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THE PREVALENCE OF SELF-REPORTED SYSTEMIC ALLERGIC REACTION TO *HYMENOPTERA* VENOM IN BEEKEEPERS WORLDWIDE: A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

OCENA GLOBALNE PREVALENCE SAMOPOROČANE SISTEMSKE ALERGIJSKE REAKCIJE ZA STRUP KOŽEKRILCEV PRI ČEBELARJIH: SISTEMATIČNI PREGLED LITERATURE IN META-ANALIZA

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ABSTRACT

Background: Beekeepers represent a high-allergic risk population group due to their unavoidable seasonal or persistent exposure to the elicitors of *Hymenoptera* venom allergy, bees in particular. A systematic literature review and meta-analysis aimed to estimate the prevalence of self-reported systemic allergic reaction to *Hymenoptera* venom among beekeepers worldwide.

Methods: We rigorously reviewed and conducted meta-analysis on observational studies retrieved from seven electronic databases (MEDLINE via PubMed, Web of Science Core Collection, Scopus, Academic Search Complete, ScienceDirect, Cumulative Index to Nursing and Allied Health Literature, Zoological Record), spanning data from inception to August 1, 2023. The Joanna Briggs Institute Prevalence Critical Appraisal Tool was employed to assess the risk of bias. A meta-analysis was conducted to synthesize evidence.

Results: Out of 468 studies, eight original articles met the inclusion criteria. The estimated overall lifetime and one-year prevalence of self-reported systemic allergic reaction to bee venom were 23.7% (95% CI: 7.7-53.4) and 7.3% (95% CI: 5.8-9.2), respectively. The estimated lifetime prevalence of self-reported systemic allergic reaction to bee venom for grades III-IV (severe systemic allergic reaction) was 6.0% (95% CI: 3.0-11.7). In general, substantial heterogeneity and a high risk of bias were observed across the majority of studies. The impact of geographical location and climate differences on the estimated lifetime prevalence is suggestive for severe systemic allergic reaction.

Conclusions: Future observational cross-sectional studies should employ rigorous study designs, using validated questionnaires, and thoroughly report the observed health outcomes, verified by physicians.

Keywords:
Public health
Venom hypersensitivity
Prevalence
Beekeeping

IZVLEČEK

Uvod: *Izpostavljenost ponavljajočim se pikom kožekrilcev (čebele, ose, čmrlji) je glavni okoljski dejavnik tveganja za razvoj alergijske reakcije. Čebelarji sodijo med ogrožene populacijske skupine, saj je sezonska ali celoletna izpostavljenost pikom kožekrilcev (zlasti čebelam) pomembno večja v primerjavi s splošno odraslo populacijo. Namen sistematičnega pregleda literature in meta-analize je oceniti globalno prevalenco samoporočane sistemske alergijske reakcije za strup kožekrilcev med čebelarji.*

Metode: *Časovno okno pregleda je segalo od prvih objav na področju opazovanja do 1. avgusta 2023. Iskanje virov je potekalo v sedmih elektronskih podatkovnih zbirkah (MEDLINE z iskalnim sistemom PubMed, Web of Science Core Collection, Scopus, Academic Search Complete, ScienceDirect, Cumulative Index to Nursing and Allied Health Literature, Zoological Record). V analizo so bile vključene epidemiološke opazovalne raziskave v vseh tujih jezikih. Za oceno tveganja pristranosti je bilo uporabljeno orodje za kritično vrednotenje raziskav o prevalenci Inštituta Joanne Briggs. Meta-analiza je bila izvedena v programskem okolju R (paket »meta«), pri čemer je bil uporabljen model naključnih učinkov.*

Rezultati: *Od 468 zadetkov je bilo v končno analizo vključenih 8 izvirnih znanstvenih člankov, ki so ustrezali vključitvenim kriterijem. Ocenjena globalna vseživljenjska in enoletna prevalenca samoporočanih sistemskih alergijskih reakcij po piku čebele je bila 23,7 % (95-% IZ: 7,7-53,4) in 7,3 % (95-% IZ: 5,8-9,2). Ocenjena globalna vseživljenjska prevalenca samoporočanih sistemskih alergijskih reakcij po piku čebele za razrede III-IV (težka sistemska alergijska reakcija) je bila 6,0 % (95-% IZ: 3,0-11,7). Vključene raziskave so bile heterogene z visokim tveganjem za pristranost. Vpliv geografske lege in podnebnih razlik na ocenjeno globalno vseživljenjsko prevalenco je bil nakazan za težko sistemsko alergijsko reakcijo.*

Zaključki: *Pri načrtovanju epidemioloških presečnih raziskav s področja opazovanja bi bilo potrebno uporabiti veljavna orodja in izboljšati kakovost navajanja podatkov, relevantnih za opazovani zdravstveni izid. Objektivizacija sistemske alergijske reakcije po piku čebele s strani specialista alergologa bi pomenila nadgradnjo in s tem klinično uporabno vrednost zbranih podatkov.*

Ključne besede:
javno zdravje
preobčutljivost
prevalenca
čebelarjenje

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1 INTRODUCTION

Hymenoptera, including bees, wasps, ants and sawflies, comprises over 150,000 described species (1). Widely distributed across terrestrial ecosystems (2), this insect order is among the most species-rich and abundant, (3), playing crucial roles as pollinators, herbivores, and natural enemies within ecosystems (2). Despite their ecological significance, direct interactions with humans – often prompted by perceived threats from human activities or competition for food (4) – pose a risk of stinging and venom injection. The likelihood of encountering a specific stinging insect can vary depending on geographical, environmental, and ecological factors in the living environment, as well as the types of activities individuals engage in (5, 6).

In most healthy individuals without *Hymenoptera* venom allergy (HVA), a sting typically results in a well-tolerated, albeit temporarily painful local reaction, characterized by swelling, redness, and itching (7), usually resolving on its own within 24 to 48 hours (8). Conversely, for those sensitized to *Hymenoptera* venom, symptomatic allergic reaction (AR) may occur, with large local reaction (LLR) and systemic allergic reaction (SAR) as the most frequent clinical patterns. Medically important species capable of stinging and causing HVA belong to the *Apidae*, *Vespidae*, and *Formicidae* families (9).

*Hymenoptera*s are also a leading cause of occupational anaphylaxis due to the heightened risk associated with exposure to repeated stings, a key factor in the development of AR (6). In terms of exposure intensity, certain population groups, particularly those in outdoor professions and specific occupational settings (6), face increased vulnerability to HVA. Beekeepers, in particular, face a specific risk (10), and epidemiological review findings have consistently reported higher estimated (self-reported) prevalence rates of SAR to bee venom in beekeepers (14%-30% (10); 4%-26% (11)) compared to the general population, affecting up to 3.3% of adults in the USA (12) and 8.9% in Europe (13).

However, none of the existing reviews (10, 11) systematically assessed observational studies among beekeepers worldwide, addressing the epidemiology of SAR to *Hymenoptera* venom. This study aims to fill this gap by conducting the first comprehensive systematic literature review and meta-analysis with the following objectives: 1) to assess the estimated prevalence of self-reported SAR to *Hymenoptera* venom in beekeepers worldwide, and 2) to explore whether geographical location and climate differences affect the estimated self-reported prevalence. Aligning with the observed population, we focused on the most common culprits of HVA among beekeepers (bee, wasp, hornet). In addition, our research specifically focuses on one species of bee, the honeybee (*Apis mellifera*), rather than bees in general, hereinafter referred to as the "bee".

2 METHODS

A comprehensive systematic literature review and meta-analysis were performed following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (14). The study protocol was preregistered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identification number CRD42021260922 and is described elsewhere (15).

2.1 Eligibility criteria

We included questionnaire-based observational (cohort, cross-sectional) studies, assessing the estimated prevalence of self-reported SAR to *Hymenoptera* (bee, wasp, hornet) or *Hymenoptera* venom among beekeepers of any age, engaged in beekeeping activities. There were no language restrictions, and translations were performed when necessary for literature in languages other than English.

Exclusion criteria comprised studies assessing reactions other than self-reported SAR to *Hymenoptera* venom (e.g., LLR, systemic toxic reaction) or those investigating other causes of SAR. We excluded meta-analysis, (systematic) literature reviews, clinical and qualitative studies, case reports/case series, experimental ex vivo/in vivo studies, articles reporting editorials/comments/opinions and other types of papers that did not report original research data, conference abstracts, articles not related to the systematic literature review and studies not available in a full form.

2.2 Information sources and search strategy

A systematic electronic literature search was carried out by two reviewers (TC, AK) across seven databases: MEDLINE via PubMed, Web of Science Core Collection, Scopus, Academic Search Complete (EBSCO host), ScienceDirect, Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCO host), and Zoological Record (Web of Science). The search spanned from their inception up to August 3, 2021, and was subsequently repeated between July 11, 2022, and finalized on August 1, 2023. The search strategy, employing two search terms ("hypersensitivity" AND "beekeeping"), was reviewed by an experienced librarian and initially formulated in MEDLINE via PubMed, with subsequent adaptation for use in other electronic databases (data available on request). Manual search of the reference lists was conducted to identify any relevant publications that might have been missed in the electronic search.

2.3 Selection process

The search results underwent initial screening for duplicate removal and record management using the Zotero reference manager, either automatically or through manual upload. The selection process, encompassing title and/or abstract screening, as well as a full-text review based on the eligibility criteria, was independently conducted by two reviewers (TC, AK). When necessary, a third reviewer (IL) was consulted.

2.4 Data collection process and data items

Prior to final data tabulation, a pre-designed data extraction form in Excel was prepared. Two independent reviewers (TC, AK) manually extracted the following data of interest: study characteristics (first author; year of publication; location, study design, aim); observed population characteristics (sample size, age, gender); observed health outcome, method of data collection and statistical analysis. The observed health outcome was defined as the estimated lifetime (≥10 years) and/or one-year prevalence of self-reported SAR to *Hymenoptera* venom, with grading of the severity of clinical symptoms according to the classification, whenever possible. Prevalence of self-reported SAR was defined as the number of beekeepers who reported at least one SAR within a certain time period (lifetime or one-year). In cases where the information was unclear or missing, several efforts were made to contact the authors of the original articles, and the data were updated accordingly.

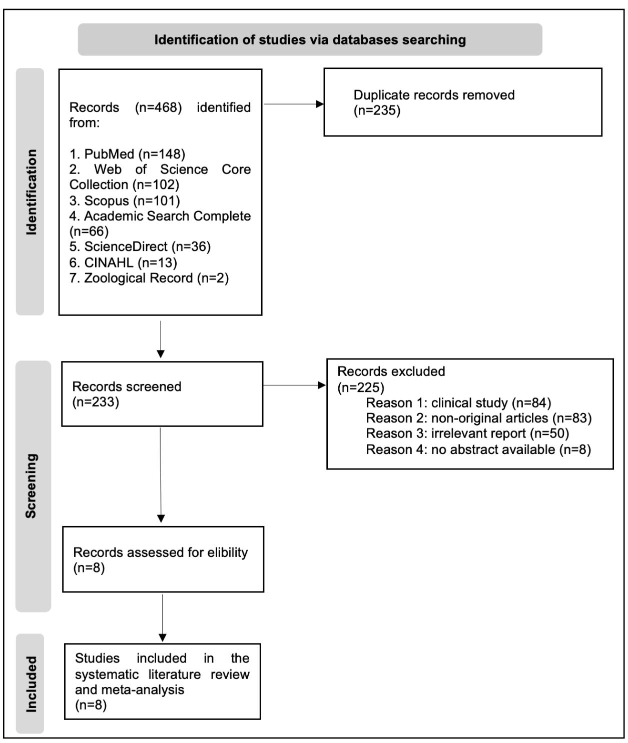

Figure 1. PRISMA 2020 flow diagram of the study selection process.

2.5 Study risk of bias assessment

The quality assessment of the included studies was conducted using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data (16) (data available on request).

2.6 Data synthesis

The meta-analysis of the prevalence data and forest plot construction were performed under the R statistical environment (version 4.3.1), utilizing the function metaprop within the "meta" package. Due to expected high heterogeneity, the random effect model was applied and the restricted maximum-likelihood estimator (REML) was used for calculating between-study variance (¤2). Overall prevalence was calculated using the logit transformation. Confidence intervals of prevalence for individual studies were calculated based on exact binominal intervals.

3 RESULTS

3.1 Study selection

The initial database search yielded a total of 468 publications. After removing duplicates (n=235) and conducting screening based on titles and/or abstracts (n=233), we identified eight articles that met the criteria for full-text assessment. All of these (17-24) were eligible for inclusion and no additional studies from the reference lists were added. The PRISMA 2020 flow diagram (Figure 1) outlines the selection process.

3.2 Study characteristics

The majority of the included studies (n=5) were conducted outside Europe, with four in Turkey (18, 22-24) and one in Mexico (21) (Table 1). There was one study each from Northern (Finland) (17), Central (Germany) (19) and Western Europe (Great Britain) (20). The studies were published between 1996 and 2020, and the majority were published after the year 2000 (18-24).

The primary objectives of the studies were to assess the prevalence and types of HVA, specifically stinging *Hymenoptera*-induced SAR (17, 18, 22-24). In two studies (18, 19), the authors initially reported estimating the incidence of bee venom allergies. However, after a detailed text analysis and consensus with reviewers (TC, AK, IL), it became evident that these two studies were also assessing the prevalence of HVA. Therefore, we categorize them as prevalence studies. All studies included beekeepers (17-24) and one study used food-service staff from a restaurant as an occupational control group (24). The sample size of the studies varied substantially, ranging from 69 (24) to 1,541 (21), with a mean (standard deviation) age from 48.2±11.5 (18) to 61.8±13.9 years (19), and with 4,025 men out a total of 5,473 participants.

Table 1. Key items of the self-reported observed health outcome.

	Country	Sample size (N)	Male	Age, years (mean, SD)	1-year	≥10 years	Classification of systemic allergic reaction	Culprit *Hymenoptera*
Annila et al., 1996 (17)	Finland	191	164	51.8±12.3	✓	✓	Müller	bee wasp (*Vespula* spp.)
Celikel et al., 2006 (18)	Turkey	1245	489	48.2±11.5			NA	bee
Münstedt et al., 2008 (19)	Germany	1053	973	61.8±13.9	✓	✓	Müller	bee
Richter et al., 2011 (20)	Great Britain	852	545	range 51-60		✓	modified Müller	bee
Becerril-Ángeles et al., 2013* (21)	Mexico	1541	1289	average 37		✓	Müller	bee
Çeliksoy et al., 2014* (22)	Turkey	301	295	48.2±11.5	✓		Müller Ring-Messmer	bee
Ediger et al., 2018 (23)	Turkey	221	213	49.9±11.8		✓	Ring-Messmer	bee
Demirkale et al., 2020 (24)	Turkey	69	57	48.4±12.0		✓	NA	bee

Legend: N=number of participants; NA=not available; SD=standard deviation
a:*additional data gathered upon request
b: ✓ indicates the observed measure(s) of occurrence

Epidemiological data were collected using questionnaires, distributed through various methods, (sending by mail (17, 21), being included in selected journals and sent to subscribers, or made available in electronic form on the internet (19), or only in electronic form (20)). In one study, printed questionnaires were completed during a beekeeping congress meeting under the supervision of the researchers (24). In a few studies how the questionnaires were distributed was not clearly specified (18, 22, 23). Survey response rates varied widely, ranging from as low as 3.0% (19) to 79.6% (17).

Except for three studies (17, 18, 22), the prevalence period for the estimated lifetime self-reported SAR to *Hymenoptera* venom remained unclear, and an assumption was made according to the sociodemographic data (mean age, duration of beekeeping). In most cases, SAR was graded according to the Müller classification (17, 19, 20-22), and bees were the most frequently reported culprit (17-24). A comprehensive summary of the main study characteristics is available on request.

3.3 Methodological quality

A summary of the RoB assessments for each study is available on request. None of the studies met all 10 evaluation points for quality assessment, with more than half (n=5) exhibiting a high RoB. Measurements of the outcome (Q7.1 and Q7.2) and the statistical analysis (Q8) applied to a high RoB in most cases.

3.4 Meta-analysis results

The estimated overall lifetime prevalence of self-reported SAR to bee venom, graded for severity according to different classification systems, was 23.7% (95% CI: 7.7-53.4). A substantial level of heterogeneity was observed among the studies (I^2=99%, p<0.01, Figure 2A). The estimated lifetime prevalence of self-reported SAR to bee venom for grades III-IV, graded for severity according to different classification systems (classification data not provided in one study (24)), was 6.0% (95% CI: 3.0-11.7). A significant degree of variability in reported event rates was observed (I^2=93%, p<0.01, Figure 2B).

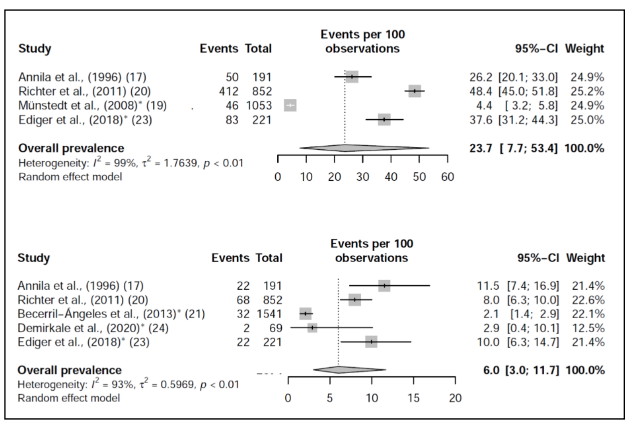

Figure 2. Forest plot of the estimated overall lifetime (≥10 years) prevalence of self-reported systemic allergic reaction to bee venom among beekeepers (A) and self-reported systemic allergic reaction to bee venom for grades III-IV (B). *Studies with high risk of bias.

The estimated overall one-year prevalence of self-reported SAR to bee venom, graded for severity according to different classification systems (classification data not provided for one study (18)), was 7.3% (95% CI: 5.8–9.2). There was no heterogeneity observed among the studies (I^2=0%, p=0.43, Figure 3).

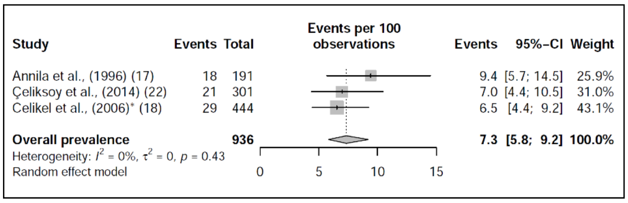

Figure 3. Forest plot of the estimated overall one-year prevalence of self-reported systemic allergic reaction to bee venom among beekeepers.* Studies with high risk of bias.

4 DISCUSSION

To the best of our knowledge, this systematic literature review and meta-analysis represents the first comprehensive attempt to estimate the global prevalence of self-reported SAR to *Hymenoptera* venom among beekeepers. Compared to the previous reviews, our findings (23.7%) align within the estimated clinical data on SAR, as objectively assessed by physicians (14%-21%) or assessed through interviews (30%), and self-reported data (4%-26%) (10, 11). The estimated lifetime prevalence of self-reported SAR (grades III-IV) to bee venom and overall one-year prevalence of self-reported SAR to bee venom were, as expected, lower, at 6.0% (95% CI: 3.0-11.7) and 7.3% (95% CI: 5.8–9.2), respectively. The observed heterogeneity across the studies was substantial, with I^2 values of 99% for estimated overall lifetime prevalence, and 93% for grades III-IV. The majority of studies were characterized by a high RoB.

Two major reasons could contribute to the observed heterogeneity in the study. Firstly, they may reflect methodological differences, including data collection technique, definition of AR and utilization of diverse classification systems for grading the severity of SAR across different regions (12, 25, 26).

With regard to the definition of AR, variability in how studies categorized and reported AR was observed. With the exception of one study (23), the questionnaires did not distinguish between allergic and non-allergic reactions (i.e., systemic toxic reactions, psychogenic reactions), raising the potential for a false history of self-reported SAR to *Hymenoptera* venom. This is because psychogenic reactions, which can imitate the symptoms of SAR, are relatively common following insect stings (27), and the high estimated overall lifetime prevalence of self-reported SAR to bee venom among the British beekeepers (48.4%) (20) could be attributed to misinterpretations of anxiety or pain following bee stings. This difference is particularly noteworthy, since the British study included a substantial number of women compared to other studies (see Table 1). Gender differences in self-reported emotional experiences have been well-documented, with previous research indicating that women often report experiencing negative emotions (fear) more frequently and intensely than men (28). Moreover, in this study the absence of a reported response rate, coupled with insufficient information for recalculation, may have caused a selection-bias, as individuals who had experienced SAR might have been more inclined to complete the questionnaire, driven by their heightened awareness of the potential severity of SAR. This selective participation could have led to an overestimation of the overall lifetime prevalence of self-reported SAR to bee venom, particularly for mild grades (grade I: 233 out of 852 (27.3%); grade II: 111 out of 852 (13.0%)) (20). The phenomenon of overestimation in both parental and self-reported data is a well-documented issue in assessing the prevalence of food allergies (29), and has also been reported in the context of HVA. Studies conducted in Poland revealed an overestimation in the prevalence of LLR and mild SAR when comparing self-reported estimates to those objectively assessed by a physician (30).

Importantly, putting aside the fact that a classification other than Müller was used, a high estimated overall lifetime prevalence of self-reported SAR to bee venom (37.6%) was also reported by Ediger et al. (23). However, these results may actually reflect the incidence of new cases rather than the overall prevalence, as the authors observed the course of symptoms over the years following bee stings. Meanwhile, Münstedt et al. (19), aimed to report the incidence of bee venom allergy, but a detailed textual analysis revealed that they reported the prevalence instead. Compared to the other studies, the authors also reported the lowest overall lifetime prevalence of self-reported SAR to bee venom, partly attributed to variations in the age of participants, with the mean age being approximately a decade higher compared to the data from other studies (17, 18, 22-24). Nevertheless, an important shortcoming of the German study is its very low response rate (3.0%), which may affect the accuracy of the prevalence estimates.

Secondly, the observed heterogeneity might be attributed to genuine disparities in sting exposure across different regions, influenced by geographic locations, climate, and beekeeping practices (11, 12, 25, 26).

In relation to bee sting exposure, Bousquet et al. (31) noted a strong correlation between the degree of sensitization to bee venom and the annual number of bee stings. This correlation is most prominent when the annual number of stings falls below 25 and reaches an optimum when it exceeds 200 (31). Aligning with this data, the potential protective effect of higher sting frequencies, as observed in Turkish studies (18, 22), and less so in the Finnish beekeepers (17), may explain the lower estimated overall one-year prevalence of self-reported SAR to bee venom in Turkey (6.5% (18), 7.0% (22)) compared to Finland (9.4%) (17). However, in Bousquet et al.'s study (31) the specific selection criteria employed (exclusion of numerous allergic beekeepers and individuals with variations in the number of annual bee stings over the previous five years) may have influenced the study's outcomes.

Nonetheless, an intriguing pattern emerges within the estimated lifetime prevalence of self-reported SAR to bee venom in grades III-IV (severe SAR). Studies consistently indicate a higher estimated prevalence of severe self-reported SAR to bee venom in colder European regions (Finland, Great Britain) (17, 20), and a lower one in warmer non-European ones (Mexico, Turkey) (21, 24). In the latter case, it is plausible that favourable climatic conditions permit beekeepers to be exposed to bees throughout most of the year (18, 22, 32), leading to a lasting form of immunological protection (33), presumably on an immunological basis. Notably, heavily exposed beekeepers exhibit higher levels of bee-venom specific IgG4 (sIgG4), reflecting their degree of exposure to stings and believed to induce immune tolerance while mitigating the inflammatory response (34). However, the results of one Turkish study led by Ediger et al. (23) deviate from this expected pattern. It is suggestive that these findings may not be solely attributable to geographic location and climatic conditions, as observed in other studies. Instead, it is conceivable that methodological concerns, as mentioned previously, could significantly impact the observed outcome. However, the risk of developing SAR to bee venom cannot be entirely ruled out, even among beekeepers with a history of numerous bee stings and no prior AR (35, 36).

In contrast to beekeeping in regions with milder climates, apiculture in Europe is inherently seasonal, characterized by the distinct absence of bee sting exposure during the winter months, with this seasonal break lasting from the end of October throughout the entire winter (33). Moreover, the length of the beekeeping season varies across the regions, i.e., in Finland it extends from May to August (17), while in France it spans from early spring to late fall (31). It is conceivable that the natural history of sting reactions may exhibit disparities between the northern and southern regions (17). Moreover, it is plausible that differences between countries may also be due to beekeeping with different subspecies of honeybees (e.g., *Apis mellifera carnica, Apis mellifera ligustica*, etc.), because they are not all equally aggressive. Although Richter (20) noted that beekeeping with a particular subspecies did not increase susceptibility to SAR (data not shown in the original article), future studies should incorporate species-specific behavioural trait data to gain further insights into this research area.

However, regardless of the location, the temporal gap between two working seasons may potentially attenuate the protective effect conferred by prior bee stings, consequently increasing the susceptibility to the development of AR (37). This aligns with the conclusions drawn from a literature review (10), as initial stings in spring were identified as a definitive risk factor for the onset of allergic bee sting reactions among beekeepers. Furthermore, Münstedt et al. (19), reported the occurrence of more severe non-allergic reactions to bee venom during the spring months when compared to later periods. It is also important to consider the impact of climate change, as the available data support the presence of positive correlations between climate change and HVA (38).

Knowing that factors such as geographical location, climate differences, temperature fluctuations, and insect behaviour patterns can heighten the risk of insect stings within this population group, targeted public health interventions are essential. This includes implementing comprehensive risk assessment and management strategies, as well as launching public health campaigns and educational initiatives aimed at raising awareness about SAR and promoting preventive measures.

For allergic beekeepers, the most critical measure to mitigate risk is to reduce exposure by considering cessation of beekeeping activities. However, our meta-analysis reveals that many allergic beekeepers continue beekeeping, thereby exposing themselves to recurrent and potentially life-threatening SAR. Therefore, allergologists, public health professionals, and occupational, traffic and sports medicine specialists should intensify efforts in counselling, emphasizing 1) the importance of wearing full protective equipment during all beekeeping activities, 2) self-medication in emergencies, including regular training in proper use of adrenaline autoinjectors, and 3) considering Venom Immunotherapy (VIT) as a causal treatment option when indicated. In particular, life-long VIT should be considered for individuals with inherited or acquired risk factors.

Finally, when considering the extent of exposure, the differences in beekeepers' status (professional or hobbyist) may also affect the outcome. As only one study included professional beekeepers (17), it would be intriguing to investigate potential differences between these two groups in future research. Moreover, an important knowledge gap is the lack of information regarding the location of hives (i.e., in a rural or urban environment). Urban beekeeping considerations are essential for public safety, as the estimated prevalence of self-reported SAR to *Hymenoptera* venom among individuals living in close proximity to beehives remains unreported (11).

For future cross-sectional studies, detailed reporting of study design, settings, study participants, and the use of validated questionnaires should be employed to ensure high-quality assessment of the observed health outcomes. In order to reduce the overestimation of the self-reported data, the observed health outcomes should be confirmed by an allerogologist. In terms of data collection, comprehensive reporting of health outcomes should include essential elements such as the classification system used (e.g., Müller grading system), grade of SAR, identified culprit *Hymenoptera* species, type and number of bees causing AR, and the prevalence period. Standardizing these parameters will enhance data uniformity, completeness, and comparability across studies. Statistical analyses should employ multivariate regression models to control for potential confounders effectively. Furthermore, distinguishing between family members and first-degree relatives (parents, children, siblings) will provide valuable insights into the heritable risks associated with SAR.

4.1 Limitations and strengths

The quality of our work is subject to several limitations, primarily stemming from the high heterogeneity in self-reported data among the included studies and a high RoB. Additionally, the predominant reliance on Turkish data in more than half of the eligible publications, along with the absence of data about the beekeepers' status, raises concerns about the generalizability of these findings. Therefore, caution is needed when interpreting the results, especially considering the exclusion of clinical studies from our analysis. Specifically, the lack of conformity between self-reported SAR to bee venom observed by beekeepers and verification by physicians suggests potential overestimation, particularly for mild/moderate SAR (grades I-II).

Moreover, the meta-analysis was conducted on cross-sectional studies, thereby limiting the ability to infer causality or temporal relationships. Additionally, our study was constrained by the small number of available studies, which is reflected in the very wide confidence intervals of the reported estimates. However, our research was able to clearly distinguish between the one-year and lifetime prevalence of self-reported SAR to bee venom, thereby explaining much of the variability in the results. Consequently, individual forest plots included only three, four or five studies. We acknowledge that some of the studies are of poor quality, with inadequate reporting. However, the estimates provide valuable indicative trends that can guide further research and highlight areas where larger, better designed, and more comprehensive studies are needed. For public health professionals and policymakers, even these unstable estimates can raise awareness about the significance of SAR among beekeepers, prompting preliminary guidelines and interventions aimed at mitigating risks until more robust data become available.

Nonetheless, our study's main strength lies in its rigorous methodology. It included comprehensive searches across seven electronic databases without language or publication date restrictions, adhering to PRISMA 2020 guidelines. We made extensive efforts to obtain additional information from the authors, not available in the original articles, and used a JBI algorithm with predetermined criteria, facilitating objective quality assessments. Moreover, we identified methodological aspects warranting improvement in future research, which will help mitigate potential sources of bias and enhance the robustness of estimates. By identifying research gaps and exploring the major sources of heterogeneity across the included studies, our findings could contribute to a more comprehensive understanding of the existing research limitations in this field of science.

CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

FUNDING

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ETHICAL APPROVAL

The method used in this systematic review involves no ethical issues, hence no ethical approval was needed.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study can be obtained upon request from the corresponding author.

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