MS. YICHAO WANG (Orcid ID : 0000-0002-1166-3796)

PROF. KATRINA J ALLEN (Orcid ID : 0000-0002-1921-4493)

DR. JENNIFER KOPLIN (Orcid ID : 0000-0002-7576-5142)

Article type : Review

Allergy

The global incidence and prevalence of anaphylaxis in children in the general population: a systematic review

Yichao Wang[1,2], Katrina J. Allen[1,2,3], Noor H.A. Suaini[1,2], Vicki McWilliam[1,2,3], Rachel L.Peters[1,2], Jennifer J. Koplin[1,4]

Affiliations:

[1] Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Victoria, 3052, Australia.

[2] Department of Paediatrics, University of Melbourne, Victoria, 3010, Australia.

[3] The Department of Allergy and Immunology, Royal Children's Hospital, Melbourne, Victoria, 3010, Australia.

[4] The School of Population and Global Health, University of Melbourne, Victoria, 3010, Australia.

Corresponding author:

Dr Jennifer Koplin, PhD

Murdoch Children's Research Institute

Royal Children's Hospital, Flemington Road Parkville Victoria 3052 Australia

Telephone: +61 3 83416236

Email: jennifer.koplin@mcri.edu.au

Word count – 3743

Abstract

Word count – 242

Background

Despite an increasing number of publications from individual countries and regions, there is still no systematic review of the global epidemiology of anaphylaxis in the general paediatric population.

Methods

We conducted a systematic review, using a protocol registered and published with the international prospective register of systematic reviews (PROSPERO). Results were reported following PRISMA guidelines. The search strategy was designed in Medline (ovid) and modified for Embase (ovid) and PubMed. Papers were screened by two independent reviewers following selection and exclusion criteria. Data extraction and risk of bias assessment were completed by the same two reviewers. Studies in adults only or those that did not report data in children separately were excluded.

Results

A final total of 59 articles were included. Of these, 5 reported cumulative incidence, 39 reported incidence rate and 17 reported prevalence data. The incidence of anaphylaxis in children worldwide varied widely, ranging from 1 to 761 per 100,000 person-years for total anaphylaxis and 1 to 77 per 100,000 person-years for food-induced anaphylaxis. The definition of anaphylaxis from NIAID/FAAN was the most commonly used. Gender and ethnicity were demographic risk factors associated with anaphylaxis in children. Increasing total or food-induced anaphylaxis incidence over time were reported by 19 studies.

Conclusion

The reported incidence of anaphylaxis in children varied widely. Studies in developing countries are underrepresented. To accurately compare anaphylaxis incidence between countries and investigate the time trends, further studies using a standardised definition across different countries are required.

Keywords:

Anaphylaxis, epidemiology, paediatrics

Abbreviations:

ASCIA: Australasian Society of Clinical Immunology and Allergy, ED: emergency department, FIA: food-induced anaphylaxis, NIAID/FAAN: National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network,

Introduction:

Anaphylaxis is a serious and rapid onset allergic reaction with the involvement of multiple body systems that can lead to death[1]. In 2015, Tejedor-Alonso reported an increase in both the number and quality of studies on the epidemiology of anaphylaxis over the past 10 years[2]. An increase in hospital presentation rates for anaphylaxis has been reported in western countries such as Canada[3], Finland, Sweden[4], Australia[5], the United Kingdom[6,7] and the United States[8] using data from hospital administrative and national healthcare databases. Emerging studies from Asian regions also show a rising anaphylaxis incidence in South Korea[9] and Hong Kong[10] using national insurance claims data and hospital admission databases, respectively.

A previous systematic review in 2013 by Panesar et al[11] summarized the epidemiology of anaphylaxis in Europe, but there has been no systematic review of anaphylaxis outside of Europe, and several additional studies published since late 2012 were not included in this review. Another systematic review in 2015 by Umasunthar et al reported the risk of food-induced anaphylaxis in patients with food allergy, but not in a general population and not including other non-food triggers of anaphylaxis[12]. By only reporting anaphylaxis among patients with a previous diagnosis of food allergy, patients who presented with anaphylaxis as their first food reaction might have been missed. A detailed description of the epidemiology of anaphylaxis worldwide using the latest data could help us better understand and compare the overall disease burden caused by anaphylaxis in different regions. Additionally, some

countries are challenged by the fact that it is expensive and time consuming to estimate food allergy prevalence using the gold standard method of oral food challenge. As previous studies have shown that food was the most frequent trigger of anaphylaxis in children[6,13], food-related anaphylaxis in children could be a good proxy for food allergy in those countries without convincing food allergy information although it may underestimate food allergy prevalence[10]. Finally, by comparing the risk of anaphylaxis in children by subgroups, we could obtain better insights into the aetiology and risk factors of anaphylaxis.

Despite an increasing number of publications from individual countries and regions, there is still no systematic review on the global epidemiology of anaphylaxis at any age. The absence of a systematic review in the paediatric population is problematic because this is where there is a dramatic rise in hospital admission rates for food-induced anaphylaxis[14]. Although incidence is the most adequate and frequently used measurement of anaphylaxis in general population, prevalence is also reported in studies and can be used as a complementary method[2]. Hence, we aim to describe the current epidemiology of anaphylaxis including incidence, prevalence and eliciting triggers among children in the general population worldwide, and to investigate whether there was evidence of changing time trends of anaphylaxis and whether this differed by region.

Methods:

The protocol of this systematic review has been registered and published with the international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016042080). We followed the PRISMA guidelines to report our results[15].

Search strategy

The search strategy was formed following terms and methods from previous studies[12,16], designed in Ovid MEDLINE and modified for Embase and PubMed. Although Medline and PubMed are essentially the same databases, we included both in our search strategy as PubMed includes e-publications and additional journals that were not included in Medline. Our search strategy was developed in conjunction with a librarian from the Royal Children's Hospital, Melbourne. The exact search strategies for Ovid MEDLINE, Embase and PubMed are outlined in Online Repository Table S1. The search was conducted in the above databases on 19th September 2018. The reference lists of identified paper were reviewed for additional studies. We included only published literature that has undergone peer review in our

systematic review, however, we also reviewed conference abstracts during the screening process to retrieve in-progress publications. Other source of literature were not considered in our study.

Study Selection

Identified articles were independently screened via titles and abstracts according to the selection and exclusion criteria by two reviewers (YW and NS). Screening results from two reviewers were compared. Discrepancies were resolved by reading of the full-text and discussions between the two reviewers. Reference lists of identified studies were reviewed for additional studies. Finally full-text review was undertaken by the same reviewers for all identified articles. Discrepancies were resolved by discussions between the two reviewers, if necessary, a third reviewer (JK) arbitrated.

The screening process was developed and piloted by YW. To pilot the title and abstract screen, the first 50 manuscripts were screened by title and abstract using EndNote X7, then the full text was retrieved to ensure that the initial screen had not missed any potentially relevant articles. The full text screening process was tested on 10 manuscripts. These manuscripts were labelled by YW after reading the full text and were checked again to make sure the articles had been assigned to the correct label. Then the results were discussed with NS to ensure all relevant articles had been included. Both YW and NS followed the same screening process.

Inclusion criteria were as follows:

- Original observational studies, including cross-sectional studies, cohort studies, registries (prospective/retrospective/historical cohort design) and hospital databases;
- Studies reporting the incidence and/or prevalence of anaphylaxis in a general population or studies reporting hospital and/or emergency department (ED) admission rate by using the total population in the catchment area as the denominator;
- Studies were conducted in children. Studies conducted in the whole population (adults and children) were included if they provided a breakdown by age groups, with results for children reported separately.

Exclusion criteria were as follows:

- Systematic and non-systematic reviews, non-research letters, case reports, randomized controlled trials, comments and editorials;
- Studies reporting anaphylaxis rates in patients with specific diseases (including allergic disorders) or under specific condition (e.g. anaesthesia, immunization);
- Studies did not state age group of participants or did not provide incidence or prevalence data in children separately or studies reporting hospital and/or emergency department (ED) admission rate by using the number of patients admitted as the denominator;
- Studies reporting food-dependent exercise-induced anaphylaxis only.

Risk of bias assessment

Risk of bias of included studies was assessed independently by two reviewers (YW and VM) using 10 questions assessing both external and internal validity modified from the risk of bias tool established by Hoy et.al[17].

Data extraction

Data from included articles were extracted by two reviewers (YW and VM) using the same extraction form. Any discrepancy was resolved by checking original articles and discussion. We also contacted authors of original studies to request original incidence data in children if these were not provided. Of 7 authors contacted, 2 authors[18,19] replied with the requested information and these data were included in our review. We summarized the reference details, such as study design, study population, data sources, extracted data type, denominator, data collection years, country, age of target population, definition of anaphylaxis and outcome confirmation, reported type of anaphylaxis, risk of bias, numerator of incidence and response rate of included studies. Incidence (including cumulative incidence, incidence rate and admission rate) and prevalence estimates with 95% confidence intervals (CI) of anaphylaxis for each year and/or time period were extracted. In our review, studies that reported hospital and/or emergency department (ED) admission rate of anaphylaxis per 100,000 person-years were considered as a measure of incidence if they used the total population in the catchment area as the denominator. The number of cases and person-time at risk or size of sample population were also extracted if the incidence or prevalence was not provided. Incidence rate ratios were calculated based on extracted data to assess the association between demographic factors (e.g. sex and ethnicity) and anaphylaxis where possible. Other risk ratio results (e.g.

odds ratio) reported by the studies was extracted directly if there was not enough original data to calculate incidence rate ratios.

Outcomes

In our systematic review, the main outcomes of interest were the incidence and/or prevalence of anaphylaxis in children in the general population. Incidence included incidence rate and cumulative incidence. Incidence is defined as the number of new cases of anaphylaxis that occur during a given time period in a defined population[11]. Most studies of hospital admissions data claimed to report anaphylaxis incidence, but did not state whether they only included new cases/first onset of anaphylaxis. For this review, we included these studies under the heading of incidence. Incidence is reported as incidence rate (IR) and cumulative incidence (CI):

$$Incidence\ rate\ (IR) = \frac{\text{Number of people who developed anaphylaxis}}{\text{Number of person} - \text{years when people were at risk of developing anaphylaxis}}$$

$$Cumulative\ incidence\ (CI) = \frac{\text{Number of people who developed anaphylaxis in a specified period}}{\text{Number of people at risk of developing anaphylaxis at the start of the period}}$$

Prevalence estimates what proportion of a population has a history of anaphylaxis at a specific point in time[20] and is calculated as follows:

$$Prevalence = \frac{\text{Number of people with a history of anaphylaxis at a given point in time}}{\text{Total number of people in the population}}$$

Data synthesis and analysis

Incidence rate, cumulative incidence or prevalence estimates were extracted where available, or calculated from available data if these estimates were not provided in the paper. A random effects model using the method of Der Simonian and Laird was applied for the meta-analysis. The heterogeneity was estimated by the Mantel-Haenszel model. We use I-squared statistic to examine and quantify between-study heterogeneity. Very high heterogeneity was found in all analyses. The I-squared statistic was above 95% for all primary and subgroup analyses. According to the Cochrane handbook, if substantial heterogeneity (*I-square* > 50%) is found, pooling data using meta-analysis is not recommended[21]. Hence, we have not pooled the results. There is no limitation of anaphylaxis definition used for including studies. We

performed sensitivity analyses to examine the effect of using different definitions of total anaphylaxis and food-induced anaphylaxis on our results.

To assess gender differences, we calculated incidence rate ratios (IRR) and 95% confidential intervals (CI) using Poisson regression models. Statistical analyses were undertaken using STATA 15 (Stata Corp, College Station, TX, USA).

Results

Study selection

Figure 1 outlines the search results and results of the article screening. We identified 3997 original references from 3 databases after removing duplicates and additional articles from the reference lists of identified paper. Title and abstract review excluded 3813 articles as they did not meet the inclusion criteria. The remaining 184 articles underwent full-text screening. A final total of 59 articles were included in the qualitative synthesis and 4 of them were excluded from quantitative analysis as they only reported anaphylaxis incidence in children in their figures. Among the included studies, 42 of them reported anaphylaxis incidence, 15 of them reported anaphylaxis prevalence, 2 studies reported both anaphylaxis incidence and prevalence.

Study characteristics and risk of bias

The main characteristics of the studies are listed in Table 1. Of the included studies, seventeen only measured and reported total anaphylaxis, nineteen studies only reported food-induced anaphylaxis and nineteen studies measured total anaphylaxis and also reported anaphylaxis separately by specific triggers. The remaining four studies measured only anaphylaxis induced by hen's egg, peanut, hazelnut and drugs specifically.

The risk of bias assessment results are listed in online Table S2. High risk of bias was found in 2 (3.4%) study, moderate risk in 8 (13.6%) and low risk of bias in 49 (83.1%) studies.

The majority of studies (42/44) reporting anaphylaxis incidence were conducted based on registry databases and most (34/42) were from hospital and/or ED admission databases. Only two studies were conducted in population-based birth cohorts. Only a minority of studies (12/44) stated that only first onset anaphylaxis episodes were used to calculate incidence. Most of studies (12/17) that reported anaphylaxis prevalence were cross-sectional studies and more than half (8/12) were conducted in a school environment. Among these studies, nine

had a participation rate above 70%, six between 50 and 70%, and two below 50% or unknown.

The age of the study population varied in included studies, from 0 to 90 years of age, although only data from children was included in this study. The data collection period of studies was also different, from 1995 to 2016.

Anaphylaxis in children by trigger

The incidence of anaphylaxis in children by trigger is shown in Figure 2a. Of 44 studies, 29 reported total anaphylaxis with a wider incidence range of 1 to 761 per 100,000 person-years, 17 reported incidence of food-induced anaphylaxis, ranging from 1 to 77 per 100,000 person-years and 6 reported incidence of drug-induced anaphylaxis, with range between 0.3 and 10.6 per 100,000 person-years. The incidence of anaphylaxis triggered by other agents such as insect, anaesthesia, venom, serum and individual foods (peanut, nuts, fruit, milk, seafood and egg) are also depicted in the figure. Anaphylaxis induced by individual food triggers had higher incidence (0.1 to 9.7 per 100,000 person-years) compared with insect, anaesthesia and serum triggers.

The prevalence of anaphylaxis by trigger is listed in Figure 2b. Prevalence estimates for total anaphylaxis ranged from 0.04% to 1.8% (four studies). The prevalence of food-induced anaphylaxis ranged from 0.3% to 1.2% (ten studies).

Total and food-induced anaphylaxis in children by definition of anaphylaxis

The incidence of total and food-induced anaphylaxis in children stratified by definition of anaphylaxis is shown in Figure 2c and Figure 2d. The definition from NIAID/ FAAN was the most widely applied definition in included studies (n=17) although 17 studies relied on ICD-9/ICD-10 codes alone to define anaphylaxis.

Total and food-induced anaphylaxis in children by region

Figure 2e and Figure 2f summarize the incidence of total anaphylaxis and food-induced anaphylaxis by region. Most studies were from Europe (n=16), followed by America (n=10) and Oceania (n=5). Additionally, 5 studies from Asia reported a lower incidence of total and food-induced anaphylaxis in children. The range for total anaphylaxis incidence in studies from Europe was between 2.3 and 761 per 100,000 person-years, and in America was between 0.8 and 70 per 100,000 person-years. Incidence of food-induced anaphylaxis was

higher in studies from Europe (from 1.4 to 76.7 per 100,000 person-years) compared with studies from other regions.

Figure 3 shows countries with available data on anaphylaxis incidence or prevalence. The United States, Chile, Spain, Finland, Italy, Singapore, New Zealand and countries from Europrevall study (UK, the Netherlands, Germany, Poland, Lithuania, Spain, Italy and Greece) reported anaphylaxis incidence in children, while Mexico, Portugal, Turkey, Germany and Thailand reported anaphylaxis in children using prevalence. The United Kingdom, China (Hong Kong SR), Denmark, Sweden, South Korea and Australia have provided both incidence and prevalence information of anaphylaxis in children.

Demographic factors associated with anaphylaxis (male gender, and ethnicity)

Eleven studies reported incidence rate of anaphylaxis by gender as shown in online Table S4. Boys had a higher incidence rate of total anaphylaxis than girls based on results from studies by Wang et al. and Bohlke et al. ($P < 0.001$, IRR=1.31, 95%CI: 1.10-1.55). Boys under 10 years of age had higher risk of anaphylaxis incidence than girls. However, as the children grew older (≥10 years), girls tended to have a comparable or even higher rate of anaphylaxis compared with boys.

A study published recently explored the association between anaphylaxis and ethnicity and found South Asian children living in the UK were more likely to have anaphylaxis compared with white children living in the UK (OR: 2.37, 95%CI 1.83-2.90)[22]. Another study in the USA reported the rates of hospital presentation due to food-induced anaphylaxis was highest in Asian children, followed by black children, white children and then Hispanic children[23]. The study in New Zealand also found paediatric food-induced anaphylaxis hospital presentations were highest in Asian children, followed by Pacific people[24].

Time trends of anaphylaxis in included studies

Increasing anaphylaxis incidence over time was reported by studies from the United States[25,26], Spain[18], Australia[5,27,28], Denmark[29], South Korea[30], Hong Kong[31] Finland and Sweden[4] for total anaphylaxis, and from UK[6], Spain[18], Italy[19,32,33], Australia[5,27], Hong Kong[31], New Zealand[24], Sweden[34] and United States[23,35,36] for food-induced anaphylaxis. The incidence of total anaphylaxis and food-induced anaphylaxis for available years from 1990 to 2013 were extracted from these studies and are shown in online Figure S1 and online Figure S2.

Studies by Bohlke et al., Lee et al. (not shown in the figure as data was not available) and Hoyos-Bachiloglu et al. (not shown in the figure as data was not available) reported no significant increase in total anaphylaxis incidence during 1991-1997 in western Washington State, USA[37], during 2001-2010 in Olmsted County, USA[38] and during 2001-2010 in Chile[39].

Discussion

This systematic review identified 59 studies measuring incidence and prevalence of anaphylaxis from more than 20 countries located in four continents. Seventeen studies reported incidence or prevalence of total anaphylaxis and did not distinguish by sub-type of anaphylaxis triggers. In childhood, male gender was associated with a higher incidence of anaphylaxis. Increasing trends of total anaphylaxis or food-induced anaphylaxis incidence between 1990 and 2013 were reported by 18 studies, while three studies did not find an increase in anaphylaxis incidence over a similar time period.

Our review is the first study to investigate worldwide anaphylaxis data in children in the general population up to 2018 using a robust systematic review methodology. We stratified the incidence and prevalence of anaphylaxis in children by triggers, definitions, regions and time trends. However, we are unable to provide a single overall estimate of anaphylaxis for children worldwide according to the Cochrane handbook because the heterogeneity in our results was high (*I-square* > 95%)[21]. It is difficult to compare between studies due to differences in study design, anaphylaxis definitions, and the regions and years in which the study was conducted. To explore potential sources of the observed heterogeneity, we conducted sub-group analyses e.g. by anaphylaxis definition, region, and study design, however substantial heterogeneity remained (*I-square* > 90% in all sub-groups). Even among studies that used the same definitions of anaphylaxis, misclassification is possible and could affect the estimates. Since most of the studies reporting anaphylaxis incidence were registry or hospital admission databases, the characteristics of the databases will affect the estimates. Given that food allergy prevalence and triggers vary by region it is likely that anaphylaxis prevalence and triggers would vary by region too[40,41]. An additional factor that could affect incidence of anaphylaxis, which was not measured in most of the included studies, is the presence of coexisting conditions such as asthma. A limitation of the publications identified by our systematic review was the use of hospital databases which rely on both optimal recognition by clinicians and optimal coding by database staff which may be challenging in a busy hospital setting. When hospital presentation of anaphylaxis is used as the proxy of

anaphylaxis incidence, it would be more reliable if patient signs and symptoms were also captured so that cases could be confirmed and validated using standardised objective criteria. Another limitation was that some of the studies which asserted to report incidence of anaphylaxis did not state whether the cases in the numerator were new cases or repeat admissions. Overestimation of anaphylaxis incidence (new cases only) in these studies was possible because some children might be counted more than once. It is important to differentiate whether the reported cases were first onset or not. Including the first onset of anaphylaxis estimates the incidence of anaphylaxis i.e. new cases of anaphylaxis, whereas including all occurrences of anaphylaxis without differentiating whether the anaphylactic reaction was first or subsequent reactions would estimate the rate. Interpreting the rate as anaphylaxis incidence, and counting some anaphylaxis patients more than once, may overestimate the true incidence. We conducted a subgroup analysis including only studies that specified that they used first onset anaphylaxis as the numerator, however few studies made this distinction (n=9) and there was still substantial heterogeneity between studies (*I-Square* = 100%, $p < 0.001$). Additionally, among those studies reporting hospital presentations of anaphylaxis, different patient groups were included, such as outpatients, hospitalized patients and/or ED patients. Furthermore, time trends of anaphylaxis incidence in our review could only be shown in individual studies rather than by combining results because of the limited number of studies that provided the risk data for each year and also the high heterogeneity of these studies.

The range of total anaphylaxis incidence in our review (from 1 to 761 per 100,000 person-years) was wider than the range reported (range 1.5-32 per 100,000 person-years) by Panesar in their systematic review of European studies in 2013[11]. The highest incidence of total anaphylaxis (761 per 100,000 person-years) was reported in Sweden by Vetander et al. using parent-reported questionnaire in a population-based birth cohort[42]. There could be overestimation in the study by Vetander et al. due to the reliance on parent-report, although they defined anaphylaxis according to symptoms recorded in the questionnaire using NIAID/FAAN criteria. Their study was not included in any previous systematic reviews because it was only published in 2016. Their study was also the only one among included studies that reported anaphylaxis estimates based on parent-reported survey. We did a sensitivity analysis removing this study to investigate the heterogeneity in the remaining subset and still observed a high heterogeneity (*I-square* > 95%, $p < 0.001$) by using random effects model.

Panesar et al. performed a meta-analysis of anaphylaxis prevalence, reporting a pooled anaphylaxis prevalence of 0.3%[11]. However, there was significant heterogeneity (*I-square* = 94.6%, p<0.0001) in their meta-analysis, and it was based on only three studies. We chose not to present a pooled estimate due to the limited number of comparable studies, referring to studies undertaken applying the same definition within the same trigger from same region.

In our review, we found evidence of an association between gender and ethnicity and risk of anaphylaxis, consistent with previous individual studies[43]. Relationships between ethnicity and risk of food allergy have also been reported by previous studies. Children with Asian ethnicity who were born in Australia were reported to have higher risk of eczema, egg allergy and peanut allergy compared with children of other ethnicities[44,45]. Similar to food allergy, our systematic review also identified a higher risk of anaphylaxis in children with Asian ethnicity compared with other ethnicity from 3 studies[22-24].

The incidence and prevalence reported in this systematic review provide us with improved clarity about anaphylaxis, including its frequency in several specific subgroups by trigger, definition and region. However, high heterogeneity (*I-square* > 90%) limits our interpretation of an overall incidence and prevalence. Studies in developing countries are also underrepresented. Future studies across different countries using a consistent, accurate definition of anaphylaxis and using the correct epidemiological method to define incidence and prevalence would help to identify any true difference between countries, and help to provide an overall estimate of prevalence.

Acknowledgements

We would like to acknowledge Miguel A. Tejedor-Alonso and Roberto Berni Canani for replying and sharing their original data with us. We acknowledge Poh Chua from the Royal Children's Hospital for her help with developing and revising the search strategy for this review. The authors also would like to acknowledge Jing Wang for her suggestions on this study.

Funding

YW was supported by the Melbourne International Research Scholarship (MIRS) and Melbourne Internal Fee Remission Scholarship (MIFRS) from The University of Melbourne

and MCRI Top-up Scholarship from Murdoch Children's Research Institute. Noor H.A. Suaini's PhD scholarship was funded by National Health and Medical Research Council of Australia (NHMRC) funded Centre for Food and Allergy Research (CFAR).

Author contributions

YW, JK and KA conceived this review. The review was undertaken by YW, NS and VM. JK, KA and RP helped YW with the data analysis and interpretation of data. YW led the drafting of the manuscript. All authors critically commented on the drafts of manuscript and finally approve this version to be published.

Conflicts of interest

The authors have no conflict of interest to declare.

References

1. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 2006;117(2):391-397.
2. Tejedor-Alonso MA, Moro-Moro M, Mugica-Garcia MV. Epidemiology of Anaphylaxis: Contributions From the Last 10 Years. *J Investig Allergol Clin Immunol.* 2015;25(3):163-175; quiz follow 174-165.
3. Hochstadter E, Clarke A, LaVieille S, et al. C-care: Comparing two years of anaphylaxis in a Canadian pediatric emergency department. *Paediatrics and Child Health (Canada).* 2014;19 (6):e105.
4. Kivisto JE, Protudjer JLP, Karjalainen J, Wickman M, Bergstrom A, Mattila VM. Hospitalizations due to allergic reactions in Finnish and Swedish children during 1999-2011. *Allergy: European Journal of Allergy and Clinical Immunology.* 2016;71(5):677-683.

5. Mullins RJ, Dear KB, Tang ML. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. *The Journal of allergy and clinical immunology.* 2015;136(2):367-375.
6. Turner PJ, Gowland MH, Sharma V, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *The Journal of allergy and clinical immunology.* 2015;135(4):956-963.e951.
7. Sheikh A, Hippisley-Cox J, Newton J, Fenty J. Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England. *Journal of the Royal Society of Medicine.* 2008;101(3):139-143.
8. Lee S, Hess EP, Lohse C, Gilani W, Chamberlain AM, Campbell RL. Trends, characteristics, and incidence of anaphylaxis in 2001-2010: A population-based study. *J Allergy Clin Immunol.* 2017;139(1):182-188 e182.
9. Yang MS, Kim JY, Kim BK, et al. True rise in anaphylaxis incidence: Epidemiologic study based on a national health insurance database. *Medicine (Baltimore).* 2017;96(5):e5750.
10. Wang Y, Koplin JJ, Ho MHK, Wong WHS, Allen KJ. Increasing hospital presentations for anaphylaxis in the pediatric population in Hong Kong. *The journal of allergy and clinical immunology In practice.* 2018;6(3):1050-1052 e1052.
11. Panesar SS, Javad S, de Silva D, et al. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy.* 2013;68(11):1353-1361.
12. Umasunthar T, Leonardi-Bee J, Turner PJ, et al. Incidence of food anaphylaxis in people with food allergy: a systematic review and meta-analysis. *Clin Exp Allergy.* 2015;45(11):1621-1636.
13. Grabenhenrich LB, Dolle S, Moneret-Vautrin A, et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. *J Allergy Clin Immunol.* 2016;137(4):1128-1137 e1121.
14. Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. *J Allergy Clin Immunol.* 2009;123(2):434-442.
15. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.
16. Panesar SS, Nwaru BI, Hickstein L, et al. The epidemiology of anaphylaxis in Europe: protocol for a systematic review. *Clin Transl Allergy.* 2013;3(1):9.

17. Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol.* 2012;65(9):934-939.
18. Tejedor-Alonso MA, Moro-Moro M, Mosquera Gonzalez M, et al. Increased incidence of admissions for anaphylaxis in Spain 1998-2011. *Allergy: European Journal of Allergy and Clinical Immunology.* 2015;70(7):880-883.
19. Parekh D, O'Hickey S, Nocerino R, Leone L, Cosenza L, Berni Canani R. Increasing rate of hospitalizations for food-induced anaphylaxis in Italian children: An analysis of the Italian Ministry of Health database. *Allergy.* 2015;135(3):833-835.e833.
20. Penny Webb CBaSP. *Essential epidemiology: an introduction for students and health professionals.* Cambridge university press; 2005.
21. Ryan R; Cochrane Consumers and Communication Review Group. 'Heterogeneity and subgroup analyses in Cochrane Consumers and Communication Group reviews: planning the analysis at protocol stage. http://cccrg.cochrane.org, December 2016. Accessed July 1, 2018.
22. Buka RJ, Crossman RJ, Melchior CL, et al. Anaphylaxis and ethnicity: Higher incidence in British South Asians. *Allergy: European Journal of Allergy and Clinical Immunology.* 2015;70(12):1580-1587.
23. Dyer AA, Lau CH, Smith TL, Smith BM, Gupta RS. Pediatric emergency department visits and hospitalizations due to food-induced anaphylaxis in Illinois. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology.* 2015;115(1):56-62.
24. Speakman S, Kool B, Sinclair J, Fitzharris P. Paediatric food-induced anaphylaxis hospital presentations in New Zealand. *J Paediatr Child Health.* 2018;54(3):254-259.
25. Wright BL. Anaphylaxis and epinephrine in North Carolina public schools. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology.* 2015;115(1):75-77.
26. Lin RY, Anderson AS, Shah SN, Nurruzzaman F. Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990 -2006. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology.* 2008;101(4):387-393.
27. Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993-1994 to 2004-2005. *The Journal of allergy and clinical immunology.* 2007;120(4):878-884.

28. Andrew E, Nehme Z, Bernard S, Smith K. Pediatric Anaphylaxis in the Prehospital Setting: Incidence, Characteristics, and Management. *Prehosp Emerg Care.* 2018;22(4):445-451.
29. Jeppesen AN, Christiansen CF, Froslev T, Sorensen HT. Hospitalization rates and prognosis of patients with anaphylactic shock in Denmark from 1995 through 2012. *J Allergy Clin Immunol.* 2016;137(4):1143-1147.
30. Yang MS, Kim JY, Kim BK, et al. True rise in anaphylaxis incidence. *Medicine (United States).* 2017;96 (5) (no pagination)(00033).
31. Wang Y, Koplin JJ, Ho MHK, Wong WHS, Allen KJ. Increasing hospital presentations for anaphylaxis in the pediatric population in Hong Kong. *Journal of Allergy and Clinical Immunology: In Practice.* 2018;6(3):1050-1052.e1052.
32. Canani RB, Nocerino R, Terrin G, Leone L, Troncone R. Hospital admissions for food-induced anaphylaxis in Italian children. *Clinical and Experimental Allergy.* 2012;42(12):1813-1814.
33. Calvani M, Di Lallo D, Polo A, Spinelli A, Zappala D, Zicari AM. Hospitalizations for pediatric anaphylaxis. *International journal of immunopathology and pharmacology.* 2008;21(4):977-983.
34. Osterlund J, Winberg A, West CE. A 10-year review found increasing incidence trends of emergency egg allergy reactions and food-induced anaphylaxis in children. *Acta Paediatrica, International Journal of Paediatrics.* 2018.
35. Michelson KA, Hudgins JD, Burke LG, et al. Trends in Severe Pediatric Emergency Conditions in a National Cohort, 2008 to 2014. *Pediatr Emerg Care.* 2018;16:16.
36. Okubo Y, Nochioka K, Testa MA. Nationwide Survey of Hospitalization Due to Pediatric Food-Induced Anaphylaxis in the United States. *Pediatr Emerg Care.* 2018;14:14.
37. Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *The Journal of allergy and clinical immunology.* 2004;113(3):536-542.
38. Lee S, Hess EP, Lohse C, Gilani W, Chamberlain AM, Campbell RL. Trends, characteristics, and incidence of anaphylaxis in 2001-2010: A population-based study. *Journal of Allergy and Clinical Immunology.* 2017;139(1):182-188.e182.
39. Hoyos-Bachiloglu R, Morales PS, Cerda J, et al. Higher latitude and lower solar radiation influence on anaphylaxis in Chilean children. *Pediatric allergy and*

immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2014;25(4):338-343.

40. Nwaru BI, Hickstein L, Panesar SS, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy.* 2014;69(8):992-1007.
41. Koplin JJ, Wang, Y. The epidemiology of food allergy. *Curr Pediatr Rep* 2016;4(2016):117-128.
42. Vetander M, Protudjer JLP, Lilja G, et al. Anaphylaxis to foods in a population of adolescents: incidence, characteristics and associated risks. *Clinical and Experimental Allergy.* 2016;46(12):1575-1587.
43. Koplin JJ, Martin PE, Allen KJ. An update on epidemiology of anaphylaxis in children and adults. *Curr Opin Allergy Clin Immunol.* 2011;11(5):492-496.
44. Martin PE, Koplin JJ, Eckert JK, et al. The prevalence and socio-demographic risk factors of clinical eczema in infancy: a population-based observational study. *Clinical and Experimental Allergy.* 2013;43(6):642-651.
45. Koplin JJ, Peters RL, Ponsonby AL, et al. Increased risk of peanut allergy in infants of Asian-born parents compared to those of Australian-born parents. *Allergy.* 2014;69(12):1639-1647.

Legends of Figures

Figure 1. PRISMA diagram of literature search and study selection

Figure 2a. Incidence of anaphylaxis in children by trigger

Figure 2b. Prevalence of anaphylaxis in children by trigger

Figure 2c. Incidence of total anaphylaxis in children by definition

Figure 2d. Incidence of food-induced anaphylaxis in children by definition

Figure 2e. Incidence of total anaphylaxis in children by region

Figure 2f. Incidence of food-induced anaphylaxis in children by region

Figure 3. Map of countries that reported the incidence and/or prevalence of anaphylaxis in children.

Table 1. Summary of the characteristics of studies included

Studies reported incidence												
Study ID	**Study Design**	**Study Population**	**Data source characteristic**	**Extracted data type (original reported type in the study)**	**Denominator (population)**	**Data collection years**	**Country**	**Age of study population**	**Definition of anaphylaxis and outcome confirmation**	**Reported type of anaphylaxis**	**Risk of bias**	**Numerator of incidence**
Andrew, E. 2018	Registry	Paediatric patient from emergency medical services (EMS)	EMS is a state-wide provider in Victoria	Incidence rate (incidence)	Victorian population in relevant year and the population in 2001 as the standard population	01/07/2008-30/06/2016	Australia	0-16 years	NIAID/FAAN equivalent (patients with a sudden onset of two or more of: respiratory distress, abdominal symptoms, skin/ mucosal symptoms or hypotension); patients received emergency treatment with epinephrine	Total anaphylaxis and specific agents triggered anaphylaxis	Low	NA
Michelson, K. A. 2018	Registry	Children from ED visits	Nationwide Emergency Department Sample (NEDS)	Incidence rate (incidence)	National population estimates	01/01/2008-31/12/2014	United States	0-18 years	NA; serious diagnosis	Total anaphylaxis (only)	Low	NA
Okubo, Y. 2018	Registry	Hospitalization patients (inpatient) for anaphylaxis, not include ED patients	National representative Kids' Inpatient Database (KID), National estimates of hospitalizations	Incidence rate (hospitalization rate)	Not mentioned	2006, 2009, 2012	United States	0-20 years	ICD-9 (995.6x); Primary diagnoses for hospitalization discharge records	Only food-induced anaphylaxis	Low	NA

			was calculated using discharge-level weight variables (DISCWT)									
Osterlund, J. 2018	Registry	Children presented to Umea University hospital	Paediatric emergency visits to Umea University hospital in Vasterbotten county, Sweden	Cumulative incidence (hospitalization rate)	Population data from Statistics Sweden	01/01/2006-31/12/2015	Sweden	0-18 years	NIAID/FAAN; ICD-10 diagnostic code	Only food-induced anaphylaxis	Low	NA
Speakman, S. 2018	Registry	Paediatric ED presentations from public hospital for food-induced anaphylaxis	Routine coded discharge data from the Ministry of Health's National Minimum Dataset (NMDS)	Incidence rate (admission rate)	Population data from NZ census	01/01/2006-31/12/2015	New Zealand	0-14 years	ICD-10 (T78.0, T78.2) ; First two diagnostic fields	Only food-induced anaphylaxis	Low	NA
Wang, Y. 2018	Registry	Hospital and ED admission for anaphylaxis in paediatric population	Clinical Data Analysis and Reporting System coving records for all public hospitals in Hong Kong, coving 78% of total inpatients	Incidence rate (incidence)	Population estimated from Centre for Health Protection, Department of Health, Hong Kong SAR.	01/07/2001-30/06/2015	Hong Kong, China.	0-18 years	ICD-9 (995.0, 995.60-995.69); Diagnosis codes	Total anaphylaxis and specific agents triggered anaphylaxis	Low	Yes, first onset

Ruiz Oropeza, A. 2017	Registry	All patients seen at the ED and the Acute Paediatric Ward (APW), Odense University Hospital (OUH)	OUH served for a mixed rural-urban population of 288587 persons	Incidence rate (incidence)	Population living in the hospitals catchment area from the StatBank Denmark website	01/05/2013-30/04/2014	Denmark	0-18+ years, breakdown with 0-17 age group	NIAID/FAAN equivalent (WAO/EAACI diagnostic criteria); Review records in the ED	Total anaphylaxis and specific agents triggered anaphylaxis	Low	Yes, first onset
Yang, M.S. 2017	Registry	All patients from Korean National Health Insurance (NHI) claims database	Korean NHI is a mandatory health insurance program and covers 97.9% of the population in Korea	Incidence rate (incidence)	Number of beneficiaries from National Health Insurance Statistical Yearbook	01/01/2008-31/12/2014	South Korea	0-70+ years breakdown with 0-19 age group	ICD-10 (T78.0, T78.2, T80.5, T88.6); ICD-10 Principal diagnoses	Total anaphylaxis (only)	Low	NA
Lee, S. 2017	Registry	All Olmsted County residents from Rochester Epidemiology Project (REP)	REP captures 98.7% of the population in Olmsted County	Incidence rate (incidence)	Population of Olmsted County, adjusted to US 2010 white population	01/01/2001-31/12/2010	United States	0-60+ years breakdown with 0-9, 10-19 age groups	NIAID/FAAN; Review records	Total anaphylaxis and specific agents triggered anaphylaxis	Low	NA
Liu, F.C. 2017	Registry	Citizens from the National Health Insurance (NHI) research database	NHI is a single-payer program and covers 99% of the population	Incidence rate (incidence)	Population of Taiwan in 2012	01/01/2005-31/12/2012	Taiwan	0-80+ years breakdown with 0-9, 10-19 age groups in figures	ICD-9 (995.0, 995.4, 995.6); ICD-9 diagnostic code	Total anaphylaxis and specific agents triggered anaphylaxis	Low	Yes, first onset
Xepapadaki, P. 2016	Cohort Study	Children from EuroPrevall birth cohort	Children recruited from 9 countries across Europe	Cumulative incidence (NA, was calculated	Number of children recruited in the birth cohort	01/10/2005-31/03/2007	UK, the Netherlands, Germany,	2 years	Not mentioned	Hen's egg induced anaphylaxis only	Moderate	Yes, first onset

				based on cases and person-time at risk)			Poland, Lithuania, Spain, Italy, Greece					
Jeppesen, A. N. 2016	Registry	Hospitalization for anaphylaxis, not include ED patients	Danish National Patient Registry and Danish Civil Registration System	Incidence rate (hospitalization rate)	Population living in Denmark between 1995 and 2012 (person time at risk)	01/01/1995-31/12/2012	Denmark	0-75+ years breakdown with 0-14 years	ICD-10 (T78.0, T78.2, T80.5, T88.6, T634F); ICD-10 primary and secondary diagnoses	Total anaphylaxis (only)	Low	Yes, first onset
Vetander, M. 2016	Cohort Study	People from the birth cohort	BAMSE, a population-based, unselected birth cohort of children in 1994-1996	Incidence rate (incidence)	The number of adolescent in the study population (person time at risk)	01/01/2009-31/12/2011	Sweden	16 years old	NIAID/FAAN; Questionnaire of survey	Only food-induced anaphylaxis	Moderate	NA
Kim, S. H. 2016	Registry	Inpatient and outpatient for anaphylaxis	Health Insurance Review and Assessment Service (HIRA)	Incidence rate (incidence)	Korean population in 2012	01/01/2011-31/12/2013	South Korea	0-60+ years, breakdown with 10-19 years	ICD-10 (T78.0, T78.1, T78.2); ICD-10 diagnostic code	Only food-induced anaphylaxis	Low	NA
Kivisto, J. E. 2016	Registry	Hospitalization for anaphylaxis, not include ED patients	National Hospital Discharge Register (NHDR) in Finland and the National Patient Register (NPR) in Sweden	Incidence rate (incidence)	Mid-populations from the Official Statistics of Finland and Statistics Sweden	01/01/1999-31/12/2011	Finland, Sweden	0-19 years	ICD-10 (T78.0, T78.2); ICD-10 diagnostic code	Total anaphylaxis (only)	Low	NA
Wright, B. L. 2015	Registry	North Carolina public school	North Carolina Annual School	Incidence rate (incidence)	Total students in all North Carolina	01/01/2004-31/12/2014	United States	Students from elementary	Not mentioned	Total anaphylaxis (only)	High	NA

		students reported of anaphylaxis	Health Services Report		public schools			school to high school				
Turner, P. J. 2015	Registry	Hospital admissions for anaphylaxis, not include ED visits only	Hospital Episodes Statistics database and the Patient Episode Data base for Wales	Incidence rate (hospital admission rate)	Population in mid-2001 and mid-2006 from the Office for National Statistics	01/01/1992-31/12/2012	United Kingdom	0-85+ years, breakdown with 0-4, 5-9, 10-14, 15-19 age groups in figures	ICD-9 (995.0, 995.6), ICD-10 (T78.0, T78.2, T88.6); ICD-9 and ICD-10 diagnostic code	Total anaphylaxis and specific agents triggered anaphylaxis	Low	NA
Tejedor-Alonso, M. A. 2015	Registry	Hospital admissions for anaphylaxis	Spanish Minimum Basic Data Set (MBDS)	Incidence rate (incidence)	Population in Spain	01/01/1998-31/12/2011	Spain	0-75+ years, data received for age 0-14 years from author	NIAID/FAAN; ICD-9 diagnostic code	Total anaphylaxis and specific agents triggered anaphylaxis	Low	NA
Parekh, D. 2015	Registry	Hospital admissions for food-induced anaphylaxis, not state whether include ED patients	Database of the Italian Ministry of Health, Hospital admissions	Incidence rate (incidence)	Italian paediatric population	01/01/2006-31/12/2011	Italy	0-14 years	ICD-9 (did not provide detailed codes); ICD-9 diagnostic code	Only food-induced anaphylaxis	Low	NA
Mullins, R. J. 2015	Registry	Hospital admissions for anaphylaxis (include ED and inpatient)	Australian Institute of Health and Welfare (AIHW)	Incidence rate (hospital admission rate)	National population estimates from Australian Bureau of Statistics	01/07/1998-30/06/2012	Australia	0-30+ years, breakdown with 0-4, 5-14 years	ICD-10 (T78.0, T80.5, T78.2, T88.6, L50, T78.3, J45, J46); ICD-10 diagnostic code	Total anaphylaxis and specific agents triggered anaphylaxis	Low	NA
Dyer, A. A. 2015	Registry	Hospital admissions for food-induced	Illinois hospital discharge data (COMPdata),	Incidence rate (admission rate)	Illinois population estimated from the US Census	01/01/2008-31/12/2012	United States	0-19 years	ICD-9 (995.60-995.69); ICD-9 diagnostic code	Only food-induced anaphylaxis	Low	NA

		anaphylaxis (include ED and inpatient)			Bureau							
Buka, R. J. 2015	Registry	ED attendances for anaphylaxis	National Health Service (NHS) organizations in the UK	Incidence rate (incidence)	Population in catchment area	01/01/2012-31/12/2012	United Kingdom	0-90 years, breakdown with 0-15 years	NIAID/FAAN equivalent (WAO diagnostic criteria); Electronic database search for key words	Total anaphylaxis (only)	Moderate	NA
Hoyos-Bachiloglu, R. 2014	Registry	Hospital admissions for anaphylaxis, not state whether include ED patients	National hospital discharge database	Incidence rate (admission rate)	Chilean population	01/01/2001-31/12/2010	Chile	0-97 years, breakdown with 0-9, 10-19 years	ICD-10 (T78.0, T78.2, T88.6, T78.3 to avoid miscoding as angioedema); ICD-10 diagnostic code	Total anaphylaxis (only)	Low	NA
Liew, W. K. 2013	Registry	Hospital admissions, Department of Children's Emergency, Allergy service outpatient clinics in KK Women's and Children's Hospital	The largest paediatric tertiary referral centre in Singapore	Incidence rate (incidence)	Singapore residents ≤ 18 years	01/01/2005-131/12/2009	Singapore	0-18 years	NIAID/FAAN; Review records	Total anaphylaxis and specific agents triggered anaphylaxis	Low	Yes, first onset
Rolla, G. 2013	Registry	Patients reporting severe allergic reactions in Reference Centre	Reference Center for Severe Allergic Reactions in	Incidence rate (incidence)	Population in Piemonte during 2010	01/01/2010-31/12/2010	Italy	0-87 years, breakdown with 0-17 years	NIAID/FAAN (Brighton Collaboration); Patients reported severe allergic reactions	Only food-induced anaphylaxis	Low	NA

			Piemonte Region									
Vetander, M. 2012	Registry	ED attendances for anaphylaxis	Three paediatric hospitals in Stockholm County	Incidence rate (incidence)	The population of all children in Stockholm	01/01/2007-31/12/2007	Sweden	0-17 years	NIAID/FAAN equivalent (Modified EAACI task force anaphylaxis paper); ICD-10 diagnostic code	Total anaphylaxis and food-induced anaphylaxis	Low	Yes, first onset
Tejedor Alonso, M. A. 2012	Registry	Anaphylaxis patients from primary care, ED, Inpatient and outpatient clinic	Cases from public health settings in Alcorcon	Incidence rate (incidence)	The population in Alcorcon	01/01/2004-31/12/2005	Spain	0-85+ years, breakdown with 0-4, 5-9, 10-14, 15-19 years	NIAID/FAAN; Retrieve from database by alphanumeric strings searching	Total anaphylaxis and specific agents triggered anaphylaxis	Low	No
Canani, R. B. 2012	Registry	Hospital admissions for anaphylaxis, not state whether include ED patients	Hospital episode statistics system database	Cumulative incidence (hospital admission rate)	Italian population under 14 years of age	01/01/2001-31/12/2005	Italy	0-14 years	ICD-9 (995.60-995.68); ICD-9 diagnostic code	Only food-induced anaphylaxis	Low	NA
Mulla, Z. D. 2011	Registry	Hospitalization statistics (inpatient) for anaphylaxis, not include ED patients	Texas Department of State Health Services	Incidence rate (hospitalization rate)	Texas resident population estimate	01/01/2004-31/12/2007	United States	0-24 years, breakdown with 0-4, 5-9, 10-14, 15-19 years	ICD-9 (995.61); ICD-9 principal discharge diagnosis or one of the secondary diagnosis	Peanut-induced anaphylaxis only	Low	NA
Moro Moro, M. 2011	Registry	Emergency department attendances for anaphylaxis	Hospital Universitario Fundacion Alcorcon (HUFA)	Cumulative incidence (incidence)	Catch population of HUFA in 2005	01/01/2004-31/12/2005	Spain	0-69+ years, breakdown with 0-4, 5-9, 10-14, 15-19 years	NIAID/FAAN; Electronic clinical records search using alphanumeric strings	Total anaphylaxis and specific agents triggered anaphylaxis	Moderate	NA
Harduar-	Registry	Emergency	Florida Agency	Incidence rate	Florida population	01/01/2005-	United	0-85+ years,	NIAID/FAAN;	Total anaphylaxis	Low	NA

Morano, L. 2011		department attendances for anaphylaxis	for Health Care Administration	(incidence)	estimated for 2005 and 2006	31/12/2006	States	breakdown with 0-4, 5-14 years	ICD-9 (995.60-995.69, 995.0) diagnostic code	and specific agents triggered anaphylaxis		
Iribarren, C. 2010	Registry	Hospital admissions for anaphylaxis (include ED and inpatient)	Kaiser Permanente of Northern California (KPNC)	Cumulative incidence (incidence)	The population in the cohort	01/01/1996-31/12/2006	United States	0-65+ years, breakdown with 0-11, 12-18 age groups in figures	NIAID/FAAN; ICD-9 (995.6, 999.40, 995.0, 708.0, 989.5, 995.1) diagnostic code	Total anaphylaxis and specific agents triggered anaphylaxis	Low	Yes, first onset
Ho, M. 2010	Registry	Hospital admissions for anaphylaxis (include ED and inpatient)	Hospital Authority central computer system CDARS	Incidence rate (admission rate)	Hong Kong population	01/01/1997-31/12/2007	Hong Kong, China	0-17 years	NIAID/FAAN equivalent (Defined by author); ICD-9 diagnostic code	Total anaphylaxis and specific agents triggered anaphylaxis	Low	NA
Gonzalez-Perez, A. 2010	Registry	Individuals enrolled for at least 1 year with a general practitioner	The Health Improvement Network (THIN) database	Incidence rate (incidence)	Each member of the cohort as the time contributed to the study period (person time at risk)	01/01/1996-31/12/2005	United Kingdom	10-79 years, breakdown with 10-19 years by gender	ICD-9 (995.0, 995.4, 995.6, 693.1, 695.1, 708.0, 708.9, 989.5, 995.1, 995.3); Contacting general practitioner with a completed questionnaire	Total anaphylaxis (only)	Low	Yes, first onset
Sheikh, A. 2008	Registry	Patients had a computer-recorded diagnostic read code for anaphylaxis	QRESEARCH database	Incidence rate (incidence)	Number of patient years of observation standardized by mid-year population estimates for England	01/01/2001-31/12/2005	United Kingdom	0-90+ years, breakdown with <5, 5-9, 10-14 age groups in figures	NA; Computer-recorded diagnostic read code for anaphylaxis in the electronic health record	Total anaphylaxis (only)	Low	Yes, first onset

Lin, R. Y. 2008	Registry	Hospital admissions for anaphylaxis, did not state whether include ED patients	Statewide Planning and Research Cooperative System (SPARCS) database	Incidence rate (hospitalization rate)	The resident population estimates in New York State from the US Census Bureau	01/01/1990-31/12/2006	United States	0-19 years	ICD-9 (995.6, 999.4, 995.0, 708.0, 995.1, 995.3) and Common Procedural Terminology; ICD-9 diagnostic code	Total anaphylaxis (only)	Low	NA
Decker, W. W. 2008	Registry	Patients from all medical care providers (inpatient and outpatient)	The Rochester Epidemiology Project	Incidence rate (incidence)	Population in Olmsted County, Minnesota, adjusted for US population in 2000	01/01/1990-31/12/2000	United States	0.8-78.2 years, breakdown with 0-9, 10-19, 0-19 years	NIAID/FAAN equivalent (Defined by author); ICD-9 diagnostic code and hospital adaptation of the ICD-2 codes.	Total anaphylaxis (only)	Low	Yes, first onset
Calvani, M. 2008	Registry	Hospital admissions for anaphylaxis (ED+inpatient)	Sistema Informativo Ospedaliero (SIO) and the Sistema informativo Emergenza Sanitaria (SIES) system	Incidence rate (incidence)	The average children resident for 2 subsequent years (person time at risk)	01/01/2000-31/12/2003	Italy	0-17 years	ICD-9 (995.0, 995.4, 995.60-995.69, 999.4); ICD-9 diagnostic code	Total anaphylaxis and specific agents triggered anaphylaxis	Low	Yes, first onset
Poulos, L. M. 2007	Registry	Hospitalization for anaphylaxis (inpatient), did not include ED patients	National Hospital Morbidity Database	Incidence rate (hospitalization rate)	Australian population in mid-2001	01/07/1993-30/06/2005	Australia	0-65+ years, breakdown with 0-4, 5-14 years	ICD-9 (995.0, 995.6, 999.4),ICD-10 (T78.2, 88.6, 78.0, 80.5); ICD-9 and ICD-10 principal diagnosis	Total anaphylaxis (only)	Low	NA
Braganza, S. C. 2006	Registry	Emergency department	One Australian paediatric	Incidence rate (incidence)	Local catchment population in	01/07/1998-30/06/2001	Australia	0.2-14.1 years	ASCIA definitions; ICD-9 diagnostic code	Total anaphylaxis and specific	Moderate	NA

		attendances for anaphylaxis	emergency department		Brisbane, Australia					agents triggered anaphylaxis		
Bohlke, K. 2004	Registry	Patients for anaphylaxis from automated hospital, emergency department, and outpatient clinic	Group Health Coorperative	Incidence rate (incidence)	Each member of the cohort as the time enrolled in the HMO during study period (person time at risk)	01/03/1991-31/12/1997	United States	0-17 years	Defined by author own algorithm; ICD-9 (995.0, 995.6, 999.4, 995.4) diagnostic code	Total anaphylaxis and specific agents triggered anaphylaxis	Low	NA
Ruffoni, S. 2015	Registry	Phone calls and medical visits for anaphylaxis	Liguria Medical emergency service	Incidence rate (NA, was calculated based on cases and person-time at risk)	Population in Liguria in 2013	01/01/2013-31/12/2013	Italy	0-17 years	NIAID/FAAN equivalent (Defined by author); Calls due to suspected anaphylaxis recorded by Liguria Medical Emergency Service	Total anaphylaxis (only)	Low	NA
West, S. L. 2007	Registry	ED visits and hospital admissions for drug-related anaphylaxis	South Carolina Emergency Room Hospital Discharge Database (SCERHDD)	Incidence rate (admission rate)	SC paediatric population from 2000 US census	01/01/2000-31/12/2002	United States	0-18 years	The algorithm defined by author based on ICD-9 and E-codes; ICD-9 (995.0, 995.3, 785.50, 708.0, 708.1, 708.9, 995.1, 478.75, 478.8, 786.05, 786.07, 786.09, 786.1,458.9, 785.0, 693.0, 995.2) diagnostic code	Drug-related anaphylaxis	Low	NA
Gupta, R. 2004	Registry	Hospital admissions for	Health Survey for England, Scottish	Incidence rate (hospital	Mid-year population	01/07/2000-30/06/2001	United Kingdom	0-45+ years, breakdown	ICD-9 (995.0, 999.4), ICD-10 (T78.0, T78.2,	Total anaphylaxis (only)	Low	NA

		anaphylaxis, did not state whether include ED patients	Health Survey, International Study of Allergies and Asthma in Childhood (ISAAC) and the European Community Respiratory Health Survey (ECRHS)	admission rate)	estimated from National Statistics			with 0-14 years	T80.5, T88.6); ICD-9 and ICD-10 diagnostic code			
Studies reported prevalence												
Study ID	**Study Design**	**Study Population**	**Data source characteristic**	**Extracted data type (original reported type in the study)**	**Denominator (population)**	**Data collection years**	**Country**	**Age of study population**	**Definition of anaphylaxis and outcome confirmation**	**Reported type of anaphylaxis**	**Risk of bias**	**Response Rate (%)**
McWilliam, V. L. 2018	Cross-sectional study	Students reported to have experienced food-induced anaphylaxis in the past 12 months	SchoolNuts study, students from 229 schools from greater metropolitan Melbourne area	Prevalence	9663 consented students with completed questionnaires	01/07/2011-31/12/2014	Australia	10-14 years	ASCIA definition; Questionnaire	Only food-induced anaphylaxis	Low	51.1
Jeong, K. 2018	Registry	Patients designated as “absolutely confirmed” and “confirmed” of	Korean National Health Insurance (NHI) database, covers about 98% of the overall	Prevalence	Korean population from beneficiaries of health insurance and medical aid in	01/01/2010-31/12/2014	South Korea	0-80+ years, breakdown with 0-2, 3-6, 7-12, 13-17, 18-19 age	Defined by authors, using ICD-10 codes and combine with EAI management information; ICD-10 diagnostic codes	Total anaphylaxis (only)	Low	100.00

		anaphylaxis	Korean population		2010-2014 NHI statistical yearbooks			groups in figures				
Ruiz Oropeza, A. 2017	Registry	All patients seen at the ED and the Acute Paediatric Ward (APW), Odense University Hospital (OUH)	OUH served for a mixed rural-urban population of 288587 persons	Prevalence	Population living in the hospitals catchment area from the StatBank Denmark website	01/05/2013-30/04/2014	Denmark	0-18+ years, breakdown with 0-17 age group	NIAID/FAAN equivalent (WAO/EAACI diagnostic criteria); Review records in the ED	Total anaphylaxis and specific agents triggered anaphylaxis	Low	100.00
Kim, M. 2017	Cross-sectional study	Children reported to have food-induced anaphylaxis in questionnaire	Survey in 50000 schoolchildren from 17 cities and provinces.	Prevalence	29842 children returned questionnaire with valid responses	01/09/2015-30/09/2015	South Korea	6-16 years	NIAID/FAAN; Questionnaire	Only food-induced anaphylaxis	Low	59.70
Chan, J. C. K. 2017	Cohort study	Children was confirmed to have anaphylaxis during oral food challenge	HealthNuts study, recruited 5276 12-month-old children across Melbourne between September 2007 and August 2011	Prevalence	5276 children agreed to participate in this study	01/09/2007-31/08/2015	Australia	1 years and 4 years	Defined by author, Anaphylaxis was defined as evidence of circulatory or respiratory compromise (eg, hypotension, persistent cough, or wheeze); Oral food challenge induced anaphylaxis	Only food-induced anaphylaxis (Peanut, raw egg, sesame-induced anaphylaxis)	Low	74.00
Ontiveros, N. 2016	Cross-sectional study	Children reported to have food-induced anaphylaxis in	Survey in 10 elementary schools (private and public	Prevalence	1049 children returned questionnaire with valid responses	01/09/2014-31/08/2015	Mexico	5-13 years	NIAID/FAAN (WAO); Questionnaire and parent reported	Only food-induced anaphylaxis	Low	84.00

		questionnaire	schools) in Culiacan									
Protudjer, J. L. 2016	Cohort study	Children reported to have anaphylaxis at 16 years	BAMSE project, a birth cohort of 4089 children between 1994 and 1996	Prevalence	2572 children with available information from follow-up questionnaires	01/01/2010-31/12/2012	Sweden	16 years	NIAID/FAAN; Questionnaire	Only food-induced anaphylaxis	Low	62.90
Dereci, S. 2016	Cross-sectional study	Schoolchildren in the city of Rize	20800 school children	Prevalence	15783 people returned questionnaire	01/01/2013-29/02/2013	Turkey	6-18 years	NA; Questionnaire	Hazelnut-induced anaphylaxis	Moderate	75.90
Kilger, M. 2015	Cross-sectional study	Children reported to have primary anaphylactic reactions	16644 children from 86 primary school and kindergartens	Prevalence	5981 children returned questionnaire and were included in the study	01/03/2011-30/06/2011	Germany	Children from primary school and kindergarten, average age was 7 years	NIAID equivalent (EAACI position paper); Questionnaire	Total anaphylaxis (only)	Low	35.93
Gaspar, A. 2015	Cross-sectional study	Children diagnosed as anaphylaxis in an allergy outpatient clinic	Allergy outpatient clinic	Prevalence	3646 children from allergy outpatient clinic	01/01/2011-31/12/2011	Portugal	0-17 years	NIAID/FAAN; Questionnaire	Total anaphylaxis (only)	Moderate	NA
Park, M. 2014	Cross-sectional study	Children reported to have current food allergy with anaphylaxis as the symptoms	16982 children were recruited from 301 public child care centers	Prevalence	16749 children returned valid questionnaires	01/09/2011-31/10/2011	South Korea	0-6 years	NIAID/FAAN; Questionnaire	Only food-induced anaphylaxis	Low	98.63
Gaspar-Marques,	Cross-sectiona	Children reported to have	Children health questionnaire in	Prevalence	1217 children returned	01/01/2014-31/12/2014	Portugal	0-6 years	NIAID equivalent (EAACI position paper);	Only food-induced	Low	54.60

J. 2014	l study	anaphylaxis in questionnaire	the frame of the ENVIRH Project (Environment and Health in Children Day Care Centres)		questionnaire				Questionnaire	anaphylaxis		
Lao-araya, M. 2012	Cross-sectional study	Children from selected kindergartens reported having anaphylaxis in questionnaire	9 kindergartens selected by multistage random sampling	Prevalence	452 children returned questionnaire	01/01/2010-31/12/2010	Thailand	3-7 years	NIAID equivalent (anaphylaxis defined as ≥2 organ systems involved); Questionnaire	Only food-induced anaphylaxis	Low	82.80
Ho, M. H. 2012	Cross-sectional study	Children reported having anaphylaxis to foods	Child Health Survey (CHS)	Prevalence	7393 land-based non-institutionalized children	01/09/2005-31/08/2006	Hong Kong, China	0-14 years	NA; Reported anaphylaxis as symptom	Only food-induced anaphylaxis	Moderate	73.30
Sheikh, A. 2008	Registry	Patients had a computer-recorded diagnostic read code for anaphylaxis	QRESEARCH database	Prevalence	Number of patients observed standardized by mid-year population estimates for England	01/01/2001-31/12/2005	United Kingdom	0-90+ years, breakdown with <5, 5-9, 10-14 age groups in figures	NA; Computer-recorded diagnostic read code for anaphylaxis in the electronic health record	Total anaphylaxis (only)	Low	100.00
Touraine, F. 2002	Cross-sectional study	Children were reported as anaphylactic shock	1086 questionnaires were distributed to 4 primary schools, 2 colleges and	Prevalence	748 returned questionnaire	2000-2001 school year	France	5-17 years	NA; Questionnaire	Only food-induced anaphylaxis	High	69.00

			public high school, 1 private college and high school in Limoges									
Boros, C. A. 2000	Cross-sectional study	Children from selected schools for the project	Children from preschools, schools, and child-care centres	Prevalence	4173 South Australian children	01/01/2000-31/12/2000	Australia	3-17 years	Defined by author: Anaphylaxis was defined as rapid onset with symptoms of airway tract obstruction, skin rash, gastrointestinal involvement, and cardiovascular involvement; Questionnaire and parent reported	Total anaphylaxis and specific agents triggered anaphylaxis	Moderate	60.00

NA: refers to relevant information was not available in including studies.

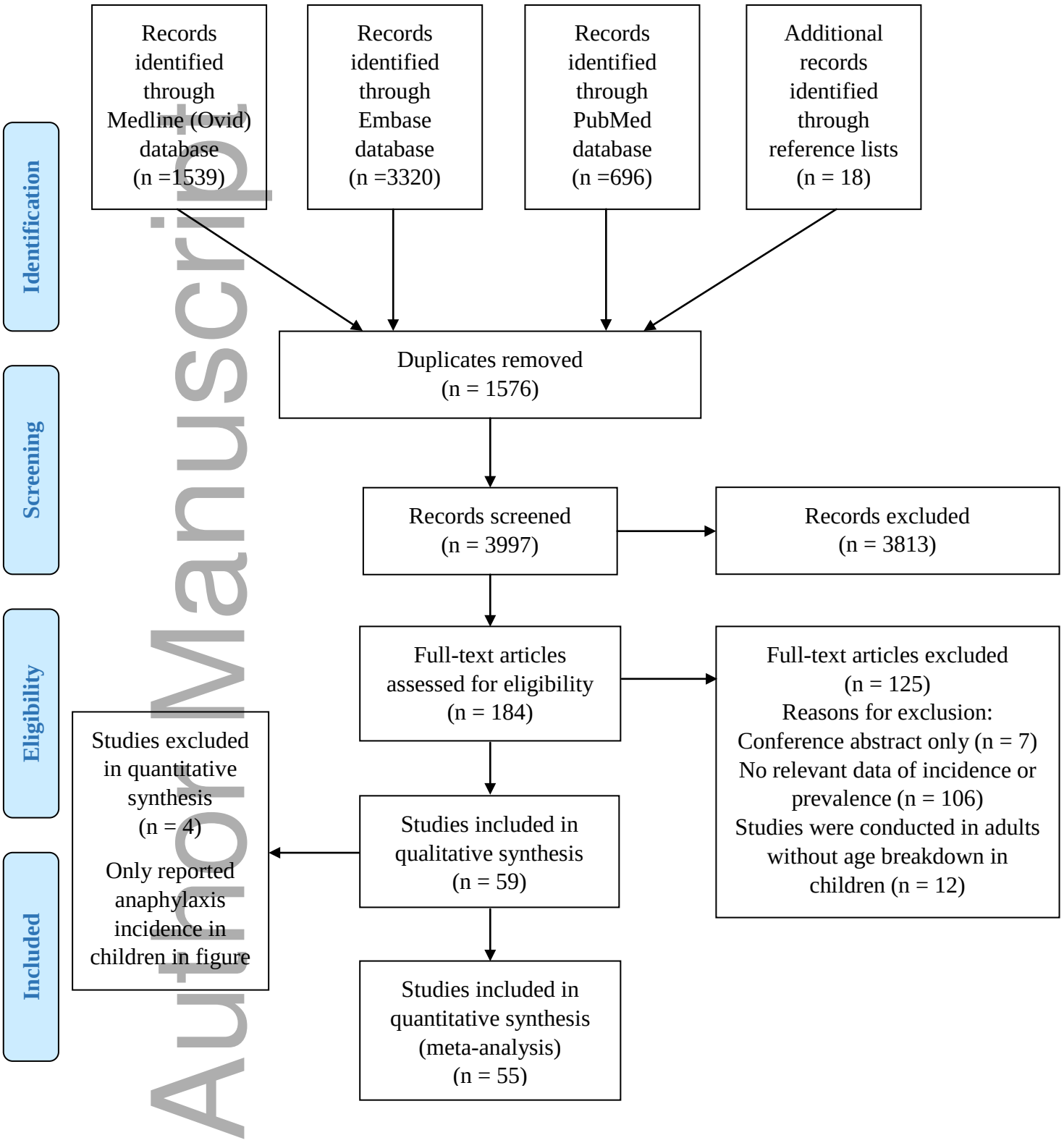
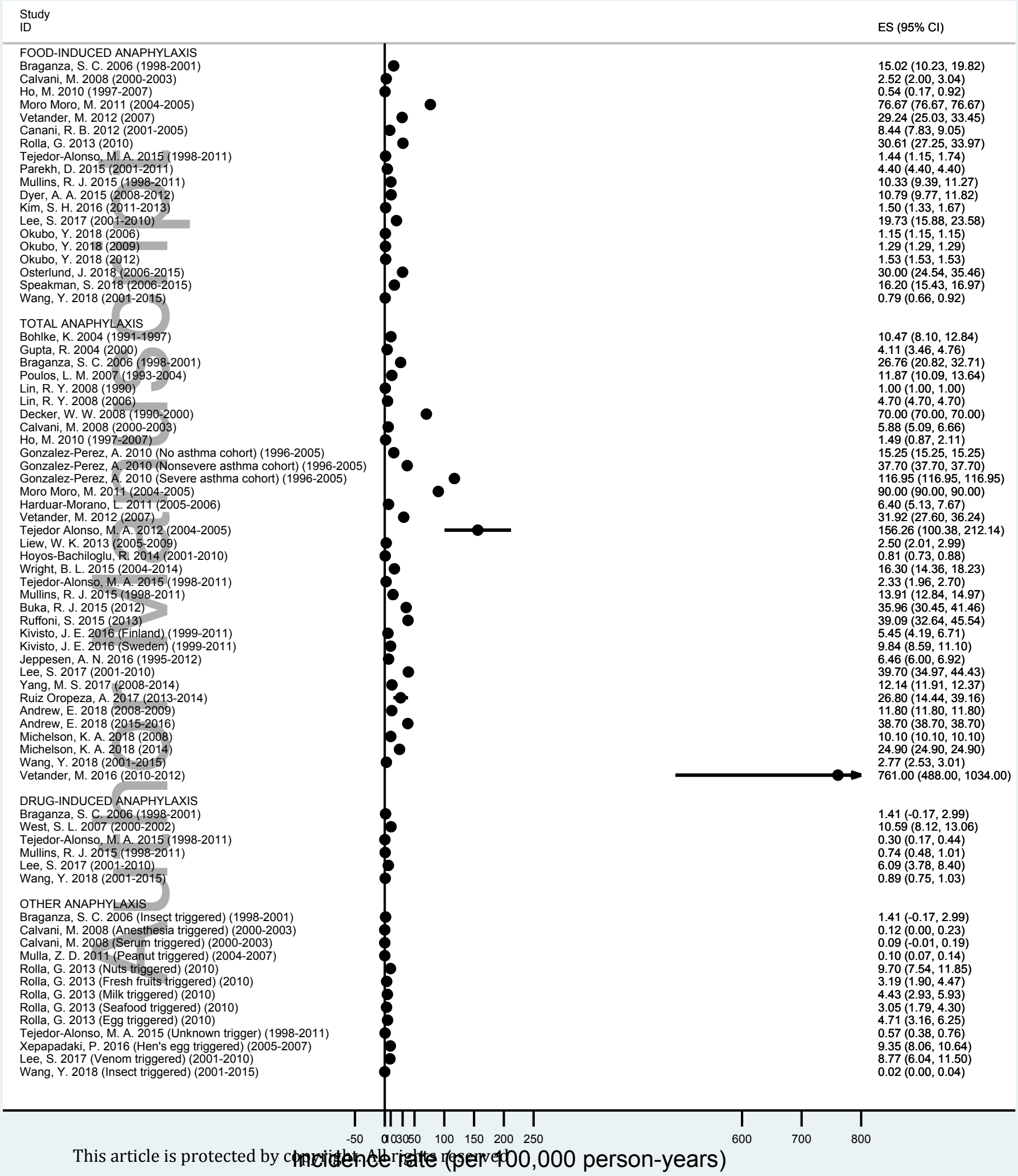
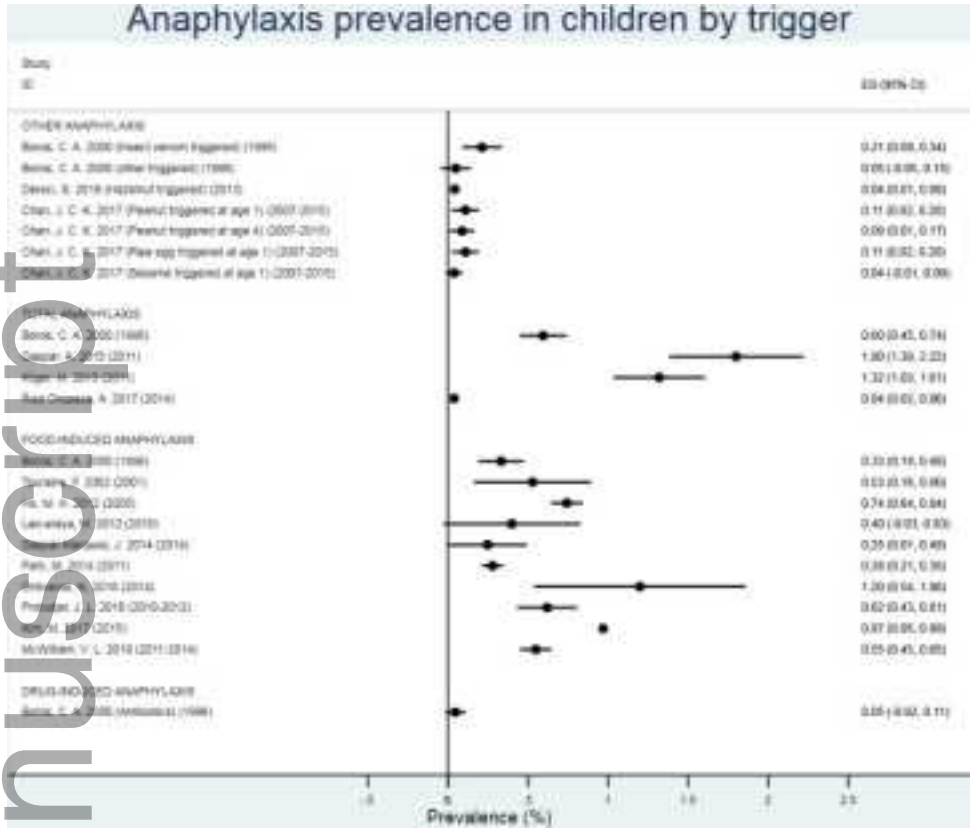


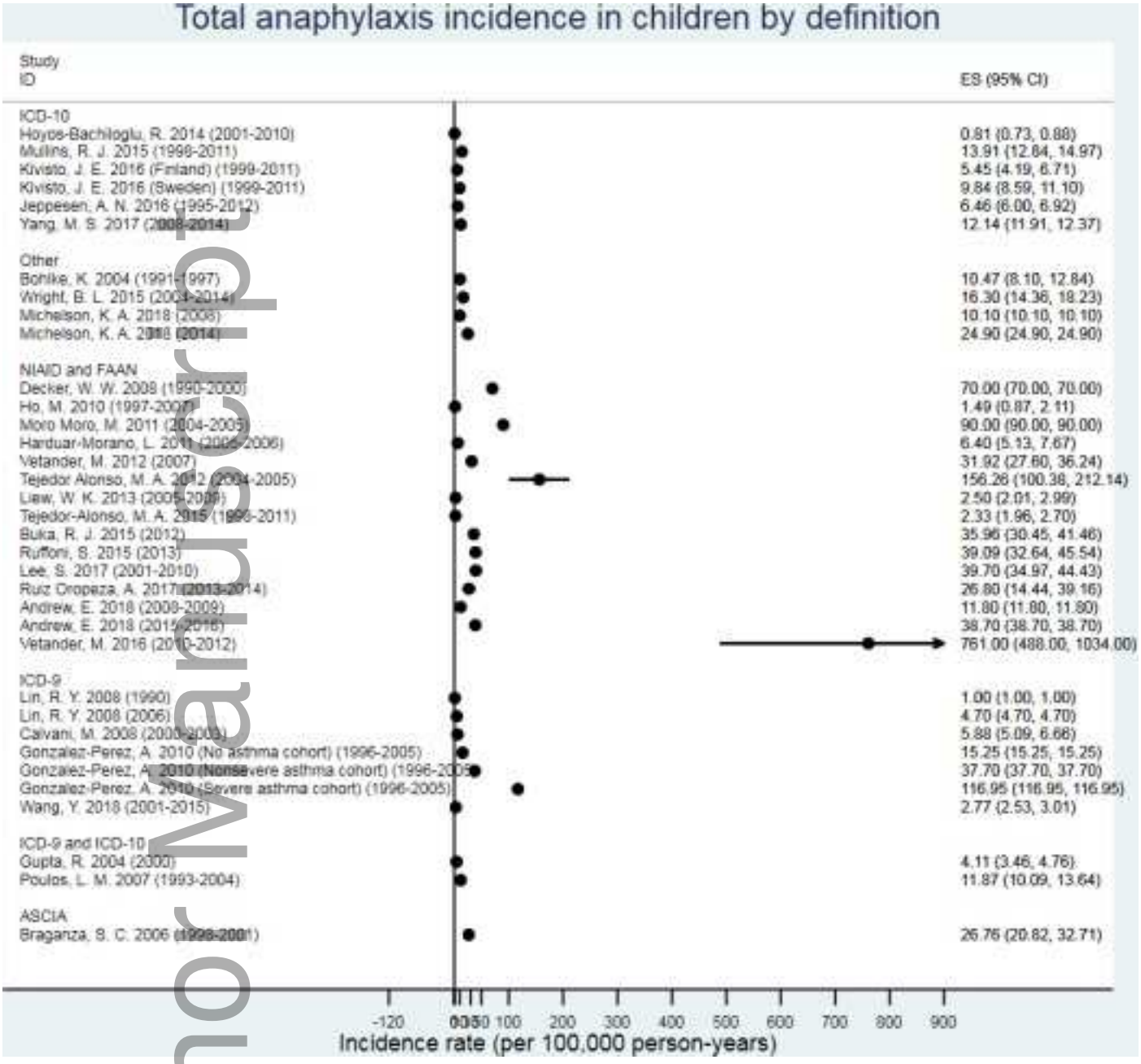
Figure 1. PRISMA diagram of literature search and study selection

Anaphylaxis incidence in children by trigger

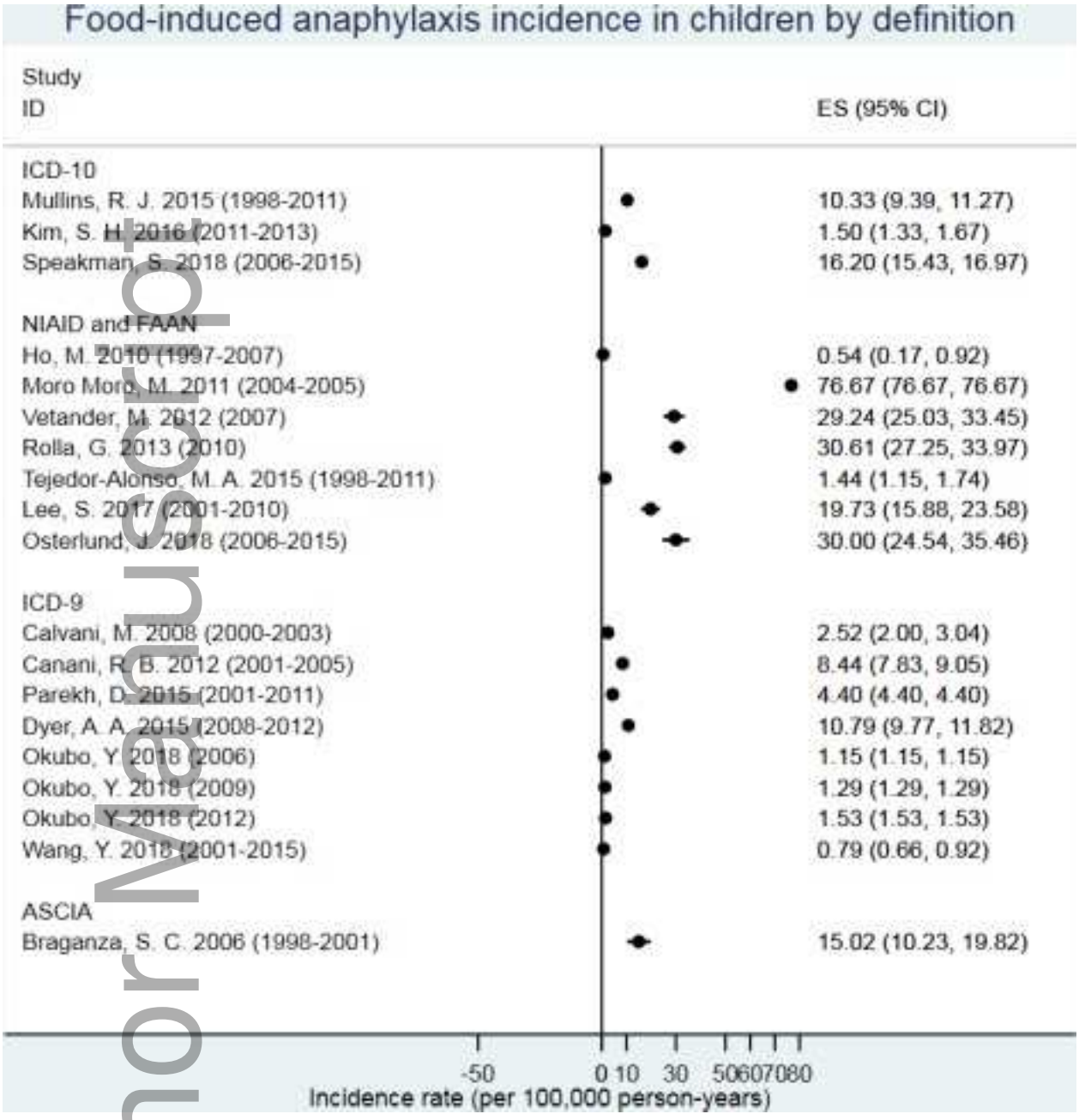




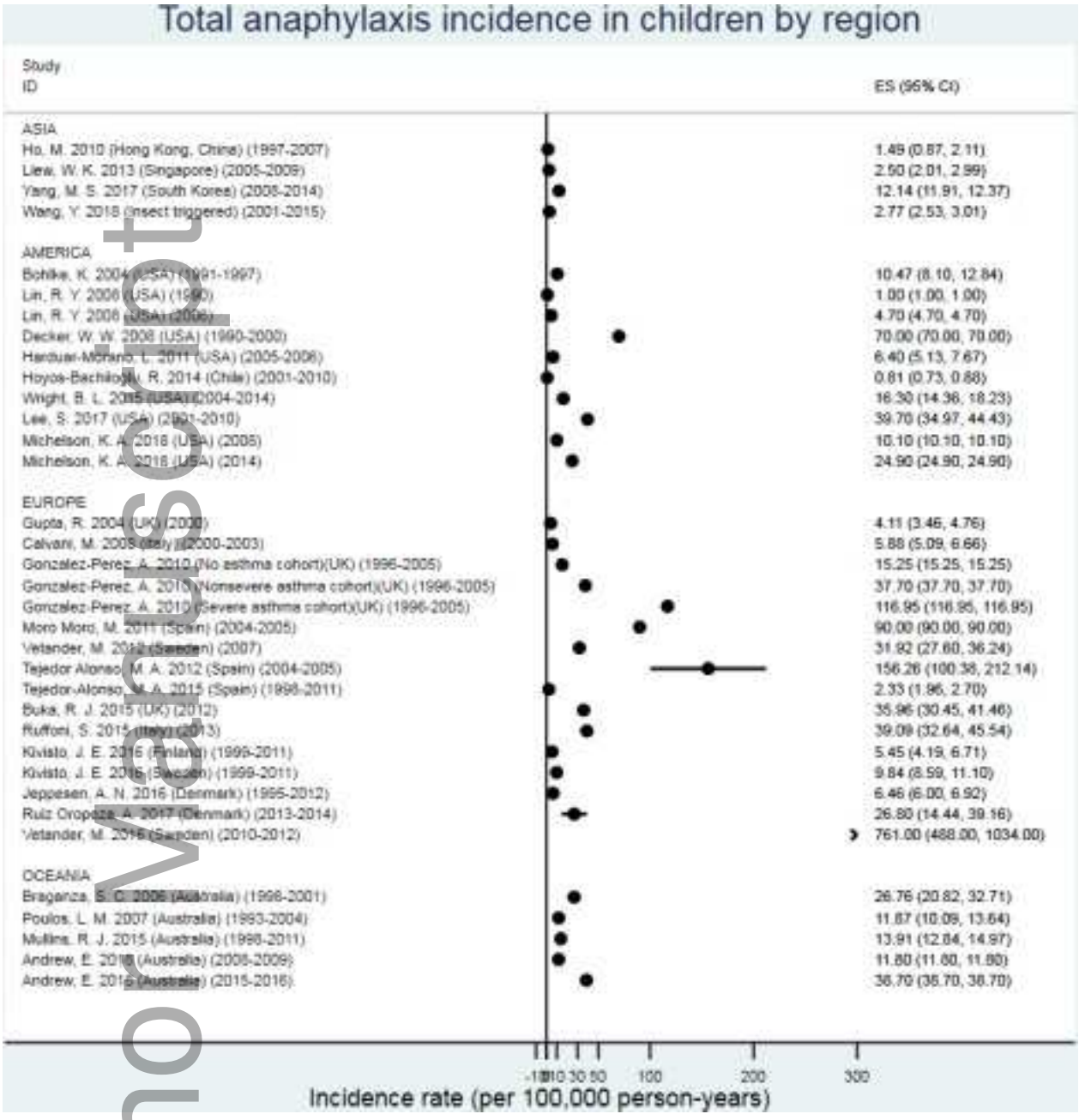
all_13732_f2b.tif



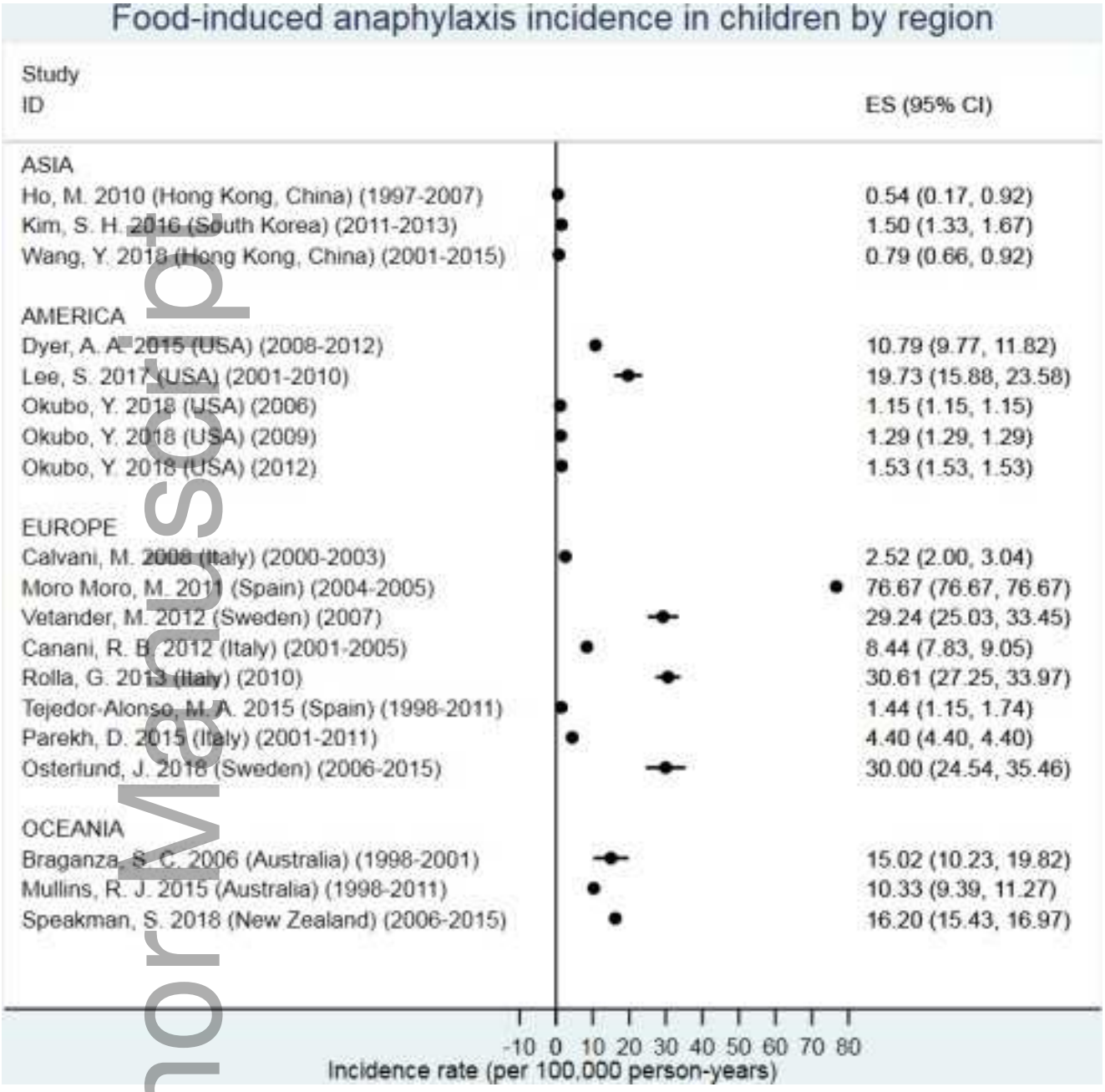
all_13732_f2c.tif



all_13732_f2d.tif



all_13732_f2e.tif



all_13732_f2f.tif

all_13732_f3.tif

all_13732_f3bw.tif

Author/s:
Wang, Y; Allen, KJ; Suaini, NHA; McWilliam, V; Peters, RL; Koplin, JJ

Title:
The global incidence and prevalence of anaphylaxis in children in the general population: A systematic review

Date:
2019-06-01

Citation:
Wang, Y., Allen, K. J., Suaini, N. H. A., McWilliam, V., Peters, R. L. & Koplin, J. J. (2019). The global incidence and prevalence of anaphylaxis in children in the general population: A systematic review. ALLERGY, 74 (6), pp.1063-1080. https://doi.org/10.1111/all.13732.

Persistent Link:
http://hdl.handle.net/11343/285560

File Description:
Accepted version