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Association Between Severity of Anaphylaxis and Co-occurrence of Respiratory Diseases: A Systematic Review and Meta-analysis of Observational Studies

Tejedor-Alonso MA[1,2], Farias-Aquino E[1,3], Pérez–Fernández E[1], Moro-Moro M[1], Rosado-Ingelmo A[1], Alberti Masgrau N[4], Pérez-Codesido S[1], Privitera-Torres M[1]

[1]Hospital Universitario Fundación Alcorcón, Alcorcón (Madrid), Spain
[2]Facultad Ciencias de la Salud, Universidad Rey Juan Carlos, Alcorcón (Madrid), Spain
[3]Escuela Internacional de Doctorado, Universidad Rey Juan Carlos, Alcorcón (Madrid), Spain
[4]Pathology Department, Hospital Universitario 12 de Octubre, Madrid, Spain
*Enrique Farias-Aquino and Miguel A Tejedor-Alonso contributed equally to this work.

■ **Abstract**

Background: Asthma is very prevalent in all grades of severity of anaphylaxis. Asthma and chronic obstructive pulmonary disease (COPD) have been associated with the 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), as did asthma (OR, 1.89; 95%CI, 1.26-2.83). For the meta-analysis of all studies (adjusted and nonadjusted), COPD increased the severity of anaphylaxis (OR, 2.47; 95%CI, 1.46-4.18). In the case of 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**

Antecedentes: El asma es muy frecuente en todos los grados de gravedad de la anafilaxia y así mismo el asma y 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. Meta-análisis.

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 3 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 February 28, 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 (ie, food, drugs) or a specific cause of anaphylaxis (ie, 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 (antihypertensive 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 (eg, 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%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

Table 1. Characteristics of Studies Included in Both Meta-analyses: Severity of Anaphylaxis and Respiratory Diseases

Autor/ Country/ Year	Design	Type of Records	Type of Anaphylaxis/ Criteria for Diagnosis of Anaphylaxis	Outcome of Severity	Type of Respiratory Disease	Adjustment	Quality of Study	No.
Lang et al [8]	Case-control	Structured questionnaire of anaphylaxis in patients with use of RCM	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	Hypotension OR stridor	Asthma	Confounders (same iodinated radiologic contrast, age, date of study) and in the multivariate analysis (asthma, cardiovascular diseases and BBs). Use of binomial logistic regression	7	105
Summers et al [11] UK 2008	Cross-sectional	Outpatient allergy clinic	Peanut and tree nut anaphylaxis Not specified	Loss of consciousness	Moderate-severe asthma	List of adjusted covariables: Upper airway disease, lower airway disease, eczema, age, use of binomial logistic regression	7	1094
Ahner et al [28] Turkey 2009	Cross-sectional	Outpatient allergy clinic	Food Urticaria or angioedema plus upper respiratory tract or lower respiratory tract or gastro-intestinal tract involvement which was temporally related to food consumption	3-MURARO	Asthma	Bronchial asthma, multiple food allergy and house dust mite allergy	4	129
Calvani et al [14] Italy 2012	Cross-sectional	Outpatient allergy clinic	Food NIAID/FAAN criteria	4-5 SAMPSON	Asthma	Age, parents' asthma, previous episodes, history of asthma, and chronic/relapsing gastrointestinal symptoms	7	163
Brown et al [2] Australia 2013	Cross-sectional	Emergency department	All subtypes NIAID/FAAN criteria	Hypotension	Respiratory diseases	List several adjusted covariables (age, gender, respiratory diseases, drug anaphylaxis, cardiovascular diseases, cardiovascular medication). Use of binomial logistic regression, gender, other food allergy, IgE for peanut, IgE for Ara h 2, previous reaction to peanut	7	315
Van Erp, et al [29] The Netherlands 2013	Cross-sectional	Peanut challenges in children	Food Following grades of severity of Sampson score	4-5 SAMPSON	Asthma treated with ICS		7	225
Mulla and Simons [1] USA 2013	Cross-sectional	Admissions for anaphylaxis in the Texas Hospital System (USA)	All subtypes ICD-9-CM codes related to anaphylaxis	Mechanical ventilation	COPD	List several adjusted covariates (age, gender, Charlson-Deyo score [47], autoinjectors, previous visit to allergist, ACEIs, BBs, previous laboratory tests, previous visit to emergency department, previous hospitalization, cardiovascular disease)	7	2410

(continued)

Table 1. Characteristics of Studies Included in Both Meta-analyses: Severity of Anaphylaxis and Respiratory Diseases (*continued*)

Autor/Country/Year	Design	Type of Records	Type of Anaphylaxis/Criteria for Diagnosis of Anaphylaxis	Outcome of Severity	Type of Respiratory Disease	Adjustment	Quality of Study	No. Study
Clark et al [9] USA 2014	Cross-sectional	No state health system record, several HMOs including Medicare	All subtypes; ICD-9-CM codes related to anaphylaxis	Admission to hospital	COPD	List several adjusted covariates (age, gender, Charlson-Deyo score [47], filled adrenaline devices, previous visit to allergist, ACEIs, BBs, previous diagnostic laboratory tests, previous visit to emergency department, previous hospitalization, cardiovascular disease)	7	11972
Mirone et al [3] Italy 2015	Cross-sectional	Retrospective data from all of the patients with a history of perioperative hypersensitivity referred to allergy clinic of authors	Drug anaphylaxis; Following grades of severity of Messner-Ring score	3-4 REISNER-RING	Respiratory diseases	Not adjusted	5	193
Ha et al [27] Korea 2016	Cross-sectional	Iodinated contrast	Drug anaphylaxis; Not specified	Severe anaphylaxis according to ACR	Asthma	Age, sex, time of onset, previous allergy to LOCMs, change of contrast, pretreatment	7	70
Nieto-Nieto et al [12] Spain 2017	Cross-sectional	Admissions for anaphylaxis in the Spanish Hospital System	All subtypes; ICD-9-CM codes related to anaphylaxis	Mechanical ventilation	Respiratory diseases	Adjusted according to the Elixhauser score [45]	7	5261
Motosue et al [4] USA 2017	Cross-sectional	Emergency department	All subtypes; ICD-9-CM codes related to anaphylaxis	Mechanical ventilation	Respiratory diseases	Age groups, gender, census region, cause of anaphylaxis, heart disease, asthma, respiratory diseases, eczema, allergy visit, Charlson comorbidity index	7	38695
Worm et al [13] Europe 2018	Cross-sectional	European anaphylaxis registry	All subtypes; NIAID/FAAN criteria	$SatO_2 < 92\%$, collapse, systolic blood pressure <90, altered consciousness, or incontinence	Asthma	Age, gender, asthma, mastocytosis, thyroid disease, exercise, psychological burden, ACEIs, BBs, causes of anaphylaxis	7	7316
Total with quantitative data	13							67948

Abbreviation: ACEI, angiotensin-converting enzyme inhibitor; ACR, American College of Radiology; BB, beta-blocker; HMOs, health management organizations; ICS, inhaled corticosteroid; LOCMs, low osmolar contrast media; NIAID/FAA, National Institute of Allergy and Infectious Diseases/Food Allergy Anaphylaxis Network.

of the studies, we performed the meta-analysis using a random-effects model following the DerSimonian and Laird approach. 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 the Egger test in the case of the meta-analysis based on ≥10 studies owing to the low power associated with such 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 (StataCorp LLC).

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<.001). The study of Ha et al [27] 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<.001). The OR was also significant in the 4 nonadjusted studies (OR, 2.77; 95%CI, 1.05-7.32). Examination of this meta-analysis did not reveal heterogeneity (I^2=42.5%, P=.16) (Figure 2, Table 3). The meta-regression analysis did not reveal any variants that could explain 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%; P<.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 nonadjusted studies showed that asthma was associated with greater severity of anaphylaxis (Table 3). The meta-analysis of adjusted studies showed heterogeneity, whereas that of nonadjusted 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=.036) (Figure 3).

Presence of COPD

Only 3 studies [1,9,12] were available to assess the relationship between COPD and severity of anaphylaxis (2 with adjusted studies and 1 with nonadjusted studies). For the meta-analysis of all studies (adjusted and nonadjusted), 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=.033). The meta-analysis of 2 adjusted studies showed similar ORs, although heterogeneity was high without reaching statistical significance (I^2=70.5%; P=.066) (Table 3).

Table 2. Contingency Table for Studies Included in the Meta-Analysis of Severity of Anaphylaxis and Concomitant Presence of Cardiovascular and Respiratory Diseases

Autor/ Year	Type of Patients	Exposure and Diagnosis of Exposure	Outcome	Exposed, Cases	Not Exposed, Cases	Exposed, Not Cases	Not Exposed, Not Cases	OR	95% CI Lower Limit	95% CI Upper Limit	Adjusted OR
Lang et al [8]/ 1993	Iodinated contrast	Asthma (clinical criteria)	Hypotension OR stridor	2	8	8	87	5.91	0.60	58.50	Yes
Calvan et al [14]/ 2003	Outpatient allergy clinic	Asthma (clinical records)	4-5 SAMPSON	20	16	39	88	7.10	2.50	20.20	Yes
Summers et al [11]/2008	Outpatient allergy clinic	Moderate-severe asthma (clinical records)	Loss of conscious-ness	43	113	149	787	2.00	0.80	5.20	Yes
Ahner et al [28]/ 2009	Outpatient allergy clinic	Asthma (not shown)	3-MURARO	Not reported				3.41	1.18	9.82	Yes
Brown et al [2]/ 2013	Emergency department	Respiratory diseases (clinical records)	Hypotension	Not reported				0.89	0.42	1.90	Yes
Mulla and Simons [1]/2013	Hospital admissions	COPD (codes system)	Mechanical ventilation	32	332	116	1928	1.61	1.06	2.46	Yes
Van Erp et al [29]/ 2013	Peanut challenges in children	Asthma using ICS (clinical criteria)	4-5 SAMPSON	9	15	74	127	1.13	0.36	3.50	No
Clark et al [9]/ 2014	Emergency department and admissions	COPD (clinical records)	Hospital admission	8	2614	4	9346	7.15	2.15	23.77	No
Mirone et al [3]/2015	Periopera-tive anaphylaxis	Respiratory diseases (clinical records)	3-4 REISNER-RING					3.43	0.93	12.66	No
Ha et al [27]/2016	Iodinated contrast	Asthma (clinical records)	Severe anaphylaxis according to ACR	0	37	0	33	0.89	0.02	47.28	No
Motosue et al [4]/ 2017	Emergency department	Respiratory diseases (clinical criteria)	Mechanical ventilation	124	443	173	3630	1.21	1.08	1.36	Yes
Nieto-Nieto et al [12]/2017	Hospital admissions	Respiratory diseases (codes system)	Mechanical ventilation	112	206	818	4125	2.57	2.00	3.32	Yes
Worm [13]/2018	European anaphylaxis registry	Asthma (European register of anaphylaxis)	$SatO_2$<92%, collapse, systolic blood pressure <90, altered conscious-ness, or incontinence	Not reported				0.75	0.61	0.89	Yes

Abbreviations: ACR, American College of Radiology; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid.

Table 3. Synthesis and Heterogeneity Statistics in the Meta-Analysis of Severity of Anaphylaxis and Respiratory or Cardiovascular Diseases

Exposure	Number of Studies	Type of Study	Overall OR, Meta-analysis Random Effects	Lower limit, 95% CI	Upper limit, 95% CI	Heterogeneity, I^2	Heterogeneity, P
Respiratory disease	13	All studies	1.87	1.30	2.70	87.3%	<.001
Respiratory disease	12	Cross-sectional studies	1.82	1.26	2.64	88.2%	<.001
Respiratory disease	1	Case-control studies	5.91	0.60	58.50	Only 1 study	
Respiratory disease	9	Adjusted OR	1.71	1.15	2.54	90.5%	<.001
Respiratory disease	4	Nonadjusted OR	2.77	1.05	7.32	42.6%	.156
COPD	3	All studies	2.47	1.46	4.18	70.6%	.033
COPD	2	Adjusted OR	2.10	1.33	3.30	70.5%%	.066
COPD	1	Nonadjusted OR	7.15	2.15	23.77	Only 1 study	
Asthma	13	All studies	1.89	1.26	2.83	91.1%	<.001
Asthma	12	Cross-sectional studies	1.83	1.22	2.76	91.7%%	<.001
Asthma	1	Case-control studies	5.91	0.60	58.50	Only 1 study	
Asthma	9	Adjusted OR	1.80	1.14	2.85	93.2%	<.001
Asthma	4	Nonadjusted OR	2.35	1.36	4.05	18.9%	.296

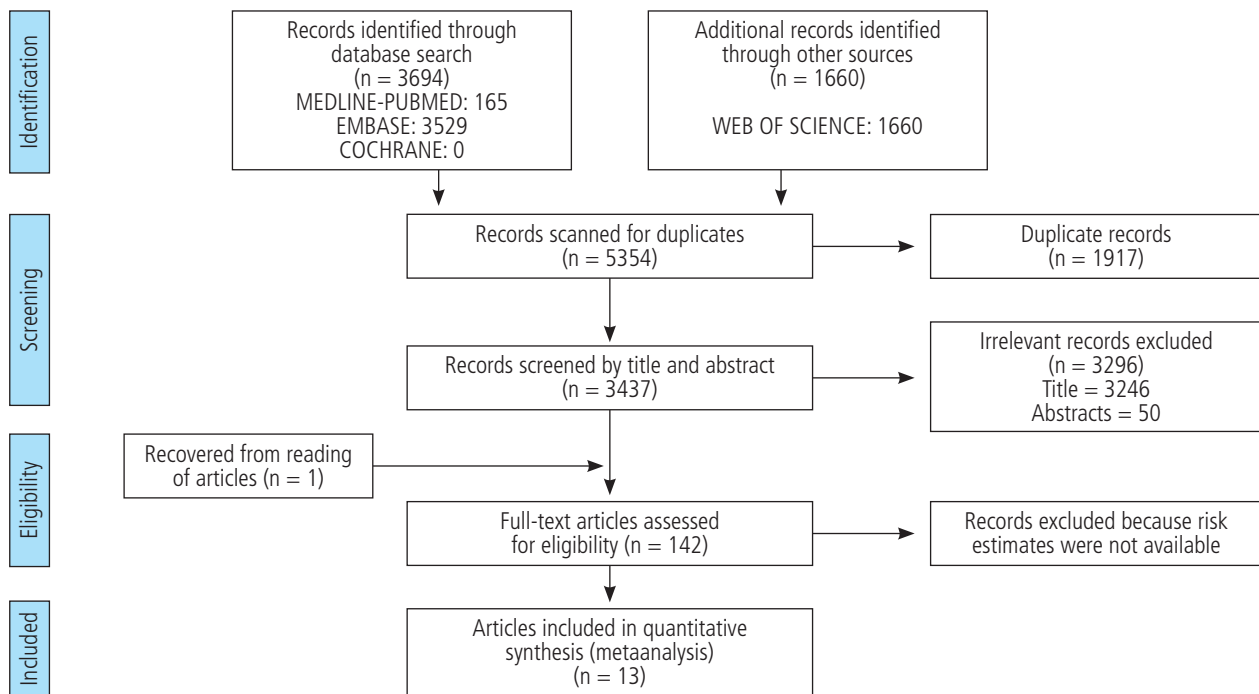Abbreviations: COPD, chronic obstructive pulmonary disease.

Figure 1. PRISMA flow diagrams summarizing the study selection process for respiratory diseases.
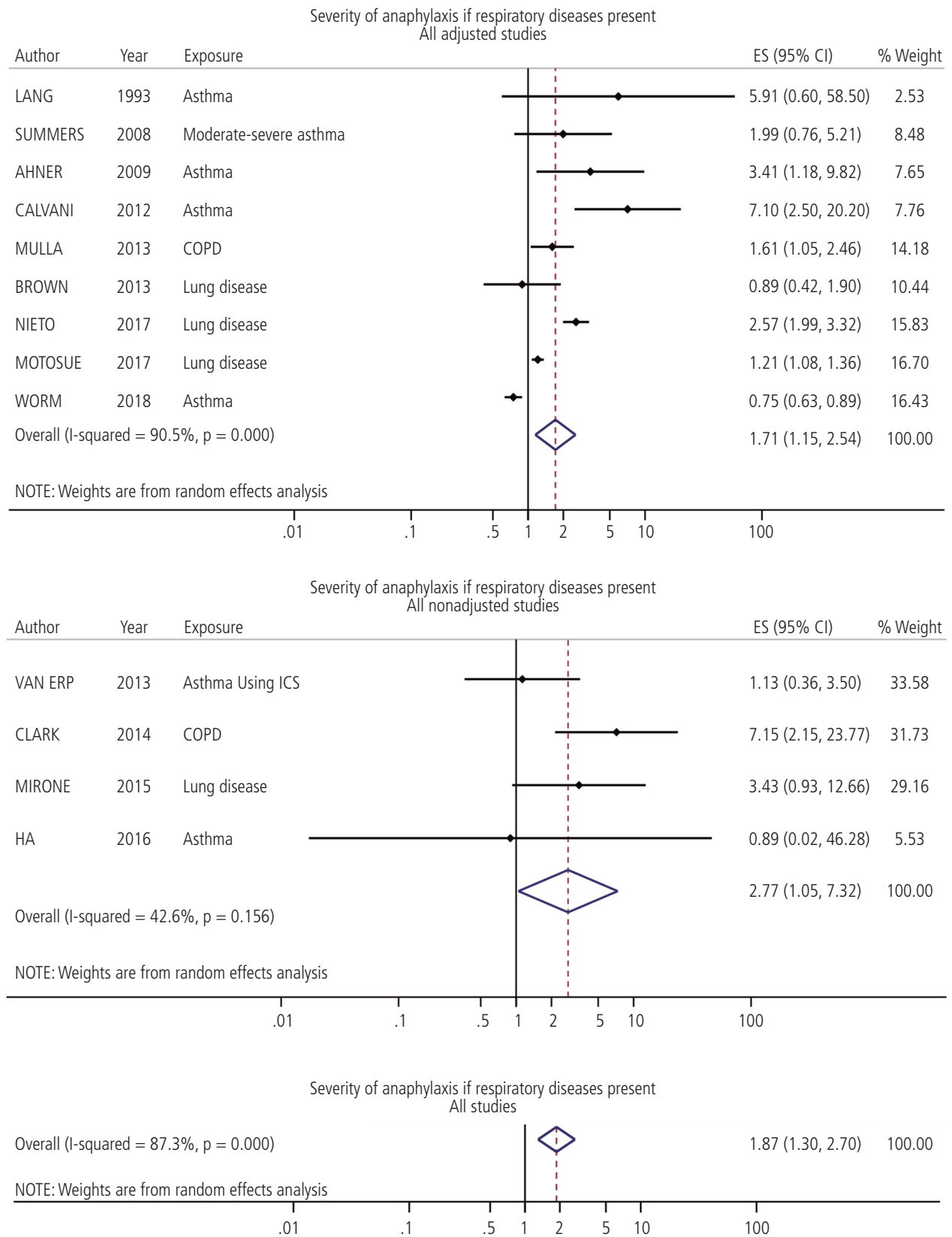
Figure 2. Meta-analysis of respiratory disease and severity of anaphylaxis (adjusted, nonadjusted). ES indicates effect size.
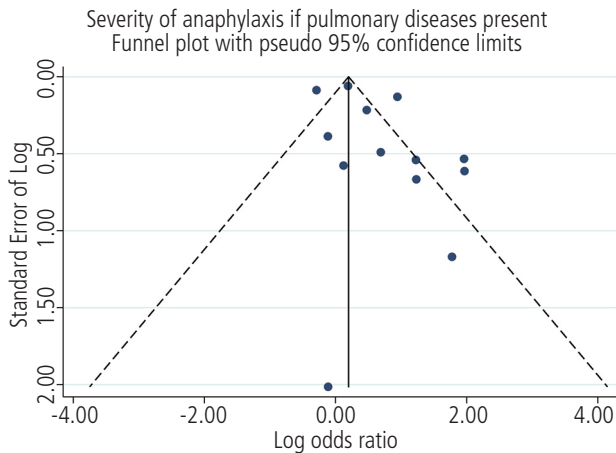
Severity of anaphylaxis if pulmonary diseases present
Funnel plot with pseudo 95% confidence limits

Figure 3. Funnel plots for the meta-analysis of respiratory diseases assessing small study bias.

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 nonadjusted studies), and very low for all respiratory diseases based on 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 the exposure and the 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 [9], although it was controlled for in the studies by Mulla and Simons [1] and Worm et al [13]. 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 and Gowland [15] reported that many deaths involved patients with uncontrolled asthma. However, in our review, only the study by Summers et al [11] analyzed whether moderate or severe asthma increased the severity of anaphylaxis more than mild asthma and found nonsignificant differences between both.

Age can also 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 once the studies were excluded (data not shown).

In assessments of 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 [23] considered the Egger test to be conservative and recommended caution 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 were no 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
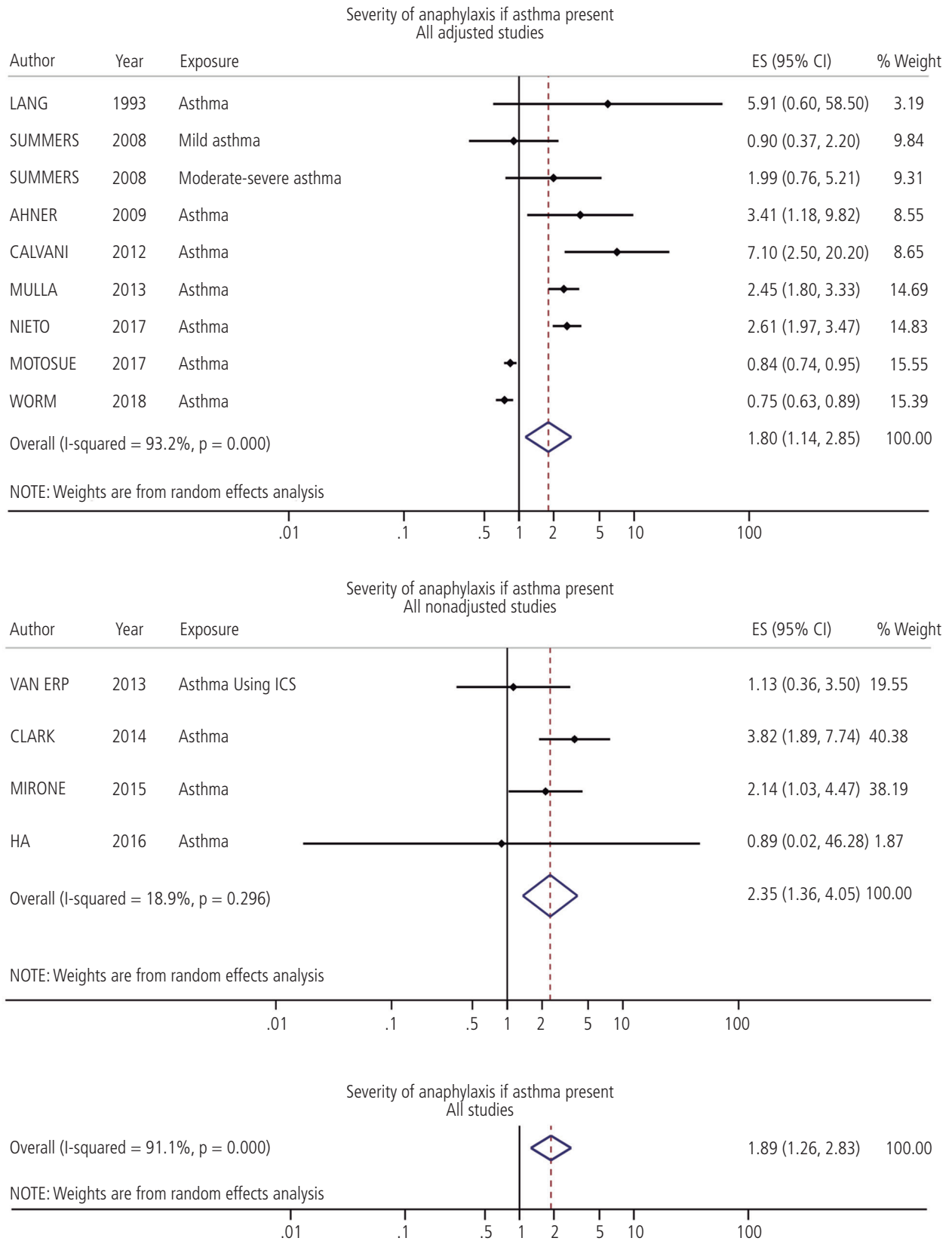
Severity of anaphylaxis if asthma present
All adjusted studies

Author	Year	Exposure		ES (95% CI)	% Weight
LANG	1993	Asthma		5.91 (0.60, 58.50)	3.19
SUMMERS	2008	Mild asthma		0.90 (0.37, 2.20)	9.84
SUMMERS	2008	Moderate-severe asthma		1.99 (0.76, 5.21)	9.31
AHNER	2009	Asthma		3.41 (1.18, 9.82)	8.55
CALVANI	2012	Asthma		7.10 (2.50, 20.20)	8.65
MULLA	2013	Asthma		2.45 (1.80, 3.33)	14.69
NIETO	2017	Asthma		2.61 (1.97, 3.47)	14.83
MOTOSUE	2017	Asthma		0.84 (0.74, 0.95)	15.55
WORM	2018	Asthma		0.75 (0.63, 0.89)	15.39
Overall (I-squared = 93.2%, p = 0.000)				1.80 (1.14, 2.85)	100.00

NOTE: Weights are from random effects analysis

.01   .1   .5   1   2   5   10   100

Severity of anaphylaxis if asthma present
All nonadjusted studies

Author	Year	Exposure		ES (95% CI)	% Weight
VAN ERP	2013	Asthma Using ICS		1.13 (0.36, 3.50)	19.55
CLARK	2014	Asthma		3.82 (1.89, 7.74)	40.38
MIRONE	2015	Asthma		2.14 (1.03, 4.47)	38.19
HA	2016	Asthma		0.89 (0.02, 46.28)	1.87
Overall (I-squared = 18.9%, p = 0.296)				2.35 (1.36, 4.05)	100.00

NOTE: Weights are from random effects analysis

.01   .1   .5   1   2   5   10   100

Severity of anaphylaxis if asthma present
All studies

			ES (95% CI)	% Weight
Overall (I-squared = 91.1%, p = 0.000)			1.89 (1.26, 2.83)	100.00

NOTE: Weights are from random effects analysis

.01   .1   .5   1   2   5   10   100

Figure 4. Meta-analysis of presence of asthma and severity of anaphylaxis. ES indicates effect size.

Table 4. Analysis of the Quality of Evidence of the Different Meta-analyses Using the GRADE Guidelines

No. of Studies	Study design	Certainty Assessment					No. of Patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory diseases	Comparison	Relative (95%CI)	Absolute (95%CI)		
Respiratory diseases and severity of anaphylaxis, all studies (assessed with: OR meta-analysis)												
13	Observational studies	Serious[a]	Serious[b]	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	350/3326 (10.5%)	3784/23395 (16.2%)	OR 1.87 (1.30 to 2.70)	103 more per 1000 (from 39 more to 181 more)	⊕◯◯◯ VERY LOW	Critical
Respiratory diseases and severity of anaphylaxis, all non-adjusted studies (assessed with: OR meta-analysis)												
4	Observational studies	Serious[c]	Serious[b]	Not serious	Serious[d]	Strong association, all plausible residual confounding would reduce the demonstrated effect, dose-response gradient	17/95 (17.9%)	95/2666 (3.6%)	OR 2.77 1.05 to 7.32)	57 more per 1000 (from 2 more to 177 more)	⊕⊕◯◯ LOW	Critical
Respiratory diseases and severity of anaphylaxis, all adjusted studies (assessed with: OR meta-analysis)												
9	Observational studies	Serious[c]	Serious[e]	Not serious	Not serious	None	333/3231 (10.3%)	1118/10645 (10.5%)	OR 1.71 (1.15 to 2.54)	62 more per 1000 (from 14 more to 125 more)	⊕◯◯◯ VERY LOW	Critical
Asthma and severity of anaphylaxis, all studies (assessed with: OR meta-analysis)												
13	Observational studies	Not serious	Not serious	Not serious	Not serious	None	581/11428 (5.1%)	7536/49585 (15.2%)	OR 1.89 (1.26 to 2.83)	101 more per 1000 (from 32 more to 185 more)	⊕⊕◯◯ LOW	Critical
COPD and severity of anaphylaxis, all studies (assessed with: OR meta-analysis)												
3	Observational studies	Serious[f]	Not serious	Not serious	Not serious	Strong association, all plausible residual confounding would reduce the demonstrated effect	271/1023 (26.5%)	3033/18618 (16.3%)	OR 2.47 (1.46 to 4.18)	162 more per 1000 (from 58 more to 286 more)	⊕⊕⊕◯ MODERATE	Critical

[a] No adjustment in studies with cardiovascular disease.
[b] Overall ($I^2=87.3\%$; $P<.001$).
[c] No adjustment in studies with cardiovascular disease.
[d] Small number of cases.
[e] Overall ($I^2=90.5\%$; $P<.001$).
[f] No adjustment in studies with cardiovascular disease.

been too broad and ambiguous (Tables 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 of 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 approach 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 has only moderate internal validity.

Conclusions

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 nonsevere 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

Association between severity of anaphylaxis and coexistence of respiratory diseases: a systematic review and meta-analysis of observational studies. EAACI Congress 2019, Lisbon, Portugal, June 1-5, 2019.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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▌ **Miguel A Tejedor-Alonso**

Allergy Unit, Hospital Universitario Fundación Alcorcón, Madrid
Avda Budapest 1
28922 Alcorcón (Madrid), Spain
E-mail: m914674227@telefonica.net;
matejedor@fhalcorcon.es