

Received Date : 21-Sep-2015

Revised Date : 18-Dec-2015

Accepted Date : 30-Dec-2015

Article type : Original Article

Title: Epidemiology of chronic spontaneous urticaria: results from a nationwide, population-based study in Italy

Running head: Epidemiology of chronic spontaneous urticaria in Italy

F. Lapi¹, N. Cassano², V. Pegoraro³, N. Cataldo³, F. Heiman³, I. Cricelli¹, M. Levi¹, D. Colombo⁴, E. Zagni⁴, C. Cricelli⁵, G.A. Vena²

¹Health Search, Italian College of General Practitioners and Primary Care, Florence, Italy; ²Dermatology and Venereology Private Practice, Bari and Barletta, Italy; ³IMS Health Information Solutions Medical Research srl, Milan, Italy; ⁴Novartis Farma S.p.A., Origgio, Varese, Italy; ⁵Italian College of General Practitioners and Primary Care

Correspondence

Francesco Lapi, PharmD, PhD
Health Search, Italian College of General Practitioners and Primary Care
Via Sestese 61
50141 Florence, Italy
Telephone: +39 055 4590716
Fax: +39 055 494900
Email address: lapi.francesco@simg.it

Statement of funding: The present study was funded by Novartis.

Conflict of interest: F. Lapi and I. Cricelli provided consultancies in protocol preparation for epidemiological studies and data analyses for Novartis, Bayer and Abbvie. G. A. Vena has been a speaker and/or a scientific consultant and/or an Advisory Board member for Novartis, Abbvie, MSD, Pfizer, and Leo Pharma. N. Cassano has been a scientific consultant and/or a speaker for Novartis, Abbvie, Leo Pharma, MSD and Pfizer. V. Pegoraro, N. Cataldo and F. Heiman, all received grants from Astellas, Astra Zeneca, Bayer, DOC Generici, Helsinn, Hisamitsu, Kyowa, Lundbeck, Merck Serono, Novartis, Otsuka, Pfizer, Pierre Fabre, Recordati. C. Cricelli provided clinical consultancies for Novartis and Bayer. D. Colombo and E. Zagni are employees of Novartis Farma Italy. M. Levi has no conflict of interest to disclose.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.14470

This article is protected by copyright. All rights reserved.

What's already known about this topic?

- Precise information on the epidemiology of chronic spontaneous urticaria (CSU) in Italy is lacking.

What does this study add?

- Annual incidence and prevalence rates of CSU in Italy were calculated from 2002 to 2013 using data from a national database of general practitioners.
- Demographic and clinical determinants associated with the occurrence of CSU were determined.

Summary

Background: Chronic spontaneous urticaria (CSU) is a common skin disease, but there is a paucity of precise epidemiological data on this disease.

Objective: To obtain information on the epidemiology of CSU in Italy.

Methods: The data source was the Health Search IMS Longitudinal Patient Database (HSD). The study population was formed by patients aged 15 years or older being registered with 700 general practitioners, homogeneously distributed across Italy. An ICD-9-CM-based algorithm was used for the identification of patients with CSU. The annual prevalence and incidence rates of CSU over a 12-year period (2002-2013) were estimated, along with demographic and clinical determinants.

Results: The annual prevalence of CSU ranged from 0.02% in 2002 to 0.38% in 2013. The incidence was within 0.10 to 1.50/1000 person-years. For both prevalence and incidence rates, females outnumbered males. The risk of CSU was statistically significantly higher in the presence of the following variables: obesity; anxiety; dissociative and somatoform disorders; malignancies; use of immunosuppressive drugs; chronic use of systemic corticosteroids. History of autoimmune thyroiditis showed a trend towards an increased risk of CSU, even if not statistically significant. Smoking was instead associated with a significantly reduced risk of CSU.

Conclusions: Our findings on CSU prevalence are consistent with those obtained in previous studies. Furthermore, this large population-based study provides important information regarding the association of CSU with demographic and clinical determinants, which have been examined in the primary care setting.

Keywords

Epidemiology; urticaria.

Introduction

Urticaria is a common disorder characterized by pruritic wheals and/or angioedema that affects 20-25% of the population at some point in their lifetime.¹ Chronic urticaria (CU) is defined as the occurrence of daily or almost daily wheals, angioedema, or both, for at least six weeks. Unlike physical and other inducible urticarias, in chronic spontaneous urticaria (CSU), the appearance of clinical manifestations is spontaneous and not evoked by physical and/or environmental stimuli.²

Many aetiological factors have been associated with the development of CSU, but most cases remain without any obvious aetiology^{1,3,4} from which the previous definition of “chronic idiopathic urticaria” (CIU) is currently abandoned. Autoimmune mechanisms have been implicated in the pathogenesis of CSU, at least in a subgroup of patients, based on the presence of functional histamine-releasing autoantibodies.⁴⁻⁶

Even if generally not life-threatening, CSU is a disabling disease whose management can be complex and challenging, with an important impact on the health-related quality of life and a relevant socio-economic burden.^{7,8}

Few data regarding CSU epidemiology are available. The existing literature reports estimates for the prevalence of CU, in the community setting, ranging from 0.05% to 3%.⁹⁻¹¹ However, prior investigations might suffer from limitations likely due to social desirability (i.e., tendency of the surveyed subjects to answer favourably), recall bias and low response rate, or to the adopted data sources.⁹⁻¹³ Furthermore, the precise epidemiological picture of CSU in Italy is unknown. In Italy, the General Practitioner (GP) acts as gatekeeper of the healthcare system. As such, general practice databases are able to track patients in a long-term fashion,¹⁴ and to generate information that faithfully reflects the health status of the general population. In light of this scenario, the primary objective of this study was to obtain information on the epidemiology of CSU in Italy, using a national database of GPs. Specifically, the annual prevalence and incidence rates over a 12-year period were estimated, along with the demographic and clinical determinants for CSU.

Materials and methods

Data source

The data source was the Health Search IMS Health Longitudinal Patient Database (HSD), a longitudinal observational database, established in 1998 by the Italian College of GPs, containing the electronic patient records from approximately 1000 GPs throughout Italy. Computer-based patient records collected by a selected group of 700, who met standard quality criteria regarding the levels of data entry, were included in the present study. These GPs cover almost one million patients, and were selected on a geographical basis to include patients representative of the whole Italian population and to ensure the completeness and consistency of medical records.¹⁵⁻¹⁹

A number of studies have been published, documenting the research validity of the HSD.^{20–23} Records consisted in demographic details, medical information, such as diagnoses, drugs and diagnostic tests prescriptions, specialist referrals, lifestyle characteristics, and mortality. All these data are linked through a unique identification number for an individual patient. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Drug prescriptions comprised information on trade name, formulation, and active substance, and were encoded with Anatomic Therapeutic Chemical (ATC) and Health Ministry coding systems.

Study population

We selected from HSD all patients aged ≥ 15 years who were alive and registered in the list of the 700 selected GPs within the study period (1 January 2002 to 31 December 2013), and with at least 1 year of medical history in the database.

CSU definition

A specific ICD-9-CM code for CSU is lacking. Similarly, there is not a specific code for CIU, the definition commonly adopted in the past for CSU, as well as the approved indication for some second-generation antihistamines. In order to overcome this limitation, we adopted a modified version of the algorithm previously used by Zazzali et al.¹¹ to identify CIU/CSU cases through the ICD-9-CM classification and medications use and subsequently tested by Cherepanov et al.²⁴ by reviewing medical charts.

In particular, the ICD-9-CM code 708 refers to urticaria, that, in turn, may be distinguished into idiopathic (708.1), other specified (708.8), or unspecified (708.9) urticaria. CSU diagnosis was supported by the presence of at least one outpatient ICD-9-CM code of 708.1, 708.8, or 708.9 combined with a) a second diagnosis of 708.1, 708.8, or 708.9 coded six or more weeks later; b) an ICD-9-CM code of 995.1 for angioedema at least six weeks from the urticaria diagnosis; or c) a 90-day or longer period of an overlapping supply of a prescription antihistamine and a second prescription medication commonly used to treat CSU (i.e., a second antihistamine, montelukast, cyclosporine, methotrexate, or oral corticosteroids) occurring within 6 months after the first ICD-9-CM diagnosis. This last temporal criterion was the only change introduced to the original algorithm adopted by Zazzali et al.¹¹ Patients with different urticarias recognizable by distinct ICD-9-CM codes (e.g., allergic urticaria and inducible urticarias) were excluded.

Data analyses

The annual prevalence and incidence rates of CSU were calculated for the period 2002-2013. As for the annual prevalence, for each year of observation the number of patients with old and new diagnoses of CSU, alive and present in the GPs' lists up to 31 December of the year (numerator), was divided by the total number of active (currently alive) patients in the same year (denominator). Given that most cases of CSU showed a duration ranging between 6 weeks and 1 year,⁹ we defined old cases as those occurring in the year prior to the year of observation.

The annual incidence was calculated by dividing the number of new cases (excluding those with CSU in the previous year) in each year of observation (numerator) by the person-time at risk of developing CSU (denominator) on the 1st of January for each year of observation. For the calculation of the incidence rate, person-time of follow-up was accumulated until the occurrence of one of the following events, whichever came first: occurrence of CSU, transferring out of general practice, death or the 31st December of the year of observation. The prevalence and incidence were calculated as rates per 100 inhabitants and 1000 person-years, respectively.

The role of variables associated with CSU was assessed in a cohort of patients aged ≥ 15 years with a first visit (index date) with their GPs recorded between 01/01/2002 and 31/12/2012. From this cohort, we excluded patients with less than 1-year medical history before the index date, as well as those with a diagnosis of CSU preceding or on the index date. These patients were followed up until the occurrence of any of the following events, whichever came first: diagnosis of CSU, transferring out of general practice, death, or end of the study period (31/12/2013). The potential determinants were therefore defined prior or on the index date, and included gender, age, smoking status, obesity [(ICD-9-CM code 278.0 or body mass index ≥ 30 (last information recorded before the index date)], excessive alcohol intake (i.e., more than 20 mg or 40 mg per day in women and men, respectively) and related diseases identified by specific ICD-9-CM codes, use of immunosuppressants, or chronic use (at least 180 days) of systemic corticosteroids. The following diseases were also examined: insomnia; acute reaction to stress; anxiety, dissociative and somatoform disorders; human immunodeficiency virus infection; neoplasms (of any kind); Hashimoto thyroiditis and other forms of autoimmune thyroiditis; allergy (not specified). Selection of determinants of CSU was performed by a backward stepwise (p values < 0.10 for entering and < 0.15 for exiting variables) procedure using multivariable Cox regression. The use of p values > 0.05 prevented the automatic exclusion of determinants with clinical significance but reduced

statistical power.²⁵ Hazard Ratios (HRs) and related 95% Confidence Intervals (CIs) were estimated for each determinant.

Given that the CSU diagnosis might be prone to misclassification, the role of the explicative variables was further assessed in a sensitivity analysis in which we limited CSU cases to those coupled with a referral to a dermatologist in the six months before/after the event date.

Results

In the observed period, 14,859 patients (mean age, 46.43 ± 20.35 years) received a diagnosis consistent with CSU. The annual prevalence of CSU ranged from 0.02% in 2002 to 0.38% in 2013, with a trend towards progressive increase (Fig. 1). The incidence rate was comprised within 0.10 to 1.50/1000 person-years (Fig. 2). For both prevalence and incidence rates, females consistently outnumbered males.

Table 1 depicts the results concerning the identification of the baseline determinants of CSU. We observed some discontinuity across age categories. Namely, patients younger than 20 years showed a greater risk to develop CSU than those aged 20 to 49. In contrast, patients in the 50-74 years age group showed an increased risk, although marginally significant, while subjects aged ≥ 75 years had a lower risk. The incidence rates of CSU were statistically significantly higher for females [(adjusted (aHR), 1.84; 95% CI, 1.77-1.91)], obesity (aHR, 1.40; 95% CI, 1.17-1.67), anxiety, dissociative and somatoform disorders (aHR, 1.22; 95% CI, 1.08-1.37), malignancies (aHR, 1.14; 95% CI, 1.02-1.27), use of immunosuppressive drugs (aHR 2.19; 95% CI, 1.67-2.88), and chronic use of systemic corticosteroids (aHR, 1.95; 95% CI, 1.48-2.57). A trend towards an increased risk of CSU was observed in patients with a history of autoimmune thyroiditis, even though this association did not reach statistical significance. Smoking was associated with a significantly reduced risk of CSU (aHR, 0.75; 95% CI, 0.63-0.88) (Table 1).

The sensitivity analysis in which CSU cases were restricted to those preceded or followed by a specialist referral (n=3,489) gave rise to aHRs consistently similar to those obtained for the primary analysis (Table 2).

Discussion

This study represents the first nationwide, population-based, epidemiological study on CSU in Italy. To the best of our knowledge, this was the first investigation that assessed the association of CSU with demographic and clinical determinants in primary care.

Although CSU is frequently encountered in clinical practice and has a considerable psychosocial burden, there is a paucity of epidemiological information about this condition. Some of the data in the literature show inconsistencies, mainly due to the heterogeneity of populations examined and the diagnostic criteria used.²⁶⁻²⁹

The methodology and results of the main epidemiological studies in CU/CSU patients are summarized in Table 3. Gaig et al.⁹ conducted a cross-sectional study among adults in Spain using a validated questionnaire, and found a 0.6% point prevalence of CU. A representative cross-sectional population survey in Germany detected a period prevalence of CU within the previous 12 months of 0.8%.¹⁰ A CU prevalence of 0.4% was reported in Taiwan, although no methodological details were provided. Instead, Zazzali et al.,¹¹ using a large insurance database in the USA, identified claims consistent with the diagnosis of CIU/CSU, estimating 1-year period prevalence of 0.08%. The variability in the aforementioned estimates is likely due to the different methodologies adopted to select the target population and to define the disease: social desirability,^{9-11,13} self-reporting and/or recall bias, low response rate,¹⁰ and the use of claims databases^{11,12} might have biased the results. In questionnaire-based studies, the occurrence of the disease is self-reported by patients and therefore lacks an actual confirmatory diagnosis.^{9,10,13} Claims of administrative/insurance databases, generated for billing purpose, may lack of clinical details so leading to under- or over-coding.^{11,12} Indeed, although we used an algorithm similar to that used by Zazzali et al.,¹¹ we obtained different results given the difference between data sources. Namely, insured populations are generally less representative of the general population than clinical databases. Then, considering the young age of the cohort examined by Zazzali et al.¹¹ (mean age, 36; SD, 19.6), these individuals were likely to have less comorbidities than ours. Finally, younger individuals are more prone to use over-the-counter medications, which are not registered in claims/insurance databases.

The incidence of CSU in our study population was in the range of 0.10-1.50 per 1,000 person-years; the annual prevalence of CSU was comprised between 0.02% and 0.40%. The estimates in the first two years were particularly lower, but a trend towards a progressive increase up to more steady values was observed. This result might be attributed to the improvement of data quality in the HSD over recent years. Given the natural course of CSU, the fact that the prevalence estimates were stable over 2008-2013 period is reassuring.

Our findings on CSU prevalence roughly agree with the results of previous studies. However, we attempted to minimize the aforementioned biases using a clinical-based data source, instead of administrative data, and an algorithm previously tested to identify cases of

CSU.^{11,24} Furthermore, our analyses were longitudinally performed, thus reducing any recall bias, which may occur with cross-sectional design. Finally, some differences with previous studies can be due to the age of the target populations. The mean age of CSU patients in our population was 46.43 years (SD, 20.35). The greatest risk of CSU, even if only marginally significant, was observed for patients aged 50 to 75, whereas subjects aged ≥ 80 had the lowest risk. Consistently, a population-based study in Taiwan disclosed a very low proportion of CU cases among patients ≥ 80 years.¹² Older patients are likely to have a lower access to GP services because of higher rates of hospitalization or institutionalization. However, the role of immunosenescence in decreasing the frequency of CSU in the oldest people cannot be ruled out.

When examining the role of other candidate determinants, we confirmed a greater risk for females,¹¹ who represented two-thirds of CSU patients in our cohort (most authors found a male/female ratios of 1:2 up to 1:4).^{1,5,9,10,26,30} The reasons for this gender-related disparity are not completely understood. A plausible explanation may be the autoimmune nature of the disease at least in a subgroup of CSU patients.³⁰ In fact, in the light of recent evidence, CSU has been proposed to be an autoimmune disorder characterized by circulating functional IgG autoantibodies directed against IgE and/or the alpha-chain of the high-affinity IgE receptor and detectable in approximately 27-50% of cases.⁵ Other indirect hints for the possible autoimmune nature of CSU are its predilection for middle-aged women and its frequent association with autoimmune thyroid disorders,^{31–35} which has been repeatedly recognized as significant in previous works.^{30–32} In most reports, autoimmune thyroid disorders were defined on the basis of the presence of high titers of anti-thyroid autoantibodies.³⁰ The pathophysiology of the association between CSU and thyroid autoimmunity is not well understood, although it seems that anti-thyroid antibodies are not directly linked to CSU pathogenesis but simply represent a marker of autoimmunity.^{31,32} A recent study in Israel on 12,778 patients who received a diagnosis of CSU by either allergy or dermatology specialists during 17 years confirmed the association of CSU with hypothyroidism, hyperthyroidism, and anti-thyroid autoantibodies.³⁰ The same study also demonstrated that females with CSU had a significantly higher incidence of autoimmune disorders mostly diagnosed during the 10 years following the CSU diagnosis.³⁰ In our database, a tendency towards an increased risk of CSU was revealed in patients with a history of autoimmune thyroiditis, although this trend did not reach significance, possibly because of lack of statistical power. The absence of a systematic recording of anti-thyroid autoantibodies might be responsible for this underestimation.

We found an increased frequency of CSU in patients treated with systemic corticosteroids and other immunosuppressants. As these medications are commonly prescribed for many immune-mediated disorders, patients receiving such treatments could correspond to patients more susceptible to autoimmune disorders.

Our findings also show a higher risk of developing CSU in obese subjects, as well as in patients with history of malignancies, and in those who suffer from anxiety, dissociative and somatoform disorders.

The significant association observed in our study between CSU and obesity is particularly intriguing, and might suggest the pathogenetic involvement of shared factors and/or adipokine-mediated inflammation. After the discovery of the activity of adipokines on immunity and inflammation, growing evidence has highlighted the link between obesity and autoimmunity.³⁵ Obesity is characterized by a chronic, systemic low-grade inflammatory state,³⁴ and can result in a decreased immunological tolerance to antigens, thus increasing the risk of allergy and of various immune-mediated diseases.^{36,37} Human mast cells may also be a direct target of adipokine activity.³⁸ The serum levels of mast cell-derived tryptase and the number of adipose tissue mast cells were reported to be increased in obese patients and high fat diet-fed mice, respectively.^{39,40} Comparison of individual components of metabolic syndrome between patients with CU and controls revealed that central obesity was more prevalent in subjects with CU, and significantly correlated with levels of tumour necrosis factor-alpha, serum total IgE and eosinophil cationic protein.⁴¹

The association between CU and malignant tumours is still controversial. An increased overall risk of cancer, especially for hematologic cancers and among young and middle-aged individuals, was observed in patients with CU, in a recent nationwide population-based study in Taiwan.¹² Malignant diseases were mostly identified in the first year after the diagnosis of CU. Our study supported also the opposite correlation, namely that patients with cancer are at increased risk of CSU. It is not known whether the coexistence of CSU with malignancies implies shared etiologic factors and/or pathomechanisms or if it is only a coincidental finding.

Similar considerations may be applied to the association between CSU and anxiety, dissociative and somatoform disorders emerged from our results. In the study carried out by Zazzali et al.,¹¹ anxiety and depression were common among CSU patients, with both being identified in 9.4% of the population. Patients with CSU have frequently been reported to have high rates of psychiatric comorbidities (particularly anxiety, depression and somatoform disorders).⁴²⁻⁴⁴ Psychiatric comorbidity, in turn, can be an important driver of emotional

distress and quality of life impairment in subjects with CSU.⁴⁴ Of note, our study supports that the psychological status is not only a mere consequence of CSU, as the presence of pre-existing anxiety, dissociative and somatoform disorders significantly augmented the risk of CSU. The link between CSU and mental disorders deserves further studies in order to better define any causal relationship and possible implications.

Interestingly, we found that smoking seems to have a protective effect on the risk of CSU. The role of smoking in inflammatory and immune-mediated disorders is complex and multi-faceted. For instance, current epidemiological data point out that smoking can contribute to the development of rheumatoid arthritis, lupus erythematosus, and Crohn's disease, while being a protective factor for ulcerative colitis.⁴⁵ Modest associations have been seen between smoking and some allergic diseases.⁴⁶ Large cross-sectional population-based surveys and prospective observational studies have emphasized the protective effects of smoking against autoimmune hypothyroidism.^{47,48} Experimental evidence documented the ability of nicotine to modulate inflammatory and allergic processes through multiple mechanisms.^{49,50}

The present study has some limitations. The lack of a specific ICD-9-CM code for CSU, along with the absence of a formal validation of the individual diagnoses, might have misclassified some cases of CSU. We adopted criteria previously used and verified to identify patients with CIU/CSU.¹¹ Although in the study performed by Cherepanov et al.²⁴ CSU was not confirmed by direct physical examination, the ICD-9-CM-based algorithm was tested by reviewing the medical charts, and showed a positive predictive value greater than 90% along with 71.1% sensitivity, which increased up to 83.3% when diagnoses were complemented by medication use. In addition, the fact that our prevalence estimates were stable over the 2008-2013 period, and that, in the analysis restricted to cases preceded or followed by a specialist visit CSU, determinants were consistent with those emerged from the primary analysis was reassuring.

In conclusion, we assessed the epidemiology of CSU in the Italian HSD, along with the related determinants. These findings may contribute to increase the knowledge of CSU. In particular, the knowledge of determinants of CSU might support clinicians to appropriately manage and treat this condition.

References

- 1 Champion RH, Roberts SO, Carpenter RG, Roger JH. Urticaria and angio-oedema. A review of 554 patients. *Br J Dermatol* 1969; **81**:588–97.
- 2 Zuberbier T, Aberer W, Asero R, *et al.* The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: The 2013 revision and update. *Allergy* 2014; **69**:868–87.
- 3 Najib U, Sheikh J. The spectrum of chronic urticaria. *Allergy* 2009; **30**: 1–10.
- 4 Saini SS. Chronic spontaneous urticaria. Etiology and pathogenesis. *Immunol Allergy Clin North Am* 2014; **34**:33–52.
- 5 Greaves M. Chronic urticaria. *J Allergy Clin Immunol* 2000; **105**:664–72.
- 6 Altman K, Chang C. Pathogenic intracellular and autoimmune mechanisms in urticaria and angioedema. *Clin Rev Allergy Immunol* 2013; **45**:47–62.
- 7 Delong LK, Culler SD, Saini SS *et al.* Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 nonimmunosuppressed patients. *Arch Dermatol* 2008; **144**:35–9.
- 8 O'Donnell BF. Urticaria. Impact on quality of life and economic cost. *Immunol Allergy Clin North Am* 2014; **34**:89–104.
- 9 Gaig P, Olona M, Muñoz Lejarazu D *et al.* Epidemiology of urticaria in Spain. *J Investig Allergol Clin Immunol* 2004; **14**:214–20.
- 10 Zuberbier T, Balke M, Worm M *et al.* Epidemiology of urticaria: A representative cross-sectional population survey. *Clin Exp Dermatol* 2010; **35**:869–73.
- 11 Zazzali JL, Broder MS, Chang E *et al.* Cost, utilization, and patterns of medication use associated with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol* 2012; **108**:98–102.
- 12 Chen Y-J, Wu C-Y, Shen J-L *et al.* Cancer risk in patients with chronic urticaria: a population-based cohort study. *Arch Dermatol* 2012; **148**:103–8.
- 13 Nederhof A, Nederhof AJ. Methods of coping with social desirability bias: A review. *Eur J Soc Psychol* 1985; **15**:263–80.
- 14 Ferré F, de Belvis A, Valerio L, *et al.* Italy: Health System Review. *Health Syst Transit* 2014; **16**: 1-168.
- 15 Fleming DM, Schellevis FG, Van Casteren V. The prevalence of known diabetes in eight European countries. *Eur J Public Health* 2004; **14**:10–4.
- 16 Gijzen R, Poos MJJC. Using registries in general practice to estimate countrywide morbidity in The Netherlands. *Public Health* 2006; **120**:923–36.
- 17 Mazzaglia G, Sessa E, Samani F. Use of Computerized General Practice Database for epidemiological studies in Italy: a comparative study with the official national statistics. *J Epidemiol Community Health* 2004; **58**.
- 18 Sessa E, Samani F, Niccolai C *et al.* La creazione di un campione validato di medici di medicina generale nel database di Health Search. *SIMG* 2004; **3**:10–4.
- 19 Bianchini E, Brignoli O, Cricelli C *et al.* VIII Report Health Search. Anno 2013/2014. Firenze, 2014 URL http://healthsearch.it/documenti/Archivio/Report/VIIIReport_2013-2014/index.html

[accessed on 18 December 2015].

- 20 Filippi A, Vanuzzo D, Bignamini AA *et al.* The database of Italian general practitioners allows a reliable determination of the prevalence of myocardial infarction. *Ital Heart J* 2005; **6**:311–4.
- 21 Cricelli C, Mazzaglia G, Samani F *et al.* Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. *J Public Health Med* 2003; **25**:254–7.
- 22 Mazzaglia G, Ambrosioni E, Alacqua M *et al.* Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 2009; **120**:1598–605.
- 23 Vena GA, Altomare G, Ayala F *et al.* Incidence of psoriasis and association with comorbidities in Italy: A 5-year observational study from a national primary care database. *Eur J Dermatol* 2010; **20**:593–8.
- 24 Cherepanov D, Raimundo K, Chang E *et al.* Validation of an ICD-9-based claims algorithm for identifying patients with chronic idiopathic/spontaneous urticaria. *Ann Allergy Asthma Immunol* 2015; **114**:393–8.
- 25 Steyerberg E. Clinical prediction models. A practical approach to development, validation, and updating., 1st ed. New York, Springer-Verlag New York, 2009.
- 26 Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981; **104**:369–81.
- 27 Paul E, Greilich K. Zur Epidemiologie der Urtikariaerkrankungen. *Hautarzt* 1991; **42**:366–75.
- 28 Kulthanan K, Jiamton S, Thumpimukvatana N, Pinkaew S. Chronic idiopathic urticaria: prevalence and clinical course. *J Dermatol* 2007; **34**:294–301.
- 29 Zhong H, Song Z, Chen W *et al.* Chronic urticaria in Chinese population: A hospital-based multicenter epidemiological study. *Allergy* 2014; **69**:359–64.
- 30 Confino-Cohen R, Chodick G, Shalev V *et al.* Chronic urticaria and autoimmunity: Associations found in a large population study. *J Allergy Clin Immunol* 2012; **129**:1307–13.
- 31 Asero R. Sex differences in the pathogenesis of chronic urticaria. *J Allergy Clin Immunol* 2003; **111**:425–6.
- 32 Missaka RFBG, Penatti HC, Silveiras MRC *et al.* Autoimmune thyroid disease as a risk factor for angioedema in patients with chronic idiopathic urticaria: a case-control study. *Sao Paulo Med J* 2012; **130**:294–8.
- 33 Pan X-F, Gu J-Q, Shan Z-Y. The prevalence of thyroid autoimmunity in patients with urticaria: a systematic review and meta-analysis. *Endocrine* 2015; **48**:804–10.
- 34 Rodríguez-Hernández H, Simental-Mendía LE, Rodríguez-Ramírez G, Reyes-Romero MA. Obesity and inflammation: Epidemiology, risk factors, and markers of inflammation. *Int J Endocrinol* 2013; **2013**:678159.
- 35 Abella V, Scotece M, Conde J *et al.* Adipokines, metabolic syndrome and rheumatic diseases. *J Immunol Res* 2014; **2014**:343746.
- 36 Hersoug LG, Linneberg A. The link between the epidemics of obesity and allergic diseases: Does obesity induce decreased immune tolerance? *Allergy* 2007; **62**:1205–13.

- 37 Versini M, Jeandel PY, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: Not a passive bystander. *Autoimmun Rev* 2014; **13**:981-1000.
- 38 Sismanopoulos N, Delivanis DA, Mavrommati D *et al*. Do mast cells link obesity and asthma? *Allergy* 2013; **68**:8–15.
- 39 Moreno M, Puig J, Serrano M *et al*. Circulating tryptase as a marker for subclinical atherosclerosis in obese subjects. *PLoS One* 2014; **9**:e0097014.
- 40 Liu J, Divoux A, Sun J *et al*. Genetic deficiency and pharmacological stabilization of mast cells reduce diet-induced obesity and diabetes in mice. *Nat Med* 2009; **15**:940–5.
- 41 Ye Y-M, Jin H-J, Hwang E-K *et al*. Co-existence of chronic urticaria and metabolic syndrome: Clinical implications. *Acta Derm Venereol* 2012; **93**:156-60.
- 42 Pasaoglu G, Bavbek S, Tugcu H *et al*. Psychological status of patients with chronic urticaria. *J Dermatol* 2006; **33**:765–71.
- 43 Engin B, Uguz F, Yilmaz E *et al*. The levels of depression, anxiety and quality of life in patients with chronic idiopathic urticaria. *J Eur Acad Dermatol Venereol* 2008; **22**:36–40.
- 44 Staubach P, Dechene M, Metz M *et al*. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. *Acta Derm Venereol* 2011; **91**:557–61.
- 45 de Carvalho JF, Pereira RMR, Shoenfeld Y. The mosaic of autoimmunity: the role of environmental factors. *Front Biosci (Elite Ed)* 2009; **1**:501–9.
- 46 Saulyte J, Regueira C, Montes-Martínez A *et al*. Active or passive exposure to tobacco smoking and allergic rhinitis, allergic dermatitis, and food allergy in adults and children: a systematic review and meta-analysis. *PLoS Med* 2014; **11**:e1001611.
- 47 Dong YH, Fu DG. Autoimmune thyroid disease: mechanism, genetics and current knowledge. *Eur Rev Med Pharmacol Sci* 2014; **18**:3611–8.
- 48 Wiersinga WM. Smoking and thyroid. *Clin Endocrinol (Oxf)* 2013; **79**:145–51.
- 49 Nizri E, Irony-Tur-Sinai M, Lory O *et al*. Activation of the cholinergic anti-inflammatory system by nicotine attenuates neuroinflammation via suppression of Th1 and Th17 responses. *J Immunol* 2009; **183**:6681–8.
- 50 Mishra NC, Rir-sima-ah J, Boyd RT *et al*. Nicotine inhibits Fc epsilon RI-induced cysteinyl leukotrienes and cytokine production without affecting mast cell degranulation through alpha 7/alpha 9/alpha 10-nicotinic receptors. *J Immunol* 2010; **185**:588–96.

Table 1 Determinants of CSU calculated on the new (incident) cases over the follow-up period

	Patients with CSU	Patients without CSU	Crude HR*	Adjusted HR*
<i>Gender</i>				
Males	4297 (31.88)	800434 (46.95)	1	1
Females	9182 (68.12)	904322 (53.05)	1.84 [1.77 - 1.91]	1.84 [1.77 - 1.91]
<i>Age groups (years)</i>				
14-19	1271 (9.43)	181440 (10.64)	1	1
20-24	676 (5.02)	101550 (5.96)	0.80 [0.73 - 0.88]	0.79 [0.72 - 0.87]
25-29	790 (5.86)	122295 (7.17)	0.79 [0.72 - 0.86]	0.77 [0.71 - 0.85]
30-34	946 (7.02)	145653 (8.54)	0.80 [0.73 - 0.87]	0.78 [0.72 - 0.85]
35-39	1090 (8.09)	156077 (9.16)	0.84 [0.77 - 0.91]	0.81 [0.75 - 0.88]
40-44	1148 (8.52)	146060 (8.57)	0.92 [0.85 - 1.00]	0.90 [0.83 - 0.97]
45-49	1061 (7.87)	130820 (7.67)	0.93 [0.85 - 1.01]	0.91 [0.83 - 0.98]
50-54	1138 (8.44)	121765 (7.14)	1.04 [0.96 - 1.12]	1.01 [0.93 - 1.09]
55-59	1117 (8.29)	115193 (6.76)	1.06 [0.98 - 1.15]	1.03 [0.95 - 1.12]
60-64	1130 (8.38)	109334 (6.41)	1.14 [1.05 - 1.24]	1.10 [1.02 - 1.19]
65-69	1125 (8.35)	101676 (5.96)	1.24 [1.15 - 1.35]	1.19 [1.10 - 1.29]
70-74	925 (6.86)	91864 (5.39)	1.18 [1.08 - 1.28]	1.11 [1.02 - 1.21]
75-79	621 (4.61)	77960 (4.57)	1.02 [0.93 - 1.12]	0.93 [0.85 - 1.03]
80-84	297 (2.20)	53824 (3.16)	0.83 [0.73 - 0.94]	0.74 [0.66 - 0.85]
85-89	100 (0.74)	28150 (1.65)	0.68 [0.55 - 0.83]	0.59 [0.48 - 0.73]
90-94	28 (0.21)	13526 (0.79)	0.48 [0.33 - 0.70]	0.42 [0.29 - 0.61]
≥95	16 (0.12)	7569 (0.44)	0.53 [0.32 - 0.87]	0.45 [0.27 - 0.73]
Obesity	185 (1.37)	20792 (1.22)	1.57 [1.32 - 1.87]	1.40 [1.17 - 1.67]
Smoking	168 (1.25)	43301 (2.54)	0.64 [0.55 - 0.76]	0.75 [0.63 - 0.88]
Excessive alcohol consumption	6 (0.04)	2302 (0.14)	0.45 [0.20 - 1.01]	-
Insomnia	29 (0.22)	5055 (0.30)	1.30 [0.90 - 1.87]	-
Anxiety, dissociative and somatoform disorders	266 (1.97)	30872 (1.81)	1.36 [1.20 - 1.54]	1.22 [1.08 - 1.37]
Acute reaction to stress	15 (0.11)	1571 (0.09)	1.27 [0.77 - 2.11]	-
HIV infection	3 (0.02)	718 (0.04)	0.81 [0.27 - 2.49]	-
Neoplasm	330 (2.45)	50753 (2.98)	1.24 [1.12 - 1.39]	1.14 [1.02 - 1.27]
Autoimmune thyroiditis	34 (0.25)	3952 (0.23)	1.73 [1.24 - 2.42]	1.39 [0.99 - 1.95]
Allergy (unspecified)	171 (1.27)	27448 (1.61)	1.13 [0.98 - 1.32]	-
Use of immunosuppressive drugs	54 (0.40)	2797 (0.16)	2.47 [1.89 - 3.23]	2.19 [1.67 - 2.88]
Chronic use of systemic corticosteroids	53 (0.39)	3506 (0.21)	2.43 [1.85 - 3.18]	1.95 [1.48 - 2.57]

CSU= chronic spontaneous urticaria; HIV= human immunodeficiency virus; HR= hazard ratio

*significant hazard ratios are shown in bold

Table 2 Determinants of CSU calculated on the new (incident) cases with a diagnosed of CSU combined with a specialist referral

	Patients with CSU	Patients without CSU	Crude HR*	Adjusted HR*
<i>Gender</i>				
Males	1.135 (32.53)	803.596 (46.86)	1	1
Females	2.354 (67.47)	911.150 (53.14)	1.78 [1.66 - 1.91]	1.77 [1.65 - 1.90]
<i>Age groups (years)</i>				
<20	313 (8.97)	182398 (10.64)	1	1
20-29	371 (10.63)	224940 (13.12)	0.82 [0.71 - 0.96]	0.82 [0.70 - 0.95]
30-39	467 (13.38)	303299 (17.69)	0.77 [0.66 - 0.89]	0.75 [0.65 - 0.87]
40-49	516 (14.79)	278573 (16.25)	0.88 [0.77 - 1.02]	0.87 [0.75 - 1.00]
50-59	577 (16.54)	238636 (13.92)	1.10 [0.96 - 1.26]	1.08 [0.94 - 1.24]
60-69	680 (19.49)	212585 (12.40)	1.47 [1.29 - 1.68]	1.43 [1.25 - 1.63]
70-79	458 (13.13)	170912 (9.97)	1.34 [1.16 - 1.55]	1.27 [1.10 - 1.46]
80-89	93 (2.67)	82278 (4.80)	0.75 [0.59 - 0.94]	0.68 [0.54 - 0.85]
≥90	14 (0.40)	21125 (1.23)	0.64 [0.37 - 1.09]	0.55 [0.32 - 0.94]
Obesity	47 (1.35)	20.930 (1.22)	1.53 [1.08 - 2.17]	-
Smoking	41 (1.18)	43.428 (2.53)	0.65 [0.47 - 0.90]	0.78 [0.56 - 1.08]
Excessive alcohol consumption	1 (0.03)	2.307 (0.13)	0.29 [0.04 - 2.06]	-
Insomnia	8 (0.23)	5.076 (0.30)	1.35 [0.68 - 2.71]	-
Anxiety, dissociative and somatoform disorders	74 (2.12)	31.064 (1.81)	1.45 [1.15 - 1.83]	1.28 [1.01 - 1.61]
Acute reaction to stress	4 (0.11)	1.582 (0.09)	1.31 [0.49 - 3.49]	-
HIV infection	2 (0.06)	719 (0.04)	2.03 [0.51 - 8.12]	-
Neoplasm	107 (3.07)	50.976 (2.97)	1.55 [1.28 - 1.88]	1.40 [1.15 - 1.69]
Autoimmune thyroiditis	11 (0.32)	3.975 (0.23)	2.13 [1.18 - 3.84]	1.74 [0.96 - 3.14]
Allergy (unspecified)	49 (1.40)	27.570 (1.61)	1.24 [0.94 - 1.65]	1.27 [0.96 - 1.68]
Use of immunosuppressive drugs	15 (0.43)	2.836 (0.17)	2.64 [1.59 - 4.38]	2.57 [1.55 - 4.27]
Chronic use of systemic corticosteroids	10 (0.29)	3.549 (0.21)	1.75 [0.94 - 3.25]	-

CSU= chronic spontaneous urticaria; HIV= human immunodeficiency virus; HR= hazard ratio

*significant hazard ratios are shown in bold

Table 3 Epidemiological studies on chronic urticaria: methodology details and results

R ef.	Count ry	Study population (n)	Definition of CU/CSU	Study design and methodology	No. of cases of CU/CSU	Prevalence of CU/CSU
9	Spain	Patients aged 18 years or older (105,603; respondents=5,003)	Presence of hives with or without angioedema more than twice a week for at least 6 weeks	Cross-sectional design Randomly selected sample; sample size calculated assuming a 1.4% error for global results and a 95% CI Phone survey performed using a validated questionnaire	30 CU patients	Point prevalence: 0.6% (95% CI: 0.4%-0.8%)
10	Germany	Patients of any age (13,300; respondents=4,093)	Presence of continuous or recurrent wheals and/or angioedema for at least 6 weeks	Cross-sectional design Representative random sample Initial contact by means of a standardized questionnaire Of the subjects interviewed by phone, those who reported active symptoms in the previous 3 years were invited for further investigations	767 suspected cases of urticaria, 189 confirmed after investigations*	Lifetime prevalence: 1.8% (95% CI 1.4-2.3%) Period prevalence (yearly): 0.8% (95% CI 0.6-1.1%)
11	USA	Patients of any age (7,555,991 residents)	Presence of at least 1 outpatient ICD-9-CM code of 708.1, 708.8, or 708.9 combined with 1) a second such code 6 or more weeks later; 2) an ICD-9-CM code for angioedema (995.1) at least 6 weeks from the urticaria diagnosis; or 3) a 90-day or longer period of an overlapping supply of a prescription antihistamine and a second prescription medication commonly used to treat CIU/CSU. Codes for allergic (708.0), heat or cold (708.2), dermatographic (708.3), vibratory (708.4), or cholinergic (708.5) urticarias were excluded	Cross-sectional study Retrospective analysis using health insurance claims databases of patients enrolled from July 1, 2007 through June 30, 2008 CIU (CSU) diagnosis not confirmed by manual review of medical charts Data on OTC drugs not available This algorithm has been tested by a subsequent study (Cherepanov et al. ²⁴)	6,019 CIU/CSU patients	Period prevalence (yearly): 0.08%

CI = confidence interval; CU= chronic urticaria; CIU= chronic idiopathic urticaria; CSU= chronic spontaneous urticaria; ICD-9-CM= International Classification of Diseases, 9th Revision, Clinical Modification;

OTC= over-the-counter

*the distinction between acute and chronic cases cannot be derived from the study results, as well as the absolute number of CU cases

Figure legends

Fig 1. Prevalence rates of chronic spontaneous urticaria

Fig 2. Incidence rates of chronic spontaneous urticaria

