

## Original Article

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# No gender differences in patients with eosinophilic oesophagitis

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**ABSTRACT**

**INTRODUCTION.** Gender difference in the incidence of eosinophilic oesophagitis (EoE) is well-known as more men than women are affected. However, knowledge of gender differences is lacking for most other aspects of EoE. In this population-based adult EoE cohort, the aim was to study if gender differences exist with respect to 1) clinical phenotype, 2) treatment response and 3) complications.

**METHODS.** This was a retrospective, registry-based DanEoE cohort study of 236 adult patients with EoE (178 adult men and 58 adult women) diagnosed in 2007-2017 in the North Denmark Region. Medical registries were searched for patient records and pathology reports.

**RESULTS.** No statistically or clinically significant differences were recorded in the phenotype regarding symptoms reported, macroscopic or histological findings at diagnosis (all  $p > 0.3$ ). A comparable number of men and women were followed up symptomatically and histologically (all  $p > 0.3$ ). More men than women reported "no symptoms" on proton pump inhibitor (56% men versus 39% women,  $p = 0.04$ ), although the histological response was similar between genders ( $p = 0.4$ ). The proportions of food bolus obstructions and dilations were comparable (all  $p > 0.4$ ).

**CONCLUSION.** This study found very few gender differences. Results suggest that men and women with EoE may receive the same treatment.

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Eosinophilic oesophagitis (EoE) is classified as a clinicopathological disease characterised by symptoms of oesophageal dysfunction such as food impaction and dysphagia, and histologically by the presence of  $\geq 15$  eosinophils per high-power field (HPF) [1]. In recent decades, the number of patients with EoE has increased rapidly. The formal consensus-based diagnostic criteria were established in 2007 and updated in 2011 and 2018 [1-3]. EoE is associated with autoimmune diseases, allergic rhinosinusitis and asthma [3, 4]. EoE is more prevalent in men than women, approximately at a 3:1 ratio, although autoimmune diseases are more common in females [3, 5]. The diagnostic delay in establishing the EoE diagnosis is generally up to ten years, and the age for men and women at the time of diagnosis is similar [5-7].

In the literature, the male-female health survival paradox describes how women experience more medical conditions and disability during their lives but have a lower mortality than men [8]. The most common explanations for these gender differences involve biological variance, social roles, health and lifestyle behaviour and differences in healthcare utilisation [8, 9]. Moreover, evidence shows that men report poor health at a more severe stage of disease [8] and men are more likely to be hospitalised and to die from these conditions [10]. Based on this evidence, it is possible that men would have more complications than women. Conversely, in clinical practice, women tend to be regarded as more demanding in relation to sedation when undergoing painful or uncomfortable procedures, e.g., gastroscopy.

The DanEoE database is a regional, population- and registry-based cohort based on the Danish Patho-histology Registry of EoE patients diagnosed in the North Denmark Region (580,000 inhabitants) between 2007 and 2017 with follow-up until December 2018 [5]. Gender has not been shown to affect diagnostic delay in the DanEoE cohort [5].

To our knowledge, the gender effect on complications in patients with EoE has not previously been examined. Based on the general differences between gender and disease, this study hypothesised that men would have a more severe disease phenotype, a lower treatment response and a higher prevalence of complications than women. The aim of this study was to estimate gender-based differences in complications among patients with EoE in a population-based setting in the North Denmark Region.

## METHODS

The study database was approved by the Danish Data Protection Agency, ID number 2018-59. Under Danish law, this study does not require ethical approval. All hospitals in the North Denmark Region approved the project for quality assessment of EoE treatment; ID number 2017-011259.

The study was a retrospective, cross-sectional cohort study using the DanEoE database, which was previously described in detail [11]. DanEoE is a registry-based database based on the Danish Patho-histology Registry using the SNOMED system [11]. The unique personal identification number assigned to all Danish citizens is used to register all individuals in a region with oesophageal eosinophilia based on the SNOMED codes for topography (oesophagus mucosa (T62010)), and morphology (eosinophilia defined as  $\geq 15$  eosinophils in 1 HPF (M47150)) [11]. The personal identification number facilitates assessment of all medical information providing ideal possibilities for conducting population-based studies [12]. The DanEoE database includes all patients with oesophageal eosinophilia (236 adults with EoE) in the North Denmark Region diagnosed between 1 January 2007 and 31 December 2017 with follow-up until 31 December 2018 [5]. For the purpose of the present study, all patient records, radiology reports, histology reports, medication history and referral documents were reviewed in detail by two EoE experts and reported as data in the tables.

Patients with EoE were diagnosed according to the international diagnostic criteria for EoE from the AGREE 2 consensus [13]. Some patients had comorbid gastro-oesophageal reflux disease, such as Barrett's oesophagus and erosive oesophagitis; Barrett's oesophagus was defined as intestinal metaplasia in salmon-coloured oesophageal mucosa [14]. Erosive oesophagitis was defined according to the Los Angeles (LA) classification and grouped into *mild* (LA grades A + B) or *moderate to severe* (LA grades C + D). When the endoscopist did not use the LA classification, the description in the patient record was used to assess severity when possible [11]. We identified 178 men and 58 women who were comparable with respect to age at symptom debut, diagnosis and diagnostic delay [5]. However, 14 men and three women declined treatment or further investigation. Thus, we have missing data on symptomatic and histological follow-up.

## Statistics

Descriptive statistics were given as median and interquartile range (25-75 percentile) for continuous variables or mean ( $\pm$  standard deviation), as appropriate. For categorical variables, counts and percentages were displayed. Comparison between genders for continuous variables was performed using the t-test, and results were given as mean with 95% confidence interval. Comparison of proportions between genders was made using the  $\chi^2$  test if the number of observations was  $\geq 5$ ; otherwise, no comparison was made. Data management and statistics were performed using SAS enterprise guide 71 (SAS Institute Inc., Cary, NC, USA) and SigmaPlot 11.0 Build 11.1.0.102 (Systat Software Inc., CA, USA).

*Trial registration: not relevant.*

## RESULTS

Data for this study were almost complete (Table 1, Table 2, Table 3) for the 178 adult men and 58 adult women in the DanEoE cohort. A total of 14 male and three female patients with EoE declined treatment or further investigation and clinical information was sparse. These missing values were omitted from the data presented in Table 3.

**TABLE 1** Characteristics of all adults with eosinophilic oesophagitis in 2007-2017 in the North Denmark Region (580,000 inhabitants).

	Men (N <sub>tot</sub> = 178)	Women (N <sub>tot</sub> = 58)	p value
<i>Descriptive statistics [N]</i>			
Age at diagnosis, mean ( $\pm$ SD), yrs	48 ( $\pm$ 15) [178]	44 ( $\pm$ 14) [58]	0.1
Age at symptom debut, mean ( $\pm$ SD), yrs	38 ( $\pm$ 16) [139]	35 ( $\pm$ 17) [45]	0.2
Proportion with comorbid GORD, %	29 [52]	24 [14]	0.5
Delay from 1st hospital contact to diagnosis, mean ( $\pm$ SD), yrs	2.2 ( $\pm$ 4.5)	3.2 ( $\pm$ 5.3)	0.1
<i>Phenotype: proportion of group, % [N]</i>			
Dysphagia without stenosis or severe EE	85 [150]	81 [47]	0.6
Allergies, unspecified	61 [108]	47 [27]	0.06
Barrett's oesophagus, currently or previously	5.5 [8]	0.0 [0]	0.2
Oesophagitis at debut or previously:			
Any severity	14 [24]	14 [8]	1.0
Severe: LA C or D	0 [1]	0 [0]	-

EE = erosive oesophagitis; GORD = gastro-oesophageal reflux disease; LA = Los Angeles Classification; SD = standard deviation.

**TABLE 2** Gender differences at index endoscopy in adults with eosinophilic oesophagitis.

	<b>Men (N<sub>tot</sub> = 178)</b>	<b>Women (N<sub>tot</sub> = 58)</b>	<b>p value</b>
On PPI at index endoscopy, % [N]	19 [30]	20 [10]	1.0
<i>Indication for index endoscopy, % [N]</i>			
EoE symptoms, any:	38 (± 16) [139]	35 (± 17) [45]	0.2
“EoE obs pro” in the medical record	93 [166]	97 [56]	0.5
Dysphagia	64 [113]	69 [40]	0.5
Dysphagia	62 [111]	64 [37]	0.9
Food impaction	22 [39]	22 [13]	1.0
<i>Sedation at index endoscopy: proportion of patient group, % [N]</i>			
No sedation or local anaesthetics	56 [80]	52 [27]	0.6
Local anaesthetics	9.2 [13]	7.7 [4]	-
IV sedation	9.9 [14]	12 [6]	0.6
General anaesthesia	22 [32]	25 [13]	0.7
<i>Macroscopic changes at the index endoscopy: proportion of patient group, % [N]</i>			
Macroscopically normal	29 [52]	38 [22]	0.3
Endoscopic EoE sign:			
Any	45 [80]	40 [23]	0.5
Inflammatory: oedema, exudates, furrows	14 [24]	8.6 [5]	0.3
Fibrotic: rings, strictures, narrow oesophagus	31 [56]	31 [18]	1.0
FBO	13 [23]	14 [8]	0.9
<i>Biopsy practice if presenting with dysphagia [N]</i>			
Biopsies if dysphagia, median (IQR), n	8.0 (5.0-9.0)	7.0 (5.0-9.0)	0.3
Patients with ≥ 8 biopsies, Danish guidelines, %	57 [101]	55 [32]	0.9
Patients with ≥ 6 biopsies, %	71 [126]	72 [42]	0.9
Max eos/HPF, median (IQR), n	30 (23-50)	40 (25-65)	0.4

EoE = eosinophilic oesophagitis; eos/HPF = eosinophils per high-power field; FBO = food bolus obstruction; IQR = interquartile range; IV = intravenous; PPI = proton pump inhibitor.

**TABLE 3** Gender differences in eosinophilic oesophagitis and treatment initiation.

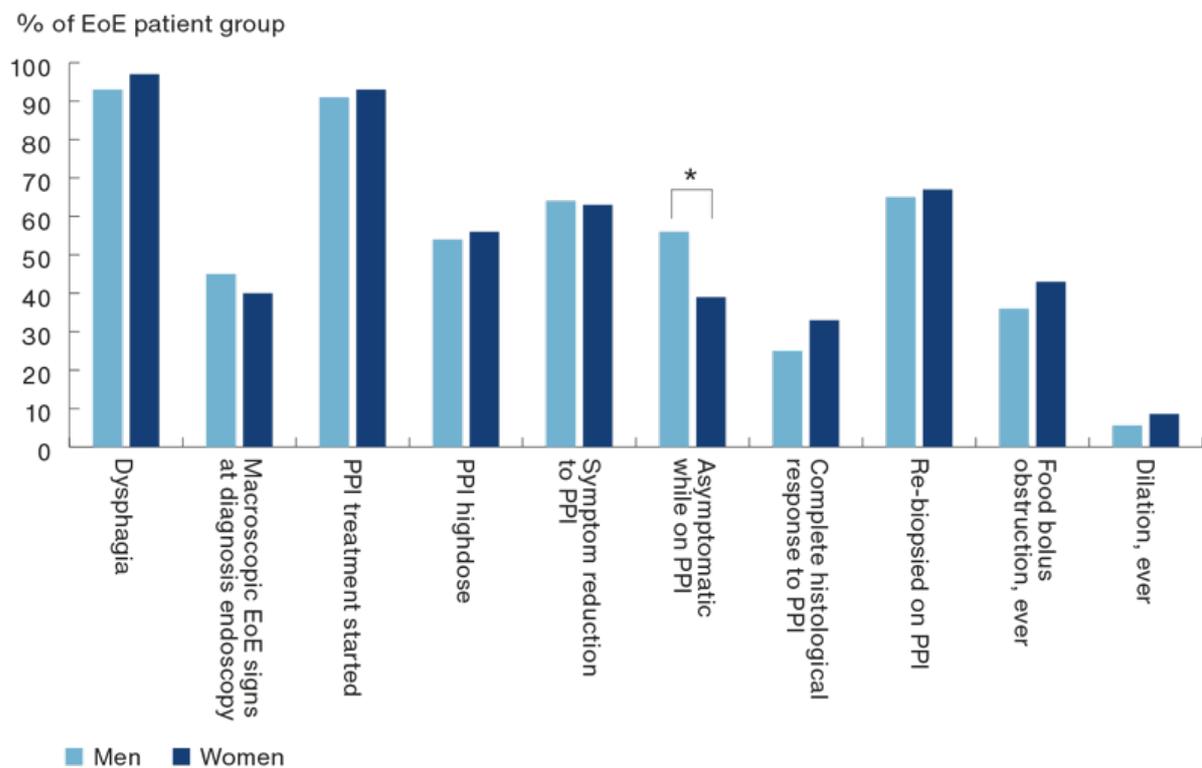
	Men (N <sub>tot</sub> = 178)	Women (N <sub>tot</sub> = 58)	p value
<i>1st line treatment of EoE patients, % [N]</i>			
Treatment offered within 3 months	82 [146]	85 [49]	0.8
No treatment offered	18 [32]	15 [9]	0.7
Treatment or further investigation declined	7.9 [14]	5.2 [3]	
<i>PPI treatment [N]</i>			
Delay, diagnosis to PPI initiation, mean (± SD) weeks	12 (± 23) [80]	8.4 (± 14) [32]	0.3
PPI treatment started at any time, %	91 [162]	93 [54]	0.5
High dose: % of PPI-treated patients	54 [88]	56 [30]	1.0
Low dose: % of PPI-treated patients	46 [74]	44 [24]	1.0
Symptomatic follow-up: % of PPI-treated patients	90 [146]	85 [46]	0.3
Symptom reduction: % of PPI-treated patients	64 [103]	63 [34]	1.0
Asymptomatic: % of PPI-treated patients	56 [91]	39 [21]	0.04
Histological follow-up: % of PPI-treated patients	65 [105]	67 [36]	0.9
PPI duration at follow-up, mean (± SD) weeks	33 (± 55)	32 (± 62)	0.9
Histological remission: % of PPI-treated patients	25 [41]	33 [18]	0.3
Treatment failure: eos/HPF ≥ 15, or if not biopsied, % of PPI-treated patients	46 [74]	52 [28]	0.4
<i>Other treatment initiated if PPI failed [N]</i>			
Second treatment started, % of treatment failure	54 [40]	57 [16]	0.8
Second treatment started within 6 months, % of started	85 [34]	94 [15]	0.7

EoE = eosinophilic oesophagitis; eos/HPF = eosinophils per high-power field; IQR = interquartile range; PPI = proton pump inhibitor; SD = standard deviation.

**Few phenotype differences between men and women**

Table 1 shows descriptive data on EoE phenotype. No significant differences were recorded in the proportion of men and women presenting with dysphagia, comorbid Barrett’s oesophagus or erosive oesophagitis (Table 1). A trend was observed towards men having allergic disease 14% more often than women (p = 0.06), but allergies are unspecified in the medical records. No differences or trends were observed in the indications for the index endoscopy or the macroscopic changes (Table 2, **Figure 1**). Furthermore, the number of biopsies and the extent of inflammation in the biopsies were comparable between men and women.

**FIGURE 1** In this retrospective, registry-based eosinophilic oesophagitis (EoE) cohort study in North Denmark Region, data from 178 adult men and 58 adult women with EoE were examined for gender differences in complication development. Food bolus obstruction and strictures in need of dilation were similar between men and women. Few and subtle differences were observed in baseline data and treatment. More men than women were described as asymptomatic after proton pump inhibitor (PPI) treatment, but the proportion of patients in histological remission was comparable between genders.



\*)  $p < 0.05$ .

**More men reported no symptoms despite a comparable histological response between genders**

No differences were found in treatment patterns between genders (Table 3, Figure 1). When proton pump inhibitor (PPI) treatment was initiated, men and women were prescribed high-dose PPI to the same extent and followed up in comparable patterns (Table 3, Figure 1). However, 17% more men than women were described as asymptomatic ( $p = 0.04$ ).

No differences in complication rate between genders was observed.

Food bolus obstruction was a common problem before treatment initiation and was rare after initiation of PPI. Dilations were very rare, especially during treatment with PPI ( $< 5\%$ ), and both genders were equally affected (Figure 1).

## DISCUSSION

This was a retrospective cross-sectional study of gender differences in the 236 patients with EoE in the population-based DanEoE cohort. The phenotype of men and women was comparable apart from the trend towards men having more allergies, though these allergies were not further specified. PPI treatment was the first-line choice and prescribed to almost all men and women, and did not result in gender differences in terms of outcome. The histological response rate was similar between genders, although more men than women were described as asymptomatic. In our studies, food bolus obstruction was observed just before treatment initiation in a fifth of all men and women, but it is already known from other studies that this occurs in more than a third of all men and women at any time before treatment initiation [11]. Food bolus obstruction is rarely observed after treatment initiation with PPI. Strictures and dilations were rare.

For both men and women, the time from obtaining a biopsy to treatment initiation was three months. This is due to the structure of Danish outpatient clinics as biopsy results are usually present a month after the sampling, and an appointment for treatment is scheduled once the endoscopist sees the results.

### Strengths and limitations

The strength of this study was its population- and registry-based design. The Danish health registries have a high validity and completeness, producing strong epidemiological research. In the DanEoE cohort, patient phenotype was determined in 97% of the cases [5].

Among the limitations of the study was missing data on new biopsies in one-third of male and female patients with EoE who initiated treatment. Furthermore, 8% of male and 5% of female patients with EoE had not initiated treatment, and clinical information on these patients was sparse. These missing data were omitted, and we therefore do not know if they developed complications.

We only included one of the five geographical regions in Denmark, including all hospitals in the studied region. However, the regions are similar with respect to geographical and demographical data [15]. Since the study was retrospective, clinical information from the medical records was not always described systematically and dysphagia scoring by a validated questionnaire was not available. The number of patients was small, limiting sub-group analyses. When conducting medical record reviews, it is important to be aware of possible incomplete or incorrect registrations.

### Gender differences

Men are more frequently diagnosed with EoE than women [16-19], up to 2-3 times [18]; but why they are overrepresented remains unclear [16]. Previous studies investigating gender-based differences in the presentation of EoE are few and have yielded conflicting findings. In our study, very few differences in clinical presentation or endoscopic findings were observed between males and females. Lynch et al. [15] reported that males more often than females experienced food impaction, but no differences were recorded in the prevalence of strictures, rings or furrows. Sperry et al. [20] found that males were more likely than females to report dysphagia or food impaction; but on endoscopic evaluation, no significant differences were recorded between male and females with EoE. In our study, we found that men more often than women reported no symptoms on PPI although the histological response was the same for both genders. It is unknown if this may be explained by the DanEoE symptoms being obtained directly from the ordinary medical records and not from a standardised questionnaire. The influence of gender differences in patients with EoE related to recording of medical history or completion of questionnaires has not been investigated.

Two previous studies have reported that stricture development is more often seen in males than females; this was not the case in our study [6, 17]. This may be a true difference between patients with EoE in Denmark and

the United States of America (USA). Another possible explanation is selection bias as more males than females in the US may afford health insurance and thus have easier access to diagnostics and treatment as reported in the study by Moawad et al.. Warners et al. [6] found male gender to be an independent risk factor for oesophageal stricture in EoE, speculating that males are predisposed to fibrosis due to lack of oestrogen. However, in their study, two thirds of the population data were extracted from electronic medical charts including both academic and non-academic centres. Data could not be extracted from the remaining third of the population data due to logistic or cooperative reasons, and no analysis was thus made. If the third of patients omitted from the study had less complex disease, this would lead to selection bias towards patients having more complex disease and therefore a higher risk of complications.

Moawad et al. [17] also reported strictures to be more frequent in males than females; however, dilation frequency was similar between genders. Similar to Moawad, we found that the proportion of men and women being dilated was comparable, but we reported fewer strictures. The differences between our study and the studies above regarding stenosis may, in part, be explained by a lack of international consensus on a definition of stenosis and strictures. It may potentially also be explained by differences in EoE populations as the Moawad population was partly based on referrals, which often results in selection bias towards more complex cases of EoE. In the DanEoE cohort in the present study, a stricture was defined as a stenosis not passable by a standard scope. This rough definition was necessary as the stenosis was rarely described in detail in the endoscopy reports. All strictures were dilated. Since the definitions used in the literature vary, this may account for the different results.

## CONCLUSION

This retrospective, registry- and population-based DanEoE study of patients with EoE in the North Denmark Region showed very few gender differences. Most importantly, food bolus obstruction and strictures in need of dilation were similar between men and women.

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