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Bidirectional association between GERD and asthma: Two longitudinal follow-up studies using a national sample cohort

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Competing interests

The authors declare that they have no competing interests.

Highlight

1. What is already known about this topic?

It was speculated that GERD could elevate the risk of asthma. On the other hand, asthma has also been proposed to impact the development of GERD.

2. What does this article add to our knowledge?

This study demonstrated the bidirectional relation between asthma and GERD, independent of demographic factors, medical histories, and lifestyle factors.

3. How does this study impact current management guidelines?

The development of GERD should be assessed in the patients with asthma, and patients with GERD should be evaluated for asthma development.

Abbreviations

GERD: gastroesophageal reflux disease; HR: hazard ratio; LES: low esophageal sphincter ; HIRA-NSC: Korean Health Insurance Review and Assessment Service-National Sample Cohort; PPI: proton pump inhibitor; ICSs: inhaled corticosteroids; LABAs: long-acting β 2-agonists; LTRAs: leukotriene antagonists; SABAs: short-acting β 2-agonists; CCI: Charlson comorbidity index; SD: standard deviation; COPD: Chronic obstructive pulmonary disease; LAMAs: long-acting muscarinic antagonists

Abstract

Background: A relation between gastroesophageal reflux disease (GERD) and asthma has been suggested; however, causality has not been investigated.

Objective: This study aimed to delineate the causal relation between GERD and asthma.

Methods: Participants of the Korean National Health Insurance Service-National Sample Cohort 2002-2013 who were ≥ 20 years old were selected for this study. In study I, 116,502 GERD patients were matched in a 1:2 ratio to 233,004 control I participants, and the hazard ratio (HR) of asthma in GERD patients was analyzed. In study II, 104,146 asthma patients were matched in a 1:1 ratio to 104,146 control II participants, and the HR for GERD in asthma patients was analyzed. A stratified Cox-proportional hazards model was used. Subgroup analyses were performed according to age and sex.

Results: In study I, 12.5% (14,595/116,502) of the GERD group and 7.8% (18,135/233,004) of the control I group presented asthma ($P < 0.001$). The GERD group demonstrated a 1.46-fold higher HR for asthma than the control I group (95% confidence interval [CI] = 1.42-1.49, $P < 0.001$). In study II, 16.9% (17,582/104,146) of the asthma group and 11.9% (12,393/104,146) of the control II group presented GERD ($P < 0.001$). The asthma group showed a 1.36-fold higher HR for GERD than the control II group (95% CI = 1.33-1.39, $P < 0.001$). All age and sex subgroups presented consistent results.

Conclusion: GERD and asthma had a bidirectional relation in the study population.

Key words: Gastroesophageal Reflux; Asthma; Risk Factors; Cohort Studies; Epidemiology

Introduction

Asthma is a chronic disease with respiratory symptoms that include wheezing, cough, and breathlessness. The prevalence of asthma was estimated to be approximately 4.3% in the worldwide population according to data from the Centers for Disease Control ¹. In Korea, the annual incidence of asthma was approximately 3.63-6.07 per 1,000 people in the adult population ². Although most asthma can be managed with asthma medications such as long-acting β 2-agonists and inhaled corticosteroids, approximately 3.6% of asthma patients have severe refractory asthma (95% CI = 3.0-4.1) ³. In these severe asthma patients, other comorbidities, such as rhinosinusitis and obesity, are a concern, as they could be an underlying cause for asthma symptoms such as wheezing, dyspnea, cough, and chest tightness ⁴. In addition, multiple pathophysiologies of both allergic and nonallergic inflammatory responses were suggested to induce asthma ^{5,6}. Thus, chronic diseases related to inflammation, including metabolic syndromes, diabetes, hypertension, and coronary heart diseases, were suggested to increase the risk of asthma ⁷.

GERD is a chronic disease with reflux symptoms. Its prevalence in the USA was estimated to be as high as 30% ⁸. In Korea, approximately 7.1% of the adult population had GERD, and 7.7% had uninvestigated dyspepsia ⁹. In addition to gastroesophageal reflux symptoms, several secondary extraesophageal, laryngopharyngeal and respiratory symptoms were documented in GERD patients ¹⁰. For instance, approximately 18% (56/299) of GERD patients presented chronic respiratory symptoms ¹¹. Thus, it was speculated that the direct impact of microaspiration or the indirect impact of vagal neuronal hyperactivation could elevate the risk of asthma in GERD patients ^{12,13}.

On the other hand, asthma has also been proposed to impact the development of GERD. Researchers have suggested that the physical influence of hyperinflation and air trapping or the neuronal influence of high vagal tone disturbs the low esophageal sphincter (LES) reflex,

resulting in an increase in GERD in asthma patients^{12,13}. Indeed, the prevalence of GERD symptoms was 3.5 times higher in asthma patients than in the control group (95% CI = 2.5-5.3)¹⁴. A systemic review indicated that the prevalence of GERD symptoms in asthma patients was approximately 59.2%, which was higher than that in the controls (38.1%)¹⁵.

Thus, a bidirectional relation between asthma and GERD could be postulated; however, most previous studies used a cross-sectional design that could not determine causality¹⁵. To confirm this hypothesis, this study performed two different analyses. In study I, the GERD group was compared with the control group to determine the risk of subsequent asthma. In study II, the asthma group was compared to the control group to determine the risk of subsequent GERD.

Methods

Study Population and Data Collection

The ethics committee of Hallym University (2017-I102) approved the use of these data. Written informed consent was exempted by the institutional review board.

This national cohort study relied on data from the Korean Health Insurance Review and Assessment Service-National Sample Cohort (HIRA-NSC). A detailed description of the data is provided in our previous studies^{16,17}.

Participant Selection

There were 1,125,691 cases with 114,369,638 medical claim codes, and of these, we included participants who were treated for GERD. GERD was defined using the ICD-10 code K21 from 2002 through 2013. We selected participants who were treated for GERD ≥ 2 times and prescribed a proton pump inhibitor (PPI) for ≥ 2 weeks ($n = 137,807$)¹⁸. We included GERD patients with ≥ 2 diagnoses because in Korea, due to the national healthcare insurance

system, a tentative diagnosis of GERD is registered at the initial clinical visit to conduct diagnostic evaluations, including endoscopy and laboratory tests. Then, the confirmative diagnosis of GERD is registered at the second clinical visit. This method was modified from a previous study¹⁹ and was used in our previous study¹⁶.

We included participants who were diagnosed with asthma (ICD-10: J45) or status asthmaticus (J46) from 2002 through 2013. Among them, we selected participants who were diagnosed with asthma by a physician more than 2 times and who were treated with asthma-related medications, including inhaled corticosteroids (ICSs) or ICSs combined with long-acting β 2-agonists (LABAs), oral leukotriene antagonists (LTRAs), short-acting β 2-agonists (SABAs), systemic LABAs, xanthine derivatives, or systemic corticosteroids (n = 230,764). This method was modified from a previous study²⁰ and was used in our previous study²¹.

Study I

The GERD patients were matched in a 1:2 ratio with control I participants who were not diagnosed with GERD from 2002 through 2013. The control group was selected from a population (n = 987,884) without a history of GERD. Matching for age group, sex, income group, and region of residence was performed. To prevent selection bias when selecting the matched participants, the control I participants were first sorted using a random number order and then selected from top to bottom. We set the index date as the date of the GERD diagnosis. It was assumed that the matched control I participants were examined at the same time as each matched GERD participant (index date). Therefore, participants in the control group who died before the index date were excluded. Participants who had a history of asthma before the index date were excluded from both the GERD group and the control I group. In the GERD group, 18,291 participants were excluded. The GERD patients for whom we could not identify sufficient matching participants were excluded (n = 519), and we

excluded participants who were under 20 years old ($n = 2,495$). The mean follow-up time from the index date to the end date (Dec. 31, 2013) or death date was similar in both the GERD (73.2 months, standard deviation [SD] = 38.6) and the control I groups (72.2 months, SD = 38.7). Finally, 1:2 matching resulted in the inclusion of 116,502 GERD patients and 233,004 control I participants (Fig. 1). We analyzed the occurrence of asthma in both the GERD and the control I groups.

Study II

Asthma patients were matched in a 1:1 ratio with control II participants who were not diagnosed with asthma from 2002 through 2013. The control group was selected from a population ($n = 894,927$) without a history of asthma. Matching for age group, sex, income group, and region of residence was performed. To prevent selection bias when selecting the matched participants, the control II participants were sorted using a random number order and then selected from top to bottom. We set the index date as the date of the asthma diagnosis. It was assumed that the matched control II participants were examined at the same time as each matched asthma participant (index date). Therefore, participants in the control group who died before the index date were excluded. Participants who had a history of GERD before the index date were excluded from both the asthma group and the control II group. In the asthma group, 14,634 participants were excluded. Asthma patients for whom we could not identify sufficient matching participants were excluded ($n = 21,531$), and we excluded participants who were under 20 years old ($n = 90,453$). The mean follow-up time from the index date to the end date (Dec. 31, 2013) or death date was similar in both the asthma (83.0 months, SD = 40.9) and the control II groups (82.8 months, SD = 41.2). Finally, 1:1 matching resulted in the inclusion of 104,146 asthma patients and 104,146 control II participants (Fig. 1). We analyzed the occurrence of GERD in both the asthma and the control II groups.

Variables

The age groups were categorized using 5-year intervals, i.e., 20-24, 25-29, 30-34, ..., and 85+ years old; a total of 14 age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 5 classes (class 1 [lowest income]-5 [highest income]). The regions of residence were divided into 16 areas according to administrative districts. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The past medical histories of the participants were evaluated using ICD-10 codes. The Charlson comorbidity index (CCI) for 16 comorbidities, except pulmonary disease, was considered a continuous variable (0 [no comorbidity] through 28 [multiple comorbidities])²². Depression, which was diagnosed by a psychiatrist ≥ 2 times, was defined using the ICD-10 codes F31 (bipolar affective disorder) through F39 (unspecified mood disorder)¹⁶. Chronic obstructive pulmonary disease (COPD) was defined by codes J43 (emphysema) through J44 (other COPD) and the administration of SABAs, LABAs, long-acting muscarinic antagonists (LAMAs), and corticosteroids²³. Obstructive sleep apnea (OSA) was defined by code G473 (sleep apnea). Central sleep apnea was not considered due to its rarity, with a less than 1% incidence in the general population²⁴. Body mass index (BMI, kg/m²) information was available in the participants who underwent Korean National Health Insurance Service-Health Screening (NHIS-HEALS). BMI was evaluated as a continuous variable.

Statistical Analyses

A chi-square test was used to compare the general characteristics of the GERD and control groups (study I) and the asthma and control groups (study II).

In study I, a stratified Cox-proportional hazards model was used to analyze the hazard ratio (HR) of asthma (dependent variable) in patients with GERD (independent variable). In study II, another stratified Cox-proportional hazards model was used to analyze the HR for GERD (dependent variable) in patients with asthma (independent variable). Crude (simple) and adjusted (CCI, depression, OSA, and COPD history) models were used. The interactions of exposure and age and exposure and sex were analyzed for both study I and study II. In addition, the risk of asthma in study I and GERD in study II were analyzed according to the number of clinical visits. In the analyses, age, sex, income, and region of residence were stratified, and the 95% confidence interval (CI) was calculated. A Kaplan-Meier curve and log-rank test were employed.

For the subgroup analysis, we divided the participants by age and sex (<40 years old, 40-59 years old, 60+ years old; men and women) because we suspected these associations differed among the subgroups. Age groups were classified <40 years old and 40-59 years old because adult-onset asthma peaked in the 40-59 year-olds, and the phenotypes of asthma in these age groups were considered specific in a previous study²⁵.

For the sensitivity analyses, we analyzed the association between asthma and GERD using the different inclusion criteria. First, we included GERD and asthma diagnosed more than 6 months after the index dates (Table E1). Second, we limited the analysis to those who visited the clinics ≥ 3 times, 4 times, and 5 times for GERD and asthma (Tables E2). In addition, we evaluated the interaction of GERD with age and sex (Table E3).

To attenuate the possible confounding effect of obesity, additional analyses including BMI were conducted for the study I, study II, and sensitivity analyses using the NHIS-

HEALS cohort. The logistic regression analyses were performed without stratification due to unmatched control groups.

Two-tailed analyses were conducted, and P values less than 0.05 were considered to indicate significance. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY, USA).

Results

Study I

The average time duration from January 1, 2002 to GERD diagnosis was 69.1 months (SD = 38.6). The 1.87% (2,179/ 116,502) of GERD patients died during follow-up periods. The time duration from the index date to asthma diagnosis was 40.0 months (SD =31.6) in the GERD group and 38.8 months (SD = 32.1) in the control I group. The rate of asthma was higher in the GERD group (12.5% [14,595/116,502]) than in the control I group (7.8% [18,135/233,004], $P < 0.001$, Table 1). The general characteristics (age, sex, income, and region of residence) of the participants were exactly the same due to matching ($P = 1.000$). The rates of depression, COPD, and OSA were higher in the GERD group than in the control I group ($P < 0.001$ for each comparison). The CCI values of the GERD and control I groups also differed ($P < 0.001$).

The adjusted HR for asthma in the GERD group was 1.46 (95% CI = 1.42-1.49, $P < 0.001$, Table 2 and Fig. 2a). The high adjusted HR for asthma in the GERD group was consistent after the considerations of the interactions of GERD and age and GERD and sex (Table E3). In addition, the adjusted HR for asthma in the GERD group increased with the higher number of clinical visit for GERD (Table E4).

In the subgroup analyses, all the adjusted HRs for asthma were increased in the GERD group (each $P < 0.001$, Table 3). 13.1% (15,275/116,502) of the GERD group and 24.6%

(57,279/233,004) of the control I group had BMI records (Table E5). Compared to patients without a BMI record, patients with a BMI record were younger, more likely female, had lower income, were more likely from an urban region, were more likely to have no co-morbidities, and less likely to have asthma (Table E6). In the analyses adjusted for BMI, the GERD group demonstrated increased adjusted HRs for asthma compared to the control I group for the total sample (1.41, 95% CI 1.38-1.44) (Table E7) and in all subgroup and sensitivity analyses (Tables E8, E9, and E10).

Study II

The mean time duration from January 1, 2002 to asthma diagnosis was 55.8 months (SD = 40.4). The 7.46% (7,773/ 104,146) of asthma patients died during follow-up period. The time duration from the index date to GERD diagnosis was 43.5 months (SD = 32.4) in the asthma group and 46.7 months (SD = 34.2) in the control II group. The rate of GERD was higher in the asthma group (16.9% [17,582/104,146]) than in the control II group (11.9% [12,393/104,146], $P < 0.001$, Table 1). The general characteristics (age, sex, income, and region of residence) of the participants were exactly the same due to matching ($P = 1.000$). The rates of depression, COPD, and OSA were higher in the asthma group than in the control II group ($P < 0.001$ for each comparison). The CCI values of the asthma and control II groups also differed ($P < 0.001$).

The adjusted HR for GERD in the asthma group was 1.36 (95% CI = 1.33-1.39, $P < 0.001$, Table 2 and Fig. 2b). The high adjusted HR for GERD in the asthma group was consistent after the considerations of the interactions of asthma and age and asthma and sex (Table E3). In addition, the adjusted HR for GERD in the asthma group increased with the higher number of clinical visit for asthma (Table E4).

In the subgroup analyses, all the adjusted HRs for GERD were higher in the asthma group than in the control II group (each $P < 0.001$, Table 4)..

23.1% (24,021/104,146) of the asthma group and 27.7% (28,881/104,146) of the control II group had BMI records (Table E5). Compared to patients without a BMI record, patients with a BMI record were younger, more likely female, had lower income, were more likely from an urban region, were more likely to have no co-morbidities, and less likely to have GERD (Table E11). In the analyses adjusted for BMI, the asthma group demonstrated increased adjusted HRs for GERD compared to the control II group for the total sample (1.30, 95% CI 1.27-1.34) (Table E7) and in all subgroup and sensitivity analyses (Tables E8, E9, and E12).

Discussion

The GERD group demonstrated a 1.46-fold (95% CI = 1.42-1.49) higher risk of asthma than the control I group, independent of the demographic factors and medical histories, including COPD and OSA. Likewise, the asthma group showed a 1.36-fold (95% CI = 1.33-1.39) higher risk of GERD than the control II group. All subgroup analyses presented consistent results. When the PubMed and EMBASE databases were searched for the key words “asthma”, “GERD”, and “bidirectional” or “reciprocal”, no studies concurrently investigating the bidirectional relation between asthma and GERD were identified through April 11, 2019. In addition, comprehensive matching, stratification, and adjustments for demographic factors and numerous past medical histories minimized the confounding effects on the association between asthma and GERD.

Similar to the present results, several previous studies reported a high incidence of GERD in asthma patients²⁶⁻²⁸. The GERD symptoms of acid regurgitation (28.3% vs. 6.7%), heartburn (28.2% vs. 16.7%), and dysphagia (38.3% vs. 1.7%) were more common in the asthma patients than in the control group²⁶. Another case-control study demonstrated that the

odds of heartburn were 19.5 times higher in the asthma group than in the control group (95% CI = 4.5-85.7)²⁷. In addition to a higher prevalence of GERD in asthma patients (58% vs. 32.75%), upper gastrointestinal symptoms, including heartburn, retrosternal pain, and regurgitation, were more prevalent in the asthma patients than in the control participants (52% vs. 28%)²⁸. However, because of the cross-sectional study design, the causality between GERD and asthma could not be elucidated in these previous studies. Using two respective study and control groups, the present study demonstrated a reciprocal temporal and potentially causal relation between asthma and GERD. Asthma was diagnosed approximately 40.0 months after the index date in GERD patients and GERD was diagnosed approximately 43.5 months after the index date in the asthma patients in this study. Although the underlying pathophysiology is still elusive, there is putative evidence for the relation between asthma and GERD, which supports the current results.

Asthma could influence the risk of GERD by inflation pressure or hyperventilation-induced LES dysfunction, vagal stimulation, and asthma medication effects. A cough or elevated respiratory effort may induce lung hyperinflation and the subsequent herniation or dysfunction of the LES²⁹. The common vagal innervation between the esophagus and airway may cause the bronchoconstriction stimuli to influence LES relaxation¹². Because both the esophagus and the airway are innervated by the vagus nerve, it is possible that chronic bronchoconstriction could initiate or aggravate esophageal dysfunction. In addition, the chronic use of asthma medications, including corticosteroids, theophylline, and β -agonists, could decrease the LES pressure and promote GERD³⁰⁻³². For instance, the β -agonist albuterol reduced the LES basal tone in a dose-response relationship even in healthy individuals ($P = 0.01$)³².

GERD could elevate the risk of asthma via increased microaspiration and abnormal vagal activation. Although a number of physical barriers, such as the upper esophageal

sphincter, esophageal motility, gastric emptying, and clearance reflexes, prevent the microaspiration of gastric contents¹², the degradation of elastin in the lung tissue and the elevated number of polymorphonuclear cells were reported following a single instillation of gastric fluid in rats and humans³³. The loss of elastin and the pulmonary inflammation response in GERD patients could mediate the risk of asthma. In addition to histological changes, the microaspiration of gastric contents was related to respiratory symptoms associated with asthma. It has been reported that acid reflux decreased the peak expiratory flow in asthma patients³⁴. Because both the esophagus and the airway are innervated by the vagus nerve, it was suggested that distal esophageal stimuli could initiate or aggravate bronchoconstriction¹². This esophageal-bronchial neural crosstalk could result in an elevated risk of asthma in GERD patients.

The shared etiologic factors, such as inflammatory conditions or environmental irritants, could increase the risks of both asthma and GERD. In addition to type 2 inflammation, there are a number of T helper 2-low asthma endotypes associated with airway inflammation³⁵. For example, type 1 inflammation was reported to contribute to obesity-related asthma, systemic inflammation and metabolic dysregulation³⁶. Likewise, GERD is related to mucosal inflammation with increased secretion of inflammatory mediators and neurotransmitters³⁷. GERD, in turn, may contribute to extraesophageal inflammation and may be associated with obesity³⁸. Moreover, there are several common aggravating or risk factors, such as smoking and irritants, for both asthma and GERD^{39,40}. Although information on smoking and obesity was not available from the National Health Insurance Service (NHIS) data, the participants of NHIS-HEALS with BMI records were analyzed. The reciprocal relation between asthma and GERD was consistent. There were demographic and clinical differences between participants with versus without BMI records, but the direction of any bias introduced by these differences is not clear. OSA was also adjusted to attenuate the

343 confounding effects of obesity in the total population. In addition, we adjusted for the CCI,
344 which included diabetes, hypertension, and other metabolic diseases. COPD was adjusted to
345 minimize the possible confounding effects of COPD, especially in current or past smokers.
346 Furthermore, we additionally analyzed the bidirectional relation between asthma and GERD
347 in groups with more than 6 months of follow-up and multiple treatment histories (≥ 3 , ≥ 4 , and
348 ≥ 5 times) to improve the validity of our results and explore the effects of the disease severity
349 on the bidirectional associations (Tables E1-E4). The results of these sensitivity analyses
350 showed that the bidirectional association between asthma and GERD was consistent.

351 This study used a large sample size, thereby potentiating the statistical power. The
352 representative, nationwide population was selected and verified in a previous study⁴¹.
353 Because all Koreans are legally registered in the NHIS system and all medical records are
354 tracked using the Health Insurance Review and Assessment (HIRA) system, there was no
355 missing participants in this study. Both asthma and GERD were classified based on the
356 multiple and objective measures of ICD-10 codes and medication histories. Additionally, bias
357 in the control groups was prevented by matching for age, sex, income, and region of
358 residence. In addition to age and sex, matching for socioeconomic factors is imperative in
359 studies using health claim codes because medical accessibility is largely determined by
360 socioeconomic factors. The very large study cohort enabled the random selection of each
361 control participant matched for these confounders. The stratified and adjusted models for
362 demographic and comorbidity factors improved the viability of the reciprocal relation
363 between asthma and GERD. However, there were still potential confounders that could not be
364 assessed in this study. Firstly, because this study did not have wash out periods, there were
365 potentials for the length time bias and the lead time bias. Lifestyle factors such as diet,
366 smoking, obesity in the total cohort, and stress could not be considered due to a lack of
367 information in the NHIS database, as mentioned above. Although we could not adjust for

stress, depression, which is related to stress, was adjusted for in this study. An association between asthma and depression has been previously reported²¹. The E-value were 2.27 for study I and 2.06 for the study II⁴². It means that the association between GERD and asthma (HR = 1.46 for study I and HR = 1.36 for study II) could be explained by an un-measured confounder if that was associated with GERD and asthma at a risk ratio of 2.27 fold or greater for Study I and 2.06 or greater for study II. These values were higher than the ORs of asthma for smoking, which was estimated 2.18 or less⁴³. For GERD, the ORs for smoking was estimated 1.7 or less³⁹. Although the OR of asthma for obesity was as high as 2.5 in previous study⁴³, the adjusted HRs of asthma in GERD (study I) and GERD in asthma (study II) were high after adjusting BMI in the present study (Table E7). The E-values were 2.34 for study I and 2.24 for study II when the BMI was adjusted. In addition, subclinical cases of asthma and GERD might have been excluded in this study because this study was based on health claim codes. Although medication histories were used for the identification of asthma and GERD patients, detailed prescription information, treatment compliance data, and the severity of disease were heterogeneous among the study participants. Previous studies reported the improvement of symptoms of asthma as well as GERD following the proton pump inhibitor (PPI) medications⁴⁴⁻⁴⁶. Thus, further studies considering the PPI medication histories will be warranted to delineate the bidirectional association between asthma and GERD excluding the potential effects of PPI use.

Conclusions

GERD increased the risk of asthma, and asthma increased the risk of GERD.

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Availability of data and materials

Releasing of the data by the researcher is not allowed legally. All of data are available from the database of National health Insurance Sharing Service (NHIS) <https://nhiss.nhis.or.kr/> NHIS allows all of this data for the any researcher who promises to follow the research ethics with some cost. If you want to access the data of this article, you could download it from the website after promising to follow the research ethics.

Authors contributions

HCG performed the literature search, data analysis and interpretation, and wrote the first draft of the manuscript. SYK, CM, and DJO contributed to the study design, data collection, data interpretation and writing of the manuscript. All authors read and approved the final manuscript.

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539

540 **Table 1** General Characteristics of Participants

Characteristics	Study I			Study II		
	GERD (n, %)	Control I (n, %)	P-value	Asthma (n, %)	Control II (n, %)	P-value
Age (years old)			1.000			1.000
20-24	4,235 (3.6)	8,470 (3.6)		4,410 (4.2)	4,410 (4.2)	
25-29	6,793 (5.8)	13,586 (5.8)		6,930 (6.7)	6,930 (6.7)	
30-34	9,262 (8.0)	18,524 (8.0)		10,204 (9.8)	10,204 (9.8)	
35-39	11,518 (9.9)	23,036 (9.9)		10,179 (9.8)	10,179 (9.8)	
40-44	15,048 (12.9)	30,096 (12.9)		9,710 (9.3)	9,710 (9.3)	
45-49	15,737 (13.5)	31,474 (13.5)		9,951 (9.6)	9,951 (9.6)	
50-54	15,646 (13.4)	31,292 (13.4)		9,392 (9.0)	9,392 (9.0)	
55-59	11,951 (10.3)	23,902 (10.3)		8,945 (8.6)	8,945 (8.6)	
60-64	10,169 (8.7)	20,338 (8.7)		9,190 (8.8)	9,190 (8.8)	
65-69	7,590 (6.5)	15,180 (6.5)		9,124 (8.8)	9,124 (8.8)	
70-74	4,922 (4.2)	9,844 (4.2)		7,350 (7.1)	7,350 (7.1)	
75-79	2,392 (2.1)	4,784 (2.1)		4,817 (4.6)	4,817 (4.6)	
80-84	901 (0.8)	1,802 (0.8)		2,701 (2.6)	2,701 (2.6)	
85+	338 (0.3)	676 (0.3)		1,243 (1.2)	1,243 (1.2)	
Sex			1.000			1.000
Male	54,451 (46.7)	108,902 (46.7)		37,968 (36.5)	37,968 (36.5)	
Female	62,051 (53.3)	124,102 (53.3)		66,178 (63.5)	66,178 (63.5)	
Income			1.000			1.000
1 (lowest)	17,974 (15.4)	35,948 (15.4)		17,307 (16.6)	17,307 (16.6)	
2	16,922 (14.5)	33,844 (14.5)		15,633 (15.0)	15,633 (15.0)	
3	21,096 (18.1)	42,192 (18.1)		18,774 (18.0)	18,774 (18.0)	
4	26,459 (22.7)	52,918 (22.7)		23,733 (22.8)	23,733 (22.8)	
5 (highest)	34,051 (29.2)	68,102 (29.2)		28,699 (27.6)	28,699 (27.6)	

Region	of	1.000	1.000
residence			
Urban	54,335 (46.6)	108,670 (46.6)	47,727 (45.8)
Rural	62,167 (53.4)	124,334 (53.4)	56,419 (54.2)
CCI (score) [†]		<0.001*	<0.001*
0	42,280 (36.3)	123,367 (53.0)	38,339 (36.8)
1	17,328 (14.9)	30,915 (13.3)	15,657 (15.0)
2	18,433 (15.8)	25,358 (10.9)	14,354 (13.8)
3	13,239 (11.4)	18,330 (7.9)	11,016 (10.6)
4	9,640 (8.3)	13,114 (5.6)	8,444 (8.1)
5	6,084 (5.2)	8,090 (3.5)	5,796 (5.6)
≥ 6	9,498 (8.2)	13,830 (5.9)	10,540 (10.1)
Depression	14,744 (12.7)	16,772 (7.2)	<0.001* 11,659 (11.2)
COPD	8,079 (6.9)	9,960 (4.3)	<0.001* 20,173 (19.4)
OSA	913 (0.8)	1,073 (0.5)	<0.001* 190 (0.6)
Asthma	14,595 (12.5)	18,135 (7.8)	<0.001* 104,146
			0 (0.0)
			(100.0)
GERD	116,502	0 (0.0)	<0.001* 17,582 (16.9)
	(100.0)		12,393 (11.9)

* Chi-square test, Significance at $P < 0.05$

[†] Charlson Comorbidity Index was calculated without pulmonary disease

Abbreviation: COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease; IHD, Ischemic heart disease; OSA, obstructive sleep apnea

Table 2 Crude and adjusted hazard ratios (95% confidence interval) of asthma in GERD (study I) and GERD in asthma (study II)

Characteristics	Hazard ratios			
	Crude†	P-value	Adjusted†‡	P-value
Study I				
GERD	1.65 (1.61-1.68)	<0.001*	1.46 (1.42-1.49)	<0.001*
Control	1.00		1.00	
Study II				
Asthma	1.48 (1.45-1.52)	<0.001*	1.36 (1.33-1.39)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Stratified model for age, sex, income, and region of residence.

‡ Adjusted model for COPD, depression, OSA histories, and Charlson Comorbidity Index calculated without pulmonary disease.

Abbreviation: COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease; OSA, obstructive sleep apnea

Table 3 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of asthma in GERD according to age and sex (study I)

Characteristics	Hazard ratios for asthma			
	Crude†	P-value	Adjusted†‡	P-value
Age < 40 years old, men (n = 43,854)				
GERD	2.02 (1.85-2.19)	<0.001*	1.80 (1.65-1.96)	<0.001*
Control	1.00		1.00	
Age < 40 years old, women (n = 51,570)				
GERD	1.67 (1.57-1.77)	<0.001*	1.47 (1.39-1.56)	<0.001*
Control	1.00		1.00	
Age ≥ 40 years old & < 60 years old, men (n = 83,895)				
GERD	1.82 (1.73-1.92)	<0.001*	1.56 (1.48-1.65)	<0.001*
Control	1.00		1.00	
Age ≥ 40 years old & < 60 years old, women (n = 91,251)				
GERD	1.63 (1.57-1.69)	<0.001*	1.45 (1.39-1.51)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 35,604)				
GERD	1.48 (1.39-1.57)	<0.001*	1.23 (1.15-1.31)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 43,332)				
GERD	1.52 (1.45-1.60)	<0.001*	1.35 (1.28-1.42)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Stratified model for age, income, and region of residence.

562 ‡ Adjusted model for COPD, depression, OSA histories, and Charlson Comorbidity Index
563 calculated without pulmonary disease.
564 Abbreviation: COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal
565 reflux disease; OSA, obstructive sleep apnea
566

Table 4 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of GERD in asthma according to age and sex (study II)

Characteristics	Hazard ratios for GERD			
	Crude†	P-value	Adjusted†‡	P-value
Age < 40 years old, men (n = 20,850)				
Asthma	1.69 (1.55-1.85)	<0.001*	1.57 (1.43-1.71)	<0.001*
Control	1.00		1.00	
Age < 40 years old, women (n = 42,596)				
Asthma	1.48 (1.39-1.57)	<0.001*	1.35 (1.27-1.43)	<0.001*
Control	1.00		1.00	
Age ≥ 40 years old & < 60 years old, men (n = 27,836)				
Asthma	1.66 (1.56-1.76)	<0.001*	1.51 (1.42-1.61)	<0.001*
Control	1.00		1.00	
Age ≥ 40 years old & < 60 years old, women (n = 48,160)				
Asthma	1.46 (1.40-1.52)	<0.001*	1.33 (1.28-1.39)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 27,250)				
Asthma	1.34 (1.25-1.43)	<0.001*	1.23 (1.15-1.32)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 41,600)				
Asthma	1.42 (1.34-1.49)	<0.001*	1.28 (1.22-1.35)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Stratified model for age, sex, income, and region of residence.

572 ‡ Adjusted model for COPD, depression histories, OSA and Charlson Comorbidity Index
573 calculated without pulmonary disease.
574 Abbreviation: COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal
575 reflux disease; OSA, obstructive sleep apnea
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Figure Legend

Fig. 1 Schematic illustration of the participant selection process that was used in the present study. Of a total of 1,125,691 participants, 116,502 GERD patients were matched with 233,004 control I participants for age, group, sex, income group, region of residence, and past medical histories (a). Of a total 1,125,691 participants, 104,146 asthma patients were matched with 104,146 control II participants for age, group, sex, income group, region of residence, and past medical histories (b).

Fig. 2 Kaplan-Meier survival analysis. (a) the group with GERD demonstrated a higher cumulative rate of asthma than the control I group. (b) the group with asthma demonstrated a higher cumulative rate of GERD than the control II group.

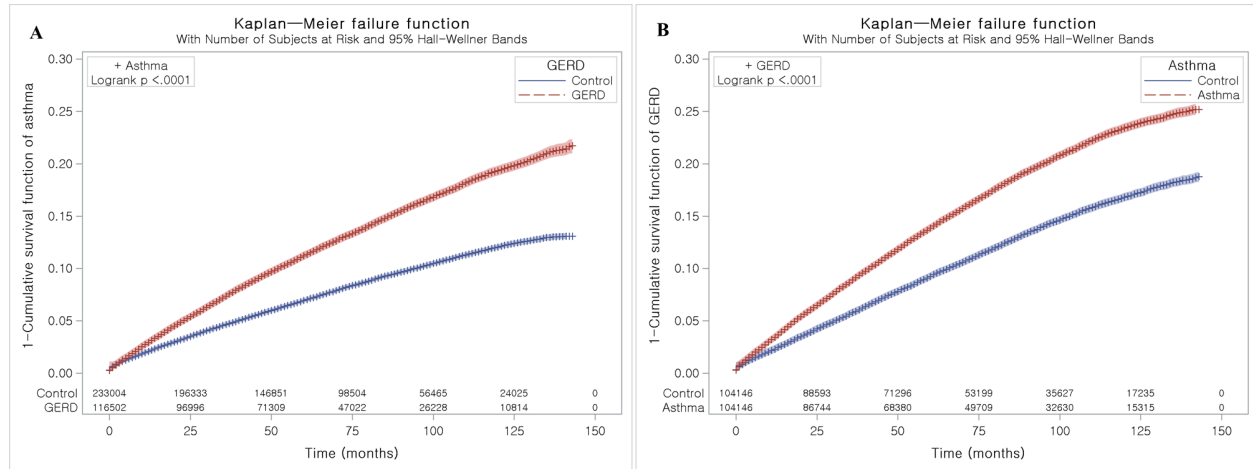


Table E1 Analysis of crude and adjusted hazard ratios (95% confidence interval) of asthma in GERD (study I) and of GERD in asthma (study II) in the periods after 6 months of index dates.

Characteristics	Hazard ratios			
	Crude†	P-value	Adjusted†‡	P-value
Study I				
GERD	1.77 (1.73-1.81)	<0.001*	1.57 (1.54-1.61)	<0.001*
Control	1.00		1.00	
Study II				
Asthma	1.50 (1.46-1.54)	<0.001*	1.39 (1.35-1.42)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Stratified model for age, sex, income, and region of residence.

‡ Adjusted model for COPD, depression, OSA histories, and Charlson Comorbidity Index calculated without pulmonary disease.

Abbreviation: COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease; OSA, obstructive sleep apnea

Table E10 Crude and adjusted hazard ratios (95% confidence interval) of asthma in GERD (study I) and GERD in asthma (study II) with those who had BMI records in a sensitivity analysis**

Characteristics	Hazard ratios			
	Crude†	P-value	Adjusted†‡	P-value
GERD $\geq$ 3 times (n = 114,125)				
Study I				
GERD	1.65 (1.60-1.70)	<0.001*	1.45 (1.41-1.50)	<0.001*
Control	1		1	
Study II				
Asthma	1.47 (1.43-1.52)	<0.001*	1.37 (1.32-1.41)	<0.001*
Control	1		1	
GERD $\geq$ 4 times (n = 95,244)				
Study I				
GERD	1.71 (1.65-1.78)	<0.001*	1.49 (1.44-1.55)	<0.001*
Control	1		1	
Study II				
Asthma	1.59 (1.53-1.65)	<0.001*	1.44 (1.39-1.50)	<0.001*
Control	1		1	
GERD $\geq$ 5 times (n = 80,467)				
Study I				
GERD	1.79 (1.72-1.87)	<0.001*	1.53 (1.47-1.60)	<0.001*
Control	1		1	
Study II				

Asthma	1.60 (1.53-1.67)	<0.001*	1.46 (1.40-1.53)	<0.001*
Control	1		1	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Adjusted model for age, sex, income, region of residence, COPD, depression, OSA histories, Charlson Comorbidity Index calculated without pulmonary disease, and BMI.

Abbreviation: BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease; OSA, obstructive sleep apnea

**In these analyses, GERD was defined using the ICD-10 code K21 from 2002 through 2013. We selected participants treated for GERD ≥ 3 times, GERD ≥ 4 times, and GERD ≥ 5 times and prescribed a proton pump inhibitor (PPI) for ≥ 2 weeks.

Asthma was defined as asthma (ICD-10: J45) or status asthmaticus (J46) from 2002 through 2013. Among them, we selected the participants who were diagnosed with asthma by a physician more than 3 times, and who were treated with asthma-related medications including inhaled corticosteroid(ICS), ICSs combined with long-acting $\beta 2$ -agonists (LABAs), oral leukotriene antagonists (LTRAs), short-acting $\beta 2$ -agonists (SABAs), systemic LABAs, xanthine derivatives, and systemic corticosteroids ($n = 176,510$).

Table E11 The differences of general characteristics of the participants in study II according to with/without BMI record

Characteristics	Study I					
	Asthma	Asthma with	P-value	Control II	Control II with	P-value
	without BMI record (n, %)	BMI record (n, %)		without BMI record (n, %)	BMI record (n, %)	
Obesity record	80,125 (76.9)	24,021 (23.1)	<0.001*	75,265 (72.3)	28,881 (27.7)	<0.001*
Age (years old)			<0.001*			<0.001*
20-24	2,238 (2.8)	2,172 (9.0)		2,309 (3.1)	2,101 (7.3)	
25-29	4,101 (5.1)	2,829 (11.8)		4,194 (5.6)	2,736 (9.5)	
30-34	7,002 (8.7)	3,202 (13.3)		6,626 (8.8)	3,578 (12.4)	
35-39	7,973 (10.0)	2,206 (9.2)		7,431 (9.9)	2,748 (9.5)	
40-44	8,145 (10.2)	1,565 (6.5)		7,618 (10.1)	2,092 (7.2)	
45-49	8,631 (10.8)	1,320 (5.5)		8,031 (10.7)	1,920 (6.7)	
50-54	8,319 (10.4)	1,073 (4.5)		7,844 (10.4)	1,548 (5.4)	
55-59	7,881 (9.8)	1,064 (4.4)		7,593 (10.1)	1,352 (4.7)	
60-64	8,002 (10.0)	1,188 (5.0)		7,554 (10.0)	1,636 (5.7)	
65-69	7,550 (9.4)	1,574 (6.6)		6,902 (9.2)	2,222 (7.7)	
70-74	5,462 (6.8)	1,888 (7.9)		4,978 (6.6)	2,372 (8.2)	
75-79	2,971 (3.7)	1,846 (7.7)		2,676 (3.6)	2,141 (7.4)	
80-84	1,391 (1.7)	1,310 (5.5)		1,139 (1.5)	1,562 (5.4)	
85+	459 (0.6)	784 (3.3)		370 (0.5)	873 (3.0)	
Sex			<0.001*			<0.001*
Male	30,254 (37.8)	7,714 (32.1)		28,132 (37.4)	9,836 (34.1)	
Female	49,871 (62.2)	16,307 (67.9)		47,133 (62.6)	19,045 (65.9)	
Income			<0.001*			<0.001*
1 (lowest)	12,395 (15.5)	4,912 (20.5)		10,944 (14.5)	6,363 (22.0)	
2	12,187 (15.2)	3,446 (14.4)		11,486 (15.3)	4,147 (14.4)	
3	14,633 (18.3)	4,141 (17.2)		13,876 (18.4)	4,898 (17.0)	

4	18,619 (23.2)	5,114 (21.3)		17,808 (23.7)	5,925 (20.5)	
5 (highest)	22,291 (27.8)	6,408 (26.7)		21,151 (28.1)	7,548 (26.1)	
Region of residence			<0.001*			<0.001*
Urban	36,401 (45.4)	11,326 (47.2)		34,077 (45.3)	13,650 (47.3)	
Rural	43,724 (54.6)	12,695 (52.9)		41,188 (54.7)	15,231 (52.7)	
CCI (score) [†]			<0.001*			<0.001*
0	28,798 (35.9)	9,541 (39.7)		34,875 (46.3)	15,222 (52.7)	
1	11,480 (14.3)	4,177 (17.4)		10,032 (13.3)	3,900 (13.5)	
2	11,116 (13.9)	3,238 (13.5)		8,900 (11.8)	2,872 (9.9)	
3	8,892 (11.1)	2,124 (8.8)		6,800 (9.0)	2,062 (7.1)	
4	6,885 (8.6)	1,559 (6.5)		5,248 (7.0)	1,527 (5.3)	
5	4,727 (5.9)	1,069 (4.5)		3,406 (4.5)	1,034 (3.6)	
≥ 6	8,227 (10.3)	2,313 (9.6)		6,004 (8.0)	2,264 (7.8)	
Depression	9,154 (11.4)	2,505 (10.4)	<0.001*	6,414 (8.5)	2,158 (7.5)	<0.001*
COPD	15,308 (19.1)	4,865 (20.3)	<0.001*	3,693 (4.9)	1,148 (4.0)	<0.001*
OSA	429 (0.5)	89 (0.4)	<0.001*	310 (0.4)	55 (0.2)	<0.001*
GERD	15,591 (19.5)	1,991 (8.3)	<0.001*	10,897 (14.5)	1,496 (5.2)	<0.001*

* Chi-square test, Significance at $P < 0.05$

[†] Charlson Comorbidity Index was calculated without pulmonary disease

Abbreviation: COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease; IHD, Ischemic heart disease; OSA, obstructive sleep apnea

Table E12 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of GERD in asthma according to age and sex (study II) who had BMI records

Characteristics	Hazard ratios for GERD			
	Crude†	P-value	Adjusted†‡	P-value
Age < 40 years old, men (n = 15,086)				
Asthma	1.57 (1.43-1.73)	<0.001*	1.46 (1.33-1.61)	<0.001*
Control	1.00		1.00	
Age < 40 years old, women (n = 26,788)				
Asthma	1.45 (1.35-1.56)	<0.001*	1.33 (1.24-1.43)	<0.001*
Control	1.00		1.00	
Age ≥ 40 years old & < 60 years old, men (n = 23,076)				
Asthma	1.54 (1.45-1.64)	<0.001*	1.42 (1.34-1.52)	<0.001*
Control	1.00		1.00	
Age ≥ 40 years old & < 60 years old, women (n = 40,986)				
Asthma	1.38 (1.33-1.45)	<0.001*	1.28 (1.23-1.34)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 20,224)				
Asthma	1.23 (1.15-1.32)	<0.001*	1.15 (1.07-1.24)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 29,230)				
Asthma	1.30 (1.23-1.38)	<0.001*	1.23 (1.16-1.30)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at P < 0.05

† Adjusted model for age, sex, income, region of residence, COPD, depression, OSA histories, Charlson Comorbidity Index calculated without pulmonary disease, and body mass index.

Abbreviation: BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease; OSA, obstructive sleep apnea

Table E2 Crude and adjusted hazard ratios (95% confidence interval) of asthma in GERD (study I) and GERD in asthma (study II) in a sensitivity analysis**

Characteristics	Hazard ratios			
	Crude†	P-value	Adjusted†‡	P-value
GERD $\geq$ 3 times (n = 114,125)				
Study I				
GERD	1.74 (1.70-1.79)	<0.001*	1.52 (1.48-1.56)	<0.001*
Control	1		1	
Study II				
Asthma	1.57 (1.53-1.62)	<0.001*	1.44 (1.39-1.48)	<0.001*
Control	1		1	
GERD $\geq$ 4 times (n = 95,244)				
Study I				
GERD	1.80 (1.74-1.86)	<0.001*	1.55 (1.50-1.60)	<0.001*
Control	1		1	
Study II				
Asthma	1.69 (1.63-1.75)	<0.001*	1.51 (1.46-1.57)	<0.001*
Control	1		1	
GERD $\geq$ 5 times (n = 80,467)				
Study I				
GERD	1.88 (1.81-1.96)	<0.001*	1.659(1.53-1.66)	<0.001*
Control	1		1	
Study II				
Asthma	1.72 (1.65-1.79)	<0.001*	1.54 (1.48-1.61)	<0.001*

Control	1	1
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* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Stratified model for age, sex, income, and region of residence.

‡ Adjusted model for COPD, depression, OSA histories, and Charlson Comorbidity Index calculated without pulmonary disease.

Abbreviation: COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease; OSA, obstructive sleep apnea

**In these analyses, GERD was defined using the ICD-10 code K21 from 2002 through 2013. We selected participants treated for GERD ≥ 3 times, GERD ≥ 4 times, and GERD ≥ 5 times and prescribed a proton pump inhibitor (PPI) for ≥ 2 weeks ($n = 114,125$).

Asthma was defined as asthma (ICD-10: J45) or status asthmaticus (J46) from 2002 through 2013. Among them, we selected the participants who were diagnosed with asthma by a physician more than 3 times, and who were treated with asthma-related medications including inhaled corticosteroid(ICS), ICSs combined with long-acting β_2 -agonists (LABAs), oral leukotriene antagonists (LTRAs), short-acting β_2 -agonists (SABAs), systemic LABAs, xanthine derivatives, and systemic corticosteroids ($n = 176,510$).

Table E3 Crude and adjusted hazard ratios (95% confidence interval) of asthma in GERD (study I) and GERD in asthma (study II)

Characteristics	Hazard ratios							
	Crude†	P-value	Model 1†‡	P-value	Model 2§	P-value	Model 3	P-value
Study I								
GERD	1.67 (1.64-1.71)	<0.001*	1.50 (1.47-1.53)	<0.001*	2.12 (1.94-2.31)	<0.001*	1.58 (1.46-1.71)	<0.001*
Age*GERD					0.97 (0.96-0.97)	<0.001*		
Sex*GERD							0.95 (0.91-1.00)	0.029*
Control	1.00		1.00		1.00		1.00	
Study II								
Asthma	1.49 (1.45-1.52)	<0.001*	1.37 (1.34-1.41)	<0.001*	1.67 (1.54-1.81)	<0.001*	1.52 (1.40-1.65)	<0.001*
Age*asthma					0.98 (0.98-0.99)	<0.001*		
Sex*asthma							0.94 (0.90-0.99)	0.011*
Control	1.00		1.00		1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Stratified model for age, income, and region of residence.

‡ Model 1 was adjusted for COPD, depression histories, and Charlson Comorbidity Index calculated without pulmonary disease.

§ In study I, model 2 was adjusted for age, age*GERD (interaction), sex, income, region of residence, COPD, depression histories, and Charlson Comorbidity Index calculated without pulmonary disease. In study II, model 2 was adjusted for age, age*asthma (interaction), sex, income, region of residence, COPD, depression histories, and Charlson Comorbidity Index calculated without pulmonary disease.

|| In study I, model 3 was adjusted for age, sex, sex*GERD (interaction), income, region of residence, COPD, depression histories, and Charlson Comorbidity Index calculated without pulmonary disease. In study II, model 3 was adjusted for age, sex, sex*asthma (interaction), income, region of residence, COPD, depression histories, and Charlson Comorbidity Index calculated without pulmonary disease.

Abbreviation: COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease

Table E4 Crude and adjusted hazard ratios (95% confidence interval) of asthma in GERD (study I) according to the numbers of the visit for GERD

Characteristics	Hazard ratios			
	Crude†	P-value	Adjusted†‡	P-value
GERD $\leq$ 3 times (n = 108,816)				
GERD	1.17 (1.11-1.23)	<0.001*	1.10 (1.04-1.16)	0.001*
Control	1.00		1.00	
GERD > 3 and $\leq$ 8 times (n = 124,650)				
GERD	1.53 (1.47-1.59)	<0.001*	1.37 (1.32-1.43)	<0.001*
Control	1.00		1.00	
GERD $\geq$ 9 times (n = 116,040)				
GERD	1.97 (1.91-2.03)	<0.001*	1.70 (1.65-1.75)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Stratified model for age, income, and region of residence.

‡ Adjusted model for COPD, depression histories, and Charlson Comorbidity Index calculated without pulmonary disease.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease

Table E5 General characteristics of participants who had BMI records

Characteristics	Study I			Study II		
	GERD (n, %)	Control I (n, %)	P-value	Asthma (n, %)	Control II (n, %)	P-value
Age (years old)			<0.001*			<0.001*
20-24	2,208 (2.2)	4,031 (2.3)		2,238 (2.8)	2,309 (3.1)	
25-29	4,540 (4.5)	8,541 (4.9)		4,101 (5.1)	4,194 (5.6)	
30-34	6,865 (6.8)	12,414 (7.1)		7,002 (8.7)	6,626 (8.8)	
35-39	9,723 (9.6)	16,724 (9.5)		7,973 (10.0)	7,431 (9.9)	
40-44	13,849 (13.7)	23,283 (13.3)		8,145 (10.2)	7,618 (10.1)	
45-49	14,595 (14.4)	25,189 (14.3)		8,631 (10.8)	8,031 (10.7)	
50-54	14,721 (14.5)	25,557 (14.5)		8,319 (10.4)	7,844 (10.4)	
55-59	11,330 (11.2)	19,918 (11.3)		7,881 (9.8)	7,593 (10.1)	
60-64	9,620 (9.5)	16,825 (9.6)		8,002 (10.0)	7,554 (10.0)	
65-69	7,019 (6.9)	11,909 (6.8)		7,550 (9.4)	6,902 (9.2)	
70-74	4,232 (4.2)	7,146 (4.1)		5,462 (6.8)	4,978 (6.6)	
75-79	1,788 (1.8)	3,006 (1.7)		2,971 (3.7)	2,676 (3.6)	
80-84	567 (0.6)	913 (0.5)		1,391 (1.7)	1,139 (1.5)	
85+	170 (0.2)	269 (0.2)		459 (0.6)	370 (0.5)	
Sex			0.078			0.121
Male	48,398 (47.8)	83,407 (47.5)		30,254 (37.8)	28,132 (37.4)	
Female	52,829 (52.2)	92,318 (52.5)		49,871 (62.2)	47,133 (62.6)	
Income			<0.001*			<0.001*
1 (lowest)	14,696 (14.5)	24,127 (13.7)		12,395 (15.5)	10,944 (14.5)	
2	14,813 (14.6)	25,153 (14.3)		12,187 (15.2)	11,486 (15.3)	
3	18,519 (18.3)	32,064 (18.3)		14,633 (18.3)	13,876 (18.4)	
4	23,381 (23.1)	41,144 (23.4)		18,619 (23.2)	17,808 (23.7)	
5 (highest)	29,818 (29.5)	53,237 (30.3)		22,291 (27.8)	21,151 (28.1)	
Region of residence			0.133			0.542
Urban	46,994 (46.4)	81,060 (46.1)		36,401 (45.4)	34,077 (45.3)	

Rural	54,233 (53.6)	94,665 (53.9)		43,724 (54.6)	41,188 (54.7)	
CCI (score) [†]			<0.001*			<0.001*
0	36,285 (35.9)	89,462 (50.9)		28,798 (35.9)	34,875 (46.3)	
1	14,486 (14.3)	23,573 (13.4)		11,480 (14.3)	10,032 (13.3)	
2	15,996 (15.8)	20,241 (11.5)		11,116 (13.9)	8,900 (11.8)	
3	11,859 (11.7)	14,876 (8.5)		8,892 (11.1)	6,800 (9.0)	
4	8,753 (8.7)	10,572 (6.0)		6,885 (8.6)	5,248 (7.0)	
5	5,484 (5.4)	6,514 (3.7)		4,727 (5.9)	3,406 (4.5)	
≥ 6	8,364 (8.3)	10,487 (6.0)		8,227 (10.3)	6,004 (8.0)	
Depression	12,693 (12.5)	12,886 (7.3)	<0.001*	9,154 (11.4)	6,414 (8.5)	<0.001*
COPD	7,319 (7.2)	7,981 (4.5)	<0.001*	15,308 (19.1)	3,693 (4.9)	<0.001*
OSA	827 (0.8)	933 (0.5)	<0.001*	429 (0.5)	310 (0.4)	<0.001*
Asthma	13,027 (12.9)	14,667 (8.4)	<0.001*	80,125 (100.0)	0 (0.0)	<0.001*
GERD	101,227 (100.0)	0 (0.0)	<0.001*	15,591 (19.5)	10,897 (14.5)	<0.001*

* Chi-square test, Significance at P < 0.05

[†] Charlson Comorbidity Index was calculated without pulmonary disease

Abbreviation: BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease; IHD, Ischemic heart disease; OSA, obstructive sleep apnea;

Table E6 The differences of general characteristics of the participants in study I according to with/without BMI records

Characteristics	Study I					
	GERD without	GERD with	P-value	Control I without	Control I with	P-value
	BMI record	BMI record		BMI record	BMI record	
	(n, %)	(n, %)		(n, %)	(n, %)	
Obesity record	101,227 (86.9)	15,275 (13.1)	<0.001*	175,725 (75.4)	57,279 (24.6)	<0.001*
Age (years old)			<0.001*			<0.001*
20-24	2,208 (2.2)	2,027 (13.3)		4,031 (2.3)	4,439 (7.8)	
25-29	4,540 (4.5)	2,253 (14.8)		8,541 (4.9)	5,045 (8.8)	
30-34	6,865 (6.8)	2,397 (15.7)		12,414 (7.1)	6,110 (10.7)	
35-39	9,723 (9.6)	1,795 (11.8)		16,724 (9.5)	6,312 (11.0)	
40-44	13,849 (13.7)	1,199 (7.9)		23,283 (13.3)	6,813 (11.9)	
45-49	14,595 (14.4)	1,142 (7.5)		25,189 (14.3)	6,285 (11.0)	
50-54	14,721 (14.5)	925 (6.1)		25,557 (14.5)	5,735 (10.0)	
55-59	11,330 (11.2)	621 (4.1)		19,918 (11.3)	3,984 (7.0)	
60-64	9,620 (9.5)	549 (3.6)		16,825 (9.6)	3,513 (6.1)	
65-69	7,019 (6.9)	571 (3.7)		11,909 (6.8)	3,271 (5.7)	
70-74	4,232 (4.2)	690 (4.5)		7,146 (4.1)	2,698 (4.7)	
75-79	1,788 (1.8)	604 (4.0)		3,006 (1.7)	1,778 (3.1)	
80-84	567 (0.6)	334 (2.2)		913 (0.5)	889 (1.6)	
85+	170 (0.2)	168 (1.1)		269 (0.2)	407 (0.7)	
Sex			<0.001*			<0.001*
Male	48,398 (47.8)	6,053 (39.6)		83,407 (47.5)	25,495 (44.5)	
Female	52,829 (52.2)	9,222 (60.4)		92,318 (52.5)	31,784 (55.5)	
Income			<0.001*			<0.001*
1 (lowest)	14,696 (14.5)	3,278 (21.5)		24,127 (13.7)	11,821 (20.6)	
2	14,813 (14.6)	2,109 (13.8)		25,153 (14.3)	8,691 (15.2)	
3	18,519 (18.3)	2,577 (16.9)		32,064 (18.3)	10,128 (17.7)	

4	23,381 (23.1)	3,078 (20.2)		41,144 (23.4)	11,774 (20.6)	
5 (highest)	29,818 (29.5)	4,233 (27.7)		53,237 (30.3)	14,865 (26.0)	
Region of residence			<0.001*			<0.001*
Urban	46,994 (46.4)	7,341 (48.1)		81,060 (46.1)	27,610 (48.2)	
Rural	54,233 (53.6)	7,934 (51.9)		94,665 (53.9)	29,669 (51.8)	
CCI (score) [†]			<0.001*			<0.001*
0	36,285 (35.9)	5,995 (39.3)		89,462 (50.9)	33,905 (59.2)	
1	14,486 (14.3)	2,842 (18.6)		23,573 (13.4)	7,342 (12.8)	
2	15,996 (15.8)	2,437 (16.0)		20,241 (11.5)	5,117 (8.9)	
3	11,859 (11.7)	1,380 (9.0)		14,876 (8.5)	3,454 (6.0)	
4	8,753 (8.7)	887 (5.8)		10,572 (6.0)	2,542 (4.4)	
5	5,484 (5.4)	600 (3.9)		6,514 (3.7)	1,576 (2.8)	
≥ 6	8,364 (8.3)	1,134 (7.4)		10,487 (6.0)	3,343 (5.8)	
Depression	12,693 (12.5)	2,051 (13.4)	0.002*	12,886 (7.3)	3,886 (6.8)	<0.001*
COPD	7,319 (7.2)	760 (5.0)	<0.001*	7,981 (4.5)	1,979 (3.5)	<0.001*
OSA	827 (0.8)	86 (0.6)	<0.001*	933 (0.5)	140 (0.2)	<0.001*
Asthma	13,027 (12.9)	1,568 (10.3)	<0.001*	14,667 (8.4)	3,468 (6.1)	<0.001*

* Chi-square test, Significance at $P < 0.05$

[†] Charlson Comorbidity Index was calculated without pulmonary disease

Abbreviation: COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease; IHD, Ischemic heart disease; OSA, obstructive sleep apnea

Table E7 Crude and adjusted hazard ratios (95% confidence interval) of asthma in GERD (study I) and GERD in asthma (study II) who had BMI records

Characteristics	Hazard ratios			
	Crude	P-value	Adjusted†	P-value
Study I				
GERD	1.58 (1.54-1.62)	<0.001*	1.41 (1.38-1.44)	<0.001*
Control I	1.00		1.00	
Study II				
Asthma	1.39 (1.36-1.43)	<0.001*	1.30 (1.27-1.34)	<0.001*
Control II	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Adjusted model for age, sex, income, region of residence, COPD, depression, OSA histories, Charlson Comorbidity Index calculated without pulmonary disease, and body mass index.

Abbreviation: BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease; OSA, obstructive sleep apnea

Table E8 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of asthma in GERD according to age and sex (study I) who had BMI records

Characteristics	Hazard ratios for asthma			
	Crude†	P-value	Adjusted†‡	P-value
Age < 40 years old, men (n = 32,263)				
GERD	1.93 (1.76-2.11)	<0.001*	1.74 (1.58-1.91)	<0.001*
Control	1.00		1.00	
Age < 40 years old, women (n = 32,783)				
GERD	1.64 (1.53-1.76)	<0.001*	1.46 (1.36-1.57)	<0.001*
Control	1.00		1.00	
Age ≥ 40 years old & < 60 years old, men (n = 70,110)				
GERD	1.73 (1.64-1.83)	<0.001*	1.51 (1.42-1.60)	<0.001*
Control	1.00		1.00	
Age ≥ 40 years old & < 60 years old, women (n = 78,332)				
GERD	1.55 (1.49-1.62)	<0.001*	1.42 (1.36-1.48)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 29,432)				
GERD	1.42 (1.33-1.51)	<0.001*	1.18 (1.11-1.27)	<0.001*
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 34,032)				
GERD	1.45 (1.37-1.53)	<0.001*	1.31 (1.24-1.39)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at P < 0.05

† Adjusted model for age, sex, income, region of residence, COPD, depression, OSA histories, Charlson Comorbidity Index calculated without pulmonary disease, and body mass index.

Abbreviation: BMI, body mass index COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease; OSA, obstructive sleep apnea

Table E9 Analysis of crude and adjusted hazard ratios (95% confidence interval) of asthma in GERD (study I) and of GERD in asthma (study II) in the periods after 6 months of index dates with those who had BMI records

Characteristics	Hazard ratios			
	Crude	P-value	Adjusted†	P-value
Study I				
GERD	1.68 (1.63-1.72)	<0.001*	1.51 (1.47-1.55)	<0.001*
Control	1.00		1.00	
Study II				
Asthma	1.41 (1.37-1.44)	<0.001*	1.33 (1.29-1.36)	<0.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Adjusted model for age, sex, income, region of residence, COPD, depression, OSA histories, Charlson Comorbidity Index calculated without pulmonary disease, and BMI.

Abbreviation: BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro esophageal reflux disease; OSA, obstructive sleep apnea