction (ICD-9-CM code: 309); and depressive disorder, not elsewhere classified (ICD-9-CM code: 311).

Psychiatric medication use was defined as patients who had been prescribed anxiolytics (ATC code N05B), anti-depressants (ATC code N06A), or sleeping pills for insomnia (ATC code N05CF) in at least 4 outpatient visits in 2011.

Statistical analyses

First, Pearson chi-square tests were performed to examine differences in demographic variables, prevalence of psychiatric disorders, as well as prevalence of psychiatric anxiolytics use between CSU cases and comparison. Second, a generalized linear model (GLM) was used to predict the relative risk (RR) of psychiatric disorders and of psychiatric medication use between cases and comparison by disease severity. All analyses were performed using the SAS/Stat system for Windows, version 9.3 (SAS Institute, Cary, NC).

Results

There were 167,132 cases of CU identified in 2011 from NHIRD. Among them, 689, 28,414, and 138,029 patients were classified as severe, moderate, and mild cases, respectively (Fig. 1); 56.5% of them were females. The majority of CU patients was in the age range of 30-59 years old (51.2%). CU was more common in the residential areas with the highest urbanization level (Table 1).

The observed prevalence of psychiatric disorders in the mild, moderate, and severe CU patients were 7.00%, 7.49%, and 11.76%, respectively. When compared with their comparison, CU patients had consistently higher prevalence in specific disorders of

sleep of nonorganic origin and adjustment reaction among each of the 3 severity groups.

The mild and moderate CU patients also had higher prevalence of major depression, anxiety, dissociative and somatoform disorders, nondependent abuse of drugs, and depressive disorder (not elsewhere classified). Drug dependence was more prevalent in the mild CU cases, while bipolar disorder and paranoid status only had significantly higher prevalences in the severe CU group. In contrast, the prevalence of schizophrenic disorder was significantly lower among mild and severe CU patients (Table 2).

Around 20-30% of the CU patients had used psychiatric medication. Anxiolytics was the most commonly prescribed psychiatric medication among each of the 3 CU severity groups, followed by sleeping pills and anti-depressants. When compared with comparisons, CU patients had significantly higher prevalence of psychiatric medication use among each of the 3 severity groups (Table 2).

Results from multivariate analysis showed that severe CU patients had the highest relative risk of psychiatric disorders (RR 2.32, 95% CI 1.80-3.00), followed by moderate CU (RR 1.50, 95% CI 1.43-1.57) and mild CU (RR 1.43, 95% CI 1.40-1.46). In contrast, moderate CU had the highest relative risk of psychiatric medication use (RR 2.70, 95% CI 2.64-2.76), followed by severe CU (RR 2.09, 95% CI 1.77-2.48) and mild CU (RR 1.95, 95% CI 1.93-1.98) (Table 3).

Results from subgroup analysis showed that, when compared with their respective comparisons, both female and male patients had significantly higher prevalence of having psychiatric disorders in each of the 3 severity groups. Male patients had a significantly higher RR of psychiatric disorders than the female patients only in the mild group but not in the moderate and severe groups (Figure 2). Patients aged ≥ 50 years old had higher prevalence of psychiatric disorders in each of the 3 severity groups, but the RR of psychiatric disorders in comparison to their comparisons was significantly lower than those of patients aged < 50 years old in the mild and moderate groups (Figure 2).

Similarly, when compared with their respective comparisons, both female and male, as well as younger and older patients had significantly higher prevalence of psychiatric medication prescription in each of CU severity groups. CU patients < 50 years old had significantly higher RR of psychiatric medication prescription among each of the severity groups (Figure 3).

Discussion

Only limited studies of the association of psychiatric disorders and psychiatric medication prescription with CU severity in national populations have been conducted. In this study, we tried to divide the CU patients into mild, moderate, and severe groups according to their medication types based on the national guidelines of CU treatment in

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Taiwan.¹⁹ The advantage of this approach was avoiding the misclassification of severity based only on subjective judgements and clinical impressions from a few visits. However, the limitations of the approach may include non-adherence to the current treatment guidelines, failure to detect self-paid medications, and the misclassification of severity due to intermittent treatment in the studied period. The above limitations may also contribute to the higher prevalence and risk of psychiatric medication prescription observed in the moderate CU group than in the severe CU group, as some severe cases might have been classified into the moderate group. Nonetheless, the reported data still reflect the clinical situation in daily practice because the prevalences and risks of psychiatric disorders were correlated with the CU severity levels. Taking the above points into consideration, the risk was significantly different in all comparisons if we combined the moderate and severe CU groups together (Supplementary Table S1 and Supplementary Figure S1).

The current study reported that the overall prevalence of psychiatric disorders in CU ranged from 7.0-11.76%, which is similar to the rates indicated in some previous reports,^{21, 23, 24} but lower than those indicated in others.^{5, 7, 9, 13, 16} Previous hospital-based studies using questionnaires may have identified higher percentages of patients with psychiatric or mental symptoms rather than the prevalence of real clinical diagnoses. This discrepancy in the prevalences is also evidenced by those studies using

questionnaires in the general population²¹ or using health insurance databases,¹⁸ both of which showed a similar or lower prevalence of psychiatric disorders in urticaria patients in comparison to the current report. If we consider CU patients with psychiatric medication prescription as potentially having psychiatric symptoms, the prevalence was higher (20.37-29.55%). Therefore, a comprehensive approach to assessing mental health status and psychiatric medication prescription is needed in managing CU patients. In this study, specific disorders of sleep of nonorganic origin and adjustment reaction both showed consistently higher prevalences in the CU patients of the 3 different severity groups than in the controls. The mild and moderate CU groups also had higher prevalences of major depression, anxiety, dissociative and somatoform disorders, nondependent abuse of drugs, and depressive disorder than the controls. The above findings are consistent with those of previous reports.⁵⁻¹⁶ The failure to detect significant differences of prevalence of the above-mentioned psychiatric disorders in the severe CU group might just reflect the relatively low number of patients in this group.

We also found that the CU patients younger than 50 had significantly higher risks of psychiatric disorders in the mild and moderate CU groups, and also a higher risk of psychiatric medication prescription in all the CU severity groups. Young adult patients may face more life events and stress from work, family, and urticaria itself. The

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influences of age and gender are associated with different degrees of social support and also different levels of personal coping ability. When facing stressful life events, younger patients and females tend to obtain less family support and exhibit poor coping ability, which might predispose them to the development of urticaria.¹⁵

In conclusion, we found that the prevalence and risk of psychiatric disorders (specific disorders of sleep of nonorganic origin, adjustment reaction, major depression, anxiety, dissociative and somatoform disorders, nondependent abuse of drugs, and depressive disorder) and psychiatric medication prescription were significantly higher in CU patients than in controls in the general population. The above findings indicate that mental health evaluations and management should be included in routine clinical practice in managing CU patients.

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Figure legends

Figure 1 Selection process for cases of CU in 2011.

Figure 2 Subgroup analysis of the prevalences of psychiatric disorders in CU patients.

Figure 3 Subgroup analysis of the prevalence and risk of psychiatric medication prescription in CU patients of different severities.

Table 1. Patient profile of CU patients versus their comparisons

	Total				Mild *				Moderate*				Severe*			
	cases		comparisons		cases		comparisons		cases		comparisons		cases		comparisons	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total	167,132	100	668,528	100	138,029	100	552,116	100	28,414	100	113,656	100	689	100	27,56	100
Age																
<20	25,834	15.46	103,336	15.46	23,102	16.74	92,408	16.74	2,705	9.52	10,820	9.52	27	3.92	108	3.92
20-29	18,476	11.05	73,904	11.05	15,231	11.03	60,924	11.03	3,160	11.12	12,640	11.12	85	12.34	340	12.34
30-39	26,921	16.11	107,684	16.11	21,556	15.62	86,224	15.62	5,218	18.36	20,872	18.36	147	21.34	588	21.34
40-49	30,274	18.11	121,096	18.11	24,076	17.44	96,304	17.44	6,041	21.26	24,164	21.26	157	22.79	628	22.79
50-59	28,391	16.99	113,564	16.99	23,167	16.78	92,668	16.78	5,070	17.84	20,280	17.84	154	22.35	616	22.35
60-69	17,332	10.37	69,328	10.37	14,373	10.41	57,492	10.41	2,885	10.15	11,540	10.15	74	10.74	296	10.74
≥70	19,904	11.91	79,616	11.91	16,524	11.97	66,096	11.97	3,335	11.74	13,340	11.74	45	6.53	180	6.53
Gender																
Male	72695	43.50	290,780	43.50	59,316	42.97	237,264	42.97	13,097	46.09	52,388	46.09	282	40.93	1,128	40.93
Female	94,437	56.50	377,748	56.50	78,713	57.03	314,852	57.03	15,317	53.91	61,268	53.91	407	59.07	1,628	59.07
Urbanization Level																
1	49,843	29.82	199,372	29.82	40,322	29.21	161,288	29.21	9,186	32.33	36,744	32.33	335	48.62	1,340	48.62
2	47,337	28.32	189,348	28.32	39,283	28.46	157,132	28.46	7,906	27.82	31,624	27.82	148	21.48	592	21.48
3	33,960	20.32	135,840	20.32	28,397	20.57	113,588	20.57	5,465	19.23	21,860	19.23	98	14.22	392	14.22
4	21,375	12.79	85,500	12.79	17,724	12.84	70,896	12.84	3,581	12.6	14,324	12.6	70	10.16	280	10.16
5	3,031	1.81	12,124	1.81	2,577	1.87	10,308	1.87	447	1.57	1,788	1.57	7	1.02	28	1.02
6	5,648	3.38	22,592	3.38	4,707	3.41	18,828	3.41	927	3.26	3,708	3.26	14	2.03	56	2.03
7	5,938	3.55	23,752	3.55	5,019	3.64	20,076	3.64	902	3.17	3,608	3.17	17	2.47	68	2.47

* P-value=1

Table 2. Prevalence of psychiatric disorders and psychiatric medication use among CU cases vs. comparisons

	Mild					Moderate					Severe				
	cases		comparisons		<i>P-value</i>	cases		comparisons		<i>P-value</i>	cases		comparisons		<i>P-value</i>
	n	%	n	%		n	%	n	%		n	%	n	%	
Psychiatric disorders	9,658	7.00	26,945	4.88	<.0001	2,129	7.49	5,665	4.98	<.0001	81	11.76	138	5.01	<.0001
Dementias (ICD-9=290)	745	0.54	3,106	0.56	0.309	174	0.61	623	0.55	0.195	3	0.44	10	0.36	0.781
Alcoholic psychoses (ICD-9 =291)	27	0.02	89	0.02	0.378	8	0.03	23	0.02	0.419	0	0.00	0	0.00	—
Drug psychoses (ICD-9 =292)	16	0.01	39	0.01	0.092	3	0.01	8	0.01	0.547	0	0.00	0	0.00	—
Transient organic psychotic conditions (ICD-9 =293)	60	0.04	208	0.04	0.328	18	0.06	32	0.03	0.005	0	0.00	0	0.00	—
Other organic psychotic conditions (ICD-9 =294)	272	0.20	1,077	0.20	0.881	72	0.25	210	0.18	0.020	2	0.29	7	0.25	0.868
Schizophrenic disorders (ICD-9 =295)	450	0.33	2,362	0.43	<.0001	92	0.32	505	0.44	0.005	0	0.00	20	0.73	0.025
Major Depression (ICD-9 =296.2/296.3)	1,086	0.79	2,683	0.49	<.0001	253	0.89	550	0.48	<.0001	6	0.87	17	0.62	0.464
Bipolar disorder (ICD-9 =296.1/296.4/296.5)	195	0.14	679	0.12	0.087	48	0.17	157	0.14	0.221	3	0.44	1	0.04	0.006
Paranoid states (ICD-9 =297)	48	0.03	206	0.04	0.660	12	0.04	56	0.05	0.628	2	0.29	1	0.04	0.043
Other nonorganic psychoses (ICD-9=298)	110	0.08	316	0.06	0.003	27	0.10	71	0.06	0.062	0	0.00	3	0.11	0.386
Psychoses with origin specific to childhood (ICD-9=299)	74	0.05	219	0.04	0.025	11	0.04	32	0.03	0.360	0	0.00	1	0.04	0.617
Anxiety, dissociative and somatoform disorders (ICD-9=300)	8,303	6.02	19,748	3.58	<.0001	2,025	7.13	4,117	3.62	<.0001	35	5.08	105	3.81	0.131
Obsessive-compulsive personality disorder (ICD-9=301.4)	11	0.01	30	0.01	0.274	1	0.00	6	0.01	0.706	0	0.00	1	0.04	0.617
Drug dependence (ICD-9=304)	57	0.04	123	0.02	<.0001	6	0.02	26	0.02	0.860	0	0.00	0	0.00	—
Nondependent abuse of drugs (ICD-9=305)	257	0.19	492	0.09	<.0001	92	0.32	117	0.10	<.0001	1	0.15	1	0.04	0.289
Specific disorders of sleep of nonorganic origin (ICD-9=307.4)	2,559	1.85	5,752	1.04	<.0001	611	2.15	1,226	1.08	<.0001	15	2.18	31	1.12	0.031
Adjustment reaction (ICD-9=309)	266	0.19	672	0.12	<.0001	83	0.29	150	0.13	<.0001	3	0.44	2	0.07	0.025
Depressive disorder, not elsewhere classified (ICD-9=311)	644	0.47	1,669	0.30	<.0001	166	0.58	352	0.31	<.0001	5	0.73	8	0.29	0.096
Psychiatric medication use	28,121	20.37	56,123	10.17	<.0001	8,395	29.55	11,779	10.36	<.0001	154	22.35	284	10.3	<.0001
Anxiolytics (N05b)	23,273	16.86	43,514	7.88	<.0001	7,297	25.68	9,065	7.98	<.0001	132	19.16	218	7.91	<.0001
Anti-depressants (N06a)	5,625	4.08	14,008	2.54	<.0001	1,446	5.09	2,994	2.63	<.0001	28	4.06	66	2.39	0.0162
Sleep pills for insomnia (N05cf)	7,877	5.71	16,060	2.91	<.0001	1,820	6.41	3,422	3.01	<.0001	42	6.1	92	3.34	0.001

Table 3. Risk of psychiatric disorders and psychiatric medication use in CU patients of different severity

	Crude RR	95% CI		<i>P-value</i>	Adjusted RR*	95% CI		<i>P-value</i>
Psychiatric disorders								
Mild CU	1.43	1.40-	1.47	<.0001	1.43	1.40-	1.46	<.0001
Moderate CU	1.50	1.43-	1.58	<.0001	1.50	1.43-	1.57	<.0001
Severe CU	2.35	1.81-	3.05	<.0001	2.32	1.80-	3.00	<.0001
Psychiatric medication use								
Mild CU	2.00	1.98-	2.03	<.0001	1.95	1.93-	1.98	<.0001
Moderate CU	2.85	2.78-	2.92	<.0001	2.70	2.64-	2.76	<.0001
Severe CU	2.17	1.82-	2.59	<.0001	2.09	1.77-	2.48	<.0001

*Adjusted for age and sex

Patients who had at least 2 outpatient visits with primary/secondary ICD-9-CM codes of 708.1 (idiopathic urticaria), 708.8 (other specified urticaria) or 708.9 (urticaria unspecified) and with anti-histamine prescription in 2011 NHIRD (N=294,337)

Exclusion Criteria

1. The interval between the 1st CSU outpatient visit and the last CSU visit in 2011 was less than 6 weeks (N=127,025)
2. Patients who had at least 2 outpatient visits with primary/secondary ICD-9-CM code of 287.0 (vasculitis and allergic purpura) within 3 months before or after the 1st CSU outpatient visit (N=83)

167,229 patients were enrolled

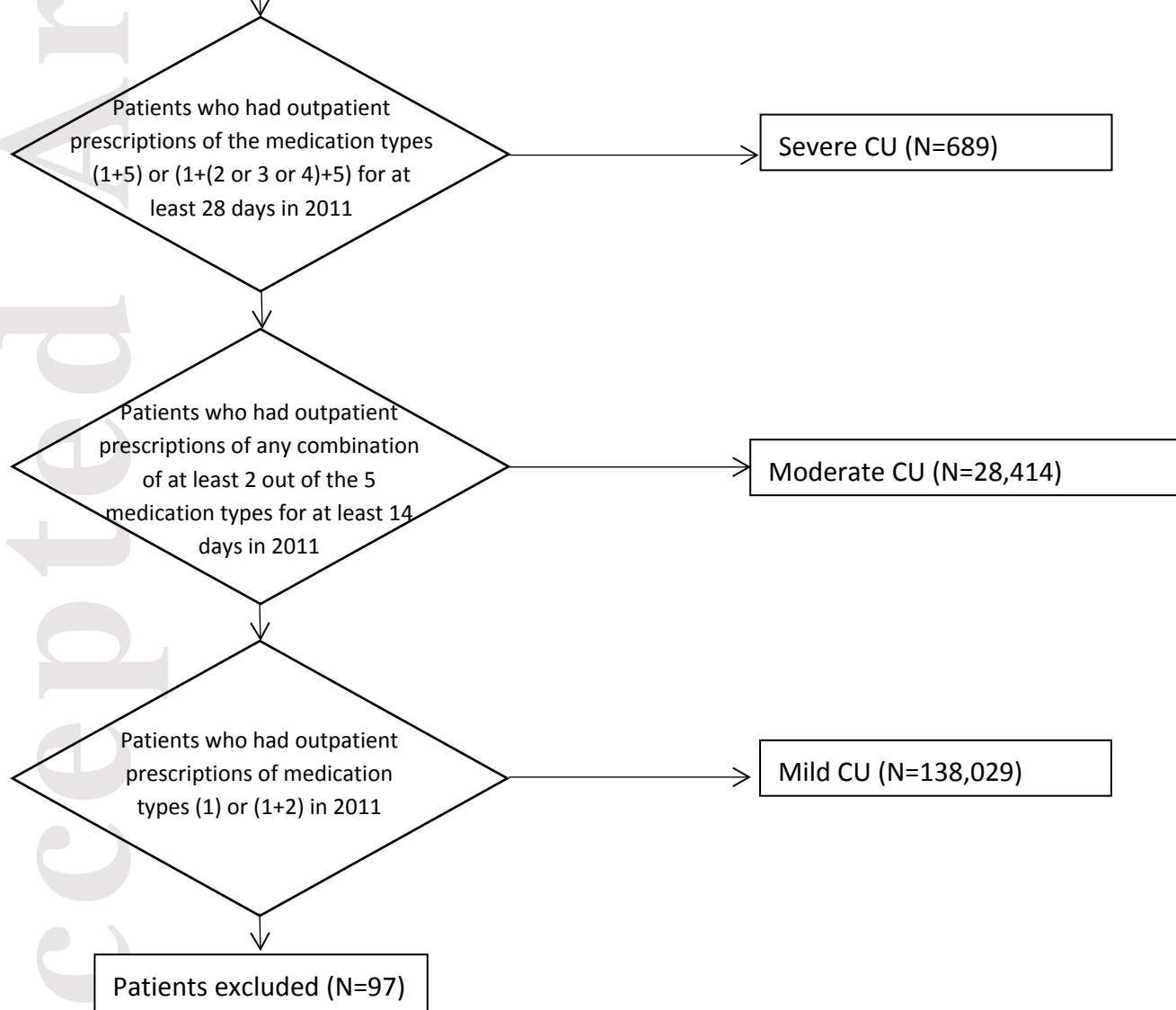


Figure 1. Patient selection process

*** Types of medication associated with CU treatment**

Medication types	Description
1	Monotherapy with 1st generation or 2nd generation H1 antihistamines
2	Combination therapies with 1st generation H1 antihistamines, 2nd generation H1 antihistamines, and H2 antihistamines
3	Systemic corticosteroids
4	Use of either ketotifen, oxatomide, doxepin, colchicine, hydroxychloroquine, leukotriene, nifedipine, or warfarin
5	Use of cyclosporine, azathioprine, cyclophosphamide, mycophenolic acid, omalizumab, methotrexate, or interferon

Figure 2. Subgroup analysis on the prevalence of psychiatric disorders in CU patients

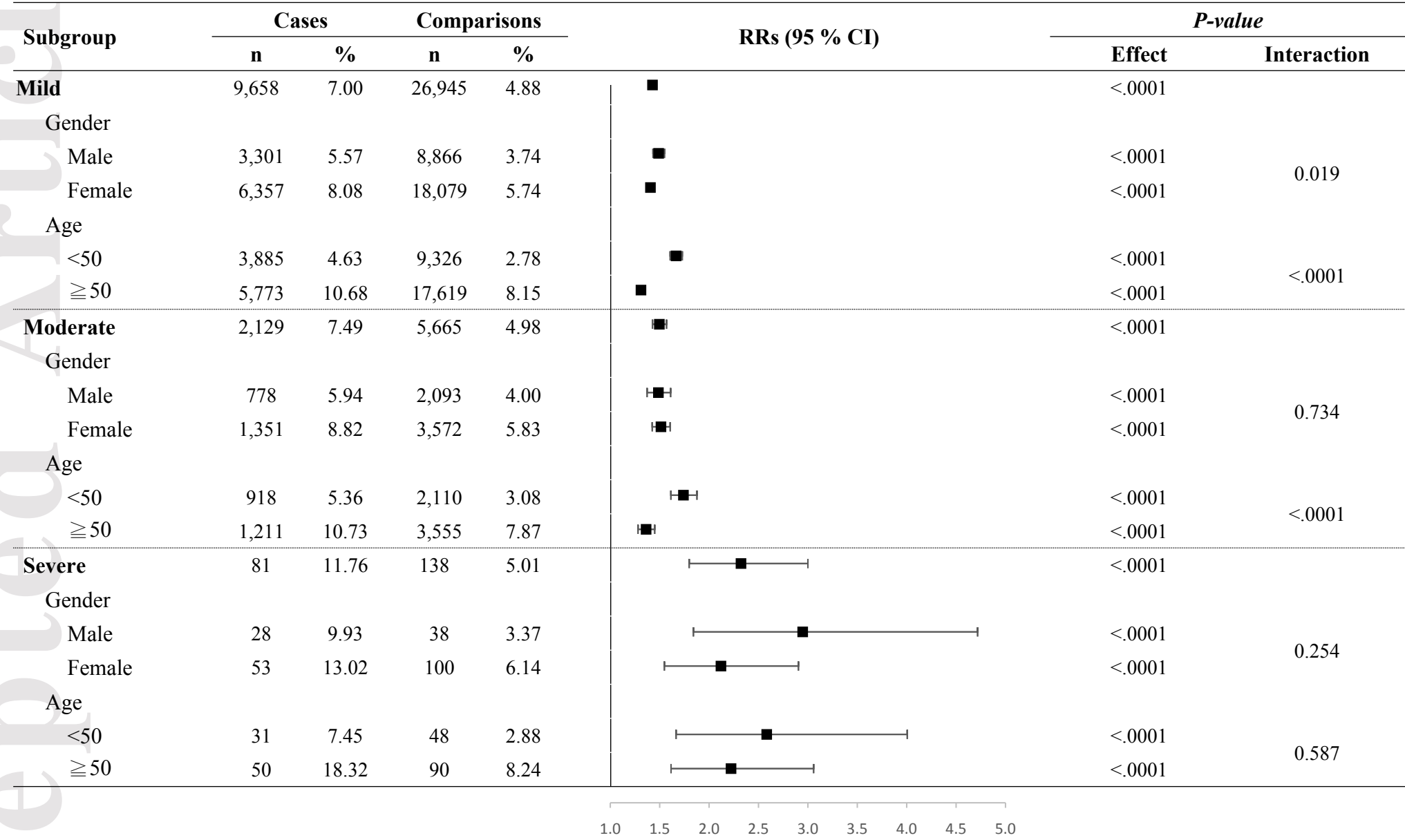
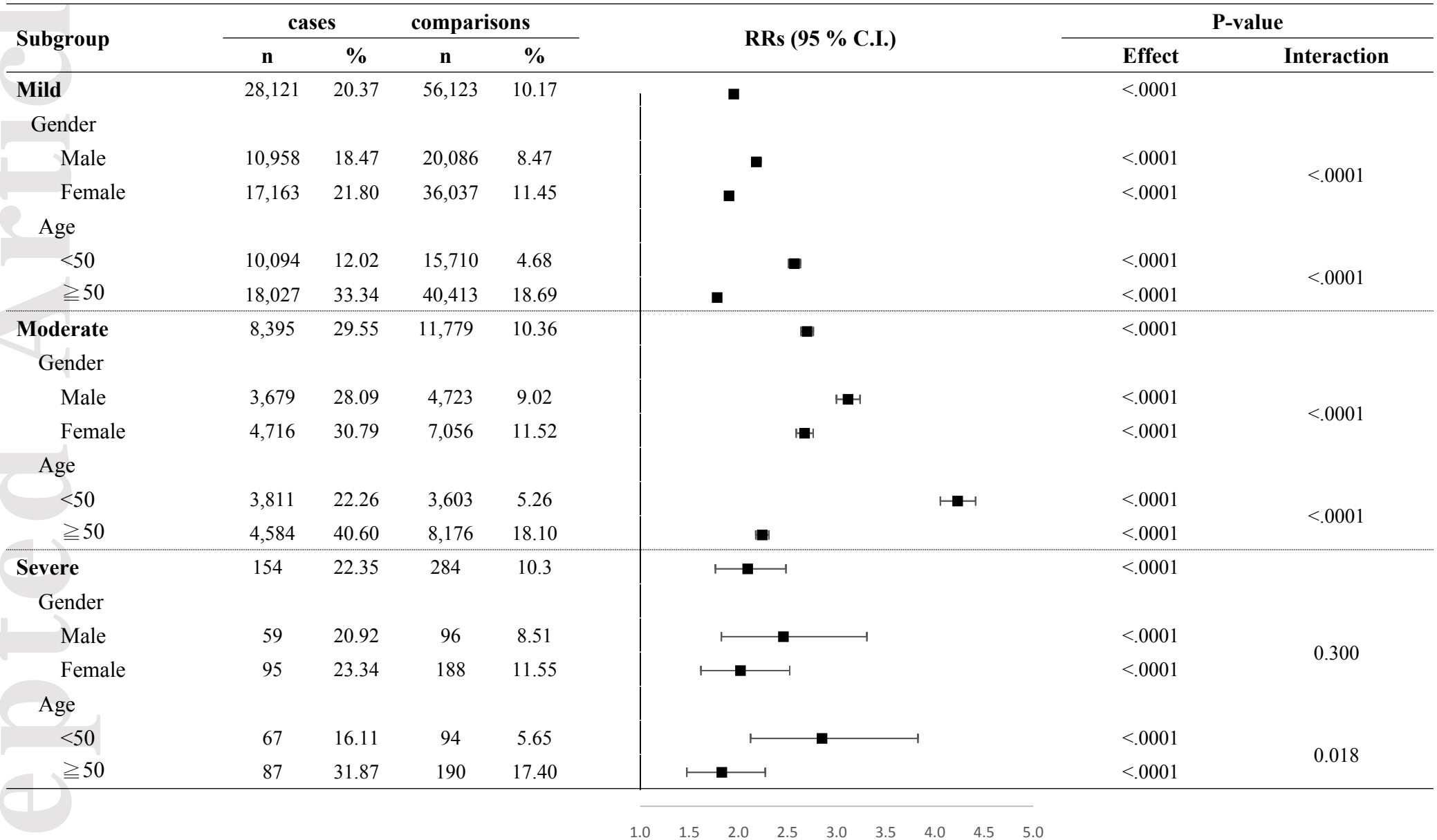


Figure 3. Subgroup analysis on the prevalence and risk of psychiatric medication use in CU patients of different severity



Supplementary Table S1. Risk psychiatric disorders and psychiatric medication use in CU patients of different severity (combining moderate and severe groups)

	Crude RR	95% CI		P-value	Adjusted RR*	95% CI		P-value
Psychiatric disorders								
Mild	1.43	1.40-	1.47	<.0001	1.43	1.40-	1.46	<.0001
Moderate to Severe	1.52	1.45-	1.60	<.0001	1.52	1.45-	1.59	<.0001
Psychiatric medication use								
Mild	2.00	1.98-	2.03	<.0001	1.95	1.93-	1.98	<.0001
Moderate to Severe	2.83	2.77-	2.91	<.0001	2.68	2.62-	2.75	<.0001

* Adjusted for age and sex

Supplementary Figure S1. Subgroup analysis on the prevalence and risk of psychiatric medication use in CU patients of different severity (combining moderate and severe group)

