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Novel questionnaires for assessing signs and symptoms of eosinophilic esophagitis in children

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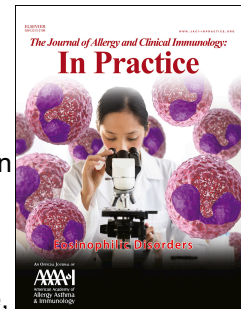
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Title: Novel questionnaires for assessing signs and symptoms of eosinophilic esophagitis in children

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26 **Conflicts of interest:** SK is an employee of Regeneron Pharmaceuticals, Inc. AY, LLK, MM, RL, CL, and DMTB
27 are employees of Adelphi Values. MK was an employee of Adelphi Values at the time of the research. IG
28 was an employee of Sanofi at the time of the research and is now an employee of IQVIA. Adelphi Values
29 conducted the qualitative research activities, sponsored by Regeneron/Sanofi. MC is an employee of the
30 Icahn School of Medicine at Mount Sinai and provided expert clinical advice during all research steps
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34 Children's Hospital of Philadelphia, Perelman School of Medicine at University of Pennsylvania and
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36 employee of the Duke University School of Medicine and served as a paid consultant to provide input on
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Abstract (current word count: 248/250)

Background: Pediatric patients with eosinophilic esophagitis (EoE) experience heterogeneous symptoms and patients' age may preclude reliable self-report of symptoms.

Objective: The goal of this study was to develop a patient-reported outcome (PRO) and an observer-reported outcome (ObsRO) questionnaire to evaluate the signs and symptoms of EoE in pediatric patients (≥ 1 to < 12 years of age) in a clinical trial setting.

Methods: A concept-focused literature review, expert advice meetings (EAM), and concept elicitation (CE) interviews with pediatric EoE patients and their caregivers were conducted to identify disease-related signs and symptoms. Instructions, items, and response options were drafted. Cognitive debriefing (CD) interviews were conducted to evaluate children and caregivers' ability to understand and respond to the questionnaires, and to evaluate the comprehensiveness of the concepts measured.

Results: Results from the literature review, EAM ($n=6$), and CE interviews ($n=24$) informed the development of the Pediatric EoE Sign/Symptom Questionnaire intended for use by patients with EoE ≥ 8 to < 12 years of age (PESQ-P) and an ObsRO questionnaire planned for use by caregivers of patients ≥ 1 to < 12 years of age (PESQ-C). Both questionnaires measure the same concepts; the PESQ-P assesses the frequency, duration, and/or severity of symptoms and the PESQ-C assesses the presence/absence of the signs/symptoms. CD interviews ($n=17$) demonstrated that participants were able to comprehend and complete the questionnaires as intended.

Conclusion: This study provides evidence of content validity of two novel questionnaires, PESQ-P and PESQ-C, designed to evaluate the symptom experience of pediatric EoE patients in a clinical trial setting.

Highlights

- **What is already known about the topic?** Eosinophilic esophagitis (EoE) is a rare, chronic inflammatory disease associated with a high eosinophil count and a heterogeneous symptom experience that may preclude reliable self-report of symptoms in pediatric patients. While treatment can reduce eosinophil levels, this reduction may not correspond with symptom experience; there are no questionnaires that can reliably and consistently assess observable EoE-related signs and symptoms across age groups
- **What does this article add to our knowledge?** Two clinical outcome assessment questionnaires that consider the age of patients and the heterogeneity of symptoms were developed to assess the signs and symptoms of pediatric EoE in a clinical trial setting from patients and caregivers
- **How does this study impact current management guidelines?** The two clinical outcome assessment questionnaires can be used to assess the signs and symptoms of pediatric EoE in pediatric patients, as well as from the perspective of caregivers of patients who may be too young to respond themselves

Keywords: eosinophilic esophagitis; EoE; symptoms; quality of life; patient-reported outcome; observer-reported outcome; pediatric; allergy; clinical outcome assessment

List of abbreviations: CD = cognitive debriefing, CE = concept elicitation, COA = clinical outcome assessment, EAM = expert advice meeting, EoE = eosinophilic esophagitis, FDA = Food and Drug Administration, HRQoL = health-related quality of life, ObsRO = observer-reported outcome, PESQ-C = Pediatric EoE Sign/Symptom Questionnaire for Caregivers, PESQ-P = Pediatric EoE Sign/Symptom Questionnaire for Patients, PRO = patient-reported outcome, US = United States

Introduction (402 words)

Eosinophilic esophagitis (EoE) is a rare, chronic type 2 inflammatory disease that is histologically characterized by eosinophilic infiltration of the esophageal epithelium.^{1,2} Clinically, EoE manifests with an array of symptoms that can significantly impair the daily activities and health-related quality of life (HRQoL) of patients and their families.^{3,4} While the histopathology of EoE is the same across age groups, the symptom experience differs.⁵ Infants primarily present with failure to thrive, school age pediatric children (<12 years of age) experience heterogeneous symptoms such as abdominal pain, vomiting, gastroesophageal reflux, and older patients (i.e., adolescents and adults) predominantly experience dysphagia.⁶⁻¹¹ Children that present with non-specific symptoms of EoE (e.g., vomiting, feeding difficulties) from a very young age may have poor symptom recognition and difficulty attributing their symptoms specifically to the condition.^{12,13}

Studies have shown that pharmacological treatment can improve the histopathological features of EoE (e.g., reduced eosinophil counts), but this does not always correlate with symptom improvement.^{14,15} This potential for contrast between objective histological improvements and the subjective patient symptom experience underscores the need to assess symptom burden via clinical outcomes. Evaluation of new treatments for pediatric patients with EoE requires a symptom-focused clinical outcomes assessment (COA) measurement strategy that considers the age and heterogeneity of EoE symptoms among patients.¹⁶

In a recent guidance on development of treatments for EoE, the United States (US) Food and Drug Administration (FDA) reported that no COA questionnaires have been widely accepted to evaluate the signs and symptoms of EoE among pediatric EoE patients.¹⁶ Existing questionnaires have limitations for use in younger patients enrolled in clinical trials.¹⁷⁻²³ These questionnaires do not adequately capture the perspective of both pediatric patients (i.e., <12 years of age), and the caregivers of patients with EoE who

are not old enough to reliably self-report their daily symptom experience, in ways that align with regulatory expectations or best measurement practice²⁰⁻²² (e.g., use of a one-month recall period as opposed to the preferred briefer recall periods).

To address this gap, two novel COA questionnaires were developed to assess the signs and symptoms of EoE in pediatric patients ≥ 1 to <12 years of age in a clinical trial setting: a patient-reported outcome (PRO) questionnaire intended for use by patients ≥ 8 to <12 years of age, the Pediatric EoE Sign/Symptom Questionnaire for Patients (PESQ-P), and an observer-reported outcome (ObsRO) questionnaire planned for use by the caregivers of patients <12 years of age, the PESQ for Caregivers (PESQ-C).

Methods (1,004 words)

Concept-focused literature review

A targeted review of published literature was conducted to identify relevant pediatric EoE-related signs and symptoms. Articles were identified using a search strategy including terms related to EoE (e.g., eosinophilic, esophagitis, allergic); signs, symptoms, and impacts; the target patient population (e.g., child, pediatric); and qualitative research (e.g., interview, patient experience, caregiver-report). The search was run via OvidSP on 31 July 2018 in the MEDLINE®, Embase, and PsycINFO® databases and was limited to peer-reviewed, English-language articles that were published within 15 years of the search being conducted. Additional articles were identified through a supplemental search via Google Scholar and input from medical experts consulting on the study. Articles were selected for full-text review and data extraction only if they focused on the signs, symptoms, and/or HRQoL impacts of EoE among children < 12 years of age. Articles were excluded if they focused only on aspects of EoE unrelated to the sign, symptom, and/or impact experience (e.g., biology, treatment efficacy), reported only data relevant to adult patients with EoE, were not peer-reviewed, and/or were not available in English.

Advice meetings with therapeutic area experts

Individual expert advice meetings (EAMs) were conducted with clinicians who treat pediatric patients with EoE in order to gather expert opinions on the symptom experience of pediatric patients. Moderators used a semi-structured EAM interview guide that included open-ended questions designed to spontaneously elicit feedback from the experts. Transcripts of these meetings were qualitatively coded and analyzed.

Concept elicitation interviews

All study documents were reviewed and approved by a centralized institutional review board, Sterling IRB, prior to interview conduct. The CE activities targeted both male and female patients ages ≥ 3

to <12 years and/or their caregivers for conducting face-to-face or telephone interviews to understand the signs and symptoms that characterize the experience of pediatric patients. Eligible pediatric participants and their caregivers were identified from a clinical site (located in Atlanta, GA) who consented, screened, and scheduled each participant ahead of the interview. To be included in the CE study, patients had to be ≥ 3 to <12 years of age with a clinician-confirmed diagnosis of EoE by upper endoscopy with biopsies and an experience with at least one active EoE symptom in the four weeks prior to screening. Patients were excluded from participating if they were diagnosed with conditions that may confound the symptom experience of pediatric EoE including hypereosinophilic syndromes, eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis), and/or eosinophilic gastroenteritis. Caregivers were eligible to participate if they were ≥ 18 years of age and provided daily care to a patient who met the inclusion criteria.

Sixty-minute interviews were conducted using a semi-structured interview guide that included open-ended and targeted follow-up questions designed to understand the patient and caregiver experience with EoE-related signs and symptoms. Though both patients and caregivers participated in the interviews, the primary respondent during the interviews was dependent upon the ability of the child. It was anticipated that the primary respondent during interviews with patients eight years of age and older would be from the child, whereas the primary respondent during interviews with patients younger than 8 years of age was anticipated to be the caregiver. Questions were targeted toward the primary respondent, but the other respondent was asked questions as well to collect additional information. Each interview was audio-recorded, transcribed, and anonymized for formal qualitative data coding and analysis.^{19,20,33}

Saturation of concept (i.e., the point at which no new relevant information would be gained from the conduct of additional CE interviews) was also analyzed to evaluate the adequacy of the sample size.^{19,20} Interviews were ordered chronologically into transcript groups and coded data were used to

determine the first transcript group in which a concept was first mentioned. The adequacy of the sample size (e.g., saturation) was determined by a downward trend in new concepts identified in the groups of interviews, and all concepts relevant to EoE reported within the first 75% of interviews (i.e., by the first three groups of interviewed participants.¹⁹ Following saturation, a conceptual model, which describes the relationship between a disease process and its signs, symptoms, and impacts, was developed based on the concepts elicited during the concept elicitation interviews with patients ≥ 3 to < 12 years of age with EoE.³⁴

As stated previously, the COA questionnaires were being developed for use in a clinical trial setting with pediatric patients with EoE. After CE activities were completed, the decision was made to extend the target age range to include patients ≥ 1 to ≤ 2 years of age. A single hybrid CE/cognitive debriefing (CD) interview was conducted with the caregiver of a child with EoE who was two years of age to explore the sign and symptom experience of patients with EoE in this age group.

Concept selection and questionnaire construction

Spontaneously reported unique concepts, representing signs or symptoms of EoE, which were either directly observed by caregivers or expressed by children were considered for selection for the questionnaires. Once concepts were selected, each questionnaire's instructions, items, and response options were drafted based on best-practice guidelines for clinical outcome assessment measurement^{20,22} and regulatory guidance documents.^{16,21,22}

Cognitive debriefing interviews

After drafting the PESQ-P and PESQ-C, cognitive debriefing (CD) interviews with patients and/or caregivers were conducted by telephone to evaluate participants' ability to understand the questionnaire content, select responses that reflect the health status of the patient, and assess the comprehensiveness of the questionnaires to assess EoE-related signs and symptoms relevant to pediatric patients.

Eligible pediatric participants and their caregivers were identified from two clinical sites located in Atlanta, GA and New York, NY who consented, screened, and scheduled each participant ahead of the interview. The same recruitment methods were followed as in the CE interviews with an adjustment to the inclusion/exclusion criteria to include interviews with caregivers of pediatric patients ≥ 1 to ≤ 2 years of age. As previously noted, one caregiver of a child with EoE who was two years of age participated in a CD interview that also included a CE component to elicit information about the patient experience on the signs and symptoms of the condition.

Results (1,425 words)

The concept-focused targeted literature search identified 12 relevant publications (Figure 1) from which a total of 21 sign and symptom concepts were identified (Supplemental Table E1). All articles focused on pediatric EoE patients with ages ranging from infants who were >0 years of age to older children (up to <18 years of age), though the focus was on the results for patients ≥ 2 to <12 years of age. The concepts most frequently identified within the literature were abdominal pain, dysphagia, vomiting, food impaction, nausea, chest pain, heartburn, and gastroesophageal reflux (hereafter referred to as 'reflux').

EAMs were conducted with six US-based medical experts who practiced in an academic setting and reported specializing in allergy-immunology (n=3), pediatric gastroenterology (n=2), or general pediatrics (n=1). Experts reported 13 disease-related signs and symptoms associated with pediatric EoE (Supplemental Table E1), including stomach pain, reflux, heartburn, trouble swallowing, and vomiting, each of which were reported by all six experts. Experts indicated that symptoms varied by age group, noting that vomiting and abdominal pain were more prevalent among patients two to seven years of age while difficulty swallowing and food impaction were more prevalent in patients ≥ 8 years of age. Most experts (n=4/6, 66.7%) reported that reducing the severity and frequency of symptoms were indicators of treatment benefit in EoE, while two of these experts also noted that assessing the presence/absence of symptoms could indicate treatment benefit.

A total of 24 CE interviews (Table I) were conducted with patients and each of their caregivers: 10 with patients 8 to <12 years old and 14 with patients 2-7 years old. The mean age of patients who participated in the CE interviews was 6.6 years of age (standard deviation was 2.9). Most patients were White/Caucasian (n=14, 58.3%) and male (n=15, 62.5%). Patient health and treatment information as reported by recruiting clinicians (Table II) indicated that patients were treated with a variety of EoE

therapies, including elimination diet and swallowed topical corticosteroids. Patients also presented with a variety of comorbid health conditions including a range of atopic conditions (i.e., food allergy, allergic rhinitis, and atopic dermatitis). Among the caregivers who participated in the interviews (N=24), ages ranged from 27.5 to 48.8 years with a mean of 37.6 years (SD=6.0). Most caregivers were female (n=23, 95.8%), more than half were white/Caucasian (n=15, 62.5%).

Patients and/or caregivers reported 25 EoE-related signs and symptoms during the CE interviews (Supplemental Table E1), with vomiting as the most frequently reported, followed by stomach pain, coughing, reflux, throat pain, and bloating. Choking, food getting stuck, trouble swallowing, chest pain and constipation were also reported by approximately half of the sample. Similar symptoms were reported by participants across age groups. Participants also reported nine food-modification behaviors (i.e., changes to the way the patient eats food to cope with symptoms) that were deemed to be signs of the condition. The most frequently reported food-modification behaviors were avoiding specific foods and eating slowly.

Saturation analysis found that the majority of the 25 reported signs and symptoms (n=20, 76.9%) were reported in the first ~25% of interviews and the remaining five symptoms were reported within the first ~75% of interviews, demonstrating that saturation of concept was achieved, providing evidence for the adequacy of the sample size. Following completion of the CE interview analysis, a conceptual model was developed presenting the signs, symptoms, and impacts reported by participants in these CE interviews (Figure 2).

To draft the PESQ-P and PESQ-C, eight concepts were selected: stomach pain, heartburn, acid reflux, regurgitation, vomiting, food refusal, trouble swallowing food, and food getting stuck in the throat. Concepts were selected if they were spontaneously reported by $\geq 30\%$ of CE interview participants (i.e. at least 8 out of 24 participants), were considered severe and/or bothersome, able to be reported by

caregivers via direct observation or what the child or other caregivers told them, were unique concepts (i.e., did not overlap with other reported concepts selected for measurement), and were identified as core disease-related concepts based on the EAM and literature review. The 30% cut-off for inclusion of CE concepts was pre-specified to ensure selection of concepts reported by a sufficient number of patients while excluding any concepts that were idiosyncratic. Items for the PESQ-P and PESQ-C were drafted for the eight sign/symptom concepts (Table III) using language reflecting the terms used by participants during interviews. Because patients and caregivers reported that the signs and symptoms of EoE can be experienced daily, the questionnaires were designed to be completed each day, in the evening, on an electronic device using a 24-hour recall period.

For the patient-reported PESQ-P, the first item is a checklist for patients to report which signs/symptoms they experienced in the past 24 hours. Following the checklist, patients are presented with follow-up items for the symptoms they reported to evaluate symptom severity using a 5-point numeric rating scale [NRS], period(s) of the day in which the symptom occurred (last night, morning, afternoon, evening), number of times the sign/symptom was experienced, and/or duration using a 4-point verbal rating scale of each reported concept at its worst (a little of the time, some of the time, most of the time, all of the time), as applicable. If patients report having trouble swallowing or food getting stuck, they are presented with a list of coping mechanisms and asked to select any action they took to cope with it.

For the observer-reported PESQ-C, caregivers are first asked to report the time periods of the day (last night, morning, afternoon, evening) during which the caregivers were present with their child. Subsequently, caregivers are asked if the patient experienced a given symptom, during which time period the symptom occurred, and the source of information used to report the symptom (i.e., direct observation or feedback from the patient or another caregiver). Severity and duration are not evaluated by the PESQ-C as these subjective aspects of the sign/symptom experience cannot be evaluated by an observer.¹⁶ For the concept of vomiting, caregivers are also asked to report how many times the child vomited. The same

260 coping mechanism response options used in the PESQ-P are presented in the PESQ-C. To encourage
261 objective and consistent reporting, the PESQ-C includes instructions to explain that a primary caregiver
262 should complete the diary each day and that caregivers should only answer questions based on what their
263 child has told them, what they have directly observed, and/or what another caregiver has told them.

264 To evaluate patient and caregiver understanding of the draft questionnaires, a total of 17 CD
265 interviews were conducted with patients and caregivers. A total of 8 patients (ages ≥ 8 to <12 years old)
266 were debriefed on the PESQ-P and a total of 9 caregivers of patients ages >1 to <8 years old were debriefed
267 on the PESQ-C, both across three waves (Supplemental Table E2 and Table E3). Wave 1 included four
268 patients who were debriefed on the PESQ-P and one caregiver who was debriefed on the PESQ-C. Wave
269 2 included four caregivers who were debriefed on the PESQ-C, and Wave 3 included four patients who
270 were debriefed on the PESQ-P and four caregivers who were debriefed on the PESQ-C (including one
271 caregiver of a 2-year-old). Most patients were White/Caucasian ($n=10$, 58.8%) and male ($n=12$, 70.6%).

272 The relevance of the concepts evaluated by the questionnaires was confirmed (Table III), as the
273 majority of patients experienced all eight of the sign/symptom concepts evaluated by the questionnaires.
274 The one exception was “food getting stuck” associated with trouble swallowing, which was only reported
275 by three patients (all of whom were ≥ 8 to <12 years of age).

276 Most patients debriefed on the PESQ-P and most caregivers debriefed on the PESQ-C understood
277 the instructions, items, recall period, and response options as intended. The readability of the PESQ-P and
278 the PESQ-C were both assessed and have a Flesch-Kinkaid 3rd and 4th grade reading level, respectively.
279 Additionally, participant suggestions for revising content pertaining to each questionnaire were minimal;
280 however minor changes were made to the questionnaires throughout interview waves. Specifically, to
281 improve patient interpretation of items and respond to patient feedback, the items evaluating “trouble
282 swallowing food” and “food getting stuck” were revised following Wave 2 of the interviews. These

283 revisions were made because participants described these two concepts as being on the same spectrum,
284 with “food getting stuck” being on the most severe end of trouble swallowing. This perspective was
285 confirmed by the two consulting medical experts. Following the completion of patient interviews,
286 additional minor revisions were made to both questionnaires to simplify content based on internal
287 discussions, which included removing instruction text that was identified as redundant.

Discussion (1,097 words)

The PESQ-P and the PESQ-C were developed to assess pediatric EoE patient signs and symptoms in a clinical trial setting across a range of pediatric patient ages (i.e., patients ≥ 1 to <12 years of age) and in accordance with best practice guidelines.^{20,28}

Studies have indicated that while most pediatric EoE patients can experience similar symptoms, the presence, frequency, and severity of these symptoms may vary by patient, and some are more common in older pediatric patients (e.g., dysphagia, food impaction, chest pain, and heartburn).^{18,23,25} The PESQ-P and PESQ-C address the challenges of evaluating a fluctuating and heterogenous symptom experience among pediatric patients and fills the need for suitable questionnaires developed according to FDA Guidance specific to EoE¹⁶. Specifically, these PRO and ObsRO questionnaires both assess the signs and symptoms of EoE in a similar manner¹⁶ by measuring the presence and frequency of relevant signs and symptoms. While the PESQ-C only measures sign/symptom frequency (in comparison to the PESQ-P which also assesses severity and duration), this provides researchers with the ability to consistently assess objective and observable aspects of the pediatric patient experience across age groups.

Both questionnaires comprehensively assess the range of signs and symptoms experienced by pediatric EoE patients using a brief recall period, simple language drawn from words/phrases used by participants during CE, and clear instructions to respondents. This is particularly critical for the PESQ-P given the targeted respondent age (i.e., patients ≥ 8 to <12 years of age). The caregiver-specific instructions provided with the PESQ-C are provided to encourage consistency (i.e., only the primary caregiver should complete the questionnaire throughout the study) and reliability (i.e., caregivers should only report on symptoms that they can objectively report on). Overall, both pediatric patients and caregivers interpreted the questionnaire content as intended and were able to use the instructions to complete the questionnaires.

While the questionnaires' instructions were well understood by patients and caregivers alike, when implementing the questionnaires in clinical trials, training and instructions should be provided to participants, and in particular to caregivers, to ensure proper data collection. The PESQ-C may be used by the caregivers of all pediatric patients with EoE but is critical to measuring observable signs of EoE in patients who are <8 years of age. In studies with older pediatric patients (i.e., ≥8 to <12 years of age), caregivers should be instructed to encourage regular completion of the PESQ-P by the patient to promote compliance. During the course of a clinical trial, there may be instances when children are not with their parents for extended periods of time. The design of the PESQ-C allows data to be collected during such periods based on what the patient or another caregiver tells them, providing data that could be used in sensitivity analyses when analyzing trial endpoints based on the PESQ-C.

Quantitative research is needed to evaluate the structure of each questionnaire and the associated psychometric performance for scoring algorithms. We anticipate that these questionnaires can be used to measure an endpoint that assesses the change in proportion of cumulative days or time-periods, without any sign or symptom of EoE, or an endpoint such as sign/symptom-free days. While the potential for item-level scores to be combined and yield domain-level total scores should be explored, ultimately an approach that calculates a total symptom score may not be viable in this patient population given the heterogeneity of the symptom experience for some patients (e.g., some patients may experience a very low frequency of symptoms).

A limitation to this study was a small sample size due to the rarity of the disease. However, despite the relatively small sample size of this study and the known heterogeneity of the disease experience, saturation of the signs and symptoms of EoE was met as all concepts were reported in the first 75% of interviews. In addition, the sample that was recruited reflected the epidemiology of the disease (i.e., the prevalence of EoE is three to four times higher among males compared to females, and commonly affects those who are White/Caucasian^{31,32}). A limitation in the design of PESQ-C is that it allows for the primary

caregiver to report on what another caregiver told them. While this is a novel aspect of the PESQ-C that may be advantageous in situations where the primary caregiver is not present, it may not be as reliable or ideal when compared to reports that are limited to direct observations or based on what the child told the caregiver. However, utilizing such an approach allows for the collection of descriptive data that can be used in sensitivity analyses to see if patterns of response are affected by the “reporting circumstances.” Another limitation is that most caregivers debriefed on the PESQ-C had a college (N=7, 41.2%) or graduate (N=4, 23.5%) degree which could have resulted in a biased sample of participants in terms of education level; this may have impacted understanding of the questionnaire. However, the PESQ-C when assessed in Word for readability, had a Flesch reading ease of 86.8 and a Flesch-Kincaid grade level of 4.5. Finally, another limitation is that while the PESQ-C was planned for use with the caregivers of patients ≥ 1 to <12 years of age, only one caregiver of a patient who was 2 years of age participated in an interview and no caregivers of patients between one and two years old participated due to recruitment limitations (i.e., difficulty recruiting younger patients due to average diagnostic age of 5.9 to 12 years³⁵). Future qualitative research in this younger age group to further confirm content validity of the PESQ-C would be suggested for patients 1-3 years of ages.

The PESQ-P and PESQ-C are novel COA questionnaires that were developed to comprehensively assess the breadth of signs and symptoms relevant to pediatric patients <12 years of age with EoE in the context of a clinical trial setting. The results of this study provide evidence supporting the content validity of these questionnaires in patients >2 to <12 years old. As a next step in the development of the PESQ-P and PESQ-C, the psychometric properties of the questionnaires should be evaluated to generate further evidence of the validity, reliability, and responsiveness of these questionnaires. Such research can also be utilized to generate guidelines to inform the interpretation of the scores generated by these questionnaires. Additionally, as previously highlighted, further qualitative research should be conducted to test the PESQ-C with caregivers of patients ≥ 1 to ≤ 2 years of age to further demonstrate content validity

359 in the younger patient population. Following such future research, the intention is for both the PESQ-P
360 and the PESQ-C to be made available through licensing.

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Figures

Figure 1. Flowchart of targeted literature search

Figure 1 Legend: Key terms related to EoE were used to identify relevant qualitative research articles that were peer-reviewed, in English, and published within the last 15 years of the search being conducted. Articles were excluded if they failed to meet inclusion criteria.

Figure 2. Pediatric EoE sign, symptom, and impact conceptual model

Figure 2 Legend: Concepts elicited from pediatric patients and their caregivers during the concept elicitation interviews were organized into a conceptual model detailing important signs, symptoms, and impacts.

Tables

Table I. Patient-reported demographic information (content evaluation interviews)

	Overall patient sample* Total (N=24 [†])	Patients 2-7 years old Total (n=14)	Patients 8 to <12 years old Total (n=10)
Age (years)			
Range	2.7–11.8 [†]		
Mean (standard deviation)	6.6 (2.9)		
Sex - n (%)			
Male	15 (62.5)	9 (64.3)	6 (60.0)
Female	9 (37.5)	5 (36.7)	4 (40.0)
Race - n (%)			
White/Caucasian	14 (58.3)	8 (57.1)	6 (60.0)
Black or African American	5 (20.8)	3 (21.4)	2 (20.0)
Other	1 (4.2)	1 (7.1)	0 (0.0)
Not answered	4 (16.7)	2 (14.3)	2 (20.0)

*Patient demographic information was self-reported by the patient and/or caregiver-reported

[†]Following the first n=23 interviews with patients and caregivers 3-11 years old, the age range of the target patient population was expanded down to include patients 1 to 2 years old. Recruitment was challenging given the rarity of the condition of this younger group, and only one caregiver of a patient 2 years of age was successfully enrolled

Table II. Patient health and treatment information (content evaluation interviews)

	Overall patient sample* Total (N=24)	Patients 2-7 years old Total (n=14)	Patients 8 to <12 years old Total (n=10)
Patients currently on a food elimination diet - n (%)			
No	11 (45.8)	4 (28.6)	7 (70.0)
Yes	9 (37.5)	8 (57.1)	1 (10.0)
Not answered	4 (16.7)	2 (14.3)	2 (20.0)
Treatments reported for EoE symptoms[†] - n (%)			
Swallowed topical corticosteroids	13 (54.2)	6 (42.8)	7 (100.0)
Proton-pump inhibitors	12 (50.0)	8 (57.1)	4 (33.3)
Systemic corticosteroids	3 (12.5)	3 (21.4)	0 (0.0)
Dietary therapy	2 (8.3)	2 (8.3)	0 (0.0)
Leukotriene antagonists (montelukast)	2 (8.3)	1 (7.1)	1 (14.3)
Comorbid health conditions that the patient currently has - n (%)			
Food allergy	14 (58.3)	8 (57.1)	6 (60.0)
Asthma	11 (45.8)	7 (50.0)	4 (40.0)
Other[†]	6 (25.0)	4 (28.6)	2 (20.0)
Allergic rhinitis	4 (16.7)	3 (21.4)	1 (10.0)
Atopic dermatitis	3 (12.5)	2 (14.3)	1 (10.0)
None	1 (4.2)	1 (7.1)	0 (0.0)
Not answered	4 (16.7)	2 (14.3)	2 (20.0)

*Patient health and treatment information was reported by a practicing clinician at the recruitment site

474 †Various treatments reported are not mutually exclusive, and percentage is based on the number of caregivers who reported the
475 child they cared for was currently receiving treatment for EoE symptoms

476 ‡Other conditions included gastroesophageal reflux disease (GERD; n=2 in 2-7 age group), cerebral palsy (n=1 in 2-7 age group),
477 eczema (n=1 in 2-7 age group), hydrocephalus (n=1 in 8 to <12 years age group), and sleep apnea (n=1 in 8 to <12 years age
478 group)

479 Note: EoE=eosinophilic esophagitis

Table III. Clinical terms, item wording, and dimensions to be evaluated

Clinical term concept (item concept wording)*	PESQ-P (PRO)					PESQ-C (ObsRO)		
	Frequency			Severity	Duration	Frequency		
	Yes/ No [†]	Time period of day	# of times			Yes/ No [†]	Time period of day	# of times
Stomach pain	X	X		X	X	X	X	
Heartburn ("Burning feeling in chest")	X	X		X	X	X	X	
Acid reflux ("Acid coming up from stomach into throat")	X	X		X		X	X	
Regurgitation ("Food came up from stomach into mouth")	X	X	X	X		X	X	
Vomiting ("Threw up")	X	X	X	X		X	X	X
Food refusal ("Refused to eat a meal")	X	X [‡]		X		X	X [‡]	
Trouble swallowing food	X	X [§]		X		X	X [§]	
Food got stuck in throat	X	X [§]		X		X	X [§]	

*Item concept wording is included in quotations only when the item concept differs from the clinical term

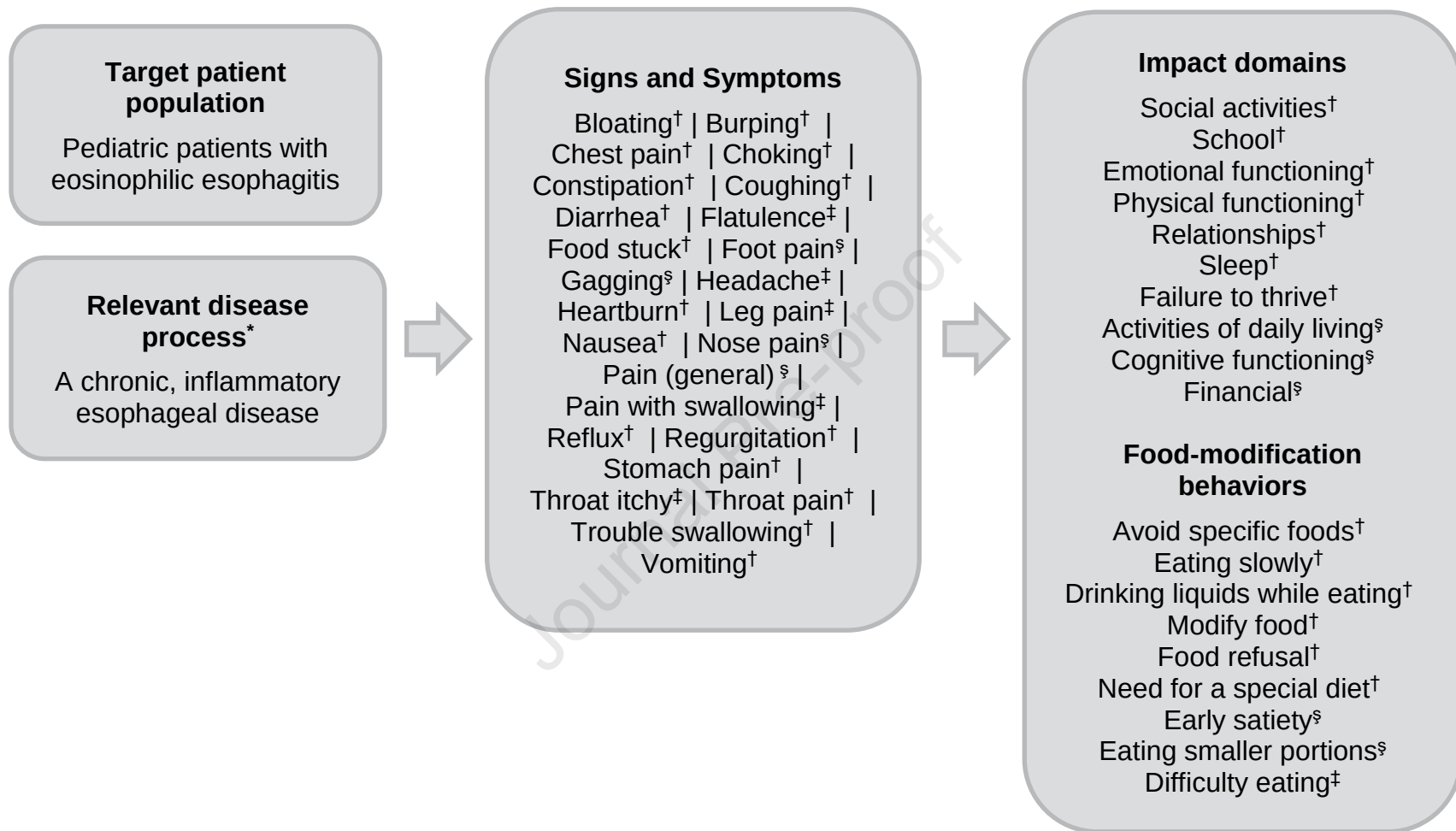
[†]Assesses whether or not the symptom was or was not experienced within the recall period

[‡]Assessed as meal(s) the child refused to eat

[§]Also assessed: Actions taken by patient to swallow food (i.e., "swallow several times," "drink liquids," "cough," "gag," "spit out the food," and "throw up")

Note: EoE=eosinophilic esophagitis; Pediatric EoE Sign/Symptom Questionnaire – Patient (Patient-reported outcome measure);

Pediatric EoE Sign/Symptom Questionnaire – Caregiver (Observer-reported outcome measure)

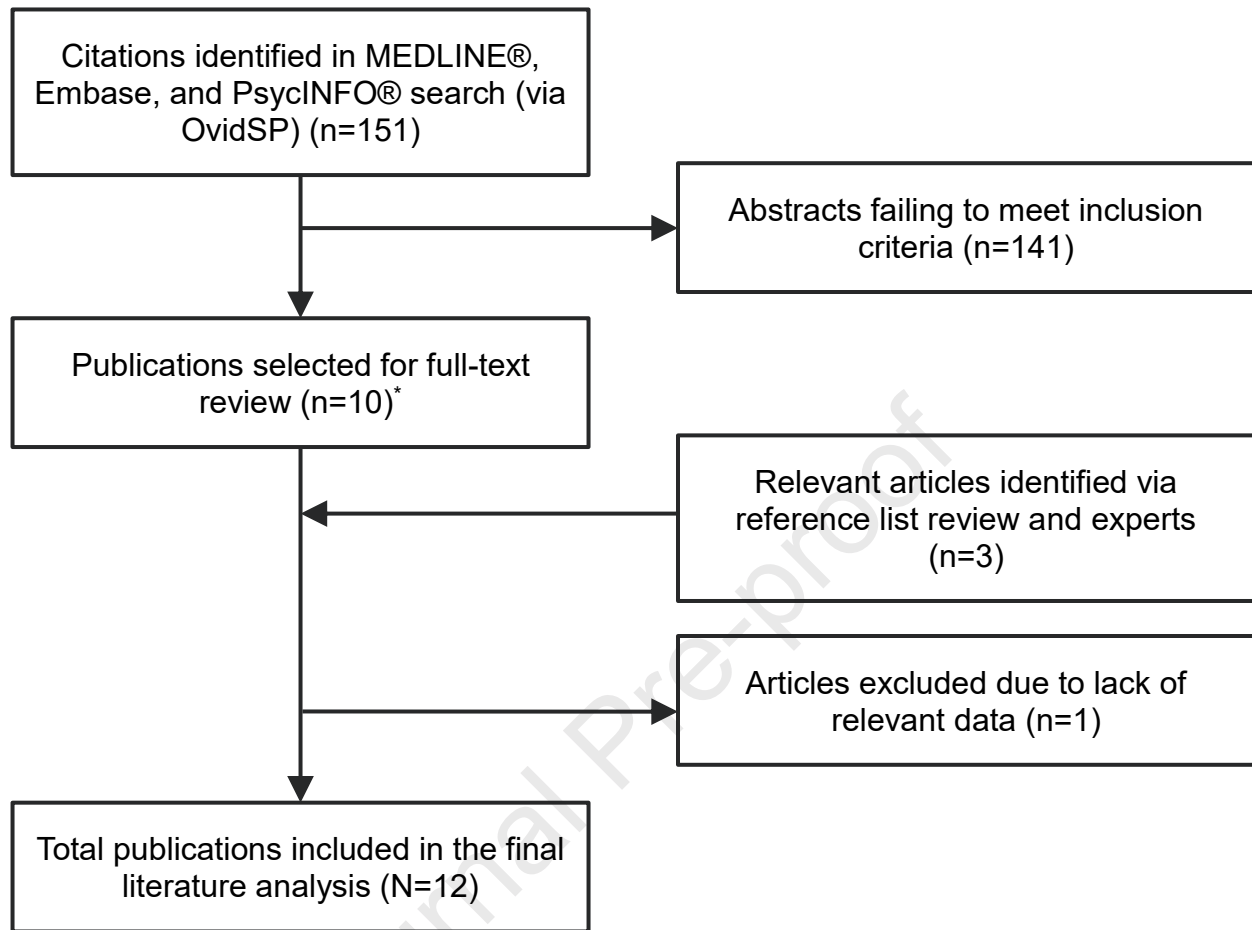
Figure 2. Pediatric eosinophilic esophagitis disease sign, symptom, and impact conceptual model

*Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clinical Gastroenterology and Hepatology*. 2005;3(12):1198-1206.²⁷

[†]Concepts reported by >30% of patients overall.

[‡]Concepts reported by <30% of patients overall.

[§]Concepts reported by <30% of patients overall and in only one age group.

Figure 1. Literature search flow diagram

*Abstracts that best met the screening criteria and that presented the strongest likelihood of providing detailed information were selected for full-text review