

Comparison of clinical features in patients with eosinophilic esophagitis living in an urban and rural environment

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SUMMARY. Eosinophilic esophagitis (EoE) has been associated with exposure to aeroallergens. Living in different locations (urban vs. rural) could potentially expose individuals to different environmental factors. Currently, there is limited data on the matter, and all was based on small population studies that did not exclude proton pump inhibitor (PPI)-responsive esophageal eosinophilia in their cohort. The primary aim of this study was to determine the prevalence of EoE in an urban versus rural population and compare demographic and clinical characteristics in patients that had been treated with high-dose PPI prior to diagnosis. Esophageal biopsies were obtained from a cohort of patients who presented with symptoms of dysphagia, odynophagia, globus sensation, and heartburn during a 10-year period. Only patients who had biopsies from the mid and distal esophagus with ≥ 20 eosinophils per high-power field while on high-dose PPI treatment during endoscopy were included. Urban population was defined as >1000 people/square mile, and rural population was defined as ≤ 1000 people/square mile (U.S. Census Bureau). Demographic data from each group was analyzed for age, sex, body mass index, duration of symptoms, and tobacco use. Chi-square analysis was used for frequencies with statistical significance defined as $P \leq 0.05$. A total of 20 718 patients were identified and their records evaluated. From this cohort, 57 (0.28%) symptomatic patients (male/female: 39/18, mean age = 29.5 years) had biopsy-proven EoE (≥ 20 eosinophils/hpf) while on PPI treatment. Of those EoE patients, 29 (50.9%) reported living in rural area versus 28 (49.1%) living in the urban area. The most common medical history components included asthma (12.3%), and the most common presenting symptoms included dysphagia (50.9%), heartburn (26.3%), and nausea/vomiting (22.8%). The average duration of symptoms, body mass index, and smoking habits did not differ between the groups. Dysphagia was significantly more prevalent in the urban population (37.9% vs. 64.3% $P = 0.047$), while heartburn and reflux were more prevalent in the rural population (37.9% vs. 14.3% $P = 0.043$). Asthma was prevalent in both populations without a significant difference ($P =$ not significant). There is no residential variation in the incidence of EoE among patients with non-PPI-responsive esophageal eosinophilia. Dysphagia was more prevalent in the urban population, while heartburn and reflux symptoms were more prevalent in the rural environment. Further exploration of environmental factors and specific allergens may help explain the varying symptoms and causes of EoE.

KEY WORDS: aeroallergen, environment, migration, PPI-responsive esophageal eosinophilia.

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INTRODUCTION

Eosinophilic esophagitis (EoE) was primarily reported by Landres *et al.* in 1978 and since then has been increasingly recognized as one of the major etiologies for dysphagia, food impaction, and food regurgitation.^{1–3} Its prevalence is estimated to be 0.4% in an asymptomatic adult population.⁴ Among patients undergoing outpatient upper endoscopy for any indication, the prevalence of EoE varies between 5% and 16%, and is highest in patients with dysphagia.^{5,6} The proposed diagnostic criteria for EoE includes demonstration of ≥ 15 eosinophils per high-power field (HPF) in the esophageal epithelium.⁷ Although true pathophysiology of EoE remains unknown, the literature has attributed the main etiology of EoE to allergic and genetic causes.^{8–10}

Many studies have investigated epidemiologic and endoscopic characteristics of the disease and suggest that EoE is more prominent in male children and young adults commonly associated with a personal and family history of allergic conditions.^{11–15} EoE is also reported to be more prevalent in urban areas.¹⁶ The reported geographic prevalence of EoE appears to be worldwide including the United States, Europe, Asia, and Middle East, and is increasing likely because of both increased recognition and incidence.^{17–25} However, there is insufficient data regarding specific factors that contribute to the development of EoE. Immune and allergic disorders such as asthma as well as exposure to aeroallergens have been reported to be associated with the development of EoE. There is limited data exploring the effects of regional variation such as urban versus rural environment on EoE incidence. Our hypothesis was that residing in different environments may affect prevalence and demographic characteristics of EoE by potentially exposing individuals to different factors. In recent years, studies have demonstrated the effectiveness of proton pump inhibitors (PPIs) in reducing symptoms and histopathology in a subset of patients with esophageal eosinophilia and suspected EoE. Patients with a density of eosinophils < 15 /hpf after PPI therapy are categorized as PPI-responsive esophageal eosinophilia (PPI-REE).^{26,27} As a tertiary referral center and main pathology laboratory of the state of Iowa, the aim of our study was to investigate prevalence of EoE in both rural and urban non-PPI-REE cohort and compare demographic characteristics in both population groups.

MATERIALS AND METHODS

Study design

We retrospectively evaluated electronic records using the current procedural terminology code for upper endoscopies performed for patients for due to dysphagia, odynophagia, globus sensation, and heart-

burn at the Digestive Disease Center at the University of Iowa Hospitals Clinics from May 2003 through January 2013. The study was approved by the University of Iowa Hospitals and Clinics Institutional Review Board.

Previous studies have defined EoE as the presence of eosinophil numbers of > 20 /hpf in squamous epithelium at any of the levels, and current guidelines adapted ≥ 15 /hpf in multiple levels as sufficient for diagnosis.^{28,29} This definition was adopted by our pathology laboratory, and we undertook this study from the starting point of the histopathologic finding of ≥ 20 eosinophils/hpf in a biopsy from esophageal squamous epithelium when we searched our patient data.

Our pathology laboratory has coded for the last decade all esophageal biopsies from the distal and mid-esophagus with ≥ 20 eosinophils/hpf as EoE. A single microscopic field with the highest eosinophilic infiltration was used for diagnostic evaluation at $\times 400$ power field of microscopic analysis equals 0.24 mm^2 . The diagnosis of EoE was defined by the presence of the following histological features: (i) peak eosinophil counts ≥ 15 – 20 /hpf; (ii) eosinophil microabscess; (iii) superficial layering of eosinophils; (iv) basal cell hyperplasia; (v) extracellular eosinophil granules; and (vi) subepithelial or lamina propria fibrosis. Demographic data from each group were analyzed for age at diagnosis, gender, body mass index (BMI), duration of symptoms, past medical history, presenting symptoms, tobacco use (including both current and/or former use), and use of PPI prior to endoscopy. All presenting symptoms and allergy history were obtained from the initial primary care or gastroenterology clinic note. The use of PPI therapy was based upon prescriptions in our electronic medical record or documentation of such therapy in clinic notes, and only patients treated with high-dose PPI (omeprazole 40 mg every day, or equivalent) ≥ 4 weeks prior to endoscopy were included in the study. Patients were excluded if there was inadequate chart information from which to extrapolate the aforementioned data. Date of diagnosis was the date of first esophageal biopsy showing EoE features.

Demographics

Patients were assigned to the urban or the rural group based on the primary address for the patient available in the electronic medical records. Rural versus urban area was defined using the U.S. Census Bureau 2010 Urban and Rural Classification System. The system defines urban population as > 1000 people/square mile and defines rural population as ≤ 1000 people/square mile.³⁰ We excluded patients that moved in and out of their county within 4 years prior to diagnosis. BMI categories were further divided into three groups (BMI < 25 , BMI 25–30, and BMI > 30) at diagnosis.

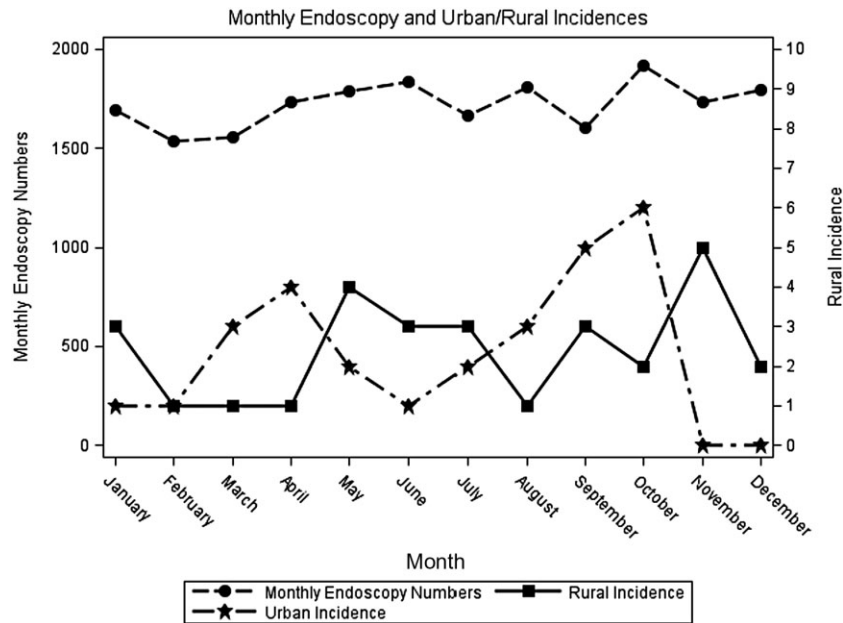


Fig. 1 Monthly endoscopy rates and incidence of eosinophilic esophagitis (EoE) among rural and urban population.

Statistical analysis

Patient characteristics were analyzed as follows: continuous variable of age using *t*-test and analysis of variance, and categorical/frequency variables (gender, race, rural/urban locale, presenting symptoms, medical history, and BMI) with chi-square test or Fisher's exact test in the case of having cells with small frequencies. SAS 9.3 was used for statistical analysis (2011, SAS Institute, Cary, NC, USA).

RESULTS

A total of 20 718 patients were identified and their records evaluated. From this cohort, 57 (0.28%) symptomatic patients had biopsy proven EoE (≥ 20 eosinophils/hpf) while on ≥ 4 weeks of high-dose PPI treatment. A total of 29 (50.9%) patients reported living in rural area versus 28 (49.1%) in urban area, demonstrating no significant difference in the incidence of EoE between these populations. The male : female ratio was 2:1, with 39 males (68.4%)

and 18 females (31.6%). The mean age of diagnosis was 26.7 years (standard deviation = 17.2). Our population included 91.2% Caucasians. There was no significant difference between the monthly endoscopy rates and incidence of EoE among rural and urban population (Fig. 1). The average duration and treatment of symptoms prior to diagnosis did not significantly differ among the groups (Table 1). Both rural and urban adult groups did not differ in BMI (24 ± 8.2 vs. 27 ± 11.7 , $P = 0.271$) or smoking habits (13.8% vs. 18.5%, $P = 0.725$, respectively). We did not find a significant difference between the mean ages at diagnosis and different BMI categories (<25, 25–30, and >30). In addition, there was no significant difference in age at diagnosis between rural and urban population (24.7 ± 20 vs. 28.7 ± 13.8 , $P = 0.388$) (Table 1).

Dysphagia was significantly more prevalent in the urban population (37.9% vs. 64.3% $P = 0.047$), while heartburn and reflux were more prevalent in the rural population (37.9% vs. 14.3% $P = 0.043$). The most common medical history component in the rural and urban population included asthma (6.9% vs. 17.9%, $P = 0.253$) (Table 2). Other presenting

Table 1 Patient demographics and characteristics

	Total cohort	Rural	Urban	P-value
Number of patients	57	29 (50.9%)	28 (49.1%)	
Male	39 (68.4%)	19 (65.5%)	20 (71.4%)	0.631
Age at diagnosis, mean (SD)	26.7 (17.2)	24.7 (20.0)	28.7 (13.8)	0.388
Smokers	9 (15.7%)	4 (13.8%)	5 (17.9%)	0.725
BMI (SD)	25.5 (10.1)	24.0 (8.2)	27.0 (11.7)	0.271
Caucasian	52 (91.2%)	27 (93.1%)	25 (89.3%)	0.670
Average PPI treatment duration in months (SD)	19.7 (31.4)	20.4 (27.1)	18.9 (35.8)	0.854

BMI, body mass index; PPI, proton pump inhibitor; SD, standard deviation.

Table 2 Medical history

Medical history	Total	Rural	Urban	P-value
Asthma	7 (12.3%)	2 (6.9%)	5 (17.9%)	0.253
Food allergy	2 (3.5%)	0 (0.0%)	2 (7.1%)	0.237
Seasonal allergy	1 (1.8%)	0 (0.0%)	1 (3.6%)	0.491
Allergic rhinitis	1 (1.8%)	0 (0.0%)	1 (3.6%)	0.491

symptoms like regurgitation, nausea, food impaction, and globus sensation did not differ between the groups (Table 3).

DISCUSSION

Our study shows a 0.28% prevalence of EoE in our cohort, which is less than the estimated prevalence of EoE in asymptomatic patients or with dysphagia (~4%).⁴ In view of current data, the consensus is to include only non-PPI-REE patients in any EoE study cohort; hence, a trial of PPI therapy remains an important prerequisite to the diagnosis EoE.³¹ Our study is unique by the fact we are the first to evaluate the effect of residential variation on the incidence of a non-PPI-REE cohort.

Our study did not find any statistical difference in the incidence of EoE in a rural versus an urban environment (50.9% vs. 49.1%). Our study population encompassed a large, homogenous, mainly Caucasian (90.4%) upper Midwest cohort of patients with a low migratory profile, similar to the state of Iowa general population. According to the 2010 Census, 91.3% of the population of Iowa was Caucasian, 5.0% was of Hispanic or Latino origin, 2.9% Black or African-American, and all the rest were American Indian and Alaska Native, Asian, Native Hawaiian, and other Pacific Islander.³² Our study confirmed that EoE tends to occur in younger populations (median age 27) and is more frequent in men (68.2%) than women (31.8%) as seen in previous studies.^{33,34} However, we did not find any significant gender or age differences among the different populations.

The nature of our study merits comparison with the previous study done by Franciosi *et al.*, which investigated sociodemographic and geographic characteristics of children with EoE.³⁵ Their study included

only pediatric population as opposed to adult population in our study and also showed that EoE patients were predominantly Caucasian and male. One of differences in our study was that we did not use a matched control population group. In addition, the Franciosi study demonstrated that EoE subjects were more affluent, educated, and resided in suburban areas. This is a contrast to our finding that showed no residential variation in the incidence of EoE. Furthermore, the Franciosi study noted that Caucasian race was a significant confounding variable that accounted for geographic differences among EoE subjects. However, given the homogeneity of Iowan population with above 90% of the population being Caucasian, the race was not considered to be a confounder in our study.

Another major difference from the Franciosi study is that we examined associated presenting symptoms of EoE in our cohorts (Table 3). Interestingly, dysphagia was significantly more prevalent in the urban population ($P = 0.047$), while heartburn and reflux were more prevalent in the rural population ($P = 0.043$). This difference could be possibly explained by a relative lack of access to gastroenterologists in the rural area. As heartburn and reflux are relatively less of alarming symptom compared with dysphagia, patients presenting with heartburn and reflux in the rural area are likely managed by their primary care doctors for a longer duration of time before they are referred to gastroenterologists. In contrast, patients in the urban area who have easier access to subspecialists are likely referred to gastroenterologists earlier.

Other presenting symptoms like regurgitation, nausea, and globus sensation did not differ between the groups. Food bolus impaction is more commonly seen in adult patients, and EoE is becoming a more common etiology.^{36,37} However, although the age of presentation is becoming younger with an increased prevalence of EoE, thus far most studies did not differentiate the groups to PPI-REE and non-PPI-REE. In our study, food bolus impaction was prevalent in only 17.5% of our population. This is low compared with previous studies, and we hypothesize that the low prevalence is due to a long average duration of PPI treatment prior to diagnosis, hence decreasing the severity of symptoms.

Table 3 Presenting symptoms

Symptoms	Total	Rural	Urban	P-value
Dysphagia	29 (50.9%)	11 (37.9%)	18 (64.3%)	0.047*
Heartburn/reflux	15 (26.3%)	11 (37.9%)	4 (14.3%)	0.043*
Regurgitation	8 (14.0%)	3 (10.3%)	5 (17.9%)	0.470
Nausea/vomiting	13 (22.8%)	8 (27.6%)	5 (17.9%)	0.382
Food impaction	10 (17.5%)	5 (17.2%)	5 (17.9%)	1.000
Globus sensation	5 (8.8%)	3 (10.3%)	2 (7.1%)	1.000

* is clinically significant, less than 0.05.

As demonstrated in previous studies, the prevalence of asthma, food, and/or seasonal allergens appears to be associated with EoE in our population as well. This supports an allergy-mediated pathophysiology for EoE.^{38,39} We did not find a difference in the prevalence of asthma, food allergy, seasonal allergy, or allergic rhinitis between the groups.

We evaluated BMI and prevalence of smoking in our adult population (age ≥ 18 years). BMI was evaluated only in the adult populations because of the fact that the weight in the pediatric population has to be adjusted to percentile scales, hence hampering any statistical analysis when combined with adult population as a uniform group. In our adult cohort, the median BMI was 25.5, defined as overweight. We did not find a significant difference between the mean ages at diagnosis and different BMI categories (<25, 25–30, and >30). Because of the fact that the average age of diagnosis was similar among all BMI subgroups, we assume that there is no correlation between obesity and the development of EoE. This finding is in contrast to gastroesophageal reflux disease (GERD), where there is a known correlation between obesity and disease development.⁴⁰ The prevalence of smokers was the same among both populations (11.4% vs. 12.5%, $P =$ not significant) and is lower than the average U.S. prevalence (~19%).⁴¹ This fact implies that smoking probably does not attribute to development of EoE.

One weakness of our study is that we may have not captured all of the patients with EoE if they were referred to other surrounding medical centers. Another potential weakness of our study is the fact that our cohort encompassed upper gastrointestinal symptoms including globus sensation and GERD that may have influenced our relatively low prevalence. Although most of Iowa habitants reside in urban areas, the vast majority of the state is rural environment.³⁰ Thus far, most of the population studies in the literature were conducted mostly on urban area populations, and contrasting incidence and prevalence of EoE in rural areas possibly could have been overlooked until now. Despite our non-PPI-REE study, we are aware of the emerging difficulties in the differentiation between true EoE and esophageal eosinophilia. Thus far, the interaction among EoE, GERD, and PPI therapy has not been totally understood. Whether these patients represent a subphenotype of GERD, EoE, or a combined mechanism of both disorders remains unknown. Currently, no histological specific features, pH esophageal monitoring, nor quantitative immunohistochemistry for mast cells are capable to differentiate between the groups.⁴² Although current guidelines do suggest a PPI trial prior to diagnosis, there is a lack of consensus on the assumption that a positive response to PPI therapy distinguishes EoE from GERD.⁴³

The unique strength of our study is that our cohort had low migration profiles from their original childhood residential area, which stabilizes a patient's exposure to the same allergens confined to their environment prior to and during the development of EoE. As evidence, Iowa's net migration rate change in year 2000–2009 ranged from –2.8% to 1.2% per U.S. Bureau of the Census.³² Hence, there may be specific allergens that trigger EoE in distinct environments.

A complete patient's profile assessment analyzing the sensitization to common inhalant and food allergens and patch test for food allergens demonstrated an increase of sensitization to aeroallergens, in particular ages ≥ 4 in patients with EoE, and a decrease of sensitization to food allergens with increasing age.^{44,45} We tried to differentiate zones by their agricultural products (wheat vs. corn), but could not find distinctive patterns.

Currently, we are trying to specify local allergens that lead to development of EoE of varying severities and symptoms. Further exploration of environmental factors and specific allergens may help to understand the causes of EoE. Despite our findings of lack of residential variation, we still do believe that different allergens in distinct environments play a role in predisposing patients to developing EoE of varying severity and complications, and patients may need different treatment approaches based on their living environment. These aspects of our hypothesis merit further investigation.

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