Diagnostic Delay in Patients With Eosinophilic Esophagitis Has Not Changed Since the First Description 30 Years Ago: Diagnostic Delay in Eosinophilic Esophagitis

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INTRODUCTION: **Eosinophilic esophagitis (EoE) is a chronic progressive disease. Diagnostic delay (DD) is associated with increased risk of esophageal strictures and food impactions. We aimed to assess the evolution of DD since the first description of EoE in 1993 until 2021.**

METHODS: **We analyzed data from patients prospectively included in the Swiss EoE database. DD was calculated as the time interval between the first occurrence of EoE symptoms and the confirmed diagnosis. DD was analyzed annually over time (1989–2021) and according to milestone publications in the field (1993: first description; 2007: first consensus recommendations; and 2011: updated consensus recommendations). In addition, a Cox proportional hazards model has been used to describe the relation between DD and covariates.**

RESULTS: **Complete data of 1,152 patients (857 male [74%]; median age at diagnosis: 38 years, interquartile range: 28–49, range: 1–86) were analyzed. Overall, median DD was 4 years (interquartile range: 1–11, range, 0–56), with DD ≥ 10 years in 32% of the population. Over time, DD did not significantly change, neither annually nor according to release dates of milestone publications with a persistently stable fraction of roughly one-third of all patients with a DD of ≥10 years. Both ages at diagnosis ($P < 0.001$, with an increase in DD up to the age of 31–40 years) and at symptom onset (younger patients had a longer DD; $P < 0.001$) were significantly associated with DD.**

DISCUSSION: **DD has not changed since the first description of EoE almost 30 years ago and remains substantial. Even today, one-third of patients have a persistently high DD of ≥10 years. Substantial efforts are warranted to increase awareness for EoE and its hallmark symptom, solid food dysphagia, as an age-independent red-flag symptom among healthcare professionals and presumably the general population alike to lower risk of long-term complications.**

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INTRODUCTION

Eosinophilic esophagitis (EoE) has emerged as one of the major disease states in gastroenterology, causing a variety of upper gastrointestinal symptoms. EoE is the major cause of solid food bolus impaction (1), which may result in serious complications such as esophageal perforation or aspiration pneumonia. However, the broad clinical picture may also consist of only mild symptoms. Incidence rates are continuously increasing, presumably because of yet insufficiently identified environmental factors and altered compositional food intake rather than an increase in awareness or esophageal biopsy rates (2,3). As of today, the overall pooled prevalence is estimated around 34 cases of 100,000 with considerable geographic and population-based heterogeneity (1,4).

Untreated disease results in remodeling of the esophagus with a progressive increase in esophageal wall stiffness and stricture formation in direct correlation with the length of diagnostic delay (DD) (5,6). Every additional year of DD increases the risk of fibrostenotic changes in the esophagus by 5% (7). This not only affects potential serious clinical sequelae, including food impaction, but also affects therapeutic management because early disease changes with mucosal inflammation may more readily respond to

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anti-inflammatory measures such as elimination diets or medical treatment, whereas later stages often require invasive treatment strategies (1). In inflammatory bowel disease—a group of chronic immune-mediated inflammation of the luminal gastrointestinal tract—a similar increase in risk of complications and lower response rates to medical treatment with increased DD have been robustly demonstrated (5,8,9).

The wide spectrum of clinical presentation, including symptoms and at times mild endoscopic appearance, might prolong the physician-attributed delay. However, according to a large retrospective long-term analysis from Italy, a large portion of the overall DD seems to be attributed to patients (10). This could be, among others, explained by a lack of awareness and symptoms, modifiable by behavioral adaptations, such as avoidance of certain foods or reduced velocity of food intake.

In recent years, EoE has emerged as an increasingly prominent topic in gastroenterology, in general, and published literature as well as educational events in specific. However, little is known on whether increased awareness and efforts to educate health professionals about EoE translate into decreasing DD over time. The purpose of this study was, therefore, to assess the evolution of DD in Switzerland from 1993 to 2021 and to examine the potential influence of milestone publications including the first description of EoE in 1993 (11,12) and consensus recommendations in 2007 and 2011 (13,14) as well as patient-specific and disease-specific characteristics on DD. We also examined whether DD in patients with typical EoE symptoms but not fulfilling diagnostic criteria for EoE and, hence, categorized as EoE-like disease or lymphocytic esophagitis (15,16) differs from DD in patients with EoE .

METHODS

Study design and patient population

We conducted a retrospective observational study of patients with EoE of all age groups included in the Swiss EoE database (SEED) initiated by one of the coauthors (A.S.) of this study and continued by the EoE clinic of the University Hospital of Zurich (Switzerland). At the time of analysis (November 2021), the SEED included 1,380 patients (first patient diagnosed in 1989). All included patients were diagnosed according to established EoE criteria (1,17). A detailed description of the SEED was published previously (18). Before inclusion, all patients gave their written consent, and this study was approved by the Ethics Commitee (EKNZ 2006/058). Inclusion criteria for this analysis were as follows: known year of the first appearance of EoE symptoms and known year of EoE affirmative diagnosis. In the case of missing data, a retrospective chart review was conducted. DD was defined as the interval between first occurrence of EoE symptoms and confirmed diagnosis.

To further evaluate the sources of the DD, we additionally performed a subanalysis focusing on the first medical contact after disease manifestation, the first contact with a gastroenterologist, and the number of esophagogastroduodenoscopies before diagnosis. Because these information are not included in the SEED, we randomly selected patients from each 5-year time interval (whenever possible 20 patients) and searched their medical records for the aforementioned data.

Statistical analysis

Statistical analysis was performed using R statistical software (version 4.0.3). Normal quantile-quantile plots were applied to visualize quantitative data distribution. Non-normally distributed data were presented as median, interquartile range (IQR), and range. For reasons of overview, age at symptom onset and at diagnosis was additionally grouped by 10-year intervals. Differences of numeric non-normally distributed data by (sub)groups were analyzed using the Kruskal-Wallis test. Categorical data were presented as number (n) and percentage (%) of group totals. A multivariate analysis of these variables was performed using the Cox proportional hazard regression model with DD, patients' characteristics and years. $P < 0.05$ was regarded as statistically significant.

RESULTS

Patient characteristics

At the time of the analysis, the SEED included 1,380 patients. After excluding missing data on symptom onset and/or date of confirmed diagnosis (n = 208 patients) as well as patients diagnosed incidentally and labeled asymptomatic (n = 20), 1,152 patients were included in the analysis. Most of the patients were males (857, 74%; median age at diagnosis: 38 years, IQR: 28–49, range: 1–86). Age at diagnosis showed a normal distribution with its peak between 30 and 40 years, with 25% of the study population being diagnosed with EoE during that period (Figure 1). The median age at symptom onset was 30 years (IQR: 18–43, range: 0–85). Fifty-one percent of patients first experienced EoE symptoms between the ages of 10 and 30 years. Individuals aged 10 years or younger and 51 years or older were less likely to first experience EoE symptoms when compared with those between 11 and 50 years (Figure 1).

Overall DD and its evolution over time

The median DD during the entire observational period of this study (1989–2021) was 4 years (IQR: 1–11, range, 0–56). Of note, one-third of the population (n = 363, 32%) had a DD of ≥10 years. Over time, DD did not change, neither when examined on an yearly basis ($P = 0.716$, Figure 2a) nor when DD was stratified into periods (1993–2007, 2008–2011, and 2012–2021) based on aforementioned EoE milestone publications ($P = 0.387$, Figure 2b). In addition, in all 3 time intervals, a persistently stable fraction of roughly one-third of all patients had a DD of ≥10 years (1993–2007: n = 85, 32%; 2008–2011: n = 124, 33%; 2021-2021: n = 154, 30%).

DD, sex, and age at the time of diagnosis

Overall, DD did not differ between sexes (Figure 3). However, the length of DD differed with age at the time of diagnosis. DD increased from a median of 0 years for persons aged 10 years or younger to 5 years for persons between 31 and 40 years ($P < 0.001$, Figure 3). When examining variation in DD based on age at symptom onset, we observed an inverse association of age at symptom onset and DD ($P < 0.001$, Figure 4), with longest DD observed in children.

DD and food bolus impaction before EoE diagnosis

One-third (n = 361, 31%) of the study population suffered from at least 1 food impaction requiring endoscopic removal before diagnosis. DD was longer in patients requiring endoscopic disimpaction before diagnosis when compared with patients who did not undergo endoscopic disimpaction (with endoscopic disimpaction median DD of 6 years, IQR: 2–14, range: 0–45; without endoscopic disimpaction: median DD of 3 years, IQR: 1–10, range: 0–56, $P < 0.001$).

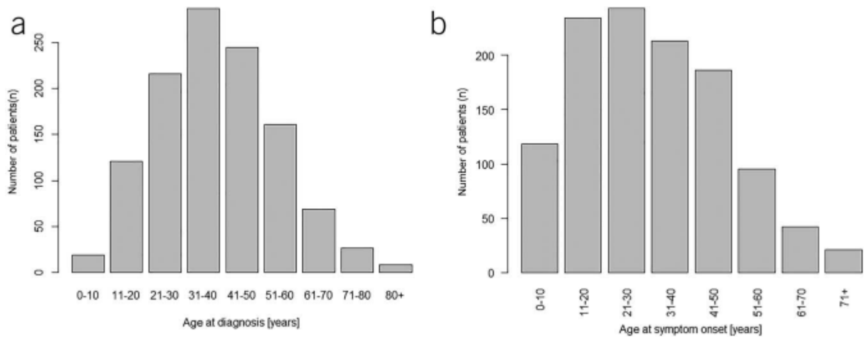

Figure 1. Distribution of patients grouped by 10-year intervals of age at diagnosis (**a**) and age at symptom onset (**b**).

DD according to concomitant atopic diseases

Three quarters (74%, n = 853) of the population had confirmed atopic conditions other than EoE. In the remaining patients, it was either not known whether patients had other atopic conditions (n = 146, 13%) or else patients did not suffer from concomitant atopic conditions (n = 153, 13%). When compared with patients without concomitant atopic conditions, patients with concomitant atopic conditions were younger at the time of symptom onset (with concomitant atopic condition: median age: 29 years, IQR: 17–41, range: 0–81; without concomitant atopic condition: median age: 34 years, IQR: 21–50, range: 0–85, $P < 0.001$) and at the time of diagnosis (with concomitant atopic condition: median age: 38 years, IQR: 28–47, range: 1–82; without concomitant atopic condition: median age: 41 years, IQR: 28–54, range: 3–86, $P < 0.001$). Diagnostic delay (DD) in patients without concomitant atopic conditions was shorter (median age: 3 years, IQR: 1–9, range: 0–45 vs median age: 5 years, IQR: 2–12, range: 0–56, $P < 0.001$).

Cox proportional hazards model

The multivariable analysis confirms the longer DD in patients with food bolus impaction. For details of all included variables, see Table 1.

DD in EoE variants

Two percent (n = 23) of this study population was diagnosed with EoE-like disease or lymphocytic esophagitis. Compared with classic EoE, DD in EoE variants did not significantly differ (classic EoE: median: 4 years, IQR: 1–11, range, 0–56; EoE variants: median: 3 years, IQR: 2–6.5, range: 0–23, $P = 0.704$).

Analysis of patient and gastroenterologist DD

In a subanalysis, we reviewed the medical charts of 123 patients, accounting for 10.7% of the entire cohort (male: 97 [79%], median age 38 years, range: 11–79). No robust data were found concerning the first medical consultation (with any type of physician) after the manifestation of symptoms. In this subgroup, 38 patients (31%) were evaluated by a gastroenterologist before diagnosis (gastroenterologist-related DD). Thirty-five of these patients (97%) received at least 1 esophagogastroduodenoscopy (range 1–5), with biopsies obtained in 17%. In the remaining 85 patients (69%), diagnosis was made at the first contact with a gastroenterologist (patient-related delay).

DISCUSSION

In our study, we demonstrated that, despite considerable research (>2,000 publication on EoE on PubMed [www.pubmed.gov]

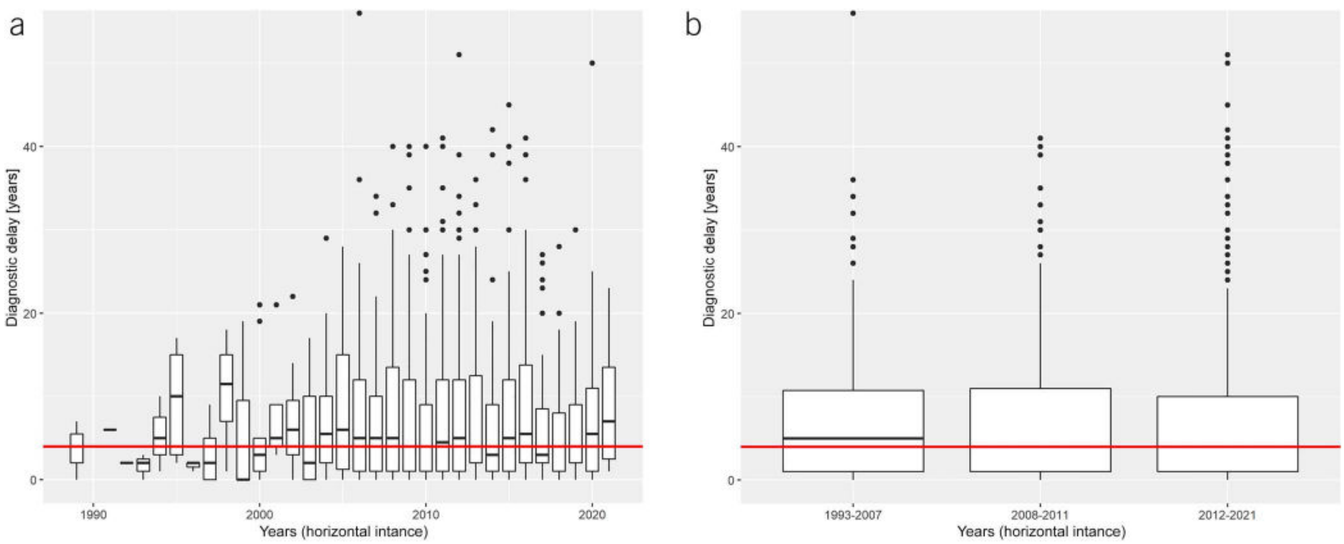

Figure 2. Diagnostic delay visualized over the entire observational period from 1989 to 2021 (**a**) and according to milestone publications (**b**). The red line represents the overall median diagnostic delay of 4 years.

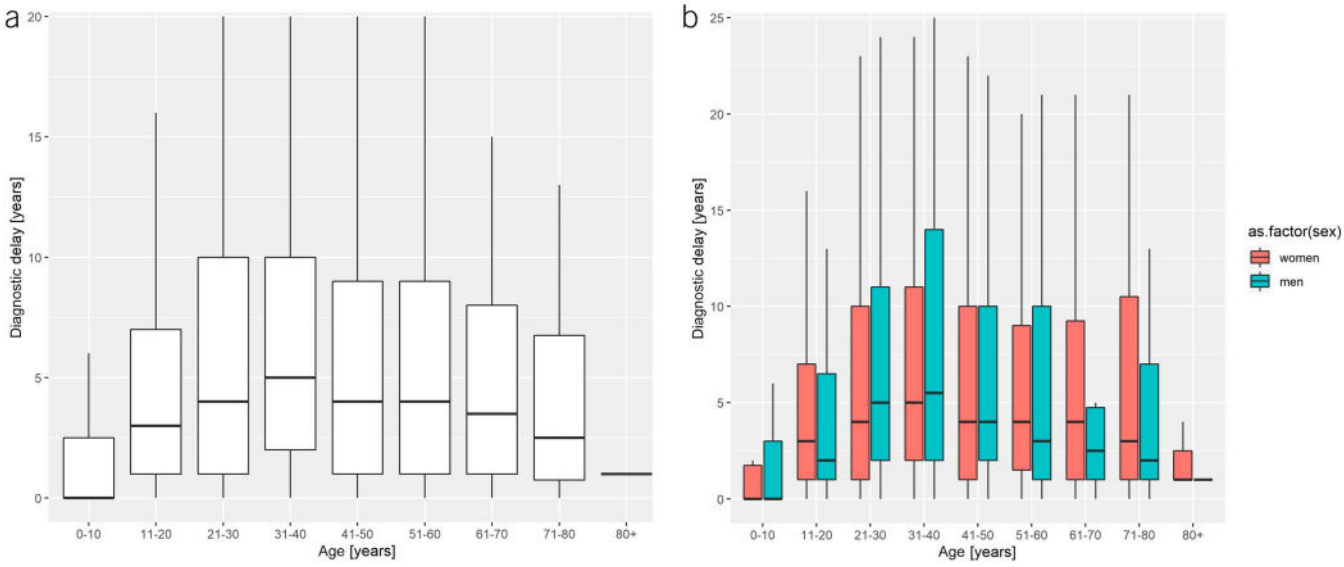

Figure 3 . Diagnostic delay according to age at diagnosis visualized in 10-year intervals. (**b**) represents the same values as (**a**) further divided into women (red) and men (green).

since 2014) and numerous educational events in recent years, the DD has not changed since the first description of EoE almost 30 years ago. In fact, DD remains substantial with an overall median delay of 4 years, comparable with that described in previously published studies from Europe and the United States (5,19–21). In addition, approximately one-third of patients with EoE have a DD of ≥10 years. Bearing in mind that EoE is a chronic and progressive disease, which, if left untreated, leads to esophageal stricturing ultimately, causing food impaction, the results of our analysis are a cause for concern (5,20,22).

Esophageal remodeling not only causes symptoms such as dysphagia but also is responsible for food bolus impactions (20,23). Importantly, the length of DD (untreated disease) directly correlates with the occurrence of esophageal strictures (5). Schoepfer et al. (5) showed that the prevalence of strictures increases from 17% to 71% in patients with a delay between 0 and 2

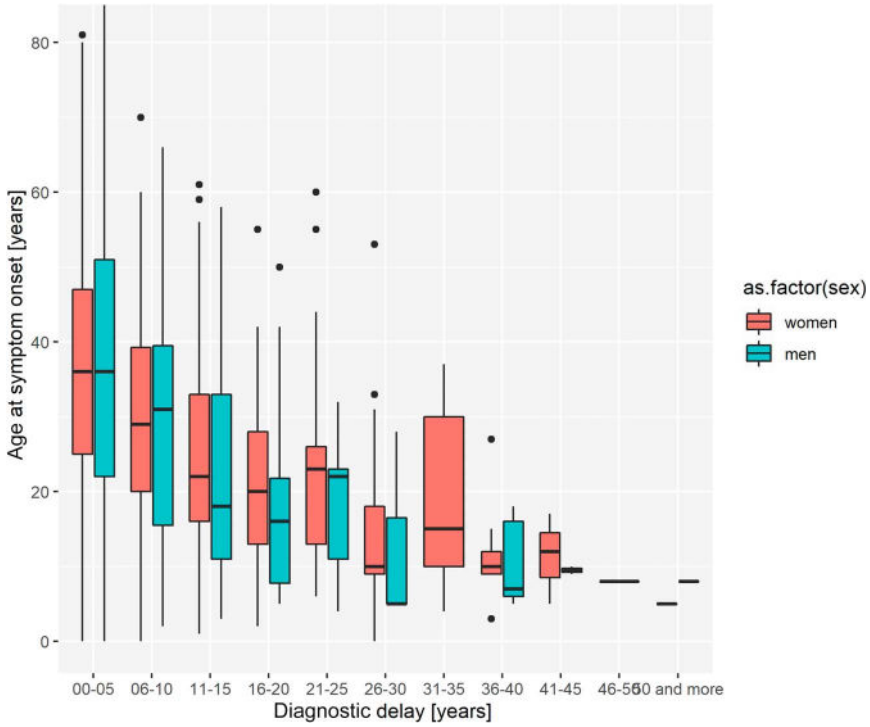

Figure 4 . Diagnostic delay according to age at symptom onset grouped in 5-year intervals and further visualized according to sex (red = women, green = men).

Table 1. Cox proportional hazards: diagnostic delay by patient characteristic/variable and year

		95% confidence interval		
Univariable	**HR**	**Lower limit: 2.5%**	**Upper limit: 97.5%**	***P* value**
Age at diagnosis	0.99	0.98	0.99	<0.001
Sex (m/f)	0.96	0.84	1.10	0.593
Year	0.99	0.98	1.01	0.387
Bolus impaction (y/n)	0.76	0.67	0.86	<0.001
Atopic disease (y/n)	0.78	0.68	0.89	<0.001
Age*atopic disease	—	—	—	—
		95% confidence interval		
Multivariable	**HR**	**Lower limit: 2.5%**	**Upper limit: 97.5%**	***P* value**
Age at diagnosis	0.99	0.98	0.99	0.014
Sex (m/f)	1.01	0.88	1.15	0.920
Year	0.99	0.98	1.01	0.555
Bolus impaction (y/n)	0.76	0.67	0.86	<0.001
Atopic disease (y/n)	0.95	0.64	1.40	0.787
Age*atopic disease	0.99	0.99	1.00	0.204

f, female; HR, hazard ratio; m, male; n, no; y, yes.

years and >20 years ($P < 0.001$). Esophageal strictures were present in around 38% of patients with a delay between 8 and 11 years, a delay that is prevalent in approximately one-third of our study population. However, even a median delay of 4 years resulted in strictures in around 31% of untreated patients (5). This was just recently confirmed by Lenti et al. (10), who reported a significantly longer median DD in patients with EoE complications (complications present in 14% of the study population; 92% of these were strictures) when compared with patients without EoE complications (60 vs 35 months). The risk of esophageal strictures seems to increase by as much as 9% with each year of untreated EoE (20). Thus, reducing the DD in patients with EoE is of importance.

One reason for the persisting long DD might be the patient-dependent delay, defined by the period from the occurrence of first symptoms to the initial medical evaluation. In a recently published retrospective, multicenter study including 261 consecutive Italian patients over a period of 5 years (10), the overall DD was 3 years (IQR 12–88; DD > 10 years in 15% of the population). The patient-dependent delay was significantly longer (median: 18 months, IQR 5–49) than the physician-dependent delay (median: 6 months, IQR 1–24), giving evidence that part of the observed overall delay results from patients coping with (i.e., changes in diet and/or eating behavior) or denying symptoms—sometimes for years. There is a lack of information regarding the first medical contact because of EoE-like symptoms in our database, which hinders us to state on the patient-dependent delay. This is unfortunate because in our personal experience, the patient-dependent delay plays a critical role in the overall DD. However, in our subsequently conducted extensive subgroup analysis, we were able to deduce that patients (or a physician other than a gastroenterologist) are responsible for the largest part of the overall DD. This fact indicates that future efforts should target the general population and potentially primary physicians to strengthen the awareness for EoE as a potential underlying condition in patients with dysphagia. Regarding the patient-dependent delay, future studies should also try to analyze the type of coping behavior and its influence on the delay. Nowadays, even a substantial change in diet may not necessarily be suspicious for underlying dysphagia. However, a change in eating behavior, especially in cases with prolonged chewing, slow swallowing, or even the necessity of drinking fluids after swallowing of solid food, should raise suspicion also in the general population.

Analyzing age at symptom onset (51% younger than 31 years and 30% younger than 21 years) once more illustrates that EoE affects young individuals. This is of major clinical relevance because young age (at onset of symptoms and at diagnosis) was associated with long DD confirming previously published data (5,20). It is likely that young patients (age younger than 10 years at symptom onset in 10% of patients in our population) face many hurdles that undoubtedly lead to increased length of DD in this population. They may have difficulties reporting their symptoms. While in adolescent and adult EoE patients, solid food dysphagia is the most common symptom, younger children may also experience regurgitations, emesis, abdominal pain, failure to thrive, and food refusal (20,24). Finally, the standard clinical management of young patients differs from adults, and when compared with adult population, endoscopic investigations are performed less frequently in the pediatric population for safety and logistic reasons (i.e., necessity of general anesthesia). Nevertheless, solid food dysphagia should be regarded as an alarming symptom in all age groups and should lead to endoscopic examination.

Just as in our analysis, Lenti et al (10) reported that patients who experienced food bolus impactions have longer DD than patients who did not. It is likely that EoE diagnosis is missed in individuals who might have relatively mild endoscopic presentation and are not biopsied. However, in our own experience, this patient group often consists of patients who are specifically at risk to notoriously and stoically cope for years with dysphagia

using various behavioral adaptations. In addition, history taking in these patients may unfortunately often be only superficial and inadequate. In these individuals, untreated EoE ultimately leads to strictures and food impactions, which often (in our experience) resemble the first contact to a gastroenterologist.

Concomitant atopic conditions are known to be associated with the diagnosis of EoE in all age groups, including the very young children (25,26). Especially in children with a symptom complex of atopy and vomiting or failure to thrive, further diagnostic workup to rule out EoE should be considered (25). In our study population, 3 quarters (74%) had atopic features, confirming the association of atopy and EoE. Median DD in patients without atopy seemed to be shorter than that in patients with atopy. However, after adjusting for age, the difference in DD between the 2 groups was not significant anymore, which is most likely explained by the significant younger median age of patients with atopy, which was shown to be associated with a longer DD. The last objective in our analysis was EoE variants. Those manifest clinically just as the classic EoE and, therefore, lead to similar diagnostic management, explaining similar lengths of DD in both groups.

The reasons for the persisting long DD are multifactorial. Lenti et al (10) argued that the vast clinical picture of EoE with differing symptoms is probably the most important influencing factor, but that argument is more likely to be relevant for pediatric than adult patients with EoE. In addition, the urge to seek medical advice because of symptoms suggestive for gastroesophageal reflux disease (GERD), a condition not always easily distinguishable from EoE, is influenced by symptom-related and patient-related factors (27,28). Mild symptoms, for example, lead to the underestimation of symptoms, both by patients and physicians. Especially if behavior changes (i.e., diet or drinking of water with solid food) decrease the severity of complaints to some extent, patients do not seek medical advice. Even if they do, physicians might not schedule further potentially invasive diagnostic workup (biopsies) in those cases. In addition, typical symptoms of GERD can be mimicked by EoE (inflammation can induce acid hypersensitivity), and the standard GERD therapy with proton pump inhibitors can also reduce symptoms caused by EoE (29–31). One additional physician-related factor contributing to the persisting long DD is that physicians do not obtain esophageal biopsies during upper endoscopy for the purposes of diagnostic exploration even in the event of prior food impaction in an apparently healthy patient. Endoscopic findings are often prematurely rated as normal or else are normal during index endoscopy resulting in a missed chance for diagnosis and loss to follow-up (in up to 50% of patients) (32,33). In fact, it is of utmost importance to keep in mind that endoscopic features of EoE vary, ranging from classic features such as exudates, rings, edema, furrows, strictures, and narrowing or crepe-paper mucosae to completely normal-appearing mucosae (1,34). In addition, endoscopic findings of whitish plaque-like lesions may be interpreted as esophageal candidiasis or as white exudates, both potentially expressing similar symptoms (35). Because the specificity of endoscopic diagnosis of Candida is at most 80%, histopathologic confirmation is essential (35,36). In addition, patients with esophageal motility disorders are at risk to develop esophageal candidiasis, adding another argument to obtain biopsies whenever the endoscopist sees white exudates and, especially, if the leading symptom is dysphagia (37). Krarup et al (34) recently demonstrated that prospectively implementing a biopsy protocol during the diagnostic workup for patients with dysphagia, regardless of the endoscopic appearance of the esophagus, resulted in doubling of the number of biopsies obtained per patient, and the EoE detection rate increased 50-fold per year. Remarkably, one-third of all patients with EoE had a macroscopically normal-appearing esophagus but eventually received diagnosis and treatment as a consequence of the biopsies obtained.

We, unfortunately, do not have a precise understanding of a potential influence of the type of physician that the patients first seek medical advice from. It seems obvious that general practitioners are not as familiar with EoE and its symptoms as gastroenterologists. But even amongst gastroenterologists the knowledge of an accurate diagnosis of EoE is not optimal. Unfortunately, our database neither includes the type of physician at the first medical attendance nor (in the case of gastroenterologists) information regarding the education or location of practice (e.g., specialty center vs rural practice). Future studies should try to implement these factors to implement tailored educational programs.

Our study has several limitations and strengths. One limitation is its retrospective design and the confinement to a single country. In addition, we were not able to dissect the patient-related delay from the physician-related one. Furthermore, the exact time point of symptom manifestation could only be estimated to a certain year in many cases. Strengths of this study are that the analysis was performed using a large number of patients with EoE who were recruited over a long period.

With a North-South diameter of 220 km and a West-East diameter of 350 km, Switzerland is geographically a small country located in the middle of Europe and has currently a population of approximately 8.8 million inhabitants. There exists a tight network of medical services with 52.3 hospitals per 1 million inhabitants and 4.5 active physicians per 1,000 inhabitants. Family doctors, specialists, and hospitals are, therefore, easily accessible. The national gastroenterology service is provided by around 430 board-certified gastroenterologists (240 in a private practice, 190 in hospitals). Of note, in Switzerland, health insurance is mandatory by law for all inhabitants independent of their socioeconomic status. Ninety percent of the costs for medical services are covered by the insurances. We do not know the proportion of referred in the SEED. However, considering a pooled prevalence of 34 of 100,000 cases (4), around 3,000 people in Switzerland should be affected by EoE, and with 1,380 patients included, the SEED is a representative cross-section of Swiss EoE patients, allowing the conclusion that the DD remains high (DD in one-third of patients older than 10 years) in Switzerland. Improving awareness through educational events not only for patients and parents but also for primary physicians with special focus on the young generation; sending all patients with solid food dysphagia, regardless of their age, for endoscopy; and adapting protocols to obtain several biopsies separately in the distal and proximal esophagus in all patients with dysphagia are steps needed to be taken to shorten DD in Switzerland.

CONFLICTS OF INTEREST

Guarantor of the article: Fritz R. Murray, MD.
Specific author contributions: F.R.M. and A.S.K.: conceptualization, formal analysis, and writing of the original manuscript. T.G., S.N., C.S., C. Schlag, A.M.S., and P.S.: review and editing. S.N.: review and editing. E.S.: review and editing. A.S.: conceptualization, data curation, formal analysis, and writing and editing. L.B.: formal analysis and writing and editing.

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Study Highlights

WHAT IS KNOWN

- ✓ Eosinophilic esophagitis (EoE) is a progressive disease resulting in an increased risk of fibrostenotic disease and esophageal food impactions in patients with longer diagnostic delay.
- ✓ Although the number of published literature in EoE is increasing rapidly, it is unknown whether this higher awareness results in a shorter diagnostic delay.

WHAT IS NEW HERE

- ✓ Median diagnostic delay was 4 years and did not change over time.
- ✓ One-third of patients had a diagnostic delay of more than 10 years.
- ✓ Diagnostic delay was not different between men and women, but differed between age at symptom onset.

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