

Accepted Manuscript

Prevalence Estimates For Chronic Urticaria in the United States: a gender and age adjusted population analysis

Sara Wertenteil, BA, Andrew Strunk, MA, Amit Garg, MD



PII: S0190-9622(19)30362-7

DOI: <https://doi.org/10.1016/j.jaad.2019.02.064>

Reference: YMJD 13246

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 19 December 2018

Revised Date: 22 January 2019

Accepted Date: 27 February 2019

Please cite this article as: Wertenteil S, Strunk A, Garg A, Prevalence Estimates For Chronic Urticaria in the United States: a gender and age adjusted population analysis, *Journal of the American Academy of Dermatology* (2019), doi: <https://doi.org/10.1016/j.jaad.2019.02.064>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title: Prevalence Estimates For Chronic Urticaria in the United States: a gender and age adjusted population analysis.

Sara Wertenteil, BA, Andrew Strunk, MA, Amit Garg, MD

Department of Dermatology, Donald and Barbara Zucker School of Medicine at Hofstra / Northwell, New Hyde Park, NY

Word count: 1559

Abstract word count: 195

Capsule summary: 50

Figures: 0

Tables: 3

References: 35

Corresponding Author:

Amit Garg, MD

Donald and Barbara Zucker School of Medicine at Hofstra / Northwell

1991 Marcus Avenue, Suite 300

New Hyde Park, NY, 11042

Email: amgarg@northwell.edu

Other Authors:

Sara Wertenteil swertenteil@northwell.edu

Andrew Strunk astrunk1@northwell.edu

Funding Sources: none

25 **Conflict of Interest:** Dr. Garg has served as an advisor for AbbVie, Pfizer, Janssen, and Asana
26 Biosciences, and has received honoraria.

27 **Role of Sponsor:** N/A

28 **Prior Presentation:** There is no prior presentation of this work.

29 **IRB Statement:** This investigation was approved by the IRB of the Feinstein Institute for Medical
30 Research at the Northwell Health.

31 **Acknowledgements:** None

32 **Acronym List**

33 CU: chronic urticaria

34 CSU: chronic spontaneous urticaria

35 ICD: International Classification of Diseases

36 SNOMED-CT: Systemized Nomenclature of Medicine—Clinical Terms

37 LOINC: Logical Observation Identifiers Names and Codes

Background: Disease burden in chronic urticaria (CU) is poorly understood.

Objective: To estimate standardized overall and gender-, age-, and race-specific prevalence estimates for CU among adults in the United States.

Methods: Cross-sectional analysis using electronic health records data for a demographically heterogeneous population-based sample of over 55 million patients across all four census regions.

Results: The overall CU prevalence was 0.23%, or 230 CU patients per 100,000 adults. The adjusted prevalence in women was 310 (95% CI 307-312) per 100,000, more than twice that of men [146 (95% CI 143-148) per 100,000, $p < 0.001$]. CU prevalence was highest among patients aged 40-49 years [256 (95% CI 252-261) per 100,000] and 50-59 years [246 (95% CI 242-251) per 100,000] compared with all other age groups ($p < 0.0001$). Adjusted prevalences for African American [292 (95% CI 285-298) per 100,000] and 'other' [331 (95% CI 323-328) per 100,000] patients were higher than for Caucasians [262 (95% CI 260-264) per 100,000; $p < 0.001$].

Limitations: Use of administrative data has the potential to underestimate burden.

Conclusion: There are over 500,000 people estimated to have CU in the United States, most of whom are women and adults aged 40 years or older.

Introduction:

Urticaria is characterized by transient wheals which may itch or burn, and which may be accompanied by angioedema. Most patients who experience urticaria have acute disease which resolves within 6 weeks. In chronic urticaria (CU), patients experience daily or almost daily wheals, angioedema, or both for at least 6 weeks.¹

In more than half of patients, symptoms may persist for up to 10 years after initial diagnosis.² CU patients experience significant health related reductions in quality of life. Visible presence of wheals may also lead to emotional upset, causing patients to withdraw from social activities.^{3,4} CU patients may also sense a loss of control due to unpredictability of flares.⁵ Patients suffer from sleep disturbances, fatigue and irritability due to pruritus, as well as psychiatric comorbidities including anxiety, depression, somatization, and obsessive-compulsive disorder.⁶⁻⁹ CU is also linked to socioeconomic burden related to direct health costs^{10,11} and loss of work productivity.¹²⁻¹⁴

While CU results in significant morbidity, the overall burden of disease is poorly understood. The purpose of this study was to establish standardized prevalence estimates for CU among adults in the United States.

Methods:

This was a cross sectional analysis using a multi-health system data analytics and research platform (Explorys) developed by International Business Machines (IBM) Corporation, Watson Health™.¹⁵ Clinical information from electronic medical records, laboratories, practice management systems, and claims systems is matched using the single set of Unified Medical Language System ontologies to create longitudinal records for unique patients. The data are standardized and curated according to common controlled vocabularies and classifications systems including International Classification of Diseases (ICD), Systemized Nomenclature of Medicine—Clinical Terms (SNOMED-CT), Logical Observation Identifiers Names and Codes (LOINC), and RxNorm.¹⁶⁻¹⁹ At present, the database encompasses 27 participating integrated healthcare organizations. Over 55 million unique lives representing approximately 17% of the population across all four census regions of the United States are

captured. Patients with all types of insurance as well as those who are self-pay are represented. Population counts are reported by the database to the nearest 10, or represented as <10 if between zero and nine, to prevent patient identification. Human Subjects Committee review was waived by the Feinstein Institute for Medical research at Northwell Health since there are no identifiers associated with the data.

The case cohort was established using the SNOMED-CT term 'urticaria', associated with ICD-9 codes 708.1 (idiopathic urticaria), 708.8 (other specified urticaria), and 708.9 (unspecified urticaria), which was followed by a second diagnosis code at least 6 weeks later for either 'urticaria' or the SNOMED-CT term 'angioedema' which is associated with ICD-9 code 995.1 (angioneurotic edema). This method has been previously validated and shown to have a positive predictive value of 90.4% for identifying cases of CU.²⁰

Statistical Analysis:

We calculated the overall prevalence of CU among patients aged 18 years or older who were active in the Explorys database from 2012 to 2017, as well as the prevalence of CU within subgroups according to age, gender, and race. Patients were categorized into one of four race categories: Caucasian alone, African American alone, Other (Biracial, Hispanic/Latino, Asian, Multi-racial, and Other), and unknown. Patients who were neither Caucasian nor African American were classified as Other due to the relatively small number of CU cases within other race groups. Prevalence estimates are based on records for which age and gender information was available. Direct standardization was used to account for differences in gender and age distributions when comparing CU prevalence across subgroups. The age and gender composition of the 2010 United States Census population was used as the standard population, with five age groups: 18-29, 30-39, 40-49, 50-59, and 60+.²¹ Estimates were age adjusted for comparison between males and females, sex adjusted for age group comparisons, and sex and age adjusted for race comparisons. Confidence intervals for crude and standardized prevalences were computed based on the Poisson and gamma distributions,²² respectively. Standardized prevalences were compared assuming the prevalence ratio follows a log-normal distribution. A 2-sided α level of .05 was

applied to determine statistical significance. All analyses were performed using SAS software (version 9.4; SAS Institute, Inc).

Results:

Table I lists demographic characteristics of adult CU patients in the population-based sample. We identified 69,570 adult patients with CU. The ratio of women to men with CU was 2.7 to 1. CU patients were most frequently Caucasian (70.0%).

Crude and standardized group-specific prevalences of CU among adult patients are listed in **Table II**. We observed an overall standardized point prevalence of 0.23%, or 229.8 (95% CI 228.0-231.5) CU patients per 100,000 adults in the United States. The standardized prevalence was two-fold greater in women [309.3 (95% CI 306.6-312.1) per 100,000] as compared with men [145.5 (95% CI 143.4-147.7, $p < 0.001$]. Standardized prevalence was similar among all age groups and ranged from 0.21% among patients aged 18-29 years and 30-39 years to 0.26% among those aged 40-49 years. Standardized prevalence was highest among 'Other' race category [330.5 (95% CI 323.2-337.8) per 100,000]), followed by African Americans [291.6 (95% CI 285.4-297.9) per 100,000] and Caucasians, [261.9 (95% CI 259.5-264.3) per 100,000] ($p < 0.001$).

Age-specific prevalences by gender are listed in **Table III**. Females had greater prevalence of CU across all age-groups. The highest prevalence of CU was observed among women aged 40-49 years [513.8 (95% CI 485.9-542.9) per 100,000]. Men aged 40-49 years also had higher prevalence of CU than men in all other age groups.

Discussion:

In this study, we have estimated overall and group-specific standardized prevalence estimates for CU among adults in the United States. The overall point prevalence of CU is 0.23%, or 230 CU patients per 100,000 adults. The standardized prevalence of CU among women was twice that of men. Patients aged 40-49 years had the highest age-specific CU prevalence. Women in this age group had the highest prevalence among all age and gender subgroups.

Epidemiologic studies estimating disease burden for CU are sparse, particularly in the United States. Moreover, there are limitations to the existing studies, which include use of interview or questionnaires not specifically designed to identify CU, self-report of diagnosis, selection and recall biases within samples, or non-standardization of prevalence estimates to a national reference population. Reports of worldwide prevalence estimates for CU range widely from 0.08% to 3.08%,²³⁻³⁵ which may be a reflection of these different methods of case cohort identification (i.e., self report of diagnosis vs diagnosis codes) and which may be a result of differing sample types (i.e., population vs single-center), study periods, and inclusion criteria (i.e., age, insurance type)

In the largest European study, 175,923 adults across five countries self-identified their diagnosis of CU. The prevalence of CU was 0.51%, and women had a prevalence that was approximately twice that of men. While the data were weighted to account for probability sampling, they were not standardized.²³ A questionnaire-based study in Poland included 4,897 individuals. The overall prevalence of CU was 0.6%. However patients who were at least 15 years of age were also included in this analysis which was not standardized to the population.³² In the largest American questionnaire based study, 0.4% of 197,463 adults self-reported having ever been diagnosed with CU. Women had over twice the standardized prevalence of men. Standardized prevalence was observed to be lowest among those aged 18-24 years and highest in the 45- to 54-year age group.²⁸

Claims analyses have also been applied to establish disease burden in CU. In an Italian analysis involving 14,859 CU patients, the point prevalence in 2013 was estimated to be 0.38%. This study included patients who were at least 15 years of age.²⁹ In an American claims based analysis, the 1-year period prevalence of CU was estimated to be of 0.08%. However, this study may have underestimated disease burden by only including patients with commercial insurance.³¹ Neither claims analysis standardized estimates to their respective population, which limits the interpretation of true burden. Race information was not reported. In a Korean analysis including patients aged at least 10years, the prevalence of chronic or recurrent urticaria over 5 years was estimated to be 0.38%. The prevalence was highest among patients aged 50-59 years.³³ In a separate Korean claims analysis which included patients

of all ages, the prevalence of CU was 3.08%. Those aged 0-9 years and 70-79 years had the highest prevalences.³⁴ Finally, a small study analyzing claims from a single health organization in Buenos Aires identified 395 adults with CU which yielded a crude point prevalence of 0.34%.³⁵

There are limits which warrant consideration when interpreting the results of our study. We could not capture patients who did not seek care in health systems included in the database. The extent to which our cohort underestimates CU frequency for this reason is unknown. While the case cohort was identified using a previously validated method, use of administrative data for case identification is an imperfect standard which may result in misclassification bias. This study also has several strengths. The prevalence estimate is based on one of the largest and most ethnically diversified population samples in the United States. It is also drawn from patients with all insurance types and self-pay patients across various types of health care settings and from all census regions. For these reasons, we believe these results may be generalized in the United States.

In conclusion, we estimate that over 500,000 people living in the United States suffer from CU, most of whom are women and adults aged 40-59 years.

References:

1. Bernstein D, Lang DM, Khan DA. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133:1270-1277.
2. van der Valk PG, Moret G, Kiemeny LA. The natural history of chronic urticaria and angioedema in patients visiting a tertiary referral centre. *Br J Dermatol*. 2002; 146(1):110-113.
3. O'Donnell BF, Lawlor F, Simpson J, et al. The impact of chronic urticaria on the quality of life. *Br J Dermatol*. 1997;136:197-201.
4. Kang MJ, Kim HS, Kim HO, Park YM. The impact of chronic idiopathic urticaria on quality of life in Korean patients. *Ann Dermatol*. 2009;21(3):226-229.
5. O'Donnell BF. Urticaria. Impact on quality of life and economic cost. *Immunol Allergy Clin North Am* 2014; 34:89-104.
6. Weldon DR. Quality of life in patients with urticaria. *Allergy Asthma Proc*. 2006;27:96-99.
7. Maurer M, Ortonne J, Zuberbier T. Chronic urticaria: a patient survey on quality-of-life, treatment usage and doctor patient relation. *Allergy*. 2009;64:581-588.
8. Ben-Shoshan M, Blinderman I, Raz A. Psychosocial factors and chronic spontaneous urticaria: a systematic review. *Allergy*. 2013;68:131-141.
9. Staubach P, Eckhardt-Henn A, Dechene M, et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol*. 2006;154:294-298.
10. Sabroe R, Greaves M. What is urticaria? anatomical, physiological, and histological considerations and classification. In: Kaplan A, Greaves M, eds. *Urticaria and Angioedema*. New York, NY: Informa Healthcare; 2009:1-14.
11. Ferrer M. Epidemiology, healthcare, resources, use and clinical features of different types of urticaria. *J Investig Allergol Clin Immunol*. 2009;2(suppl.2):21-26.
12. 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; 144:35-39.

13. Cooper C, Dewe P. Well-being, absenteeism, presenteeism, costs and challenges. *Occup Med* (London). 2008;58:522-524.
14. Kapp A, Demarteau N. Cost effectiveness of levocetirizine in chronic idiopathic urticaria: a pooled analysis of two randomized controlled trials. *Clin Drug Investig*. 2006;26:1-11.
15. Explorys, Inc. The IBM Explorys Platform. Somers, NY: IBM Corporation; June 2016. <https://public.dhe.ibm.com/common/ssi/ecm/hp/en/hps03052usen/HPS03052USEN.PDF>. Accessed December 26, 2017.
16. U.S. National Library of Medicine Unified Medical Language System (UMLS): Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT). Available at http://www.nlm.nih.gov/research/umls/Snomed/snomed_main.html [last accessed 2017 March 4].
17. Nelson SJ, Zeng K, Kilbourne J, Powell T, Moore R. Normalized names for clinical drugs: RxNorm at 6 years. *J Am Med Inform Assoc* 2011;18(4):441–448.
18. McDonald CJ, Huff SM, Suico JG, Hill G, Aller R, Forrey A, Mercer K, De Moor G, Hook J, Williams W, Case J, Maloney P. LOINC, a universal standard for identifying laboratory observations: a 5-year update. *Clin Chem* 2003;49(4):624–633.
19. Shen JJ, Wan TT, Perlin JB. An exploration of the complex relationship of socioecologic factors in the treatment and outcomes of acute myocardial infarction in disadvantaged populations. *Health Serv Res* 2001;36(4):711-732.
20. Cherepanov D, Raimundo K, Chang E, Eagan M, Zazzali JL, Solari PG, DeCotiis B, Hussain I, Rehman SM, Shahab N, Tilles SA, Broder MS. Validation of an ICD-9-based claims algorithm for identifying patients with chronic idiopathic/spontaneous urticaria. *Ann Allergy Asthma Immunol*. 2015;114(5):393-398.
21. U.S. Census Bureau. 2010 Census Summary File 1, Table PCT12. Generated by Andrew Strunk using American FactFinder. <https://factfinder.census.gov>. Last accessed December 26, 2017.
22. Fay MP, Feuer EJ. Confidence intervals for directly standardized rates: a method based on the gamma distribution. *Stat Med*. 1997; 16(7):791-801.

- 221 23. Balp MM, Vietri J, Tian H, Isherwood G. The Impact of Chronic Urticaria from the Patient's
222 Perspective: A Survey in Five European Countries. *Patient*. 2015;8(6):551-558.
- 223 24. Balp M-M, Lopes da Silva N, Vietri J, Tian H, Ensina LF. The Burden of Chronic Urticaria from
224 Brazilian Patients' Perspective. *Dermatology and Therapy*. 2017;7(4):535-545.
- 225 25. Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of urticaria: a
226 representative cross-sectional population survey. *Clin Exp Dermatol*. 2010 Dec;35(8):869-873.
- 227 26. Gaig P, Olona M, Muñoz Lejarazu D, Caballero MT, Domínguez FJ, Echechipia S, García Abujeta
228 JL, Gonzalo MA, Lleonart R, Martínez Cócera C, Rodríguez A, Ferrer M. Epidemiology of urticaria in
229 Spain. *J Investig Allergol Clin Immunol*. 2004;14(3):214-220.
- 230 27. Hellgren L. The prevalence of urticaria in the total population. *Acta Allergol*. 1972;27:236e240.
- 231 28. Vietri J, Turner SJ, Tian H, Isherwood G, Balp MM, Gabriel S. Effect of chronic urticaria on US
232 patients: analysis of the National Health and Wellness Survey. *Ann Allergy Asthma Immunol*.
233 2015;115(4):306-311.
- 234 29. Lapi F, Cassano N, Pegoraro V, Cataldo N, Heiman F, Cricelli I, Levi M, Colombo D, Zagni E,
235 Cricelli C, Vena GA. Epidemiology of chronic spontaneous urticaria: results from a nationwide,
236 population-based study in Italy. *Br J Dermatol*. 2016 May;174(5):996-1004.
- 237 30. Chen Y, Wu C, Shen J, Chen T, Chang Y. Cancer Risk in Patients With Chronic UrticariaA
238 Population-Based Cohort Study. *Arch Dermatol*. 2012;148(1):103-108.
- 239 31. Zazzali JL, Broder MS, Chang E, Chiu MW, Hogan DJ. Cost, utilization, and patterns of medication
240 use associated with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2012;108(2):98-102.
- 241 32. Raciborski F, Kłak A, Czarnecka-Operacz M, et al. Epidemiology of urticaria in Poland - nationally
242 representative survey results. *Postepy Dermatol Alergol*. 2018;35(1):67-73.
- 243 33. Seo JH, Kwon JW. Epidemiology of urticaria including physical urticaria and angioedema in Korea.
244 *Korean J Intern Med*. 2018. doi: 10.3904/kjim.2017.203.
- 245 34. Kim BR, Yang S, Choi JW, Choi CW, Youn SW. Epidemiology and comorbidities of patients with
246 chronic urticaria in Korea: A nationwide population-based study. *J Dermatol*. 2018;45(1):10-16.

- 247 35. Parisi CA, Ritchie C, Petriz N, Torres CM, Gimenez-Arnau A. Chronic urticaria in a health
248 maintenance organization of Buenos Aires, Argentina - new data that increase global knowledge of this
249 disease. *An Bras Dermatol.* 2018;93(1):76-79.

250 **Table I: Demographic Characteristics for Adults with Chronic Urticaria (N=69,570)**

Characteristic	n (%)
Gender	
Female	51,010 (73.3%)
Male	18,560 (26.7%)
Age	
18-29	11,690 (16.8%)
30-39	10,540 (15.2%)
40-49	11,880 (17.1%)
50-59	12,560 (18.1%)
60+	22,900 (32.9%)
Race	
Caucasian alone	48,700 (70.0%)
African American alone	8,660 (12.4%)
Other ^a	8,090 (11.6%)
Unknown	4,120 (5.9%)

251 ^{*} Sum of group-specific counts may not equal total N since the database rounds counts to the nearest 10.

252 ^a Other includes patients whose race was recorded as "Hispanic/Latino", "Asian", "Multi-racial", or

253 "Other", as well as patients with two or more races on record.

Table II: Crude and Standardized Group-Specific Prevalence Estimates for Chronic Urticaria in the United States

	Number of urticaria cases ^a	Population size ^a	Crude Prevalence per 100,000 population (95% CI)	Crude Prevalence (%)	Standardized prevalence per 100,000 population (95% CI) ^{bc}	Standardized Prevalence (%)
Overall Population	69,570	29,248,110	237.9 (236.1-239.6)	0.24	229.8 (228.0-231.5)	0.23
Gender						
Female	51,010	16,570,240	307.8 (305.2-310.5)	0.31	309.3 (306.6-312.1)	0.31
Male	18,560	12,677,870	146.4 (144.3-148.5)	0.15	145.5 (143.4-147.7)	0.15
Age (years)						
18-29	11,690	5,327,420	219.4 (214.5-223.4)	0.22	213.5 (209.6-217.4)	0.21
30-39	10,540	4,777,460	220.6 (216.4-224.9)	0.22	207.2 (203.2-211.2)	0.21
40-49	11,880	4,432,000	268.1 (263.3-272.9)	0.27	256.3 (251.7-261.0)	0.26
50-59	12,560	4,954,020	253.5 (249.1-258.0)	0.25	246.1 (241.8-250.5)	0.25
60-69	22,900	9,757,210	234.7 (231.7-237.8)	0.23	228.3 (225.3-231.3)	0.23

Race						
Caucasian	48,690	17,971,380	270.9 (268.5-273.3)	0.27	261.9 (259.5-264.3)	0.26
African American	8,670	2,827,520	306.6 (300.2-313.2)	0.31	291.6 (285.4-297.9)	0.29
Other	8,110	2,386,140	339.9 (332.5-347.4)	0.34	330.5 (323.2-337.8)	0.33
Unknown	4,120	6,063,120	68.0 (65.9-70.1)	0.07	68.2 (66.1-70.4)	0.07

a – Sum of group-specific counts may not equal total N since the database rounds counts to the nearest 10.

b – Gender comparisons are adjusted for age. Age group comparisons are adjusted for gender. Race comparisons are adjusted for gender and age.

The gender and age distribution of the 2010 U.S. Census population was used as the standard population, with 5 age groups: 18-29, 30-39, 40-49, 50-59, and 60+.

c – Reference groups for gender, age, and race comparisons were female, age group 40-49 years, and Caucasian, respectively. All comparisons between standardized subgroups were significant with a p-value < 0.001, except for age groups 40-49 years and 50-59 years where p = 0.0016.

Table III: Age-Specific Prevalences of Chronic Urticaria by Gender

Age group (years)	Male		Female	
	CU Cases	Prevalence per 100,000	CU Cases	Prevalence per 100,000 population
18-29	520	245.2 (224.5-267.2)	970	342.2 (321.0-364.5)
30-39	310	168.9 (150.6-188.8)	1,020	355.0 (333.6-377.5)
40-49	450	259.6 (236.1-284.7)	1,270	513.8 (485.9-542.9)
50-59	410	256.1 (231.9-282.2)	1,070	503.9 (474.1-535.0)
60+	620	232.0 (214.1-251.0)	1,470	408.8 (388.2-430.2)

Abbreviation: CU, chronic urticaria

P < .001 for all age-specific comparisons between males and females.

Capsule Summary

- Disease burden of chronic urticaria in the United States is poorly understood.
- Over 500,000 people living in the United States are estimated to suffer from CU, most of whom are women and adults aged 40-59 years, who may benefit from engaging a dermatologist.