Received: 12 February 2021 | Accepted: 20 April 2021

DOI: 10.1002/ueg2.12092

ORIGINAL ARTICLE

UNITED EUROPEAN GASTROENTEROLOGY ueg journal WILEY

A diagnostic delay of 10 years in the DanEoE cohort calls for focus on education - a population-based cross-sectional study of incidence, diagnostic process and complications of eosinophilic oesophagitis in the North Denmark Region

Dorte Melgaard[1,3] | **Signe Westmark**[1] | **Peter Thaysen Laurberg**[2] | **Anne Lund Krarup**[1,2,3,4]

[1]Centre for Clinical Research, North Denmark Regional Hospital, Hjørring, Denmark

[2]Department of Neurogastroenterological Research, North Denmark Regional Hospital, Hjørring, Denmark

[3]Institute of Clinical Medicine, Aalborg University, Aalborg, Denmark

[4]Department of Acute Medicine and Trauma Care, Aalborg University Hospital, Hobrovej, Aalborg, Denmark

Correspondence
Anne Lund Krarup, Department of Acute Medicine and Trauma Care, Aalborg University Hospital, Hobrovej 18-20, DK-9800 Aalborg, Denmark.
Email: apslk@rn.dk

Funding information
Marie Pedersen og Jensine Heibergs Foundation, Grant/Award Number: 00026

Abstract

Background: In the North Denmark Region with a population of 580,000 the awareness of eosinophilic oesophagitis (EoE) increased after 2011 due to a regional biopsy guideline. However, very little was known of the incidence, diagnostic process, or complications of EoE in Denmark.

Objective: The objectives of the study were to establish a cohort of EoE patients and describe the incidence, diagnostic process, and complications of EoE.

Methods: Patient files and histology reports for the 308 DanEoE cohort of patients with eosinophilia in the oesophagus in 2007–2017 identified by the histopathology registry were analyzed.

Results: The incidence of EoE in the North Denmark Region increased to 5.5–8.7/100,000 after 2011, where the regional biopsy guideline was implemented. The diagnostic delay was 10 (12) years for the EoE population. There was an insufficient number of biopsies sampled in 40 % of the patients. At the diagnostic endoscopy, the macroscopic appearance of the oesophagus was often described as normal (24%), and infrequently having one or more macroscopic signs of EoE (43%). Food bolus obstruction was observed in 38%, and strictures in 7.5% of EoE patients. In 22.2% of EoE patient's treatment was not initiated at debut.

Conclusions: The EoE incidence was documented. The diagnostic process was analyzed and showed an unmet need for education among referring physicians and endoscopists: A diagnostic delay of a decade, infrequently noted macroscopic EoE changes and lack of treatment at the debut in one fifth. Strictures in the DanEoE cohort were rare whereas food bolus obstruction was frequent.

KEYWORDS
cohortstudies, complications, diagnostic delay, eosinophilia, eosinophilic esophagitis, esophagus, gastroesophageal reflux, incidence, population, registry, retrospective studies, stricture

INTRODUCTION

Eosinophilic oesophagitis (EoE) is a clinico-pathological diagnose requiring symptoms of oesophageal dysfunction, often dysphagia in adults and eosinophilic.[1–4] The incidence is increasing across the western world and is now as frequent as Crohn's disease.[5,6] In countries that would be expected to be comparable, the incidence of EoE differs, and the diagnostic delay is long suggesting a lack of awareness amongst physicians.[6,7] A lack of knowledge has also been suggested by the fact that expert centers document macroscopic changes of EoE in patients far more often than low volume centers.[8] In the North Denmark Region (NDR) of 580,000 citizens the histopathology registry-based cohort DanEoE of patients with oesophageal eosinophilia documented a 50-fold increase when a standardized biopsy protocol was implemented in 2011.[9] The protocol dictated that at least eight biopsies should be sampled from all dysphagia patients with no exception.[9] Registry wise it was still not possible to divide the eosinophilia patients into EoE and other, as (1) the diagnose code for EoE was only recently instated, (2) the phenotype of a patient is still not included in the registries, and (3) overlap with gastro-oesophageal reflux disease (GORD) can be present. The solution was a detailed clinical description of a defined population-based cohort as the DanEoE cohort in order to calculate a more precise incidence of EoE in Denmark. The study aimed to establish the incidence of EoE in the NDR and to describe the diagnostic process in the secondary and tertiary setting from the first symptom to first treatment.

Key Summary

Summarize the established knowledge on this subject

- The incidence of EoE varies between otherwise comparable European countries partly due to the changing definition of EoE over time, last updated in 2018.
- Since 2018 it has been a clinical decision based on phenotyping to differentiate between EoE and GORD since they overlap with regards to symptoms and histology.
- In 2011 in the North Denmark Region the incidence of oesophageal eosinophilia increased 50-fold due to systematically biopsying all with dysphagia. On an organizational level, this was easy and at almost no costs.

What are the significant and/or new findings of this study?

- The population-based incidence of adults EoE in the North Denmark Region was 5.5–8.7/100.000 in 2012–2017 diagnosed according to the 2018 consensus.
- Despite the 50-fold increase in cases, the current study showed that the regions referring physicians and endoscopists lacked knowledge of EoE as patients had a mean diagnostic delay of 10 years, a total of one fifth of the patients were not treatment initially, and macroscopic signs of EoE were reported in less than half of inflamed patients.
- Despite this lack of EoE knowledge, strictures were rare with 7.5 % of patients needing dilation, whereas food bolus obstruction had occurred in 38%.

METHODS

The study database was approved by the Danish Data Protection Agency via the Department of Clinical Medicine, Aalborg University, with ID number 2018-59. The Regional Ethics Committee evaluated the project as not needing ethical approval within Danish law.

The North Denmark region

The NDR is a geographically well-defined area comprising approximately 10% of the Danish population (red area in Figure S1). It was administratively designed in 2008 to service all citizens in the area with medical treatment and comprise both rural areas and a university city. The composition of citizens matches that of the rest of the four regions in Denmark.

Definition of the study population in DanEoE the retrospective database of oesophageal eosinophilia

The study was a retrospective, cohort study using the population-based DanEoE cohort in the NDR including all patients with oesophageal eosinophilia. DanEoE is a histopathology registry based cohort as previously described in detail.[9] It's based on the national "SNOMED" codes for topography and morphology of tissue.[10] All patients living in the NDR and for the first time having at least one biopsy coded with both the SNOMED code for esophagus mucosa (T62010) and inflammation with eosinophilia defined as 15+

eosinophils (eos) in one high power field (hpf) (M47150) in 2007–2017 were included.[9] The index endoscopy was defined as the first endoscopy where the biopsy was sampled. In Denmark, every individual in the country is assigned a unique social security number and this is linked to the national population-based medical registries, including medical records, diagnostic codes, microbiology, biochemistry, and pathology findings.[11,12] For the current study, all patient files, endoscopy reports, radiology reports, histology reports, biochemistry results, and referral documents until the 31st of December 2008 were reviewed in detail by a gastroenterologist (ALK) and a gastroenterologist in training (PTL).

Patient groups

The patients with oesophageal eosinophilia were divided into four groups: EoE patients, GORD patients, other explanations for eosinophilia, and a rest group. All patients were manually checked twice by a gastroenterologist (ALK) for correct placement in groups as described below.

EoE group

The EoE group was defined as patients fulfilling the international diagnostic criteria for EoE: Symptoms of oesophageal dysfunction for example dysphagia without stenosis or stenosis not described as peptic and eosinophilic inflammation.[2] The diagnose was supported by concomitant atopic conditions, and endoscopic findings typical of EoE for example rings, furrows, exudates, edema, strictures, narrowings, and crepe-paper. Eosinophilic inflammation was defined as ≥15 eos/hpf (~60 eos/mm2) in at least one oesophageal biopsy, eosinophilic infiltration should be isolated to the oesophagus. If patients had eosinophilia outside the oesophagus, they were excluded from the EoE group. In general, patients were only biopsied outside oesophagus if presenting symptoms of stomach or bowel disease. The EoE group was sub grouped according to whether they had comorbid GORD (EoE + GORD) or not (Pure EoE).

EoE + GORD was defined as EoE patients with a clear EoE phenotype and comorbid objective findings of GORD: Oesophagitis, abnormal pH testing, or Barrett's oesophagus.

Pure EoE was defined as patients having EoE and no signs of GORD symptomatically or objectively.

GORD group

GORD was defined according to the Montreal consensus.[13] Patients were allocated to the GORD group if they presented with only heartburn and/or regurgitation. Dysphagia was accepted in case of severe oeosophagitis if disappearing when oesophagitis was healed, or in case of a Schatzky ring described as "peptic", if the patient did not display any other phenotypical signs of EoE. If any signs of comorbid EoE were present, they were placed in the EoE subgroup EoE + GORD.

Barrett's esophagus was defined as intestinal metaplasia in salmon colored oesophageal mucosa.[14] Oesophagitis was defined according to the LA classification and grouped into mild (LA-grade A + B) or moderate to severe (LA grade C + D), where the LA classification was not used the endoscopist's description was used to grade the severity when possible.[15]

Other explanation for the eosinophilia group

The "Other" group consisted of patients where neither EoE or GORD explained their eosinophilia for example cancer, Crohn's disease, hypereosinophilic disorder, or Achalasia.

Rest group

The Rest group was defined as patients so poorly described, that it was impossible to categorize the reason for the eosinophilia.

Complications were defined as strictures in need of dilation and food bolus obstructions requiring hospitalization.

STATISTICS

Descriptive statistics were given as median and range (25-75 percentile [IQR]) for continuous variables or mean (standard deviation (SD)) as appropriate. For categorical variables, counts and percentages were displayed. Comparing of the three groups of 1) pure EoE, 2) EoE + GORD, with the 3) GORD group, was done by one or two-way ANOVAs, and results given as mean and 95% confidence interval (95% CI)). The data management and statistics were done using SAS enterprise guide 71 (SAS Institute Inc., Cary, NC., USA), and figures using Sigmaplot 11.0 Build 11.1.0.102 (Systat Software Inc., CA, USA).

RESULTS

Patient groups and descriptive data

For simplicity Table 1 shows descriptive data of the EoE patients, whereas Table S1 shows data on EoE patients in comparison to GORD with oesophageal eosinophilia. Of the 309 adults in the DanEoE, one child was falsely registered as an adult and was removed leaving 308 patients with oesophageal eosinophilia. Of the remaining 308 adults with oesophageal eosinophilia, 76% fulfilled the EoE criteria, 18% had GORD and eosinophilia, 3% were in the "Other group", and 3% were so poorly described that they could not be categorized and constituted the "Rest group". In the "Other group" the nine patients identified

TABLE 1 Descriptive data of all adults with eosinophilic oesophagitis 2007 and 2017 in the North Danish Region with 580,000 inhabitants

	All EoE patients (subgroups in grey)		
		Pure EoE	EoE + GORD
Proportion of patients: %, number			
% of all 308 patients with oesophageal eosinophilia (*n*)	76, *n* 236	55, *n* 170	21, *n* 66
% of all EoE patients (236)	100, *n* 236	72, *n* 170	28, *n* 66
% of diseased of all 308	0, *n* 0	0, *n* 0	0, *n* 0
<2011: % of all 9 with eosinophilia	67, *n* 6	56, *n* 5	11, *n* 1
2012–14: % of all 142 with eosinophilia	75, *n* 106	55, *n* 78	20, *n* 28
2015–17: % of all 152 with eosinophilia	81, *n* 122	57, *n* 86	24, *n* 36
Ratio w:m	1:3.1	1:2.9	1:3.7
Age at diagnose: Mean (SD) years, number			
All	47 (15), *n* 236	45 (15), *n* 170	50 (14), *n* 66
Men	48 (15), *n* 178	46 (15), *n* 126	50 (14), *n* 52
Women	44 (14), *n* 60	42 (14), *n* 44	49 (15), *n* 14
Age at symptom debut: Mean (SD) years, number			
All	37 (16), *n* 184	36 (17), *n* 130	41 (16), *n* 54
Men	38 (16), *n* 139	38 (17), *n* 96	40 (16), *n* 43
Women	35 (17), *n* 45	31 (16), *n* 34	45 (15), *n* 11
Diagnostic delay: Mean (SD) years, number			
All	10 (12), *n* 184	9.6 (11), *n* 130	11 (15), *n* 54
Men	10 (13), *n* 139	9.6 (11), *n* 96	11 (16), *n* 43
Women	9.3 (9.2), *n* 45	9.9 (9.8), *n* 34	7.4 (6.7), *n* 11
Endoscopies before the index endoscopy: % Of patient group, number			
Information of previous endoscopies	43, *n* 102	38, *n* 64	58, *n* 38
No previous endoscopies	22, *n* 22	25, *n* 16	16, *n* 6
One or more previous endoscopies	78, *n* 80	75, *n* 48	9.4, *n* 6
Of these: >4 endoscopies, n	8.8, *n* 9	4.7, *n* 3	16, *n* 6
Mean (SD) number of previous endoscopies	2.0 (1.4)	1.7 (1.1)	2.4 (1.6)
Phenotype: % Of patient group, number/number of patients where data is available			
Dysphagia not explained by stenosis, or severe oesophagitis	84, *n* 197/235	86, *n* 146/170	78, *n* 51/65
Any type/allergic disease	41, *n* 97/236	44, *n* 74/170	35, *n* 23/66
Asthma	28, *n* 57/201	30, *n* 43/143	24, *n* 14/58
Allergy, rhinitis, food	36, *n* 87/236	39, *n* 66/170	29, *n* 19/66
Food impaction before diagnosis	22, *n* 51/236	24, *n* 40/170	17, *n* 11/66
Barrett's oesophagitis current or previously	3.4, *n* 8/236	0.0, *n* 0/170	12, *n* 8/66
Oesophagitis at debut or previously	14, *n* 32/236	0.0, *n* 0/170	49, *n* 32/66
Any severity			
Mild (LA A or B)	13, *n* 31/236	0.0, *n* 0/170	47, *n* 31/66
Severe (LA C or D)	0.4, *n* 1/54	0.0, *n* 0/170	1.5, *n* 1/66

Abbreviations: EoE, eosinophilic oesophagitis; GORD, gastro-oesophageal reflux disease; LA, Los Angeles classification; *n*, Number.

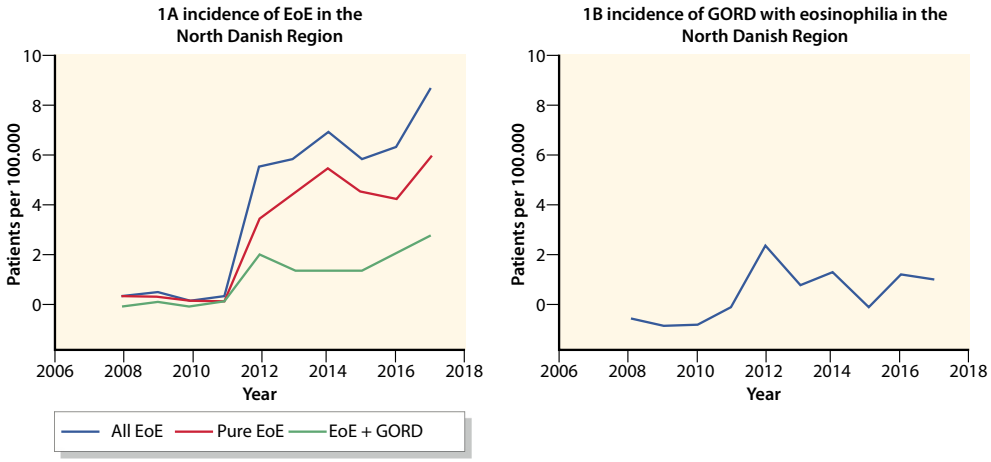

FIGURE 1 Incidence/eosinophilic oesophagitis (EoE) and gastro-oesophageal reflux disease (GORD) with eosinophilia in the North Denmark Region. Figure 1a shows incidence for EoE patients in total and sub divided into ± comorbid GORD (pure EoE and EoE + GORD resp.). Figure 1b shows the incidence for GORD patients with oesophageal eosinophilia who did not have the EoE phenotype

were: Three patients with oesophageal carcinoma, one with Crohn's disease where dysphagia disappeared when his dental status was improved, one with hypereosinophilic syndrome, one without oesophageal dysfunction, and three with achalasia.

EoE subgroups: Of the 236 EoE patients 76% had pure EoE without comorbid GORD, and 24% had comorbid GORD. The pure EoE group were 4.9 (CI: −9.8—0.0) years younger than the EoE + GORD who were 6.5 (95% CI: −13—0.3) years younger than the GORD group ($F = 14$, $p < 0.0001$, Table 1 and Table S1). Comorbid Barrett's oesophagus was rare in the EoE + GORD group, but 49% had had mild oesophagitis at some point before, during, or after the index endoscopy. These patients did however also have a very clear EoE phenotype.

The incidence of EoE in the North Denmark region was 5.5–8.7/100,000

The incidence of EoE patients per 100,000 as well as for the EoE subgroups are shown in Figure 1a and the Figure 1b shows the incidence of GORD patients with oesophageal eosinophilia. In winter 2011 a regional consensus was made to increase detection of EoE patients as previously been described in detail.[9] The true incidence of EoE is, therefore, better reflected in the data from 2012. As the regions in Denmark were formed in 2008, it was not possible to calculate the incidence from 2007.

There is still a lack of knowledge of EoE among endoscopists and referring physicians

Despite the previous easily implemented change in biopsy practice, the data from the current study indicated insufficient knowledge of EoE in the endoscopist group and referring physicians in the region. First, the diagnostic delay from symptom debut to histology-based diagnosis in EoE patients was 10 (12) years and did not change over time (Figure 2a, Figure S2a). Secondly, only 56%-61% of EoE subgroups had been biopsied according to the guideline (Figure 2b) and this trended towards decreasing over time (Figure S2b). Thirdly, less than half of EoE patients were described as having at least one macroscopic sign of EoE at diagnosis (Figure 2c, Table 2). This did not improve over time (Figure S2c). Furthermore, none of the descriptions at any time used the eosinophilic oesophagitis reference (EREFS) score.[8] Last, one fifth of the EoE patients ended up without treatment at the debut. Usually this was because the endoscopist neither offered the patient treatment nor referral to a gastroenterologist (Figure 2d) (Table 3).

EoE induced food bolus obstruction was common in the cohort, but strictures were not

Food bolus obstruction was the most common complication of EoE and occurred in approximately one third of EoE patients (Figure 3a). The number of food bolus obstructions before or during the index endoscopy did not decrease over time (Figure S3). Strictures in need of dilation were only seen in 1.7% of EoE patients before the diagnosis (Figure 3). Only one case of narrow oesophagus was observed in a non-compliant pure EoE patient who was also a heavy drinker. Perforation was observed in one patient, who was in the "Other group". No EoE patient was found to have experienced Boerhaave's syndrome, or perforations during dilations. Small ulcers after prolonged food bolus obstruction were rarely observed and healed in all patients before the next endoscopy.

The subgroups of EoE compared to the GORD patients with oesophageal eosinophilia

The two subgroups of EoE were very similar with regards to indication for endoscopy, allergies, asthma, food impactions before

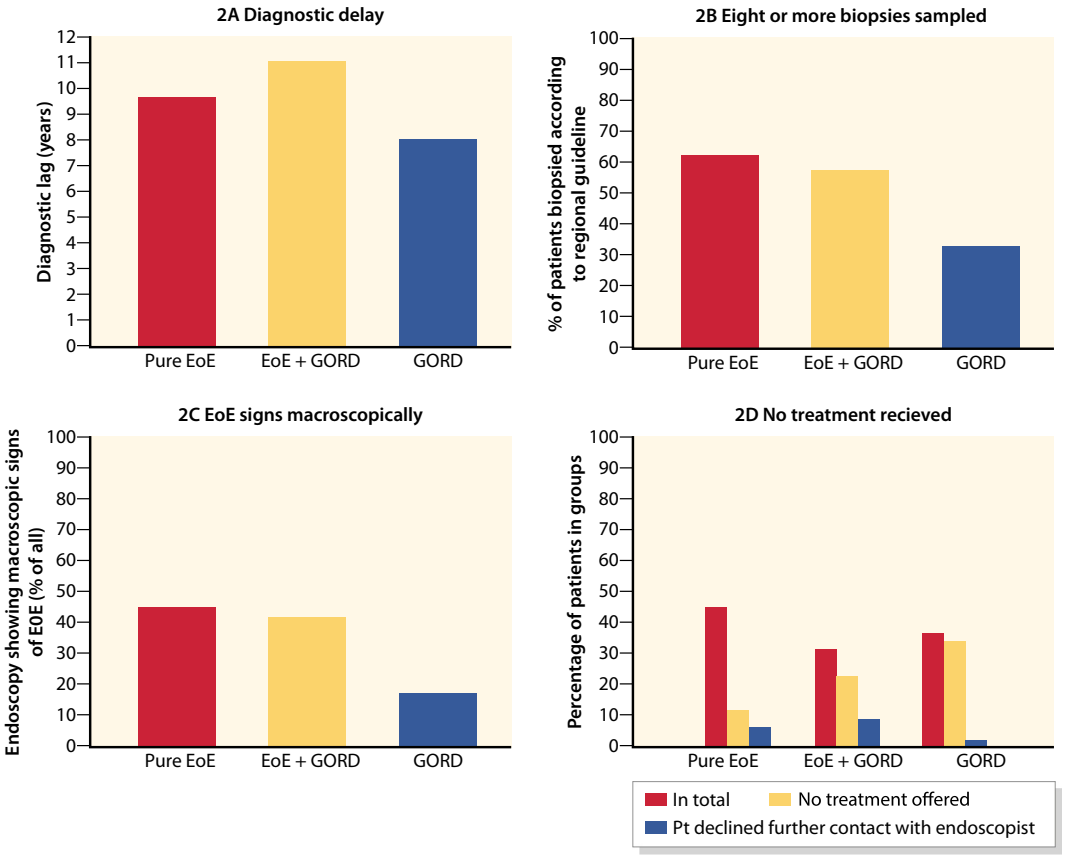

FIGURE 2 Data suggesting a lack/knowledge/EoE among endoscopists and referring doctors with regards to EoE. The diagnostic lag is shown in Figure 2a for subgroups/EoE and GORD patients with eosinophilia. Figure 2b shows adherence to the regional biopsy guideline/sampling eight or more biopsies in all patients with dysphagia. Figure 2c shows the percentage/patients having a macroscopic esophagus description showing any EoE sign (white dots, furrows, edema, rings or, strictures) at the index endoscopy. Figure 2d shows how many patients did not receive treatment

the index endoscopy, and macroscopic signs of EoE at the debut endoscopy (Table 1). Compared to the GORD group the pure EoE group had a higher percentage of allergies or asthma in the patient history, and an EoE related indication for endoscopy ($p < 0.001$, $p < 0.001$, Tables 1 and 2). The macroscopic changes also differed between these groups with the pure EoE usually having an index endoscopy description of either normal, a food bolus present, or with any signs of EoE (*p*-values all below <0.01). EoE + GORD patients compared to the GORD group more often had an EoE related indication and any macroscopic sign of EoE, and less often severe oesophagitis (*p-values all below* 0.001, Tables 1 and 2).

DISCUSSION

In this register based retrospective study, the incidence of EoE in the North Denmark Region. Patients were described with regards to the diagnostic process and complications. Despite the increase in incidence due to changed biopsy practice in 2011, we found the diagnostic delay to be 10 years and stable over time, the biopsy rate low despite guidelines, the macroscopic EoE findings rarely found, and treatment not started in one fourth of patients.

The method enabled a population-based cohort of EoE patients

The registry-based approach using the national unique identification number assigned to all Danish citizens was a strength.[11,12] As the quality of the Danish Pathology Registry is high we were certain to find all cases of oesophageal eosinophilia resulting in an expected good external validity.[9] Another strength was the phenotyping of 97% of cases using the unique citizen identification number and the Danish health registries.

The patient-groups

The diagnose of EoE has been developing since the first consensus in 2007.[1,3,4] One of the problems addressed in these consensus updates has been the overlap of GORD.[2,12] The problem of determining the phenotype of a patient in this regard is highlighted by the fact that GORD can mimic EoE and EoE can mimic GORD with regards to symptoms, histology, and complication.[1,13,16] Furthermore, that the diagnose of GORD is complicated by lack of gold standard and low sensitivity and specificity for most diagnostic tests.[1,13] Another reason may be that many GORD

TABLE 2 Descriptive data from the index endoscopy for adults with eosinophilic oesophagitis diagnosed in the North Danish Region in 2007 and 2017

	All EoE patients (subgroups in grey)		
		Pure EoE	EoE + GORD
On PPI at the index endoscopy, in proportion/patient group, number	7.2, *n* 17/236	5.3, *n* 9/170	12, *n* 8/66
Indication for index endoscopy: % of patient group, number			
EoE symptoms, any	94, *n* 222	97, *n* 165	86, *n* 57
"EoE obs pro" in the file	65, *n* 153	69, *n* 117	55, *n* 36
Dysphagia	63, *n* 148	64, *n* 108	61, *n* 40
Food impaction	22, *n* 52	24, *n* 41	17, *n* 11
GORD	13, *n* 30/236	7.1, *n* 12/170	27, *n* 18/66
Barrett control program	1.3, *n* 3	0.0, *n* 0	4.6, *n* 3
Other indications	2.5, *n* 6	2.4, *n* 4	3.0, *n* 2
Sedation at the index endoscopy: % of patient group, number			
No sedation or local anaesthetics	46, *n* 107	42, *n* 69	59, *n* 38
Local anaesthetics	7.3, *n* 17	7.8, *n* 13	6.2, *n* 4
IV Sedation	8.7, *n* 20	8.4, *n* 14	9.2, *n* 6
General anaesthesia	20, *n* 45	20, *n* 33	19, *n* 12
Missing	*n* 5	*n* 4	*n* 1
Macroscopic changes at the index endoscopy: % of patient group, number			
Macroscopic normal	24, *n* 74	36, *n* 61	18, *n* 13
Any endoscopic EoE sign (oedema, rings, exudates, furrows, strictures)	43, *n* 102	44, *n* 74	42, *n* 28
Rings	23, *n* 54	22, *n* 37	25, *n* 17
Strictures			
All	11, *n* 27	12, *n* 21	9.0, *n* 6
Not passable	1.7, *n* 4	1.8, *n* 3	1.5, *n* 1
Narrow oesophagus	0.59, *n* 1	0.42, *n* 1	0.0, *n* 0
Furrows	11, *n* 27	12, *n* 21	9.1, *n* 6
Oedema	5.1, *n* 12	6.5, *n* 11	1.5, *n* 1
White dots	4.2, *n* 10	2.9, *n* 5	7.6, *n* 5
Laceration	1.3, *n* 3	1.8, *n* 3	0, *n* 0 *n* 0
Food bolus present	13, *n* 31	14, *n* 24	11, *n* 7
Barrett's oesophagus	2.5, *n* 6	0.0, *n* 0	9.1, *n* 6
Oesophagitis, all	14, *n* 32	0.0, *n* 0	49, *n* 32
LA A-B/mild	13, *n* 31	0.0, *n* 0	47, *n* 31
LA C-D/severe	0.4, *n* 1	0.0, *n* 0	1.5, *n* 1
Not characterized	0.0, *n* 0	0.0, *n* 0	0.0, *n* 0
Oesophageal ulcer	2.5, *n* 6	3.5, *n* 6	0.0, *n* 0
Hiatal hernia	24, *n* 57	23, *n* 39	27, *n* 18
Biopsy sampling at the index endoscopy			
Number/biopsies if dysphagia			
All, median (IQR), *n*	8.0 (6.0; 9.0), *n* 222	8.0 (6.0; 9.0), *n* 165	8.0 (6.0; 9.0), *n* 57

TABLE 2 (Continued)

	All EoE patients (subgroups in grey)		
		Pure EoE	EoE + GORD
4 cm, median (IQR), *n*	4.0 (3.0; 5.0), *n* 219	4.0 (3.0; 5.0), *n* 162	4.0 (3.0; 5.0), *n* 57
14 cm, median (IQR), *n*	4.0 (3.0; 4.0), *n* 216	4.0 (3.0; 4.0), *n* 161	4.0 (2.0; 4.0), *n* 55
Dysphagia patients biopsied according to guidelines: %, number/patients where data is available			
DK guidelines (min 8 biopsies)	60, *n* 133/222	61, *n* 101/165	56, *n* 32/57
EUREOS guidelines (min 6 biopsies)	76, *n* 168/222	76, *n* 125/165	75, *n* 43/57
Max. eosinophil count, median (IQR)	32 (25; 50), *n* 234	38 (25; 60), *n* 169	28 (20; 50), *n* 65

Abbreviations: EoE, eosinophilic oesophagitis; GORD, gastro-oesophageal reflux disease; Max, Maximum; *n*, Number; PPI, proton pump inhibitor.

TABLE 3 Complications of EoE and treatment initiation in the North Danish Region (2007–2017)

	All EoE patients (Subgroups in grey)		
		Pure EoE	EoE + GORD
Food bolus obstruction (FBO): % of patient group, number			
Never FBO before, during or after the debut endoscopy	62, *n* 146	63, *n* 106	61, *n* 40
FBO At any time before or after the index endoscopy	38, *n* 90	27, *n* 64	39, *n* 26
FBO before the index endoscopy			
Once	17, *n* 40	17, *n* 28	18, *n* 12
Twice	4.6, *n* 11	4.1, *n* 7	6.1, *n* 4
3 times	2.5, *n* 6	2.4, *n* 4	3.0, *n* 2
FBO at the index endoscopy	13, *n* 31	14, *n* 24	11, *n* 7
FBO after the index endoscopy			
Once	7.2, *n* 17	7.1, *n* 12	7.6, *n* 5
Twice	0.7, *n* 1	0.6, *n* 1	0.0, *n* 0
3 times	0.4, *n* 1	0.6, *n* 1	0.0, *n* 0
Strictures dilated and perforations: % Of patient group, number			
Strictures dilated in total	7.5, *n* 18	7.1, *n* 12	9.1, *n* 6
Before the index endoscopy	2.5, *n* 6	1.8, *n* 3	4.6, *n* 3
At the index endoscopy	2.5, *n* 6	2.9, *n* 5	1.5, *n* 1
After the index endoscopy	2.5, *n* 6	2.4, *n* 4	3.0, *n* 2
Perforation/oesophagus, ever	0.0, *n* 0	0.0, *n* 0	0.0, *n* 0
Treatment/EoE patients: % of patient group, number			
Treatment offered at the debut	83, *n* 195	84, *n* 143	79, *n* 52
No treatment offered	15, *n* 35	12, *n* 20	23, *n* 15
Treatment or further investigation declined	7.2, *n* 17	6.4, *n* 11	9.1, *n* 6

Abbreviations: EoE, eosinophilic oesophagitis; FBO, food bolus obstruction; GORD, gastro-oesophageal reflux disease; *n*, Number.

patients are asymptomatic and many healthy volunteers are described with mild oesophagitis when endoscoped purely for research purposes.[17,18] The last international consensus decided at the AGREE conference in 2017 stressed that separating EoE from GORD is a clinical decision.[2] This was possible in the current study due to detailed medical history and objective findings which was a major strength. However, we are still in need of a clearer separation of EoE and GORD with eosinophilia than what was possible to find consensus for in the AGREE paper from 2018. The findings of HH hernia in the database must be seen in the light that most of them are described in retroflection as an insufficient cardia and not measured the length and therefore less valid.

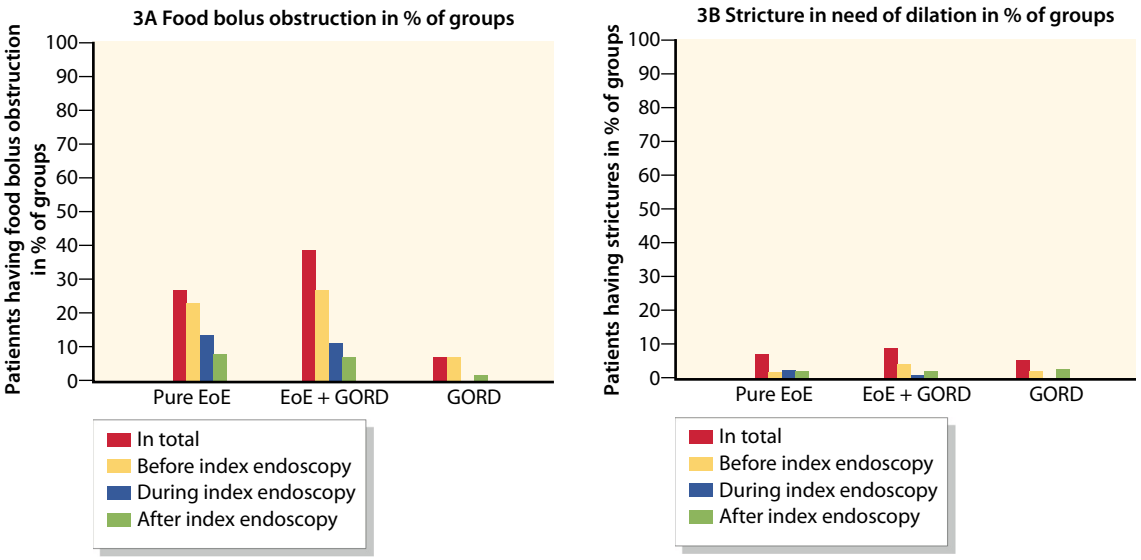

FIGURE 3 Percentage/patients having complications with oesophageal eosinophilia. Figure 3a Food bolus obstruction, and Figure 3b strictures in need/dilation

Incidence

This is to our knowledge the first population-based incidence estimates from Scandinavia where patients have been individually assessed based on all clinical material according to the EoE definition of the AGREE consensus. Since the AGREE consensus, an estimate of the EoE incidence requires the time-consuming clinical phenotype as in the current study. If trying to study EoE based on a purely registry-based EoE definition the estimate will be higher or lower depending on if the definition accepts or omits GORD. When the ICD10 code for EoE has been implemented clinically this will make registry-based EoE definitions easier. The incidence of 6-8/100,000 measured in the current study is significantly higher than the 2.6/100,000 from a previous study in Denmark. It could reflect a true increasing incidence in Denmark or the use of different EoE definitions and study methodology.[19] The incidence in the present study is also higher compared to the Netherlands (registry based estimate), but comparable to Switzerland in 2007–2009 and central Spain.[20–23]

Diagnostic delay

The diagnostic lag of a decade was high and unchanging over time in this study and possibly reflects a lack of awareness from both general practitioners and endoscopists. This was despite the previous easily implemented change of biopsy practice resulting in the 50-fold incidence increase in oesophageal eosinophilia. EoE patients were often endoscoped several times before being biopsied for the first time it is therefore highly likely that the true incidence is higher and that there are EoE patients endoscoped before 2011 that as still not diagnosed. We have previously shown that although it is possible to change the biopsy practice in our region, the peripheral hospitals within the region without endoscopists in training were less likely to adapt to new guidelines.[9] In comparison with Olten county in Switzerland, our diagnostic delay was high and probably reflected that EoE was almost non-existing in the NDR until the regional biopsy guidelines for endoscopists were published in 2012. There is no requirement of systematic training after specialization has been completed in Denmark and it can be difficult to reach out too all endoscopists for educational purposes. Furthermore, the first EoE review in Danish was not published until 2014 reaching out to general practitioners as readers for the first time.[24] It is a bit discouraging that the regional biopsy guidelines are only complied to in 60% of cases, but probably not surprising as this has been documented previously in other countries.[25] As a result, the percentage of EoE patients with normal mucosa has probably been overestimated and with likely decrease with the training of the endoscopists. The diagnostic delay was not a result of delayed coding in the Institutes of Pathology as this was done as part of the process of describing the biopsies.

Complications apart from food bolus obstruction were very rare

The percent of patients having had a food bolus obstruction at any time point was high with 27%–39% of EoE patient groups. This was in line with previous studies from Switzerland where 35% had impaction during an 18 years time period.[26] On the other hand, the risk of having a stricture requiring a dilation was, very low despite the diagnostic delay of 10 years (2% before the index endoscopy, 7.5% in total). In comparison to the Swiss cohort, this was low as they reported a stricture risk of 17% in patients with diagnostic delays of 0%–2%, 31% if the delay were 2–5 years, and 38% if the delay were 8–11 years.[7] If this means, that the natural history of EoE is milder in Denmark remains to be seen. It could, however, also reflect that the population-based design in the current study

includes the mild EoE patients that might not be referred to EoE centres. As of now fibrotic disease does not seem to develop as fast in our region as suggested by a previous American analysis and it will be very interesting to see what happens in the future[27]; Does EoE have a milder development in Denmark? Or has it just started later leaving us with a tidal wave of strictures in the years to come?

Initiating treatment

Patients with EoE in the NDR were not offered treatment in 15% of cases despite the guideline. The study did not ask the endoscopists why the lack of comments on eosinophilia suggests a lack of knowledge. Most likely the way forward is a direct education, as the published guideline or the later Danish EoE review did not relieve the problem.[24] In the NDR we will try to improve the treatment rate by direct education in the units.

CONCLUSION

The DanEoE cohort in the North Denmark Region showed an incidence of EoE in adults of 6–8/100,000 which is comparable to results from Switzerland and Spain. The study showed a lack of EoE knowledge within treating endoscopists even though they had increased biopsy sampling and consequently the incidence of EoE dramatically. Despite this, complication rates were low.

ACKNOWLEDGMENTS

The authors thank Natalia Pedersen for her substantial help with language revision. The study was supported in part by an unrestricted grant by Marie Pedersen og Jensine Heibergs Foundation (grant number: 00026).

CONFLICT OF INTEREST

The authors declares that there are no conflicts of interest.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. The Regional Ethics Committee evaluated the project as not needing ethical approval within Danish law.

AUTHOR CONTRIBUTIONS

Guarantor of article: Anne Lund Krarup. Specific author contributions: Anne Lund Krarup and Peter Thaysen Laurberg *performed the research*. Anne Lund Krarup and Peter Thaysen Laurberg *collected the data*. Anne Lund Krarup, Peter Thaysen Laurberg, Signe Westmark, and Dorte Melgaard *analyzed the data*. Anne Lund Krarup *designed the research study*. Anne Lund Krarup, Peter Thaysen Laurberg, Signe Westmark, and Dorte Melgaard *wrote the paper*. All authors approved the final version of the article, including the authorship list.

DATA AVAILABILITY STATEMENT

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

Dorte Melgaard https://orcid.org/0000-0002-5656-402X
Signe Westmark https://orcid.org/0000-0001-8456-8063
Anne Lund Krarup https://orcid.org/0000-0002-2228-7132

REFERENCES

1. Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology 2018;155:1022–1033.
2. Lucendo AJ, Molina-Infante J, Arias Á, von Arnim U, Bredenoord AJ, Bussman C, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J. 2017;5:335–358.
3. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology 2007;133:1342–1363.
4. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128:2–3.
5. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol. 2015;50:942–951.
6. Arias Á, Pérez-Martínez I, Tenías JM, Lucendo AJ. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther. 2016;43:3–15.
7. Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon H-U, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology 2013;145:1230–1236.
8. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013;62:489–495.
9. Krarup AL, Drewes AM, Ejstrud P, Laurberg PT, Vyberg M. Implementation of a biopsy protocol to improve detection of esophageal eosinophilia: a Danish registry-based study. Endoscopy 2020;53:15–24. https://doi.org/10.1055/a-1206-0852
10. 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.
11. Frank L. Epidemiology. When an entire country is a cohort. Science 2000;287:2398–2399.
12. Frank L. Epidemiology. The epidemiologist's dream: Denmark. Science 2003;301:163.
13. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900–1920.
14. Shaheen NJ, Richter JE. Barrett's oesophagus. Lancet 2009;373:850–861.
15. Armstrong D, Bennett JR, Blum AL, Dent J, De Dombal FT, Galmiche JP, et al. The endoscopic assessment of esophagitis: a progress report on observer agreement. Gastroenterology 1996;111:85–92.

16. Collins MH. Histopathologic features of eosinophilic esophagitis and eosinophilic gastrointestinal diseases. Gastroenterol Clin North Am. 2014;43:257–268.
17. Krarup AL, Gunnarsson J, Brun J, Poulakis A, Edebo A, Ringström G, et al. Exploration of the effects of gender and mild esophagitis on esophageal pain thresholds in the normal and sensitized state of asymptomatic young volunteers. Neurogastroenterol Motil. 2013; 25:766-e580.
18. Ronkainen J, Aro P, Storskrubb T, Johansson S-E, Lind T, Bolling-Sternevald E, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: A Kalixanda study report. Scand J Gastroenterol. 2005;40:275–285.
19. Dellon ES, Erichsen R, Pedersen L, Shaheen NJ, Baron JA, Sørensen HT, et al. Development and validation of a registry-based definition of eosinophilic esophagitis in Denmark. World J Gastroenterol. 2013;19:503–510.
20. Warners MJ, de Rooij W,van Rhijn BD, Verheij J, Bruggink AH, Smout AJPM, et al. Incidence of eosinophilic esophagitis in the Netherlands continues to rise: 20-year results from a nationwide pathology database. Neurogastroenterol Motil. 2018;30:e13165. https://doi.org/10.1111/nmo.13165
21. Hruz P, Straumann A, Bussmann C, Heer P, Simon H-U, Zwahlen M, et al. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. J Allergy Clin Immunol. 2011;128:1349–1350.e5.
22. Molina-Infante J, Gonzalez-Cordero PL, Ferreira-Nossa HC, Mata-Romero P, Lucendo AJ, Arias A. Rising incidence and prevalence of adult eosinophilic esophagitis in midwestern Spain (2007–2016). United European Gastroenterol J. 2018;6:29–37.
23. Arias Á, Lucendo AJ. Incidence and prevalence of eosinophilic oesophagitis increase continuously in adults and children in Central Spain: a 12-year population-based study. Dig Liver Dis. 2019;51: 55–62.
24. Krarup, AL, Vyberg, M, Ejstrud, P. [Eosinophilic oesophagitis in adults]. Ugeskr Laegers. 2014;176:V12130723.
25. García-Compeán D, González-Moreno EI, González-González JA, Borjas-Almaguer OD, Maldonado-Garza HJ. Lack of compliance with consensus recommendations on the diagnosis of eosinophilic esophagitis (EoE) in published prevalence studies. A clinical and systematic review. J Dig Dis. 2016;17:660–669.
26. Straumann A, Bussmann C, Zuber M, Vannini S, Simone H-U, Schoepfer A. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. Clin Gastroenterol Hepatol. 2008;6:598–600.
27. Dellon ES, Kim HP, Sperry SLW, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc. 2014;79: 577–585.e4.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Melgaard D, Westmark S, Laurberg PT, Krarup AL. A diagnostic delay of 10 years in the DanEoE cohort calls for focus on education - a population-based cross-sectional study of incidence, diagnostic process and complications of eosinophilic oesophagitis in the North Denmark Region. United European Gastroenterol J. 2021;9(6):688–98. https://doi.org/10.1002/ueg2.12092