

Prevalence of concomitant angioedema in chronic spontaneous urticaria: A systematic review and meta-analysis

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Abstract

Background: Angioedema (AE) is a condition associated with considerable morbidity and mortality that can significantly affect quality of life. AE often occurs in patients with CSU although the true prevalence remains unknown. Therefore, we conducted this systematic review and meta-analysis to summarize the available data.

Objectives: This study is conducted with the aim of retrieving data from all published studies and create the pooled prevalence of AE in CSU patients.

Methods: Narrative reviews of AE and CSU, a systematic review, and a meta-analysis were conducted. The Ovid Medline and Embase databases were systematically searched per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. Studies were eligible if they were in English and measured the prevalence of AE in CSU in adults or children. Two reviewers independently extracted data and appraised each study's quality. Estimated prevalence and 95% confidence interval (CI) values were pooled using random-effects meta-analysis.

Results: Seventeen studies from 16 countries were included. The pooled prevalence of AE in patients with CSU was 36.5% (95%CI, 30.9–42.5%; $I^2 = 96\%$). The pooled estimated prevalence of AE in patients with CSU was 44.0% (95%CI, 34.1–54.5%) in Europe, 44.5% (95%CI, 28.5–61.8%), America, and 29.4% (95%CI, 24.7–34.7%) in Asia.

Conclusions: Our systematic review and meta-analysis showed that AE affects over one-third of CSU patients, although the prevalence from individual study varied considerably, ranging from 5 to 67 percent. Subgroup-analysis found that AE is more prevalent in Europe and America than in Asia.

Key words: Angioedema, Chronic urticaria, Meta-analysis, Prevalence, Systematic review

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Abbreviations:

AE angioedema
CIU chronic inducible urticaria
CSU chronic spontaneous urticaria
CU chronic urticaria
QoL quality of life

Introduction

Urticaria is characterized by the development of wheals (hives), angioedema (AE), or both. Urticaria must be differentiated from other medical conditions that have the same symptoms as part of their clinical spectra. The EAACI/GA²LEN/EDF/WAO guidelines of 2021 classify urticaria into 2 main groups based on its duration, acute urticaria and chronic urticaria (CU). The presence of wheals and flares and/or AE for more than 6 weeks is the cut-off duration for CU. CU can be subdivided into chronic spontaneous urticaria (CSU), when trigger factor cannot be identified, and chronic inducible urticaria (CIU) which specific trigger factor is involved in the development of CU. CSU is much more common than CIU.¹

AE is a sudden, pronounced, circumscribed, nonpitting swelling of the lower dermis, subcutaneous tissue, or mucous membranes. It affects the lips, face, neck, oral cavity, larynx, gastrointestinal tract, and extremities.² AE usually presents with pain rather than itch, and resolution can take up to 72 hours. It is one of the most frequent disorders leading to a medical practitioner consultation.³⁻⁵ Patients with CSU can be divided clinically into (1) CU with concomitant AE, (2) CU without AE, and (3) recurrent AE without wheals.⁶ In a study by O'Donnell et al,⁷ 59% of patients with CU reported that the worst aspect of their urticaria was its swelling. Additionally, multiple studies have employed various questionnaires to investigate the burden of illness and the quality of life (QoL) of patients with AE, CSU, and CIU. The studies revealed significantly lower QoL in patients with AE than those with only urticaria.⁸⁻¹⁰ On the other hand, the review by Caballero et al showed some contradictory results from several included studies.¹¹ This review found that the patients from 3 out of 6 articles did not show significant influence of angioedema on quality-of-life scores.

From our literature search, AE in conjunction with CSU showed a substantial impact on patients' health-related QoL and produced significant humanistic and economic burdens. AE may become life-threatening if it involves the larynx.² Hereditary AE was not included in our search.

To date, few published studies have investigated the prevalence of AE in patients with CSU. The incidence of AE with CSU varies markedly globally, with studies reporting concomitant AE in 33% to 67% of CSU cases. Among these studies, 1% to 13% of patients exhibited only AE.⁶ The true prevalence of AE among patients with CSU remains unknown and no published work has yet pooled the global prevalence of AE in patients with CSU. Understanding the etiology of AE and its global burden is an essential step in improving the care for this group of patients. Our work set out to retrieve data from all published studies to create the pooled prevalence of AE in these patients and to establish whether it varies by geographical region, population age, setting, study period, or study quality. We conducted a systematic review with a meta-analysis of relevant studies to ascertain the prevalence of AE among patients with CSU.

Methods

Search strategy and study eligibility

This systematic review was registered with PROSPERO (CRD42021281158; <https://www.crd.york.ac.uk/prospero>) in October 2021. The literature search was conducted using the Embase and Ovid Medline databases, from inception to July 2021. The search terms used were "chronic spontaneous urticaria," "angioedema," and "prevalence." All studies in English that provided number of cases or the prevalence of AE among patients with CSU were included. In addition, the authors manually screened the reference lists of identified articles. This study was conducted in accordance with the approaches suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology reporting guidelines for additional relevant studies.

Eligibility criteria

The inclusion criteria were as follow: 1) Studies of patients with CSU, 2) Studies of which provided the prevalence rate (percentage) of AE among patients with CSU who had wheals and angioedema, and not patients with angioedema only. In the case of population duplicates (e.g., studies based on the same database in the same time period or follow-ups of older studies), the newest study or the one that reported on the comprehensive outcome was included.

Data extraction and study quality assessment

Two authors (P.W. and K.K.) independently screened the abstracts and the full texts of the eligible studies. The following data were extracted using a standardized form: title, authors, design, country of origin, geographic location, year of study, year of publication, number of participants, participant age, sex profile of the participants, diagnostic or screening methods, disease definitions, and AE prevalence estimates. Drawing on the World Health Organization criteria, the geographic locations were Africa, the Americas, Southeast Asia, Europe, the Eastern Mediterranean, and the Western Pacific. The 2 authors also independently assessed the risks of bias of nonrandomized studies using the Newcastle–Ottawa scale, with ≥ 3 points representing low risk and < 3 points denoting high risk. Disagreements and discrepancies between the 2 reviewers were resolved through discussion or adjudication with the third author (P.U.). The quality of studies was assessed with the Joanna Briggs Institute critical appraisal tool for prevalence studies¹² and the Newcastle–Ottawa scale (scores ≥ 7 on the scale signified good quality).¹³

Statistical analysis

Data analyses were conducted using the Metaprop package in R, version 3.3.6 (R Program for Statistical Computing). The pooled prevalence and 95% confidence intervals (CIs) of the overall prevalence of AE in patients with CSU were calculated using a generalized linear mixed-model random-effects meta-analysis.¹⁴ A proportion meta-analysis was performed to obtain the pooled prevalence

with 95% CIs. The heterogeneity of the studies was assessed using Cochran's Q test and I² statistics, which provided a quantitative estimate of t variability across the studies. A high I² percentage suggests that variation is likely due to study heterogeneity, whereas a zero percentage suggests that any variation is likely due to chance. The I² values were classified as follows: an I² of 0% to 25% indicated insignificant heterogeneity; 26% to 50%, low heterogeneity; 51% to 75%, moderate heterogeneity; and > 75%, high heterogeneity.¹⁴ Our analysis was based on a heterogeneous pool of studies, and we opted to use the random-effects model.

Results

The literature search yielded 280 distinct records (215 from Embase and 65 from Ovid Medline). An additional 19 articles were retrieved after a manual search of the relevant articles' references. Fifty-two duplicated articles were removed using the Systematic Review Accelerator (SRA) tool¹⁵ (in addition to manual removal). The titles and abstracts of the remaining 247 articles were reviewed. Of these, 41 were excluded because they did not meet the inclusion criteria (eg, studies on hereditary AE or inducible urticaria or no data on the prevalence of AE). A thorough, full-text review of the remaining 206 articles was performed, and 189 were found to be ineligible. They had irrelevant contexts (n = 134);

did not report the AE prevalence (n = 21) or differentiate CSU from other urticaria types (n = 16); had no full text (n = 11) available; were not in English (n = 6); or were case reports (n = 1). Seventeen eligible studies were included in the meta-analysis. The literature review and identification process are illustrated in **Figure 1**.

Baseline patient characteristics

Table 1 summarizes the baseline demographic data of the 8777 patients with CSU from the 17 eligible studies entered the meta-analysis. The studies were drawn from 16 countries, and their sample sizes ranged from 75 to 1845 patients per study.

The prevalence of concomitant AE in CSU

Overall pooled prevalence

Across the 17 included studies, the pooled estimate prevalence of AE in patients with CSU using a random effects model was 36.5% [95%CI, 30.9–42.5%]. The I² variation was 96% (**Figure 2**).

Pooled prevalence of AE by region

The pooled estimated prevalence of AE in patients with CSU was 44.0% [95%CI, 34.1–54.5%] in Europe, 44.5% [95%CI, 28.5–61.8%] in America, and 29.4% [95%CI, 24.7–34.7%] in Asia (**Figure 3**).

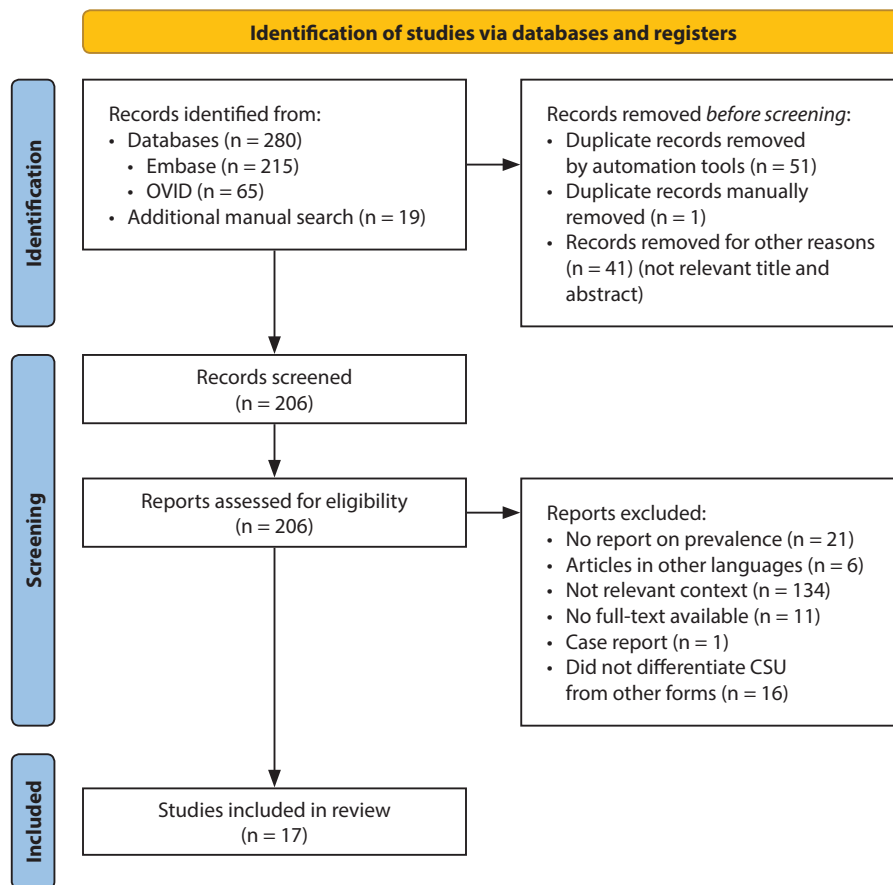


Figure 1. PRISMA flow diagram depicting the process of the literature search for our meta-analysis.

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Table 1. Baseline characteristics of the studies included in the meta-analysis.

No.	Authors	Publication year	Country	Region	WHO region	Urticaria type	Age (years)	n	Wheals + AE (n)	Wheals (n)	AE (n)	Type of study	Year of study	Instruments
1	Juhlin et al.	1981	Sweden	Europe	Europe	CSU	N/A	345	230	100	15	Retrospective	1972-1978	Medical records
2	Quaranta et al.	1989	USA	The Americas	The Americas	CSU	4-79	86	46	31	9	Retrospective	1968-1990	Medical records
3	Kozel et al.	2001	Netherlands	Europe	Europe	CSU	15-79	220	119	73	29	Prospective	N/A	Questionnaire
4	Toubi et al.	2004	Israel	Asia	Europe	CSU	17-66	139	56			Prospective	1998-2003	Medical records
5	Magen et al.	2013	Israel	Asia	Europe	CSU	18->65	1051	375	651	24	Retrospective	2002-2010	Medical records
6	Zhong et al.	2014	China	Asia	Western Pacific	CSU	mean 35	1845	531	N/A	N/A	Prospective, cross-sectional	2011	Questionnaire
7	Dionigi et al.	2015	Brazil	The Americas	The Americas	CSU	mean 44	100	36	64	0	Prospective, cohort	N/A	Medical records
8	Van den elzen et al.	2015	Netherlands	Europe	Europe	CSU	20-87	200	91	60	49	Retrospective	2012-2014	Medical records
9	Al-Ahmad et al.	2016	Kuwait	Asia	Eastern Mediterranean	CSU (refractory)	> 14	1293	345	N/A	N/A	Retrospective	2014	Medical records
10	Boonpiyathad et al.	2016	Thailand	Asia	South-East Asia	CSU	mean 35	128	7	N/A	N/A	Prospective	2012-2015	Medical records
11	Choi et al.	2016	Korea	Asia	Western Pacific	CSU	> 20	308	120	N/A	N/A	Cross-sectional	2009-2012	Medical records
12	Kumar et al.	2016	India	Asia	South-East Asia	CSU	5-60	110	21	N/A	N/A	Prospective	2012-2013	Medical records
13	Sussman et al.	2016	International*	Europe	Europe	CSU	19-89	643	259	N/A	N/A	Observational	N/A	ASSURE
14	Ye et al.	2016	Korea	Asia	Western Pacific	CSU	19-69	75	29	N/A	N/A	Prospective	2011-2013	Medical records
15	Barredo et al.	2018	Spain	Europe	Europe	CSU	mean 52	438	72	N/A	N/A	Retrospective	2001-2014	Medical records
16	Maurer et al.	2018	Germany	Europe	European	CSU (refractory)	18-75	1544	678	N/A	N/A	Prospective	2014	AWARE
17	Savic et al.	2020	UK	Europe	Europe	CSU (refractory)	18-75	252	120	N/A	N/A	Prospective	2014-2017	AWARE

Abbreviations: AE, angioedema; CSU, chronic spontaneous urticaria; n, number of patients/subjects; N/A, data not reported
*Canada, France, Germany, Italy, the Netherlands, Spain, and the UK

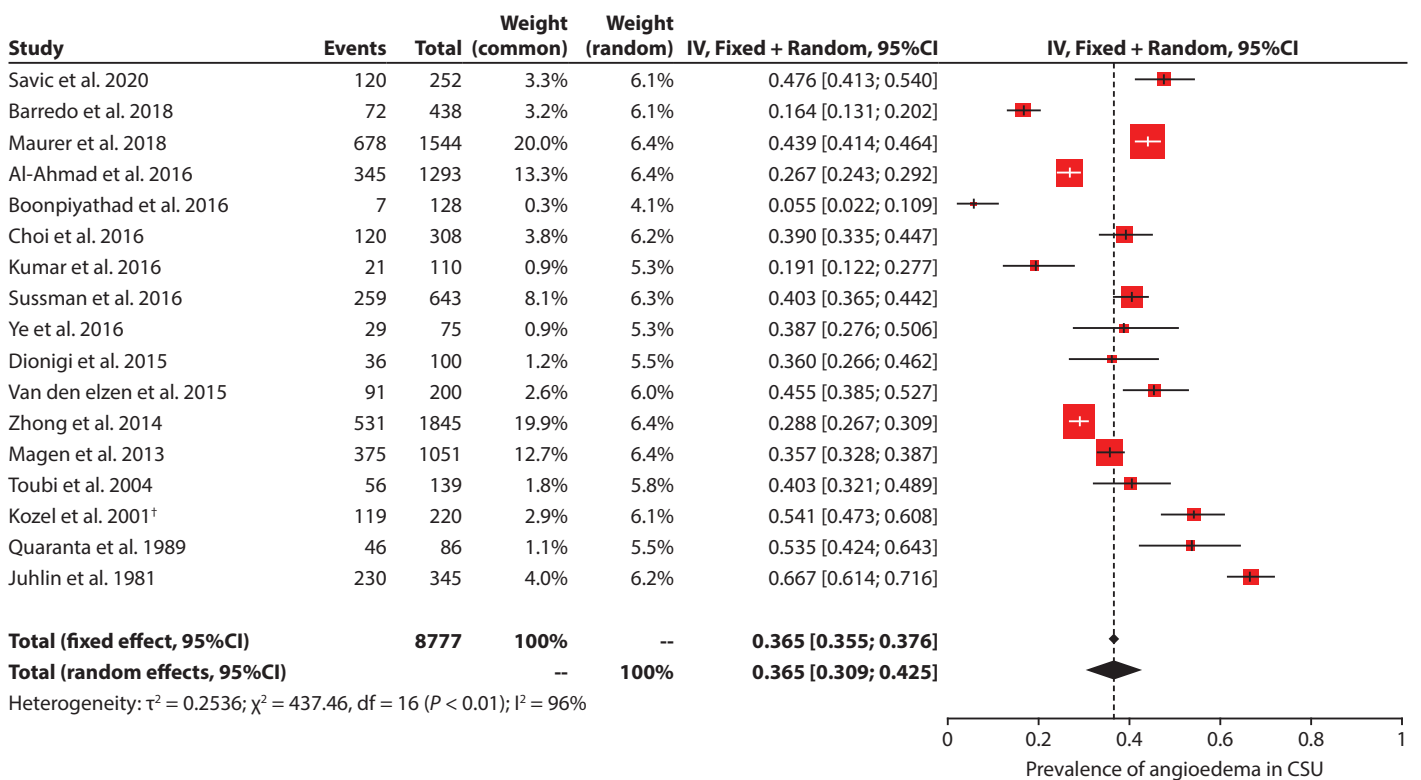


Figure 2. Pooled prevalence (as a percentage) of concomitant angioedema (AE) in patients with chronic spontaneous urticaria (CSU).

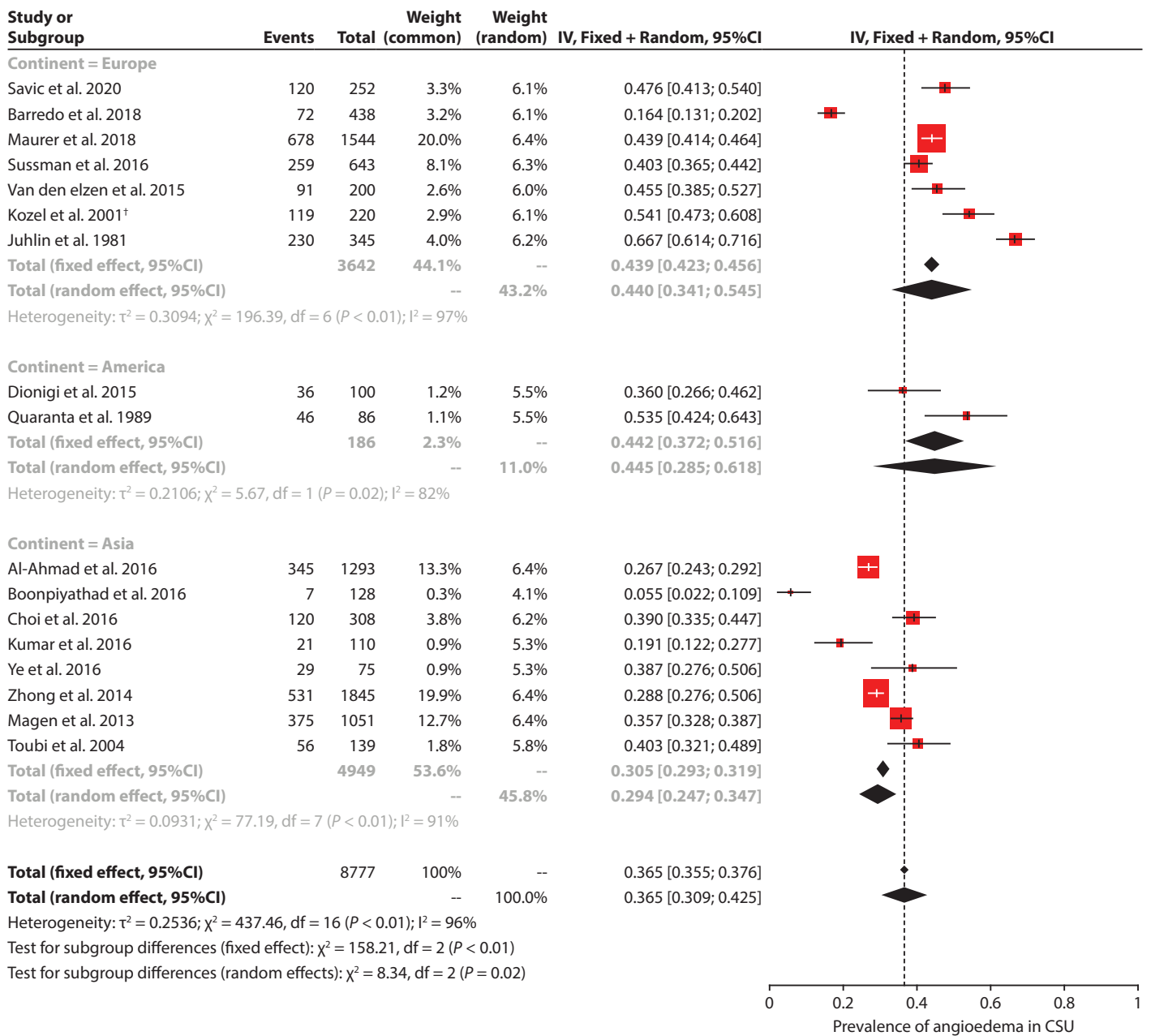


Figure 3. Pooled prevalence (as a percentage) of concomitant angioedema (AE) in patients with chronic spontaneous urticaria (CSU), classified by world region.

Discussion

Main findings

Our systematic review and meta-analysis showed that AE affects over one-third of patients with CSU, although the prevalence reported by individual studies ranged widely (from 5% to 67%), varying by country and region. Subgroup analysis found that AE is more prevalent in Europe and the Americas than in Asia, which may reflect true variations or differences in study design and diagnostic methods.

Zhong et al¹⁶ studied 3027 patients and found that patients with CSU had a significantly higher prevalence of concurrent AE (28%) than patients with other types of urticaria. Furthermore, they also found that CSU patients who had positive autologous serum skin test (ASST) had a significantly higher prevalence of AE compared to those with negative ASST.

A few studies also highlighted a compelling perspective of AE with CSU in childhood compared with adults. Balp et al¹⁷ found AE rates between 5% and 14% in patients with CSU under 17 years of age in 5 European countries. A study from Israel found that elderly patients (≥ 65 years) with CSU had a significantly lower rate of concomitant AE (14%) than adults aged 18 to < 65 (37.8%; $P < 0.001$). Furthermore, no case of only AE was observed in the elderly group compared with 2.5% in adults aged 18 to < 65 .¹⁸ Hence, concomitant AE seems to be less common in children and elderly patients with CSU. Previous study on CSU previously discussed that it might be the result of over-the-counter medications used by parents to treat their own children causing underestimated number pediatric population.¹⁷ While some studies pointed that fewer CSU symptoms in the elderly might be associated with lower numbers of mast cells in aged skin or with lower histamine release by aged mast cells.¹⁸

Some studies found a difference in the prevalence of AE among males and females. For example, a recent large study from Poland determined a prevalence of AE of 2.5% and 4.0% in men and women, respectively.¹⁹ A study by Ue et al⁸ found that women were more likely to have AE than men (84.4% versus 52.9%). Champion et al²⁰ demonstrated that no boys under the age of 15 had AE alone and few had AE concomitant with urticaria. In contrast, more girls under 15 experienced AE with or without urticaria and fewer girls than boys had urticaria alone. Unfortunately, the included studies did not provide enough data for us to perform subgroup meta-analysis based on sex.

Disease duration and prognosis

Some studies suggested that duration of CSU could be associated with various clinical parameters, such as severity and the presence of AE. Toubi et al²¹ found a strong association between duration of CSU and the presence of AE as up to 45% of patients with concomitant AE continued to suffer from urticaria at 5 years of follow-up compared with only 12% of patients without AE. Similarly, Kozel et al²² found that 80% and 41% of patients with CSU with and without AE, respectively, still had symptoms after a 1-year follow-up.

On the other hand, study by Ye et al²³ did not find an association between AE and the duration of CSU or between the presence of AE and the urticaria controlled/remission state. Similarly, Barredo et al²⁴ demonstrated no correlation between AE and disease durations or higher disease activities.

Effect of AE on quality of life

There are conflicting results in the previous studies. Choi et al⁹ found that the presence of AE was a key predictor of impaired QoL in Korean adults with CSU. Another study by Sussman et al²⁵ used multiple QoL tools, including the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and the Dermatology Life Quality Index (DLQI). Their research revealed that patients with CSU and concomitant AE had a worse health-related QoL than those with wheals only. Maurer et al²⁶ demonstrated the high impact of concomitant AE on QoL persisted after a 12-month follow-up. Moreover, Savic et al²⁷ indicated that more than 75% of patients with AE and CSU had at least a moderate disease intensity, which likely impacts QoL negatively. However, additional impairment on QoL in patients with CSU presenting with AE was not evident in some prior studies using a different QoL measurement.^{28,29} Thus, future research should draw upon the angioedema activity score (AAS), a specific instrument to measure AE activity and AE-related QoL impairment in patients with CSU and AE with or without wheals.

Limitations

Our study has some limitations. First, the data were derived from studies with different designs and screening instruments, and very few papers focused on AE in CSU. Moreover, a sizeable proportion of our included studies derived patient information on AE episodes from questionnaires or patient interviews without having diagnoses confirmed by trained physicians or dermatologists. This approach might have resulted in over- or underestimations of the prevalence of concomitant AE. The substantial heterogeneity among the studies remained largely unexplained by the variables inspected. Furthermore, analyses were typically based only on patients with CSU; to compound the situation, classifications of urticaria have substantially changed during recent decades. Consequently, we could not differentiate the specific types of urticaria from earlier studies which meant that percentages were based on smaller-than-desirable patient numbers. In terms of some factors such as age, gender, background diseases and precipitating factors, just limited information could be extracted from primary studies and subgroup analysis could not be performed based on such variables. Additionally, our analyses relied on aggregated published data. Multicenter prospective studies using validated measures and diagnostic tools in random subsets of participants would provide accurate estimates of the prevalence of AE among patients with CSU.

Future research

Determining the incidence rate of a rare disease such as AE poses methodological difficulties. More high-quality research is required to better understand the prevalence of both AE alone and AE with wheal in CSU patients. Better disease registration of rare diseases, such as AE, in accessible electronic health records would greatly facilitate future research. Careful attention must be paid to the design of such studies to ensure the complete capture of cases within the at-risk population.

Conclusions

Our systematic review and meta-analysis showed that AE affects over one-third of patients with CSU, although the prevalence from individual study varied considerably, ranging from 5 to 67 percent. Subgroup-analysis showed considerable regional differences, that AE is more prevalent in Europe and America than in Asia. Some studies found a difference in prevalence of AE among males and females although the included studies did not provide enough data for us to perform subgroup meta-analysis based on sex. There is still a need to conduct further population-based studies on the prevalence of AE, especially regarding specific age groups, sex-specific differences, and regions. Future research should focus on children and adolescents and clearly define each CU subtype. The need for worldwide studies may be facilitated by the global network of urticaria centers of reference and excellence (UCARE).

Conflicts of interest

None to declare.

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