

Lifestyle factors associated with gastroesophageal reflux disease in the Japanese population

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Abstract

Background We aimed to clarify the lifestyle factors associated with erosive esophagitis and non-erosive reflux disease (NERD) in a Japanese population.

Methods Among 886 subjects who underwent health screening, we selected, according to their scores on the FSSG (frequency scale for symptoms of gastroesophageal reflux disease; GERD) questionnaire and the findings of upper gastrointestinal endoscopy, 138 subjects with erosive esophagitis (EE), 148 subjects with NERD (absence of esophagitis, FSSG score ≥ 8 , and acid reflux-related symptoms score ≥ 4), and 565 control subjects (absence of esophagitis and FSSG score ≤ 7). We compared clinical characteristics and various lifestyle factors in these three groups.

Results The lifestyle factors significantly associated with NERD compared with findings in the control group were intake of egg (odds ratio [OR] 1.89, 95 % confidence interval [CI] 1.01–3.50), sleep shortage (OR 2.44, 95 % CI 1.54–3.88), and strong psychological stress (OR 1.77, 95 % CI 1.18–2.62). In male subjects, current smoking (OR 2.06,

95 % CI 1.13–3.74; OR 1.87, 95 % CI 1.09–3.20) was a significant risk factor for both NERD and EE. Moreover, alcohol >200 kcal/day (OR 3.99, 95 % CI 1.03–15.55) and intake of a large quantity of food at supper (OR 7.85, 95 % CI 1.66–37.05) were significant risk factors for EE in subjects with hiatal hernia. Intake of a large quantity of food at supper (OR 2.09, 95 % CI 1.06–4.13) was more common in the NERD group than in the EE group.

Conclusions There were differences in the associated lifestyle factors between patients with NERD and those with EE, and there was also a gender-related difference between these groups.

Keywords Gastroesophageal reflux disease · Erosive esophagitis · Non-erosive reflux disease · Lifestyle factor · Risk factor

Introduction

Symptoms of gastroesophageal reflux disease (GERD), which is well known as a disease that reduces the quality of life, are among the most frequent health problems in Western countries [1]. The prevalence of heartburn or acid regurgitation varies between 9 and 42 % depending on the population [2, 3]. In Asian countries, including Japan, the prevalence of GERD has gradually increased [4, 5], and GERD is recognized as a common gastrointestinal disease [6].

On the basis of the findings of upper gastrointestinal endoscopy, patients with GERD symptoms are divided into two categories: those with erosive esophagitis (EE), which is characterized by endoscopically detectable esophageal mucosal damage, and those with non-erosive reflux disease (NERD), in which esophageal mucosal damage is not observed endoscopically despite the presence of GERD

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symptoms [7]. The results of epidemiologic studies have suggested that the proportion of patients with NERD among those with GERD-related symptoms is between 50 and 70 % [7–15]. Differences in clinical features between EE and NERD have been reported, but there are few reported studies investigating the differences in lifestyle factors associated with these differences. Considering that the effectiveness of proton pump inhibitor (PPI) therapy in NERD patients is lower than that in EE patients [16–18], it is important to identify the risk factors that we can control, such as lifestyle factors. In this study, we aimed to clarify the lifestyle factors associated with EE and NERD in a Japanese population.

Methods

Study population

This study included 886 subjects who underwent upper gastrointestinal endoscopy during health screening at Yodogawa Christian Hospital between May and September 2007 and were asked to complete the frequency scale for symptoms of GERD (FSSG) questionnaire. Subjects with the following criteria were excluded from this study: evidence of gastric or duodenal ulcer; history of upper gastrointestinal tract surgery; undergoing treatment with a PPI or histamine type 2-receptor antagonist (H2RA); and evidence of malignancy. We collected and examined patient data according to the ethics rules of Yodogawa Christian Hospital.

Frequency scale for symptoms of GERD (FSSG) questionnaire

The FSSG questionnaire is a self-reported questionnaire for evaluation of the symptoms of GERD, developed in 2004 by Kusano et al. [19], and is widely used in Japan. The FSSG questionnaire consists of the following 12 questions: (1) “Do you get heartburn?” (2) “Does your stomach get bloated?” (3) “Does your stomach ever feel heavy after meals?” (4) “Do you sometimes subconsciously rub your chest with your hand?” (5) “Do you ever feel sick after meals?” (6) “Do you get heartburn after meals?” (7) “Do you have an unusual (e.g., burning) sensation in your throat?” (8) “Do you feel full while eating meals?” (9) “Do some things get stuck when you swallow?” (10) “Do you get bitter liquid (acid) coming up into your throat?” (11) “Do you burp a lot?”, and (12) “Do you get heartburn if you bend over?” The subjects answered these questions according to the frequency of their symptoms as follows: never = 0, occasionally = 1, sometimes = 2, often = 3, and always = 4. The total FSSG score was defined as the

score obtained by adding the scores from these 12 questions. The score obtained by adding the first, fourth, sixth, seventh, ninth, tenth, and twelfth questions was defined as the score for acid reflux-related symptoms. The score obtained by adding the second, third, fifth, eighth, and eleventh questions was defined as the score for dyspeptic symptoms. It was reported that the sensitivity and specificity of FSSG for the diagnosis of GERD were 62 and 59 %, respectively, when the cut-off score was set at 8 points [19]. In addition, it has also been reported that there was no difference between the FSSG and the questionnaire for the diagnosis of reflux esophagitis (QUEST) assessment systems in sensitivity, specificity, or accuracy for the diagnosis of GERD [20].

Dietary questionnaire, dietary behavior, mental and physical stress, and sleep

Dietary intake was assessed using the brief-type self-administered diet history questionnaire (BDHQ), which is a simplified version of the DHQ questionnaire (self-administered diet history questionnaire). The DHQ is a questionnaire developed for the Japanese to examine the intake of nutrients and food quantitatively [21–25]. Study participants were asked to estimate their usual frequency of consumption of various foods (seafood, meat, egg, soybean, fish, vegetable, fruit, potato, grain, oil and fat, sugar, cake, and snacks) and beverages (milk, soft drinks, alcohol). It takes about 15 min to complete the BDHQ. We calculated the daily average calory intake from various types of food and beverages using the answers to the BDHQ.

Dietary behaviors were assessed by the following seven questions: (1) “Do you have a habit of skipping breakfast more than three times a week?” (2) “Is the time for your meals irregular?” (3) “Do you eat a snack after supper more than three times a week?” (4) “Do you have a habit of skipping meals?” (5) “Do you have more food at supper than at breakfast and lunch?” (6) “Do you eat out at supper more than twice a week?” and (7) “Do you eat lunch from a convenience store more than twice a week?” These questions were answered with “Yes” or “No”.

Questions about psychological and physical stress were answered according to degree as follows: “extremely strong”, “strong”, “normal”, “weak”, and “extremely weak”. The subjects whose answers were “extremely strong” and “strong” were defined as positive in terms of having stress.

Sleep was assessed by the following two questions: (1) “How is your sleep?” and (2) “How many hours do you sleep on average?” The possible answers to the first question were as follows: “sleep soundly”, “normal”, and “sleep shortage”. The possible answers to the second question were: “less than five hours”, “between five and eight hours”, or “more than eight hours”.

Endoscopic findings

All endoscopic examinations were digitally recorded. A diagnosis of EE was based on the endoscopic appearance of a definite mucosal break. Erosive esophagitis was graded according to the Los Angeles (LA) classification. Hiatal hernia was diagnosed on the basis of proximal translocation of the esophagogastric junction of more than 2 cm above the diaphragmatic hiatus. Atrophic gastritis was endoscopically diagnosed, and the endoscopic extent of atrophic mucosa was graded according to the Kimura–Takemoto classification from C-1 to O-3 [26]. Subjects with atrophic mucosa graded as C-2, C-3, O-1, O-2, and O-3 were defined as positive for atrophic gastritis.

Definitions of EE and NERD

Regardless of the FSSG scores, subjects with EE were defined as the EE group. The EE group was divided into two subgroups according to the FSSG scores: the symptomatic EE group (subjects with a total FSSG score of more than eight points) and the asymptomatic EE group (subjects with a total FSSG score of less than seven points). Subjects who had no evidence of EE with an FSSG score of eight points or more and an FSSG score of four points or more for acid reflux-related symptoms were defined as the NERD group. Subjects who had no evidence of EE with an FSSG score of seven points or less were defined as the Control group.

Statistical analysis

Differences among the three groups (EE group, NERD group, and Control group) were analyzed by the χ^2 test for categorical variables and Student's *t*-test for continuous variables. In multivariate analyses, the variables with *p* values of less than 0.1 by the χ^2 test or Student's *t*-test were used for multiple logistic regression analyses. Statistical analyses were performed using the STATA/SE statistical software system version 11 (StataCorp., College Station, TX, USA). Differences were considered as significant when the *p* value was <0.05.

Results

Clinical characteristics and FSSG scores of the participants

Of the 886 subjects enrolled in this study, 547 were male and 339 were female. The mean age was 52.7 years.

The EE group and the Control group consisted of 138 (15.6 %) and 565 (63.7 %) subjects, respectively. The

number of subjects who had no evidence of EE with an FSSG score of eight points or more was 183 (20.7 %), and among these subjects, the NERD group (acid reflux-related symptoms score of more than four points) consisted of 148 (16.7 %) subjects. In the EE group, the numbers of subjects according to the LA classification were as follows: LA-A 100 (11.3 %), LA-B 33 (3.7 %), and LA-C 5 (0.6 %).

Distributions of the FSSG scores of the EE group and the non-EE group are shown in Figs. 1 and 2, respectively. The mean scores of the EE group and the non-EE group were 6.47 ± 5.00 and 5.08 ± 4.90 , and the proportions of subjects with eight points or more in the EE group and the non-EE group were 34.1 and 24.5 %, respectively. A score of zero points was most common in the non-EE group, whereas four points was most common in the distribution of the FSSG score in the EE group.

Univariate and multivariate analyses for the factors associated with NERD

In the univariate analysis, the proportion of subjects with current smoking was significantly higher in the NERD group than in the Control group (24.3 vs. 16.3 %, $p < 0.05$) (Table 1).

As for the endoscopic findings, there were no differences between the NERD group and the Control group (Table 2).

In regard to food and beverages, the NERD group had a significantly higher total calorie intake than the Control group (25.00 points vs. 22.99 points, $p < 0.01$). In addition, compared with the Control group, the NERD group had significantly higher intakes of meat (1.45 points vs. 1.20 points, $p < 0.01$), egg (0.56 points vs. 0.46 points, $p < 0.01$), oil and fat (2.24 points vs. 1.93 points, $p < 0.01$), and milk (1.51 points vs. 1.30 points, $p < 0.05$) (Table 3).

Regarding dietary behavior, the NERD group had a higher proportion of subjects who answered “yes” to the following three questions than the Control group: “Is the time for your meals irregular?” (22.3 vs. 15.0 %, $p < 0.05$), “Do you have more food at supper than at breakfast and lunch?” (69.6 vs. 59.6 %, $p < 0.05$), and “Do you eat out for supper more than twice a week?” (25.0 vs. 15.2 %, $p < 0.01$) (Table 4).

Table 5 shows the univariate analysis of intergroup comparisons of psychological stress, physical stress, and sleep. The NERD group had a significantly higher proportion of subjects who had psychological stress than the Control group (54.7 vs. 35.6 %, $p < 0.01$), but there were no significant differences in physical stress between the two groups. The NERD group had a significantly higher proportion of subjects who experienced sleep shortage than the Control group (32.4 vs. 14.7 %, $p < 0.01$), and there were significantly more subjects in the NERD group than

Fig. 1 Distribution of FSSG scores in the EE group. The grades of erosive esophagitis shown are according to the Los Angeles classification. FSSG frequency scale for symptoms of gastroesophageal reflux disease (GERD), EE erosive esophagitis

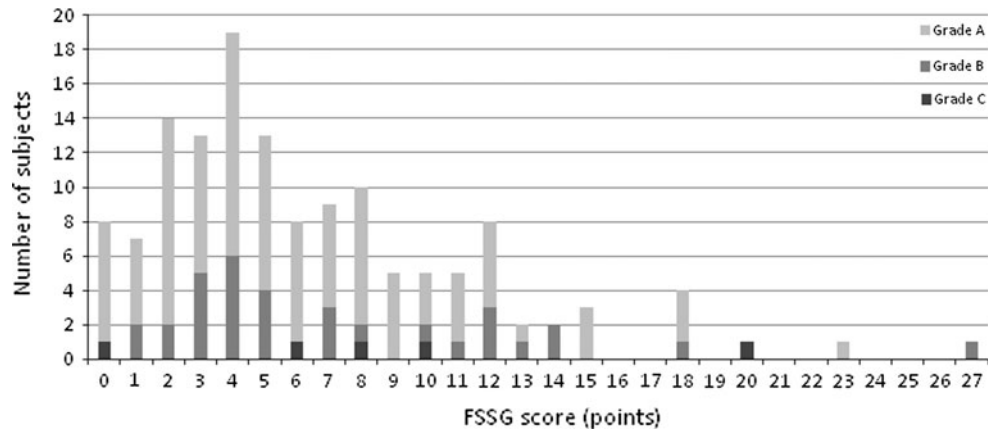


Fig. 2 Distribution of FSSG scores in the non-EE group. FSSG frequency scale for symptoms of GERD, EE erosive esophagitis

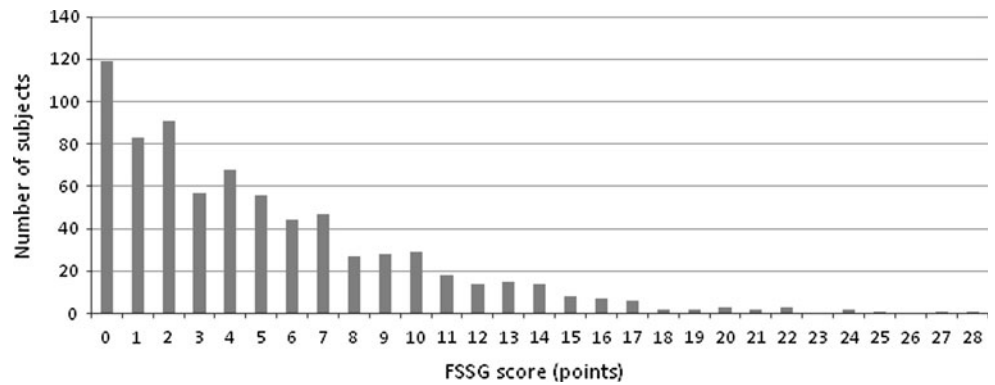


Table 1 Clinical characteristics

	EE (n = 138)	NERD (n = 148)	Control (n = 565)	Symptomatic EE (n = 47)	Asymptomatic EE (n = 91)
Age (mean ± SD, years)	52.3 ± 9.5	51.8 ± 10.5	53.2 ± 11.1	52.6 ± 9.8	52.1 ± 8.8
Male [n (%)]	119 (86.2) ^a	83 (56.1)	328 (58.1)	39 (83.0)	80 (87.9)
BMI (mean ± SD, kg/m ²)	24.3 ± 3.2 ^a	22.7 ± 3.5	22.5 ± 3.1	23.8 ± 3.2	24.5 ± 3.2
BMI ≥25 [n (%)]	54 (39.1) ^a	27 (18.2)	115 (20.4)	17 (36.2)	37 (40.7)
BMI ≥30 [n (%)]	5 (3.6)	5 (3.4)	11 (1.9)	1 (2.1)	4 (4.4)
Body fat ratio (mean ± SD, %)	23.5 ± 5.3	23.0 ± 5.9	22.6 ± 5.6	23.5 ± 5.6	23.5 ± 5.2
High body fat ratio, male ≥25 %, female ≥30 % [n (%)]	43 (31.2) ^a	25 (16.9)	99 (17.5)	14 (29.8)	29 (31.9)
Hypertension [n (%)]	12 (8.7)	16 (10.8)	40 (7.1)	5 (10.6)	7 (7.7)
Diabetes [n (%)]	4 (2.9)	1 (0.7)	15 (2.7)	2 (4.3)	2 (2.2)
Hyperlipidemia [n (%)]	67 (48.6)	58 (39.2)	231 (40.9)	19 (40.4)	48 (52.7)
Current smoking [n (%)]	46 (33.3) ^b	36 (24.3) ^c	92 (16.3)	18 (38.3)	28 (30.8)

BMI body mass index, EE erosive esophagitis, NERD non-erosive reflux disease

^a *p* < 0.01 versus NERD and *p* < 0.01 versus Control

^b *p* < 0.01 versus Control

^c *p* < 0.05 vs. Control

in the Control group whose average sleeping time was less than 5 h (25.7 vs. 17.2 %, *p* < 0.05).

The multivariate analysis revealed that a greater intake of egg (OR 1.89, 95 % CI 1.01–3.50, *p* = 0.045), strong psychological stress (OR 1.77, 95 % CI 1.18–2.62,

p = 0.005), and sleep shortage (OR 2.44, 95 % CI 1.54–3.88, *p* < 0.001) were significant risk factors for NERD (Table 6).

Furthermore, we evaluated risk factors for NERD separately in male subjects and female subjects.

Table 2 Endoscopic findings

	EE (<i>n</i> = 138)	NERD (<i>n</i> = 148)	Control (<i>n</i> = 565)	Symptomatic EE (<i>n</i> = 47)	Asymptomatic EE (<i>n</i> = 91)
Atrophic gastritis [<i>n</i> (%)]	16 (11.6) ^a	80 (54.1)	277 (49.0)	7 (14.9)	9 (9.9)
Hiatal hernia [<i>n</i> (%)]	31 (22.5) ^a	9 (6.1)	23 (4.1)	10 (21.3)	21 (23.1)

EE erosive esophagitis, NERD non-erosive reflux disease

^a *p* < 0.01 versus NERD and *p* < 0.01 versus Control

Table 3 Food and beverages

	EE (<i>n</i> = 138)	NERD (<i>n</i> = 148)	Control (<i>n</i> = 565)	Symptomatic EE (<i>n</i> = 47)	Asymptomatic EE (<i>n</i> = 91)
Total calories (mean ± SD, points/day)	24.69 ± 5.29 ^a	25.00 ± 5.69 ^a	22.99 ± 5.27	25.11 ± 5.24	24.48 ± 5.33
Seafood (mean ± SD, points/day)	0.98 ± 0.67	0.96 ± 0.54	0.90 ± 0.53	1.01 ± 0.67	0.96 ± 0.71
Meat (mean ± SD, points/day)	1.22 ± 0.76	1.45 ± 0.91 ^a	1.20 ± 0.77	1.32 ± 0.84	1.17 ± 0.71
Egg (mean ± SD, points/day)	0.52 ± 0.33 ^b	0.56 ± 0.36 ^a	0.46 ± 0.30	0.54 ± 0.34	0.51 ± 0.32
Soybean (mean ± SD, points/day)	0.99 ± 0.76	1.01 ± 0.72	1.05 ± 0.79	0.83 ± 0.50	1.07 ± 0.85
Fish (mean ± SD, points/day)	0.24 ± 0.21	0.25 ± 0.23	0.27 ± 0.26	0.22 ± 0.16	0.26 ± 0.23
Vegetable (mean ± SD, points/day)	0.65 ± 0.28	0.69 ± 0.24	0.70 ± 0.29	0.65 ± 0.29	0.66 ± 0.27
Fruit (mean ± SD, points/day)	0.47 ± 0.38 ^c	0.64 ± 0.52	0.57 ± 0.49	0.45 ± 0.37	0.48 ± 0.39
Potato (mean ± SD, points/day)	0.22 ± 0.18 ^c	0.31 ± 0.19	0.27 ± 0.21	0.23 ± 0.18	0.22 ± 0.18
Grain (mean ± SD, points/day)	9.92 ± 3.33 ^a	9.26 ± 2.88	9.15 ± 2.99	9.65 ± 3.49	10.06 ± 3.25
Cake and snacks (mean ± SD, points/day)	2.09 ± 1.98 ^d	2.60 ± 2.17	2.35 ± 2.19	1.86 ± 1.87	2.20 ± 2.04
Oil and fat (mean ± SD, points/day)	2.07 ± 0.96	2.24 ± 0.99 ^a	1.93 ± 0.96	2.14 ± 0.85	2.03 ± 1.01
Sugar (mean ± SD, points/day)	0.93 ± 0.37	0.93 ± 0.34	0.93 ± 0.33	0.95 ± 0.36	0.92 ± 0.37
Salt (mean ± SD, g/day)	11.7 ± 1.76	11.7 ± 1.96	11.3 ± 1.81	11.64 ± 1.79	11.70 ± 1.76
Milk (mean ± SD, points/day)	1.25 ± 1.15 ^d	1.51 ± 1.18 ^b	1.30 ± 1.06	1.22 ± 1.38	1.26 ± 1.04
Soft drinks (mean ± SD, points/day)	0.41 ± 0.59	0.41 ± 0.79	0.31 ± 0.61	0.56 ± 0.77 ^f	0.33 ± 0.46
Alcohol (mean ± SD, kcal/day)	218.4 ± 223.2 ^e	152.8 ± 198.5	128.0 ± 175.2	282.6 ± 241.8 ^f	184.9 ± 205.9
Alcohol >200 kcal/day [<i>n</i> (%)]	62 (44.9) ^e	43 (29.1)	139 (24.6)	26 (55.3)	36 (39.6)

1 point 80 kcal, EE erosive esophagitis, NERD non-erosive reflux disease

^a *p* < 0.01 versus Control

^b *p* < 0.05 versus Control

^c *p* < 0.01 versus NERD and *p* < 0.05 versus Control

^d *p* < 0.05 versus NERD

^e *p* < 0.01 versus NERD and *p* < 0.01 versus Control

^f *p* < 0.05 versus asymptomatic EE

Current smoking (OR 2.06, 95 % CI 1.13–3.74, *p* = 0.018), total calories (OR 1.08, 95 % CI 1.01–1.16, *p* = 0.021), having strong psychological stress (OR 1.77, 95 % CI 1.01–3.11 *p* = 0.046), and sleep shortage (OR 2.44, 95 % CI 1.27–4.70, *p* = 0.007) were significant risk factors for NERD in the male subjects. On the other hand, hiatal hernia (OR 7.33, 95 % CI 1.42–37.83, *p* = 0.017), greater intake of oil and fat (OR 1.67, 95 % CI 1.06–2.62, *p* = 0.027), and sleep shortage (OR 2.38, 95 % CI 1.17–4.84, *p* = 0.017) were significant risk factors for NERD in the female subjects (Table 6).

Univariate and multivariate analyses for the factors associated with EE

In the univariate analysis, the EE group had significantly more men (86.2 vs. 58.1 %, *p* < 0.01), a higher body mass index (BMI; 24.3 ± 3.2 vs. 22.5 ± 3.1, *p* < 0.01), a higher proportion of subjects with BMI ≥ 25 % (39.1 vs. 20.4 %, *p* < 0.01), and a higher proportion of subjects with a high body fat ratio (31.2 vs. 17.5 %, *p* < 0.01) than the Control group. In addition, the proportion of subjects with current smoking was significantly higher in the EE group than in the Control group (33.3 vs. 16.3 %, *p* < 0.01) (Table 1).

Table 4 Dietary behaviors

	EE (n = 138)	NERD (n = 148)	Control (n = 565)	Symptomatic EE (n = 47)	Asymptomatic EE (n = 91)
Skipping breakfast more than three times a week [n (%)]	18 (13.0)	18 (12.2)	54 (9.6)	9 (19.1)	9 (9.9)
The time for meals is irregular [n (%)]	23 (16.7)	33 (22.3) ^b	85 (15.0)	9 (19.1)	14 (15.4)
Eating a snack after supper more than three times a week [n (%)]	21 (15.2) ^a	39 (26.4)	109 (19.3)	7 (14.9)	14 (15.4)
Having a habit of skipping a meal [n (%)]	39 (28.3)	37 (25.0)	121 (21.4)	16 (34.0)	23 (25.3)
Having more food at supper than at breakfast and lunch [n (%)]	78 (56.5) ^a	103 (69.6) ^b	337 (59.6)	30 (63.8)	48 (51.6)
Eating out for supper more than twice a week [n (%)]	30 (21.7)	37 (25.0) ^c	86 (15.2)	14 (29.8)	16 (17.6)
Eating lunch from a convenience store more than twice a week [n (%)]	31 (22.5)	42 (28.4)	123 (21.8)	12 (25.5)	19 (20.9)

EE erosive esophagitis, NERD non-erosive reflux disease

^a $p < 0.05$ versus NERD

^b $p < 0.05$ versus Control

^c $p < 0.01$ versus Control

Table 5 Psychological stress, physical stress, and sleep

	EE (n = 138)	NERD (n = 148)	Control (n = 565)	Symptomatic EE (n = 47)	Asymptomatic EE (n = 91)
Having strong psychological stress [n (%)]	65 (47.1) ^a	81 (54.7) ^c	201 (35.6)	23 (48.9)	42 (46.2)
Having strong physical stress [n (%)]	4 (2.9)	6 (4.1)	25 (4.4)	1 (2.1)	3 (3.3)
Sleep shortage [n (%)]	25 (18.1) ^b	48 (32.4) ^c	84 (14.7)	9 (19.1)	16 (17.6)
Sleeping time ≤ 5 h [n (%)]	25 (18.1)	38 (25.7) ^a	97 (17.2)	9 (19.1)	16 (17.6)

EE erosive esophagitis, NERD non-erosive reflux disease

^a $p < 0.05$ versus Control

^b $p < 0.01$ versus NERD

^c $p < 0.01$ versus Control

As for the endoscopic findings, atrophic gastritis was less frequently observed in the EE group than in the Control group (11.6 vs. 49.0 %, $p < 0.01$), whereas hiatal hernia was more frequently observed in the EE group than in the Control group (22.5 vs. 4.1 %, $p < 0.01$) (Table 2).

In regard to food and beverages, the EE group had significantly higher intakes of total calories (24.69 vs. 22.99 points, $p < 0.01$), egg (0.52 vs. 0.46 points, $p < 0.05$), grain (9.92 vs. 9.15 points, $p < 0.01$), and alcohol (218.4 vs. 128.0 kcal/day, $p < 0.01$) than the Control group. On the other hand, the intakes of fruit (0.47 vs. 0.57 points, $p < 0.05$) and potato (0.22 vs. 0.27 points, $p < 0.05$) in the EE group were significantly lower than those in the Control group (Table 3).

Regarding dietary behavior, there were no significant differences between the EE group and the Control group (Table 4).

The EE group had a significantly higher proportion of subjects with psychological stress than the Control group

(47.1 vs. 35.6 %, $p < 0.05$). There were no significant differences in physical stress or in sleep factors between the two groups (Table 5).

The multivariate analysis revealed that male gender (OR 4.60, 95 % CI 1.74–12.14, $p = 0.002$) and hiatal hernia (OR 4.03, 95 % CI 2.08–7.79, $p < 0.001$) were significant risk factors for EE. In addition, atrophic gastritis (OR 0.13, 95 % CI 0.07–0.23, $p < 0.001$) was found to be a significant protective factor for EE (Table 7).

Because sex, hiatal hernia, and atrophic gastritis are not lifestyle factors, we performed sub-classification analysis to identify the lifestyle factors associated with EE. It was revealed that current smoking (OR 1.87, 95 % CI 1.09–3.20, $p = 0.024$) was a significant risk factor for EE in male subjects. In addition, alcohol consumption of more than 200 kcal/day (OR 3.99, 95 % CI 1.03–15.5, $p = 0.046$) and having more food at supper than at breakfast and lunch (OR 7.85, 95 % CI 1.66–37.1, $p = 0.009$) were significant risk factors for EE in the

Table 6 Multivariate analysis of the risk factors for NERD

	OR	95 % CI	<i>p</i> value
Risk factors for NERD			
Egg	1.89	1.01–3.50	0.045
Having strong psychological stress	1.77	1.18–2.62	0.005
Sleep shortage	2.44	1.54–3.88	<0.001
Risk factors for NERD in male subjects			
Current smoking	2.06	1.13–3.74	0.018
Total calories	1.08	1.01–1.16	0.021
Having strong psychological stress	1.77	1.01–3.11	0.046
Sleep shortage	2.44	1.27–4.70	0.007
Risk factors for NERD in female subjects			
Hiatal hernia	7.33	1.42–37.83	0.017
Oil and fat	1.67	1.06–2.62	0.027
Sleep shortage	2.38	1.17–4.84	0.017

OR odds ratio, CI confidence interval

subjects with hiatal hernia (Table 7). Furthermore, in the multivariate analysis of the risk factors for EE in female subjects, atrophic gastritis (OR 0.09, 95 % CI 0.02–0.51, $p = 0.006$) and a greater intake of cake and snacks (OR 1.00, 95 % CI 1.00–1.01, $p = 0.036$) were significant factors associated with EE (Table 7).

Comparison between the symptomatic EE group and the asymptomatic EE group revealed that the symptomatic EE group had greater intakes of soft drinks (0.56 vs. 0.33 points, $p < 0.05$) and alcohol (282.6 vs. 184.9 kcal/day, $p < 0.05$) than the asymptomatic EE group (Table 3). No significant lifestyle factor was identified as a risk for symptomatic EE in the sub-classification analysis (Table 7).

Comparison between NERD and EE

In the multivariate analysis comparing the NERD group and the EE group, male gender (OR 0.31, 95 % CI 0.13–0.70, $p = 0.005$) and hiatal hernia (OR 0.28, 95 % CI 0.10–0.77, $p = 0.014$) were less common, whereas atrophic gastritis (OR 15.61, 95 % CI 7.03–34.64, $p < 0.001$) and intake of a larger quantity of food at supper than at breakfast and lunch (OR 2.09, 95 % CI 1.06–4.13, $p = 0.034$) were more common in the NERD group than in the EE group (Table 8).

Discussion

Various lifestyle factors, such as smoking, alcohol intake, psychological stress, a high-fat diet, and recumbent position after a meal, have been reported to be risk factors for

GERD [27, 28]. However, there are few reports of lifestyle factors involved in the development of NERD.

In the present study, the EE group and the NERD group had a higher intake of total calories than the Control group, a finding which is consistent with previous studies [27, 29]. Our multivariate analysis revealed that the total number of calories was a significant risk factor for NERD in male subjects. In addition, the intake of oil and fat was significantly higher in the NERD group than in the Control group, and oil and fat intake was a significant risk factor for NERD in female subjects.

As for food factors, intake of egg was found to be a risk factor for NERD in the present study. It is reported that eating of egg yolk induces an increase in the plasma level of cholecystokinin (CCK) [30], which is involved in the occurrence of transient lower esophageal sphincter relaxation (TLESR) [31]. This association might be one of the mechanisms that explain the result that intake of egg was a risk factor for NERD.

Smoking decreases lower esophageal sphincter (LES) pressure and affects esophageal defense mechanisms; for example, by causing reduction of esophageal clearance and saliva secretion [32–34]. Consistent with previous studies [34–38], the EE group and the NERD group in the present study had higher proportions of subjects with smoking habits than the Control group. In our multivariate analysis, current smoking was a significant risk factor for both NERD and EE in male subjects. Nozu and Komiyama. [39] reported that smoking was an independent factor associated with asymptomatic esophagitis. However, in the present study, the proportion of subjects with smoking was somewhat higher in the symptomatic EE group than in the asymptomatic EE group.

Alcoholic beverages are considered to be associated with the impairment of primary peristalsis, an increase in gastric acid secretion, and a decrease in LES pressure [28]. In the present study, the EE group had a significantly greater alcohol intake than the NERD group and the Control group. In the multivariate analysis, alcohol consumption of more than 200 kcal/day was a significant risk factor for EE in subjects with hiatal hernia. In addition, a greater intake of alcohol was observed in the symptomatic EE group than in the asymptomatic EE group.

In this study, we investigated the regularity of dietary behavior by having the subjects respond to a questionnaire. In the NERD group, there were more subjects who had meals at irregular times, had a larger quantity of food at supper, and had a habit of eating out compared with the Control group. The multivariate analysis revealed that intake of a large quantity of food at supper was a significant risk factor for EE in subjects with hiatal hernia. There are some reports demonstrating that late-evening meals increase the supine acid reflux [40–42]. There is a

Table 7 Multivariate analysis of the risk factors for EE

	OR	95 % CI	p value
Risk factors for EE			
Male	4.60	1.74–12.14	0.002
Atrophic gastritis	0.13	0.07–0.23	<0.001
Hiatal hernia	4.03	2.08–7.79	<0.001
Risk factors for EE in male subjects			
Current smoking	1.87	1.09–3.20	0.024
Atrophic gastritis	0.11	0.06–0.22	<0.001
Hiatal hernia	4.16	2.06–8.42	<0.001
Risk factors for EE in female subjects			
Atrophic gastritis	0.09	0.02–0.51	0.006
Cake and snacks	1.00	1.00–1.01	0.036
Risk factors for EE in subjects without atrophic gastritis			
Age	1.03	1.00–1.05	0.029
Male	2.92	1.48–5.79	0.002
Hiatal hernia	2.53	1.22–5.23	0.012
Risk factors for EE in subjects with hiatal hernia			
Alcohol >200 kcal/day	3.99	1.03–15.55	0.046
Having more food at supper than at breakfast and lunch	7.85	1.66–37.05	0.009
Risk factors for symptomatic EE			
Atrophic gastritis	0.17	0.07–0.41	<0.001
Hiatal hernia	3.46	1.34–8.90	0.01
Risk factors for asymptomatic EE			
Male	3.29	1.50–7.22	0.003
Atrophic gastritis	0.12	0.05–0.24	<0.001
Hiatal hernia	4.19	2.03–8.65	<0.001

OR odds ratio, CI confidence interval

Table 8 Comparison between the NERD group and the EE group

	OR ^a	95 % CI	p value
Male	0.31	0.13–0.70	0.005
Atrophic gastritis	15.61	7.03–34.64	<0.001
Hiatal hernia	0.28	0.10–0.77	0.014
Having more food at supper than at breakfast and lunch	2.09	1.06–4.13	0.034

^a Odds ratio of NERD over EE

OR odds ratio, CI confidence interval

possibility that having more food at supper than at breakfast and lunch might also be associated with an increase of the supine acid reflux.

In regard to psychological stress, it is reported that psychosocial stress triggers reflux symptoms in GERD patients [43] and that the presence of a severe major life stressor exacerbates reflux symptoms [28, 44]. It is also

reported that response to PPI treatment in GERD patients may be dependent on the level of psychological distress [45, 46]. In the present study, the EE group and the NERD group had higher proportions of subjects who had psychological stress than the Control group, a finding which was consistent with previous studies. In the multivariate analysis, psychological stress was a significant risk factor for NERD, but not for EE.

Recent studies have demonstrated a bidirectional relationship between sleep and GERD, where night-time reflux leads to sleep deprivation and sleep deprivation per se can exacerbate GERD by enhancing the perception of intra-esophageal stimuli [47]. In our study too, the NERD group had a significantly higher proportion of subjects whose average sleeping time was less than 5 h than the Control group, and sleep shortage was found to be a significant risk factor for NERD. There was no significant relationship between sleep shortage and EE, a finding which was consistent with a previous report [48].

Consistent with previous studies on the Japanese population [6, 49, 50], the NERD group in the present study had significantly more females, lower BMI, a higher proportion of subjects with atrophic gastritis, and a lower proportion of subjects with hiatal hernia than the EE group.

In addition, intake of a large quantity of food at supper was found to be a significant risk factor for the NERD group compared with the EE group. This difference between the NERD group and the EE group might be due to the fact that only 35 % of subjects in the EE group were symptomatic. The proportion of subjects having more food at supper than at breakfast and lunch in the symptomatic EE group was higher than that in the asymptomatic EE group (63.8 vs. 52.7 %, $p = 0.21$). Intake of a large quantity of food at supper might be a factor associated with symptomatic GERD.

There are several differences associated with the development of GERD between the Japanese population and the Western population. The first difference is that the prevalence of obesity is lower in the Japanese population than that in the Western population, although the Japanese lifestyle, including dietary habits, has been westernized. Reports from Western countries show that the proportion of GERD patients with a BMI of more than 25 is 61–75 % [29, 51]. On the other hand, the proportions of subjects with a BMI of more than 25 in our EE group and NERD group were 39.1 and 18.2 %, respectively. Consequently, the contribution of obesity to the development of GERD might be relatively small in the Japanese population.

The second difference between Japanese and Western populations is that the prevalence of *Helicobacter pylori* infection and the prevalence of atrophic gastritis that is caused by *H. pylori* infection are higher in the Japanese population than in the Western population. Female gender, lower BMI, and absence of hiatal hernia were reported to

be associated with NERD in Western countries [7, 12]. However, there have been no reports demonstrating that atrophic gastritis is a significant risk factor for NERD. Atrophic gastritis might be a characteristic of NERD patients in countries such as Japan in which the prevalence of *H. pylori* infection is high.

The third difference between the populations is related to the length of working hours. It is reported that Japanese people work longer hours than European people [52]. The long working hours might be associated with the development of psychological stress and sleep disturbance, and contribute to the development of GERD.

There are some limitations of the present study. First, the subjects in the NERD group and the EE group were those who underwent health screening, and not patients who were receiving medical treatment. Second, the allocation of subjects to the NERD group might change depending on the definition of NERD. Third, the questionnaire for psychological stress, physical stress, and sleep used in this study was simple, and might have been insufficient. Fourth, the factors identified in this study may not necessarily be causes of GERD, but rather the results of GERD. Fifth, in this study we were not able to evaluate the effects of *H. pylori* infection or the effects of concomitant medications such as aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), and Ca-blockers.

In conclusion, there were differences in the associated lifestyle factors between patients with NERD and those with EE, and there was also a gender-related difference. The lifestyle factors associated with NERD were egg intake, strong psychological stress, and sleep shortage. In male subjects, current smoking was a significant risk factor for both NERD and EE. Alcohol intake of >200 kcal/day and intake of a large quantity of food at supper were significant risk factors for EE in subjects with a hiatal hernia. We consider that modification of lifestyle factors, such as the amount of food eaten at supper, psychological stress, and duration of sleep, might become a form of therapy for GERD patients. Further studies are necessary to determine whether intervention for lifestyle factors is effective as treatment in GERD patients.

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Conflict of interest The authors declare that they have no conflict of interest.

References

- Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*. 2005;54(5):710–7.
- Delaney BC. Review article: prevalence and epidemiology of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2004;20(Suppl 8):2–4.
- Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Prevalence of gastro-oesophageal reflux symptoms and the influence of age and sex. *Scand J Gastroenterol*. 2004;39(11):1040–5.
- Goh KL. Changing epidemiology of gastroesophageal reflux disease in the Asian-Pacific region: an overview. *J Gastroenterol Hepatol*. 2004;19(Suppl 3):S22–5.
- Fujimoto K. Review article: prevalence and epidemiology of gastro-oesophageal reflux disease in Japan. *Aliment Pharmacol Ther*. 2004;20(Suppl 8):5–8.
- Fujiwara Y, Arakawa T. Epidemiology and clinical characteristics of GERD in the Japanese population. *J Gastroenterol*. 2009;44(6):518–34.
- Hershcovici T, Fass R. Nonerosive reflux disease (NERD)—an update. *J Neurogastroenterol Motil*. 2010;16(1):8–21.
- Johansson KE, Ask P, Boeryd B, Fransson SG, Tibbling L. Oesophagitis, signs of reflux, and gastric acid secretion in patients with symptoms of gastro-oesophageal reflux disease. *Scand J Gastroenterol*. 1986;21(7):837–47.
- Winters C Jr, Spurling TJ, Chobanian SJ, Curtis DJ, Esposito RL, Hacker JF 3rd, et al. Barrett's esophagus. A prevalent, occult complication of gastroesophageal reflux disease. *Gastroenterology*. 1987;92(1):118–24.
- Lind T, Havelund T, Carlsson R, Anker-Hansen O, Glise H, Hernqvist H, et al. Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. *Scand J Gastroenterol*. 1997;32(10):974–9.
- Galmiche JP, Barthelemy P, Hamelin B. Treating the symptoms of gastro-oesophageal reflux disease: a double-blind comparison of omeprazole and cisapride. *Aliment Pharmacol Ther*. 1997;11(4):765–73.
- Carlsson R, Dent J, Watts R, Riley S, Sheikh R, Hatlebakk J, et al. Gastro-oesophageal reflux disease in primary care: an international study of different treatment strategies with omeprazole. International GORD Study Group. *Eur J Gastroenterol Hepatol*. 1998;10(2):119–24.
- Robinson M, Earnest D, Rodriguez-Stanley S, Greenwood-Van Meerveld B, Jaffe P, Silver MT, et al. Heartburn requiring frequent antacid use may indicate significant illness. *Arch Intern Med*. 1998;158(21):2373–6.
- Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand J Gastroenterol*. 2005;40(3):275.
- Zagari RM, Fuccio L, Wallander MA, Johansson S, Fiocca R, Casanova S, et al. Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano–Monghidoro study. *Gut*. 2008;57(10):1354–9.
- Miwa H, Sasaki M, Furuta T, Koike T, Habu Y, Ito M, et al. Efficacy of rabeprazole on heartburn symptom resolution in patients with non-erosive and erosive gastro-oesophageal reflux disease: a multicenter study from Japan. *Aliment Pharmacol Ther*. 2007;26(1):69–77.
- Dean BB, Gano AD Jr, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol*. 2004;2(8):656–64.
- Miyamoto M, Manabe N, Haruma K. Efficacy of the addition of prokinetics for proton pump inhibitor (PPI) resistant non-erosive reflux disease (NERD) patients: significance of frequency scale for the symptom of GERD (FSSG) on decision of treatment strategy. *Intern Med*. 2010;49(15):1469–76.
- Kusano M, Shimoyama Y, Sugimoto S, Kawamura O, Maeda M, Minashi K, et al. Development and evaluation of FSSG:

- frequency scale for the symptoms of GERD. *J Gastroenterol.* 2004;39(9):888–91.
20. Danjo A, Yamaguchi K, Fujimoto K, Saitoh T, Inamori M, Ando T, et al. Comparison of endoscopic findings with symptom assessment systems (FSSG and QUEST) for gastroesophageal reflux disease in Japanese centres. *J Gastroenterol Hepatol.* 2009;24(4):633–8.
 21. Sasaki S, Yanagibori R, Amano K. Validity of a self-administered diet history questionnaire for assessment of sodium and potassium: comparison with single 24-hour urinary excretion. *Jpn Circ J.* 1998;62(6):431–5.
 22. Sasaki S, Yanagibori R, Amano K. Self-administered diet history questionnaire developed for health education: a relative validation of the test-version by comparison with 3-day diet record in women. *J Epidemiol.* 1998;8(4):203–15.
 23. Sasaki S, Ushio F, Amano K, Morihara M, Todoriki O, Uehara Y, et al. Serum biomarker-based validation of a self-administered diet history questionnaire for Japanese subjects. *J Nutr Sci Vitaminol (Tokyo).* 2000;46(6):285–96.
 24. Okubo H, Sasaki S, Rafamantanantsoa HH, Ishikawa-Takata K, Okazaki H, Tabata I. Validation of self-reported energy intake by a self-administered diet history questionnaire using the doubly labeled water method in 140 Japanese adults. *Eur J Clin Nutr.* 2008;62(11):1343–50.
 25. Murakami K, Sasaki S, Takahashi Y, Okubo H, Hirota N, Notsu A, et al. Reproducibility and relative validity of dietary glycaemic index and load assessed with a self-administered diet-history questionnaire in Japanese adults. *Br J Nutr.* 2008;99(3):639–48.
 26. Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy.* 1969;3:87–97.
 27. Festi D, Scaiola E, Baldi F, Vestito A, Pasqui F, Di Biase AR, et al. Body weight, lifestyle, dietary habits and gastroesophageal reflux disease. *World J Gastroenterol.* 2009;15(14):1690–701.
 28. Vemulapalli R. Diet and lifestyle modifications in the management of gastroesophageal reflux disease. *Nutr Clin Pract.* 2008;23(3):293–8.
 29. El-Serag HB, Satia JA, Rabeneck L. Dietary intake and the risk of gastro-oesophageal reflux disease: a cross sectional study in volunteers. *Gut.* 2005;54(1):11–7.
 30. Mitsukawa T, Takemura J, Ohgo S, Mizuta M, Ii T, Kuribayashi T, et al. Gallbladder function and plasma cholecystokinin levels in diabetes mellitus. *Am J Gastroenterol.* 1990;85(8):981–5.
 31. Hershcovici T, Mashimo H, Fass R. The lower esophageal sphincter. *Neurogastroenterol Motil.* 2011;23(9):819–30.
 32. Thomas GA, Rhodes J, Ingram JR. Mechanisms of disease: nicotine—a review of its actions in the context of gastrointestinal disease. *Nat Clin Pract Gastroenterol Hepatol.* 2005;2(11):536–44.
 33. Dodds WJ, Dent J, Hogan WJ, Helm JF, Hauser R, Patel GK, et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *N Engl J Med.* 1982;307(25):1547–52.
 34. Fujiwara Y, Kubo M, Kohata Y, Machida H, Okazaki H, Yamagami H, et al. Cigarette smoking and its association with overlapping gastroesophageal reflux disease, functional dyspepsia, or irritable bowel syndrome. *Intern Med.* 2011;50(21):2443–7.
 35. Isolaure J, Laippala P. Prevalence of symptoms suggestive of gastro-oesophageal reflux disease in an adult population. *Ann Med.* 1995;27(1):67–70.
 36. Locke GR 3rd, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ 3rd. Risk factors associated with symptoms of gastroesophageal reflux. *Am J Med.* 1999;106(6):642–9.
 37. Watanabe Y, Fujiwara Y, Shiba M, Watanabe T, Tominaga K, Oshitani N, et al. Cigarette smoking and alcohol consumption associated with gastro-oesophageal reflux disease in Japanese men. *Scand J Gastroenterol.* 2003;38(8):807–11.
 38. Gunji T, Sato H, Iijima K, Fujibayashi K, Okumura M, Sasabe N, et al. Risk factors for erosive esophagitis: a cross-sectional study of a large number of Japanese males. *J Gastroenterol.* 2011;46(4):448–55.
 39. Nozu T, Komiya H. Clinical characteristics of asymptomatic esophagitis. *J Gastroenterol.* 2008;43(1):27–31.
 40. Duroux P, Bauerfeind P, Emde C, Koelz HR, Blum AL. Early dinner reduces nocturnal gastric acidity. *Gut.* 1989;30(8):1063–7.
 41. Lanzon-Miller S, Pounder RE, McIsaac RL, Wood JR. The timing of the evening meal affects the pattern of 24-hour intragastric acidity. *Aliment Pharmacol Ther.* 1990;4(5):547–53.
 42. Piesman M, Hwang I, Maydonovitch C, Wong RK. Nocturnal reflux episodes following the administration of a standardized meal. Does timing matter? *Am J Gastroenterol.* 2007;102(10):2128–34.
 43. Fass R, Tougas G. Functional heartburn: the stimulus, the pain, and the brain. *Gut.* 2002;51(6):885–92.
 44. Naliboff BD, Mayer M, Fass R, Fitzgerald LZ, Chang L, Bolus R, et al. The effect of life stress on symptoms of heartburn. *Psychosom Med.* 2004;66(3):426–34.
 45. Nojkov B, Rubenstein JH, Adlis SA, Shaw MJ, Saad R, Rai J, et al. The influence of co-morbid IBS and psychological distress on outcomes and quality of life following PPI therapy in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.* 2008;27(6):473–82.
 46. Zheng Z, Nordenstedt H, Pedersen NL, Lagergren J, Ye W. Lifestyle factors and risk for symptomatic gastroesophageal reflux in monozygotic twins. *Gastroenterology.* 2007;132(1):87–95.
 47. Fass R. Effect of gastroesophageal reflux disease on sleep. *J Gastroenterol Hepatol.* 2010;25(Suppl 1):S41–4.
 48. Kusano M, Kouzu T, Kawano T, Ohara S. Nationwide epidemiological study on gastroesophageal reflux disease and sleep disorders in the Japanese population. *J Gastroenterol.* 2008;43(11):833–41.
 49. Fujiwara Y, Higuchi K, Shiba M, Yamamori K, Watanabe Y, Sasaki E, et al. Differences in clinical characteristics between patients with endoscopy-negative reflux disease and erosive esophagitis in Japan. *Am J Gastroenterol.* 2005;100(4):754–8.
 50. Mishima I, Adachi K, Arima N, Amano K, Takashima T, Moritani M, et al. Prevalence of endoscopically negative and positive gastroesophageal reflux disease in the Japanese. *Scand J Gastroenterol.* 2005;40(9):1005–9.
 51. Nocon M, Labenz J, Willich SN. Lifestyle factors and symptoms of gastro-oesophageal reflux—a population-based study. *Aliment Pharmacol Ther.* 2006;23(1):169–74.
 52. The Japan Institute for Labour Policy and Training. Databook of International Labour Statistics 2012. http://www.jil.go.jp/kokunai/statistics/databook/2012/06/p189-190_t6-1.pdf (in Japanese).