**Impact of asthma on severe food-induced allergic reactions: a systematic review and meta-analysis**

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**Abstract**

**Background:** Food allergy can range from mild to severe, life-threatening reactions with various symptoms and organ involvement. The impact of asthma on severe food-induced allergic reactions is not completely understood. In the hypothesis that asthma increases the risk of severe food-induced allergic reactions, the aim of this study is to compare the incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma.

**Methods:** We performed a systematic research on electronic databases, including PubMed, Scopus, and Web of Science. Observational studies, studies reporting medical characteristics of patients diagnosed with food allergy, and studies reporting medical history of patients with allergic reactions were included. The primary outcome was the incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma. The protocol of this review was registered in PROSPERO (CRD42023448293).

**Results**: Eight studies with a total of 90,367 patients met the inclusion criteria and were included, with a total population of 28,166 of patients with food allergy. The incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma was increased (OR = 1.28; 95% CI: 1.03–1.59; p = 0.03; $I^2$ = 59%).

**Conclusion:** Individuals with both food allergy and asthma are at high risk of severe, potentially fatal allergic reactions. Healthcare professionals should prioritize prevention and management strategies for these subjects.

**Keywords:** asthma, anaphylaxis, food allergy, risk factor, severe allergic reactions.

Patients with asthma and food allergy are at increased risk of potentially fatal food-induced allergic reactions. Optimal management of both diseases is necessary to prevent potentially life-threatening events.

## Background

Food allergy is responsible for a variety of symptoms and disorders which can vary widely in severity ranging from mild to severe, potentially life-threatening reactions with multiple organ involvement (1). The prevalence of food allergy in the general population ranges from approximately 1% to 10% and can vary depending on the specific geographical location or age group (2). Asthma is even more common, with approximately 262 million people worldwide suffering from this condition (3).

Despite the increasing prevalence of asthma and food allergy in general population, little is known about the coexistence of this two diseases. In addition, there appears to be a significant rise in the incidence of asthma among individuals with severe food-induced allergic reactions (4). Understanding the potential link between asthma and food allergy is of paramount importance for several reasons. Indeed, there is growing evidence that asthma can potentially worsen severe food-induced allergic reactions through various immunoinflammatory mechanisms which can lead to more pronounced respiratory and systemic symptoms contributing to a high risk of life-threatening complications, including anaphylaxis (5).

It is therefore necessary for clinicians to thoroughly investigate the simultaneous presence of both conditions in order to provide patients with the correct dietary indications and treatments for potentially life-threatening events.

In the hypothesis that asthma increased the risk of severe food-induced allergic reactions, the aim of this study is to compare the incidence of severe food-induced allergic reactions in patients with history of asthma

compared with patients without history of asthma in studies that investigate the characteristics of patients with severe food-induced allergic reactions.

**Methods**

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (6). The review question was developed using the Population, Intervention or exposure, Comparison, Outcome framework (7): Among patients with food allergy (P), those with history asthma (E), compared with patients without asthma (C), is increased the incidence severity reaction (O)? The protocol of this review was registered in PROSPERO (CRD42023448293)

Literature Search:

A systematic review of the literature was conducted to identify observational studies reporting medical characteristics of patients with food allergy. Electronic databases, including PubMed, Scopus, and Web of Science, were comprehensively searched to identify relevant studies up to July 2023. The search strategy involved using relevant keywords, Medical Subject Headings, and Boolean operators to capture relevant articles. No restrictions were applied regarding the publication date or languages.

Study Selection:

Two independent reviewers screened the titles and abstracts of the identified studies to assess their eligibility for inclusion. The full texts of potentially relevant studies were then retrieved and further evaluated. Inclusion criteria for study selection were as follows: (1) observational studies (cohort studies, case-control studies, or cross-sectional studies), (2) studies reporting medical characteristics of patients diagnosed with food allergy, and (3) studies reporting medical history of patients with allergic reaction. Disagreements between the reviewers were resolved through discussion or consultation with a third reviewer.

Data Extraction and Synthesis:

Data extraction was performed using a standardized data extraction form. Relevant information from each selected study was extracted, including study characteristics (e.g., study design, sample size, and follow-up duration), participant characteristics (e.g., age, gender, and food allergy diagnosis criteria), and outcomes of

interest (e.g., incidence of asthma in food allergy patients). Characteristics and reason for exclusion of major excluded studies were reported in supplemental table 1.

Data Analysis:

Data of incidence of severe allergic reaction to food in patients with history of asthma compared with patients without history of asthma in the entire cohort of selected studies. A qualitative analysis was also conducted to provide a comprehensive overview and synthesis of the findings from the included studies.

Ethical Approval:

As this study is a systematic review based on published literature, ethical approval was not required. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed during the conduct and reporting of this systematic review (6).

Outcomes

The primary outcome was the incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma.

Statistical analysis

Computations were performed with Review manager version 5.4.1. This meta-analysis was performed in compliance with PRISMA (8). We calculated pooled odds ratio (OR) for the primary and secondary outcomes and 95% confidence intervals (CI) using the Mantel-Haenszel method for dichotomous outcomes (9). The statistical heterogeneity hypothesis was evaluated with statistical significance set at the two-tailed 0.05 levels, whereas the extent of statistical consistency was quantified with Higgins and Thompson's $I^2$. $I^2$ values around 25, 50, and 75% were considered respectively low, moderate, and severe statistical inconsistency ($I^2 > 50\%$ was used as a threshold indicating significant heterogeneity for individual studies) (10). Pooled data were analyzed using the inverse variance method with a fixed-effect model in case of low-moderate ($I^2 < 50\%$) statistical inconsistency, or with a random-effect model when the $I^2$ was above 50% (11). A p-value less than 0.05 was considered statistically significant. The risk of bias was assessed by the tool Risk Of Bias In Nonrandomized Studies-of Interventions (ROBINS-I) (12). Results of pooled analyses

were presented with forest plots. A sensitivity analysis was performed including only the studies that report unpooled data in the results.

**Results**

Characteristics of the studies

The research strategy of electronic databases detected 9,048 potentially relevant articles (Figure 1). Eight studies with a total of 90,367 patients met the inclusion criteria and were included, with a total population of 28,166 of patients with food allergy (13-17). All studies were conducted between February 2005 and January 2022, including data of patients from 1990 and 2020. Five studies were conducted in Europe (13, 15, 18, 19, 20), three in United States (14, 16, 17). Six studies were retrospective observational studies (14, 15, 17, 18-20), two were prospective (13, 16). Five studies were multicentric (13, 15, 16, 18, 20). Three studies included only children (13, 17, 19), the other studies both adults and children (14-16, 18, 20). Five studies included only patients with food allergy (13, 15-17, 19), while three studies included patients with history of anaphylactic reactions also to other agents (14, 18. 20). Two studies defined severity of food-induced reaction according to Ring and Messmer grading scale for anaphylactic reactions (18, 20). One study used Sampson's grading system to identify the level of severity of food-induced allergic reactions (13). One study used Mueller's scale to identify the severity of anaphylaxis (19). One study defined severe anaphylaxis as an index event requiring hospitalization and identified severity of anaphylaxis as an index event resulting into cardiorespiratory failure or the need of cardiorespiratory/resuscitative intervention (14). Three studies defined the degree of severity of allergic reactions according to level of multisystem organ involvement (15-17) (Supplemental table 2). Majority of studies had a low risk of bias (Supplemental figure 1) Characteristic of the studies are reported in table 1.

Outcome

The incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma was increased (OR = 1.28; 95% CI: 1.03–1.59; p = 0.03; $I^2$ = 59%. Figure 2). We performed a sensitivity analysis including only the studies that report unpooled data in the results (706/4,427 [15.9%] vs 2,558/18,589 [13.8%]; OR = 1.26; 95% CI: 0.98–1.63; p = 0.07; $I^2$ = 66%. Figure 3).

Funnel plot show less heterogeneity in both analyses in terms of size and effect estimates of included studies. (Figure 4, 5).

**Discussion**

The main findings of this study is that there is a significant association between history of asthma and the incidence of severe food-induced allergic reactions. However, the results of the sensitivity analysis did not reach statistical significance. Individuals with asthma have an increased risk of 28% to experience severe food-induced allergic reactions compared to those without a history of asthma. The results of the sensitivity analysis, which included only studies reporting unpooled data, confirm the direction and the magnitude of the primary analysis, although they report only a trend consistent with the initial finding. One of the main reasons for the mismatch between the main analysis and the sensitivity analysis is likely the inclusion of a heterogeneous population in terms of asthma control and severity. Studies included did not distinguish between controlled and uncontrolled asthma, resulting in a heterogeneous population. Although it is not possible to confirm this from our analysis results, it is plausible that uncontrolled asthma makes individuals more susceptible to severe reactions compared to controlled asthma. Another reason was the reduction in sample size, which decreased the statistical power and led to non-significant results in the sensitivity analysis. The funnel plot analysis indicates less heterogeneity in terms of study size and effect estimates among studies included, providing additional support for the validity of the results.

Turner et al. in their meta-analysis reported that asthma increases the risk of severe allergic reactions to food, consistent with our analysis (21). However, they included studies that did not clearly report data specifically related to the population of interest. Indeed, Motosue et al. did not report specific data on exclusively food-induced allergic reactions in asthmatic population (22). The same was observed for Olabarri and colleagues who considered history of asthma as a risk factor for all the anaphylactic events and not specifically food-induced reactions (23). Furthermore, Versluis et al. in their prospective cohort study, did not include subjects with a clinically defined diagnosis of asthma (24). Finally, Gabrielli et al. did not report data on the prevalence of asthma in subjects with severe allergic reactions, but exclusively in individuals with mild and moderate reactions (25). In addition, Turner and colleagues did not report which of these individuals developed severe allergic reactions (21). We included these studies as major excluded studies, despite they

could have empowered our message. A particularly impactful finding is that among a cohort of 32 children died due to food-induced allergic reactions, 24 of them had a definitive diagnosis of asthma (26). Similarly, in a separate cohort of 12 children with fatal reactions, all of them had a history of asthma (27).

The present findings have important clinical implications. They highlight the need for increased awareness and vigilance among healthcare professionals in managing individuals with both asthma and food allergies. Patients with asthma should be closely monitored and educated about the potential risks of severe food-induced allergic reactions. Although not addressed in our review, the association between asthma and severe food-induced allergic reactions could be mediated by reduced respiratory reserve in asthmatic individuals. It can be assumed that patients with uncontrolled asthma may be more susceptible to experience severe allergic reactions to food. Indeed, latest updated GA2LEN guideline 2022 on management and treatment of food allergy report that it is good practice to optimize asthma control in people with food allergy as this reduces morbidity and mortality due to asthma (28). However, they report that the evidence on optimizing asthma control to reduce the risk of severe food-induced allergic reactions is unclear with low level of evidence for all good practice statements. In addition, they did not address that all asthmatic patients have an increased risk of severe allergic reactions, but they only hypothesized that uncontrolled asthma could be related to severe allergic reactions. EAACI guidelines emphasize that asthma is a risk factor for experiencing anaphylaxis in the context of food allergy and that reactions in individuals with severe asthma are a factor to consider for prolonged observation following anaphylaxis (29). These recommendations may act as a confounding factor in observational studies, leading to increased vigilance among clinicians and patients. This heightened awareness could potentially result in a lower prevalence of severe allergic reactions in asthmatic individuals, masking their heightened susceptibility. The underlying mechanisms linking asthma and increased susceptibility to severe food-induced allergic reactions need further investigations. It is possible that the chronic airway inflammation and bronchial hyperresponsiveness in asthma contribute to the exaggerated immune response seen in food allergies (30). Understanding these mechanisms could potentially lead to the development of targeted interventions to mitigate the risk of severe reactions in individuals with both diseases. Targeting this specific population to prevent asthmatic exacerbations may have dual benefits by addressing the underlying mechanisms of both food reactions and asthma, given the bidirectional relationship between these two conditions (4). Indeed, pharmacological interventions, such as Omalizumab,

which have a dual impact on both food allergy and asthma, may elicit a synergistic effect in the treatment of these two conditions (30). Moreover, strategies for prevention, early recognition, and prompt treatment of allergic reactions should be emphasized in this high-risk population. One of the major clinical implication of our study is to emphasize the significance of ensuring that asthmatic patients with food allergies receive adequate chronic asthma treatment to effectively prevent severe allergic reactions. The current indications for oral immunotherapy for food allergy do not specifically mention individuals with asthma, indicating that the association between asthma and the high risk of severe food-induced allergic reactions is not yet fully understood (31). Further research and investigation are needed to better understand the potential benefits in terms of prevention for individuals with coexisting asthma. Moreover, the current algorithm for the administration of self-injectable adrenaline in patients with food allergies does not include individuals with concomitant diagnosis of asthma (32). These individuals may represent the ideal population for desensitization strategies and for the prescription of adrenaline auto-injectors in out-of-hospital setting, as these interventions play a crucial role in reducing the risk of life-threatening allergic reactions and improving their overall quality of life.

To the best of our knowledge, our review includes the latest available evidence regarding the impact of asthma on significant patient-centred outcomes. Notably, it includes recent and significant data that may contribute to a more precise estimation and interpretation of treatment effects. A notable strength of our study lies in its focused examination of a single outcome, the incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma in studies that investigate the characteristics of patients with severe food-induced allergic reactions. This approach reinforces and emphasizes the crucial role and impact of asthma on the level of severity of these reactions. In this way, our study provides a clear and robust understanding of the association between asthma and the risk of potentially fatal food-induced allergic reactions. The methodological strengths of this review are attributed to its clear research question, specific population, defined interventions, and comparators. In addition, we performed a sensitivity analysis that exclusively considered studies with unpooled data, further enhancing the reliability of our findings.

However, it is important to acknowledge certain limitations associated with this review. First, the included studies used different classification system to define the level of severity of food-induced allergic reactions,

which could potentially influence the overall results. One important limitation is the lack of distinction between various levels of asthma severity in relation to the primary outcome. However, the data available in the included manuscripts did not allow for a distinction between patients with controlled and uncontrolled asthma. It is plausible that patients with uncontrolled asthma are more susceptible to severe allergic reactions, futher research are needed to address this topic. Additionally, factors such as age, concomitant allergies, and specific food allergens were not considered in subgroup analysis, as the included manuscripts did not provide the necessary data. Further studies with larger sample sizes, different populations, and comprehensive patient characteristics would provide better understanding of the relationship between asthma and severe food-induced allergic reactions.

**Conclusions**

This study provides strong evidence that individuals with both food allergy and asthma might be at high risk of severe, potentially life-threating food-induced allergic reactions. Healthcare professionals should be aware of this association and take appropriate measures to prevent and manage these potentially fatal reactions. Further studies are needed to investigate the underlying mechanisms and empower management and treatment strategies for individuals with both asthma and food allergy.

**Statements and Declarations**

The study was not funded or sponsored by industry.

There are no conflicts of interests.

**Authors' contributions**: M.B.C. : Conceptualization, Writing - Original Draft, Data Curation, Methodology, Formal Analysis, Validation. G.A.R. : Writing –Review & Editing, Visualization, Validation. C.A. : Writing –Review & Editing, Data Extraction, Validation. A.F. : Writing –Review & Editing, Data Extraction, Validation. G. B. : Writing –Review & Editing, Data Extraction, Validation. S.N. : Writing –Review & Editing, Data Extraction, Validation. R.M.A.H.: Writing –Review & Editing, Data Extraction, Validation. C.C. : Writing –Review & Editing, Data Extraction, Validation. L.D. : Conceptualization, Writing - Review & Editing, Supervision, Methodology, Validation. M.C. : Conceptualization, Writing - Review & Editing,

Supervision, Methodology, Validation. M.R.Y. : Conceptualization, Writing - Review & Editing, Supervision, Methodology, Validation.

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**Table 1.** Characteristics of included studies

| Study | Country | Population | N of patients | Number of patients with food allergy (%) | Number of severe food-induced allergic reactions (%) | Number of patients with asthma (%) | Number of patients without asthma (%) |
|---|---|---|---|---|---|---|---|
| Calvani et al (2011) [13] | Italy | Children with food allergy, 0-18 years | 163 | 163 (100%) | 36 (22%) | 59 (36%) | 104 (64%) |
| Clark (2014) [14] | United States | Adults requiring hospitalization for anaphylaxis, no age limitation | 36,943 | 11,972 (32%) | 2,622 (7%) | 1,822 (5%) | 10,150 (27%) |
| Deschildre et al (2015) [15] | France | Peanut-allergic children ≤ 6 years; school age children 6-12 years; teenagers, 12-16 years; adults ≥ 16 years | 669 | 669 (100%) | 202 (30%) | 381 (57%) | 288 (43%) |
| Gupta et al (2019) [16] | United States | Adults with suspected food allergy ≥18 years | 40,443 | 4,368 (11%) | 2,228 (51%) | NR | NR |
| Neuman-Sunshine (2011) [17] | United States | Children with peanut allergy, 0-16 years | 782 | 782 (100%) | 443 (57%) | 436 (56%) | 346 (44%) |
| Worm (2018) [18] | Germany | Individuals with immediate hypersensitivity reactions, 0-93 years | 7,316 | 7,316 (100%) | 187 (3%) | 1,125 (15%) | 6,191 (85%) |
| Blazowski (2021) [19] | Poland | Children with food-induced acute allergic reaction, 0-18 | 541 | 421 (78%) | 175 (32%) | 223 (41%) | 198 (37%) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | years | | | | | |
| Pouessel et al (2022) [20] | France | Children and adults patients with anaphylactic reactions | 3,510 | 2,475 (71%) | 42 (1.7%) | 817 (33%) | 1,658 (77%) |

33.

**Figure 1.** PRISMA flow diagram showing literature search results.

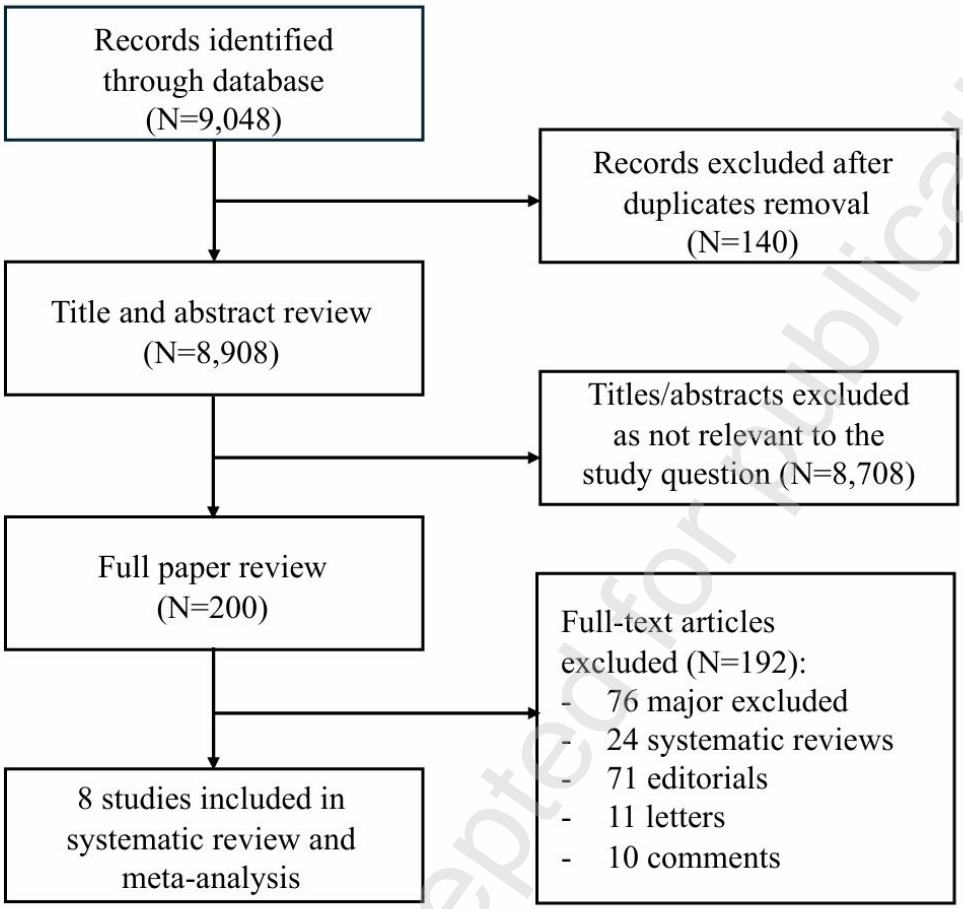


**Figure 2.** The incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma.

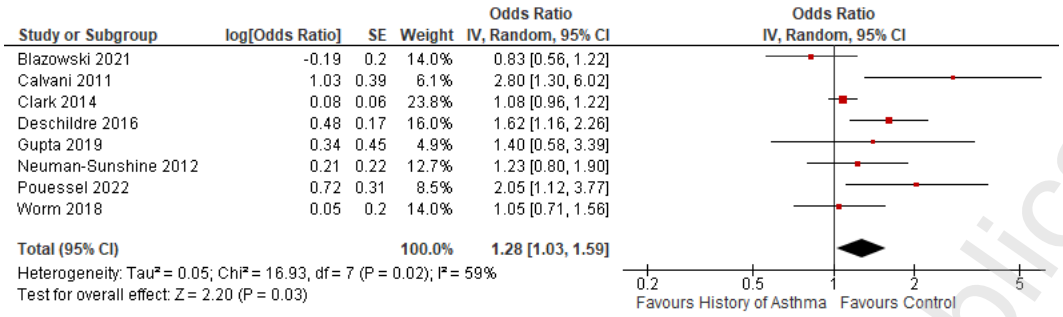


**Figure 3.** The incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma, including only the studies reporting unpooled data.

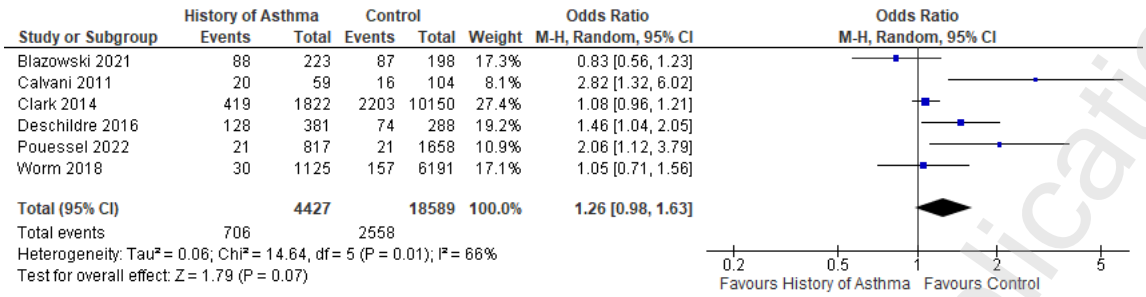


**Figure 4.** Funnel plot of the primary outcome measure: The incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma.

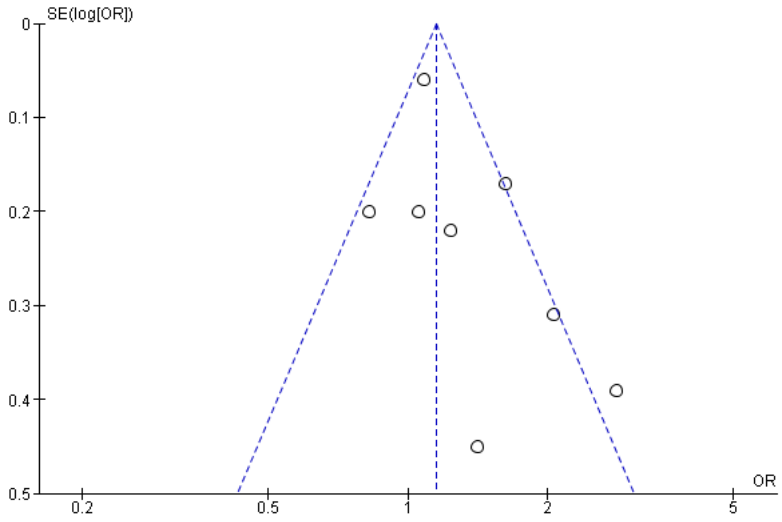
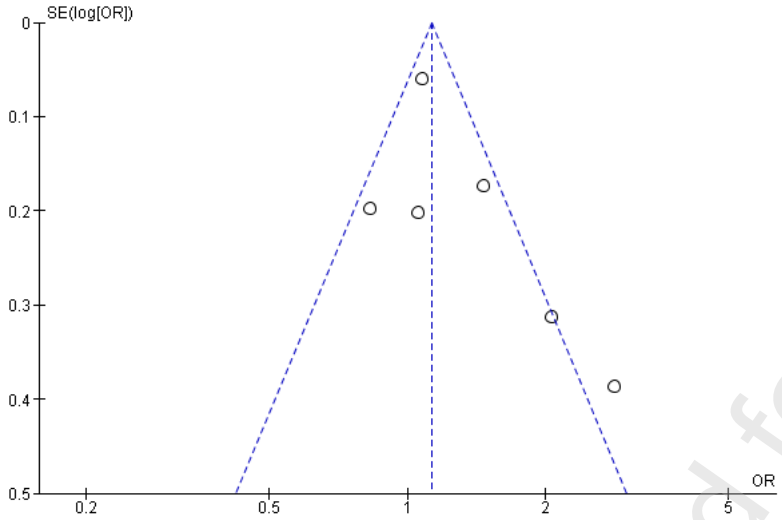


**Figure 5.** Funnel plot of the sensitivity analysis: The incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma, including only the studies reporting unpooled data.



**Supplement**

**Appendix:** Search string

((food[tiab]) OR (peanut [tiab]) OR (milk [tiab]) OR (wheat[tiab]) OR (seafood [tiab]) OR (crustac* [tiab]) OR (nut [tiab]) OR (fish [tiab])) AND ((allergic reaction [tiab]) OR (hypersensitivity [tiab]) OR (anaphyl* [tiab]))

Table 1.Characteristics of major excluded trials.

| First author | Publication date | Study design | Country | Number of patients | Allergy type | Reasons for exclusion |
|---|---|---|---|---|---|---|
| Abrams et al[1] | 2017 | Retrospective cohort study | Canada | 104 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Arkwright et al[2] | 2018 | Retrospective cohort study | UK | 525 | Peanut | No data on incidence of asthma in patients with severe food reaction |
| Ballmer-Weber et al[3] | 2019 | Prospective cohort study | Switzerland | 91 | Walnut | No data on incidence of asthma in patients with severe food reaction |
| Baseggio et al[4] | 2021 | Retrospective case series | UK | 187 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Brown et al[5] | 2013 | Prospective cohort study | Australia | 412 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Chan et al[6] | 2017 | Prospective cohort study | Australia | 726 | Peanut, egg, sesame | No data on incidence of asthma in patients with severe food reaction |
| Chinthrajah et al[7] | 2018 | Randomized controlled trial | USA | 120 | Peanut | No data on incidence of asthma in patients with severe food reaction |
| Christensen et al[8] | 2018 | Prospective cohort study | Denmark | 71 | Wheat | No data on incidence of asthma in patients with severe food reaction |
| Cianferoni et al[9] | 2012 | Retrospective cohort study | USA | 983 | Egg, milk, peanut | No data on incidence of asthma in patients with severe food reaction |
| Dang et al[10] | 2012 | Randomized controlled trial | Australia | 100 | Peanut | No data on incidence of asthma in patients with severe food reaction |
| Datema et al[11] | 2018 | Randomized | Europe | 423 | Hazelnut | No data on incidence of |

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| | | controlled trial | | | | asthma in patients with severe food reaction |
| Datema et al[12] | 2019 | Retrospective cohort study | Denmark | 181 | Peanut | No data on incidence of asthma in patients with severe food reaction |
| Datema et al[13] | 2021 | Prospective cohort study | Europe | 393 | Peanut | No data on incidence of asthma in patients with severe food reaction |
| De Schryver et al[14] | 2016 | Retrospective case series | Canada | 164 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Dua et al[15] | 2018 | Prospective cohort study | UK | 160 | Peanut | No data on incidence of asthma in patients with severe food reaction |
| Dua et al[16] | 2019 | Randomized controlled trial | UK | 100 | Peanut | No data on incidence of asthma in patients with severe food reaction |
| Eller et al[17] | 2012 | Retrospective cohort study | Denmark | 487 | Egg, milk, hazelnut, peanut | No data on incidence of asthma in patients with severe food reaction |
| Eller et al[18] | 2013 | Retrospective cohort study | Denmark | 175 | Peanut | No data on incidence of asthma in patients with severe food reaction |
| Francuzik et al[19] | 2015 | Retrospective cohort study | Europe | 5765 | All triggers | No data on incidence of asthma in patients with severe food reaction |
| Francuzik et al[20] | 2019 | Retrospective cohort study | Europe | 5765 | All triggers | No data on incidence of asthma in patients with severe food reaction |
| Gabrielli et al[21] | 2021 | Retrospective case series | Canada | 3498 | All triggers | No data on incidence of asthma in patients with severe food reaction |
| Gabrielli et al[22] | 2021 | Retrospective case series | Canada | 250 | Fruit only | No data on incidence of asthma in patients with severe food reaction |
| Goldberg et al[23] | 2021 | Retrospective case series | Israel | 120 | Walnut | No data on incidence of asthma in patients with severe food reaction |
| Grabenhenrich et al[24] | 2016 | Retrospective cohort study | Europe | 1970 | All triggers | No data on incidence of asthma in patients with severe food reaction |
| Huang et al[25] | 2012 | Retrospective | USA | 192 | Any food | No data on incidence of asthma in patients with |

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| | | case series | | | | severe food reaction |
| Jerschow et al[26] | 2014 | Retrospective case series | USA | 164 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Jiang et al[27] | 2016 | Retrospective case series | China | 1501 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Johnson et al[28] | 2014 | Retrospective case series | Sweden | 578 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Kaur et al[29] | 2021 | Retrospective case series | Australia | 89 | Peanut | No data on incidence of asthma in patients with severe food reaction |
| Kennard et al[30] | 2018 | Retrospective case series | UK | 132 | WDEIA | No data on incidence of asthma in patients with severe food reaction |
| Kennedy et al[31] | 2021 | Retrospective cohort study | USA | 675 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Kiewiet et al[32] | 2020 | Retrospective case series | Sweden | 128 | Alpha-gal (meat) | No data on incidence of asthma in patients with severe food reaction |
| Klemens et al[33] | 2013 | Retrospective cohort study | Netherlands | 93 | Peanut | No data on incidence of asthma in patients with severe food reaction |
| Kraft et al[34] | 2020 | Retrospective case series | Europe | 9171 | All triggers | No data on incidence of asthma in patients with severe food reaction |
| Kraft et al[35] | 2021 | Retrospective cohort study | Europe | 1691 | Wheat | No data on incidence of asthma in patients with severe food reaction |
| Kukkonen et al[36] | 2015 | Randomized controlled trial | Finland | 69 | Peanut | No data on incidence of asthma in patients with severe food reaction |
| Lam et al[37] | 2021 | Retrospective cohort study | UK | 15,405 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Libbers et al[38] | 2013 | Retrospective cohort study | Netherlands | 59 | Egg | No data on incidence of asthma in patients with severe food reaction |
| Lyons et al[39] | 2021 | Prospective cohort study | Europe | 531 | Walnut | No data on incidence of asthma in patients with |

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| | | | | | | severe food reaction |
| Maris et al[40] | 2021 | Retrospective cohort study | Europe | 1962 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Masthoff et al[41] | 2013 | Retrospective cohort study | Netherlands | 161 | Hazelnut | No data on incidence of asthma in patients with severe food reaction |
| Miceli Sopo et al[42] | 2021 | Retrospective cohort study | Italy | 91 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Motosue et al[43] | 2017 | Retrospective case series | USA | 10464 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Mulla et al[44] | 2013 | Retrospective cohort study | USA | 2410 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Mullins et al[45] | 2016 | Retrospective case series | Australia | 22 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Nassiri et al[46] | 2015 | Retrospective cohort study | Europe | 1222 | All foods | No data on incidence of asthma in patients with severe food reaction |
| Nguyen-Luu et al[47] | 2012 | Retrospective case series | Canada | 1411 | Peanut | No data on incidence of asthma in patients with severe food reaction |
| Nieto-Nieto et al[48] | 2017 | Retrospective cohort study | Spain | 5261 | All triggers | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Olabarri et al[49] | 2020 | Prospective cohort study | Spain | 453 | All foods | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Palosuo et al[50] | 2018 | Prospective cohort study | Finland | 124 | Egg | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Pastorello et al[51] | 2011 | Prospective cohort study | Italy | 148 | Peach | Not reporting data on incidence of asthma in patients with severe food-induced allergic |

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| | | | | | | reaction |
| Pettersson et al[52] | 2018 | Randomized controlled trial | Netherlands | 734 | Milk, egg, peanut, hazelnut, cashew | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Poirot et al[53] | 2020 | Retrospective case series | USA | 24 | All foods | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Pouessel et al[54] | 2018 | Prospective cohort study | France | 62 | All foods | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Pouessel et al[55] | 2019 | Retrospective case series | France | 18 | All foods | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Purington et al[56] | 2018 | Retrospective cohort study | USA | 410 | All foods | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Ramsey et al[57] | 2019 | Retrospective case series | USA, Canada | 1989 | All foods | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Reier-Nilsen et al[58] | 2018 | Randomized controlled trial | Norway | 96 | Peanut | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Rolinck-Werninghaus et al[59] | 2012 | Retrospective cohort study | Germany | 869 | Egg, milk, soy, wheat | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Santos et al[60] | 2020 | Prospective cohort study | UK | 117 | Peanut | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |

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| Scala et al[61] | 2018 | Retrospective case series | Italy | 626 | LTP allergy | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Song et al[62] | 2015 | Randomized controlled trial | USA | 58 | Nuts, seafood, sesame | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Su et al[63] | 2020 | Retrospective case series | USA | 203 | All triggers | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Taylor et al[64] | 2010 | Retrospective cohort study | France | 286 | Peanut | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Turner et al[65] | 2015 | Retrospective case series | UK | 124 | All foods | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Turner et al[66] | 2021 | Randomized controlled trial | UK, Spain | 83 | Cow's Milk | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Uasuf et al[67] | 2015 | Retrospective case series | Italy | 133 | Peach | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| van Erp et al[68] | 2013 | Retrospective cohort study | Netherlands | 109 | Peanut | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Versluis et al[69] | 2016 | Retrospective cohort study | Netherlands | 496 | All foods | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Versluis et al[70] | 2019 | Prospective | Netherlands | 157 | All foods | Not reporting data on |

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| | | cohort study | | | | incidence of asthma in patients with severe food-induced allergic reaction |
| Vetander et al[71] | 2012 | Retrospective case series | Sweden | 371 | All foods | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Vetander et al[72] | 2014 | Retrospective case series | Sweden | 358 | All foods | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Xu et al[73] | 2014 | Retrospective case series | Canada | 40 | All foods | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Yanagida et al[74] | 2017 | Retrospective cohort study | Japan | 393 | Milk, egg, wheat, peanut | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Yanagida et al[75] | 2018 | Retrospective cohort study | Japan | 979 | Milk, egg, wheat, peanut | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |
| Yonkof et al[76] | 2021 | Retrospective cohort study | USA | 158 | Egg, milk, nuts | Not reporting data on incidence of asthma in patients with severe food-induced allergic reaction |

**Table 2.** Definition of outcome in selected studies

| **Study** | **Definition of severe allergic reaction** |
|---|---|
| Calvani et al (2011) | Sampson's grading system to identify the level of severity. The fourth and fifth levels correspond to severe anaphylaxis. |
| Clark et al (2014) | Severe anaphylaxis was defined as an index event requiring hospitalization. Severity of anaphylaxis was identified as an index event resulting into cardiorespiratory failure or the need of cardiorespiratory/resuscitative intervention. |
| Deschildre et al (2015) | Severe or potentially severe reactions were: anaphylactic shock, laryngeal angioedema, acute asthma, and serious systemic reaction (involving two or more organs) |
| Gupta et al (2019) | Severe reaction was indicated by reporting 1 or more stringent symptoms across 2 or more of the following organ systems: skin or oral mucosa, gastrointestinal tract, cardiovascular, and respiratory tract. |
| Neuman-Sunshine (2011) | Reactions to peanut exposures were defined as severe if they resulted in: (1) cardiovascular symptoms, (2) lower respiratory symptoms, or (3) symptoms from 3 or more systems (cardiovascular, lower respiratory, upper respiratory, skin [urticaria, angioedema, eczema], |

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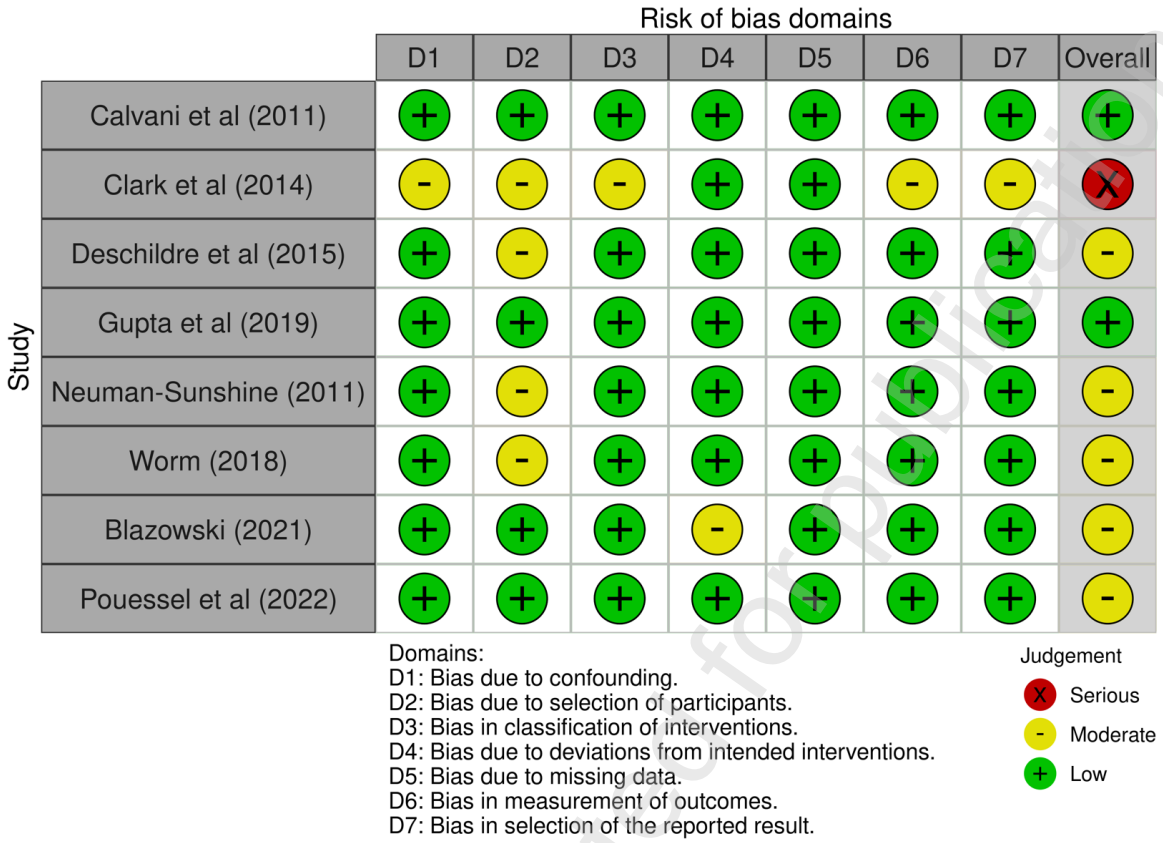
| | gastrointestinal, or oral). |
| Worm (2018) | Ring and Messmer classification to identify the level of severity. The fourth level correspond to severe anaphylaxis. |
| Blazowski (2021) | Mueller's scale used to identify the severity of anaphylaxis. Grade III-IV reactions correspond to severe anaphylaxis. Grade IV reactions include loss of consciousness, incontinence of urine or faeces, or cyanosis. |
| Pouessel et al (2022) | Ring and Messmer classification to identify the level of severity. The fourth level correspond to severe anaphylaxis. |

**Figure 1.** Risk Of Bias In Nonrandomized Studies-of Interventions (ROBINS-I)



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