Sex differences in risk factors for future onset of reflux esophagitis

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(Received 15 December, 2020; Accepted 25 December, 2020)

Reflux esophagitis is known to be more prevalent in males, and previous studies have suggested sex differences in its risk factors. However, little is known about sex differences in the time-course of risk factors before reflux esophagitis onset. Thus, we conducted a retrospective longitudinal study using health checkup records. From the records of 230,056 individuals obtained from nine institutes in Japan, we selected 1,558 male reflux esophagitis cases, 3,116 male controls, 508 female reflux esophagitis cases, and 1,016 female controls were selected. We compared time-courses of risk factors between the case and control groups and identified abdominal circumference (AC), diastolic blood pressure, alanine transaminase (ALT), and current smoking in males and body mass index (BMI) in females as sex-specific risk factors. We also found that AC and ALT in males and BMI in females were significantly different between the reflux esophagitis case and control groups during the five years before reflux esophagitis onset. Our results suggest that visceral fat-type obesity and fatty liver in males and higher BMI in females are more frequently observed in reflux esophagitis cases several years before reflux esophagitis onset, and that proactive intervention to lifestyle can help prevent reflux esophagitis in both males and females.

Key Words: sex differences, reflux esophagitis, risk factors, longitudinal study, real world evidence

Reflux esophagitis (RE) is a disease in which reflux of gastric contents into the esophagus causes superficial erosion of the lower esophagus mucosa. The prevalence of RE has increased in recent years in East Asian countries, including Japan.¹ RE is known to be more prevalent in males,² and recent studies have elucidated that there are sex-specific risk factors for RE, such as high abdominal circumference (AC),³ visceral fat-type metabolic syndrome,⁴ hypertension,⁵ and hypertriglyceridemia in males as well as risk factors common to both sexes, including obesity,⁵–⁸ advanced age,⁵–⁶ current smoking⁶ and hiatal hernia.⁵,⁶,⁷ Hyperglycemia,⁵,⁷ and absence of atrophic gastritis.⁷,⁸ However, all of these sex-specific risk factors were found in cross-sectional studies, and little is known about whether their time-courses before RE onset are different from those in healthy controls. If the time-courses of risk factors before RE onset differ from those in healthy controls, it would suggest that preventive interventions targeted at improving the risk factors may reduce the risk of developing RE. Thus, we conducted a multicenter longitudinal study to investigate sex-specific factors associated with future RE onset using health checkup records from Japanese institutions.

Materials and Methods

This was a multicenter, retrospective, longitudinal study using health checkup records from nine institution (Hidaka Hospital, Gunma; Mitsubishi Mihara Hospital, Hiroshima; Junpukai Health Maintenance Center, Okayama; Shimane Environment and Health Public Corporation, Shimane; Meitw Hospital, Hyogo; Matsue Red Cross Hospital, Shimane; Okazaki City Medical Association Public Health Center, Aichi; Saiseikai Karatsu Hospital, Saga; Shinko Hospital, Hyogo) in Japan. This study was conducted in accordance with the Declaration of Helsinki (7th revision, 2013) and was approved by the ethics committee of each institution and the Central Ethics Committee of the Japanese Association for the Promotion of State-of-the-Art in Medicine, Nagoya, Aichi, Japan.

Population. Nine Japanese institutions that met the following criteria participated in this study: 1) patient information including age, sex, body height, body weight, drinking status, smoking status, fasting blood sugar (FBS), glycated hemoglobin level (HbA1c), and records of upper gastrointestinal endoscopy were available from annual health checkup records and 2) health checkup records from at least four successive years were available. An initial dataset was obtained from individuals who participated in annual health checkups and received at least one upper gastrointestinal endoscopy in 10 years (between April 2004 and March 2014) at the participating institutions. From the individuals who were endoscopically diagnosed with RE, case candidates who met the following criteria were selected: 1) participated in four or more health checkups at the participating institutions between April 2004 and March 2014; 2) newly diagnosed with RE after April 2009; 3) completed an upper gastrointestinal endoscopy during the two years prior to their first RE diagnosis; 4) participated in three or more health checkups in the five years before their first RE diagnosis; and 5) were 30 or older at their first RE diagnosis. From the individuals without RE diagnosis, control candidates who met the following criteria were selected: 1) participated in four or more health checkups between April 2004 and March 2014 and 2) completed an upper gastrointestinal endoscopy between April 2009 and March 2014. In case-control matching, two control candidates, who were matched in age, sex, participating institution, and underwent upper gastrointestinal endoscopy in the same year as the corresponding case of RE was endoscopically diagnosed, were selected for every one case candidate.

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doi: 10.3164/jcbn.20-202

J. Clin. Biochem. Nutr. | Published online: 3 April 2021 | 1–7
During (DBP), sequel comparison was the clinical investigation of comorbidities. The criteria investigated (2) diagnosis, baseline characteristics, and matched and the continuous characteristics. Applied to implemented using R significance multivariate analysis, for group and entered characteristics. In this model, analyses assessed the between groups, and the majority analysis of each year, whose case and were analyzed. The majority case and were analyzed. For comparison, baseline variables. A forward-backward stepwise model selection method based on Akaike’s An Information Criterion was applied to determine the characteristics included in the multivariate analysis, and a pooled result of the multivariate logistic regression analyses with differently selected characteristics was estimated by referencing van Buuren’s implementation of a simple majority method.

In the time-course analysis, we performed regression analyses using a mixed-effect model for repeated measures for each of the continuous characteristics that were significantly associated with the groups in the multivariate analysis for the baseline characteristics. In this model, group, year, and their interaction were entered as fixed effects and subject ID as a random effect, and we assessed the difference in time-course of the characteristics between groups by two aspects: a longitudinal comparison over the whole period using a type III analysis of variance with Satterthwaite’s method and a cross-sectional comparison of each year before baseline based on the coefficient of the interaction term. A multivariate logistic regression model with group year, and their interaction was applied as independent variables for categorical characteristics, and the difference in time-course between the groups was assessed via a chi-square test for longitudinal comparison and via a coefficient of the interaction term for cross-sectional comparison.

All statistical tests were performed in a two-sided manner, and the significance level was set at 0.05. All statistical processing was implemented using R ver. 3.6.3 (R Foundation for Statistical Computing) with lme4, lmerTest, emmeans, and mice packages.
for RE in females, which is similar to one of the studies and differs from the other.\(^{(6,9)}\) It is likely that insufficient statistical power due to the low rate of smoking among females led to these controversial results, and a larger study is needed to investigate sex differences in smoking as a risk factor for RE. Finally, elevated DBP in males was also a significant risk factor for RE in the baseline multivariate analysis, which is partially consistent with the study by Moki et al.,\(^{(5)}\) wherein hypertension, defined as SBP \(\geq 140\) mmHg and/or DBP \(\geq 90\) mmHg, was shown to be a risk factor for RE in males. However, considering that there were no significant differences between the groups in the time-course of DBP, the impact of DBP, even if it was associated with RE, may be minor.

The presence of hiatal hernia and the absence of atrophic gastritis have been reported as risk factors for RE in many studies and were significantly associated with RE onset in the baseline comparisons in this study.\(^{(1,4-6,9)}\) The longitudinal comparisons of the prevalence of hiatal hernia between groups demonstrated significantly more hiatal hernias in the RE case group than in the control group in both males and females. Additionally, the prevalence of hiatal hernia was significantly higher in the RE case group than in the control group during the three years prior to RE onset in males, and one year prior to RE onset in females. Hiatal hernia is considered to be one of the major etiologies of RE,\(^{(21)}\) and the fact that the prevalence of hiatal hernia increased before RE onset confirms this assertion. There was no significant difference in the prevalence of atrophic gastritis in the time-course of RE between the RE case and control groups in both sexes in the longitudinal comparisons. Furthermore, the rate of atrophic gastritis was lower in the RE case group for five consecutive years prior to RE onset. This is a reasonable result as gastric mucosal atrophy, mainly caused by Helicobacter pylori, is a long-term process of deterioration over a period of years to decades and typically provokes suppression of acid secretion.\(^{(22)}\) In contrast, the differences in atrophic gastritis between groups were unclear in both the longitudinal

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**Fig. 1.** Subject flow in this study. RE, reflux esophagitis; HC, health checkup; UGE, upper gastrointestinal endoscopy.
Table 1. Baseline characteristics of the case and control groups by sex

|                  | Male                          | Female                        |
|------------------|-------------------------------|-------------------------------|
|                  | Case (n = 1,558)              | Control (n = 3,116)           | p value† | Case (n = 508) | Control (n = 1,016) | p value† |
| Age (y), Mean ± SD | 53.9 ± 9.6                    | 54.0 ± 9.7                    | 0.805     | 54.1 ± 8.4     | 53.9 ± 8.3           | 0.692    |
| BMI (kg/m²), Mean ± SD | 23.9 ± 3.1                   | 23.3 ± 2.9                   | <0.001    | 22.2 ± 3.4     | 21.6 ± 3.1           | 0.003    |
| AC (cm), Mean ± SD | 85.7 ± 8.4                    | 83.8 ± 8.0                   | <0.001    | 79.7 ± 9.4     | 78.5 ± 8.8           | 0.016    |
| FBS (mg/dl), Mean ± SD | 104.6 ± 18.8                | 102.9 ± 17.6                 | 0.002     | 96.8 ± 14.7    | 96.7 ± 13.4          | 0.807    |
| HbA1c (%), Mean ± SD | 5.71 ± 0.61                   | 5.68 ± 0.57                  | 0.098     | 5.63 ± 0.45    | 5.63 ± 0.44          | 0.935    |
| SBP (mmHg), Mean ± SD | 113.2 ± 22.9                 | 111.4 ± 22.5                 | 0.011     | 110.4 ± 20.1   | 109.7 ± 20.0         | 0.491    |
| TG (mg/dl), Mean ± SD | 86.7 ± 22.0                   | 85.5 ± 22.1                  | 0.069     | 76.6 ± 20.2    | 75.8 ± 19.5          | 0.456    |
| HDL-C (mg/dl), Mean ± SD | 137.7 ± 93.0                 | 124.7 ± 77.5                 | <0.001    | 92.0 ± 68.0    | 87.4 ± 46.9          | 0.127    |
| LDL-C (mg/dl), Mean ± SD | 57.4 ± 14.7                   | 58.5 ± 14.5                  | 0.012     | 69.7 ± 15.8    | 70.8 ± 16.0          | 0.2      |
| TC (mg/dl), Mean ± SD | 205.2 ± 32.1                  | 204.9 ± 32.5                 | 0.75      | 214.4 ± 34.6   | 215.6 ± 34.0         | 0.515    |
| UA (mg/dl), Mean ± SD | 6.08 ± 1.18                   | 5.97 ± 1.17                  | 0.004     | 4.54 ± 1.02    | 4.42 ± 0.93          | 0.027    |
| AST (IU/L), Mean ± SD | 24.9 ± 11.6                   | 23.7 ± 9.1                   | <0.001    | 21.7 ± 8.3     | 20.9 ± 6.7           | 0.059    |
| ALT (IU/L), Mean ± SD | 28.3 ± 19.1                   | 25.2 ± 15.5                  | <0.001    | 19.4 ± 12.3    | 18.1 ± 10.0          | 0.029    |
| γ-GTP (IU/L), Mean ± SD | 52.7 ± 53.5                   | 45.7 ± 47.9                  | <0.001    | 24.9 ± 22.3    | 22.9 ± 20.4          | 0.082    |
| Current drinking, n (%) | 1,237 (79.4)                  | 2,421 (77.7)                 | 0.202     | 244 (48.0)     | 463 (45.6)           | 0.378    |
| Current smoking, n (%) | 466 (29.9)                    | 826 (26.5)                   | 0.018     | 44 (8.6)       | 64 (6.3)             | 0.125    |
| Gastrointestinal symptoms, n (%) | —                            | —                             | —         | —              | —                    | —        |
| Acid reflux symptoms | 169 (10.8)                    | 131 (4.2)                    | <0.001    | 72 (14.1)      | 62 (6.1)             | <0.001   |
| Gastric pain | 111 (7.1)                      | 235 (7.5)                    | 0.712     | 84 (16.6)      | 148 (14.5)           | 0.329    |
| Heavy stomach | 267 (17.1)                      | 510 (16.4)                    | 0.674     | 100 (19.7)    | 154 (15.2)           | 0.057    |
| Feeling of fullness | 203 (13.0)                    | 387 (12.4)                    | 0.706     | 89 (17.5)      | 131 (12.9)           | 0.057    |
| Belching | 240 (15.4)                      | 428 (13.7)                    | 0.329     | 76 (14.9)      | 140 (13.8)           | 0.615    |
| Endoscopic findings, n (%) | —                            | —                             | —         | —              | —                    | —        |
| Hiatal hernia | 388 (24.9)                    | 453 (14.5)                    | <0.001    | 95 (18.7)      | 64 (6.3)             | <0.001   |
| Atrophic gastritis | 572 (36.7)                    | 1377 (44.2)                   | <0.001    | 155 (30.5)    | 339 (33.4)           | 0.282    |
| Barrett's esophagus | 44 (2.8)                      | 109 (3.5)                     | 0.22      | 13 (2.6)       | 29 (2.8)             | 0.867    |
| Comorbidities, n (%) | —                            | —                             | —         | —              | —                    | —        |
| Diabetes | 153 (9.8)                        | 258 (8.3)                    | 0.083     | 27 (5.3)       | 47 (4.6)             | 0.554    |
| Hypertension | 366 (23.5)                    | 619 (19.9)                    | 0.005     | 68 (13.3)     | 115 (11.3)           | 0.263    |
| Hyperlipidemia | 282 (18.1)                    | 492 (15.8)                    | 0.048     | 83 (16.3)     | 154 (15.1)           | 0.571    |

Missing values were imputed by chained equations. †p values were calculated based on pooled estimates of univariate logistic regression coefficients with the group as dependent variable. n, total number of subjects in the group (except subjects whose characteristics were unknown); BMI, body mass index; AC, abdominal circumference; FBS, fasting blood sugar; HbA1c, glycated hemoglobin levels; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase.

Table 2. Result of multivariate logistic regression analysis for baseline characteristics (only selected variables by stepwise method)

|                  | Male                          | Female                        |
|------------------|-------------------------------|-------------------------------|
|                  | Odds ratio [95% CI]          | p value | Odds ratio [95% CI] | p value |
| BMI (kg/m²)‡     | —                            | —       | 1.037 [1.001, 1.074] | 0.046 |
| AC (cm)          | 1.022 [1.014, 1.031]         | <0.001 | —                    | —      |
| DBP (mmHg)       | 1.003 [1.0003, 1.006]        | 0.048  | —                    | —      |
| UA (mg/dl)       | —                            | —       | —                    | —      |
| ALT (IU/L)       | 1.005 [1.001, 1.009]         | 0.009  | —                    | —      |
| Current smoking  | 1.197 [1.037, 1.382]         | 0.014  | —                    | —      |
| Acid reflux symptoms | 2.703 [2.117, 3.451]    | <0.001 | 2.548 [1.760, 3.687] | <0.001 |
| Hiatal hernia    | 2.189 [1.862, 2.574]         | <0.001 | 3.598 [2.468, 5.245] | <0.001 |
| Atrophic gastritis | 0.646 [0.565, 0.738]       | <0.001 | 0.713 [0.552, 0.920] | 0.009 |

‡Unit odds ratios were presented. BMI, body mass index; AC, abdominal circumference; UA, uric acid; DBP, diastolic blood pressure; ALT, alanine aminotransferase.
Although there is no rational explanation for this sex difference, postmenopausal progression of atrophy may have confounded the association between atrophic gastritis and RE in females. Since the prevalence of reflux symptoms was significantly higher in the RE case group than in the control group for the five years prior to RE onset, the presence of the symptoms is an obvious risk factor of RE for both males and females.
This is not surprising, given that RE is a disease primarily caused by acid reflux, but it is noteworthy that acid reflux symptoms were more prevalent for several years before RE onset in the RE case group. However, it should be noted that the prevalence of acid reflux symptoms was likely skewed toward lower values. In our cohort, the asymptomatic rate at the RE onset was 90.2% in males and 86.0% in females. This is much higher than the 33.6–41.7% reported in a systematic review. Although medication records were not available from the health checkup record database, it is speculated that this may be because some subjects were being treated for reflux symptoms.

This study has several limitations. We had planned to collect data regarding history of medications that could affect RE development, namely acid secretion inhibitors, calcium blockers, and aspirin, at first; however we abandoned because they could not be sufficiently obtained from the health checkup records. In addition, the items directly related to lifestyle habits, such as dietary and exercise habits, could not be also used for analysis because the data format was not standardized among participating institutions. Lack of information about treatment history and inconsistency in data format are major barriers to retrospective studies, in general; therefore we hope that institutions across the country will adopt a standardized format to investigate health information including treatment history and lifestyle habits for health checkup records and revitalize researches based on “real world data” in the future. Moreover, since we defined the presence or absence of RE solely on health checkup records from April 2004 to March 2013 in this study, subjects who had a history of RE before April 2004 or who had been diagnosed with RE and treated outside of their health checkup might not have been included in our cohort. Although this may have caused some bias, it is probably limited as the risk factors associated with RE in this study were consistent with previous studies.

In conclusion, the results of this study demonstrate that acid reflux symptoms, hiatal hernia, and the absence of atrophic gastritis are common risk factors for RE in both males and females, whereas AC, DBP, ALT, and current smoking are specific risk factors to males and BMI is specific to females. Moreover, significant differences between the groups in AC, ALT, acid reflux symptoms, and atrophic gastritis in males and BMI and acid reflux symptoms in females were observed during the five years prior to RE onset. Although the risk factors identified in this study are already known from the previous cross-sectional studies, this is the first study to investigate the time-courses of the factors by year during five years prior to RE onset, presenting important findings to elucidate a natural history of developing RE. In addition, these results suggest that males with visceral fat-type obesity or fatty liver and females with higher BMI are at risk for future RE onset, and that proactive intervention to their lifestyle, including dietary and exercise habit changes can help prevent RE in both males and females.

**Author Contributions**

SO, KN, KI, KH, and TJ contributed to the study conception and design. Material preparation, data collection, and analysis were performed by SO. The first draft of the manuscript was written by SO and all the other authors critically commented on previous versions of the manuscript. All authors read and approved the final manuscript.
Acknowledgments

This work was funded by AstraZeneca K.K. (Osaka, Japan), based on a contract of clinical study support. We are grateful to Yuzuru Toki (Hidaka Hospital, Gunma, Japan), Ryo Yamauchi (Mitsubishi Mihara Hospital, Hiroshima, Japan), Eizo Kayashima (Junpukai Health Maintenance Center, Okayama, Japan), Kyoichi Adachi (Shimane Environment and Health Public Corporation, Shimane, Japan), Kiyohiko Kishi (Meiwa Hospital, Hyogo, Japan), Hiroshi Suetsugu (Matsue Red Cross Hospital, Shimane, Japan), Tsuneya Wada (Okazaki City Medical Association Public Health Center, Aichi, Japan), Hiroyoshi Endo (Saiseikai Karatsu Hospital, Saga, Japan), and Hajime Yamada (Shinko Hospital, Hyogo, Japan) for providing the health checkup records to this study.

Abbreviations

AC abdominal circumference

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Conflict of Interest

No potential conflicts of interest were disclosed.

ALT alanine aminotransferase
AST aspartate aminotransferase
BMI body mass index
DBP diastolic blood pressure
FBS fasting blood sugar
γ-GTP γ-glutamyl transpeptidase
HbA1c glycated hemoglobin level
HDLC high-density lipoprotein cholesterol
LA Los Angeles
LDLC low-density lipoprotein cholesterol
RE reflux esophagitis
SBP systolic blood pressure
TC total cholesterol
TG triglyceride
UA uric acid

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