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Obesity and hiatal hernia may be non-allergic risk factors for esophageal eosinophilia in Japanese adults

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Short title: Risk factors for esophageal eosinophilia

Abstract

Background

Esophageal eosinophilia (EE) is a basal condition of eosinophilic esophageal disorders including eosinophilic esophagitis (EoE) and asymptomatic EE. EoE is considered as an allergic disorder, while it is unclear whether other non-allergic conditions are involved in the pathophysiology of EE. The aim of this study is to investigate the non-allergic risk factors for EE.

Methods

This cross-sectional study included subjects who underwent esophagogastroduodenoscopy on a medical health check-up. We compared clinical characteristics between subjects with EE (n=27) and those without EE (n=5,937).

Results

The detection rate of EE was 0.45% (27/5,964 persons). Of 27 subjects with EE, 20 subjects were symptomatic and 7 were asymptomatic. On univariate analysis, subjects with EE significantly had higher body mass index (BMI) compared to those without EE; 23.4 (4.4) vs 22.3 (4.5) kg/m^2, median (interquartile range), p=0.005. Endoscopic findings revealed that subjects with EE had significantly higher proportion of hiatal hernia (29.6% vs 14.7%; p=0.049). Subjects with EE were significantly younger and had higher proportion of bronchial asthma; 45 (11.5) vs 51 (18) years, p=0.013; 25.9% vs 5.2%, p<0.001, respectively. Multivariate analysis showed that subjects with EE were positively associated with BMI (odds ratio [OR], 1.11; 95% confidence interval [CI], 1.03-1.20; p=0.010) and hiatal hernia (OR, 2.63; 95% CI, 1.12-6.18; p=0.026) compared to those without EE. On trend test, advanced BMI classification had significant trend for increased prevalence of EE (p=0.002).

Conclusions

Obesity and hiatal hernia may be non-allergic risk factors for EE in Japanese adults.

Keywords

Eosinophilic esophagitis, Obesity, Body mass index, Hiatal hernia, Gastroesophageal reflux

Introduction

Eosinophilic esophagitis (EoE) is considered a chronic, allergic, and immune-mediated disorder clinically characterized by eosinophilic infiltration of the esophageal mucosa and symptoms of esophageal dysfunction caused by esophageal eosinophilia (EE) [1, 2]. The prevalence of EoE is increasing worldwide and some studies have estimated the prevalence as between 10 to 50 per 100,000 persons in the United States and Europe [3-6] and between 14.7 to 17.1 per 100,000 persons in Japan [7, 8].

The pathogenesis of EoE is based on environmental factors, genetic predisposition, and impaired barrier function. The environmental factors at an early age, including birth by cesarean section, antibiotic exposure during infancy, and lack of breast-feeding, may alter the immune system and increase the probability of developing EoE [9]. Lack of early exposure to microbiome and altered microbiome may play a role in the development of EoE as well as other allergic diseases such as bronchial asthma and atopic dermatitis [10]. EoE is also an allergic disorder; therefore, food antigens and inhaled aeroallergens may be involved in its pathogenesis [11].

On the other hand, in clinical settings, we sometimes encounter cases of asymptomatic EE and a previous report indicated that 80.6% of individuals with EE did not have any upper gastrointestinal symptoms in Shanghai, China, in 2015 [12]. Although asymptomatic EE may be related to EoE, whether asymptomatic EE is a preclinical phase of EoE is unknown. EE is the basal condition of eosinophilic esophageal disorders including EoE and asymptomatic EE. Therefore, it is important to know the risk factors for EE to understand the pathogenesis of eosinophilic esophageal disorders. EoE is considered as an allergic disorder, while it is unclear whether other non-allergic conditions are involved in the pathophysiology of EE.

Previous reports indicated that it is possible for EE and gastroesophageal reflux disease (GERD) to have overlapping clinical and histological features and to partially share pathogenic pathways [13-15]. In GERD, EE is considered a part of the chronic inflammatory response to acid reflux. Reflux-induced dilation of intercellular spaces in the epithelium facilitates dendritic cell and antigen movement through the mucosa [16]. Local production of eosinophil-attracting substances such as platelet-activating factor, eotaxin-1, eotaxin-2, eotaxin-3, and macrophage inflammatory protein-1α by the refluxed gastric contents in the esophagus causes EE [17]. To date, there are only few reports on the risk factors for EE, but none comparing an EE and non-EE group in the population of medical health check-ups which have screening program of the upper gastrointestinal tract. Non-allergic risk factors for EE, in particular, have not been fully elucidated.

Therefore, to clarify the pathophysiology of EE, we investigated the non-allergic risk factors for EE.

Methods

Study design and participants

This is a cross-sectional study. Between April 2015 and December 2016, a total of 6,926 consecutive Japanese subjects underwent medical health check-ups including esophagogastroduodenoscopy in our clinic 'MedCity21'. This screening program is usually performed in Japan out of health care insurance for mainly asymptomatic population. We used a 5.4-mm-diameter upper gastrointestinal endoscope (GIF-XP290N; Olympus Medical Systems Co. Ltd., Tokyo, Japan). The following subjects were excluded from the study: duplicated subjects during the observational period, subjects who had current intake of proton pump inhibitors (PPIs), potassium-competitive acid blockers (P-CABs), or steroids, subjects who did not complete to undergo endoscopy, those with lacking data, and those aged <18 years.

The following information was obtained from medical records: age, gender, body mass index (BMI), the presence of metabolic syndrome (MetS), alcohol consumption, cigarette smoking habits, Brinkman index, and comorbidities such as bronchial asthma, atopic dermatitis, chronic bronchitis, hypertension, hyperlipidemia, diabetes mellitus, and hyperuricemia. Alcohol consumption was categorized into the following 5 groups: category 0, 0 g/week (non-drinkers); 1, >0-140 g/week (light drinkers); 2, >140-280 g/week (moderate drinkers); 3, >280-420 g/week (heavy drinkers); and 4, >420 g/week (excessively heavy drinkers). Cigarette smoking was categorized into the following 4 groups: category 0, no history of smoking; 1, quit smoking; 2, less than one pack per day; and 3, more than one pack per day. Brinkman index was calculated as the number of cigarettes smoked per day multiplied by the number of years of smoking. Furthermore, we obtained the information on endoscopic findings such as reflux esophagitis (RE), hiatal hernia, Barrett's esophagus (BE), and EE. This study was registered with the university hospital medical information network (UMIN) clinical trial registry (UMIN000024444).

We compared the clinical characteristics between the subjects with and without EE and the endpoint of this study was to investigate the risk factors for EE.

Definition

According to the definition of the Japan Society for the Study of Obesity, BMI classification was divided into 6 categories; Underweight, <18.5; Normal range, 18.5-24.9; Obesity Class I, 25.0-29.9; Obesity Class II, 30.0-34.9; Obesity Class III, 35.0-39.9; Obesity Class IV, ≥40.0 kg/m^2 [18]. We used the diagnostic criteria of MetS according to the Japanese Society of Internal Medicine. The criteria were waist circumference ≥85 cm for men or ≥90 cm for women plus 2 or more of the following 3 components: systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg, triglycerides ≥150 mg/dL and/or HDL-cholesterol <40 mg/dL, and fasting plasma glucose ≥110 mg/dL [19].

EE was defined as esophageal intraepithelial eosinophil infiltration of ≥15 per high-power fields (HPF) (HPF area: 0.3 mm^2) on histological examination of a biopsy specimen. We obtained 1 to 6 esophageal biopsy specimens (median number, 5 specimens) when subjects had typical endoscopic findings for EE such as linear furrows, esophageal rings, white plaques, and mucosal edema by using forceps (Radial Jaw 4 pediatric biopsy forceps; Boston Scientific Japan Co. Ltd., Tokyo, Japan). In cases with 5 specimens, we obtained 1 of proximal esophagus, 2 of middle esophagus, and 2 of distal esophagus. Of all the subjects with EE in this study, none had eosinophilia in the stomach and duodenum. Furthermore, they did not have rare causes of EE such as parasitic infections, allergic vasculitis, achalasia, or pemphigus. On the other hand, the subjects who did not have typical endoscopic findings of EE were grouped into the non-EE group without biopsies.

The esophagogastric junction (EGJ) was defined as the most distal ends of the palisade longitudinal vessels in the esophagus. The presence of hiatal hernia was diagnosed by the proximal dislocation of the EGJ >20 mm above the diaphragmatic indentation [20, 21]. The squamocolumnar junction (SCJ) was defined as the border of the esophageal squamous epithelium and gastric columnar epithelium. The gap between SCJ and EGJ was diagnosed as endoscopically observed BE in Japan. A lining measuring less than 10 mm, reported as an ‘ultrashort segment’ of BE, was not considered to indicate BE in this study. One expert endoscopist (F.T.) checked the photographs taken by the endoscopists.

Statistical analyses

Data are expressed as median and interquartile range (IQR) for continuous variables and as numbers for categorical variables. For categorical variables, comparisons were performed by using Fisher’s exact test

or chi-square test, while continuous variables were compared by using a Mann-Whitney U test. P values <0.05 were considered statistically significant. We entered candidate risk factors such as BMI and hiatal hernia into multivariate analysis as explanatory variables by using logistic regression. We adjusted for age and bronchial asthma which represented allergic histories on multivariate analysis. Risk factors for EE were estimated by calculating the odds ratio (OR) and 95% confidence interval (CI). OR represents the relative odds of the occurrence of EE given exposure to the variable. To evaluate the presence of an association between a variable with categories, we used Cochran-Armitage trend test. All statistical analyses were performed using EZR (version 1.34, Saitama Medical Center, Jichi Medical University, Saitama, Japan) [22] which is a graphical user interface for R (version 3.3.2, The R Foundation for Statistical Computing, Vienna, Austria).

Results

Detection of EE

Of 6,926 subjects who underwent esophagogastroduodenoscopy, 773 were duplicated subjects, 139 currant intake of PPIs, 3 current intake of P-CABs, 41 current intake of steroids, 5 did not complete to undergo endoscopy, and 1 had data unavailable (Fig. 1). On duplicated subjects, we excluded the data of second visit. We excluded these 962 subjects, and the remaining 5,964 subjects were enrolled in this study. We identified 27 subjects with EE and the remaining 5,937 subjects were considered to not have EE. The detection rate of EE was 0.45% (27/5,964). Of the 27 subjects with EE, 19 had dysphagia, 1 had heartburn without dysphagia, and 7 had no symptoms. In addition, of the 19 dysphagia-positive subjects, 5 subjects also had heartburn.

Clinical characteristics of the study participants

Clinical characteristics of the study participants are shown in Table 1. On univariate analysis, subjects with EE were significantly younger and had higher BMI compared to those without EE; 45 (11.5) vs 51 (18) years, p=0.013; 23.4 (4.4) vs 22.3 (4.5) kg/m^2, p=0.005, respectively. There were no significant differences between subjects with EE and those without EE in other factors such as gender, MetS, alcohol consumption, cigarette smoking habits, and Brinkman index.

Subjects with EE significantly had a higher proportion of bronchial asthma compared to those without EE

(25.9% vs 5.2%; p<0.001). There were no significant differences between subjects with EE and those without EE in other comorbidities such as atopic dermatitis, chronic bronchitis, hypertension, hyperlipidemia, diabetes mellitus, and hyperuricemia.

Endoscopic findings revealed that subjects with EE had significantly higher proportion of hiatal hernia (29.6% vs 14.7%; p=0.049). Subjects with EE were more likely to have RE, but the difference was not statistically significant (18.5% vs 10.4%; p=0.195). Barrett's esophagus was not observed in subjects with EE (0% vs 15.5%; p=0.016).

Independent risk factors for EE

The results of multivariate analysis are shown in Table 2. Multivariate analysis indicated that subjects with EE were significantly younger (OR, 0.95; 95% CI, 0.91-0.99; p=0.007) and had bronchial asthma (OR, 5.31; 95% CI, 2.20-12.80; p<0.001). Furthermore, subjects with EE were positively associated with BMI (OR, 1.11; 95% CI, 1.03-1.20; p=0.010) and hiatal hernia (OR, 2.63; 95% CI, 1.12-6.18; p=0.026) compared to those without EE. The prevalence of EE based on BMI classification was as follows; Underweight (n=537), 0.186% (n=1); Normal range (n=4031), 0.372% (n=15); Obesity Class I (n=1153), 0.607% (n=7); Obesity Class II (n=206), 0.941% (n=2); Obesity Class III (n=32), 6.25% (n=2); Obesity Class IV (n=5), 0% (n=0). On trend test, advanced BMI classification had significant trend for increased prevalence of EE (p=0.002, Fig. 2). These results indicate that obesity and hiatal hernia may be independent non-allergic risk factors for EE.

Typical endoscopic findings for EE

The number and the rate of each typical endoscopic finding for EE in both groups are shown in Table 3. Linear furrows were the most frequent findings in the EE group (96.3%). In the non-EE group, the positive rate of each finding was very low (from 0.0674 to 0.152%). The positive rate of histologically-diagnosed EE in each finding is also shown in Table 3. The positive rate was from 74.3 to 82.6% for each finding.

Discussion

This is the first report with evidence that obesity and hiatal hernia may be non-allergic risk factors for EE in Japanese adults. Obesity and hiatal hernia were previously reported as risk factors for GERD [23-25].

Our results indicate that EE may be strongly affected by GERD. In the updated international consensus diagnostic criteria for EoE showed that EoE and GERD were not necessarily mutually exclusive, which was consistent with our results [26]. The prevalence, frequency, and severity of symptoms of GERD increase with an increase in BMI [23]. Obesity is involved in the pathogenesis of GERD mechanically and non-mechanically [27]. The mechanical effect is that the increased abdominal fat causes disruption of the gastroesophageal reflux barrier leading to increased reflux events. The non-mechanical effects may be mediated by inflammation via activated macrophages, pro-inflammatory cytokines, and adipokines such as leptin, which is likely to accelerate reflux-mediated inflammation. Hiatal hernia is considered a risk factor for nocturnal acid reflux [25]. In patients with hiatal hernia, the EGJ has increased distensibility, which can contribute to increased liquid reflux [28].

To investigate the prevalence of heartburn in our population, we used a questionnaire; however, the data of some subjects were unavailable. Based on available data, subjects with EE had a significantly higher prevalence of heartburn than those without EE (22.2% vs 6.9%, 6/27 subjects vs 389/5652 subjects, p=0.009, OR 3.86). In contrast, there were no significant difference in RE between subjects with EE and those without EE, which might indicate that EE could cause heartburn without reflux events. In our study, EE was associated with higher BMI but not MetS. This discrepancy may be based on the fact that mild obesity was mainly observed and there were few subjects who met criteria for MetS in the EE group rather than no association of central obesity. Our results indicated that advanced BMI classification had significant trend for increased prevalence of EE. Therefore, obesity may be a predominant risk factor for EE. Consequently, restoring the body weight to normal may become the new approach for the prevention of EE.

The OR of bronchial asthma was the highest among all variables: therefore, bronchial asthma might be a baseline characteristic of EE. Previous reports indicated that patients with EoE had a higher prevalence of allergic comorbidities than patients with RE [29]. Our results may imply that the allergic characteristics of our participants with EE, including EoE and asymptomatic EE, are consistent with previous reports. Furthermore, subjects with EE were significantly younger than those without EE. Previous reports showed that the susceptible age for EoE was the third or fourth decade of life [30], and our results were consistent with these reports. In this study, there were no cases with BE in EE group, though hiatal hernia and obesity were known risk factors for BE. We previously reported that BE was negatively associated with EoE [21]. This discrepancy may be due to different pathophysiology on immune response, esophageal microbiome,

food antigens, and genetic factors between BE and EE including EoE.

There were some limitations in this study. We enrolled subjects with EE and without typical endoscopic findings could be categorized as those without EE. Although the number of those subjects must be small, it was a major limitation of the study. Because study participants included subjects who underwent medical health check-ups, they might be younger than the general population. In the non-EE group, we could not perform esophageal biopsy because there was no possibility of EoE. Subjects in this group had normal endoscopic findings and no symptoms due to esophageal dysfunction. Unfortunately, in the setting of medical health check-ups, it had a difficulty to take biopsies from endoscopically-normal esophagus. This was a reason why we could not consider subjects without EE on histological examination as controls. Therefore, there is a possibility that some subjects with EE who have normal endoscopic findings may be included. The number of subjects with EE was relatively small and we could not investigate the statistical differences in clinical characteristics between symptomatic EE and asymptomatic EE. In the future, further investigation is needed by accumulation of EE cases.

In conclusion, obesity and hiatal hernia may be non-allergic risk factors for EE in Japanese adults. Obesity and hiatal hernia have possibilities to be involved in the pathogenesis for EE as well as GERD.

Notes

Authors' contributions

FT: study design, data collection, data analysis, and manuscript writing; SF, TM, KO, SH, YN, Noriko Kamata, KT, AN, TK, HY, TT, HM, TW, Norifumi Kawada, KH, and YF: critical revision of the manuscript for important intellectual content. All authors read and approved of the final manuscript.

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Compliance with ethical standards

Ethics statements

The study protocol was in accordance with the Declaration of Helsinki and was approved by the institutional review board of the Osaka City University Graduate School of Medicine (September 2016, Protocol number 3564). The need for informed consent has been waived by the institutional review board of the Osaka City University Graduate School of Medicine. We have disclosed the information about this study on our home page on the Internet and the patients had the opportunity to opt out.

Conflict of interest

The authors declare no conflict of interests for this article.

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Table 1 Clinical Characteristics of the Study Population.

Variable		Non-EE (n=5937)	EE (n=27)	OR (95% CI)	p value
Age, years		51 (18)	45 (11.5)	0.95 (0.92-0.99)	0.013
Male		2803 (47.2%)	15 (55.6%)	1.40 (0.61-3.28)	0.442
BMI, kg/m^2		22.3 (4.5)	23.4 (4.4)	1.12 (1.04-1.22)	0.005
Metabolic syndrome		854 (14.4%)	3 (11.1%)	0.74 (0.14-2.46)	0.788
Alcohol consumption					0.450
	Category 0	3018 (50.8%)	14 (51.9%)	1 (Reference)	
	Category 1	1231 (20.7%)	5 (18.5%)	0.88 (0.25-2.58)	
	Category 2	812 (13.7%)	2 (7.4%)	0.53 (0.06-2.32)	
	Category 3	674 (11.4%)	6 (22.2%)	1.92 (0.60-5.34)	
	Category 4	202 (3.4%)	0 (0%)	0 (0.00-4.54)	
Cigarette smoking habits					0.342
	Category 0	3232 (54.4%)	19 (70.4%)	1 (Reference)	
	Category 1	1715 (28.9%)	7 (25.9%)	0.69 (0.25-1.73)	
	Category 2	826 (13.9%)	1 (3.7%)	0.21 (0.00-1.30)	
	Category 3	164 (2.8%)	0 (0%)	0 (0.00-4.27)	
Brinkman index, point		0 (300)	0 (25.5)	1.00 (1.00-1.00)	0.043
Bronchial asthma		310 (5.2%)	7 (25.9%)	6.35 (2.25-15.80)	<0.001
Atopic dermatitis		303 (5.1%)	1 (3.7%)	0.72 (0.02-4.38)	1
Chronic bronchitis		28 (0.5%)	0 (0%)	0 (0.00-32.80)	1
Hypertension		927 (15.6%)	4 (11.1%)	0.68 (0.13-2.23)	0.789

Hyperlipidemia	710 (12.0%)	2 (7.4%)	0.59 (0.07-2.37)	0.764
Diabetes mellitus	278 (4.7%)	1 (3.7%)	0.78 (0.02-4.80)	1
Hyperuricemia	308 (5.2%)	1 (3.7%)	0.70 (0.02-4.31)	1
Hiatal hernia	874 (14.7%)	8 (29.6%)	2.44 (0.92-5.86)	0.049
Reflux esophagitis	617 (10.4%)	5 (18.5%)	1.96 (0.58-5.33)	0.195
Barrett's esophagus	921 (15.5%)	0 (0%)	0 (0.00-0.80)	0.016

BMI: body mass index, CI: confidence interval, EE: esophageal eosinophilia, IQR: interquartile range, OR: odds ratio

Data are expressed as median (IQR) for continuous variables and as numbers (percentage) for categorical variables.

The OR represents the relative odds of the occurrence of EE given the exposure to the variable.

Alcohol consumption; category 0=non-drinkers, 1=light drinkers, 2=moderate drinkers, 3=heavy drinkers, 4=excessively heavy drinkers.

Cigarette smoking habits; category 0=no history of smoking, 1=quit smoking, 2=less than one pack per day, 3=more than one pack per day.

Table 2 Crude and Muliple-adjusted Odds Ratios for Esophageal Eosinophilia.

	Crude-OR		Multiple-adjusted OR	
Variable	OR (95% CI)	p value	OR (95% CI)	p value
Age	0.95 (0.92-0.99)	0.013	0.95 (0.91-0.99)	0.007
BMI	1.12 (1.04-1.22)	0.005	1.11 (1.03-1.20)	0.010
Hiatal hernia	2.44 (0.92-5.86)	0.049	2.63 (1.12-6.18)	0.026
Bronchial asthma	6.35 (2.25-15.80)	<0.001	5.31 (2.20-12.80)	<0.001

OR: odds ratio, CI: confidence interval, BMI: body mass index

Table 3 Typical Endoscopic Findings for Esophageal Eosinophilia.

Endoscopic findings	Non-EE (n=5937)	EE (n=27)	Positive rate of histologically-diagnosed EE
Linear furrow	9 (0.152%)	26 (96.3%)	26/35 (74.3%)
Esophageal ring	5 (0.0842%)	21 (77.8%)	21/26 (80.8%)
White plaque	6 (0.101%)	19 (70.4%)	19/25 (76.0%)
mucosal edema	4 (0.0674%)	19 (70.4%)	19/23 (82.6%)

EE: esophageal eosinophilia

Data are expressed as numbers (percentage).

Figure Legends

Fig. 1 Flowchart of the study design. EE, esophageal eosinophilia; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

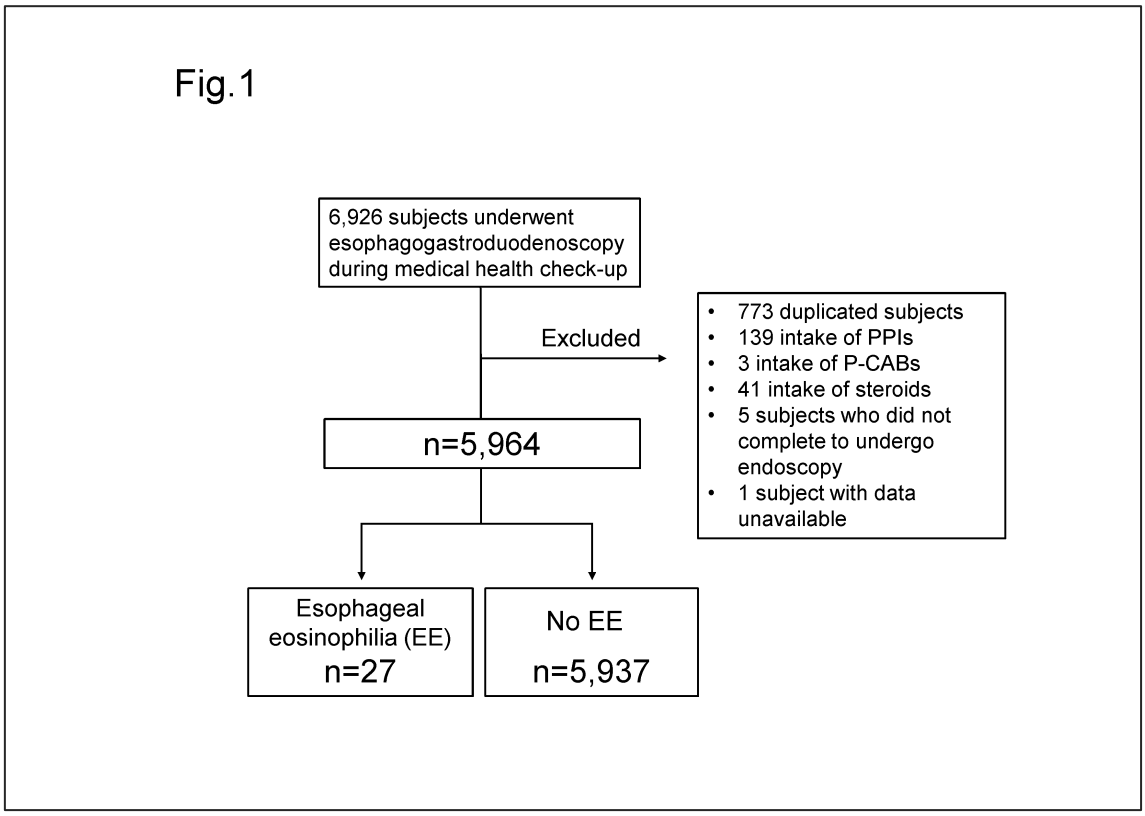

Fig. 2 The prevalence of esophageal eosinophilia based on body mass index classification.