

# Association between triglyceride-glucose index and gastroesophageal reflux disease: a health checkup cohort study

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## Research Article

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# Abstract

The triglyceride-glucose (TyG) index was proposed as a useful marker of metabolic syndrome. Insulin resistance, which is the main mechanism underlying metabolic syndrome, is related to the gastroesophageal reflux disease (GERD). This study aimed to elucidate the association between the TyG index and GERD. We retrospectively reviewed the electronic medical records of patients who underwent gastroduodenoscopy at a checkup center. The calculation of TyG index used following formula:  $\ln(\text{fasting triglycerides [mg/dL]} \times \text{fasting glucose [mg/dL]}/2)$ . We divided the patients into four groups according to the TyG index quartile (Q). We evaluated the relationship between the alteration of the TyG index and GERD in patients who received health checkup two times. Among the 52,605 enrolled patients, 3,073 (5.8%) were diagnosed with GERD. The odds ratios (ORs) for GERD in the TyG index progressively increased across quartiles ( $P < 0.001$ ): Q2 (OR = 2.477), Q3 (OR = 3.013), and Q4 (OR = 4.027) compared with Q1, which was used as a reference. Male, obesity, smoking, alcohol consumption, and hypertension were also predictive factors for GERD. Moreover, the degree of TyG index increase during the first and second tests in the GERD group was more prominent than that in the control group ( $P = 0.001$ ). In conclusion, the higher TyG index was significantly associated with GERD. The TyG index may be a novel predictive biomarker of GERD.

## Introduction

Gastroesophageal reflux disease (GERD) is a common upper gastrointestinal disorder. The prevalence of GERD in Western countries is higher as approximately 20% than that in Asian countries<sup>1,2</sup>. Because of Westernized diets and increased *Helicobacter pylori* (*H. pylori*) eradication rates, the prevalence of GERD in Asian countries has increased by approximately 15%<sup>3-5</sup>. Therefore, GERD is a health concern worldwide. GERD affects the quality of life of patients because of its various clinical symptoms<sup>6</sup> and GERD-related complications such as Barrett's esophagus and adenocarcinoma of the esophagus<sup>7</sup>. Therefore, the evaluating the predictive factors and understanding the precise pathophysiology of GERD are important.

A previous study reported that the severity of reflux esophagitis is associated with components of metabolic syndrome such as obesity, hyperglycemia, and elevated BP and triglyceride (TG) levels<sup>8</sup>. In addition to these factors, sarcopenia, which is defined as skeletal muscle attenuation and is associated with metabolic syndrome, was an independent risk factor for GERD in a recent study<sup>9</sup>. Interleukin-6 (IL-6) stimulates the secretion of hepatic TGs and plays a role in insulin resistance (IR) at the cellular level in hepatocytes<sup>10,11</sup>. Moreover, the expression of IL-6 was consistently increased in Barrett's esophagus compared to that in control tissues<sup>12</sup>. Thus, GERD is associated with metabolic syndrome.

In 2008, the triglyceride-glucose (TyG) index was introduced as a novel surrogate marker for IR in healthy individuals for the first time<sup>13</sup>. Previous studies have mainly evaluated the association between the TyG index and diabetes or cardiovascular diseases<sup>14,15</sup>. The TyG index was calculated using a simple formula

based on the TG and glucose levels in a routine laboratory test. The TyG index has clinical significance in various metabolic conditions because of the synergistic effect of lipotoxicity and glucotoxicity. Increased adipose tissue causes lipid overflow and inflammation via alteration of the secretion for adipokines and cytokines, thereby playing an important role in the development of IR<sup>16</sup>. Both lipotoxicity and glucotoxicity have vicious cycles that contribute to reducing the action of insulin on glucose metabolism<sup>17</sup>.

Since both the TyG index and GERD are related to the metabolic syndrome, we hypothesized that the TyG index is associated with GERD. However, studies conducted to identify this relationship are scarce. This study aimed to elucidate the predictive factors for GERD, with a focus on the TyG index in a large health checkup cohort.

## Results

### Baseline characteristics.

Table 1 shows the baseline characteristics of the study population. The mean age of the enrolled patients was  $48.5 \pm 11.2$  years, and 52.9% of the patients were men. The mean BMI was  $23.7 \pm 3.4$  kg/m<sup>2</sup> and 31.8% were diagnosed with obesity. The average TyG index was  $9.30 \pm 0.58$ . Approximately 11.0% of the patients had hypertension. Additionally, 27.1% of the patients had *H. pylori* infection. A total of 3,073 (5.8%) and 434 (0.8%) patients were diagnosed with GERD and ERD, respectively. Other baseline characteristics of the study population are presented in Table 1.

### Risk factors for GERD.

In the univariate analysis, male, obesity, smoking, alcohol consumption, and hypertension had a significant association with GERD (Table 2). In addition, the proportion of *H. pylori* infection in the GERD group was significantly lower than that in the control group. The mean TyG index for the GERD group was significantly higher than that for the control group ( $9.74 \pm 0.89$  vs.  $9.27 \pm 0.54$ ,  $P < 0.001$ ). The proportions of Q3 and Q4 groups in TyG index quartile were significantly higher in the GERD group than in the control group (30.4% vs. 25.1% in the Q3 group and 37.4% vs. 20.4% in the Q4 group,  $P < 0.001$ ).

In multivariate analysis, the TyG index in the quartile ( $P < 0.001$ ), male sex (odds ratio [OR] = 1.425, 95% confidence interval [CI]: 1.285–1.577,  $P < 0.001$ ), obesity (OR = 1.300, 95% CI: 1.201–1.406,  $P < 0.001$ ), smoking (OR = 1.136, 95% CI: 1.036–1.245,  $P = 0.007$ ), alcohol consumption (OR = 1.488, 95% CI: 1.359–1.629,  $P < 0.001$ ), and hypertension (OR = 1.546, 95% CI: 1.403–1.703,  $P < 0.001$ ) were identified as independent risk factors for GERD (Table 3). *H. pylori* infection was significantly negatively associated with GERD (OR = 0.678, 95% CI: 0.620–0.742,  $P < 0.001$ ). Taking Q1 as the reference, the ORs for GERD were increased according to the TyG levels for Q2, Q3, and Q4: Q2 (OR = 2.477, 95% CI: 2.142–2.863,  $P <$

0.001), Q3 (OR = 3.013, 95% CI: 2.610–3.478,  $P < 0.001$ ), and Q4 (OR = 4.027, 95% CI: 3.484–4.655,  $P < 0.001$ ).

## Risk factors for ERD.

In the univariate analysis, male sex, obesity, smoking, alcohol consumption, and hypertension were significantly associated with an increased risk for ERD (Table 4). The mean TyG index for the ERD group was significantly higher than that for the control group ( $9.94 \pm 1.08$  vs.  $9.27 \pm 0.54$ ,  $P < 0.001$ ). The TyG indices for the Q3 and Q4 groups were significantly higher in the ERD group than in the control group (29.0% vs. 25.1% in Q3 and 47.5% vs. 20.4% in Q4,  $P < 0.001$ ).

In multivariate analysis, the TyG index in the quartile ( $P < 0.001$ ), male sex (OR = 3.906, 95% CI: 2.732–5.587,  $P < 0.001$ ), obesity (OR = 1.972, 95% CI: 1.606–2.420,  $P < 0.001$ ), smoking (OR = 1.540, 95% CI: 1.233–1.924,  $P < 0.001$ ), and hypertension (OR = 1.747, 95% CI: 1.392–2.191,  $P < 0.001$ ) were independent risk factors for ERD (Table 5). With respect to the TyG index, the ORs for ERD were progressively increased according to quartiles: Q2 (OR = 4.264, 95% CI: 2.418–7.522,  $P < 0.001$ ), Q3 (OR = 4.841, 95% CI: 2.767–8.471,  $P < 0.001$ ), and Q4 (OR = 7.390, 95% CI: 4.247–12.857,  $P < 0.001$ ).

## Progression of the TyG index and GERD.

Among the study population, 1,123 patients of GERD group and 8,815 patients of control group received health checkup two times. The mean TyG index for the GERD group was  $9.41 \pm 0.02$  in the first test and  $9.66 \pm 0.02$  in the second test. Moreover, mean TyG index for the control group was  $9.27 \pm 0.01$  in the first test and  $9.28 \pm 0.01$  in the second test. The degree of the TyG index increase in the GERD group was more significant than that in the control group ( $P = 0.001$ , Figure 1A). This tendency was maintained after adjusting for obesity, hypertension, *H. pylori* infection, alcohol consumption, and smoking. After adjustment, the TyG index for the GERD group was  $9.36 \pm 0.02$  in the first test and  $9.57 \pm 0.02$  in the second test. The mean TyG index for the control group was  $9.30 \pm 0.01$  in the first test and  $9.27 \pm 0.01$  in the second test. The degree of the TyG index increase index was higher in the GERD group than in the control group ( $P = 0.001$ , Figure 1B).

## Discussion

To the best of our knowledge, this is the first study to demonstrate an association between the TyG index and GERD. To evaluate IR, various methods, such as the hyperinsulinemic-euglycemic clamp and the insulin tolerance test, have been used<sup>18,19</sup>. Since these methods are expensive and invasive, the homeostasis model assessment for IR (HOMA-IR) was introduced as an alternative method<sup>20</sup>. Recently, the TyG index, which is a simple and cost-effective marker from routine laboratory result, was identified as a useful marker for IR in recent studies<sup>13,21</sup>. Despite its simplicity, the TyG index has substantial clinical importance owing to its metabolic significance.

Although the precise mechanism underlying the relationship between the TyG index and GERD is unclear, it may be explained by the metabolic syndrome, which is a complex of various metabolic conditions such as IR, obesity, dyslipidemia, and hypertension<sup>22</sup>. Among these conditions, IR, which is the inability of insulin to transport glucose into optimal cells, is closely associated with metabolic syndrome<sup>23,24</sup>.

The relationship between GERD and IR is explained by changes in esophageal motility resulting from hyperglycemia, which increases the peristaltic wave duration and decreases peristaltic velocity in the distal esophagus, decreases lower esophageal sphincter (LES) pressure, and eventually delays gastric emptying<sup>25-27</sup>. Several pro-inflammatory cytokines are involved in insulin transport disturbances linked with insulin receptor substrate serine phosphorylation-1 and nuclear factor-kappa B<sup>28</sup>. Previous studies have reported that hyperglycemia is associated with a prolonged LES relaxation period compared with euglycemic conditions<sup>25,27</sup>, and high IR is clearly associated with increased severity and prevalence of GERD<sup>29</sup>.

In addition to the TyG index, metabolic factors such as obesity and hypertension were significantly associated with GERD in this study. Inflammation is involved in the association between obesity and IR. Obesity-associated inflammation in the adipose tissue and liver induces an increase in macrophage infiltration and the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha and IL-6. These cytokines, in addition to other inflammatory mediators are involved in the insulin signaling pathway and the induction of IR. IR, with compensatory hyperinsulinemia, is an important proposed mechanism in the pathophysiology of hypertension. IR induces increased blood pressure through various mechanisms including stimulating sympathetic nervous system activity and renal tubular sodium reabsorption. Thus, various metabolic factors and GERD are interlinked by IR.

The strength of this study was that we analyzed patients who received laboratory tests two times during the study period. The mean TyG indices for the first and second tests increased in both the GERD and control groups. This result may be associated with the aging process between the first and second tests. However, the amount of the increase was more noticeable in the GERD group than that in the control group. This tendency was maintained after adjusting for metabolic factors, *H. pylori* infection, smoking, and alcohol consumption. These findings suggest that the TyG index is not only an independent predictive factor for GERD but may also be involved in the pathogenesis of GERD. Moreover, if a patient has GERD-related symptoms and shows a noticeable increase in the TyG index compared with previous test, an upper endoscopy may be recommended.

The diagnosis of GERD is based on heterogeneous clinical symptoms such as regurgitation, heartburn, and dyspepsia<sup>30</sup>. Since our checkup center questionnaire did not have questions to evaluate these symptoms, GERD was diagnosed via endoscopic findings based on the LA classification<sup>31</sup>. To overcome this limitation, we set "ERD group (LA grades B to D reflux esophagitis)," which is a more conclusive endoscopic finding for GERD<sup>32</sup>, and performed additional analysis. In addition to the TyG index, metabolic components such as obesity and hypertension were significantly associated with GERD. The

TyG index and these metabolic factors were also independent predictive factors for ERD. Notably, regarding the TyG index, the OR for ERD was stronger than that for GERD.

This study had several limitations. First, because of the retrospective nature of this study, we might have collected some incomplete data. Second, since the study design was cross-sectional, there was a selection bias, with regards to the individual's socioeconomic status and dietary habits. Third, GERD was diagnosed based on endoscopic findings via a retrospective review of endoscopic images in our electronic medical records. However, we performed additional analysis in the ERD group, which is a more specific mucosal injury for GERD. Fourth, since enrolled patients of this study were Korean from single center, it is hard to generalize our findings. Finally, since the laboratory tests performed at our health checkup center did not include a test for the insulin level, the HOMA-IR was not considered. Further studies are needed to measure the insulin levels and to compare the TyG index with the HOMA-IR.

In conclusion, the TyG index may be a novel predictive biomarker for GERD. Notably, the amount of the increase in TyG index between the first and second tests was prominent for GERD. Therefore, the TyG index from routine laboratory tests could be helpful for diagnosing GERD in clinical practice. Moreover, treatment of high TG or glucose levels, which are determinants of TyG index, may be important for the prevention and treatment of GERD.

## Methods

### Study design and population.

We reviewed the electronic medical records of 61,014 patients who underwent upper gastrointestinal endoscopy for a routine health checkup from January 2013 to September 2020. Patients with a current medication for anti-diabetic agents ( $n = 4,473$ ) and fasting plasma glucose  $\geq 126$  mg/dL ( $n = 2,094$ ), a history of cancer ( $n = 1,461$ ) and gastric surgery ( $n = 227$ ), a current medication for TG-lowering agents ( $n = 98$ ) and high TG level ( $\geq 400$  mg/dL) ( $n = 15$ ), and an incomplete electronic medical records ( $n = 41$ ) were excluded. As a result, 52,605 patients were enrolled in this study (Figure 2).

The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board of Gangnam Severance Hospital (IRB no. 3-2020-0395). Moreover, the informed consent was waived by the Institutional Review Board of Gangnam Severance Hospital, as this study was a retrospective analysis of the existing administrative and clinical data.

### Data collection.

Data were retrospectively collected from the electronic medical records of the enrolled patients. Patients underwent a health checkup after fasting for 12 hours, and the data included laboratory and anthropometric parameters and endoscopic findings. Laboratory data included fasting glucose, total

cholesterol, TG, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein cholesterol levels. The calculation of TyG index used following formula:  $\ln(\text{fasting triglycerides [mg/dL]} \times \text{fasting glucose [mg/dL]}/2)$ . According to the TyG index, enrolled patients were classified into four groups as follows: quartile 1 (Q1), between 6.45 and 8.93; Q2 between 8.93 and 9.30; Q3 between 9.30 and 9.72; and Q4, between 9.72 and 13.52. Moreover, to evaluate the relationship between the variation of the TyG index and GERD, we compared the TyG index between the first and second tests in patients who received health checkup two times during the study period. In the case of GERD, a follow-up test was defined as test occurring at the time of GERD diagnosis.

Height, body weight, and waist circumference were measured while the patients were wearing lightweight clothing without shoes. Body mass index (BMI) was calculated as body weight divided by height squared ( $\text{kg/m}^2$ ). Obesity was defined as a  $\text{BMI} \geq 25 \text{ kg/m}^2$  according to the Asia-Pacific criteria<sup>33</sup>.

## Endoscopic evaluation of the stomach.

All enrolled patients underwent upper endoscopic examinations using an endoscope (GIF-H260; Olympus Medical Systems, Tokyo, Japan) equipped with an electronic endoscopy system (EVIS LUCERA; Olympus Medical Systems). In this study, GERD was diagnosed based on endoscopic findings, which included Los Angeles (LA) grades A to D reflux esophagitis. LA grades B to D were defined as erosive reflux disease (ERD).

The following three methods were used for *H. pylori* infection: rapid urease test (CLO test; Delta West, Bentley, Australia), pathology (Giemsa staining), and immunoglobulin G test specific for *H. pylori* in serum (enzyme-linked fluorescence assay, Vidas (bioMerieux Vitek, Inc. (Hazelwood, MO, USA)). *H. pylori* infection was diagnosed when the results of at least one of these three tests was positive.

## Questionnaire.

All patients who visited our checkup center were asked to complete the questionnaire. The questionnaire included questions on smoking, alcohol consumption, and medical history such as hypertension. A current smoker was defined as a patient who is currently smoking or has smoked 100 cigarettes in their lifetime. Alcohol consumption was defined as the consumption of alcohol at least twice per week for a year. Patients were asked to check “yes” or “no” to indicate whether they were taking medication for hypertension. A patient was considered to have hypertension if they answered “yes” on the questionnaire when asked whether they have hypertension or if they had a systolic blood pressure  $\geq 140 \text{ mmHg}$  or a diastolic blood pressure  $\geq 90 \text{ mmHg}$ <sup>34</sup>.

## Statistical analysis.

Continuous variables were shown as the mean  $\pm$  standard deviation. We used t-test to compare continuous variables between groups. Categorical variables were shown as numbers and percentages, and we performed the chi-square test to compare categorical variables between groups. To identify the predictive factors for GERD and ERD, we used the multivariate logistic regression analysis. This study has similar methods in data analyses, with previous study<sup>9</sup>, which identify the association between sarcopenia and GERD. However, the purpose and conclusion of our study was different from this previous study. Moreover, we performed a multivariate linear mixed model to evaluate the association between variation of the TyG index and GERD. Statistical analysis was performed using SPSS (version 25.0; IBM Corp., Armonk, NY, USA). A two-tailed *P*-value < 0.05 was considered significant.

## Declarations

## Author Contributions

Y.M.K. substantial contributions to conception and design, or analysis and interpretation of data and drafting the article or revising it critically for important intellectual content; J.K. substantial contributions to conception and design, final approval of the version to be published and agreement to be accountable for all aspects of the work; S.J.B. Acquisition of data; J.S.P., J.C., Y.H.Y., and H.P. revising the article critically for important intellectual content; All authors reviewed the manuscript.

## Additional Information

Competing Interests: The authors declare no competing interests.

## Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request since the datasets include patients' personal information.

## References

1. Wu, J. C. Gastroesophageal reflux disease: an Asian perspective. *J Gastroenterol Hepatol* **23**, 1785-1793.<https://doi.org/10.1111/j.1440-1746.2008.05684.x> (2008).
2. El-Serag, H. B., Sweet, S., Winchester, C. C. & Dent, J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* **63**, 871-880.<https://doi.org/10.1136/gutjnl-2012-304269> (2014).
3. He, J.*et al.* A population-based survey of the epidemiology of symptom-defined gastroesophageal reflux disease: the Systematic Investigation of Gastrointestinal Diseases in China. *Bmc Gastroenterol*

10. <https://doi.org/Artn> 94. 10.1186/1471-230x-10-94 (2010).
4. Jung, H. K. Epidemiology of Gastroesophageal Reflux Disease in Asia: A Systematic Review. *J Neurogastroenterol* **17**, 14-27. <https://doi.org/10.5056/jnm.2011.17.1.14> (2011).
  5. Dent, J., El-Serag, H. B., Wallander, M. A. & Johansson, S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* **54**, 710-717. <https://doi.org/10.1136/gut.2004.051821> (2005).
  6. Richter, J. E. & Rubenstein, J. H. Presentation and Epidemiology of Gastroesophageal Reflux Disease. *Gastroenterology* **154**, 267-276. <https://doi.org/10.1053/j.gastro.2017.07.045> (2018).
  7. Spechler, S. J. GERD and its complications. *Mt Sinai J Med* **67**, 106-111 (2000).
  8. Hsieh, Y. H. *et al.* What is the impact of metabolic syndrome and its components on reflux esophagitis? A cross-sectional study. *Bmc Gastroenterol* **19**. <https://doi.org/ARTN> 33. 10.1186/s12876-019-0950-z (2019).
  9. Kim, Y. M. *et al.* Association between skeletal muscle attenuation and gastroesophageal reflux disease: A health check-up cohort study. *Sci Rep* **9**, 20102. <https://doi.org/10.1038/s41598-019-56702-6> (2019).
  10. Nonogaki, K. *et al.* Interleukin-6 stimulates hepatic triglyceride secretion in rats. *Endocrinology* **136**, 2143-2149. <https://doi.org/10.1210/endo.136.5.7720663> (1995).
  11. Senn, J. J., Klover, P. J., Nowak, I. A. & Mooney, R. A. Interleukin-6 induces cellular insulin resistance in hepatocytes. *Diabetes* **51**, 3391-3399. <https://doi.org/10.2337/diabetes.51.12.3391> (2002).
  12. Dvorak, K. & Dvorak, B. Role of interleukin-6 in Barrett's esophagus pathogenesis. *World J Gastroenterol* **19**, 2307-2312. <https://doi.org/10.3748/wjg.v19.i15.2307> (2013).
  13. Simental-Mendia, L. E., Rodriguez-Moran, M. & Guerrero-Romero, F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord* **6**, 299-304. <https://doi.org/10.1089/met.2008.0034> (2008).
  14. Sanchez-Inigo, L., Navarro-Gonzalez, D., Fernandez-Montero, A., Pastrana-Delgado, J. & Martinez, J. A. The TyG index may predict the development of cardiovascular events. *Eur J Clin Invest* **46**, 189-197. <https://doi.org/10.1111/eci.12583> (2016).
  15. Lee, D. Y. *et al.* Predictive Value of Triglyceride Glucose Index for the Risk of Incident Diabetes: A 4-Year Retrospective Longitudinal Study. *Plos One* **11**. <https://doi.org/ARTN> e0163465. 10.1371/journal.pone.0163465 (2016).
  16. Meex, R. C. R., Blaak, E. E. & van Loon, L. J. C. Lipotoxicity plays a key role in the development of both insulin resistance and muscle atrophy in patients with type 2 diabetes. *Obes Rev* **20**, 1205-1217. <https://doi.org/10.1111/obr.12862> (2019).
  17. Scheen, A. J., Paquot, N. & Lefebvre, P. J. [Glucotoxicity and lipotoxicity, two implicated accomplices in the vicious circle of type 2 diabetes]. *Rev Med Liege* **54**, 535-538 (1999).
  18. DeFronzo, R. A., Tobin, J. D. & Andres, R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* **237**, E214-223. <https://doi.org/10.1152/ajpendo.1979.237.3.E214> (1979).

19. Bergman, R. N., Prager, R., Volund, A. & Olefsky, J. M. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. *J Clin Invest* **79**, 790-800.<https://doi.org/10.1172/JCI112886> (1987).
20. Bonora, E.*et al.* Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* **23**, 57-63.<https://doi.org/10.2337/diacare.23.1.57> (2000).
21. Unger, G., Benozzi, S. F., Perruzza, F. & Pennacchiotti, G. L. Triglycerides and glucose index: a useful indicator of insulin resistance. *Endocrinol Nutr* **61**, 533-540.<https://doi.org/10.1016/j.endonu.2014.06.009> (2014).
22. Rochlani, Y., Pothineni, N. V., Kovelamudi, S. & Mehta, J. L. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Ther Adv Cardiovasc Dis* **11**, 215-225.<https://doi.org/10.1177/1753944717711379> (2017).
23. Roberts, C. K., Hevener, A. L. & Barnard, R. J. Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training. *Compr Physiol* **3**, 1-58.<https://doi.org/10.1002/cphy.c110062> (2013).
24. Wilcox, G. Insulin and insulin resistance. *Clin Biochem Rev* **26**, 19-39 (2005).
25. Punjabi, P., Hira, A., Prasad, S., Wang, X. & Chokhavatia, S. Review of gastroesophageal reflux disease (GERD) in the diabetic patient. *J Diabetes* **7**, 599-609.<https://doi.org/10.1111/1753-0407.12279> (2015).
26. Lee, S. D., Keum, B., Chun, H. J. & Bak, Y. T. Gastroesophageal Reflux Disease in Type II Diabetes Mellitus With or Without Peripheral Neuropathy. *J Neurogastroenterol Motil* **17**, 274-278.<https://doi.org/10.5056/jnm.2011.17.3.274> (2011).
27. Krishnan, B., Babu, S., Walker, J., Walker, A. B. & Pappachan, J. M. Gastrointestinal complications of diabetes mellitus. *World J Diabetes* **4**, 51-63.<https://doi.org/10.4239/wjd.v4.i3.51> (2013).
28. Budiyan, L., Purnamasari, D., Simadibrata, M. & Abdullah, M. Insulin Resistance in Gastroesophageal Reflux Disease. *Acta Med Indones* **50**, 336-342 (2018).
29. Hsu, C. S.*et al.* Increasing insulin resistance is associated with increased severity and prevalence of gastro-oesophageal reflux disease. *Aliment Pharm Ther* **34**, 994-1004.<https://doi.org/10.1111/j.1365-2036.2011.04817.x> (2011).
30. Clarrett, D. M. & Hachem, C. Gastroesophageal Reflux Disease (GERD). *Mo Med* **115**, 214-218 (2018).
31. Lundell, L. R.*et al.* Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* **45**, 172-180.<https://doi.org/DOI10.1136/gut.45.2.172> (1999).
32. Gyawali, C. P.*et al.* Modern diagnosis of GERD: the Lyon Consensus. *Gut* **67**, 1351-1362.<https://doi.org/10.1136/gutjnl-2017-314722> (2018).
33. Pan, W. H. & Yeh, W. T. How to define obesity? Evidence-based multiple action points for public awareness, screening, and treatment: an extension of Asian-Pacific recommendations. *Asia Pac J Clin Nutr* **17**, 370-374 (2008).

34. Unger, T.*et al.* 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension* **75**, 1334-1357. <https://doi.org/10.1161/HYPERTENSIONAHA.120.15026> (2020).

## Tables

**Table 1**

## Baseline characteristics of the study population

Characteristics	All patients (N = 52,605)
Age (years, mean $\pm$ SD)	48.5 $\pm$ 11.2
Male (n, %)	27,802 (52.9)
Height (cm, mean $\pm$ SD)	166.3 $\pm$ 8.7
Weight (kg, mean $\pm$ SD)	65.8 $\pm$ 12.9
BMI (kg/m <sup>2</sup> , mean $\pm$ SD)	23.7 $\pm$ 3.4
Waist (cm, mean $\pm$ SD)	81.0 $\pm$ 10.3
SBP (mmHg, mean $\pm$ SD)	119.7 $\pm$ 13.2
DBP (mmHg, mean $\pm$ SD)	72.0 $\pm$ 9.7
Obesity (n, %)	16,721 (31.8)
TyG index (mean $\pm$ SD)	9.30 $\pm$ 0.58
Current smoker (n, %)	18,882 (35.9)
Alcohol history (n, %)	31,026 (59.0)
Hypertension (n, %)	5,767 (11.0)
<i>H. pylori</i> infection (n, %)	14,264 (27.1)
Endoscopic findings	
LA-A (n, %)	2,639 (5.0)
LA-B (n, %)	410 (0.8)
LA-C (n, %)	24 (0.05)
LA-D (n, %)	0 (0.0)
GERD (n, %)	3,073 (5.8)
ERD (n, %)	434 (0.8)
Laboratory finding (mean $\pm$ SD)	
Fasting glucose	97.0 $\pm$ 9.5
Total cholesterol	204.2 $\pm$ 37.2
Triglyceride	128.0 $\pm$ 81.1
HDL cholesterol	56.6 $\pm$ 13.2

LDL cholesterol

133.4 ± 31.7

SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TyG index, triglyceride-glucose index; *H. pylori*, *Helicobacter pylori*; LA, Los Angeles; GERD, gastroesophageal reflux disease; ERD, definite erosive reflux disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

## Table 2

Univariate analysis of the risk factors for GERD

Characteristics	Control (n = 49,532)	GERD (n = 3,073)	P-value
Age (years, mean $\pm$ SD)	48.2 $\pm$ 11.5	48.7 $\pm$ 11.4	0.401
Male (n, %)	25,551 (51.6)	2,251 (73.3)	< 0.001
Height (cm, mean $\pm$ SD)	166.1 $\pm$ 8.7	169.6 $\pm$ 8.3	< 0.001
Weight (kg, mean $\pm$ SD)	65.4 $\pm$ 12.8	72.1 $\pm$ 13.7	< 0.001
BMI (kg/m <sup>2</sup> , mean $\pm$ SD)	23.6 $\pm$ 3.4	24.9 $\pm$ 3.5	< 0.001
Waist (cm, mean $\pm$ SD)	80.7 $\pm$ 10.2	85.4 $\pm$ 10.4	< 0.001
SBP (mmHg, mean $\pm$ SD)	119.6 $\pm$ 13.2	120.8 $\pm$ 12.2	< 0.001
DBP (mmHg, mean $\pm$ SD)	72.0 $\pm$ 9.8	72.2 $\pm$ 8.4	0.273
Obesity (n, %)	15,270 (30.8)	1,451 (47.2)	< 0.001
TyG index (mean $\pm$ SD)	9.27 $\pm$ 0.54	9.74 $\pm$ 0.89	< 0.001
TyG index in quartile			< 0.001
Q1 (n, %)	13,817 (27.9)	262 (8.5)	
Q2 (n, %)	13,164 (26.6)	726 (23.6)	
Q3 (n, %)	12,445 (25.1)	935 (30.4)	
Q4 (n, %)	10,106 (20.4)	1,150 (37.4)	
Current smoker (n, %)	17,253 (34.8)	1,629 (53.0)	< 0.001
Alcohol history (n, %)	28,780 (58.1)	2,246 (73.1)	< 0.001
Hypertension (n, %)	5,173 (10.4)	594 (19.3)	< 0.001
<i>H. pylori</i> infection (n, %)	13,610 (27.5)	654 (21.3)	< 0.001
Laboratory finding			
Fasting glucose	96.9 $\pm$ 9.5	98.5 $\pm$ 9.4	< 0.001
Total cholesterol	204.1 $\pm$ 37.2	206.0 $\pm$ 38.0	0.006
Triglyceride	126.9 $\pm$ 79.6	144.3 $\pm$ 100.3	< 0.001
HDL cholesterol	56.7 $\pm$ 13.3	55.3 $\pm$ 13.1	< 0.001
LDL cholesterol	133.9 $\pm$ 31.8	126.4 $\pm$ 30.4	< 0.001

SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TyG index, triglyceride-glucose index; Q, quartile; *H. pylori*, *Helicobacter pylori*; HDL, high-

density lipoprotein; LDL, low-density lipoprotein; GERD, gastroesophageal reflux disease.

**Table 3**

Multivariate analysis of the risk factors for GERD

	OR (95% CI)	P-value
Male	1.425 (1.285–1.577)	< 0.001
Obesity	1.300 (1.201–1.406)	< 0.001
Current smoker	1.136 (1.036–1.245)	0.007
Alcohol history	1.488 (1.359–1.629)	< 0.001
Hypertension	1.546 (1.403–1.703)	< 0.001
<i>H. pylori</i> infection	0.678 (0.620–0.742)	< 0.001
TyG index in quartile		< 0.001
Q1	1	
Q2	2.477 (2.142–2.863)	< 0.001
Q3	3.013 (2.610–3.478)	< 0.001
Q4	4.027 (3.484–4.655)	< 0.001

*H. pylori*, *Helicobacter pylori*; TyG index, triglyceride-glucose index; Q, quartile; OR, odds ratio; CI, confidence interval.

**Table 4**

Univariate analysis of the risk factors for ERD

Characteristics	Control (n = 49,532)	ERD (n = 434)	P-value
Age (years, mean $\pm$ SD)	48.2 $\pm$ 11.5	49.2 $\pm$ 11.1	0.302
Male (n, %)	25,551 (51.6)	393 (90.6)	< 0.001
Height (cm, mean $\pm$ SD)	166.1 $\pm$ 8.7	171.5 $\pm$ 7.5	< 0.001
Weight (kg, mean $\pm$ SD)	65.4 $\pm$ 12.8	77.7 $\pm$ 12.9	< 0.001
BMI (kg/m <sup>2</sup> , mean $\pm$ SD)	23.6 $\pm$ 3.4	26.3 $\pm$ 3.4	< 0.001
Waist (cm, mean $\pm$ SD)	80.7 $\pm$ 10.2	90.2 $\pm$ 9.0	< 0.001
SBP (mmHg, mean $\pm$ SD)	119.6 $\pm$ 13.2	123.3 $\pm$ 12.3	< 0.001
DBP (mmHg, mean $\pm$ SD)	72.0 $\pm$ 9.8	73.8 $\pm$ 8.8	< 0.001
Obesity (n, %)	15,270 (30.8)	274 (63.1)	< 0.001
TyG index (mean $\pm$ SD)	9.27 $\pm$ 0.54	9.94 $\pm$ 1.08	< 0.001
TyG index in quartile			< 0.001
Q1 (n, %)	13,817 (27.9)	14 (3.2)	
Q2 (n, %)	13,164 (26.6)	88 (20.3)	
Q3 (n, %)	12,445 (25.1)	126 (29.0)	
Q4 (n, %)	10,106 (20.4)	206 (47.5)	
Current smoker (n, %)	17,253 (34.8)	294 (67.7)	< 0.001
Alcohol history (n, %)	28,780 (58.1)	334 (77.0)	< 0.001
Hypertension (n, %)	5,173 (10.4)	104 (24.0)	< 0.001
<i>H. pylori</i> infection (n, %)	13,610 (27.5)	124 (28.6)	0.611
Laboratory finding			
Fasting glucose	96.9 $\pm$ 9.5	100.2 $\pm$ 9.1	< 0.001
Total cholesterol	204.1 $\pm$ 37.2	209.0 $\pm$ 39.0	< 0.001
Triglyceride	126.9 $\pm$ 79.6	167.1 $\pm$ 112.7	< 0.001
HDL cholesterol	56.7 $\pm$ 13.3	51.8 $\pm$ 12.4	< 0.001
LDL cholesterol	133.9 $\pm$ 31.8	131.8 $\pm$ 31.5	0.188

SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TyG index, triglyceride-glucose index; Q, quartile; *H. pylori*, *Helicobacter pylori*; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ERD, erosive reflux disease.

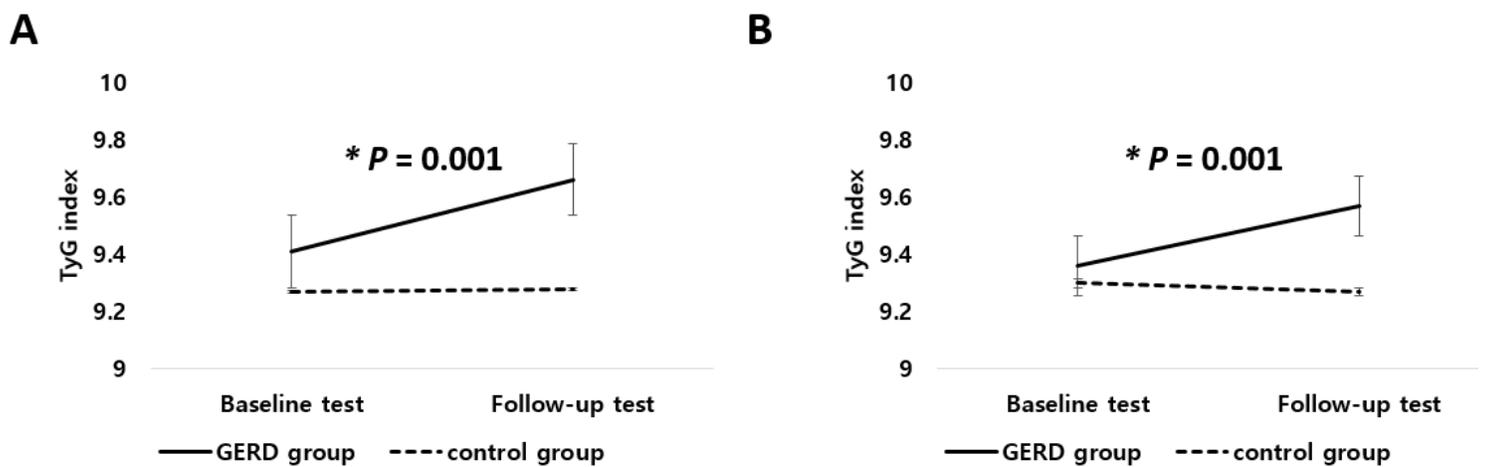
**Table 5**

Multivariate analysis of the risk factors for ERD

	OR (95% CI)	P-value
Male sex	3.906 (2.732–5.587)	< 0.001
Obesity	1.972 (1.606–2.420)	< 0.001
Current smoker	1.540 (1.233–1.924)	< 0.001
Alcohol history	1.203 (0.940–1.540)	0.142
Hypertension	1.747 (1.392–2.191)	< 0.001
TyG index in quartile		< 0.001
Q1	1	
Q2	4.264 (2.418–7.522)	< 0.001
Q3	4.841 (2.767–8.471)	< 0.001
Q4	7.390 (4.247–12.857)	< 0.001

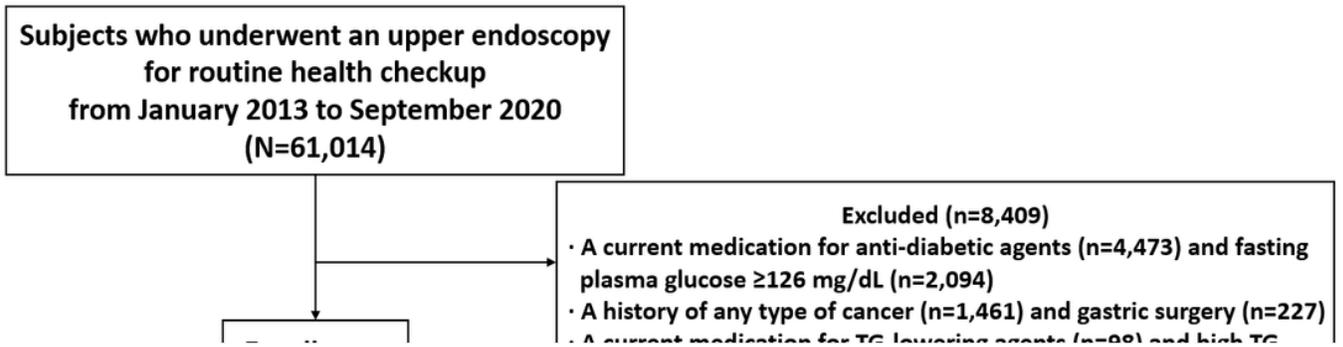
TyG index, triglyceride-glucose index; Q, quartile; OR, odds ratio; CI, confidence interval.

## Figures



**Figure 1**

Progression of the TyG index and GERD. (A) Unadjusted. (B) Adjusted for obesity, hypertension, *Helicobacter pylori* infection, smoking, and alcohol consumption.



**Figure 2**

Flow chart of the enrolled patients.