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Chronic Urticaria: A Swedish Registry-based Cohort Study on Population, Comorbidities and Treatment Characteristics

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Swedish databases present unique opportunities to research population data on diseases and treatments. The current study is, to our knowledge, the most comprehensive registry-based study on a chronic urticaria population in Sweden to date. The aim of this study was to describe the chronic urticaria population in Stockholm County regarding epidemiology, demographics, comorbidity, healthcare usage and treatment patterns in relation to current international guidelines. Real-world data were extracted between 2013 and 2019, yielding 10,642 adult patients. Study period prevalence of chronic urticaria was 0.53%, the mean annual incidence was approximately 0.08%, and 68% of patients were female. Regarding diagnosis, 58% were first diagnosed in primary care, approximately 50% were diagnosed before the age of 40 years. Regarding type of urticaria, 89% had chronic spontaneous urticaria, 11% had chronic inducible urticaria, and 5% of patients with chronic urticaria had coexisting angioedema. Common coexisting diagnoses were, for example, asthma, allergy, psychiatric and behavioural disorders and cardiometabolic disorders. Treatment patterns generally followed guidelines, yet data indicated that guidelines were not fully implemented, especially in primary care.

Key words: urticaria; chronic urticaria; therapeutics; adult; child; comorbidity; guideline; angioedema; dermatology.

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SIGNIFICANCE

Chronic urticaria can be a severely debilitating disorder, impacting quality of life. It is of great importance to understand patient and disease characteristics, including associated diseases. Furthermore, it is important to examine whether treatment adheres to guidelines to provide the best possible care. Swedish databases, containing large amounts of information both on patient characteristics and treatment, provide a great opportunity to study patients with chronic urticaria. An extensive descriptive study on both patient and disease characteristics and treatment patterns was carried out to help healthcare professionals better understand this important dermatological disease.

Chronic urticaria (CU) is defined as urticaria existing as recurring episodes of wheals over a period of 6 weeks or more. CU is commonly associated with angioedema (1, 2). According to current guidelines, CU can be divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CINDU), with several subgroups. According to a recent large systematic review and meta-analysis there appear to be regional differences, as the point prevalence of CU is reported as higher in Asia (1.4%) compared with Europe (0.5%) and North America (0.1%) (3).

CU can seriously impact patient's quality of life (4). The disorder is also linked to loss of work productivity and activity impairment (5). The association of CU with common comorbidities, such as psychiatric disorders, autoimmune disorders, asthma, hypertension and osteoporosis, has been reported previously (6–10). Since CU can be severely taxing on both the patient and healthcare system, it is of utmost importance that management and treatment follows best practice. Studies show that patients with CU, who may be diagnosed and treated by either specialists or general practitioners, frequently experience a delay in diagnosis and receive less than optimal treatment despite readily available international EAACI/GA²LEN/EDF/WAO guidelines, which were first published in 2009 and updated in 2018 (2, 11, 12). The aims of this study, which is based on real-world data, were:

- To describe the CU population in Stockholm County, Sweden, regarding prevalence, incidence, demographics, subtypes of CU and common comorbidities, including coexisting treatments.
- To describe age and clinic type at first diagnosis and healthcare usage in Stockholm County for patients with CU.
- To describe treatment patterns for CU in Stockholm County in relation to the international guidelines (2).

MATERIALS AND METHODS

This was a population-based study using real-world data retrieved from the Stockholm County Council VårdAnalysdataLagar (VAL) database, which collects and presents anonymized data from all publicly subsidized healthcare provided in Stockholm County, including the vast majority of primary care. The database covers, among other things, registered contacts with healthcare

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professionals, diagnoses and collected prescriptions for virtually all inhabitants of the county (13). Stockholm County with its 2.3 million inhabitants covers approximately 20% of the entire Swedish population and includes both city, suburban and rural areas (14). Data were compiled and analysed using statistical computing software R (15).

The study was carried out as a registry-based study in which the VAL database was used to study age, sex, comorbidities and treatment for CU.

Mean annual incidence of CU was defined for a 5-year interval as the number of incident cases of CU from 31 December 2014 to 31 December 2019 divided by the total number of person years in the population during the 5-year period.

The study population included individuals 12 years and above in Stockholm County who were alive on 1 March 2020. They had at least 1 registered contact with the Stockholm County healthcare system in which the diagnosis L50 (general International Classification of Diseases (ICD) code for all types of urticaria) was registered between January 2013 and December 2019 as a primary or secondary diagnosis were included in the study (16). The ICD codes for CINDU used were; urticaria due to cold and heat (L50.2), dermatographic urticaria (L50.3), cholinergic urticaria (L50.5), contact urticaria (L50.6), allergic contact urticaria (L50.6A), non-allergic contact urticaria (L50.6B) and urticaria unspecified (L50.6X). As there is no dedicated ICD diagnosis for CU, the CU population was defined in this study as all patients with at least 2 healthcare visits within 3 months (outpatient or inpatient care) with a primary ICD diagnosis of urticaria. The definition of CU was chosen to include as many patients with a primary urticaria diagnosis as possible within a 3-month period, while lessening the risk of missing patients with CU with longer intervals (>3 months) between doctor's visits. A sensitivity analysis was preformed to evaluate the definition used for the CU population in relation to the study reults (see Table SI[1]).

The period 2013 to 2019 was selected, because an improved system for reporting data from primary care was introduced in 2013, thus increasing population data accuracy compared with earlier years. See Fig. S1[1] for data on inclusion and exclusion.

Common coexisting disorders and potential comorbidities defined as the 10 most common additional co-reported diagnoses in the population were studied and compared with available data from specialized healthcare for a cohort of patients without CU. Coexisting disorders were also studied as broader categories of coexisting diagnoses previously reported associated with CU: psychiatric and behavioural disorders, systemic cardiometabolic diagnoses, allergy diagnoses (which may be mistaken for CU), autoimmune disease and osteoporosis (6–9, 17)).

Treatments used for CU were described based on available data on use of, for example, antihistamines, glucocorticoids, adrenaline, leukotriene antagonists (e.g. montelukast), ultraviolet (UV)-light treatment, omalizumab and cyclosporine. Data on dosage were not available.

First- and second-line treatment according to the international guideline recommendations are defined as antihistamines and up-dosing of antihistamines. Third-line add-on treatment is defined as omalizumab (i.e. if not responding to antihistamines) and fourth-line as cyclosporine (i.e. to be used after omalizumab or if use of omalizumab is not possible, as an add-on to antihistamines). Other drug treatments used in everyday practice for CU were leukotriene antagonists, methotrexate, tranexamic acid, mycophenolic acid, azathioprine and dapsone. The database does not provide information on dosage, thus eliminating the possibility to, for example, study up-dosing with antihistamines, as defined as second-line treatment per guidelines. Table SII[1] sets out the definition of drug treatment used in this study.

Ethics approval was received from the Stockholm Ethical Review Board (#2019-04002).

RESULTS

The CU study population in Stockholm County consisted of 10,642 unique patients in December 2019, a prevalence of 0.53% (entire population of Stockholm County 2,377,081) (14). The 5-year mean annual incidence was approximately 0.08% from the end of 2014 to the end of 2019. There was a predominance of female patients (68%) with a mean age of 45.6 years (Table SIII[1]). The mean time between first and last healthcare visit with the primary diagnosis of CU was 250 days and the median time between first and last visit with the primary diagnosis of CU was 38 days.

A large percentage (37%) of the CU population received a first urticaria diagnosis between ages 30 and 49 years. A small proportion of the population (9%) received their first diagnosis at the age of 70 years or older. Fig. S2[1] shows the age distribution at first diagnosis.

In patients with CU, 78% did not receive a primary or secondary CU diagnosis when seeking healthcare after 1 year, but 8% of patients still had a CU diagnosis when seeking healthcare after 5 years (**Fig. 1**).

Most patients with CU (91%) had CSU only, while a small proportion, 3.7%, of patients with CU had isolated CINDU only, and 7.7% had a combination of both types. Dermatographic urticaria was the most common diagnosis among patients with CINDU (60%), followed by urticaria due to temperature, cool and heat (23%) and cholinergic urticaria (8%) (**Fig. 2**).

At some point between 2013 and 2019, 528 out of 10,6420 patients with CU had received a coexisting

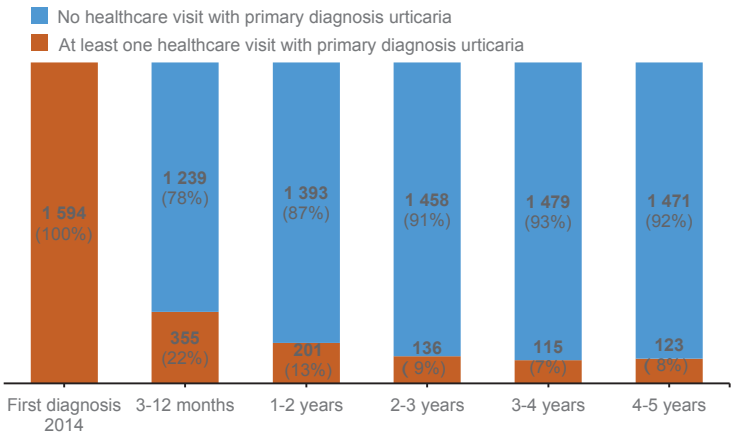

Fig. 1. Persistency of chronic urticaria diagnosis (either primary or secondary) in patients who received their first diagnosis in 2014 (*n* = 1,594), presented as remaining share of total (%) at defined time-periods 3–6 months, 6–12 months, 1–2 years, 2–3 years, 3–4 years and 4–5 years.

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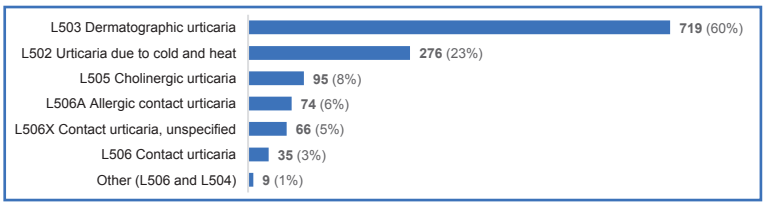

Fig. 2. Percentage of patients with chronic inducible urticaria (CINDU), divided by subtype (n = 1,207). Share of total CINDU (%).

angioedema diagnosis, rendering a prevalence of 5% for angioedema in the population.

Coexisting diagnoses

Amongst additional common coexisting diagnoses reported in 1 year in the CU population, 13% of patients were also diagnosed with a soft-tissue disorder, 13% with hypertension, and 10% with an upper respiratory tract disorder (**Table I**).

Additional coexisting diagnoses to CU were also categorized into broader diagnostic categories reported associated with CU (6–9, 17). Of all patients with CU in 2018 (not counting visits regarding CU), 19% received psychiatric and behavioural diagnoses, 17% cardiometabolic diagnoses, 4% allergy diagnoses, 2% autoimmune disease diagnoses, and 1% osteoporosis diagnoses (data not shown).

The 10 most common additional coexisting diagnoses reported in the CU population were more common compared with the same diagnoses reported in specialized care for the general population of Stockholm County (n = 1,992,147) (with and without CU), e.g. other soft-tissue disorders 7.1% vs 1.5%, other anxiety disorders 5% vs 1%, hyperkinetic disorders 2.3% vs 1.2%, respectively, in the CU vs general population (Fig. S3[1]).

Of patients diagnosed with CU in 2018 and having coexisting angioedema, 20% received a cardiometabolic disorder diagnosis, 16% psychiatric and behavioural diagnoses, 7% allergy diagnoses, 3% autoimmune diagnoses, and 1% osteoporosis diagnoses (data not shown).

Table I. The 10 most common additional diagnoses received in 2018 in the study population, presented as number of patients with chronic urticaria per diagnosis

Additional diagnosis	Patients per additional diagnosis (n = 10,642) n (%)
Other soft-tissue disorders, not elsewhere classified	1,427 (13)
Essential (primary) hypertension	1,391 (13)
Dorsalgia	1,217 (11)
Acute upper respiratory infections of multiple and unspecified sites	1,034 (10)
Abdominal and pelvic pain	1,008 (9)
Other anxiety disorders	879 (8)
Pain, not elsewhere classified	834 (8)
Other joint disorders, not elsewhere classified	824 (8)
Asthma	670 (6)
Malaise and fatigue	552 (5)

Represents all healthcare types (primary and specialized care). Share of total additional diagnoses in (%), n = 10,642. Diagnoses according to International Classification of Diseases 10th revision (ICD-10): J06, M79, J10, R10, M54, J45, F41, R52, M25, R05.

Healthcare utilization

In 2019, 35% of all healthcare visits (6,457 in total) in the CU population were to primary care, while 43% were to a dermatologist (Fig. S4[1]).

A portion of the CU population accounted for a large part of the healthcare utilization. Approximately 5% of all patients with CU in the population accounted for 28% of all healthcare visits registered with the primary diagnosis urticaria, and 20% of all patients with CU accounted for 50% of all visits with the primary diagnosis urticaria.

Treatment

Various types of prescribed medicines were received within 6 months prior to the first diagnosis. Regarding prescriptions, 27% of patients diagnosed with CU received antihistamines within 6 months prior to first CU diagnosis, 25% antibacterials, 18% analgesics, 15% psycholeptics, 14% systemic glucocorticoids, 13% topical glucocorticoids and 13% anti-inflammatory drugs (**Table II**).

Of the drugs prescribed for CU treatment, as per guidelines, antihistamines (89%) were most common. The most common antihistamines were second-generation antihistamines, such as desloratadine (78% of total prescriptions), followed by cetirizine (22%), loratadine (19%) and ebastine (3%). Of patients prescribed antihistamines, (excluding allergic diagnoses), 82% had only one type during the first 6 months after diagnosis, whereas 16% had 2 different types of antihistamine, and 1% had 3 or 4 types.

Only 17% of patients who started antihistamine treatment continued for more than 4 months and only 3% continued for 17 months or more.

Table II. The 10 most collected prescription types within 6 months prior to the first diagnosis of chronic urticaria, registered July 2013 to December 2018. n = 8,565

Most collected prescription within 6 months prior to first diagnosis	n (%)
Antihistamines for systemic use	2,339 (27)
Antibacterials for systemic use	2,115 (25)
Analgesics	1,513 (18)
Psycholeptics	1,287 (15)
Five most common in the group: hydroxyzine, zopiclone, zolpidem, oxazepam, priopriomazine	
Sex hormones and modulators of the genital system	1,284 (15)
Glucocorticoids for systemic use	1,173 (14)
Anti-inflammatory and anti-rheumatic products	1,156 (13)
Glucocorticoids, dermatological preparations	1,140 (13)
Psychoanaleptics	1,024 (12)
Drugs for acid-related disorders	947 (11)

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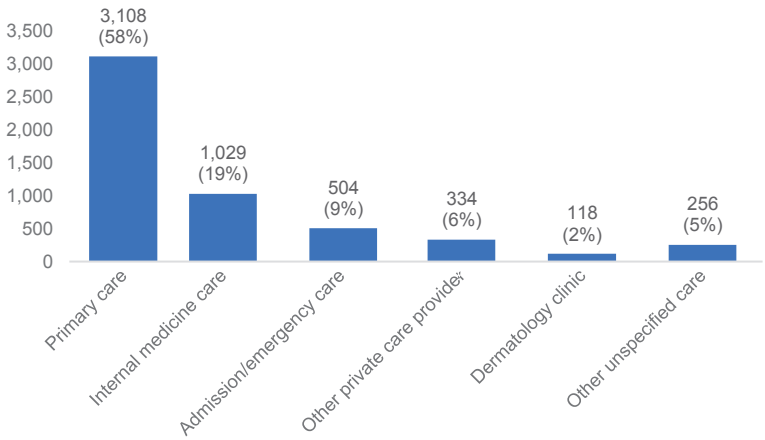

Fig. 3. Prescription of systemic glucocorticoids in chronic urticaria population, divided by healthcare provider ($n = 5{,}349$). Population limited to first diagnosis of urticaria in July 2013 to December 2018 and to patients receiving glucocorticoids within 1 month after first diagnosis.

The other most common medications prescribed to patients with CU were glucocorticoids (68%) and different types of receptor antagonists (16%). The most common types of glucocorticoids prescribed were topical betamethasone (54%) and systemic prednisolone (29%). Leukotriene antagonists consisted of montelukast (11% of prescriptions in total), antihistamines consisted of ranitidine (6%) and famotidine (<1%).

Eight percent of patients had used adrenaline and 4% had been treated with UV-light therapy.

Fifty-eight percent of glucocorticoids prescribed for the patient within the first month after diagnosis were prescribed from primary care and 28% were prescribed by internal medicine clinics and emergency care (including patients admitted to hospital). Only 2% of all glucocorticoid prescriptions for patients with CU within the first month of diagnosis were from dermatology clinics (**Fig. 3**).

A total of 543 (5.1%) patients with CU received omalizumab (third-line treatment) and 45 (0.4%) of patients received cyclosporine (fourth-line treatment) between 2013 and 2019. **Table III** gives an overview of CU treatment.

Table III. Drug treatments in the chronic urticaria (CU) population between 2013 and 2019 (n=10,642)

Number of patients by type of drug received (percentage of total population)	*n* (%)
Second-generation antihistamines (first-line)	9,491 (89)
Glucocorticoids for systemic use	7,192 (68)
Receptor antagonists	1,734 (16)
Adrenaline	895 (8)
Tranexamic acid	619 (4.3)
Omalizumab (third-line)[a]	543 (5.1)
Methotrexate	230 (2.2)
Azathioprine	61 (0.6)
Cyclosporine (fourth-line)	45 (0.4)
Mycophenolic acid	16 (0.2)
Dapsone	11 (0.1)

[a]Approved for chronic urticaria in Stockholm County in 2015.

Between 2015 and 2019, omalizumab was mainly prescribed by dermatology clinics, with 83% of the total number of omalizumab prescriptions, while methotrexate was commonly prescribed by rheumatology clinics, with 63% of the total number of methotrexate prescriptions (103 out of 137 prescriptions had a rheumatic diagnosis 12 months prior to prescription). Twenty-nine percent of all patients who received omalizumab between 2015 and 2019 did so within 30 days of first diagnosis, while 25% received omalizumab more than 6 months after first diagnosis. The number of patients who received omalizumab has increased each year since 2015, with 360 patients (3% of the CU population) receiving the drug in 2019, compared with 92 patients (1%) in 2015.

The majority (73%) of patients receiving omalizumab between 2015 and 2019 had previously received antihistamine and 36% had previously received receptor antagonists. Thirty-nine percent of patients prescribed omalizumab received prescriptions for 4 months or less, while 29% of patients received omalizumab for 13 months or more.

In patients with omalizumab prescriptions lasting less than 5 months, only 8% had an allergy diagnosis 6 months prior to or 4 months after the first omalizumab prescription.

DISCUSSION

To our knowledge, this is the largest Swedish study on CU to date with real-world data on population (incidence, prevalence, characteristics), subtypes of CU, coexisting diagnosis, healthcare usage, and treatment patterns.

This study found the prevalence of CU to be approximately 0.53% between 2013 and 2019, which is comparable to other reported prevalence data for Europe (0.5%, range 0.2–1.0) presented in a large meta-analysis by Fricke et al. (3). An earlier study from Sweden by Hellgren et al. found a lower prevalence of CU of approximately 0.1% in the total Swedish population. This particular study was performed approximately 50 years ago, hence several factors apart from increased prevalence could account for the discrepancy (e.g. criteria used, registry availability, healthcare accessibility, etc.) (18).

The results show that women have CU twice as often than men, which confirms earlier findings in European populations. The age distribution for the adult population in this study showed a peak between 30 and 49 years, which is similar to the results of a Scandinavian study from 2017 (20).

Approximately 11% of patients had CINDU, which compares well to findings by Hon et al., where the subtype accounted for 10–20% of all cases (21). Ap-

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proximately 8% of patients in the current study had both CINDU and CSU. A total of 276 patients had heat- or cold-induced urticaria, corresponding to approximately 23% of the CINDU population. Due to using the same diagnosis code, the 2 temperature-triggered subtypes could not be distinguished from each other in the current data. Cold urticaria, which in some cases may be severe and life-threatening (as may heat urticaria), is said to be more prevalent in colder climates, yet data on specific prevalence for comparison is scarce (22).

This study demonstrated that nearly 80% of patients with CU had no further primary urticaria diagnosis reported after 1 year, but 8% of the patients still had a primary CU diagnosis after 4–5 years. This may reflect the natural history of the disease and is in line with the results of in a study of 5,000 patients by Gaig et al. (23) (88% of patients had no persisting urticaria symptoms after 5 years), but is less than some other studies reporting 50–70% of patients with a persisting CU after 5 years (24, 25). Heterogenicity between studies in terms of included patients and definition of "chronic CU diagnosis" used makes comparison between studies difficult. Psychiatric and behavioural diagnoses were among the most common primary and additional coexisting diagnoses received during a 1-year period, indicating the importance of considering these diagnosis groups in patients with CU. Furthermore, these coexisting diagnoses were more common in patients with a diagnosis of CU compared with other patients without CU diagnosis in a specialized care setting. This notion is strengthened in a systematic review and meta-analysis by Konstantinou et al. (6) from 2019, in which approximately 30% of patients with CU had a coexisting psychiatric disorder. Psycholeptics were amongst the 10 most common prescriptions, including sleep medication, e.g. zolpidem and anxiety medication oxazepam. This further indicates comorbidity of psychiatric and behavioural disorders in the CU population.

Hypertension was more common in patients with CU compared with other patients in specialized care. The association between CU and hypertension has been described by, for example, Chang et al. (8) in 2016. The association with hypertension could possibly be explained by misdiagnosis of bradykinin-induced angioedema. The current study also showed a high prevalence of cardiometabolic disorders in general. Metabolic syndrome has previously been linked to CU (17). Asthma was more common in patients with CU compared with other patients, as was also reported by Vadasz et al. in 2016 (10).

The prevalence of angioedema in the current study population was lower than other reports; 5% compared with up to approximately 30% reported in some other studies (19, 20). This could be due to coexisting angioedema not receiving a ICD diagnosis separately from urticaria or receiving a more unspecific ICD diagnosis of other soft-tissue disorders. This may be reflected by the fact that other non-specified soft-tissue disorder was one of the 10 most common additional coexisting diagnoses. More research on the current population is needed to understand this discrepancy regarding angioedema. Although the angioedema sub-population was small, the coexistence of, for example, cardiometabolic disorders was slightly higher compared with patients with CU without angioedema (20% vs 17%, respectively). This may reflect that CSU with angioedema may represent a more severe disease and should mandate additional precaution in patients with CU with angioedema. Healthcare providers treating patients with CU should be aware of important coexisting diagnoses and potential comorbidities and readily provide additional investigations or referrals when needed.

In line with the EAACI/GA²LEN/EDF/WAO guidelines, the vast majority of patients with CU in the current study were prescribed second-generation H1-antihistamines (2). Although 89% collected antihistamines in line with guidelines, the remaining 11% did not collect this first-line treatment at any time. Only 17% of patients who started with antihistamines continued treatment for more than 4 months, and 18% of patients used 2 or more antihistamines. These results may reflect the natural history of CU, supported by the fact that most patients in this study did not receive another urticaria diagnosis 3–6 months after their first diagnosis. It could also indicate dissatisfaction with the effect of the first antihistamine prescribed. Unfortunately, data on specific doses was not available, thus it was not possible to analyse how many patients had been offered higher doses of antihistamines as second-line treatment according to guidelines.

Eleven percent of all prescriptions in the current study were for montelukast, a leukotriene receptor antagonist. According to international CU guidelines reported by Zuberbier et al. (2), the level of evidence for using leukotriene receptor antagonists in CU is low. The best evidence found has been for montelukast specifically, yet the guidelines still state that no recommendation can be made on its use.

Conclusively, most patients received first-line antihistamine treatment in line with guidelines, yet 11% of patients with CU did not receive any antihistamines, and many patients received glucocorticoids, anti-inflammatory (NSAIDS), antibacterials, or other symptomatic treatment with analgesics, hypnotics and psycholeptics. As this study uses data on prescriptions, there may have been patients whose symptoms resolved before antihistmines were collected, or compliance in this patient group might have been lower.

The third-line treatment option per guidelines, the biologic omalizumab, consisted of 5% of all prescriptions for CUs, while fourth-line treatment cyclosporine made up 0.4%. Other treatments not classified as first- to fourth-line treatment were, surprisingly, used in a number of cases, although they are not recommended in the EAACI/GA²LEN/EDF/WAO guidelines treatment algorithm,

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e.g. due to low-quality evidence, or that the drugs have been evaluated only in case series (2). The high share of other treatment compared with recommended treatment could, in part, be due to poor awareness or adherence to guidelines or patients receiving these drugs for diagnoses other than CU, e.g. autoimmune disorders, which were relatively common in the current population and in previous studies of CU (7). The high share of tranexamic acid, 5.8% of all prescriptions, could be due to treatment for angioedema, as this is by tradition a drug used in the treatment of the disorder.

Eight percent of patients had received adrenaline, indicating that a relatively high percentage of patients needed rescue treatment at some point, e.g. when experiencing severe angioedema.

Systemic use of glucocorticoids is, according to guidelines, not recommended for use in CU, other than a short treatment period may be considered in acute exacerbations (2). Of all patients who had received systemic glucocorticoids within the first month of diagnosis, almost 1 in 5 collected at least 3 prescriptions within the first 12 months. This indicates that prolonged use of glucocorticoids could be relatively common in the study population.

Primary care was the most frequent prescriber of systemic glucocorticoids in the current study, with 58% of prescriptions, i.e. nearly 30-fold compared with dermatology clinics. Primary care handled approximately the same number of patients with CU compared with dermatology clinics. These results may reflect a delay in patients receiving specialist care and prescription of more effective third- or fourth-line treatment options. The high share of corticosteroid prescriptions in primary care could be due to uncertainty of diagnosis and treatment. Treatments commonly prescribed to patients with CU within 6 months of first diagnosis included antibacterials and analgesics. It should be noted that analgesics in the form of NSAIDs, e.g. ibuprofen, naproxen, etc. can give rise to urticaria and are therefore not recommended for this patient group (and may therefore also be a cause for urticaria in this group) (2). This could indicate that bothersome CU symptoms, such as itch and ulcerations from scratching, might be sub-optimally treated and that there is a delay in more effective treatment for CU. The fact that 20% of patients with CU account for nearly 50% of all visits for urticaria may indicate that these patients are sub-optimally treated or treatment resistant. Healthcare utilization could be improved by improving treatment success in these patients.

The study results should be representative and generalizable, as Stockholm County is the largest county in Sweden, incorporating approximately one-fifth of the entire Swedish population. The county has a wide representation regarding demographics, with both city, suburban and rural areas (including inhabitants of remote archipelago areas). As healthcare in Stockholm County is highly accessible, this lowers the risk of patients with CU continuing undiagnosed and untreated (thus lowering the risk of not being included in this study). The study is based on registry data collected by Stockholm County over a long period of time. Publicly funded healthcare (run both privately and by the county council), which comprises the vast majority of all healthcare provided in CU, is automatically linked to the county's databases. Information covers both primary care and specialized inpatient and outpatient care. Furthermore, prescriptions collected from all healthcare providers at any pharmacy are registered, giving unique access to treatment data. The large region of Stockholm County contains several different types of areas with large variations in both demographics and age.

As the study relies on the accuracy of the individual healthcare provider registering each diagnosis, some patients may have been misclassified. Furthermore, the inclusion and classification of coexisting diagnoses in the patient with CU involves risk of error for the same reason.

As there is no CU diagnosis code in the ICD-10, patients with CU in the current study were defined by 2 primary diagnoses of urticaria within a set period of 3 months. This study definition for CU differs from the guideline definition of a minimum disease duration of 6 weeks. This definition was chosen to include as many patients with a primary urticaria diagnosis as possible within a 3-month period, while lessening the risk of missing patients with CU with longer intervals (>3 months) between doctor's visits. As the mean time between first and last visit with the primary diagnosis urticaria in the study was 250 days, patients in the current population had healthcare contacts due to urticaria over a longer period in line with a CU diagnosis. It was considered uncommon for patients with acute urticaria to receive a primary urticaria diagnosis at 2 separate doctor's appointments within a 3-month interval, as such symptoms are most commonly resolves within 24 h. The results of a sensitivity analysis using different criteria for defining CU and evaluating the effects on key outcomes support the chosen study definition for CU (see Table SI[1]).

The database introduced mandatory primary care registrations from 2013 and onward, limiting the time scope of this study.

As seen in the current and previous studies, psychiatric and behavioural (psychiatric) disorders are over-represented in CU (6). It would be of great value to further study the relationship between CU, coexisting disorders and quality of life, comparing both treatment received and level of healthcare provider (primary or dermatology care). Furthermore, it would be of interest to gather information on Swedish CU cohorts from further back in time.

CU is a relatively common disease, occurring in more than 0.5% of the population. The current study CU population matches previous reported findings regarding sex

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and age distribution, yet the proportion of patients with angioedema was considered low. Coexisting disorders reported in earlier studies were similar with respect to, for example, psychiatric and behavioural disorders, hypertension and asthma. Treatment in Stockholm County was mostly in line with the EAACI/GA²LEN/EDF/WAO guidelines, although there was also substantial treatment with, for example, anti-inflammatory drugs and antibiotics. The results suggested that there may be unnecessarily high and lengthy use of glucocorticoids for treatment of CU, especially in primary care. This mandates caution in prescription of cortisone other than for shorter episodes, especially considering the side-effects of long-term use, such as osteoporosis.

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Table SI. Sensitivity analysis: definition of chronic urticaria (CU) population

Number of patients by inclusion criteria (prevalence in Stockholm County)	*n* (%)
At least 2 healthcare visits within 3 months (outpatient or inpatient care) with a primary ICD diagnosis of urticaria	10,642 (0,53)
At least 2 healthcare visits within 3 months (outpatient or inpatient care) with a primary ICD diagnosis of urticaria – and at least 6 weeks between 2 visits during the 3-month period	3,997 (0,20)

ICD: International Classification of Diseases.

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Table SII. Overview of chronic urticaria drugs according to current international guidelines (2)

Line of treatment according to guidelines	Drug
1st line	Standard-dosed second-generation antihistamine
2nd line	Up-dosed second-generation antihistamine
3rd line	Omalizumab[a]
4th line	Cyclosporine
Other treatments[b]	E.g. methotrexate, azathioprine

[a]Approved for chronic urticaria in Stockholm County in 2015. [b]Refers to other treatment prescribed to chronic urticaria patients in Stockholm County, yet not recommended in the guidelines, e.g. off-label treatment. Special considerations must be made regarding children, see guidelines.

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Table SIII. Overview of population characteristics (*n* = 10,462)

Population characteristics	
Age, years, mean ± SD	45.6 ± 18.6
Sex, *n* (%)	
Male	3,373 (32)
Female	7,269 (68)

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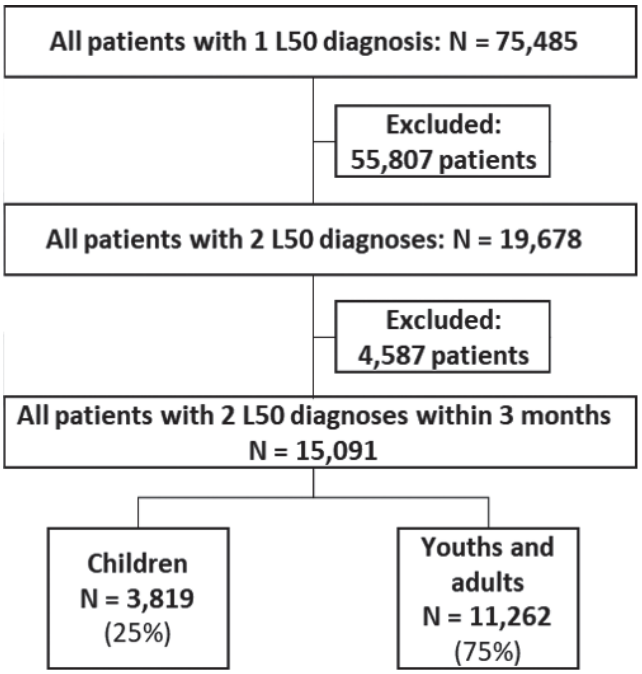

Fig. S1. Included study population, by stages of exclusion. L50 diagnosis: general International Classification of Diseases (ICD) code for all types of urticaria.

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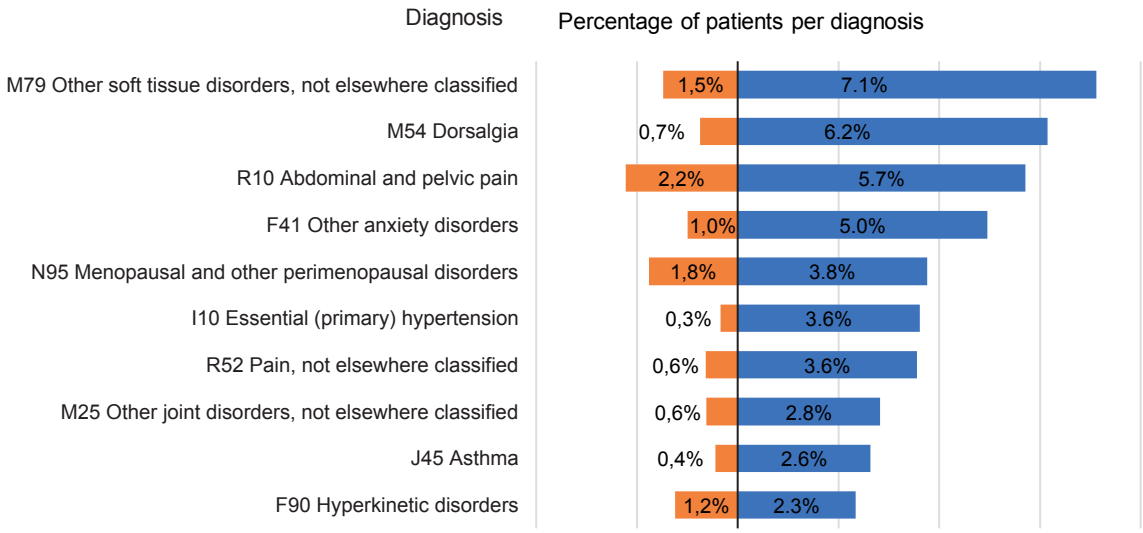

Fig. S3. The 10 most common additional diagnoses in specialized care (not including primary care) in 2018 for patients with chronic urticaria (*n* = 10,642) compared with the general population of Stockholm County (*n* = 1,992,147).

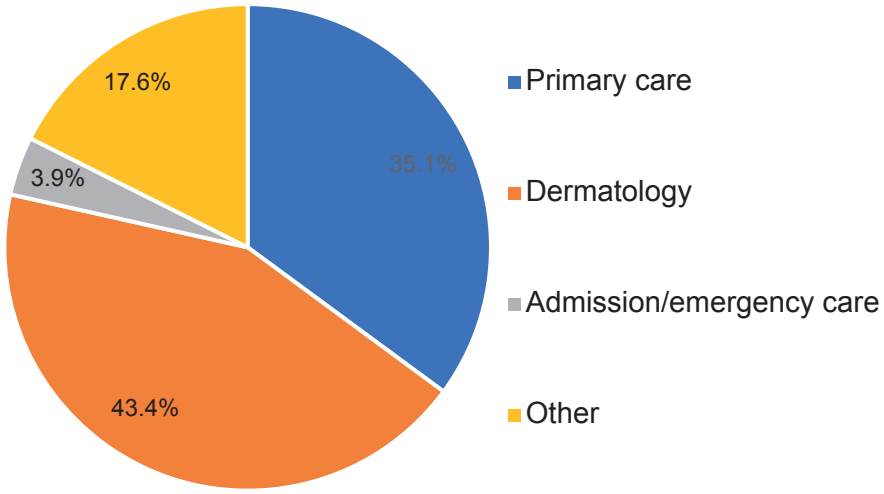

Fig. S4. Healthcare visits in the chronic urticaria population in 2019, divided by type of healthcare (number of visits in total=6,457).

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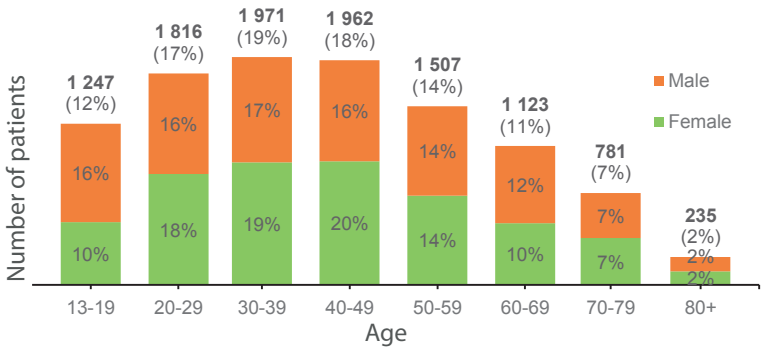

Fig. S2. Age divided by sex at first diagnosis for patients with chronic urticaria in Stockholm County (*n* = 10,642). Share of total (%).

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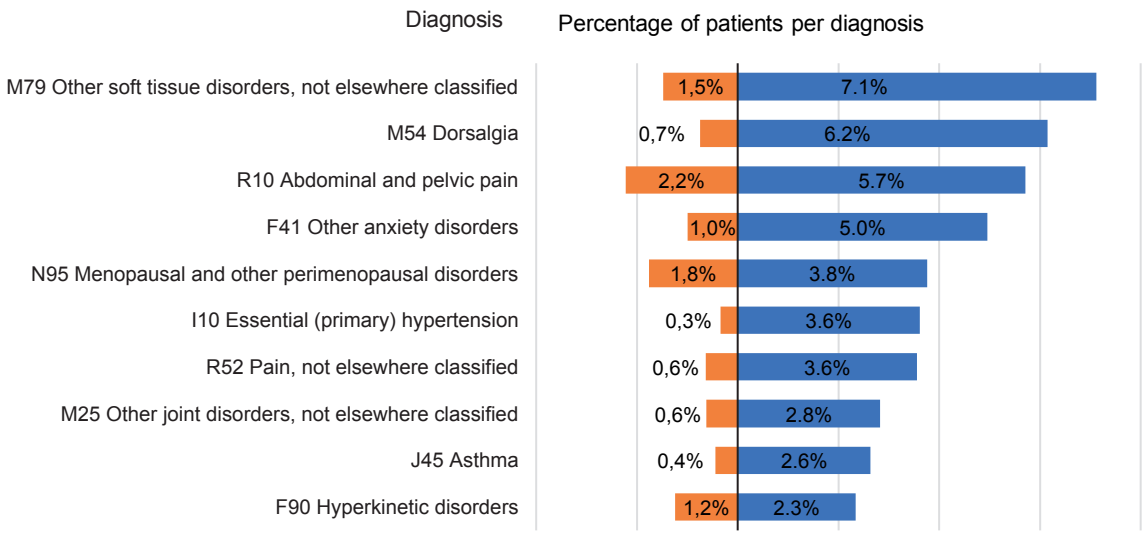

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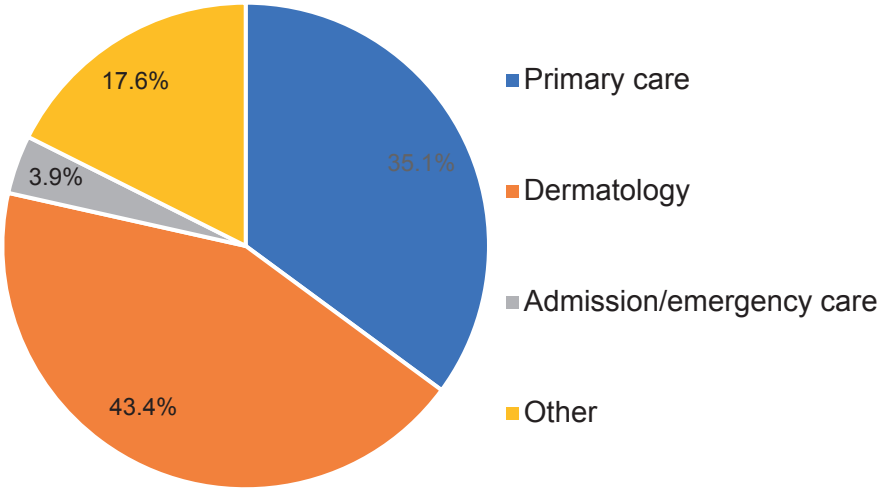

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