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Association between sleep disorders and subsequent chronic spontaneous urticaria development

A population-based cohort study

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Abstract

Patients with chronic spontaneous urticaria (CSU) often have sleep disorders (SDs) because of pruritus. However, SDs might also contribute to the development of CSU. Here, we present the first population-based cohort study on the association between SDs and subsequent CSU development.

This study investigated whether SDs increase the risk of CSU by using a population-based database in Taiwan.

This retrospective matched-cohort study included 105,892 patients with new-onset SDs (SD cohort) and 105,892 randomly selected controls (control cohort). Each patient was monitored for 10 years to individually identify patients who were subsequently diagnosed as having CSU during the follow-up period. A Cox proportional hazard regression analysis was conducted to determine the risk of CSU in patients with SDs compared with the controls.

All relevant comorbidities were more prevalent in the SD cohort than in the control cohort ($P < .001$). During the follow-up period, the incidence rates of CSU among the patients with SDs and controls were 53.4 and 28.3 per 10,000 person-years, respectively. After adjustment for age, sex, and comorbidities, the adjusted hazard ratio for CSU in the SD cohort was 1.83 (95% confidence interval = 1.73–1.93, $P < .001$).

The risk of CSU was higher in the patients with SDs than in the controls.

Abbreviations: CI = confidence interval, CRH = corticotrophin-releasing hormone, CSU = chronic spontaneous urticaria, HPA = hypothalamic–pituitary–adrenocortical, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IL = interleukin, LHID = Longitudinal Health Insurance Database, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, PY = person-year, SD = sleep disorder, Treg = regulatory T cells.

Keywords: chronic spontaneous urticaria, population-based study, retrospective cohort study, sleep disorders

1. Introduction

Chronic spontaneous urticaria (CSU) is a debilitating skin disease that affects approximately 0.5% to 1% of the general population.[1] It is characterized by persistent or recurrent eruptions of itchy wheals lasting for more than 6 weeks.[2] The disease predominantly affects adults aged 30 to 40 years and has a female preponderance (female: male ratio = 1.46:1–2:1).[3–5] Although CSU is often self-limiting, its effects on quality of life and its contribution to the economic burden are enormous.[1,6]

Unlike chronic inducible urticaria, most CSU has no obviously identifiable external triggers. Therefore, the pathogenesis of CSU has not yet been well delineated. The activation and degranulation of mast cells are the key pathophysiological events, but the underlying triggering stimuli and the complexity of effector mechanisms remain unclear. Several factors, including autoimmunity, stress, and inflammation, are considered the possible causes of CSU.[4,7] Furthermore, comorbidities such as thyroid disorders and autoimmune diseases are more prevalent among patients with CSU.[8–10]

Patients with CSU often have sleep disturbances due to pruritus. Frequent interference with sleep has been reported by more than 50% of patients with CSU.[4,11–13] By contrast, studies regarding the relationship between sleep disorders (SDs) and the subsequent development of CSU are scarce.[14] Elucidating the possible association between SDs and CSU might facilitate the prevention and treatment of CSU. Therefore, we conducted a population-based retrospective cohort study to assess the risk of CSU in patients with preceding SDs.

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2. Materials and methods

2.1. Data source

All the data for the study were obtained from the Longitudinal Health Insurance Database (LHID), which is a subset of the National Health Insurance Research Database (NHIRD). The NHIRD contains claims data from the Taiwan National Health Insurance (NHI) program, a nationwide and single-payer health insurance program for Taiwan citizens. The Taiwan NHI covered nearly 99% of 23 million Taiwan citizens in 2014. The LHID consists of 1 million randomly selected insured people between 1996 and 2000. The age and sex distribution do not differ between the LHID and NHIRD. The LHID contains data from the registry for beneficiaries, disease diagnosis records, medical prescriptions, and other medical services, and the database is updated every year. To protect the privacy of the beneficiaries, the Taiwan government removed the original identification number of beneficiaries from the database and prepared anonymous and surrogate identification codes to link the different claim files of each beneficiary. This study was approved by the Ethics Review Board of the China Medical University (approval no. CMU-REC-101–012).

The disease recording system for the LHID was based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The entire disease history for each patient and control was collected from inpatient and outpatient files.

2.2. Study population

This study had a retrospective population-based cohort study design. We established an SD cohort and a control cohort to compare the risk of CSU between the individuals with and without SDs. The SD cohort consisted of individuals who received a first SD diagnosis (ICD-9-CM 307.4 and 780.5) between 2001 and 2010. The index date of a patient with an SD was the day on which the SD was initially diagnosed. SD cohort was further divided into 2 subgroups: sleep apnea (ICD-9-CM 780.51, 780.53, and 780.57) and nonapnea SD (ICD-9-CM 307.4, 780.50, 780.52, 780.54, 780.55, 780.56, and 780.59). The control cohort consisted of individuals without a history of SDs in the LHID and was frequency matched by age (per 5 years) and sex at a 1:1 ratio; we randomly assigned a month and a day with the same index year of the matched cases as the index date. The outcome of interest was CSU, which was identified in our study as having a diagnosis of ICD-9-CM 708.1 (idiopathic urticaria), 708.8 (other specified urticaria), or 708.9 (urticaria, unspecified) at least 4 times in outpatients or at least 3 times in inpatients, with the interval of the first and the last diagnosis being more than 6 weeks. Patients with the diagnoses of ICD-9-CM 708.1, 708.8, and 708.9 before the index date were excluded from the study. We stopped the follow-up when an individual withdrew from the health insurance program, when CSU occurred, or on December 31, 2011.

The confounding factors in this study were age, sex, and comorbidities. A comorbidity was defined as a coexisting medical condition diagnosed before the index date. The relevant comorbidities to CSU were categorized into 3 groups as follows: allergic diseases, comprising asthma (ICD-9-CM 493), allergic rhinitis (ICD-9-CM 477), and atopic dermatitis (ICD-9-CM 691); autoimmune diseases, comprising systemic lupus erythematosus (ICD-9-CM 710.0), rheumatoid arthritis (ICD-9-CM 714.0), and ankylosing spondylitis (ICD-9-CM 720.0); thyroid diseases, comprising nontoxic goiter (ICD-9-CM 240, 241), thyrotoxicosis and toxic goiter (ICD-9-CM 242), hypothyroidism (ICD-9-CM 244), thyroiditis (ICD-9-CM 245), and other disorders of thyroid (ICD-9-CM 246); anxiety (ICD-9-CM 300.00); and depression (ICD-9-CM 296.2, 296.3, 300.4, and 311).

2.3. Statistical analysis

The age distribution is presented as mean and standard deviation and the sex and comorbidity distribution is represented as numbers and percentages. To assess the distribution difference between these 2 cohorts, we performed the Student *t* test for age and the Chi-squared test or Chi-square test with Yates' correction for sex and comorbidities. The chronic urticaria incidence density for the study cohorts was calculated by counting the total number of chronic urticaria events and dividing this number by the sum of the follow-up years (per 10,000 person-years). We used the Kaplan–Meier method to measure the cumulative incidence curve for the 2 study cohorts and applied the log-rank test to assess the difference between the curves representing individuals with and without SDs. To estimate the difference in the risk of chronic urticaria between the SD cohort and control cohort, we used single and multivariable Cox proportional hazard models to measure the hazard ratios (HRs) and 95% confidence intervals (95% CIs). We also implemented a stratified analysis to investigate the risk of chronic urticaria in the SD and control cohorts by using different statuses of demographic factors and comorbidities.

We used the SAS 9.4 software package (SAS Institute, Cary, NC) for data management and statistical analysis. The cumulative incidence curves were drawn using R software (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were 2-sided, and $P < .05$ was considered statistically significant.

3. Results

In total, we enrolled 105,892 patients with SDs and the same number of the controls with a similar mean age (47.7 years) and sex ratio (female: 60%) (Table 1). The percentage of allergic diseases, autoimmune diseases, and thyroid disorders in the SD cohort was higher than that in the control cohort (all $P < .001$).

The cumulative incidence in the whole SD cohort was significantly higher than that in the control cohort ($P < .001$) (Fig. 1). The overall incidence of CSU were 28.3, 53.6, 45.9, and 53.4 per 10,000 person-years in the controls without SDs, the nonapnea SD, the sleep apnea, and the SD cohorts, respectively (Table 2). The corresponding adjusted HRs (aHRs) of the CSU were 1.82 (95% CI = 1.72–1.93), 1.64 (95% CI = 1.34–2.00), and 1.81 (95% CI = 1.71–1.92) compared with control, respectively, after adjusting for age, sex, and comorbidities of atopic diseases, autoimmune diseases, thyroid diseases, anxiety, and depression. In the multivariable model, the risk of CSU increased with age from 1.05 (95% CI = 0.99–1.12) to 1.11 (95% CI = 1.03–1.20) and was 1.24-fold higher for women than for men (95% CI = 1.18–1.32). The risk of developing CSU was higher for patients with atopic diseases (aHR = 1.28, 95% CI = 1.21–1.36), autoimmune diseases (aHR = 1.33, 95% CI = 1.11–1.60), and anxiety (aHR = 1.11, 95% CI = 1.00–1.24).

Table 3 presents a comparison of the risk of CSU between the individuals with and without SDs stratified by demographic and comorbidity status. Compared with the controls, the risk of CSU was 1.92-fold, 1.73-fold, and 1.82-fold higher in the patients

Table 1

Demographic status compared between comparison cohort and sleep disorder cohort.

Variable	Comparison cohort N = 105,892 (%)	Sleep disorder cohort All N = 105,892 (%)	Sleep disorder cohort Nonapnea sleep disorder N = 102,520 (%)	Sleep disorder cohort Sleep apnea N = 3372 (%)	*P*
Age, y (SD)*	47.7 (16.4)	47.7 (16.3)	47.8 (16.4)	46.0 (14.4)	.4106
Sex					.99
Female	63,550 (60.0)	63,550 (60.0)	62,435 (60.9)	1115 (33.1)	
Male	42,342 (40.0)	42,342 (40.0)	40,085 (39.1)	2257 (66.9)	
Comorbidities					
Atopic diseases	15,840 (15.0)	27,853 (26.3)	26,748 (26.1)	1105 (32.8)	<.001
Autoimmune diseases†	1155 (1.09)	1912 (1.81)	1853 (1.81)	59 (1.75)	<.001
Thyroid diseases†	2871 (2.71)	4904 (4.63)	4738 (4.62)	166 (4.92)	<.001
Anxiety†	1975 (1.87)	8596 (8.12)	8322 (8.12)	274 (8.13)	<.001
Depression†	1221 (1.15)	6114 (5.77)	5939 (5.79)	175 (5.19)	<.001

Chi-square test.

* *t* test.

† Chi-square test with Yates' correction.

with SDs aged < 45 years (aHR = 1.91, 95% CI = 1.75–2.08), 45 to 64 years (aHR = 1.71, 94% CI = 1.56–1.88), and ≥ 65 years (aHR = 1.81, 95% CI = 1.58–2.08), respectively. Compared with the control cohort, the SD cohort had a similar risk of CSU in female (aHR = 1.85, 95% CI = 1.72–1.98) and male (aHR = 1.76, 95% CI = 1.59–1.94) patients. In both study cohorts with at least 1 comorbidity, the patients with SDs had a 1.73-fold higher risk of CSU than did the controls (aHR = 1.73, 95% CI = 1.56–1.93). Furthermore, the patients with SDs had a 1.85-fold higher risk of CSU than did the individuals without any relevant comorbidities (aHR = 1.85, 95% CI = 1.73–1.98). The results also revealed that the presence of SDs was significantly associated with an increased risk of CSU stratified by comorbidities. Among the noncomorbid subjects, patients with SD had a higher risk of CSU than the control cohort (aHR = 1.84 for atopic diseases; aHR = 1.81 for autoimmune diseases; aHR = 1.82 for thyroid diseases; aHR = 1.82 for anxiety; aHR = 1.82 for depression).

4. Discussion

The association between SDs and the subsequent development of CSU was rarely discussed before. To our knowledge, this is the first epidemiologic study to investigate SDs and subsequent CSU. In the literature, only 1 questionnaire study involving 208 subjects determined that insomnia is a predisposing factor for CSU in patients who had stress from major life events in the 6 months before symptom onset.[14] Stress can induce SDs, and sleep deprivation has itself been hypothesized to be a

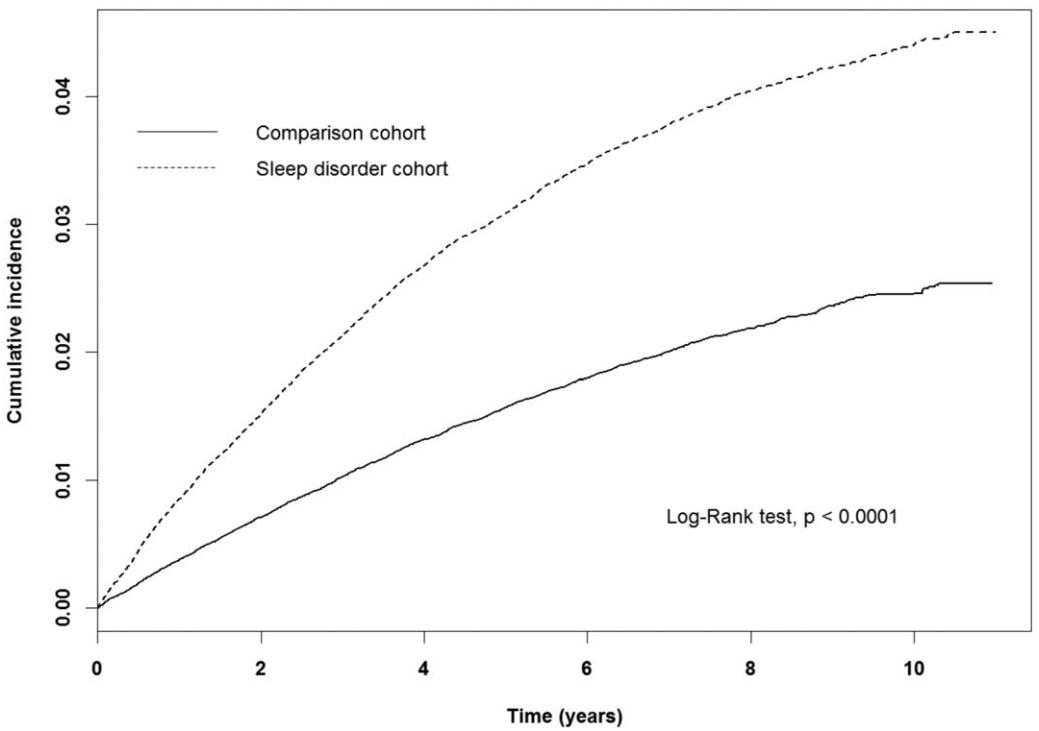

Figure 1. The chronic spontaneous urticaria incidence curves for sleep disorder and comparison cohort.

Table 2

Incidence of chronic spontaneous urticaria and multivariate cox proportional hazards regression analysis measured hazard ratio for study cohort.

Variables	Event	PYs	Rate	Crude HR 95% CI	Adjusted HR* 95% CI
Sleep disorders					
No	1895	670,782	28.3	ref	ref
Nonapnea sleep disorder	3520	656,447	53.6	1.90 (1.80–2.01)	1.82 (1.72–1.93)
Sleep apnea	100	21,805	45.9	1.63 (1.34–2.00)	1.64 (1.34–2.00)
Both	3620	678,252	53.4	1.90 (1.79–2.00)	1.81 (1.71–1.92)
Age group, y					
<45	2505	639,618	39.2	ref	ref
45–64	2061	499,229	41.3	1.06 (1.00–1.12)	1.05 (0.99–1.12)
≧65	949	210,188	45.2	1.13 (1.05–1.22)	1.11 (1.03–1.20)
Sex					
Male	1863	517,470	36.0	ref	Ref
Female	3652	831,565	43.9	1.23 (1.18–1.32)	1.24 (1.18–1.32)
Atopic diseases					
No	4100	1,094,945	37.4	ref	ref
Yes	1415	254,090	55.7	1.44 (1.35–1.53)	1.28 (1.21–1.36)
Autoimmune diseases					
No	5398	1,329,962	40.6	ref	ref
Yes	117	19,073	61.3	1.51 (1.25–1.81)	1.33 (1.11–1.60)
Thyroid diseases					
No	5282	1,300,320	40.6	ref	ref
Yes	233	48,715	47.8	1.17 (1.03–1.33)	0.99 (0.87–1.13)
Anxiety					
No	5141	1,284,760	40.0	ref	ref
Yes	374	64,274	58.2	1.43 (1.29–1.59)	1.11 (1.00–1.24)
Depression					
No	5259	1,303,586	40.3	ref	ref
Yes	256	45,448	56.3	1.39 (1.23–1.58)	1.09 (0.96–1.23)

Model adjusted for age, sex, atopic diseases, autoimmune diseases, thyroid diseases, anxiety, and depression.

CI = confidence interval, HR = hazard ratio, PYs = person-years, rate = incidence rate, per 10,000 person-years.

* Variables found to be significant in the univariable analysis were further examined in the multivariable analysis.

Table 3

Demographic factors and comorbidities stratified analysis estimated hazard ratio of chronic spontaneous urticaria risk in sleep disorder cohort compared with comparison cohort.

	Comparison cohort			Sleep disorder cohort			
Variables	Event	PYs	Rate	Event	PYs	Rate	Adjusted HR (95% CI)†
Age group, y							
<45	834	318,254	26.2	1671	321,364	52.0	1.91 (1.75–2.08)
45–64	738	249,649	29.6	1323	249,579	53.0	1.71 (1.56–1.88)
≧65	323	102,879	31.4	626	107,309	58.3	1.81 (1.58–2.08)
Sex							
Male	651	257,898	25.2	1212	259,572	46.7	1.76 (1.59–1.94)
Female	1244	412,885	30.1	2408	418,680	57.5	1.85 (1.72–1.98)
Comorbidity*							
No	1461	552,168	26.5	2095	430,747	48.6	1.85 (1.73–1.98)
Yes	434	118,614	36.6	1525	247,505	61.6	1.73 (1.56–1.93)
Atopic diseases							
No	1560	582,423	26.8	2540	512,521	49.6	1.84 (1.72–1.96)
Yes	335	88,359	37.9	1080	165,731	65.2	1.74 (1.53–1.96)
Autoimmune diseases							
No	1869	663,858	28.2	3529	666,103	53.0	1.81 (1.71–1.92)
Yes	26	6924	37.6	91	12,149	74.9	1.91 (1.23–2.96)
Thyroid diseases							
No	1841	653,405	28.2	3441	646,914	53.2	1.82 (1.71–1.93)
Yes	54	17,377	31.1	179	31,338	57.1	1.72 (1.26–2.35)
Anxiety							
No	1852	659,803	28.1	3289	624,957	52.6	1.82 (1.72–1.93)
Yes	43	10,979	39.2	331	53,295	62.1	1.63 (1.19–2.25)
Depression							
No	1868	664,093	28.1	3391	639,493	53.0	1.82 (1.72–1.93)
Yes	27	6690	40.4	229	38,759	59.1	1.49 (1.00–2.23)

Model adjusted for age, sex, atopic diseases, autoimmune diseases, thyroid diseases, anxiety, and depression.

CI = confidence interval, HR = hazard ratio, PYs = person-years, rate = incidence rate, per 10,000 person-years.

* "No" meant the individual did not have any comorbidities; "Yes" presented the individual had at least 1 comorbidity.

† Variables found to be significant in the univariable analysis were further examined in the multivariable analysis.

stressor.[15] Therefore, stress may play a major role in SD-related CSU.

Stress as a trigger of and aggravating factor for CSU, although controversial, is well documented.[16–21] The mechanism of stress-induced CSU is proposed to involve interference with inflammation. Stress was ascertained to be associated with inflammation by the activation of the central hypothalamic–pituitary–adrenocortical (HPA) axis. In acute stressful situations, corticotrophin-releasing hormone (CRH) from the hypothalamus activates pituitary adrenocorticotrophin secretion, which in turn stimulates adrenal cortisol secretion for homeostasis regulation. Nevertheless, chronic stress may reduce cortisol secretion because of HPA axis fatigue that results in the increased secretion of inflammatory cytokines, which are counter-regulated by cortisol.[22] Studies have revealed that markers of systemic inflammation, such as C-reactive protein, interleukin (IL)-17, IL-18, IL-23, IL-6, and tumor necrosis factor-alpha, are significantly elevated in patients with CSU and positively correlate with disease severity.[23–26]

In the peripheral, CRH can also directly stimulate the dermal mast cells and increase vascular permeability through CRH-R1 receptor activation.[27] Expression of high levels of CRH-R1 receptor was also observed in the skin samples from patients with chronic urticaria.[28]

In addition to the adverse effects of psychological stress, sleep disturbance itself may aggravate CSU by disrupting the circadian rhythm of cortisol secretion. Increased inflammatory cytokines and low cortisol levels have been reported in patients with sleep disturbances.[29–32] Besides, sleep deprivation would abrogated the circadian rhythm of CD4(+)CD25(+) regulatory T cells (Treg), which play critical roles in maintaining peripheral tolerance and preventing autoimmunity.[33] Arshi et al[34] had found that a significant decrease of circulating Treg cells was detected in patients with chronic urticaria. To summarize, SDs may trigger CSU by increasing CRH secretion and activating inflammation by affecting both the HPA axis and circadian rhythm.

In our study, the results reveal a female predominance [adjusted (female-to-male) HR for CSU = 1.25, 95% CI = 1.18–1.32], as previously reported. However, the mean age in our cohorts is higher than that of the normal population (47.7 years in the SD and control cohorts, with the median age of the general population in Taiwan in 2017 being 40.7 years).[35] By contrast, the mean age of patients with CSU in previous studies has been reported to be between 30 and 40 years.[4,5] This may be because we excluded patients with pre-existing CSU, who were younger on average, and enrolled patients with SDs, and the control cohort was also frequency matched by age and sex.

CSU is difficult to assess in the general population because there is no specific ICD-9-CM diagnosis code for CSU. Cherepanov et al[36] conducted a study trying to validate an ICD-9-CM based algorithm for identification of patients with CSU and thus facilitate claims-based research. The results showed a positive predictive value of 90.4% for CSU when patients had diagnoses of at least 2 outpatient ICD-9-CM codes of 708.1 (idiopathic urticaria), 708.8 (other specific urticaria), and 708.9 (unspecified urticaria) at least 6 weeks apart, or had 1 outpatient diagnosis of 708.1, 708.8, or 708.9 and 1 diagnosis of 995.1 (angioneurotic edema) at least 6 weeks apart. We defined CSU in our study more rigorously as having a diagnosis of ICD-9-CM 708.1, 708.8, or 708.9 at least 4 times in outpatients or at least 3 times in inpatients, with the interval of the first and the last diagnosis being more than 6 weeks.

It was possible that some inducible urticaria will be misclassified into CSU in our study (e.g., aquagenic urticaria and contact urticaria). However, the proportion was expected to be low because many types of inducible urticaria have their own ICD-9-CM codes (e.g., 708.5 for cholinergic urticaria, 708.2 for cold/heat urticaria, 708.3 for symptomatic dermographism, 708.4 for vibratory urticaria, and 692.72 for solar urticaria).

The most crucial strength of this study is the use of a nationwide population-based database; therefore, this study is free from the effects of selection bias. In addition, the current analysis revealed that patients with either sleep apnea or nonapnea SDs had higher risk to developing CSU. However, some limitations of this study were apparent when we interpreted these results. First, the number of patients with SDs might have been underestimated because some of them may practice self-medication with over-the-counter medication.[37] Second, because we used a claims database, we could not inspect patients' history of possible eliciting factors, such as psychologic stress events, dietary habits, alcohol consumption, smoking behavior, or family history of CSU, which could compromise our findings. The relationship between SDs and CSU might be not a direct causal association, because there are too many contributing factors of SDs. Further studies should be conducted to clarify thoroughly the underlying mechanism linking SDs and CSU. Furthermore, the etiologies of autoreactive urticaria may be different from other CSU, but we could not differentiate between the 2 in this database, as autologous serum skin test was rarely performed in Taiwan.

In conclusion, this longitudinal cohort study involving 105,892 patients with SDs demonstrated that the patients with SDs had a 1.83-fold higher risk of developing CSU than did the general population. Despite the existence of a bidirectional relationship between SDs and CSU, in addition to the mentioned study limitations, this study still provides evidence of an association between SDs and CSU from a large population database, which increases the statistical power of the study and reduces its selective bias. Therefore, the findings suggest the likely importance of holistic care for patients with CSU and with preceding or concomitant SDs. The latest guidelines for the treatment of CSU recommend nonsedating H1-antihistamines as first and second lines of treatment.[2] Considering that a possible bidirectional relationship may exist between SDs and CSU, sedating antihistamines may be administered to selective patients to attenuate the vicious cycle.

Author contributions

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