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ORIGINAL ARTICLE

Epidemiology, comorbidities, and healthcare utilization of patients with chronic urticaria in Germany

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Abstract

Background Comprehensive data on the epidemiology and comorbidities of chronic urticaria (CU) in Germany are either limited, or not contemporary.

Objectives To investigate the epidemiology of CU, overall comorbidities and healthcare resource utilized by patients with CU in Germany, using an anonymized statutory health insurance (SHI) database.

Methods Anonymized SHI claims research database of the Institute for Applied Health Research, Berlin [InGef] (01 January 2015–30 September 2018) was used to analyse insured individuals with a confirmed diagnosis of CU (ICD-10-GM codes). Twelve-month diagnosed prevalence and incidence, comorbidities (vs. atopic dermatitis and psoriasis), and healthcare utilization by patients with CU were investigated.

Results Of 4 693 772 individuals of all ages listed in the database, 3 538 540 were observable during 2017. Overall, 17 524 patients (~0.5%) were diagnosed with CU; chronic spontaneous urticaria (CSU: 71.2%), chronic inducible urticaria (CIndU: 19.7%), CSU+CIndU (9.1%). Females, vs. males, had higher diagnosed prevalence (0.62% vs. 0.37%) and diagnosed incidence (0.18% vs. 0.11%) of CU among all patients. Patients most frequently visited general practitioners (41.3% of total visits). Hypertensive diseases (43.5%), lipoprotein metabolism disorders (32.1%) and affective disorders (26.0%) were the most frequently reported comorbidities of special interest. Rates of most comorbidities of special interests were similar to atopic dermatitis and psoriasis patients, and all higher vs. overall population. More than half (54.1%) of all CU patients were not prescribed any treatment. Second-generation H_1-antihistamines were the most commonly prescribed medication for adult (17.9%) and paediatric (27.9%) patients. Patients with CIndU (paediatric, 15.5%; adult, 7.8%) were more often hospitalized versus patients with CSU (paediatric, 9.9%; adult, 4.6%).

Conclusions In Germany, prevalence of CU along with multiple comorbidities may pose increased burden on the healthcare system. Awareness of adhering to treatment guidelines, and aiming for complete control of urticaria, needs to be driven and may improve outcomes.

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Conflict of interest

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Introduction

Chronic urticaria (CU) is characterized by the repeated occurrence of itchy and sometimes painful wheals (hives) and/or angioedema for more than 6 weeks in a row. CU is one of the most common skin diseases and is divided into 2 sub-types based on triggers: chronic spontaneous urticaria (CSU), with unspecific triggers, and chronic inducible urticaria (CIndU), with specific and identifiable triggers, such as cold, heat, pressure, exercise, etc.[1] Many patients may be comorbid with both variants of CU.[2,3] Despite regional differences, publications have estimated the prevalence of CU at ~1%.[1,3,4] CU affects all age groups among both sexes, although women are more frequently affected and constitute ~70% of the patient pool; the prevalence of CU has been reported to be the highest in patients aged 30–50 years.[3,5] CU significantly affects patients' health-related quality of life. Patients often suffer from sleep disorders, depression and emotional distress[6–8] that often result in a high emotional burden, psychiatric disorders and other comorbidities.[6,9,10] Many studies have focused on specific comorbidities and their association with CU but have seldom reported the overall burden of comorbidities.[7,11–19] The international guidelines for treating CU recommend use of the approved dose and up to 4 times the approved dose of second-generation H_1-antihistamines (AH) as first- and second-line treatment options, respectively, with administration of omalizumab and ciclosporin as third- and fourth-line therapy, respectively. Corticosteroids (CS) are only recommended as a short course for exacerbations.[1] Despite these recommendations, routine administration of first-generation H_1-AH and long-term use of systemic CS have been reported in clinical practice.[20,21]

The prevalence of CU and current status of treatment have been the focus of several international surveys as well as clinical studies and database queries.[22–25] However, studies relying on data from specialist centres may introduce a selection bias, thereby inaccurately reflect epidemiology in the overall population. Particularly, data on comorbidities, treatment and prevalence of forms of urticaria in Germany are still scarce. Newer, more extensive analyses using different methodological approaches could complement previous data. Insurance and billing data can be regarded as the 'gold standard' in terms of coverage and can be used to comprehensively explore epidemiological questions and investigate comorbidities existing in the overall population. The aim of the current study was to identify the prevalence and incidence of diagnosed CU, assess the rate of comorbidities and examine the consultation and treatment patterns for adult and paediatric CU patient population, using the statutory health insurance (SHI) claims data from Germany.

Methods

Study design and data source

This non-interventional, cross-sectional study used the anonymised research database of the Institute for Applied Health Research, Berlin (InGef),[26,27] with longitudinally linkable billing and social data from ~70 statutory company health insurance funds, with ~7 million insured individuals. The sample, stratified according to age (adults and paediatric patients) and sex, comprised more than 3.5 million insured individuals between 01 January 2015 and 30 September 2018.

Study population and inclusion/exclusion criteria

Insured individuals with data between 01 January 2015 and 30 September 2018, including those who may have died during this period, were included in this analysis. The final data set refers all patients identified during the year 2017 with a confirmed diagnosis of CU, based on the respective International Classification of Diseases and Related Health Problems, 10th Revision, German Modification (ICD-10-GM) coding (Table 1). A specific ICD-10-GM code for acute urticaria does not exist. A persistent diagnosis for at least 6 weeks of the ICD-10-GM codes

specified in Table 1 was used to indicate the chronic nature of urticaria. For this, the 'Minimum 2 Quarter' (M2Q) criterion,[28] which requires diagnosis in ≥2 different quarters of a year, was followed. Patients were deemed to have CU (CSU, CIndU or CSU+CIndU) if they had either a primary or secondary diagnosis in 2017, or had an outpatient confirmed diagnosis in 2 different quarters between 01 January 2017 and 30 September 2018. Patients who were diagnosed with CU and psoriasis (PsO) or atopic dermatitis (AD) in 2017 were excluded from comorbidity assessments. All patient-related data in the SHI database are anonymized in compliance with the German data protection law, and therefore permitted for research use without approvals from an ethics committee or review board.

Primary objective

The primary objective of the study was to investigate the 12-month diagnosed prevalence and 12-month diagnosed incidence of CU in Germany in 2017. Diagnosed prevalence was defined as all CU cases identified in 2017 including new cases and those diagnosed prior to the target year, and evaluated using the M2Q criterion for CU (CSU, CIndU and CSU+CIndU) during the evaluation period. Diagnosed incidence of CU (CSU, CIndU and CSU+CIndU) in 2017 was defined as all new cases identified during that year with no diagnosis of CU in the previous 8 quarters.

Secondary objectives

Comorbidities of special interest, identified after consultation with healthcare experts in the field of urticaria management (Table S1), based on ICD-10-GM coding were evaluated in patients with CU (CSU and/or CIndU) versus those with PsO or AD, and the general SHI population. The 15 most common comorbid diseases based on ICD-10-GM codes were also evaluated. Medical procedures associated with ICD-10-GM codes in the database were excluded from comorbidity assessments. Patient sex, age group, specialists consulted, medication (Table S2) and class of medication taken (Table 2), hospitalizations and work days lost were analysed in the CU and SHI total population.

Data analysis

Diagnosed epidemiology, disease subtypes, comorbidities, treatment algorithms and hospitalization of adult and paediatric patients with CU were assessed. The entire SHI population was examined for the diagnosed prevalence and incidence of CU (total), CSU, CIndU and CSU+CIndU in 2017. Patients with CSU+CIndU were analysed under the CIndU group. Age and sex distribution of prevalence and incidence was also analysed. In order to achieve a risk-adjusted assessment of the comorbidities, an exact, step-by-step matching procedure with regard to age and sex was carried out. Patients with CSU and CIndU were age and sex matched in a 1:1 ratio to patients with AD and PsO. This CU subpopulation was then age and sex matched 1 : 4 to the rest of the insured population (i.e. 4 individuals with the same age/sex were selected from the database of SHI individuals as controls for each patient of the CU target population). CU patients who could not be matched were excluded from the comparative analysis with PsO and AD patients and with the general SHI population. Pair-wise comparisons of the proportion of individuals with the respective comorbidity between groups of matched patients were carried out for each of the comorbidities of special interest outlined in Table S2 using chi-square tests. All *P*-values were corrected for multiple testing using the Bonferroni-Holm method within each comorbidity. All analyses, except comparison of comorbidity of special interest, were descriptive in nature and no formal statistical analysis to test a hypothesis was undertaken.

Results

The diagnosed prevalence and diagnosed incidence of CU in Germany is high

During the observed period, a total of 4 693 772 individuals were listed in the SHI database. Of these, 3 538 540 individuals

Table 1 ICD-10-GM codes for diagnosis of CU, AD and PsO used in the study

ICD-10-GM Codes	Diagnosis	Diagnosis group
L50 (L50.1; L50.8; L50.9); **T78.3**	**Urticaria** (Idiopathic urticaria; Other urticaria; Unspecified urticaria); **Angioneurotic oedema**	CSU
L50 (L50.0; L50.2; L50.3; L50.4; L50.5; L50.6); **L56.3**	**Urticaria** (Allergic urticaria; Urticaria due to cold and heat; Dermatographic urticaria; Vibratory urticaria; Cholinergic urticaria; Contact urticaria); **Solar urticaria**	CIndU
L20 (L20.0, L20.8, L20.9)	**AD** (Besnier prurigo; Other atopic dermatitis; Unspecified atopic dermatitis)	AD
L40 (L40.0, L40.1, L40.2, L40.3, L40.4, L40.5, L40.8, L40.9)	**Psoriasis** (Psoriasis vulgaris; Generalized pustular psoriasis; Acrodermatitis continua; Pustulosis palmaris et plantaris; Guttate psoriasis; Arthropathic psoriasis; Other psoriasis; unspecified Psoriasis)	Psoriasis

AD, atopic dermatitis; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; ICD-10-GM, International Classification of Diseases and Related Health Problems in the 10th Revision, German Revision; PsO, psoriasis.
If patients were diagnosed with both CIndU and CSU, they were counted in the CIndU group. Bold text presents the main ICD-10-GM code and disease term used for identification, and those within brackets, ICD-10-GM code or term.

Table 2 List of treatment groups for classification according to recommended treatment during the time of the study

Treatment group	Hierarchy
Ciclosporin + second-generation H_1 -AH	1
Biologic + second-generation H_1 -AH	2
Montelukast + second-generation H_1 -AH	3
Corticosteroids (prescribed as needed for exacerbations) + second-generation H_1 -AH	4
Second-generation H_1 -AH + H_2 -AH	5
Second-generation H_1 -AH + first-generation H_1 -AH	6
Second-generation H_1 -AH + second-generation H_1 -AH	7

AH, antihistamines.
If patients were observed in more than one treatment group, they were classified under the lower hierarchical treatment group (therapeutic algorithm recommended in the treatment guidelines).

were observable in the SHI population during the year 2017 and 17 524 patients had CU, yielding a diagnosed prevalence of 0.5% in 2017. Among all patients diagnosed with CU, 71.2% were diagnosed with CSU, 19.7% were diagnosed with CIndU and the remaining 9.1% were diagnosed with CSU+CIndU (Fig. 1a). Compared with men, women were more likely to be diagnosed with CU (0.62% vs. 0.37%), CSU (0.44% vs. 0.26%), CIndU (0.12% vs. 0.07%) or CSU+CIndU (0.06% vs. 0.03%).

The diagnosed incidence of CU during 2017 was 0.15% of the total 3.53 million individuals. Among them, 65.8% were diagnosed with CSU, 18.3% with CIndU and 15.9% with CSU+-CIndU (Fig. 1b). The incidence of CU during 2017 was also higher among women versus men (CU, 0.18% vs. 0.11%; CSU, 0.12% vs. 0.08%; CIndU, 0.03% vs. 0.02%; CSU+CIndU, 0.03% vs. 0.02%). The age-distributed diagnosed incidence of CU during 2017 showed a reverse trend to its diagnosed prevalence, with the highest incidence observed in the youngest population and the lowest in the oldest (Fig. 1b).

Rates of comorbidities in patients with CU are high

Of the 17 524 patients observable in the SHI population during the year 2017, 14 246 were matched 1 : 1 with PsO and AD patients. Among comorbidities of special interest, hypertensive diseases (45.6%), lipid metabolism disorders (33.7%), affective disorders (27.0%), vasomotor and allergic rhinitis (23.5%) and somatoform disorders (21.9%) were the most frequently reported in the adult patient population with CU. Depression was the most common affective disorder recorded in 24.9% of patients with CU. Among paediatric patients, vasomotor and allergic rhinitis (24.7%), bronchial asthma (20.2%), somatoform disorders (7.7%), obesity (7.5%), and stress and adjustment disorders (6.1%) were the most frequently recorded comorbidities of special interest. Most comorbidities of special interest in CU occurred with similar rates compared to AD and PsO, and with significantly higher rates versus the general SHI population (Fig. 2a; Table S3). Vasomotor and allergic rhinitis, and bronchial asthma occurred with a higher frequency in patients with CU (23.5% and 18.6%, respectively) or AD (25.7% and 22.0%, respectively) versus patients with PsO (11.3% and 10.7%, respectively) or the general SHI population (8.6% and 7.9%, respectively; Fig. 2a). However, the frequency of vasomotor and allergic rhinitis, and bronchial asthma was significantly different between CU and AD, and interestingly not between CIndU and AD for vasomotor and allergic rhinitis ($P = 0.147$; Table S3). Angioneurotic oedema was an ICD-10-GM code that was more specifically associated with CU patients (7.0%) versus patients with AD (0.5%) or PsO (0.3%), or the general SHI population (0.1%; Fig. 2a). The frequency of comorbidities of special interest in patients with CSU or CIndU was similar to that in the overall CU patient population (Table S3).

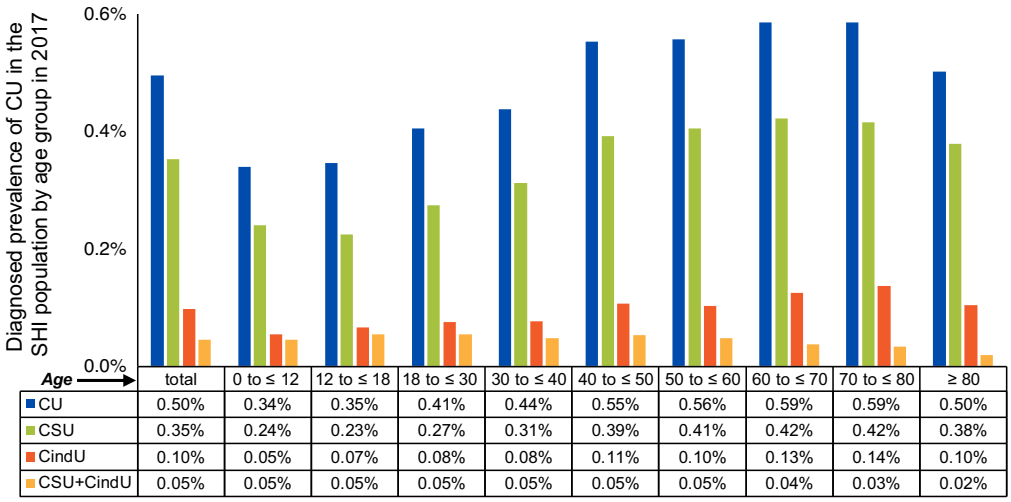
The most frequently reported comorbidities in the matched overall CU population were back pain (45.3%), essential hypertension (42.9%), lipid metabolism disorders (32.1%), disorders of refraction and accommodation (30.2%), and vasomotor and allergic rhinitis (23.5%; Fig. 2b and Table S4). All comorbidities, except those associated with atopy, were recorded at similar rates between CU, AD and PsO, and at higher rates versus the overall SHI population (Fig. 2b). For adult patients with CSU, the most frequent comorbidities were similar to those in the overall CU population, while for paediatric CSU patients, acute upper respiratory tract infections of multiple and unspecified sites (33.8%), disorders of refraction and accommodation (28.4%), vasomotor and allergic rhinitis (22.4%), bronchial asthma (21.0%), and abdominal and pelvic pain (18.4%) were the most frequently recorded comorbidities (Fig. 2c).

Most CU patients do not receive prescription treatment

Among patients with available data on consultation, general practitioners were most frequently consulted for CU [41.3% of total visits (patients with CSU, 41.5% of total visits; patients with CIndU, 40.8% of total visits)]. Dermatologists constituted only 6.6% and 6.7% of the total visits by patients with CSU and CIndU, respectively. Other specialists frequently consulted by CU patients included gynaecologists (5.6%), orthopaedists (5.3%) and ophthalmologists (3.3%). Dermatologists were the most frequent prescribers for biologics [47.2% (patients with CSU, 48.8%; patients with CIndU, 42.0%)].

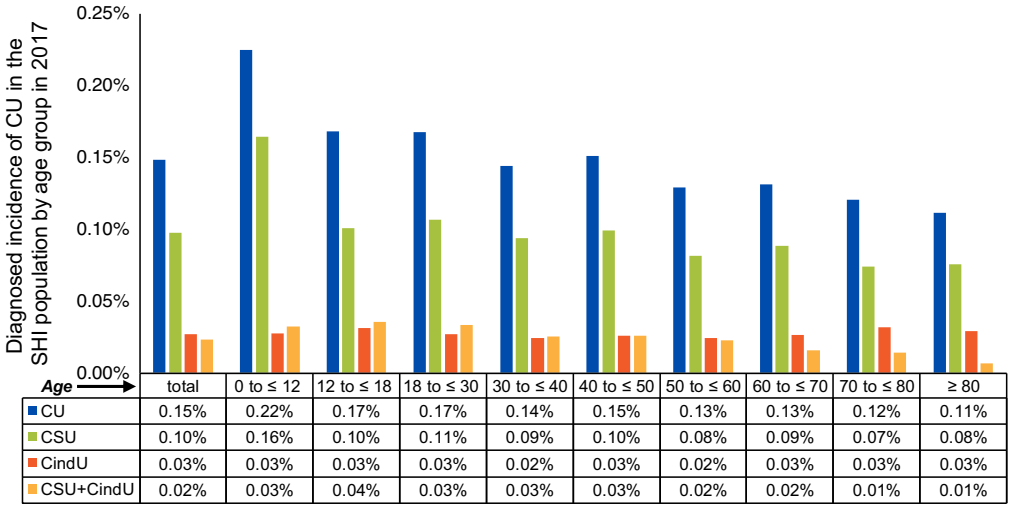
Overall, 54.1% of the patients did not have a record of treatment for CU (38.0% of paediatric patients and 56.1% of adults). In paediatric patients with CU, the most frequently prescribed treatment was second-generation H_1-AH (27.9%), followed by first-generation H_1-AH (11.9%) and CS (5.9%). In adult patients with CU, the most frequently prescribed treatment was second-generation H_1-AH (17.9%), followed by CS (12.8%) and first-generation H_1-AH (1.1%). All other treatments and treatment combinations were prescribed in <1% of the evaluated population. Treatments for CSU were similar to those for CIndU, with adult patients more likely to be untreated for both

(a)



Age	total	0 to ≤ 12	12 to ≤ 18	18 to ≤ 30	30 to ≤ 40	40 to ≤ 50	50 to ≤ 60	60 to ≤ 70	70 to ≤ 80	≥ 80
CU	0.50%	0.34%	0.35%	0.41%	0.44%	0.55%	0.56%	0.59%	0.59%	0.50%
CSU	0.35%	0.24%	0.23%	0.27%	0.31%	0.39%	0.41%	0.42%	0.42%	0.38%
CindU	0.10%	0.05%	0.07%	0.08%	0.08%	0.11%	0.10%	0.13%	0.14%	0.10%
CSU+CindU	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%	0.04%	0.03%	0.02%

(b)



Age	total	0 to ≤ 12	12 to ≤ 18	18 to ≤ 30	30 to ≤ 40	40 to ≤ 50	50 to ≤ 60	60 to ≤ 70	70 to ≤ 80	≥ 80
CU	0.15%	0.22%	0.17%	0.17%	0.14%	0.15%	0.13%	0.13%	0.12%	0.11%
CSU	0.10%	0.16%	0.10%	0.11%	0.09%	0.10%	0.08%	0.09%	0.07%	0.08%
CindU	0.03%	0.03%	0.03%	0.03%	0.02%	0.03%	0.02%	0.03%	0.03%	0.03%
CSU+CindU	0.02%	0.03%	0.04%	0.03%	0.03%	0.03%	0.02%	0.02%	0.01%	0.01%

Figure 1 Epidemiology of CU in Germany, overall, and by age group: (a) diagnosed prevalence of CU, CSU and CIndU in 2017, (b) diagnosed incidence of new reports of CU, CSU and CIndU in 2017. CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; SHI, statutory health insurance.

forms versus paediatric patients (Fig. 3). A considerable proportion of CU patients were prescribed CS alone (5.9%), or in combination with second-generation H_1-AH during the observation period. Biologics were rarely prescribed to patients with CSU (0.71%).

Hospitalization rates in CU patients are high

At least 1 hospitalization due to CU was recorded in 11.7% of paediatric and 5.5% of adult patients. Patients with CIndU (paediatric patients, 15.5%; adult patients, 7.8%) were more likely to be hospitalized versus patients with CSU (paediatric patients, 9.9%; adult patients, 4.6%). Inability to work due to CU was reported in 2.7% of adult patients, with a mean ± standard deviation of 1.3 ± 0.81 days of work lost per patient during 2017.

Discussion

CU is a common dermatological condition that imposes significant burden on patients' quality of life. While there is heterogeneity in the regional distribution of CU and its phenotypes, CSU always occurs with a higher frequency than CIndU, with comorbid CIndU likely in a fifth of the cases.[3] Using an anonymized SHI claims research database in Germany (2015–18), a large patient population was assessed, which was a close

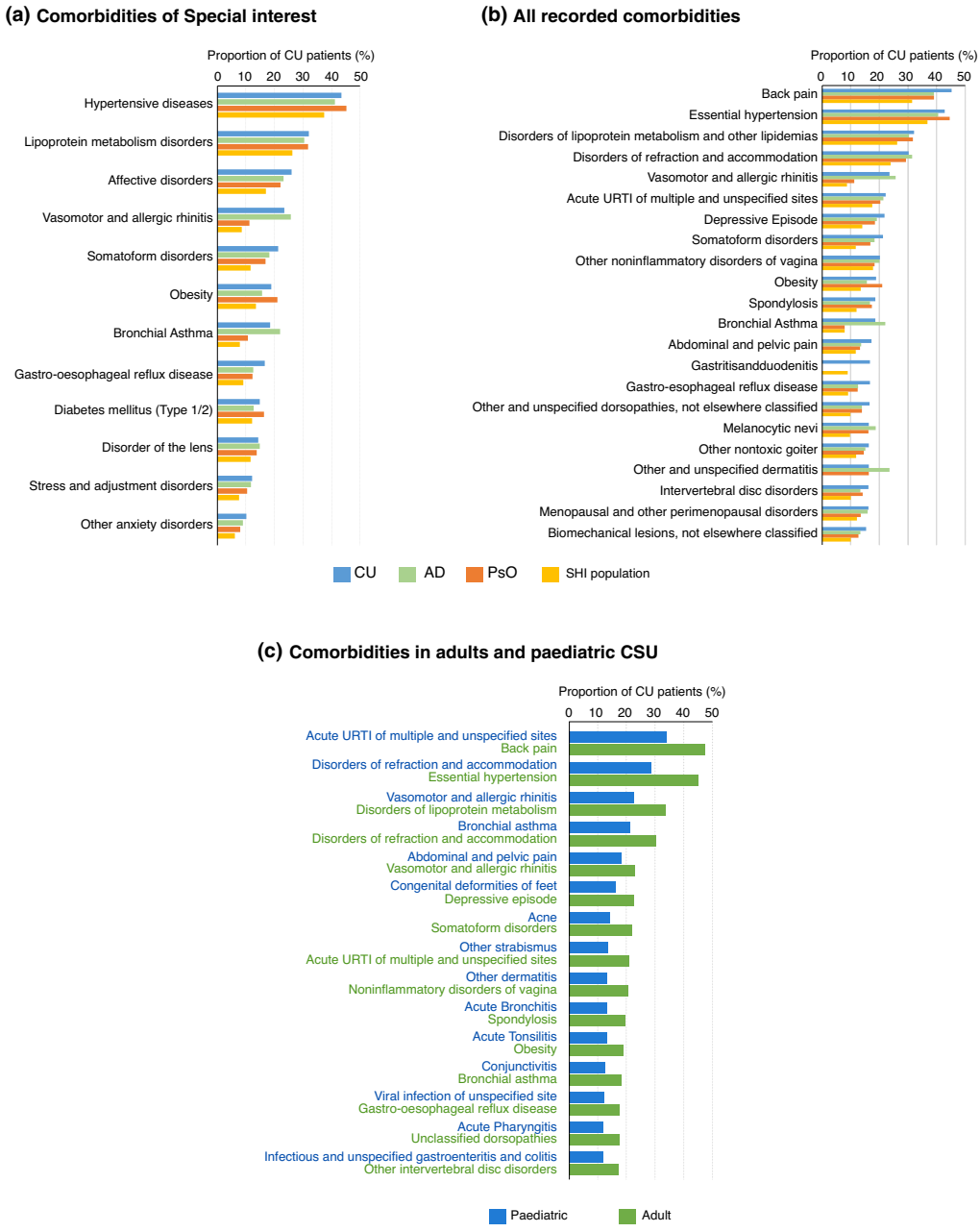


Figure 2 Comorbidities in patients with CSU from Germany documented in 2017: (a) comorbidities of special interest (rate>10%) in patients with CU, and its comparison with those recorded in patients with AD and PsO, and with the general SHI population, (b) all comorbidities (rate>10%) in patients with CU, and comparison with AD, PsO and with the general SHI population, and (c) 15 most frequent comorbidities in paediatric and adult patients with CSU observed in the SHI database. Missing data in b are a result of the data not being captured under the limited measure for the analysis. AD, atopic dermatitis; CSU, chronic spontaneous urticaria; CU, chronic urticaria; PsO, psoriasis; SHI, statutory health insurance; URTI, upper respiratory tract infection.

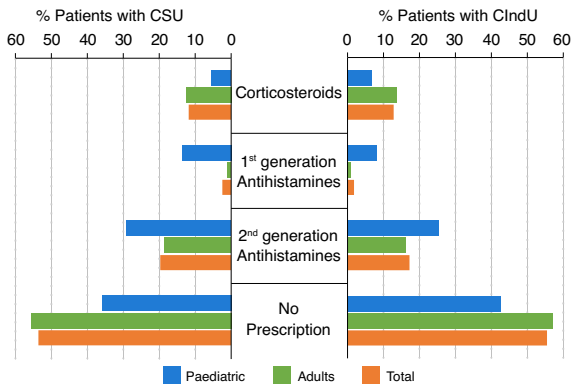


Figure 3 Treatments prescribed for CU in 2017: proportion of CSU and CIndU* patients with specific medication (guideline-recommended treatments and/or treatments prescribed in>5% of patients) prescribed in 2017. *Patients with CSU+CIndU were evaluated under CindU. CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria.

representative of previously described age, sex and burden of morbidity in Germany.[26]

Though CU is a self-limiting disease with a higher incidence in younger patients, severe CU may persist into adulthood in a sizable population, adding to other age-related comorbidities. In this study, the higher diagnosed incidence of CU in younger patients, along with its higher diagnosed prevalence in patients aged ≥40 years, reaffirms this. Additionally, we observed prevalence of CU in the elderly relatively higher than previously assumed. The distribution of prevalence by age we observed in our analysis was similar to that observed in a population-based study in Korea.[29] In agreement with previous studies, the results suggest that there is a high prevalence of CSU within the population of patients with CU in Germany.[3] However, the prevalence observed in this study is slightly lower than that observed previously[4,30–32] and should be considered as diagnosed prevalence captured in the health insurance database. Real-world prevalence may be higher due to older patients or those with mild to moderate symptoms not consulting a doctor, or may be misdiagnosed or underdiagnosed during the observation period.[33,34] The ATTENTUS online survey (>9000 participants) reported that only 40% of CU patients in Germany are under physicians' care.[32] Similar online surveys in Greece, Germany and France showed that around 17%–20% of patients were not under a physician's care.[35,36] The average time since diagnosis of over 11 years in the ATTENTUS survey contributes further to the underestimation of prevalence, since our analysis suggest a 0.15% annual rate of CU diagnosis in Germany. A lack of re-testing previously diagnosed patients in 2017 may also have contributed to the underestimation of prevalence. A 2017 study on paediatric CU prevalence in Germany showed a 1.3%, 1.5% and 0.7% prevalence in children aged 12–18, 7–11 and 0–6 years, respectively; ~3 times higher than that reported in our analysis.[4] However, the paediatric study was based on an online survey of physicians based on their recollection and not confirmed through medical record abstraction.

More than 80% of the CU patients seeking medical assistance were diagnosed with CSU. Among CU patients, <7% of all physician visits were to a specialist dermatologist, possibly due to the German insurance guidelines mandating primary visits to general practitioners or paediatricians followed by specialist referrals. General practitioners are likely to treat a higher percentage of mild CU cases and may be more conservative with respect to innovative and costly biological treatments, and in elderly patients in need of poly-pharmacotherapy.[37] Dermatologists are more likely to prescribe biologicals for severe disease and to be more aware of international guidelines. In Germany, unlike other countries such as the United States, allergology is a sub-speciality, and dermatologists are generally responsible for any conditions related to the skin. Hence, the term allergologist does not appear in the SHI database.

More than 10% of patients were prescribed CS alone or as part of a combination treatment. It was unclear if CS were prescribed as part of an on-demand rescue kit, or if the treatment duration with CS was for a short- or long-term regimen. Guideline-recommended prescription of second-generation H_1-AH was low (~20%) in CU patients possibly due to physicians not prescribing common second-generation H_1-AH such as loratadine or levocetirizine, leading to out-of-pocket expenditure for patients. Hence, these over-the-counter medications do not appear in the SHI data. A large proportion of paediatric patients were prescribed non-recommended first-generation H_1-AH, while biologics were rarely prescribed. However, it is difficult to deduce from the available data if patients are truly undertreated or underprescribed. The inclusive selection of patients, regardless of the severity of their disease, most likely contributes to a large number of patients with no record of a prescribed treatment. According to prior reports, nearly two-thirds of paediatric patients with CU in Europe show an adequate response to standard-of-care treatments, while less than half of all adult patients show a complete response to standard of care.[4,30] This may also factor the skew of a higher CU prevalence in older patients. Similar to observations highlighted in prior reports from the AWARE study and the DERMLINE survey, the analysis of the German SHI data reinforces the observation that patients do not receive guideline-recommended treatments for CU despite presenting with active disease.[20,34] Adhering to guideline-recommended treatments and aiming for complete control of urticaria are more likely to lead to better outcomes and lower healthcare utilization. Previous reports have shown a high frequency of hospitalizations and absenteeism in patients with H_1-AH-refractory CU.[3] The hospitalization rates in this study were comparatively low as the high severity of CU was not a criterion for inclusion.

Patients with CU, AD and PsO also shared similar rates of most comorbidities; however, there were more similarities between comorbidities in patients with CU, and AD, than PsO considering their common pathological link to elevated IgE. All 3 dermatological conditions recorded higher rates of comorbidities versus the overall SHI population that excluded these diseases. Comorbid incidence of cardiovascular and psychiatric disorders was slightly higher in patients with CU, AD and PsO versus in the overall general SHI population. Expectedly, comorbidities affected a lower proportion of paediatric patients compared to adults, yet with a substantial burden. Besides the well-known comorbid association of psychiatric disorders with dermatological conditions such as CU,[17,27,38,39] various cardiovascular disorders, other allergic conditions and disorders of refraction and accommodation were notable. Higher frequency of vasomotor and allergic rhinitis, and bronchial in patients with CU or AD vs. PsO was observed in the data, but the frequency of these atopic comorbidities was significantly different between CU and AD. Although CU, and more specifically CSU, is not an atopic condition, various reports have demonstrated atopic comorbidities in patients with CU.[10,39–41] Mandatory medical records of 16-year-old Israeli citizens showed a significant association of CSU (yearly prevalence ranging between 0.4% and 0.8%) with atopic diseases such as allergic rhinitis, asthma, AD and food allergy.[40] It may be interesting to investigate in future studies if high frequency of atopic comorbidities associated with CSU is disease endotype specific, i.e. type-1 auto-allergic versus type-2 auto-immune driven CSU. Auto-allergic CSU being quite common,[42,43] and possibly more likely associated with atopic comorbidities, may be the reason the high frequency of atopic comorbidities is observed in the overall CU population. A Danish study also highlighted the high burden of common comorbidities like depression, rhinoconjunctivitis, osteoporosis, AD and diabetes mellitus in patients with CU.[44] Similar to Denmark, there is a large patient population in Germany that may be at risk of developing various comorbidities along with affective disorders.

Limitations of these analyses include the fact that patients' diagnoses of CSU or CIndU were derived from pre-existing definitions, as specific ICD-10-GM codes for CSU or CIndU are not currently available. This certainly is also true for comorbidities, and may have resulted in disease misclassifications. Adding to these possible misclassifications, the initial diagnoses in the SHI database was likely done by general practitioners, who may not be familiar with differential diagnosis of various dermatological conditions. A good example of this is the term 'angioneurotic oedema' occurring in 7% of CU patients, which is high considering the prevalence of hereditary angioedema in literature, and low considering the frequent occurrence of angioedema in overall CU patients. A methodological limitation may have risen by following a stringent M2Q criteria. Patients who may have followed-up within 6 to 12 weeks of initial urticaria diagnosis, and would have been diagnosed with CU, may have contributed to underestimation of diagnosed incidence or diagnosed prevalence if they did not follow-up on subsequent quarters.

Overall, this analysis of the German SHI data provides better understanding of the diagnosed prevalence and incidence of CU in Germany, and of frequent comorbidities occurring with CU by age and in comparison with other common dermatological conditions. These results also reinforce the immediate need to spread awareness among patients and healthcare workers about the disease, the multimorbid facet of CU and the importance of adhering to recommended treatment guidelines.[45]

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Comorbidity of special interest

Table S2. Drugs prescribed for CU classified according to ATC classification system

Table S3. Pair-wise comparisons of the proportion of individuals with the respective comorbidities between groups of matched patients using Chi-square tests

Table S4. Most frequent recorded ICD 10 code diagnosis in patients with CU and comparison with the overall SHI population