

SUPPLEMENTAL MATERIAL

Supplemental methods

Statistical analysis

Once a patient was determined to have severe disease they were classed as having severe disease for the rest of the study follow-up period.

Patients with a minimum of 12 months of follow-up from their EoE diagnosis index date were included in the treatment analysis. The first recorded prescription of PPI, TCS or OCS therapy in the 12 months prior to EoE diagnosis or any time after that was defined as the therapy index date. First-, second- and third-line drug treatments were also recorded. To ensure treatment patterns over time (i.e., first-, second- and third-line drug treatments) were captured adequately, patients were required to have a minimum of 3 years of follow-up to be included in the analysis. First-line drug treatment was defined in either the pre- or post-diagnosis period. Second- and third-line drug treatments were defined as:

- **Continued** indicates no treatment change until end of follow-up for the patient.
- **Switched** indicates treatment change from one to another different drug class, (e.g. moving from PPI to TCS).
- **Addition/augmentation** indicates the addition of at least one EoE medication to the current EoE regimen. A patient was considered to have received combination therapy if prescriptions for drug treatment of at least two classes occurred within a 30-day period; otherwise, the patient was considered to have received monotherapy.
- **Removal** – moving from combination therapy to monotherapy – indicates the removal of at least one EoE medication. If a patient was on combination therapy, they were considered to have moved to monotherapy if there were no prescriptions

for one of the EoE medications after the last prescription of >60 days, with no restarting of that drug over the rest of follow-up.

- **Discontinued** indicates no prescription for the EoE medication after the last prescription of >60 days. If a patient discontinued a drug treatment but restarted it later, the treatment was considered to occur in the same line of therapy, regardless of the gap between treatments.

Patients were required to have at least 12 months of registration with the practice prior to first EoE diagnosis to be included in the stricture development analysis. Strictures were identified using diagnosis codes for oesophageal strictures. At least 12 months of follow-up from EoE diagnosis was needed to describe the proportion of patients on medication who developed strictures.

Definitions

EoE symptom onset was defined as first recording of dysphagia, food impaction, acid reflux/heartburn, non-cardiac chest pain or failure to thrive ≥ 3 years before EoE diagnosis.

Adequate disease control was defined as no change in treatment, no procedures for the management/treatment of EoE, no hospitalisations or Accident and Emergency visits and no addition of a dietary formula for ≥ 3 months. Poor disease control was defined as a change in drug class or the addition of other treatments including procedures for the management of EoE and dietary formulas.

Sensitivity analysis

A univariate sensitivity analysis was performed to determine the impact of excluding patients diagnosed with first EoE symptoms on the same day as EoE diagnosis when assessing disease severity, upper GI endoscopy and oesophageal dilation as potential determinants of time to diagnosis.

Supplemental table 1. Code lists for EoE diagnosis

MedCodeID	Term	Original ReadCode	Cleansed ReadCode	SnomedCT ConceptId	SnomedCT DescriptionId
353159016	Eosinophilic oesophagitis	J1017	J101700	235599003	353159016
5082651000006117	Eosinophilic esophagitis	^ESCTEO508265		235599003	353158012

EoE, eosinophilic oesophagitis; SnomedCT, Systematized Nomenclature of Medicine Clinical Terms

Supplemental table 2. Baseline EoE symptoms and allergic comorbidities by age group in England

EoE symptoms and allergic comorbidities	Overall (n=2381)	Age at EoE diagnosis		
		<12 years (n=165)	12–17 years (n=173)	≥18 years (n=2043)
Symptoms				
Dysphagia	952 (40.0)	19 (11.5)	43 (24.9)	890 (43.6)
Acid reflux/heartburn	515 (21.6)	43 (26.1)	41 (23.7)	431 (21.1)
Acid reflux/heartburn	220 (9.2)	21 (12.7)	20 (11.6)	179 (8.8)
GERD/GORD	359 (15.1)	29 (17.6)	28 (16.2)	302 (14.8)
Regurgitation	13 (0.6)	7 (4.2)	2 (1.2)	4 (0.2)
Vomiting and nausea	167 (7.0)	45 (27.3)	19 (11.0)	103 (5.0)
Food impaction	194 (8.2)	3 (1.8)	11 (6.4)	180 (8.8)
Non-cardiac chest pain	96 (4.0)	1 (0.6)	5 (2.9)	90 (4.4)
Abdominal pain	256 (10.8)	30 (18.2)	32 (18.5)	194 (9.5)
Failure to thrive	28 (1.2)	6 (3.6)	1 (0.6)	21 (1.0)
≥1 symptom	1581 (66.4)	100 (60.6)	108 (62.4)	1373 (67.2)
Comorbidities				
Asthma	567 (23.8)	43 (26.1)	50 (28.9)	474 (23.2)
Atopic dermatitis/eczema	118 (5.0)	31 (18.8)	14 (8.1)	73 (3.6)
Allergic rhinitis	86 (3.6)	9 (5.5)	22 (12.7)	55 (2.7)
Food allergy/oral allergy syndrome	50 (2.1)	14 (8.5)	13 (7.5)	23 (1.1)
≥1 allergic comorbidity	695 (29.2)	65 (39.4)	71 (41.0)	559 (27.4)

All data are presented as n (%)

EoE, eosinophilic oesophagitis; GERD, gastroesophageal reflux disease; GORD, gastro-oesophageal reflux disease

Supplemental table 3. Baseline comorbidities of patients with EoE and non-EoE matched controls in England

Baseline comorbidities	Patients with EoE (n=2381)	Non-EoE controls (n=9365)	p value
Concomitant allergic diseases			
Asthma	567 (23.8)	614 (6.6)	<0.001
Atopic dermatitis/eczema	118 (5.0)	199 (2.1)	<0.001
Allergic rhinitis	86 (3.6)	91 (1.0)	<0.001
Food allergy/oral allergy syndrome	50 (2.1)	11 (0.1)	<0.001
≥1 allergic comorbidity (per patient)	695 (29.2)	851 (9.1)	<0.001
Diseases associated with EoE			
Reflux oesophagitis	489 (20.5)	95 (1.0)	<0.001
Eosinophilic gastritis/gastroenteritis	10 (0.4)	0 (0.0)	<0.001
Coeliac disease	17 (0.7)	5 (0.1)	<0.001
Inflammatory bowel disease	41 (1.7)	36 (0.4)	<0.001
Hypereosinophilic syndrome	0 (0.0)	0 (0.0)	NR
Achalasia	5 (0.2)	2 (0.0)	<0.001
Drug hypersensitivity	45 (1.9)	42 (0.5)	<0.001
Vasculitis and eosinophilic granulomatosis polyangiitis	7 (0.3)	18 (0.2)	0.48
Connective tissue diseases	16 (0.7)	47 (0.5)	0.39
Graft-versus-host disease	0 (0.0)	0 (0.0)	NR
≥1 EoE-related comorbidity (per patient)	581 (24.4)	242 (2.6)	<0.001
Psychiatric comorbidities			
Depression/anxiety	223 (9.4)	483 (5.2)	<0.001
Depression	139 (5.8)	328 (3.5)	<0.001
Anxiety	51 (2.1)	46 (0.5)	<0.001
Bipolar disorder	4 (0.2)	17 (0.2)	1.00
Post-traumatic stress disorder	0 (0.0)	0 (0.0)	NR
Schizophrenia	3 (0.1)	24 (0.3)	0.34
Insomnia	20 (0.8)	34 (0.4)	<0.001

Baseline comorbidities	Patients with EoE (n=2381)	Non-EoE controls (n=9365)	p value
Chronic pain disorder	6 (0.3)	14 (0.2)	0.42
≥1 psychiatric comorbidity (per patient)	260 (10.9)	598 (6.4)	<0.001
Prescribed psychiatric medication at baseline			
SSRI	207 (8.7)	680 (7.3)	0.02
SNRI	33 (1.4)	87 (0.9)	0.06
Tricyclic antidepressant	126 (5.3)	287 (3.1)	<0.001
MAOI	2 (0.1)	0 (0.0)	0.05
Antipsychotic	70 (2.9)	166 (1.8)	<0.001
Benzodiazepine	74 (3.1)	203 (2.2)	0.01
Buspirone, and others (trazodone, pregabalin, gabapentin, and mirtazapine anxiolytics)	94 (4.0)	304 (3.3)	0.10
≥1 psychiatric medication (per patient)	439 (18.4)	1281 (13.7)	0.00

All data are presented as n (%)

EoE, eosinophilic oesophagitis; MAOI, monoamine-oxidase inhibitor; NR, not relevant; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

Supplemental table 4. English patient and clinical characteristics by time to diagnosis in patients with EoE with data available at least 3 years prior and including the EoE diagnosis date, and with EoE symptom onset on or before the diagnosis date (n=1473)

	Time to diagnosis (months)			
	0	>0–<12	12–<24	24–36
Total number of patients with EoE, n (%)	76 (5.2%)	928 (63.0%)	240 (16.3%)	229 (15.5%)
Demographic characteristics				
Sex, n (%)				
Male	46 (60.5)	660 (71.1)	162 (67.5)	151 (65.9)
Age at diagnosis, years				
<18, n (%)	6 (7.9)	81 (8.7)	36 (15.0)	45 (19.7)
BMI, kg/m ²				
Mean (SD)	26.3 (5.4)	79.5 (8.6)	25.7 (5.2)	26.0 (6.0)
Ethnicity, n (%)				
White	44 (57.9)	575 (62.0)	147 (61.3)	147 (64.2)
Black	2 (2.6)	12 (1.3)	6 (2.5)	4 (1.7)
Asian	4 (5.3)	29 (3.1)	9 (3.8)	14 (6.1)
Other	0 (0.0)	16 (1.7)	7 (2.9)	6 (2.6)
Unknown	26 (34.2)	296 (31.9)	71 (29.6)	58 (25.3)
Clinical characteristics				
Dysphagia, n (%)	37 (48.7)	658 (70.9)	140 (58.3)	131 (57.2)
Acid reflux/heartburn, n (%)	25 (32.9)	329 (35.5)	120 (50.0)	132 (57.6)
Regurgitation, n (%)	0 (0.0)	6 (0.7)	2 (0.8)	5 (2.2)
Vomiting and nausea, n (%)	11 (14.5)	68 (7.3)	24 (10.0)	42 (18.3)
Food impaction, n (%)	26 (34.2)	139 (15.0)	27 (11.3)	20 (8.7)
Non-cardiac chest pain, n (%)	0 (0.0)	44 (4.7)	54 (22.5)	74 (32.3)
Abdominal pain, n (%)	7 (9.2)	79 (8.5)	0 (0.0)	0 (0.0)
Failure to thrive, n (%)	0 (0.0)	16 (1.7)	10 (4.2)	15 (6.6)
Disease severity				
Severe disease, n (%)	26 (34.2)	221 (23.8)	55 (22.9)	52 (22.7)

	Time to diagnosis (months)			
	0	>0–<12	12–<24	24–36
Total number of patients with EoE, n (%)	76 (5.2%)	928 (63.0%)	240 (16.3%)	229 (15.5%)
Strictures or selected procedures				
Oesophageal strictures, n (%)	19 (25.0)	149 (16.1)	50 (20.8)	35 (15.3)
Endoscopic dilation, n (%)	3 (4.0)	16 (1.7)	10 (4.2)	10 (4.4)
Barium meal, n (%)	0 (0.0)	1 (0.1)	2 (0.8)	0 (0.0)
Upper GI endoscopy (with and without biopsy), n (%)	48 (63.2)	800 (86.2)	208 (86.7)	197 (86.0)
Comorbidities				
Concomitant allergic diseases				
Asthma, n (%)	18 (23.7)	250 (26.9)	69 (28.8)	83 (36.2)
Atopic dermatitis, n (%)	7 (9.2)	73 (7.9)	19 (7.9)	28 (12.2)
Allergic rhinitis, n (%)	9 (11.8)	50 (5.4)	26 (10.8)	23 (10.0)
Food allergy, n (%)	2 (2.6)	27 (2.9)	11 (4.6)	16 (7.0)
Diseases associated with EoE				
Reflux oesophagitis, n (%)	23 (30.3)	298 (32.1)	97 (40.4)	119 (52.0)
≥1 EoE-related comorbidity, n (%)	27 (35.5)	331 (35.7)	110 (45.8)	123 (53.7)
Psychiatric comorbidities				
Depression/anxiety, n (%)	14 (18.4)	124 (13.4)	39 (16.3)	46 (20.1)
≥1 psychiatric comorbidity, n (%)	16 (21.1)	144 (15.5)	44 (18.3)	56 (24.5)
≥1 psychiatric medication, n (%)	20 (26.3)	172 (18.5)	47 (19.6)	58 (25.3)

Time to diagnosis was defined as the time between EoE symptom onset and EoE diagnosis
BMI, body mass index; EoE, eosinophilic oesophagitis; GI, gastrointestinal; SD, standard deviation

Supplemental table 5. Multivariable association (IRR and 95% CI) of disease severity and EoE procedures with prolonged time to diagnosis¹

	Unadjusted incident rate ratio (95% CI)	Adjusted ² incident rate ratio (95% CI)
Analysis of patients diagnosed with first symptom prior to or on same day as EoE diagnosis		
Severe disease compared with no severe disease at baseline (262 versus 1211)	0.81 (0.69, 0.96)	0.77 (0.65, 0.91)
Oesophageal dilation compared with no oesophageal dilation at baseline (24 versus 1449)	0.84 (0.52, 1.38)	0.91 (0.56, 1.48)
Upper GI endoscopy compared with no upper GI endoscopy at baseline (977 versus 496)	1.09 (0.96, 1.25)	1.12 (0.98, 1.28)
Sensitivity analysis of those with first symptom before day of EoE diagnosis		
Severe disease compared with no severe disease at baseline (261 versus 1136)	0.76 (0.66, 0.89)	0.72 (0.62, 0.85)
Oesophageal dilation compared with no oesophageal dilation at baseline (24 versus 1373)	0.89 (0.56, 1.41)	0.96 (0.61, 1.53)
Upper GI endoscopy compared with no upper GI endoscopy at baseline (975 versus 422)	1.28 (1.12, 1.46)	1.31 (1.14, 1.49)

¹Time to diagnosis was defined as time from symptom onset to first EoE diagnosis;
²Adjusted for age (measured in years at index), gender, BMI (most recent measurement prior to index), ethnicity, and the following comorbidities, measured at baseline (12 months prior to index): concomitant allergic diseases (including asthma), oesophagitis and depression

BMI, body mass index; CI, confidence interval; EoE, eosinophilic oesophagitis; GI, gastrointestinal; IRR, incident rate ratio

Supplemental table 6. Baseline patient characteristics and development of strictures in patients in England with EoE with at least 12 months of follow-up

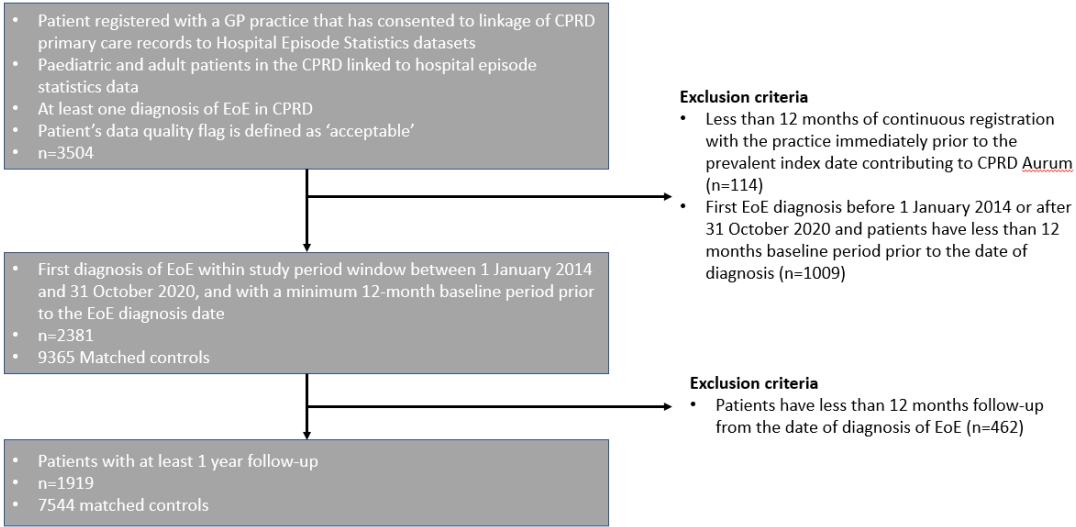
	Patients with EoE with ≥1 year of follow-up (n=1919)	Patients with incident EoE who NEVER developed strictures (baseline or follow-up) (n=1567)	Patients with incident EoE who developed strictures EVER (baseline or follow-up period) (n=352)
Duration of follow-up			
(days)			
Mean (SD)	1131.8 (529.9)	1122.7 (526.0)	1172.5 (546.1)
Demographics			
Sex, n (%)			
Male	1350 (70.4)	1085 (69.2)	265 (75.3)
Age at diagnosis (years)			
Median (IQR)	40 (25)	39 (26)	44 (22)
<18, n (%)	303 (15.8)	287 (18.3)	16 (4.6)
≥18, n (%)	1616 (84.2)	1280 (81.7)	336 (95.5)
BMI, kg/m ²			
Mean (SD)	26.8 (6.3)	25.6 (6.2)	25.7 (5.1)
Clinical characteristics			
Dysphagia, n (%)	756 (39.4)	598 (38.2)	158 (44.9)
Acid reflux/heartburn, n (%)	415 (21.6)	359 (22.9)	56 (15.9)
Food impaction, n (%)	157 (8.2)	114 (7.3)	43 (12.2)
Non-cardiac chest pain, n (%)	74 (3.9)	57 (3.6)	17 (4.8)
Regurgitation, n (%)	9 (0.5)	9 (0.6)	0 (0.0)
Vomiting and nausea, n (%)	140 (7.3)	130 (8.3)	10 (2.8)
Abdominal pain, n (%)	203 (10.6)	181 (11.6)	22 (6.3)
Failure to thrive, n (%)	19 (1.0)	17 (1.1)	2 (0.6)

	Patients with EoE with ≥1 year of follow-up (n=1919)	Patients with incident EoE who NEVER developed strictures (baseline or follow-up) (n=1567)	Patients with incident EoE who developed strictures EVER (baseline or follow-up period) (n=352)
Food refusal, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Disease severity			
Severe disease, n (%)	294 (15.3)	214 (13.7)	80 (19.2)
Comorbidities			
<i>Concomitant allergic diseases</i>			
Asthma, n (%)	452 (23.6)	371 (23.7)	81 (19.4)
Atopic dermatitis, n (%)	101 (5.3)	90 (5.7)	11 (2.6)
Allergic rhinitis, n (%)	69 (3.6)	58 (3.7)	11 (2.6)
Food allergy, n (%)	44 (2.3)	40 (2.6)	4 (1.0)
≥1 allergic comorbidity in baseline period (per patient), n (%)	559 (29.1)	459 (29.3)	100 (24.0)
<i>Diseases associated with EoE</i>			
Reflux oesophagitis, n (%)	400 (20.8)	324 (21.6)	76 (18.2)
≥1 EoE-related comorbidity in baseline period (per patient), n (%)	498 (26.0)	355 (23.6)	143 (34.3)
<i>Psychiatric comorbidities</i>			
Depression/anxiety, n (%)	158 (8.2)	128 (8.5)	30 (7.2)

	Patients with EoE with ≥1 year of follow-up (n=1919)	Patients with incident EoE who NEVER developed strictures (baseline or follow-up) (n=1567)	Patients with incident EoE who developed strictures EVER (baseline or follow-up period) (n=352)
≥1 psychiatric comorbidity in baseline period (per patient), n (%)	188 (9.8)	153 (10.2)	35 (8.4)

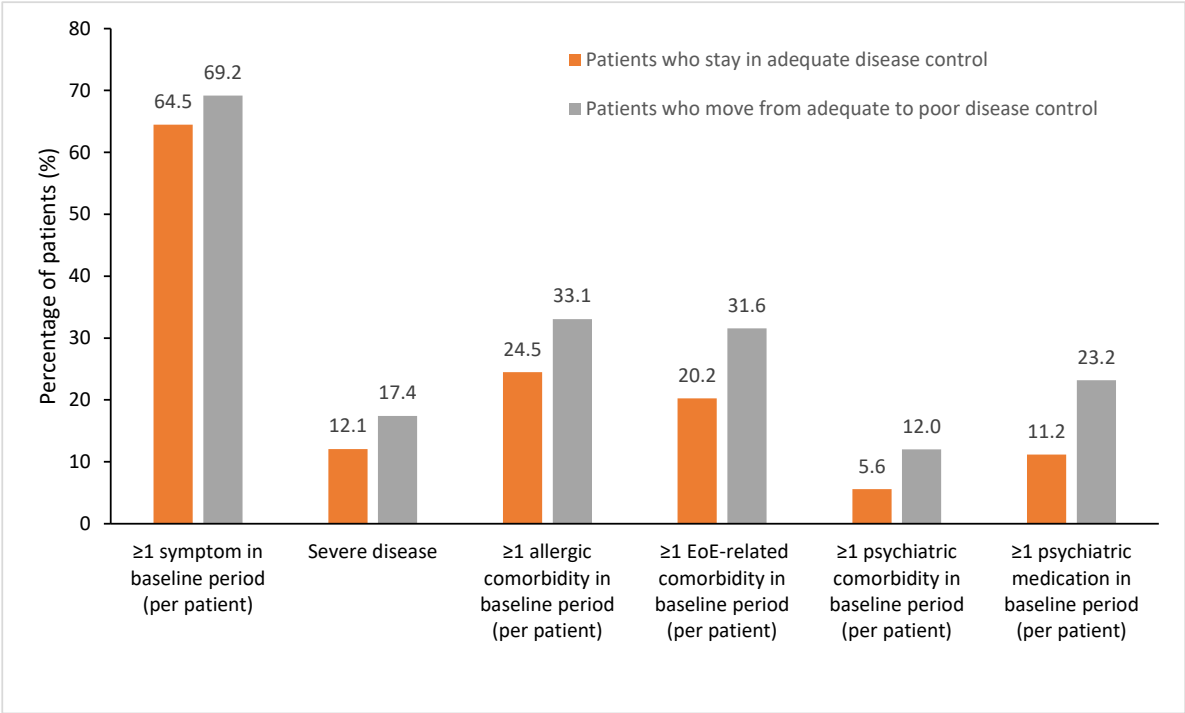
BMI, body mass index; EoE, eosinophilic oesophagitis; GI, gastrointestinal; IQR, interquartile range; SD, standard deviation

Supplemental figure 1. Flow chart of study cohort



CPRD, Clinical Practice Research Datalink; EoE, eosinophilic oesophagitis; GP, general practitioner

Supplemental figure 2. Percentage of patients with EoE in England remaining in adequate disease control and those experiencing poor disease control after achieving adequate disease control, by clinical characteristics (n=1729)



EoE, eosinophilic oesophagitis