Association between severity of anaphylaxis and coexistence of respiratory diseases: a systematic review and meta-analysis of observational studies

Running title: Anaphylaxis and respiratory disease

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Abstract

Background: Asthma is very prevalent in all grades of severity of anaphylaxis and asthma and Chronic obstructive pulmonary disease (COPD) have been associated with severity of anaphylaxis.

Objective: We carried out a systematic review and meta-analysis to assess the influence of respiratory diseases on the severity of anaphylaxis.

Methods: We searched PubMed/MEDLINE, EMBASE, and the Web of Science for observational studies. The target studies were those that compared the severity of anaphylaxis between patients who had or did not have respiratory diseases.

Results: A total of 13 studies assessed the severity of anaphylaxis in respiratory disease. Respiratory disease increased the severity of anaphylaxis (OR, 1.87; 95% CI, 1.30-2.70). Overall, asthma increased the severity of anaphylaxis (OR, 1.89; 95% CI, 1.26-2.83). For the meta-analysis of all studies (adjusted and non-adjusted), COPD increased the severity of anaphylaxis (OR, 2.47; 95% CI, 1.46-4.18). For asthma studies, only 1 study assessed the influence of severity of asthma on severity of anaphylaxis.

Conclusions: Evidence showing that respiratory disease increases the severity of anaphylaxis is low to moderate, although studies do not usually assess the importance of severity of asthma.

Key words: Severity, Anaphylaxis, Respiratory disease, COPD, Asthma, Meta-analysis
Resumen

Conocimiento previo: El asma es muy frecuente en todos los grados de gravedad de la anafilaxia y así mismo el asma y no controles no sigue la enfermedad pulmonar obstructiva crónica (EPOC) se han asociado con las anafilaxias graves.

Objetivo: Realizamos una revisión sistemática y un meta-análisis para evaluar la influencia de las enfermedades respiratorias en la gravedad de la anafilaxia.

Métodos: Se realizaron búsquedas en PubMed / MEDLINE, EMBASE y Web of Science de estudios observacionales, en donde se compararon la gravedad de la anafilaxia entre pacientes que tenían o no enfermedades respiratorias.

Resultados: Un total de 13 estudios evaluaron la influencia de las enfermedades respiratorias en la gravedad de la anafilaxia. La enfermedad respiratoria aumentó la gravedad de la anafilaxia (OR, 1.87; IC 95%, 1.30-2.70). En general, el asma también aumentó la gravedad de la anafilaxia (OR, 1.89; IC del 95%, 1.26-2.83). En el meta-análisis de todos los estudios con EPOC (ajustado y no ajustado), la misma aumentó la gravedad de la anafilaxia (OR, 2.47; IC del 95%, 1.46-4.18). En los estudios con asma, solo uno evaluó la influencia de la gravedad del asma en la gravedad de la anafilaxia.

Conclusiones: La evidencia que muestra que la enfermedad respiratoria aumenta la gravedad de la anafilaxia es baja a moderada, aunque los estudios no suelen evaluar la importancia de la gravedad del asma.

Palabras clave: Gravedad, Anafilaxia, Enfermedad respiratoria, EPOC, Asma, metanálisis
Introduction

Respiratory diseases and other factors [1-4,5] are major risk factors for increased severity of anaphylaxis [6,7]. Asthma is associated with the severity of anaphylaxis [4,8-15]. Its sensitivity for predicting severity is high, while its specificity is low, owing to the marked presence of asthma in patients with food anaphylaxis in all grades of severity [7,11,15]. When addressing the option of exploring the relationship between severity of anaphylaxis and severity of asthma, few authors have investigated the relationship between uncontrolled asthma and severity of anaphylaxis [11,15]. Chronic obstructive pulmonary disease (COPD) has been associated with severity of anaphylaxis in only three studies [1,9,12].

The influence of respiratory diseases and the weaknesses of the various studies on severity of anaphylaxis have not been examined systematically. Consequently, our aims in this study are to evaluate the quality of evidence for the relationship between presence of respiratory diseases and severity of anaphylaxis and to determine to what extent it is affected by the presence of various confounders.

Methods

The study was designed according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology [16] checklist and PRISMA Statement for systematic reviews [17]. The meta-analysis was registered in the PROSPERO database (No. CRD42018086042).
**Search strategy**

We searched PubMed/MEDLINE, EMBASE, and Web of Science to obtain titles and abstracts from relevant studies in humans with no language restrictions. The search strategy was designed to find text terms for respiratory disease (sever* and anaphylaxis and lung) or (sever* and anaphylaxis and respira*), after ruling out other less effective options and based on shortened forms of the words. The last search for respiratory disease was run on 28 February 2018 by 2 investigators (EFA and MMM). Articles cited in the articles and review papers were reviewed by the investigators to identify articles not included in the previous searches.

The abstract and title of each article were examined during identification and screening in order to choose articles that met the study criteria. Two investigators (EFA and ARI) carried out the search independently. Disagreements between reviewers were resolved by consensus and discussion.

**Selection criteria**

We searched for studies where the severity and presence of anaphylaxis episodes were compared between patients with and without respiratory diseases. There were no restrictions based on age or sex. The studies included all the major causes of anaphylaxis (i.e. food, drugs) or a specific cause of anaphylaxis (i.e. insect venom, radiographic contrast media).

We included all types of studies except the following: studies with duplicate dates, systematic reviews and/or meta-analyses, reviews, studies which did not report risks, editorials, case reports, guidelines, and animal studies. We also excluded series
involving fatal anaphylaxis in order to ensure that the pathogenic factors involved were different for severe anaphylaxis.

**Data collection and extraction**

We designed an electronic data extraction form to collect the following: (1) study data (first author, year of publication, country, type of anaphylaxis); (2) study characteristics (design [cohort, cross-sectional, case control], origin of patients [field stings, anaphylaxis registries]); (3) confounding or exposure variables (anti-hypertensive drugs, comorbidities [cardiovascular diseases, respiratory diseases, mastocytosis], sex, age); and (4) outcomes associated with severity (previously published scores [Sampson [18] and Ring and Messmer [19], admissions to hospital wards or critical care areas, hypotension, use of mechanical ventilation). One author obtained the information and the other checked its accuracy. Disagreement was resolved by consensus (EFA and MMM).

Given the observational nature of the studies included in the systematic review, our priority was to find adjusted statistics (odds ratios [OR]) (Table 1).

In order not to include the same patients several times, we chose only the most severe outcome in each study. When the same group published several reports about the same exposure in different years (for instance anaphylaxis due to hymenoptera venom), duplication of participants was ruled out if the exposure occurred under different circumstances (e.g. hymenoptera anaphylaxis in the field or after the build-up or maintenance phase of venom immunotherapy).
Risk of bias in individual studies

The quality of the studies and the presence of bias were assessed using the Newcastle-Ottawa Scale [20]. For cross-sectional and case-control studies, the highest score is 8. In addition, the quality of evidence was assessed again using the recommendations of the GRADE guidelines [21], which classify quality from very low to high based on 4 grades. The risk of bias in individual studies was assessed by EFA and MAT.

Ethical Approval

Given that our study was a review of published literature, approval was not requested from our local ethics committee.

Summary Measures and Meta-analysis

Severity of anaphylaxis was modeled as a binary variable independently of the criterion used to establish severity in each study. ORs with a 95% confidence interval (CI) were calculated as a summary measure, since some studies make it possible to conclude that for the severity of anaphylaxis, the OR is a good marker of relative risk, because of the low prevalence of severe anaphylaxis. In a meta-analysis of food anaphylaxis [22], the incidence rate of anaphylaxis requiring admission to hospital (as a proxy of severity) was 6.4% of the incidence rate of food anaphylaxis.

The heterogeneity of the studies was measured using the $I^2$ statistic (inconsistency) [23]. Given the probable heterogeneity of the studies, we performed the meta-analysis using a random-effects model following the approach of DerSimonian and Laird. In the case of cells with zero in the contingency table, 0.5 was added to enable the analysis. For this meta-analysis, we performed an additional meta-analysis without these studies in order
to assess the possible changes produced by our approach [24]. Likewise, in order to account for the heterogeneity of the studies, we used meta-regression models, by means of which we checked whether the design, type of anaphylaxis, outcome, and presence of adjustment played a relevant role in determining heterogeneity. Other variables not included in the regression models were age and population, owing to the fact that they were grouped very heterogeneously. Bias due to small sample size was assessed by analyzing the symmetry of the funnel plot and using Egger’s test in the case of the meta-analysis based on ≥10 studies owing to the low power associated with a low number of studies [25]. Therefore, this approach was only used in the meta-analyses of all respiratory and all asthma studies and in the cross-sectional studies on both diseases. All statistical analyses were carried out using STATA™, version 15.1.
Results

Selection of studies

Our literature search revealed 5354 publications on respiratory disease (Figure 1), of which 1818 (33.96%) were related to asthma (1774) or COPD (92). After exclusion of duplicate studies, the number of publications decreased to 3437. A further 3296 articles were excluded during the screening phase. One article [26] was identified by checking the references of the excluded articles. Of the remaining 142 studies, 129 were excluded because they did not have available risk estimates. Therefore, 13 met our criteria for inclusion in the review [1-4,8, 9,11-14,27-29] and had data for the quantitative analysis (Table 1). Almost all of the studies were cross-sectional observational studies, and only 1 was a case-control study [8]. The studies were published from 1993 to December 2017. All studies for cardiovascular and respiratory diseases were published in English.

Characteristics of the studies

The 13 studies on respiratory disease brought together 67,948 episodes (Table 2 and 3). With respect to severity, the most frequent analysis was carried out in studies analyzing the main causes of anaphylaxis (6 from 13 for respiratory disease), whereas anaphylaxis due to drugs was the second cause of anaphylaxis studied (3 from respiratory disease). The number of different outcomes in the severity studies was 10 for respiratory disease. Presence of respiratory disease was assessed based on the criteria used in the clinical records (9), although up to 4 additional approaches were followed by other authors (Table 2).
In the case of severity, the authors followed various strategies to control for confounders. Seven confounders were frequently identified, the most common being age, sex, cardiovascular diseases, and type of anaphylaxis (9, 7, 5, and 3 studies, respectively). Analysis of bias using the Newcastle-Ottawa scale [20] showed that except for 2 studies, the remaining studies yielded scores equal to 7.

Table 2 shows individual studies with their contingency tables.

**Effects of respiratory disease on severity of anaphylaxis**

*All respiratory diseases*

In this meta-analysis, respiratory disease increased the severity of anaphylaxis (OR, 1.87; 95% CI, 1.30-2.70). The general analysis of the studies revealed heterogeneity ($I^2=87.3\%$, $p<0.001$). The study of Ha et al [26] had 0 events in some of the cells in the contingency table (Table 2). We therefore performed an additional meta-analysis without this study, and the OR remained almost unchanged (OR, 1.89; 95% CI, 1.30-2.73). The separate analysis of adjusted studies also showed the presence of a significant OR (OR, 1.71; 95% CI, 1.15-2.54) and heterogeneity ($I^2=90.5\%$, $p<0.001$). The OR was also significant in the 4 non-adjusted studies (OR, 2.77; 95% CI, 1.05-7.32). Examination of this meta-analysis did not reveal heterogeneity ($I^2=42.5\%$, $p=0.16$) (Figure 2, Table 3). The meta-regression analysis did not reveal any variants that explained the heterogeneity.

The funnel plot did not show presence of small studies with high effects, and findings were confirmed with the Egger test ($p=0.11$) (Figure 3).

*Presence of asthma*
Overall, asthma increased the severity of anaphylaxis (OR, 1.89; 95% CI, 1.26-2.83), albeit with heterogeneity ($I^2=91.1\%$; 95% CI, 91.1% p<0.001). The study of Ha et al [26] once again had 0 values in some of the cells in the contingency table, and the OR was very similar in the meta-analysis with and without the authors’ data (OR, 1.90; 95% CI, 1.26-2.86) (Figure 4). The meta-analysis of adjusted and non-adjusted studies showed that asthma was associated with greater severity of anaphylaxis (Table 3). The meta-analysis of adjusted studies showed heterogeneity, whereas that of non-adjusted studies did not. Once again, none of the covariables used in the meta-regression model were able to account for this heterogeneity.

The funnel plot shows the absence of small studies with effects that favored severity of anaphylaxis, while the results of the Egger test for small effect bias were significant (p=0.036) (Figure 3).

**Presence of COPD**

Only 3 studies [1, 9, 12] were available to study the relationship between COPD and severity of anaphylaxis (2 with adjusted studies and 1 with non-adjusted studies). For the meta-analysis of all studies (adjusted and non-adjusted), COPD increased the severity of anaphylaxis (OR, 2.47; 95% CI, 1.46-4.18). Heterogeneity was recorded in this meta-analysis ($I^2=70.6\%$, p=0.033). The meta-analysis of 2 adjusted studies showed similar ORs, although heterogeneity was high without reaching statistical significance ($I^2=70.5\%$, p=0.066) (Table 3).

**Quality of evidence of the meta-analysis**

As for the quality of evidence for the relationship between severity of anaphylaxis and respiratory disease, application of the GRADE system showed the quality of evidence to
be moderate for studies assessing COPD, low for asthma (with no separation between adjusted and non-adjusted studies), and very low for all respiratory diseases using individual adjusted studies and all studies (Table 4).

**Discussion**

*Severity of anaphylaxis*

Our meta-analysis showed that respiratory diseases increased the severity of anaphylaxis in studies that were adjusted or not adjusted for individual studies. However, according to the recommendations of the GRADE guidelines [30], the quality of evidence was only moderate for meta-analyses of all studies on COPD and low for adjusted meta-analyses including all studies on asthma. Consequently, our initial observations must be interpreted with some degree of caution because of the known and unknown confounders that are classically associated with observational studies.

Differences in prognosis in exposed and unexposed populations mean that observational studies carry a risk of bias [21,31], since they cannot control for confounders owing to the fact that the groups are not chosen randomly [31,32].

According to the GRADE framework, evidence from observational studies is low [30]. However, the risk of bias is diminished if methodologically rigorous observational studies are performed (those that comprehensively and accurately measure prognostic factors associated with the outcome of interest), if the studies minimize loss to follow-up (the worst reported characteristic in the studies in our systematic reviews), if the 2 groups are similar (similar time, place, and population, as in our study), and if the analysis is an adjusted analysis that controls for differences in the distribution of
prognostic factors between exposure and control groups (as in 12 of 13 studies in the present review). In addition, if the studies show a sufficiently large effect (RR >2 and strength >5), it seems reasonable to consider this effect real [20,30]. These conclusions can translate to ORs if the baseline risk is 20% or lower [20,30]. If the studies meet these conditions, evidence can be upgraded to moderate.

In the case of respiratory disease, the association with advanced cardiovascular disease [33] can confound the effect of respiratory disease on severity of anaphylaxis. However, this confounding effect is mainly for COPD and other respiratory diseases and is much less pronounced for asthma, a disease associated with younger age groups. In the case of COPD, the effect of cardiovascular disease was not controlled for in the study of Clark et al [8], although it was controlled for in the studies by Mulla and Simmons and Worm et al [1,12]. This finding, together with the strength of the OR [30], means that the quality of evidence for the increase in the effect of COPD on severity of anaphylaxis is moderate according to the GRADE score (1 step below the maximum score). In the case of asthma, the quality of evidence was low (1 step below moderate) because the OR was less than 2, despite being less affected by possible confounding factors. Asthma has traditionally been considered a very sensitive risk factor for severe anaphylaxis and fatal anaphylaxis, although specificity was low for many patients with food anaphylaxis (severe and not severe) who had asthma as a comorbid condition [6]. In their fatal anaphylaxis series, Pumphrey et al [14] reported that many deaths involved patients with uncontrolled asthma. However, in our review, only the study by Summers et al [10] analyzed whether moderate or severe asthma increased the severity of anaphylaxis more than mild asthma and found non-significant differences between both.
Likewise, age can be a confounding factor for the severity of anaphylaxis and COPD. However, we cannot carry out a meta-analysis of age and severity of anaphylaxis because assessment of age was very heterogeneous in the individual studies (2 values under or over a cut-off, age-group variables).

**Limitations of the study**

We added 0.5 in those cells containing zero values. For meta-analyses that excluded or did not exclude these studies, neither the statistical significance nor the fact that the OR was higher or lower than 1 changed after excluding these studies (data not shown).

In studies assessing small study bias or publication bias, the Egger test and the funnel plots revealed bias in very few meta-analyses, as in the case of the meta-analysis of asthma effects on severity of anaphylaxis. Harris et al [22] considered the Egger test to be conservative and frequently suggest that caution is needed when interpreting the results of meta-analyses. Using the qualitative funnel plot, most studies did not seem to show the large facilitating effects of small studies.

Our findings were also limited by the heterogeneity of the studies assessed: several studies were carried out in different clinical settings, anaphylaxis occurred during different diagnostic or therapeutic protocols, there was not common criteria on the diagnosis of anaphylaxis, the types of anaphylaxis and the criteria used to diagnose respiratory diseases were different, and the categories of respiratory diseases may have been too broad and ambiguous (Table 1 and 2). Consequently, our conclusions must be
interpreted with caution owing to the heterogeneity of the studies included in our review.

Nevertheless, we did make an effort to obtain as much information as possible on the type respiratory diseases analyzed in the review. This is very evident in the analysis of respiratory disease, where characterization covers almost all of the studies (from 13 studies, asthma was the disease analyzed in 7 and COPD in 4) as shown in Tables 1 and 2.

Another weakness of our meta-analysis is that some of the markers of severity chosen by the authors of the studies reviewed, such as admissions, may be more related to prognostic factors owing to an increased number of comorbidities that force clinicians to opt for more conservative management.

To our knowledge, no studies have evaluated the correlation between the different anaphylaxis severity scores; therefore, it seems that heterogeneity of outcomes does not explain the heterogeneity of the meta-analyses. The authors use the highest grade(s) of severity, which are similar in each organ and system evaluated. On the other hand, when authors do not use these scores, individual proxies of severity belong to extreme grades or the 2 highest grades of severity.

On the other hand, analyzing more than 2 grades of severity can be more informative, although it may prove problematic, because many authors report only 2 levels of severity or it is difficult to establish limits for intermediate severity and equivalences of
intermediate severity between different outcomes. However, this choice can introduce unknown bias because not all grades of severity are reviewed.

Finally, the presence of 4 studies (from 13) where anaphylaxis was diagnosed based on ICD-9-CM codes could be considered a weakness of our study. Walsh et al. [34] found a positive predictive value of 63.1% for ICD-9-CM codes in the diagnosis of anaphylaxis and wide variability between the 5 health organizations that provided patient records (from 48.1% to 78.9%). In other words, while ICD-9-CM has considerable external validity, it only has moderate internal validity.

Summary

The authors of the GRADE guidelines recommend not rating up for a large effect size if there are major problems associated with accuracy, publication bias, and the risk of bias (a confounding factor for cardiovascular disease and COPD in the present review) [20]. Therefore, evidence obtained according to the GRADE guidelines will generally be low to moderate for the influence of respiratory diseases on severity of anaphylaxis if we apply the 4 grades for quality of evidence as a continuous scale.

In summary, for respiratory disease, the meta-analysis revealed the quality of evidence to be low to moderate, although not owing to the confounding effects, but rather to the widespread presence of asthma in severe and non-severe anaphylaxis. A series of studies should be conducted to determine whether the different degrees of severity of asthma are associated to different extents with the different grades of severity of anaphylaxis.
Previous Presentations


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Conflict of interest statement

The authors declare that they have no conflicts of interest.
References


25. Harbord RM, Harris RJ, Sterne JAC. Updated tests for small studies effects in meta-analyses. Meta-Analysis in Stata: An updated collection from the State Journal. 2nd ed. College Station (Texas, USA): Stata Press; 2016. p. 29-54


Figures

Figure 1. PRISMA flow diagrams summarizing the study selection process for respiratory diseases.
Figure 2. Meta-analysis of respiratory disease and severity of anaphylaxis (adjusted, non-adjusted).

Severity of anaphylaxis if respiratory diseases present
all adjusted studies

Severity of anaphylaxis if respiratory diseases present
all non-adjusted studies

Severity of anaphylaxis if respiratory diseases present
all studies

NOTE: Weights are from random-effects analysis.
Figure 3. Funnel plots for the meta-analysis of respiratory diseases assessing small study bias.
Figure 4. Meta-analysis of presence of asthma and severity of anaphylaxis.
Table 1. Characteristics of studies included in both meta-analyses: Severity of anaphylaxis and respiratory diseases.

<table>
<thead>
<tr>
<th>Author/Country/Year</th>
<th>Design</th>
<th>Type of Records</th>
<th>Type of Anaphylaxis/Criteria for Diagnosis of Anaphylaxis</th>
<th>Outcome of Severity</th>
<th>Type of Respiratory Disease</th>
<th>Adjustment</th>
<th>Quality of Study</th>
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<td>LANG\footnote{8}</td>
<td>Case-control</td>
<td>Structured questionnaire of anaphylaxis in patients with use of RCM</td>
<td>Drug anaphylaxis Urticaria or angioedema plus upper respiratory tract or lower respiratory tract involvement or hypotension or syncope or arrhythmia 20 minutes after infusion radiologic contrast medium</td>
<td>Hypotension OR stridor</td>
<td>Asthma</td>
<td>Confounders (same iodinated radiologic contrast, age, date of study) and in the multivariate analysis (asthma, cardiovascular diseases and BBs). Use of binomial logistic regression</td>
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<td>SUMMERS\footnote{11} UK 2008</td>
<td>Cross-sectional</td>
<td>Outpatient allergy clinic</td>
<td>Peanut and tree nut anaphylaxis Not specified</td>
<td>Loss of consciousness</td>
<td>Moderate-severe asthma</td>
<td>List of adjusted covariables: Upper airway disease, lower airway disease, eczema, age, use of binomial logistic regression</td>
<td>7</td>
<td>1094</td>
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<td>AHNER\footnote{28} TURKEY 2009</td>
<td>Cross-sectional</td>
<td>Outpatient allergy clinic</td>
<td>Food Urticaria or angioedema plus upper respiratory tract or lower respiratory tract or gastro-intestinal tract involvement which was temporarily related to food consumption</td>
<td>3-</td>
<td>Asthma</td>
<td>Bronchial asthma, multiple food allergy and house dust mite allergy</td>
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<td>CALVANI\footnote{14} ITALY 2012</td>
<td>Cross-sectional</td>
<td>Outpatient allergy clinic</td>
<td>Food NIAID/FAAN criteria</td>
<td>4-5 SAMPSON</td>
<td>Asthma</td>
<td>Age, parents’ asthma, previous episodes, history of asthma, and chronic/relapsing gastrointestinal symptoms</td>
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<td>BROWN\footnote{2} AUSTRALIA</td>
<td>Cross-sectional</td>
<td>Emergency department</td>
<td>All subtypes</td>
<td>Hypotension</td>
<td>Respiratory diseases</td>
<td>List several adjusted covariables (age, gender, respiratory diseases, drug anaphylaxis,</td>
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<td>Year</td>
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<td>Methods</td>
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<td>Adjusted Covariates</td>
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<td>2013</td>
<td>VAN ERP</td>
<td>Cross-sectional</td>
<td>Peanut challenges in children</td>
<td>Food-related</td>
<td>4-5 Sampson Asthma treated with ICS</td>
<td>Age, gender, other food allergy, IgE for peanut, IgE for Ara h2, previous reaction to peanut</td>
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<td>Admissions for anaphylaxis in the Texas Hospital System (USA)</td>
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<td>Mechanical ventilation COPD</td>
<td>List several adjusted covariates (age, gender, Charlson-Deyo score, autoinjectors, previous visit to allergist, ACEIs, BBs, previous laboratory tests, previous visit to emergency department, previous hospitalization, cardiovascular disease)</td>
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<td>No state health system record, several HMOs including Medicare</td>
<td>All subtypes</td>
<td>Admission to hospital COPD</td>
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<td>2015</td>
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<td>Retrospective data from all of the patients with a history of perioperative hypersensitivity referred to allergy clinic of authors</td>
<td>Drug anaphylaxis</td>
<td>3-4 Reisner-RING Respiratory diseases</td>
<td>Not adjusted</td>
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<td>HA</td>
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<td>Iodinated contrast</td>
<td>Drug anaphylaxis</td>
<td>Severe anaphylaxis according to ACR Asthma</td>
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<td>European anaphylaxis registry</td>
<td>All subtypes NIAID/FAAN criteria SatO₂&lt;92%, collapse, systolic blood pressure &lt;90, altered consciousness, or incontinence</td>
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</table>

Total with quantitative data 13 67948

ACR: American College of Radiology; LOCMs: low osmolar contrast media; HMOs: health management organizations; BB: beta-blocker; ACEI: angiotensin-converting enzyme inhibitor; ICS: inhaled corticosteroid; NIAID/FAA: National Institute of Allergy and Infectious Diseases/Food Allergy Anaphylaxis Network.
Table 2. Contingency table for studies included in the meta-analysis of severity of anaphylaxis and concomitant presence of cardiovascular and respiratory diseases.

<table>
<thead>
<tr>
<th>AUTHOR/YEAR</th>
<th>TYPE OF PATIENTS</th>
<th>EXPOSURE AND DIAGNOSIS OF EXPOSURE</th>
<th>OUTCOME</th>
<th>EXPSED, CASES</th>
<th>NOT EXPSED, CASES</th>
<th>EXPSED, NOT CASES</th>
<th>NOT EXPSED, NOT CASES</th>
<th>ODDS RATIO</th>
<th>95% CI LOWER LIMIT</th>
<th>95% CI UPPER LIMIT</th>
<th>ADJUSTED OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LANG 1/1993</td>
<td>Iodinated contrast</td>
<td>Asthma (clinical criteria)</td>
<td>Hypotension OR stridor</td>
<td>2 8</td>
<td>8 87</td>
<td></td>
<td></td>
<td>5.91</td>
<td>0.60</td>
<td>58.50</td>
<td>Yes</td>
</tr>
<tr>
<td>CALVAN 1/2003</td>
<td>Outpatient allergy clinic</td>
<td>Asthma (clinical records)</td>
<td>4-5 SAMPSON</td>
<td>20 16</td>
<td>39 88</td>
<td></td>
<td></td>
<td>7.10</td>
<td>2.50</td>
<td>20.20</td>
<td>Yes</td>
</tr>
<tr>
<td>SUMMERS 1/2008</td>
<td>Outpatient allergy clinic</td>
<td>Moderate-severe asthma (clinical records)</td>
<td>Loss of consciousness</td>
<td>43 113</td>
<td>149 787</td>
<td></td>
<td></td>
<td>2.00</td>
<td>0.80</td>
<td>5.20</td>
<td>Yes</td>
</tr>
<tr>
<td>AHNER 2/2009</td>
<td>Outpatient allergy clinic</td>
<td>Asthma (not showed)</td>
<td>3-MURARO</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
<td>3.41</td>
<td>1.18</td>
<td>9.82</td>
<td>Yes</td>
</tr>
<tr>
<td>BROWN 3/2013</td>
<td>Emergency department</td>
<td>Respiratory diseases (clinical records)</td>
<td>Hypotension</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
<td>0.89</td>
<td>0.42</td>
<td>1.90</td>
<td>Yes</td>
</tr>
<tr>
<td>MULLA 1/2013</td>
<td>Hospital admissions</td>
<td>COPD (codes system)</td>
<td>Mechanical ventilation</td>
<td>32 332</td>
<td>116 1928</td>
<td></td>
<td></td>
<td>1.61</td>
<td>1.06</td>
<td>2.46</td>
<td>Yes</td>
</tr>
<tr>
<td>VAN ERP 3/2013</td>
<td>Peanut challenges in children</td>
<td>Asthma using ICS (clinical criteria)</td>
<td>4-5 SAMPSON</td>
<td>9 15</td>
<td>74 127</td>
<td></td>
<td></td>
<td>1.13</td>
<td>0.36</td>
<td>3.50</td>
<td>No</td>
</tr>
<tr>
<td>CLARK 4/2014</td>
<td>Emergency department and admissions</td>
<td>COPD (clinical records)</td>
<td>Hospital admission</td>
<td>8 2614</td>
<td>4 9346</td>
<td></td>
<td></td>
<td>7.15</td>
<td>2.15</td>
<td>23.77</td>
<td>No</td>
</tr>
<tr>
<td>MIRONI 5/2015</td>
<td>Perioperative anaphylaxis</td>
<td>Respiratory diseases (clinical records)</td>
<td>3-4 REISNER-RING</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
<td>3.43</td>
<td>0.93</td>
<td>12.66</td>
<td>No</td>
</tr>
<tr>
<td>HA 7/2016</td>
<td>Iodinated contrast</td>
<td>Asthma (clinical records)</td>
<td>Severe anaphylaxis according to ACR</td>
<td>0 37</td>
<td>0 33</td>
<td></td>
<td></td>
<td>0.89</td>
<td>0.02</td>
<td>47.28</td>
<td>No</td>
</tr>
<tr>
<td>MOTOSUE 1/2017</td>
<td>Emergency department</td>
<td>Respiratory diseases (clinical criteria)</td>
<td>Mechanical ventilation</td>
<td>124 443</td>
<td>173 3630</td>
<td></td>
<td></td>
<td>1.21</td>
<td>1.08</td>
<td>1.36</td>
<td>Yes</td>
</tr>
<tr>
<td>NIETO 2/2017</td>
<td>Hospital admissions</td>
<td>Respiratory diseases (codes system)</td>
<td>Mechanical ventilation</td>
<td>112 206</td>
<td>818 4125</td>
<td></td>
<td></td>
<td>2.57</td>
<td>2.00</td>
<td>3.32</td>
<td>Yes</td>
</tr>
<tr>
<td>WORM 4/2018</td>
<td>European anaphylaxis registry</td>
<td>Asthma (European register of anaphylaxis)</td>
<td>SatO₂&lt;92%, collapse, systolic blood pressure &lt;90, altered consciousness, or incontinence</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
<td>0.75</td>
<td>0.61</td>
<td>0.89</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 3. Synthesis and heterogeneity statistics in the meta-analysis of severity of anaphylaxis and respiratory or cardiovascular diseases.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Number of studies</th>
<th>Type of studies</th>
<th>Overall OR, meta-analysis random effects</th>
<th>Lower limit, 95% CI</th>
<th>Upper limit, 95% CI</th>
<th>Heterogeneity, ( I^2 )</th>
<th>Heterogeneity, ( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory disease</td>
<td>13</td>
<td>All studies</td>
<td>1.87</td>
<td>1.30</td>
<td>2.70</td>
<td>87.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>12</td>
<td>Cross-sectional studies</td>
<td>1.82</td>
<td>1.26</td>
<td>2.64</td>
<td>88.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>1</td>
<td>Case-control studies</td>
<td>5.91</td>
<td>0.60</td>
<td>58.50</td>
<td>Only 1 study</td>
<td></td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>9</td>
<td>Adjusted OR</td>
<td>1.71</td>
<td>1.15</td>
<td>2.54</td>
<td>90.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>4</td>
<td>Non-adjusted OR</td>
<td>2.77</td>
<td>1.05</td>
<td>7.32</td>
<td>42.6%</td>
<td>0.156</td>
</tr>
<tr>
<td>COPD</td>
<td>3</td>
<td>All studies</td>
<td>2.47</td>
<td>1.46</td>
<td>4.18</td>
<td>70.6%</td>
<td>0.033</td>
</tr>
<tr>
<td>COPD</td>
<td>2</td>
<td>Adjusted OR</td>
<td>2.10</td>
<td>1.33</td>
<td>3.30</td>
<td>70.5%</td>
<td>0.066</td>
</tr>
<tr>
<td>COPD</td>
<td>1</td>
<td>Non-adjusted OR</td>
<td>7.15</td>
<td>2.15</td>
<td>23.77</td>
<td>Only 1 study</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>13</td>
<td>All studies</td>
<td>1.89</td>
<td>1.26</td>
<td>2.83</td>
<td>91.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthma</td>
<td>12</td>
<td>Cross-sectional studies</td>
<td>1.83</td>
<td>1.22</td>
<td>2.76</td>
<td>91.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthma</td>
<td>1</td>
<td>Case-control studies</td>
<td>5.91</td>
<td>0.60</td>
<td>58.50</td>
<td>Only 1 study</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>9</td>
<td>Adjusted OR</td>
<td>1.80</td>
<td>1.14</td>
<td>2.85</td>
<td>93.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthma</td>
<td>4</td>
<td>Non-adjusted OR</td>
<td>2.35</td>
<td>1.36</td>
<td>4.05</td>
<td>18.9%</td>
<td>0.296</td>
</tr>
</tbody>
</table>
Table 4. Analysis of the quality of evidence of the different meta-analyses using the GRADE guidelines.

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>No. of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Respiratory diseases [comparison]</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory diseases and severity of anaphylaxis, all studies (assessed with: OR meta-analysis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Observational studies</td>
<td>Serious *</td>
<td>Serious †</td>
<td>Not serious</td>
<td>Not serious</td>
<td>All plausible residual confounding would reduce the demonstrated effect</td>
<td>350/3326 (10.5%)</td>
<td>3784/23395 (16.2%)</td>
<td>OR 1.87 (1.30 to 2.70)</td>
<td>103 more per 1000 (from 39 more to 181 more)</td>
<td>⬤ ⬤ ◯ ◯ ◯ VERY LOW</td>
<td>Critical</td>
</tr>
<tr>
<td>Respiratory diseases and severity of anaphylaxis, all non-adjusted studies (assessed with: OR meta-analysis)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Observational studies</td>
<td>Serious †</td>
<td>Serious †</td>
<td>Not serious</td>
<td>Serious §</td>
<td>Strong association, all plausible residual confounding would reduce the demonstrated effect, dose-response gradient</td>
<td>1795 (17.9%)</td>
<td>95/2666 (3.6%)</td>
<td>OR 2.77 (1.05 to 7.32)</td>
<td>57 more per 1000 (from 2 more to 177 more)</td>
<td>⬤ ⬤ ◯ ◯ LOW</td>
<td>Critical</td>
</tr>
<tr>
<td>Respiratory diseases and severity of anaphylaxis, all adjusted studies (assessed with: OR meta-analysis)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Observational studies</td>
<td>Serious †</td>
<td>Serious ll</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>333/3231 (10.3%)</td>
<td>1118/10645 (10.5%)</td>
<td>OR 1.71 (1.15 to 2.54)</td>
<td>62 more per 1000 (from 14 more to 125 more)</td>
<td>⬤ ⬤ ◯ ◯ ◯ VERY LOW</td>
<td>Critical</td>
</tr>
<tr>
<td>Asthma and severity of anaphylaxis, all studies (assessed with: OR meta-analysis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>581/11428 (5.1%)</td>
<td>7536/49585 (15.2%)</td>
<td>OR 1.89 (1.26 to 2.83)</td>
<td>101 more per 1000 (from 32 more to 185 more)</td>
<td>⬤ ⬤ ◯ ◯ LOW</td>
<td>Critical</td>
</tr>
<tr>
<td>COPD and severity of anaphylaxis, all studies (assessed with: OR meta-analysis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Other considerations</td>
<td>No. of patients</td>
<td>Effect</td>
<td>Certainty</td>
<td>Importance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------</td>
<td>--------------</td>
<td>---------------</td>
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<td>-------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>--------</td>
<td>-----------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Observational studies</td>
<td>Serious ¶</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Strong association, all plausible residual confounding would reduce the demonstrated effect</td>
<td>271/10023 (26.5%)</td>
<td>3033/18618 (16.3%)</td>
<td>OR 2.47 (1.46 to 4.18)</td>
<td>162 more per 1000 (from 58 more to 286 more)</td>
<td>⨁⨁⨁ ⯃ MODERATE</td>
<td>Critical</td>
</tr>
</tbody>
</table>

Explanations

CI: Confidence interval; OR: Odds ratio
*No adjustment in studies with cardiovascular disease
†Overall (I²=87.3%, p<0.001)
‡ No adjustment in studies with cardiovascular disease
§ Small number of cases
Il Overall (I²=90.5%, p<0.001)
¶ No adjustment in studies with cardiovascular disease