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Prevalence of chronic urticaria in children and adults across the globe: Systematic review with meta-analysis

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Abstract

Background and objectives: Urticaria is a frequent skin condition, but reliable prevalence estimates from population studies particularly of the chronic form are scarce. The objective of this study was to systematically evaluate and summarize the prevalence of chronic urticaria by evaluating population-based studies worldwide.

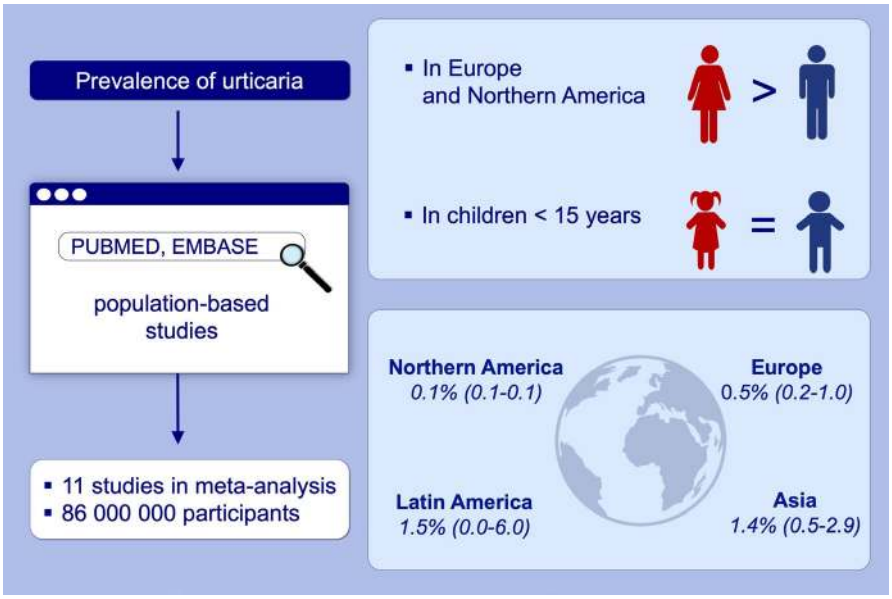
Methods: We performed a systematic search in PUBMED and EMBASE for population-based studies of cross-sectional or cohort design and studies based on health insurance/system databases. Risk of bias was assessed using a specific tool for prevalence studies. For meta-analysis, we used a random effects model.

Results: Eighteen studies were included in the systematic evaluation and 11 in the meta-analysis including data from over 86 000 000 participants. Risk of bias was mainly moderate, whereas the statistical heterogeneity (I^2) between the studies was high. Asian studies combined showed a higher point prevalence of chronic urticaria (1.4%, 95%-CI 0.5-2.9) than those from Europe (0.5%, 0.2-1.0) and Northern American (0.1%, 0.1-0.1). Women were slightly more affected than men, whereas in children < 15 years we did not find a sex-specific difference in the prevalence. The four studies that examined time trends indicated an increasing prevalence of chronic urticaria over time.

Conclusions: On a global level, the prevalence of chronic urticaria showed considerable regional differences. There is a need to obtain more sex-specific population-based and standardized international data particularly for children and adolescents, different chronic urticaria subtypes and potential risk and protective factors.

KEYWORDS

chronic urticaria, meta-analysis, prevalence, sex differences, systematic review



GRAPHICAL ABSTRACT

We evaluated the prevalence of chronic urticaria worldwide by performing a systematic search in PUBMED and EMBASE. Chronic urticaria seems to be more prevalent in Asia than in Europe and Northern America. Women in Europe and Northern America were more affected by chronic urticaria than men, whereas in children < 15 years we did not find a sex-specific difference.

1 | INTRODUCTION

Urticaria is considered by clinicians as a relatively common skin condition, characterized by the development of wheals (hives), angioedema, or both.[1] By contrast, there is a paucity of studies assessing urticaria prevalence, and usually, they do not distinguish between acute and chronic forms.[2-5] Epidemiological data are lacking especially for chronic urticaria (CU), defined as the recurrence of wheals, angioedema, or both for longer than 6 weeks.[1]

Addressing previous inconsistencies, the updated EAACI/GA^{2}LEN/EDF/WAO guideline for urticaria now clearly distinguishes two subtypes of CU: chronic spontaneous urticaria and chronic inducible urticaria—the latter including, for example, cold urticaria, cholinergic urticaria, and symptomatic dermographism.[1]

Chronic urticaria carries a substantial burden not only for affected patients but also for health care systems. In most patients, CU markedly impairs quality of life with significant impact on sleep, work performance, and social interactions.[6-8] In addition, patients with CU often present mental health problems.[9-11] Health care systems are facing high costs for managing patients with CU—including frequent health care visits, pharmacotherapy, absences from work, and loss of productivity.[12,13]

To the best of our knowledge, there is no comprehensive systematic review of population-based studies assessing the prevalence of CU worldwide. Therefore, the primary aim of this systematic review was to examine the prevalence of CU by assessing the evidence from population-based studies worldwide. As secondary outcome, the incidence of CU was investigated, if assessed within the same studies. As subgroup analyses, we planned a stratification of prevalence estimates by age, sex, and world region.

2 | MATERIAL AND METHODS

This systematic review is reported in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[14] The protocol of the present review was published on PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42017073948), an international prospective register of systematic reviews.

2.1 | Search strategy

We performed a systematic search in the major medical databases PUBMED and EMBASE. No date and language restrictions were applied. In addition to the electronic search, reference lists of selected articles were hand-searched. The results were managed using Endnote X7®. The search strategy is provided in the electronic supplement (Table S1).

2.2 | Eligibility criteria

The inclusion criteria were the following: (a) Population-based studies of cross-sectional or cohort design, register studies or studies based on health insurance or physician databases and (b) studies in which prevalence and/or incidence data for CU can be extracted or calculated (self-reported/parent-reported or diagnosed by physician).

The following studies were excluded: (a) intervention studies, (b) case reports/series, (c) ecological studies, (d) hospital/out-patient studies, (e) studies with participants based on their occupations, and (f) studies with participants of only male or only female sex.

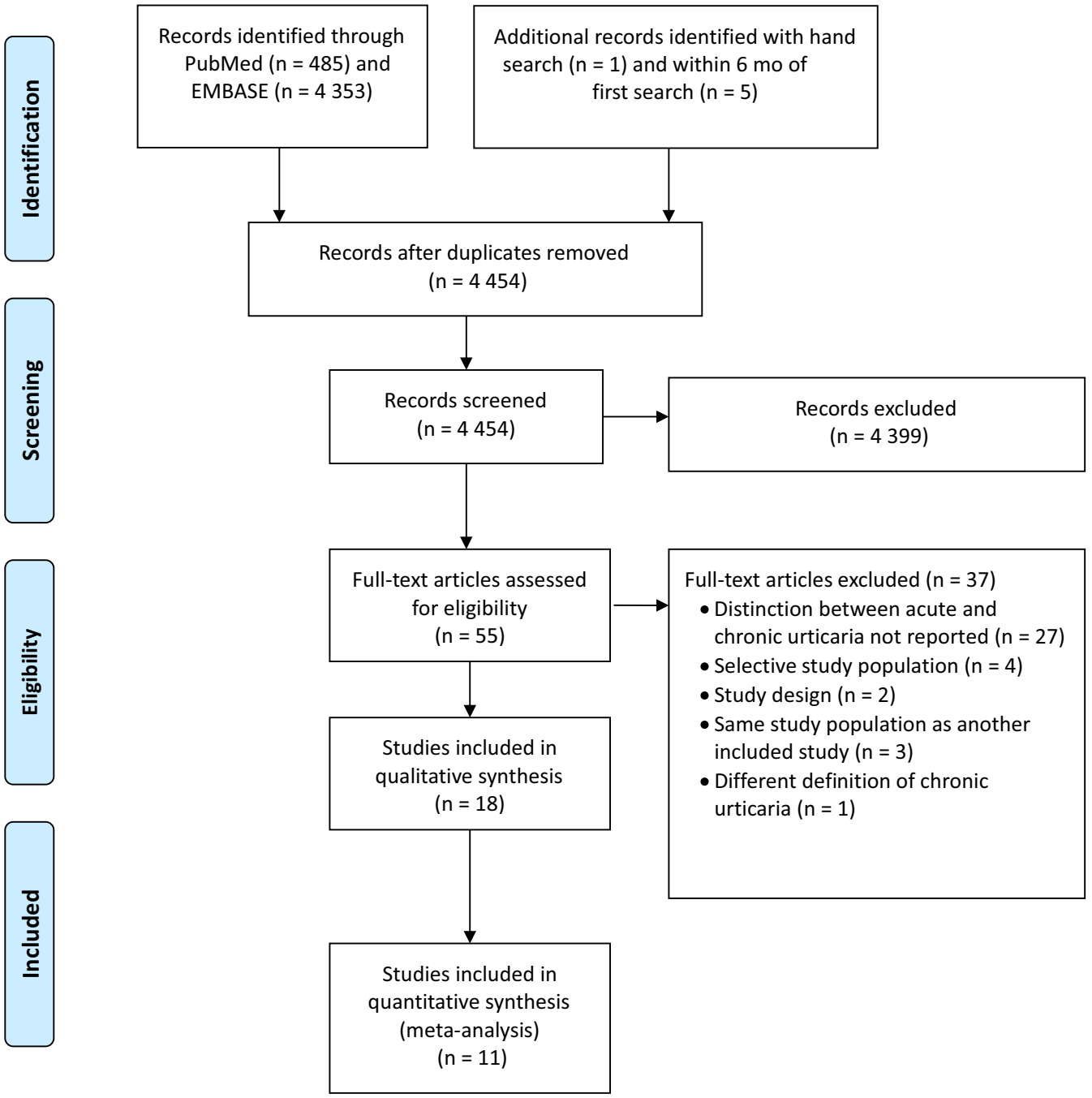


FIGURE 1 PRISMA flow chart for the literature search

Abstracts, editorials, notes, letters, and reviews were also not eligible for inclusion in the review.

2.3 | Study selection

The selection of studies was conducted in a three-stage process by two independent reviewers (JF, GA). First, each reviewer scanned the identified publications by title and classified each publication as "include","exclude", or "unclear". Second, every publication categorized as "include" or "unclear" was reviewed using the abstract. Third, full text of publications rated as "include" or "unclear" was assessed according to the eligibility criteria. Any disagreements were discussed and if necessary referred to a third reviewer (T. Keil) for final decision.

Data were extracted independently by two reviewers (JF, GA). Disagreements were solved by consensus. If necessary, a third reviewer was involved (T. Keller). The following data were extracted: continent, country, study design, sample size, database, response rate, observation period, age of participants, definition of disease, method of data collection, type of urticaria, prevalence, and incidence data. In case data were missing, authors of the article were contacted by e-mail. Only data of authors who responded within

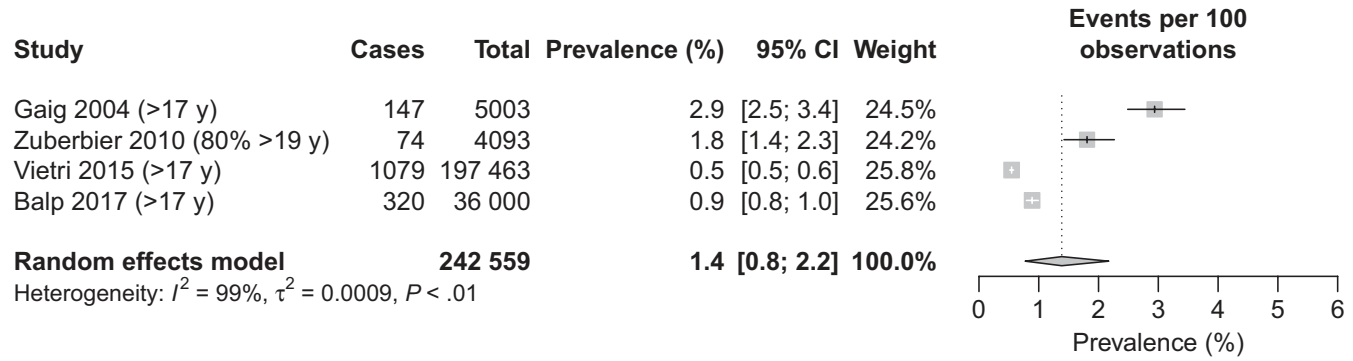


FIGURE 2 Overall lifetime prevalence of chronic urticaria

2 weeks were included in the meta-analysis. Additional data from authors were checked if it was in line with the original publication.

Risk of bias of individual studies was assessed by two reviewers (JF, GA) using a tool that was designed for population-based prevalence studies and recently modified.[15] The tool includes 10 items (external validity: representation, sampling, and random selection; internal validity: nonresponse bias, data collection, case definition, reliability/validity of tool, method of data collection, prevalence period, numerator(s), and denominator(s)) and a summary assessment (low risk, moderate risk, and high risk of bias). The scope of the tool was to identify whether studies had attempted to minimize bias and not to assess an overall numeric rating of risk of bias. The modified tool has shown to have a high interrater agreement and had been adopted previously in several studies.[16,17] Disagreements were resolved by consensus. Studies rated with a high risk of bias were not included in the meta-analysis.

2.4 | Quantitative synthesis

We extracted the prevalence of CU for each study and then calculated the pooled prevalence estimates using the arcsine transformation for variance stabilization[18] with a 95% confidence interval using random effects meta-analysis due to the expected heterogeneity of the studies. For subgroup analyses, we planned a stratification by world region, sex, and age. I^2 was calculated to quantify this heterogeneity. Statistical analyses were done with R (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Characteristics of included studies

A total of 4844 records were identified, and finally, full texts of 55 records were assessed for eligibility. Eigteen studies were included in the systematic evaluation and 11 in the meta-analysis. Selection process is shown in Figure 1.

Six of the 18 studies were carried out in Europe,[19-24] two in Latin America,[25,26] three in Northern America,[27-29] six in Asia,[30-35] and one in Africa.[36] Sixteen studies were published after 2003. Five studies comprised only adults and three only children. Ten were cross-sectional studies of primary data and eight based on cross-sectional analyses of secondary data (health insurance or national health system database). Seven studies used self-reported data, ten studies data based on physician diagnosis, and one used a 3 step assessment (self-reporting questionnaire, than telephone interview, than examination with physician diagnosis). Data on incidence were only available from three studies, but these were too heterogeneous for meta-analysis. Two authors sent additional information, and data of one author were included. A detailed summary of each study is included in Tables S2 and S3.

Most studies were rated as having a moderate risk of bias. Only Hellgren 1972[19] had a high risk of bias, and this study was not included in the meta-analysis. It should be noted that for secondary health analysis studies or survey panels response rate was not specified. Risk of bias was found most often for the external validity items representation and sampling frame. Within the internal validity section, risk of bias was more often found for the appropriateness of numerators/denominators. In case calculation or reporting of numerators/denominators contained errors, we recalculated them or, if this was not possible, excluded them from the meta-analysis. Another concern was the validity/reliability of the study instrument. It should be pointed out that validated instruments, like the widely used ISAAC questions for assessing asthma, rhinitis, and atopic eczema on a population level,[2] are lacking for the assessment of CU in population-based studies.

Four studies[23,24,31,34] provided prevalence estimates, but the published information was incomplete and therefore not included in the meta-analysis. Furthermore, El-Khateeb et al 2014[36] were included in the evaluation but excluded from the meta-analysis because it assessed only the one-day prevalence. Similarly, Ohmi et al 1984[30] were excluded because it assessed only the prevalence of one subtype of chronic inducible urticaria.[37] Finally, pooled estimates of prevalence were determined from 11 studies. In total, data from n = 86 632 267 persons were considered for meta-analysis (study samples: 2613 [minimum]-50 316 384 [maximum]). Due to the expected heterogeneity of the studies, a random effects model was chosen for meta-analysis instead of a fixed effects model. In a random effects model, the weights of the single studies are more

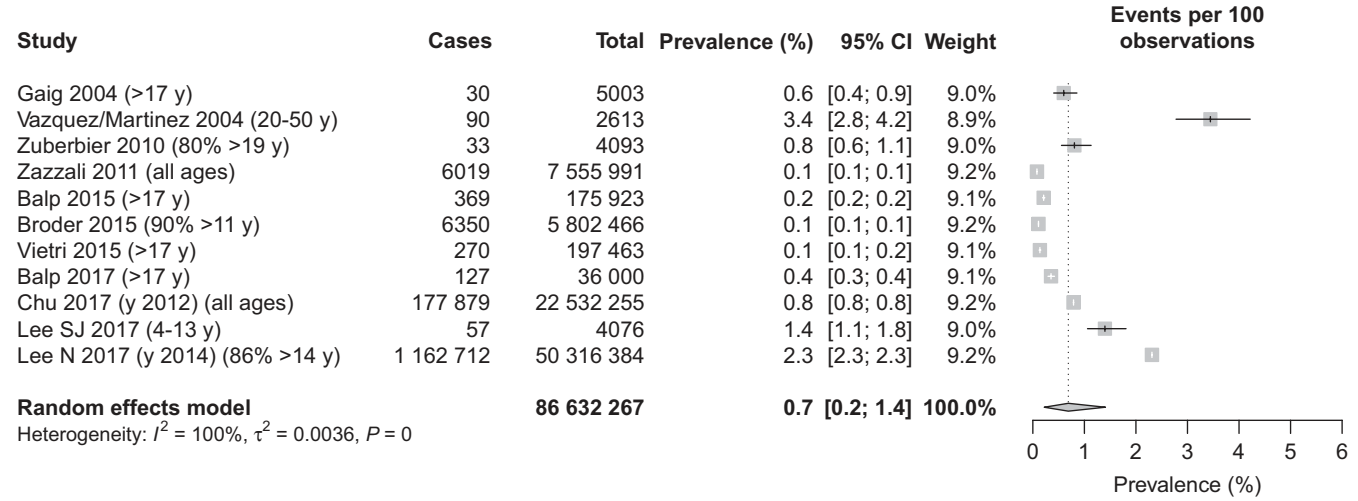


FIGURE 3 Overall point prevalence of chronic urticaria

balanced and the size of the individual boxes for each study in the forest plots is therefore not substantially different.

3.2 | Lifetime prevalence of chronic urticaria

Five studies[20,21,25,26,29] reported the overall lifetime prevalence of CU, which was on average 4.4% (95% CI 1.6-8.4). Excluding one study with an unusually high lifetime prevalence[25] in relation to the other studies, the adjusted lifetime prevalence was 1.4% (95% CI 0.8-2.2, I^2 = 98.9%, Figure 2).

3.3 | Point prevalence of chronic urticaria

Based on eleven studies,[20-22,25-29,32-34] the overall point prevalence of CU was 0.7% (95% CI 0.2-1.4, I^2 = 100%) (Figure 3). Most studies presented 12-month prevalence estimates; however, three studies assessed the prevalence of current treatment for CU[22,26,29] and one study the combination of one-week prevalence plus current treatment.[20]

3.4 | Point prevalence of chronic urticaria by world region, sex, and age

The regions with the highest point prevalence estimates were Latin America and Asia: 1.5% (95% CI 0.0-6.0) and 1.4% (95% CI 0.5-2.9), respectively. The region with the lowest prevalence was Northern America: 0.1%; 95% CI 0.1-0.1 (Figure 4).

Seven studies[20,21,25,26,28,32,33] presented data stratified by sex. The point prevalence estimate for women was slightly higher than for men with overlapping corresponding 95% CIs based on random effect meta-analysis: 1.3% (95% CI 0.1-2.2) vs 0.8% (95% CI 0.2-3.2) (Figure 5). Stratifying by world regions, we found that this difference was only statistically significant in Europe and Northern America whereas in the Asian studies we did not detect such sex-specific difference in the prevalence of CU (Figure S1-S3).

Nine studies[20-22,25,26,28,29,32,33] presented data stratified by age. Only one of the studies included in meta-analysis assessed only data on children (4-13 years).[32] Based on the available studies, we decided to calculate prevalence estimates for children (0-19 years) and adults (>19 years). For this age-specific analysis, we excluded one study that presented age strata, which did not correspond with the age strata of the other studies (≤11, 12-24, and ≥25 years[28]). The summary point prevalence estimate for children was slightly higher than for adults (Figure 6). Looking at sex-specific differences in children < 15 years[28,32,33] a subgroup analysis yielded a point prevalence of 1.0% (95% CI 0.0-3.4) for girls and of 1.1% (95% CI 0.0-3.9) for boys (Figure S4).

3.5 | Additional analysis

Studies assessing point prevalence based on self-reported questionnaires (cross-sectional studies) (0.7%, 95% CI 0.4-1.0) yielded similar prevalence estimates as studies assessing point prevalence based on physician diagnosis (secondary data) (0.6%, 95% CI 0.0-1.8) (Figure S5).

Regarding possible time trends, we identified four studies from the systematic review that assessed the point prevalence at different time points in the same region with the same methods. All four studies[23,24,33,34] showed an increasing point prevalence over time (Table S3).

4 | DISCUSSION

4.1 | Main findings

Our systematic review with meta-analysis showed that CU affects a considerable part of the population around the globe with overall lifetime and point prevalence rates of 1.4% and 0.7%, respectively. CU seems to be more prevalent in Asia than in Europe and Northern America. Regarding sex-specific analyses, women seemed to be

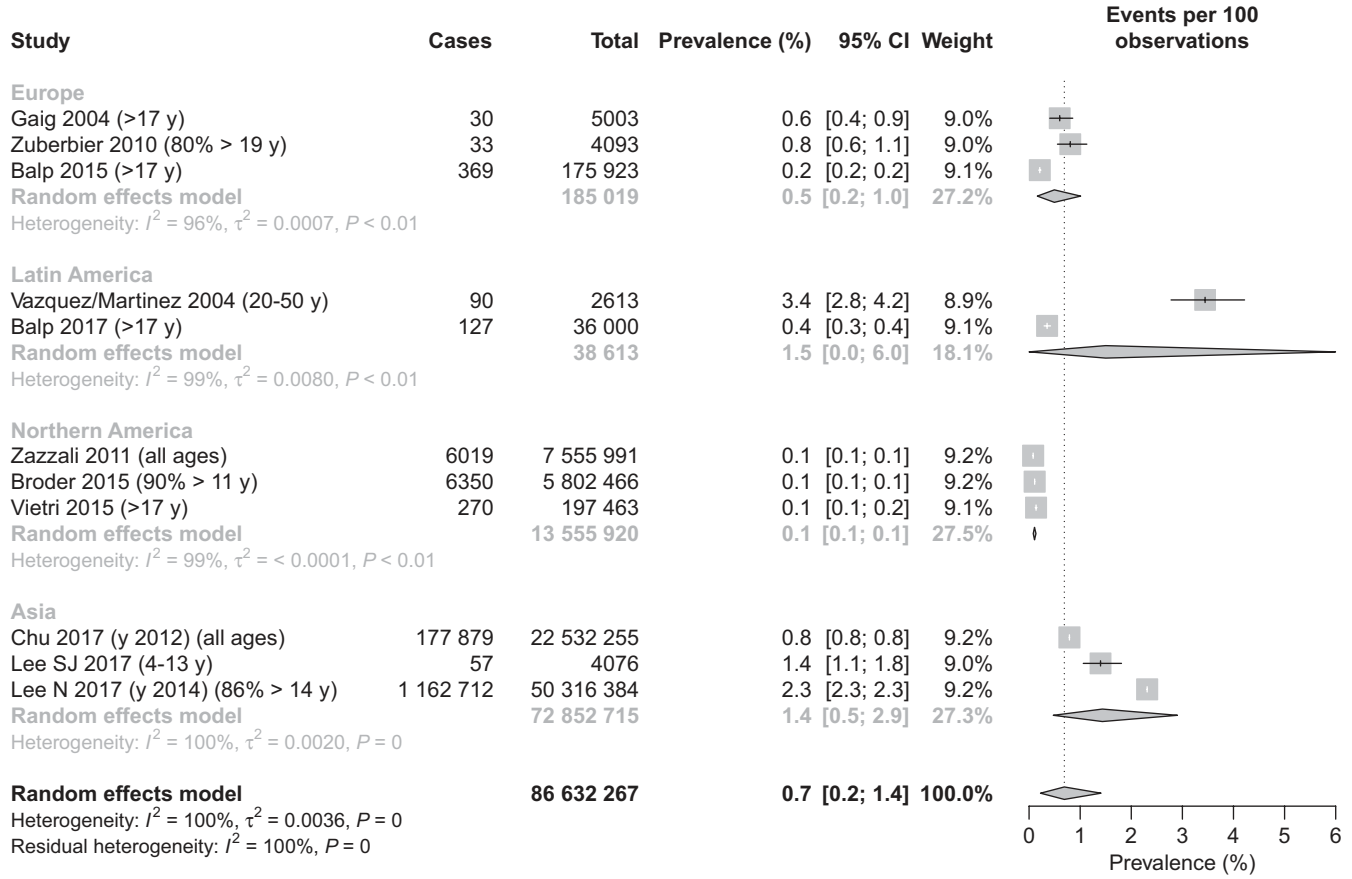


FIGURE 4 Point prevalence of chronic urticaria by world region

more affected than men. In children < 15 years, we did not find a sex-specific difference. Varying time trend evaluations showed an increasing prevalence of CU in recent years.

4.2 | Comparison with other studies

Based on four studies only, the overall lifetime prevalence of 1.4% needs to be interpreted with caution. It may be an underestimation because several studies did not ask specifically for symptoms of chronic inducible urticaria and participants may not be aware of having it because symptoms can be mild. In a selected sample of students, Zuberbier et al assessed a prevalence of 11.2% for cholinergic urticaria after presenting urticaria-specific symptoms in slides to them.[38] On the other hand, a recently published study from Poland with similar methods yielded a lifetime prevalence of CU of only 0.6%.[39]

The overall point prevalence of <1% may be also an underestimation because the definition of CU in several of the included studies required current treatment, but not all CU patients are receiving treatment continuously. In fact, only <50% of patients seem to be responsive to the first-line treatment with antihistamines.[37] Another reason may be that three studies[27,28,34] assessed only chronic spontaneous urticaria.

Latin America and Asia showed a higher point prevalence of CU than other regions. However, the estimate for Latin America, based on two studies only, yielded a very wide confidence interval. The study from Mexico[25] assessed with 3.4% specifically higher point prevalence in relation to the other studies. The authors of this study pointed out that their study was undertaken in a region of Mexico that is according to their assessment predestined for allergic diseases due to climatic reasons.[25] Opposite to the data from Mexico, a recently published study from Argentina yielded a point prevalence of only 0.29% among a highly selective sample in Buenos Aires, that is, members of a private health maintenance organization.[40] Northern America showed the lowest point prevalence. This may be explainable by the fact that two of the three studies—covering 98.5% of the Northern America sample—assessed only chronic spontaneous urticaria and not chronic inducible urticaria. More population-based studies from Latin and Northern America assessing both chronic spontaneous and chronic inducible urticaria are needed to further elucidate the prevalence patterns.

The point prevalence estimate for women was slightly higher than for men, confirming results from studies in samples of patients with chronic spontaneous urticaria.[41] Interestingly, one study from Asia found no sex-specific difference and it was the study including only children (4-13 years).[32] Evaluating sex-specific differences in children < 15 years in three studies,[28,32,33] we found again no sex-specific difference. A sex-related prevalence shift from childhood

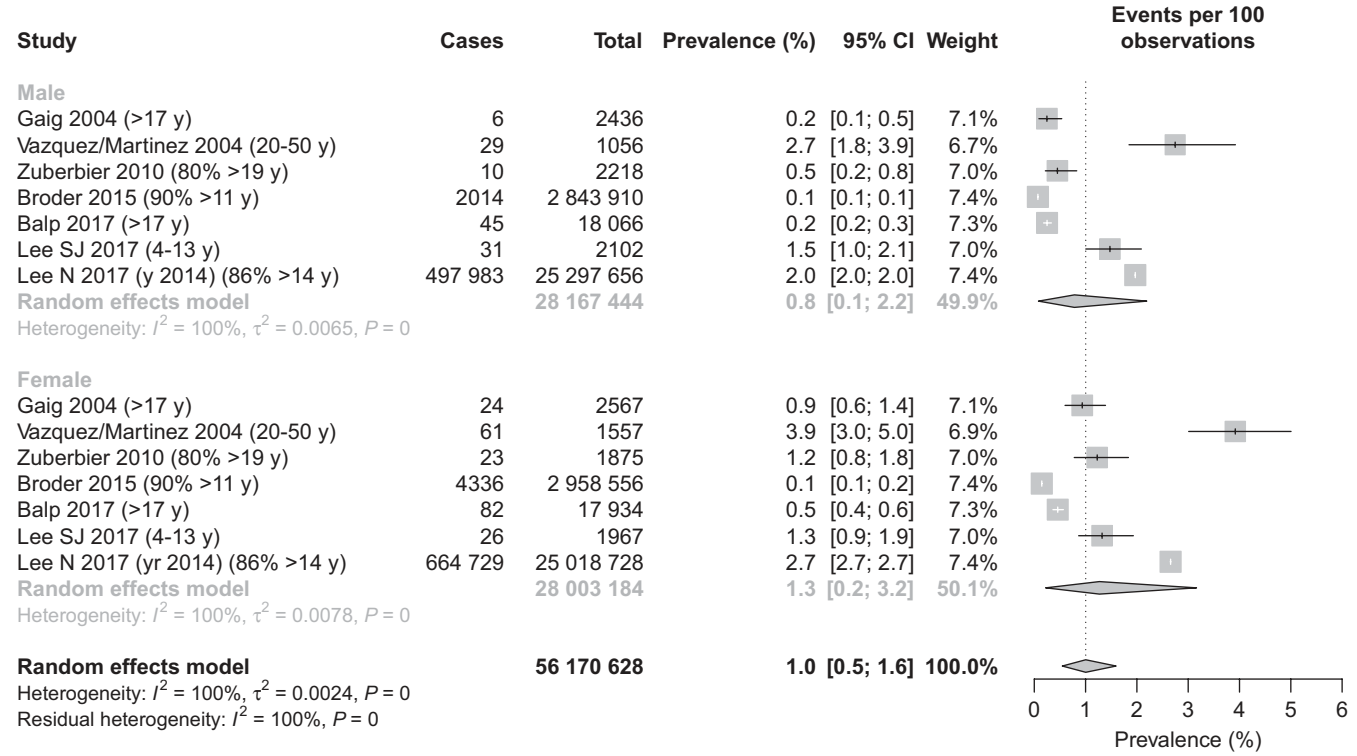


FIGURE 5 Point prevalence of chronic urticaria by sex

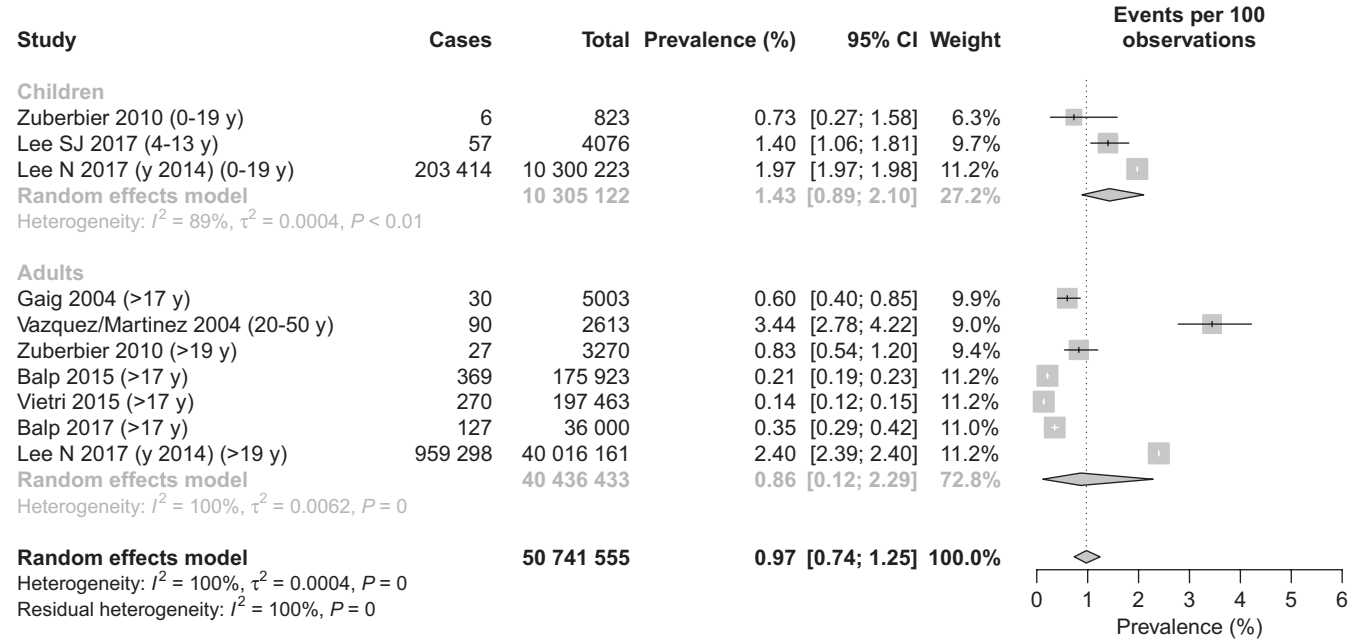


FIGURE 6 Point prevalence of chronic urticaria by age group

to adulthood has been identified for allergies, like allergic rhinitis in adolescence[42,43] and asthma after the onset of puberty.[44,45] Maybe the sex-specific difference in CU that has been shown for patients[41] results because in the transition to adulthood more females are developing urticaria? A recent study from South Korea assessed a predominance of women for new-onset urticaria only for the age group 20-64 years,[46] being a possible explanation for the preponderance of female patients with CU in this group.

The point prevalence estimate of CU for children was slightly higher than for adults, although the limited number of childhood studies is hampering valid comparisons. A recently published study among physicians from five European countries yielded a point

prevalence of 1.4% among pediatric patients,[47] which is within the range of the population-based prevalences for children in our meta-analysis. These results indicate that more studies are needed to validly assess prevalence data in children, preferably differentiating between childhood, adolescence, and early adulthood.

Prevalence rates of CU appear to be increasing. This should be confirmed and characterized in more detail in future longitudinal studies.

4.3 | Strengths and limitations

To the best of our knowledge, the current review has been the first to determine systematically the prevalence of CU worldwide. Our meta-analysis included large datasets with a total of more than 86 000 000 participants of population-based studies worldwide. We searched the two major medical databases, PUBMED and EMBASE, which cover most of the available medical literature. Although we did not restrict our search to specific languages, most publications were in English. We cannot completely rule out that we may have missed studies, however, to minimize such bias we conducted manual searches in addition to the systematic search.

Unfortunately, not all world regions were represented in this present evaluation. For Oceania, no study was identified and the only study from Africa had to be excluded from meta-analysis, but was included in the systematic review. Three of the most recent studies included in meta-analysis were from Asia, adding new evidence to the epidemiology of CU worldwide.

For some of our planned subgroup analyses, there were only few studies eligible hampering comparisons. This concerns especially the estimates for overall lifetime prevalence and point prevalence for children.

There was a great difference in sample size between cross-sectional studies and studies assessing complete health insurance/national health system databases. This may be one reason for the considerable heterogeneity in all meta-analyses as indicated by the Higgins' I^2 tests. By applying the random effects model, studies with larger samples had a smaller and studies with smaller samples had a bigger effect. Another reason for heterogeneity may be having taking into account different data collection modes like cross-sectional studies using self-reported questionnaires as well as secondary data analyses assessing physician diagnoses. More possible reasons are the inclusion of different regions and age strata.

Risk of bias assessment showed that the included studies were mainly rated as moderate risk of bias. One concern was the validity/reliability of the instruments used in the studies. Interestingly, the point prevalence did not considerably differ when comparing studies using physician diagnosis with studies administering self-reported questionnaires. So even without including a validated questionnaire for the assessment of CU, the questionnaire-based studies did not seem to over- or underestimate notably the CU prevalence.

Most studies did not distinguish between relevant CU subtypes. Future studies should address this issue and aim to assess both types of CU separately. Only a few studies assessed incidence data, which was insufficient to conduct a meta-analysis. Future cohort studies should start early in life and try to collect incidence data from childhood onwards to get a broader picture of the development of this disease and assess potential predictors, risk, and protective factors. Another potential determinant to be investigated may be urban and rural setting as rural residence has been suggested as a risk factor for urticaria.[46]

5 | CONCLUSIONS

This first systematic review on CU prevalence showed considerable regional differences. CU seems to be more prevalent in Asia than in Europe and Northern America. Women seemed to be more affected than men, whereas in children < 15 years there was no sex-specific difference in the prevalence of CU. Temporal analysis showed an increasing prevalence over time. Our quality assessment showed that the risk of bias was mainly moderate, whereas the statistical heterogeneity (I^2) between the studies included in the meta-analysis was rather high.

There is a need to conduct further properly performed population-based studies on the prevalence of CU, especially regarding certain age groups, sex-specific differences, and regions. Further research should focus specifically on children and adolescents and different CU subtypes. Prospective investigations are required to examine the incidence and potential protective and risk factors of CU in order to develop preventive strategies. The need for global studies may be facilitated by the global network of urticaria centers of reference and excellence (UCARE).[48]

CONFLICTS OF INTEREST

J. Fricke, G. Ávila, T. Keller, and T. Keil have nothing to disclose. K. Weller reports personal fees from Novartis, MOXIE, Uriach, UCB, Dr Pfleger, all outside the submitted work; S. Lau reports personal fees from Sanofi Genzyme, DBV, ALK, Allergopharma, Boehringer, all outside the submitted work; M. Maurer reports grants and personal fees from Allakos, FAES, Genentech, Menarini, Novartis, Moxie, MSD, Roche, Sanofi, UCB, and Uriach, as well as personal fees from Aralez and grants from AstraZeneca, all outside the submitted work; T. Zuberbier reports personal fees from Bayer Health Care, FAES, Novartis, Henkel, Novartis, Henkel, AstraZeneca Fee for talk, AbbVie Fee for talk, ALK Fee for talk, Almirall Fee for talk, Astellas Fee for talk, Bayer Health Care Fee for talk, Bencard Fee for talk, Berlin Chemie Fee for talk, FAES Fee for talk, HAL Fee for talk, Leti Fee for talk, Meda Fee for talk, Menarini Fee for talk, Merck Fee for talk, MSD Fee for talk, Novartis Fee for talk, Pfizer Fee for talk, Sanofi Fee for talk, Stallergenes Fee for talk, Takeda Fee for talk, Teva Fee for talk, UCB Fee for talk, Henkel Fee for talk, Kryolan Fee for talk, L'Oréal Fee for talk, all outside the submitted work.

AUTHOR CONTRIBUTIONS

All the authors conceived and designed the study project. J. Fricke and G. Ávila performed the literature search, assessed study details,

and evaluated the study quality supported by T. Keil and T. Keller. T. Keller performed the statistical analyses. J. Fricke wrote the first draft of the paper with the support of G. Ávila, which was critically revised by all the other authors. All the authors gave final approval of the version to be submitted and agreed to be accountable for the whole paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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