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The increasing incidence and prevalence of eosinophilic esophagitis outpaces changes in endoscopic and biopsy practice: National population-based estimates from Denmark

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Summary

Background—National population-based medical registries in Denmark offer a unique opportunity to study eosinophilic esophagitis (EoE) epidemiology.

Aim—To determine the incidence and prevalence of EoE in Denmark, and evaluate whether an increase in endoscopy with biopsy activity explains changes in these trends.

Methods—The Danish National Pathology Registry, Danish National Patient Registry, and Danish Registry of Medicinal Product Statistics were queried from 1997–2012. Using an EoE case-finding algorithm validated for Danish patients, EoE cases were identified during each year of the study period; we also identified all patients with esophageal eosinophilia. Using the known population of Denmark, the annual incidence and prevalence of EoE were determined. We also determined the number of esophageal biopsies performed each year in Denmark, and compared the change in the incidence rate to the change in biopsy rate.

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Authorship statement

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Specific author contributions (note that all authors approved the final draft and the authorship list):

Dellon: Project conception/design; obtained funding; data analysis/interpretation; drafting of the article; critical revision; approved final draft.

Erichsen: Project conception; data acquisition/interpretation; critical revision; approved final draft.

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Results—Between 1997 and 2012, 1708 patients had esophageal eosinophilia, of whom 844 met the case definition of EoE. There were 7 new cases of EoE in 1997 and 145 new cases in 2012, corresponding to a 19.5-fold increase in incidence (0.13/100,000 to 2.6/100,000). There were 769 total cases in 2012 (prevalence of 13.8/100,000). Over the same time frame, the esophageal biopsy rate increased only 1.9 fold, from 91.1/100,000 to 175.3/100,000.

Conclusions—The incidence and prevalence of EoE markedly increased in Denmark over the past 15 years. This increase far outpaced the increase in esophageal biopsy utilization, indicating that changes in the frequency of EoE are not due to changes in biopsy rates alone.

Keywords

Eosinophilic esophagitis; epidemiology; incidence; biopsy; population-based

Introduction

Over the past two decades, eosinophilic esophagitis (EoE) has transformed from a rarely recognized and case-reportable condition to an increasingly common cause of upper gastrointestinal morbidity in both children and adults.^{1–4} The prevalence of EoE is now estimated to be approximately 50–100 cases/100,000 persons based on studies from Western Europe, Australia, and North America,^{5–11} but can be even more common among symptomatic patients undergoing endoscopy.^{12–17} Multiple studies have shown the incidence of EoE to be continually rising as well, now reaching levels of approximately 10 cases/100,000 persons.^{5, 9, 18, 19}

However, these data are limited because most studies of the incidence and prevalence of EoE are from single referral centers, and few have population-based data. No national studies have been conducted using patient-level, rather than administrative, medical data with a validated case-finding algorithm. Moreover, with the recent explosion in research and interest in EoE,^{20, 21} it is unclear if current epidemiologic trends represent a true increase in disease burden, or simply increased knowledge and detection of a previously unrecognized condition.

National population-based medical registries in Denmark, which link medical records, diagnostic codes, pathology findings, and prescription medications via an individual identifier assigned to every person in the country,^{22–25} offer a unique opportunity to study systematically the epidemiology of eosinophilic esophagitis (EoE) and to address these issues. We recently developed and validated an EoE case-finding algorithm in Denmark with high sensitivity and specificity for identification of true cases of EoE.²⁶ The aim of the current study was to use this case definition to determine the incidence and prevalence of EoE in Denmark, and evaluate whether an increase in endoscopy with biopsy activity explains changes in these trends.

Materials and methods

Danish administrative and health registries

Denmark has a stable population of approximately 5.5 million people and is well-suited for epidemiological studies.^{22–25} When the Civil Registration System was established in 1968, it made comprehensive population-based studies possible through linkage of information about individuals across multiple independent registries using the Civilian Registration Number, a unique identifier assigned to every person in the country.^{24, 27}

We conducted a retrospective study using three Danish medical registries: the Danish National Patient Registry, which houses *International Classification of Diseases, 10th Edition* (ICD-10) codes dating from 1994, hospital admission and discharge codes, surgical procedure codes, and outpatient visit codes;²⁸ the National Pathology Registry, which contains Systematized Nomenclature of Medicine (SNOMED) codes for pathologic specimens dating from 1997;²⁵ and the Register of Medical Product Statistics, which contains community pharmacy prescription data coded using the Anatomical Therapeutic Chemical (ATC) classification system.²⁴

This study was approved by both the University of North Carolina IRB (IRB # 10–1043) and the Danish Data Protection Agency (record number 2010-41-4986).

EoE case identification and data extraction

Cases of EoE were defined using our previously validated algorithm for the Danish health registries.²⁶ In brief, the National Pathology Registry was first queried from 1997–2012 to identify all patients with esophageal eosinophilia as defined by the combination of SNOMED codes for esophageal biopsies (T62xxx) and tissue eosinophilia (M47150). We previously demonstrated that these codes accurately reflected high levels of esophageal eosinophilia (ie 15 eosinophils per high-power microscopy field).²⁶ Next, all ICD-10 diagnostic codes were obtained from the Danish National Patient Registry. Patients were excluded if they had one of 11 codes that could explain esophageal eosinophilia from a secondary cause, and were included as an EoE case meeting our primary study definition if they then had one of 13 required codes for symptoms (Supplemental Table 1). The strategy previously yielded a high sensitivity and specificity for case finding in patients with esophageal eosinophilia (88% and 80%, respectively).²⁶

Because of potential inaccuracies in this case finding strategy, we decided *a priori* to include two additional case definitions for sensitivity analyses. The first case definition was for any patient with esophageal eosinophilia. To meet this definition, a subject only had to have the two SNOMED codes specified above. The second was for a more restrictive case definition of EoE. To meet this definition, patients had to meet the primary case definition and were required to have a prescription for either a proton pump inhibitor or a H2-receptor blocker medication in the two months prior to the endoscopy and biopsy (Supplemental Table 1). The rationale for this restriction was that it closely mirrors EoE diagnostic criteria.^{2–4} While this definition of EoE was highly specific (96%) in our prior study, its low sensitivity (21%) made it less desirable as a primary definition for measuring incidence and prevalence.²⁶

In addition to data required to support the case definitions, we also extracted ICD-10, SNOMED, and ATC codes for a wide range of symptoms, diseases, and medications of interest in order to further characterize the study population (Supplemental Table 2). We also collected data on the total number of esophageal biopsies performed throughout Denmark during each year of the study period.

Statistical analyses

Descriptive statistics relating to symptoms, diseases, and other factors of interest were calculated and examined for all case definitions. Using the primary EoE definition, children with EoE (< 18 years of age) were compared to adults with EoE. Means were compared with t-tests and proportions were compared with chi-square.

To calculate the incidence of EoE, the number of new patients fulfilling each of the three case definitions was identified for each year of the study, and then divided by the total population of Denmark for the corresponding year. This resulted in an annual incidence rate of cases per 100,000 persons.

To calculate the prevalence of EoE, the total number of patients fulfilling each of the three case definitions was identified for each year of the study, and then divided by the total population of Denmark for the corresponding year. This resulted in an annual prevalence rate of cases per 100,000 persons. Prevalence patterns were further analyzed for the primary EoE case definition by stratifying the most recent cumulative prevalence by both gender and 5-year age groups.

Finally, the rate of esophageal biopsies per 100,000 persons per year was also calculated. The change in the rate of biopsies over the study time frame was also calculated and compared to the change in the incidence rate. All analyses were performed using SAS version 9.3 (Cary, NC).

Results

Characteristics of patients with esophageal eosinophilia and EoE

Between 1997 and 2012, a total of 1708 patients in Denmark were found to have incident esophageal eosinophilia. Of these, 844 (49%) met the primary case definition of EoE and 291 (17%) met the restrictive case definition. The mean age of EoE cases meeting the primary definition was 48 years; 11% of cases were below the age of 20, and 71% were male (Table 1). Esophageal symptoms and associated findings of dysphagia (20%), food impaction (22%), esophageal stricture (18%), and esophageal dilation (13%) were common in this group, with a total of 371 EoE cases (44%) having a diagnostic code for either dysphagia, esophageal foreign bodies, or strictures. Other clinical features of interest for the primary EoE group, as well as the other two case definitions, are presented in Table 1.

Clinical features were similar between children and adults (Table 2), though children were noted to have more heartburn (37% vs 19%; $p < 0.001$), nausea/vomiting (18% vs 2%; $p < 0.001$), and atopy (39% vs 10%; $p < 0.001$) than adults. Interestingly, children had a similar

rate of esophageal strictures as compared to adults (22% vs 18%; $p = 0.38$), but a higher rate of esophageal dilation (23% vs 12%; $p = 0.01$).

Incidence of EoE in Denmark

The incidences of EoE, esophageal eosinophilia, and the restricted case definition of EoE are presented in Figure 1. In 1997, there were only 7 cases of EoE that met the primary definition in Denmark, yielding an annual incidence rate of 0.13/100,000. In 2012, there were 145 new cases of EoE, for an annual incidence rate of 2.6/100,000. There were similar increases in esophageal eosinophilia (from 11 cases to 292 cases; 0.21/100,000 to 5.2/100,000) and in the restrictive definition of EoE (from 3 cases to 44 new cases; 0.06/100,000 to 0.79/100,000).

Prevalence of EoE in Denmark

The prevalences of EoE, esophageal eosinophilia, and the restricted case definition of EoE are presented in Figure 2. Over the study time frame, the prevalence of EoE steadily increased, with cumulative prevalence reaching 13.8/100,000 by the end of the study period. Increases were also seen for esophageal eosinophilia (end of study prevalence of 27.9/100,000) and the restrictive definition of EoE (end of study prevalence of 4.7/100,000).

Prevalence differed between men and women, and also by age (Figure 3). Across all groups, prevalence was higher in men than in women (24.6/100,000 vs 9.2/100,000). Prevalence in men rapidly increased with age, peaking in the 30–39 age group (31.3/100,000) and then remaining at that level. In contrast, prevalence in women slowly increased with age, reaching its peak above 80 years (21.5/100,000).

Impact of rates of esophageal biopsies

Over the time course of the study, the rate of esophageal biopsies increased (Figure 4). In 1997, 4805 esophageal biopsies were performed in Denmark, for a rate of 91.1/100,000. In 2012, 9781 biopsies were performed, for a rate of 175.3/100,000. This reflects a 1.9-fold rate increase. In contrast, the rate of esophageal eosinophilia cases increased 25.0-fold, EoE cases increased 19.5-fold, and the restrictive definition of EoE cases increased 13.9-fold.

Discussion

The incidence and prevalence of EoE have been rapidly rising over the past twenty years, but national population-based data on well characterized patients using validated case-finding algorithms have been lacking. It has also been debated whether this rise in incidence and prevalence simply reflects increasing awareness of EoE, leading to more esophageal biopsies and disease detection, rather than indicating a true increase in the disease. The current study aimed to address both questions by studying the incidence and prevalence of EoE in the national medical registries of Denmark, and examining practice patterns pertaining to esophageal biopsies.

Several of the results are striking. First, there has been a steady rise in the incidence of EoE. This has been accompanied by a concomitant rise in the disease prevalence. Second,

although the rates of esophageal biopsies in Denmark over the past 15 years increased by two-fold, the 25-fold increase in esophageal eosinophilia or the 20-fold increase in our primary case definition of EoE far outpaced the use of endoscopic biopsy.

Our calculated estimates of the incidence and prevalence of EoE (2.6/100,000 and 13.8/100,000) fall within the range of previously reported values, though they are at the lower end of the spectrum.^{15, 29} The highest incidence (10–13/100,000) and prevalence (73–90/100,000) estimates have come from single referral centers,^{8, 9, 19, 30} and a national study in the U.S. which used administrative claims data without a direct link to pathology findings.¹¹ The results of a recent study from the Netherlands using national registry-based data were on the same order of magnitude (incidence of 1.3/100,000; prevalence of 4.1/100,000),¹⁸ but these data are more directly applicable to the esophageal eosinophilia group used in our study as an EoE case finding algorithm was not used. A prior study restricted to the southern region of Denmark reported an incidence of 1.6/100,000 and a prevalence of 2.3/100,000,³¹ but its data were from 2005–2007 and were limited to a pediatric population, so also cannot be directly compared with the current study.

The continuing rise in the incidence and prevalence of EoE in Denmark is also consistent with findings from other centers that have studied this issue.^{5, 6, 8–10, 18, 32–34} However, our data indicate that the pace of increase is far greater than utilization of biopsy, arguing that increases in EoE incidence are not largely due to increased biopsy practices. A prior study in a region of Canada showed a 39% increase in EoE incidence rate, compared with a 26% increase in esophageal biopsies, concluding that a large proportion of the increasing EoE incidence was explained by increased disease detection. However, several studies from U.S. have reported incidence increases which are at least twofold higher than biopsy rate increases.^{9, 32} Our data showed, for the first time at a national level, that although biopsy rates are increasing, they do not account for the majority of the increase in the incidence and prevalence of EoE.

Nevertheless, it is important to note that awareness of EoE and the decision to obtain esophageal biopsies can impact how frequently EoE is detected. In studies from both the U.S. and the U.K., pathologists were more accurate in making the diagnosis of EoE with increasing awareness of the disease over time, and gastroenterologists were similarly more likely to obtain esophageal biopsies, leading to an increased diagnostic yield.^{35, 36} This has been observed in a recent Danish study as well.³⁷ In that study, a consensus meeting was held for endoscopy unit leaders and pathologists in the Northern region of Denmark to ensure that esophageal biopsies were obtained in patients with dysphagia, and that biopsies were being examined and coded for esophageal eosinophilia in a standard fashion. This approach drastically increased the numbers of biopsies and EoE cases detected in 2012 in this region.³⁷ Nevertheless, even with this experience in one region of the country, the incidence and prevalence of EoE still outpaced biopsy practices nationally.

It is important to acknowledge potential limitations of our study. The incidence and prevalence estimates rely on the case definitions used, the accuracy of the coding in the databases, and the performance of the case-finding algorithms. In our previously published validation work,²⁶ there was a tradeoff between high specificity and low sensitivity for the

restrictive definition of EoE, and lower specificity and higher sensitivity for the primary EoE definition. While high specificity is desirable in studies examining risk factors or disease etiologies where only true cases are desirable and not all cases need be detected, for studies investigating incidence and prevalence, there is a need to balance sensitivity and specificity, which our primary case definition has done. Accordingly, the characteristics of the EoE cases identified are consistent with those that have previously been reported in the literature,^{12–14, 38, 39} and there is the expected step down in number from those with esophageal eosinophilia from any cause to those with esophageal eosinophilia from EoE.^{4, 40} It is interesting to note, however, that children in this study had a higher rate of esophageal dilation than adults, a finding that is different from what is previously reported where adults are more frequently found to have strictures and require dilation.^{41–44} Despite the potential inaccuracies in diagnosis introduced by our case-finding algorithm, this approach is superior to previous work utilizing only pathology or administrative databases to infer epidemiological trends in EoE.^{11, 18}

There are also a number of strengths to this study. It provides the first population-based estimate of EoE incidence and prevalence using patient-level health registry data and a validated case finding algorithm within a system with free tax-supported health care. As such, we were able to study a large population over a long time frame. Moreover, because we were able to capture all esophageal biopsies in Denmark, we were able to determine, for the first time, that the incidence is truly increasing. The reasons behind this increase, however, remain to be fully elucidated.¹⁵

In conclusion, we have provided the first national population-based estimates of EoE using validated case finding algorithms, and found that the incidence and prevalence of EoE have rapidly increased over the past 15 years in Denmark. This increase far outpaces the increase in endoscopy with biopsies, indicating that the changes in the frequency of EoE are not due to changes in biopsy rates alone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci.* 1993; 38(1):109–116. [PubMed: 8420741]
2. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology.* 2007; 133(4):1342–1363. [PubMed: 17919504]

3. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: Updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011; 128:3–20. e6. [PubMed: 21477849]
4. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras C, Katzka DA. ACG Clinical Guideline: Evidence based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis. *Am J Gastroenterol*. 2013; 108:679–692. [PubMed: 23567357]
5. Hruz P, Straumann A, Bussmann C, et al. Escalating incidence of eosinophilic esophagitis: A 20-year prospective, population-based study in Olten County, Switzerland. *J Allergy Clin Immunol*. 2011; 128(6):1349–1350. e5. [PubMed: 22019091]
6. Arias A, Lucendo AJ. Prevalence of eosinophilic oesophagitis in adult patients in a central region of Spain. *Eur J Gastroenterol Hepatol*. 2013; 25(2):208–212. [PubMed: 23075697]
7. Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. *Arch Dis Child*. 2006; 91:1000–1004. [PubMed: 16877474]
8. Buckmeier BK, Rothenberg ME, Collins MH. The incidence and prevalence of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2008; 121(Suppl 2):S71. (AB 271).
9. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol*. 2009; 7(10):1055–1061. [PubMed: 19577011]
10. Syed AA, Andrews CN, Shaffer E, Urbanski SJ, Beck P, Storr M. The rising incidence of eosinophilic oesophagitis is associated with increasing biopsy rates: a population-based study. *Aliment Pharmacol Ther*. 2012; 36(10):950–958. [PubMed: 22994460]
11. Dellon ES, Jensen ET, Martin CF, Shaheen NJ, Kappelman MD. Prevalence of Eosinophilic Esophagitis in the United States. *Clin Gastroenterol Hepatol*. 2014; 12:589–596. e1. [PubMed: 24035773]
12. Veerappan GR, Perry JL, Duncan TJ, et al. Prevalence of Eosinophilic Esophagitis in an Adult Population Undergoing Upper Endoscopy: A Prospective Study. *Clin Gastroenterol Hepatol*. 2009; 7:420–426. [PubMed: 19162236]
13. Prasad GA, Talley NJ, Romero Y, et al. Prevalence and Predictive Factors of Eosinophilic Esophagitis in Patients Presenting With Dysphagia: A Prospective Study. *Am J Gastroenterol*. 2007; 102:2627–2632. [PubMed: 17764492]
14. Dellon ES, Speck O, Woodward K, et al. Clinical and Endoscopic Characteristics do Not Reliably Differentiate PPI-Responsive Esophageal Eosinophilia and Eosinophilic Esophagitis in Patients Undergoing Upper Endoscopy: A Prospective Cohort Study. *Am J Gastroenterol*. 2013; 108(12):1854–1860. [PubMed: 24145677]
15. Dellon ES. Epidemiology of eosinophilic esophagitis. *Gastroenterol Clin North Am*. 2014; 43:201–218. [PubMed: 24813510]
16. Sealock RJ, Kramer JR, Verstovsek G, et al. The prevalence of oesophageal eosinophilia and eosinophilic oesophagitis: a prospective study in unselected patients presenting to endoscopy. *Aliment Pharmacol Ther*. 2013; 37(8):825–832. [PubMed: 23441936]
17. Mackenzie SH, Go M, Chadwick B, et al. Clinical trial: eosinophilic esophagitis in patients presenting with dysphagia: a prospective analysis. *Aliment Pharmacol Ther*. 2008; 28:1140–1146. [PubMed: 18624788]
18. van Rhijn BD, Verheij J, Smout AJ, Bredenoord AJ. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol Motil*. 2013; 25(1):47–52. e5. [PubMed: 22963642]
19. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med*. 2004; 351(9):940–941. [PubMed: 15329438]
20. Dellon ES, Aderoju A, Woosley JT, Sandler RS, Shaheen NJ. Variability in diagnostic criteria for eosinophilic esophagitis: A systematic review. *Am J Gastroenterol*. 2007; 102:2300–2313. [PubMed: 17617209]
21. Katzka DA. Eosinophilic Esophagitis: From Rookie of the Year to Household Name. *Clin Gastroenterol Hepatol*. 2009; 7:370–371. [PubMed: 19049833]
22. Frank L. Epidemiology. When an entire country is a cohort. *Science*. 2000; 287(5462):2398–2399. [PubMed: 10766613]

23. Frank L. Epidemiology. The epidemiologist's dream: Denmark. *Science*. 2003; 301(5630):163. [PubMed: 12855788]
24. Sorensen, HT.; Christensen, T.; Schlosser, HK.; Pedersen, L. Use of Medical Databases in Clinical Epidemiology: Department of Clinical Epidemiology. Denmark: Aarhus University Hospital; 2008.
25. Erichsen R, Lash TL, Hamilton-Dutoit SJ, Bjerregaard B, Vyberg M, Pedersen L. Existing data sources for clinical epidemiology: The Danish National Pathology Registry and Data Bank. *Clin Epidemiol*. 2010; 2:51–56. [PubMed: 20865103]
26. Dellon ES, Erichsen R, Pedersen L, et al. Development and validation of a registry-based definition of eosinophilic esophagitis in Denmark. *World J Gastroenterol*. 2013; 19(4):503–510. [PubMed: 23382628]
27. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014; 29:541–549. [PubMed: 24965263]
28. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull*. 1999; 46(3):263–268. [PubMed: 10421985]
29. Sealock RJ, Rendon G, El-Serag HB. Systematic review: the epidemiology of eosinophilic oesophagitis in adults. *Aliment Pharmacol Ther*. 2010; 32(6):712–719. [PubMed: 20662785]
30. Gill R, Durst P, Rewalt M, Elitsur Y. Eosinophilic Esophagitis Disease in Children from West Virginia: A Review of the Last Decade (1995–2004). *Am J Gastroenterol*. 2007; 102:2281–2285. [PubMed: 17573789]
31. Dalby K, Nielsen RG, Kruse-Andersen S, et al. Eosinophilic Oesophagitis in Infants and Children in the Region of Southern Denmark: A Prospective Study of Prevalence and Clinical Presentation. *J Pediatr Gastroenterol Nutr*. 2010; 51:280–282. [PubMed: 20512060]
32. Dellon ES, Gibbs WB, Fritchie KJ, et al. Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2009; 7:1305–1313. [PubMed: 19733260]
33. DeBrosse CW, Collins MH, Buckmeier Butz BK, et al. Identification, epidemiology, and chronicity of pediatric esophageal eosinophilia, 1982–1999. *J Allergy Clin Immunol*. 2010; 126(1):112–119. [PubMed: 20620567]
34. Kidambi T, Toto E, Ho N, Taft T, Hirano I. Temporal trends in the relative prevalence of dysphagia etiologies from 1999–2009. *World J Gastroenterol*. 2012; 18(32):4335–4341. [PubMed: 22969196]
35. Patel N, Busler JF, Geisinger K, Hill I. Are Pathologists Accurately Diagnosing Eosinophilic Esophagitis in Children? A 9-Year Single Academic Institutional Experience With Interobserver Observations. *Int J Surg Pathol*. 2011; 19:260–266.
36. Kanakala V, Lamb CA, Haigh C, Stirling RW, Attwood SE. The diagnosis of primary eosinophilic oesophagitis in adults: missed or misinterpreted? *Eur J Gastroenterol Hepatol*. 2010; 22(7):848–855. [PubMed: 20453656]
37. Krarup AL, Vyberg M. Increased incidence of eosinophilic esophagitis in a Danish region after changed biopsy protocol for patients with dysphagia. *Gastroenterology*. 2014; 146(Suppl 1):S-671. (Mo1847).
38. Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology*. 2003; 125(6):1660–1669. [PubMed: 14724818]
39. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol*. 2005; 3(12):1198–1206. [PubMed: 16361045]
40. Molina-Infante J, Katzka DA, Gisbert JP. Review article: proton pump inhibitor therapy for suspected eosinophilic oesophagitis. *Aliment Pharmacol Ther*. 2013; 37(12):1157–1164. [PubMed: 23656497]
41. Moawad FJ, Cheatham JG, DeZee KJ. Meta-analysis: the safety and efficacy of dilation in eosinophilic oesophagitis. *Aliment Pharmacol Ther*. 2013; 38(7):713–720. [PubMed: 23915046]
42. Bohm ME, Richter JE. Review article: oesophageal dilation in adults with eosinophilic oesophagitis. *Aliment Pharmacol Ther*. 2011; 33(7):748–757. [PubMed: 21320137]

43. Kim HP, Vance RB, Shaheen NJ, Dellon ES. The Prevalence and Diagnostic Utility of Endoscopic Features of Eosinophilic Esophagitis: A Meta-Analysis. *Clin Gastroenterol Hepatol*. 2012; 10:988–996. e5. [PubMed: 22610003]
44. Peery AF, Shaheen NJ, Dellon ES. Practice patterns for the evaluation and treatment of eosinophilic oesophagitis. *Aliment Pharmacol Ther*. 2010; 32(11–12):1373–1382. [PubMed: 21050240]

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Figure 1.
Incidence of esophageal eosinophilia and EoE in Denmark, 1997–2012.

Figure 2.
Cumulative prevalence of esophageal eosinophilia and EoE in Denmark, 1997–2012.

Figure 3.
Prevalence of EoE in Denmark by age and gender.

Figure 4.
Comparison of esophageal eosinophilia and EoE incidence to esophageal biopsy rates in Denmark.

Table 1

Characteristics of subjects with esophageal eosinophilia and EoE

	Esophageal eosinophilia* (n = 1708)	EoE – primary definition [†] (n = 844)	EoE – restrictive definition [‡] (n = 291)
Age (mean ± SD; range)	50.6 ± 20.2	48.1 ± 20.5	52.3 ± 20.2
< 20 years of age (n, %)	159 (9)	92 (11)	27 (9)
Male (n, %)	1214 (71)	607 (71)	199 (68)
Symptoms and diagnoses (n, %)			
Dysphagia	181 (11)	167 (20)	41 (14)
Food/foreign body impaction	202 (12)	187 (22)	45 (16)
Esophageal stricture/obstruction	176 (10)	153 (18)	64 (22)
Any dysphagia/impaction/stricture	414 (24)	371 (44)	108 (37)
Esophageal diverticulum	2 (0.1)	2 (0.2)	0 (0)
Esophageal perforation	8 (0.5)	5 (0.6)	1 (0.3)
Chest pain	50 (3)	47 (6)	19 (7)
Heartburn	340 (20)	177 (21)	97 (33)
Abdominal pain	271 (16)	247 (30)	114 (39)
Nausea/vomiting	32 (2)	28 (3)	10 (3)
Feeding disorders	3 (0.2)	3 (0.4)	1 (0.3)
Atopic diseases (n, %)			
Any atopic condition	191 (11)	108 (13)	32 (11)
Rhinitis	47 (3)	39 (3)	6 (2)
Sinusitis	19 (1)	8 (1)	4 (1)
Asthma	142 (8)	82 (10)	25 (9)
Dermatitis	24 (1)	13 (2)	2 (1)
Food allergy	6 (0.4)	4 (0.5)	0 (0)
Other conditions and procedures			
HSV esophagitis	0 (0)	0 (0)	0 (0)
CMV esophagitis	0 (0)	0 (0)	0 (0)
Barrett's esophagus	51 (3)	18 (2)	12 (4)
Anti-reflux surgery	7 (0.4)	3 (0.4)	1 (0.3)
Esophageal dilation	134 (8)	111 (13)	48 (17)
Medications (n, %)			
H2 receptor blockers	305 (18)	145 (17)	86 (30)
Proton pump inhibitors	1112 (65)	529 (63)	291 (100)
Systemic steroids	429 (25)	225 (27)	79 (27)
Intestinal release steroids	14 (1)	2 (0.2)	2 (1)
Nasal steroids	461 (27)	239 (28)	88 (30)
Inhaled steroids	372 (22)	203 (24)	66 (23)
Leukotriene antagonists	43 (3)	18 (2)	13 (5)

* Defined by SNOMED codes for esophageal biopsy (T62xxx) and tissue eosinophilia (M47150)

[†] Defined by esophageal eosinophilia (as above), the presence of a qualifying symptom code, and the absence exclusion codes (see Supplemental Table 1)

[‡] Defined those who met the primary EoE definition (as above), but also had a prescription for either a proton pump inhibitor or a H2-receptor blocker medication in the two months prior to the endoscopy and biopsy (see Supplemental Table 1)

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Table 2

Features of adults and children with EoE*

	Children with EoE (n = 83)	Adults with EoE (n = 761)	p value
Age (mean $\pm$ SD; range)	10.3 $\pm$ 5.3	52.2 $\pm$ 17.0	--
Male (n, %)	62 (75)	545 (72)	0.55
Symptoms and diagnoses (n, %)			
Dysphagia	21 (25)	146 (19)	0.18
Food/foreign body impaction	19 (23)	168 (22)	0.87
Esophageal stricture/obstruction	18 (22)	135 (18)	0.38
Any dysphagia/impaction/stricture	38 (46)	333 (44)	0.72
Esophageal diverticulum	1 (1)	1 (0.1)	0.19
Esophageal perforation	0 (0)	5 (1)	1.0
Chest pain	0 (0)	47 (6)	0.01
Heartburn	31 (37)	146 (19)	< 0.001
Abdominal pain	28 (34)	219 (29)	0.35
Nausea/vomiting	15 (18)	13 (2)	< 0.001
Feeding disorders	3 (4)	0 (0)	< 0.001
Atopic diseases (n, %)			
Any atopic condition	32 (39)	76 (10)	< 0.001
Rhinitis	6 (7)	22 (3)	0.05
Sinusitis (J32.x)	0 (0)	8 (1)	1.0
Asthma	28 (34)	54 (7)	< 0.001
Dermatitis	4 (5)	9 (1)	0.03
Food allergy	1 (1)	3 (0.4)	0.34
Other conditions and procedures			
HSV esophagitis	0 (0)	0 (0)	-
CMV esophagitis	0 (0)	0 (0)	-
Barrett's esophagus	0 (0)	18 (2)	0.24
Anti-reflux surgery	1 (1)	2 (0.3)	0.27
Esophageal dilation	19 (23)	92 (12)	0.01
Medications (n, %)			
H2 receptor blockers	1 (1)	144 (19)	< 0.001
Proton pump inhibitors	45 (54)	484 (64)	0.10
Systemic steroids	5 (6)	220 (29)	< 0.001
Intestinal release steroids	0 (0)	2 (0.3)	1.0
Nasal steroids	15 (18)	224 (29)	0.03
Inhaled steroids	36 (43)	167 (22)	< 0.001
Leukotriene antagonists	3 (4)	15 (2)	0.41

* EoE is the primary case definition; children are age <18