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Seasonal distribution of initial diagnosis and clinical recrudescence of eosinophilic esophagitis: a systematic review and meta-analysis

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Abstract

Background: The association between seasonality and diagnosis and/or recrudescence of eosinophilic esophagitis (EoE) remains unclear, with some studies demonstrating a higher diagnostic rate in those months with a higher aeroallergen load while others rule out this association.

Methods: We performed a systematic search of the MEDLINE, EMBASE, and SCOPUS databases for studies on the seasonality of the initial diagnosis or recrudescence (i.e., food bolus impaction) of EoE. Summary estimates, including 95% confidence intervals, were calculated for seasonal variation in diagnosis or incidence of food bolus impaction. A random-effects meta-regression model was made using aggregate-level data to compare seasonality in EoE diagnosis and recrudescence. Publication bias risks were assessed by means of funnel plot analysis.

Results: Of 1078 references found, data were finally collected from 18 studies which included a total of 16 846 EoE patients. Of all new cases of EoE diagnosed per year, 27.1% were diagnosed in spring and 21.5% in winter. No overall statistical differences in the annual seasonal distribution of newly diagnosed EoE cases were observed in the random-effects meta-regression model ($P = 0.132$). Similarly, a homogenous distribution of episodes of EoE recrudescence throughout the year was noted, with no significant differences between seasons ($P = 0.699$). No significant publication bias was found.

Conclusions: This systematic review found no significant variations in the seasonal distribution of either the diagnosis or clinical recrudescence of EoE throughout the year.

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory disorder, defined symptomatically by esophageal dysfunction and histologically by eosinophil-predominant inflammation of the esophagus (1). Despite having first been characterized as a distinct clinicopathological disorder 20 years ago (2, 3), EoE has just recently become recognized as the most prevalent cause of chronic dysphagia among children and young adults (4–6).

From its earliest descriptions, EoE has been linked to allergy; both pediatric and adult patients commonly present a personal medical and/or family history of atopic conditions such as asthma, rhinitis, conjunctivitis, eczema, and IgE-mediated food allergies (1). Indeed, the presence of atopic manifestations in a patient who has been referred for esophageal symptoms (especially dysphagia or food impaction) has been recognized as a characteristic marker of EoE (7). Food sensitization identified through positive results in skin prick tests (SPTs) is also commonly described in patients of all ages (8, 9). The definitive categorization of EoE as a characteristic manifestation of food allergy came later, when researchers documented disease remission after feeding a series of pediatric patients exclusively with an amino acid-based elemental formula lacking any antigenic capacity, followed by disease recurrence after subjects resumed a normal diet (10). Since then, various dietary interventions have proven their efficacy in producing histologic remission in patients with EoE (11). However, such interventions are not always effective in inducing disease remission, with up to 10% of

patients failing to respond to the most effective food avoidance strategies. The fact that some reported cases of EoE appear to be triggered by aeroallergens (12–14), including several environmental allergens that cross-react with certain food allergens (15, 16), along with the finding that experimental EoE can be reproduced in murine models through exposure to aeroallergens (17, 18), provides additional evidence of the role that environmental allergies play in the origin of EoE.

Several studies in adults and children have noted seasonal variations in the diagnosis of EoE: Using the month of presentation as a surrogate marker for disease activity, several studies found a peak of presentation during months with a higher pollen concentration (19, 20). Moreover, some researchers have demonstrated that esophageal food bolus impaction in atopic patients was significantly higher in the summer and fall than in winter (21). However, because other studies have failed to demonstrate a seasonal pattern (22–24), the role of airborne allergens as a relevant trigger for initiating or aggravating EoE remains elusive and needs to be clarified.

The aim of our study was to conduct a systematic review and meta-analysis of the seasonal distribution of initial diagnosis and/or clinical recrudescence (defined as an episode of esophageal food bolus impaction) in both children and adults with EoE.

Methods

This systematic review has been registered in the PROSPERO International prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO; register no. CRD42015020867) and has been reported in accordance with the PRISMA statements (25).

Selection of studies

A systematic literature search was performed independently by two researchers (AA and AJL) in three major bibliographic databases (PubMed, EMBASE, and Scopus) for the period up to May 2015. The search was not restricted to English language manuscripts. A predetermined protocol was used in accordance with the quality of reporting meta-analyses of observational studies in epidemiology (26).

Comprehensive search criteria were used to identify articles dealing with EoE in children and adults. We consulted the thesauri for MEDLINE (MESH) and EMBASE (EMTREE) using the following search strategy: ('eosinophilic esophagitis' OR 'eosinophilic oesophagitis') AND ('season*' OR 'spring' OR 'summer' or 'autumn' OR 'fall' OR 'winter' OR 'January' OR 'February' OR 'March' OR 'April' OR 'May' OR 'June' OR 'July' OR 'August' OR 'September' OR 'October' OR 'November' OR 'December'). As for the SCOPUS database, only free text searches with truncations were carried out. To identify additional relevant studies, we also examined the reference lists from all retrieved articles as well as the abstracts of conference proceedings published in annual abstract books from the meetings of the following organizations: the American Gastroenterological Association (*Digestive Disease Week*), the American College of Gastroenterology, the American Academy of Allergy, Asthma And Immunology, and the United European Gastroenterology, for the period up to December 2014. Two reviewers (AA and JG-C) independently screened the database search for titles and abstracts. If any of the reviewers felt that a title or abstract met the study eligibility criteria, the full text of the study was retrieved.

Inclusion criteria

Observational prospective and retrospective studies, along with case series reports, were included if data on the month/season of diagnosis and/or disease recrudescence were provided and if a histologic evaluation of EoE had been undertaken. Months were included in the various seasons according to the climate zones and geographical variations provided by the authors of each document.

Exclusion criteria

Review articles on EoE that did not provide original data on seasonal variation in diagnosis and/or clinical recrudescence, clinical guidelines, and consensus documents were excluded. Studies not carried out on humans or providing duplicated information (i.e., repeated abstracts presented at different congresses or abstracts published later as a full paper) were also excluded. Subsets of cases or controls from previously published articles by the same authors were excluded as well.

Quality assessment

Cohort studies, case series, and case reports were evaluated for quality if the article described the diagnostic criteria considered for EoE, all patients' demographic data, the month and/or season of EoE diagnosis (as well as the month and/or season of esophageal food bolus impaction episodes, if provided), along with the time frame used, and the clinic or clinics in which the study was carried out. Quality assessment was checked with a specific evaluation form for observational studies developed by our group and based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement (27). Studies were considered to be at low risk for bias if each of the bias items could be categorized as low risk. On the contrary, studies were judged to have a high risk of bias if even one of the items was deemed high risk. Four investigators (AJL, AA, JG-C, and OR-G) independently gave each eligible study an overall rating of high, low, or unclear risk of bias; disagreements were resolved by consensus.

Data extraction

Four reviewers (AJL, AA, JG-C, and OR-G) independently extracted relevant information from each eligible study using a standardized data extraction sheet and then proceeded to cross-check the results. The data extracted included the last name of the first author, publication year, country, month and/or season of diagnosis/clinical recrudescence, age and gender of study participants, sample size, methodological

design, and study period, whenever possible. At the same time, data on the variation of the key outcomes throughout each month/season were extracted from all included studies. Disagreements between reviewers regarding data extraction were resolved through discussion. The authors of the various studies were contacted by e-mail for additional information if necessary.

Statistical analysis

Initial EoE diagnosis rates throughout the year/season and the different months (taking into account geographic and hemispheric variations) were summarized with the aid of a fixed- or random-effects meta-analysis weighted for inverse variance following the method elaborated by DerSimonian and Laird. We did the same for food bolus impaction episodes in patients with a previously established diagnosis of EoE (or who were later diagnosed with the disease). Summary estimates, including 95% confidence intervals (CI), were calculated for each season and month, whenever possible.

Heterogeneity between studies was assessed by means of a chi-square test (Cochran Q statistic) and quantified with the I^2 statistic. Generally, I^2 was used to evaluate the level of heterogeneity, assigning the categories low, moderate, and high to I^2 values of 25%, 50%, and 75%, respectively (28). Publication bias was evaluated with the aid of a funnel plot, the asymmetry of which was assessed with the Begg and Mazumdar correlation rank test (29) as well as with the Egger (30) and Harbord tests (31).

For the primary outcomes, planned subgroup analyses were performed based on the season EoE was diagnosed and according to the climate zone of the study population. A subgroup analysis was performed with regard to quality (risk of bias) and type of document (full-length article *vs* abstract presented at conference proceedings). All calculations were made with StatsDirect statistical software version 2.7.9 (StatsDirect Ltd, Cheshire, UK).

Estimates of both new seasonal EoE diagnoses and seasonal EoE recrudescence episodes were calculated with the aid of random-effects meta-regression using aggregate-level data, with spring as the reference season. The standard errors in each season for all studies had previously been estimated for all the aforementioned dependent variables. All analyses were carried out with Stata 12.0 (Statacorp, College Station, TX, USA).

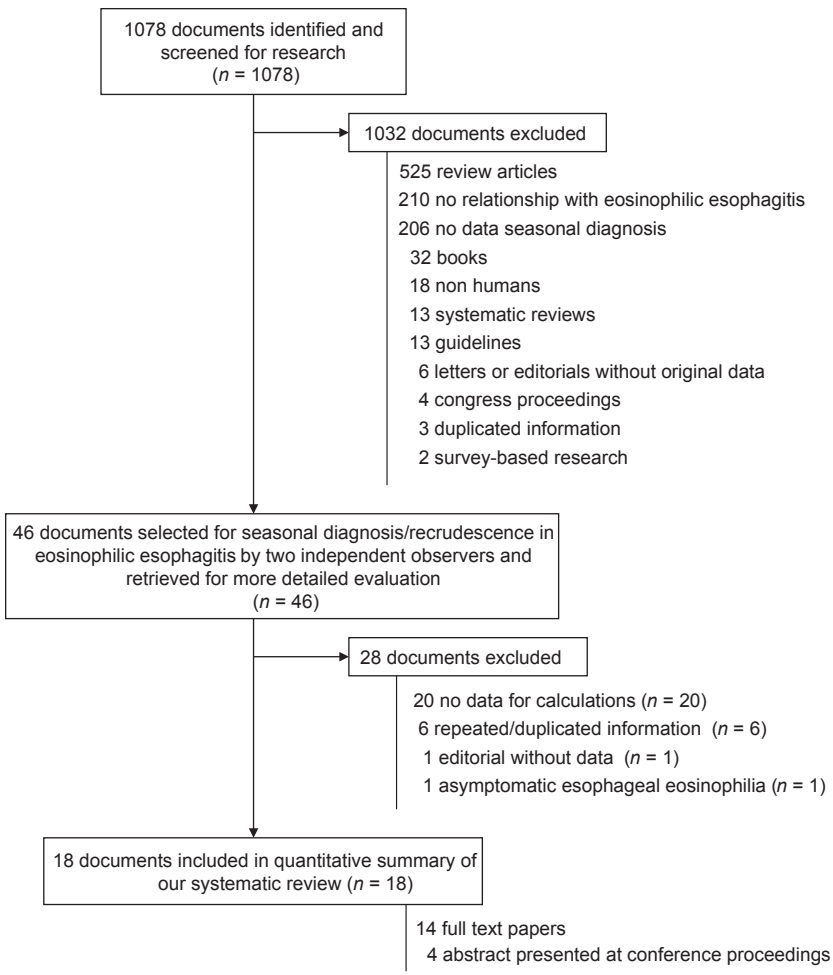

Figure 1 Flowchart for the process of identifying studies that were included in and excluded from the systematic review.

Table 1 Demographics and characteristics of seasonal diagnosis of EoE studies included in our systematic review and meta-analysis

First author, publication year	Country	% Male	N	Study design	Population	Study period	Seasonal diagnosis	Recrudescence
Wang et al. 2007 (20)	USA (Indianapolis)	66.7	234	Retrospective	Children	1998–2004	Spring (March–May): 65 (27.8%) Summer (June–August): 69 (29.5%) Fall (September–November): 58 (24.8%) Winter (December–February): 42 (17.9%)	–
Almansa et al. 2009 (19)	USA (Florida)	67.9	78	Retrospective	Adult	2002–2007	Spring (March–May): 32 (41%) March: 7; April: 14; May: 11 Summer (June–August): 21 (26.9%) June: 6; July: 10; August: 5 Fall (September–November): 12 (15.4%) September: 4; October: 3; November: 5 Winter (December–February): 13 (16.7%) December: 5; January: 4; February: 4	–
Prasad et al. 2009 (34)	USA (Minnesota)	56.4	78	Retrospective	Both	1976–2005	January: 5 (6.4%) February: 1 (1.3%) March: 3 (3.8%) April: 3 (3.8%) May: 5 (6.4%) June: 10 (12.8%) July: 10 (12.8%) August: 8 (10.3%) September: 9 (11.5%) October: 8 (10.3%) November: 12 (15.4%) December: 4 (5.1%)	–
Ding et al. 2009 (41)	Australia	–	7	Retrospective	Adult	2003–2008	Spring: 4 (57.1%)	–
Malhotra et al. 2010 (42)	USA (New Jersey)	–	24	Retrospective	Both	2007–2009	Spring–Summer: 19 (79%) Fall – Winter: 5 (21%)	–
Moawad et al. 2010 (14)	USA (Washington)	83.5	127	Retrospective	Adult	2006–2008	Spring (April–June): 42 (33%) Summer (July–September): 33 (26%) Fall (October–December): 31 (24%) Winter (January–March): 21 (16%)	–
Iwanczak et al. 2011 (35)	Poland	76.2	84	Retrospective	Children	2004–2009	Spring: 38 (45.2%) Summer: 24 (28.6%) Fall: 13 (15.5%) Winter: 9 (10.7%)	–
Larsson et al. 2011 (21)	Sweden	–	24	Retrospective	Both	2004–2009	Spring: 4 (16.7%) Summer: 5 (20.8%) Fall: 12 (50%) Winter: 3 (12.5%)	–
Van Rhijn et al. 2013 (22)	The Netherlands	74.3	674	Retrospective	Both	1996–2010	January: 46 (6.8%) February: 52 (7.7%) March: 53 (7.9%) April: 60 (8.9%) May: 41 (6.1%) June: 64 (9.5%) July: 56 (8.3%) August: 60 (8.9%) September: 57 (8.5%) October: 66 (9.8%) November: 59 (8.8%) December: 60 (8.9%)	–

Table 1 (continued)

First author, publication year	Country	% Male	N	Study design	Population	Study period	Seasonal diagnosis	Recrudescence
Elitsur et al. 2013 (24)	USA (Boston)	67.4	95	Retrospective	Children	2003–2010	Spring (March–May): 29 (30.5%) Summer (June–August): 20 (21.1%) Fall (September–November): 16 (16.8%) Winter (December–February): 30 (31.6%)	–
Sorser et al. 2013 (32)	USA (Detroit)	65.9	44	Retrospective	Both	2001–2006	Spring: 11 (25%) Summer: 7 (16%) Fall: 16 (36%) Winter: 10 (23%)	–
Frederickson et al. 2014 (33)	USA (Iowa)	65.8	193	Retrospective	Adult	2003–2013	Spring (April–June): 40 (20.7%) April: 10; May: 18; June: 12 Summer (July–September): 51 (26.4%) July: 17; August: 16; September: 18 Fall (October–December): 57 (29.5%) October: 22; November: 17; December: 18 Winter (January–March): 45 (23.3%) January: 21; February: 14; March: 10	–
Schey et al. 2014 (39)	USA (Iowa)	67.7	167	Retrospective	Both	–	Spring (Apr–Jun): 35 (21%) April: 8 (5%); May: 12 (9%); June: 15 (7%) Summer (July–September): 42 (25%) July: 13 (8%); August: 12 (7%); September: 17 (10%) Fall (October–December): 47 (28%) October: 18 (11%); November: 13 (8%); December: 15 (9%) Winter (January–March): 42 (25%) Jan: 20 (12%); Feb: 15 (9%); Mar: 7 (4%)	–
Leigh et al. 2015 (40)	USA (New York)	64	16	Retrospective	Adult	–	–	9/16 (56%) recurring symptoms Spring: 5/9 (56%) increased dysphagia Fall: 2/9 (22%) increased dysphagia
Elias et al. 2015 (23)	USA (Minnesota)	73	372	Retrospective	Adult	2002–2007	Spring: May: 41 (11%) and June: 33 (9%) Winter: December: 41 (11%) and January: 48 (13%)	–

Table 1 (continued)

First author, publication year	Country	% Male	N	Study design	Population	Study period	Seasonal diagnosis	Recrudescence
Sengupta et al. 2015 (36)	USA (Boston)	81	47	Retrospective	Adult	2004–2014	–	Spring: 13 (27.7%) Summer: 16 (34%) Fall: 8 (17%) Winter: 10 (21.3%)
Philpott et al. 2015 (37)	Australia	81.2	85	Retrospective	Adult	2002–2012	–	Spring: 23 (27.1%) Summer: 22 (25.9%) Fall: 20 (23.5%) Winter: 20 (23.5%)
Jensen et al. 2015 (38)	USA (43 Estates, DC & Puerto Rico)	64	14 524	Retrospective	Adult	2009–2012	Spring (March–May): 4150 (28.6%) Summer (June–August): 3607 (24.8%) Fall (September–November): 3066 (21.1%) Winter (December–February): 3701 (25.5%)	–

Results

Literature search

The search strategy yielded 1078 references; 1032 were excluded after examining the title and abstract because they did not fulfill the inclusion criteria. Of the remaining 46 documents retrieved for complete evaluation, 28 were excluded for the following reasons: they lacked data for calculations (20), they contained repeated or duplicated information (6), they were editorials with no original data (1), or they dealt with esophageal eosinophilia but not EoE (1). In the end, 18 studies (comprising 14 full papers (14, 19, 21–24, 31–38) and 4 abstracts (39–42)) were included in the quantitative summaries of our systematic review (Fig. 1). All the references retrieved consisted of observational studies with a retrospective design and came from the USA (13), Europe (3), and Australia (2). Characteristics of the included studies are summarized in Table 1.

Overall, data from 16 846 individual patients, with study populations ranging from 7 to 14 524 cases, were retrieved.

Seasonal distribution of newly diagnosed EoE cases

Fourteen studies examined the seasonality of EoE diagnoses; of these, eight (14, 19, 20, 34, 35, 38, 41, 42) noted a seasonal variation in the initial diagnosis of the disease, as reported by the respective authors, with most cases diagnosed in either spring/summer ($n = 7$) or summer/fall ($n = 1$).

Of all new EoE cases diagnosed per year, 27.1% were diagnosed in spring whereas 21.5% were diagnosed in winter. However, although fewer cases were diagnosed in winter ($P = 0.031$), no significant statistical differences in the annual seasonal distribution were observed with the random-effects meta-regression model ($P = 0.132$). Thus, according to our data, the incidence of EoE diagnosis shows no significant seasonal changes throughout the year, which means that the annual distribution of cases is homogeneous (Tables 2, 3 and Fig. 2).

Seasonal distribution of EoE recrudescence

Three of the four studies reporting on seasonal recrudescence of symptoms noted a seasonal variation in food impaction episodes, with most cases being reported in spring or summer (36, 40) and fall (21). Only one study showed no such variations (37).

However, and similar to our seasonality findings, a homogeneous distribution was observed for EoE recrudescence throughout the year, as no overall statistically significant differences were found with the random-effects meta-regression model ($P = 0.699$) (Tables 2 and 3; Fig. 3).

Subgroup analysis

Due to the small number of studies with a high risk of bias ($n = 4$), subgroup analysis to compare them with those considered of medium or low risk of bias ($n = 13$) was not deemed necessary. The same happened for research published

Table 2 Summary and 95% CIs for seasonal distribution of new diagnoses of EoE and recrudescence episodes (defined as food bolus impaction) in documents published for patients with eosinophilic esophagitis

Season	EoE Diagnosis (%)	*n*	I^2
Spring	27.13 (23.8–30.6)	13	79.9 (64.5–86.8)
Summer	25.51 (24.15–26.89)	11	10.8 (0–56.3)
Fall	24.76 (21.43–28.25)	11	78.5 (58.7–86.6)
Winter	21.49 (18.86–24.24)	12	72.7 (44.9–83.3)
Season	EoE Recrudescence (%)	*n*	I^2
Spring	27.86 (19.45–37.14)	4	31.1 (0–76.9%)
Summer	27.88 (21.18–35.12)	3	0 (0–72.9)
Fall	27.57 (15.96–40.97)	4	63.7 (0–85.6)
Winter	21.58 (15.53–28.33)	3	0 (0–72.9)

Table 3 A meta-regression analysis of the seasonal pattern and recrudescence of the documents dealing with EoE diagnosis included in our meta-analysis*

Seasons	β†	Lower (95% CI)	Upper (95% CI)	SE‡	*P*-value
Seasonality (global *P*-value = 0.132)					
Summer	−0.0065	−0.0604	0.0473	0.0267	0.807
Fall	−0.0228	−0.0763	0.0308	0.0265	0.396
Winter	−0.0569	−0.1083	−0.0055	0.0255	0.031
Recrudescence (global *P*-value = 0.699)					
Summer	0.0053	−0.1350	0.1457	0.0630	0.934
Fall	−0.0262	−0.1608	0.1084	0.0604	0.674
Winter	−0.0602	−0.1948	0.0744	0.0604	0.343

*Taking as reference the spring season.
†Regression coefficients.
‡Standard error.

as an abstract presented at conference proceedings ($n = 4$) compared to full-text papers ($n = 13$).

Publication bias

The funnel plot analysis for studies reporting on the seasonal distribution of initial diagnosis of EoE and/or clinical recrudescence in the form of food bolus impaction did not demonstrate a statistically significant publication bias, with no significant *P* values in the Egger, Harbord, or Begg–Mazumdar tests (see Fig. S1).

Discussion

The present systematic review and meta-analysis of 18 retrospective, observational studies comprising 16 846 individual patients found no seasonal variations in the incidence of EoE (defined as newly diagnosed EoE cases) nor in the recrudescence of the disease in the form of food bolus impaction episodes requiring medical care. No overall statistically significant differences were observed with the random-effects meta-regression model for seasonal distribution of either study endpoint ($P = 0.132$ and $P = 0.699$, respectively), indicating that the hypothesis of a seasonal predominance in the appearance of EoE is unsupported by the available data.

Some early studies in children (20, 35, 42) and adults (19, 42) had noted an increase in EoE diagnoses during the pollen season, with peaks in spring and summer. This observation supported the hypothesis of a relevant role for aeroallergens in the development and/or recrudescence of EoE in parallel to what happens with other atopic disorders frequently observed in these same patients. More recent research, however, failed to document such an association (19, 21–24, 33, 36, 37), with some authors documenting a higher incidence of EoE diagnosis during the fall (21, 32). After collecting all the published data on this topic through a systematic search in multiple databases and subsequently analyzing the data with the aid of a random-effects meta-regression model of seasonal meta-analyses, we were able to demonstrate no significant seasonal variations in the overall incidence of EoE and its flare ups.

EoE is recognized as a particular form of food allergy that in most patients is triggered and maintained by exposure to certain foods, as demonstrated by the extremely high rate of disease remission (up to 98% in some series (43)) achieved after feeding patients exclusively with an amino acid-based elemental formula. The high efficacy and extremely homogeneous effects of elemental diets in achieving EoE remission in both children and adults as demonstrated in a recent meta-analysis (11) call for a re-examination of the role that aeroallergens play in the development and/or maintenance of EoE; although they have been repeatedly recognized as triggers of the disease (12–14), this may actually occur in only a very limited number of patients. Indeed, it is worth noting that researchers have been able to induce experimental EoE in a murine model of the disease exclusively through exposure to perennial allergens such as cockroaches, dust mites, or molds (17, 44). In fact, it is well known that in many cases, EoE patients are sensitized to both seasonal and perennial allergens (45, 46). As a consequence, the role of aeroallergen exposure in the development of EoE may not be as simple as exposure to spring pollens, especially if patients are sensitized to either pollens that appear in different seasons throughout the year or exposure to indoor perennial allergens.

The increased recognition of EoE during spring and summer months does not necessarily implicate outdoor antigens as potential etiological factors for EoE, but rather indicates a greater opportunity for establishing a diagnosis of EoE in patients with mild, chronic esophageal symptoms. Indeed, the majority of EoE patients possess a personal atopic background, commonly presenting with asthma, rhinitis, conjunctivitis, and eczema with variable frequency (1), and with aeroallergen sensitization being commonly described in patients of all ages (4, 9). Thus, it is not unusual for EoE patients to suffer atopic exacerbations during the pollen season and to seek out allergist care because of it, thereby providing an increased likelihood of receiving a diagnosis of EoE during the same season. Atopic features and allergy sensitization patterns in EoE patients are similar to those of atopic non-EoE individuals living in the same geographical area and exposed to common allergens (47), with no significant differences regard-

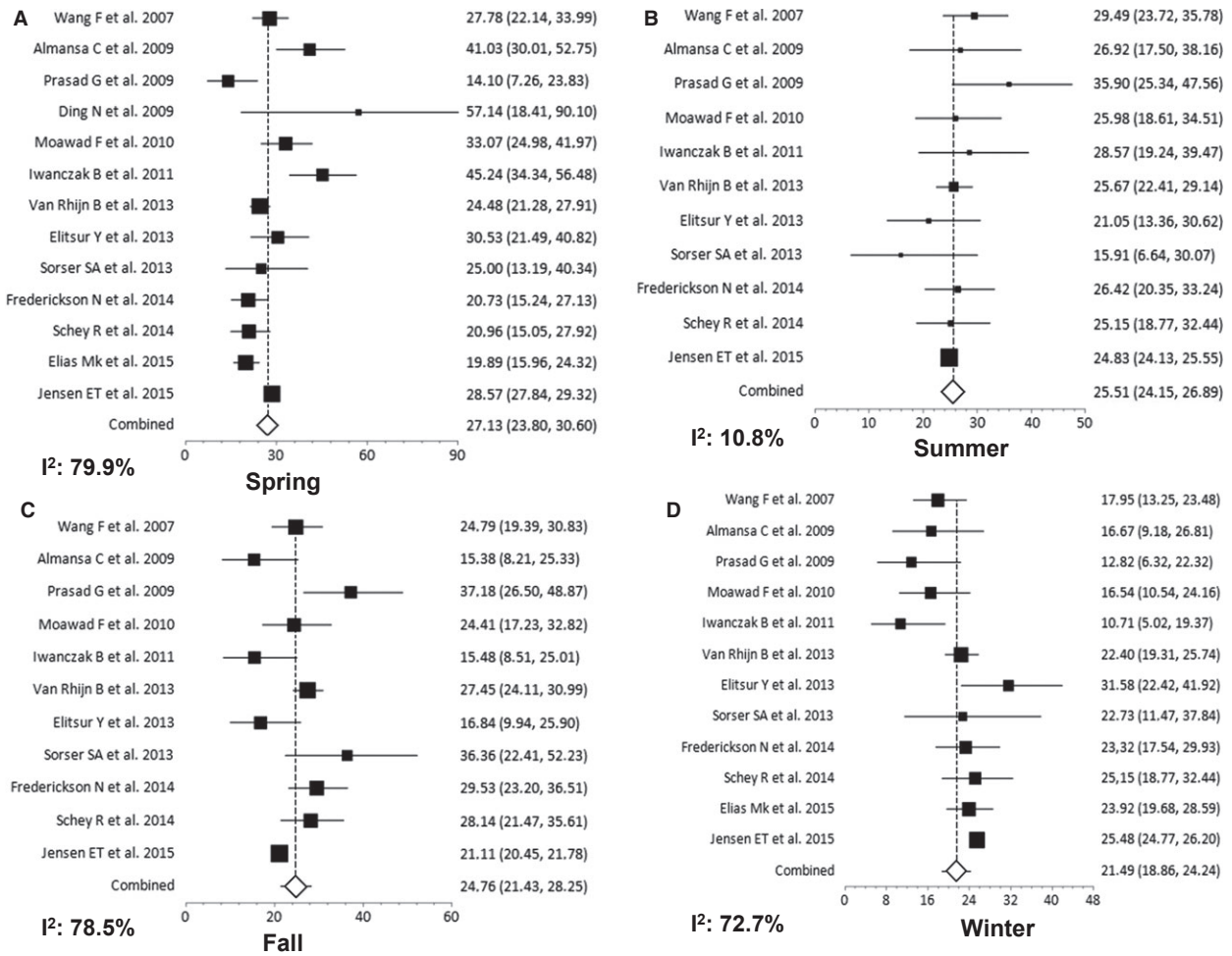

Figure 2 Overall combined seasonal incidence and 95% confidence intervals for newly diagnosed cases of EoE throughout the year, including spring (A), summer (B), winter (C), and fall (D). A random-effects model was used to calculate the overall effect size. The I^2 statistic indicates intrastudy heterogeneity.

ing family background of atopy, and personal history of allergic rhinitis, atopic dermatitis, immunoglobulin E-mediated food allergy, or sensitization to aeroallergens between the two groups, either in children or in adults (48).

Furthermore, a diagnosis of EoE can only be confirmed after an upper endoscopy with esophageal biopsies in patients complaining of symptoms of esophageal dysfunction. A long diagnostic delay from the onset of symptoms to actual diagnosis is thus extremely common for these patients, who are usually referred for esophageal symptoms several years before a definitive diagnosis is made (49–51). Several variables related to the patients themselves (underestimation of their own symptoms, avoidance of medical attention, or development of behavior modifications such as food avoidance, food modification, altered eating pace), along with variables related to the physician (lack of suspicion, lack of biopsies during endoscopic procedures) and the hospital (waiting period for endoscopic procedures), generally underlie this diagnostic delay. As such, equating the onset of clinical manifestations with a potential triggering by aeroallergens may be somewhat deceptive.

Although various atopic manifestations are present in most EoE patients, there is no solid evidence of a causal relationship, but rather both conditions seem to present independent courses. In fact, and unlike the case of atopy, a growing body of evidence indicates the absence of a relevant role for IgE-mediated immune reactions in EoE, which has been recently demonstrated to be an IgG4-associated disorder (52). To date, no peripheral markers have proven useful for monitoring EoE (53, 54), which seems to behave like a disease restricted to the esophagus, with few or no systemic manifestations. Common genetic and environmental etiological factors contributing to an independent development of atopy and EoE would thus explain the association of both entities (55, 56).

One of the major strengths of the present study is the search strategy, which included an exhaustive literature

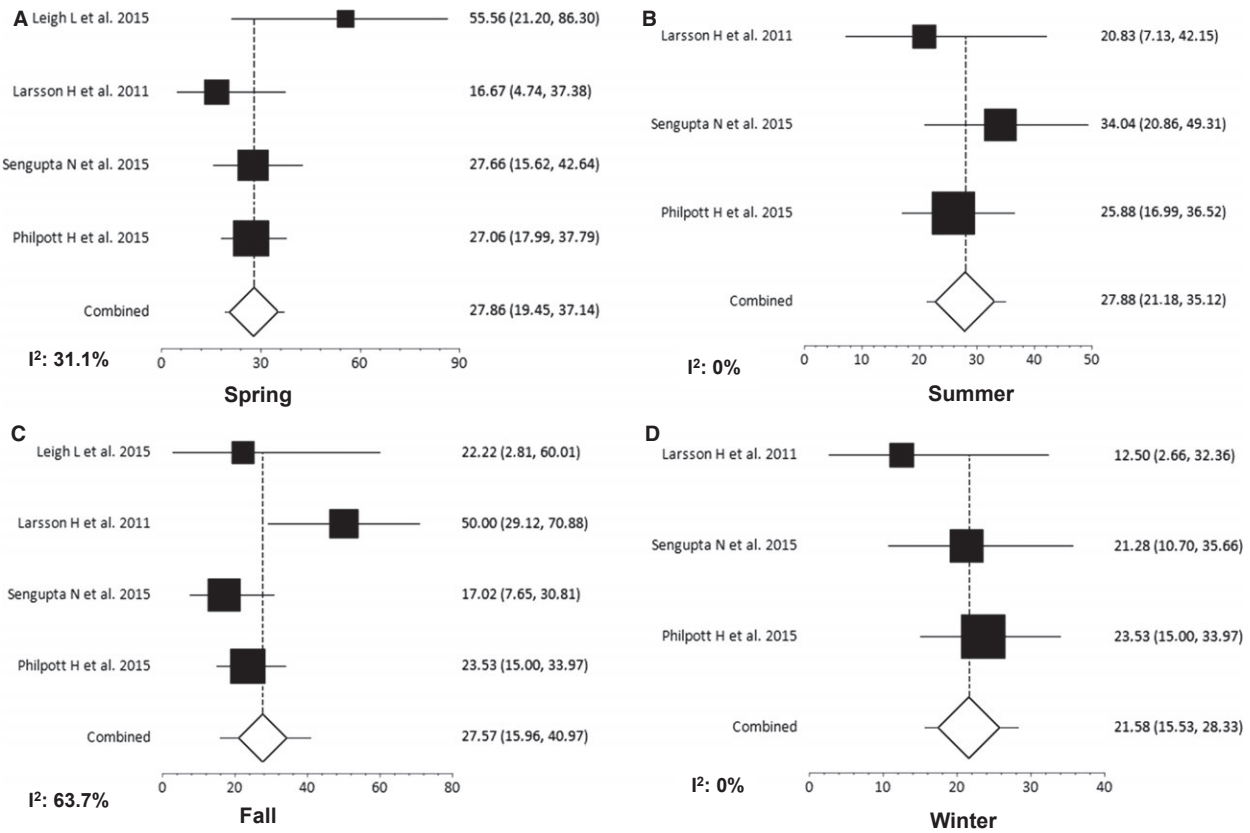

Figure 3 Overall combined incidence and 95% confidence intervals of food bolus impaction in patients with EoE, appearing in spring (A), summer (B), fall (C), and winter (D). I^2 denotes intrastudy differences or statistical heterogeneity.

search in three major databases as well as in abstract indexes of the principal allergy and gastroenterology congresses. Moreover, recovered studies were critically appraised according to their methodological aspects, and different investigators independently extracted the data from the studies included. No significant publication bias was noted in funnel plot analyses, so we are confident that the 18 documents retrieved represent all the relevant information available on this topic.

Still, several limitations should be noted for a better interpretation of our results. To begin with, the quality of the available evidence on seasonal predominance in the initial diagnosis or recrudescence of EoE was only moderate, with all the retrieved studies being of a retrospective, observational nature. Secondly, with regard to the assessment of clinical recrudescence, we only considered food bolus impaction needing medical care as it is the most reliable sign of a flare up, especially as no study assessed EoE symptoms with validated dysphagia instruments (57). Additionally, variations in the diagnostic criteria for EoE over the time period covered by our systematic review (e.g., eosinophil count threshold and exclusion of proton pump inhibitor-responsive esophageal eosinophilia) were not taken into account.

In conclusion, the present study does not support the existence of seasonal variations in the incidence of diagnosis and clinical recrudescence of EoE, both of which seem to be stable throughout the year. Our data reinforce the hypothesis that EoE predominantly constitutes a food allergy, with a minor role for aeroallergens in triggering and exacerbating the disease. Additional prospective research, specifically that focused on assessing recrudescence in accurately evaluated symptoms throughout the year, is needed to confirm our results.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Author contributions

Alfredo J Lucendo contributed to study conception and design, performed data extraction, analysis and interpretation of data, quality rating, wrote the manuscript, and approved the final version of the manuscript. Ángel Arias performed article retrieval, data extraction, analysis and interpretation of data, quality rating, and statistical analyses and approved the final version of the manuscript. Olga Redondo performed data extraction and quality rating and approved the final version of the manuscript. Jesús González-Cervera contributed to study conception and design, performed article retrieval, data extraction, analysis and interpretation of data, and quality rating, and approved the final version of the manuscript. All authors approved the final version of this manuscript, including the authorship list.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Begg funnel plot of studies on the seasonal distribution of incidence of EoE diagnoses in spring (A), summer (B), fall (C), and winter (D). The solid line in the center is the natural logarithm of pooled remission rates while the 2 oblique lines represent pseudo 95% confidence limits.

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