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ORIGINAL ARTICLE

Increased risk of osteoporosis in patients with peptic ulcer: a follow-up study using a national sample cohort

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Abstract

Summary We performed a nationwide, population-based cohort study to investigate the risk of osteoporosis in patients with peptic ulcer disease in South Korea and concluded that peptic ulcer disease is associated with an increased risk of osteoporosis.

Purpose This study aimed to evaluate the association between peptic ulcer disease (PUD) and the occurrence of osteoporosis using a national sample cohort from South Korea.

Methods Using the national cohort study from the Korean National Health Insurance Service, we extracted data for patients with PUD (n = 50,002) and for 1:1 matched control participants (n = 50,002); we then analyzed the occurrence of osteoporosis from 2002 to 2013. The patients were matched according to age, sex, income, region of residence, and past medical history. A stratified Cox proportional hazards model was used to analyze the hazard ratios (HRs) and the 95% confidence intervals (CIs). Subgroup analyses were performed based on age and sex.

Results The adjusted HR for osteoporosis was 1.36 (95% CI = 1.33–1.40, $P < 0.001$) in the PUD group. In the subgroup analysis based on age and sex, the respective adjusted HRs of PUD for osteoporosis were 1.33 (95% CI = 1.21–1.47) in the < 65-year-old group of men and 1.42 (95% CI = 1.30–1.56) in the ≥ 65-year-old group of men (each $P < 0.001$). The respective adjusted HRs of PUD for osteoporosis were 1.34 (95% CI = 1.29–1.39) in the < 65-year-old group of women and 1.38 (95% CI = 1.33–1.47) in the ≥ 65-year-old group of women (each $P < 0.001$).

Conclusion In the current nationwide cohort study, we found that PUD is associated with an increased risk of osteoporosis regardless of sex.

Keywords Cohort study · Epidemiology · Nested case-control study · Osteoporosis · Peptic ulcer

Introduction

Peptic ulcer disease (PUD) is one of the most common upper gastrointestinal disorders; in this condition, ulcers are present on the lining of the stomach or duodenum, causing burning pain and, in some cases, ulcer perforation and internal bleeding [1]. The incidence of PUD from 2008 to 2010 was estimated to be 3.4 to 3.6% of the total Korean population [2]. The risk factors for PUD include a *Helicobacter pylori*(HP) bacterial infection, the use of nonsteroidal anti-inflammatory drugs (NSIADs), the use of aspirin, a low level of physical activity, and smoking [3].

Osteoporosis is characterized by a reduction in bone mass and compromised bone strength, resulting in an increased risk of bone fractures [4]. Osteoporosis can affect both males and females, although it is most likely to occur in women after menopause due to the sudden decrease in the level of estrogen. The National Health and Nutrition Examination Survey from 2008 to 2009 reported that the prevalence of osteoporosis in the Korean population is 7.5% in males and 35% in females aged 50 years and older [5]. The risk factors for osteoporosis include sex, a low body mass index (BMI), a low calcium intake, a low level of physical activity, hypogonadism, and smoking [6].

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HP infections occur in approximately 50% of the human population worldwide and are associated with various gastrointestinal diseases and extragastric diseases driven by local and systemic inflammation [7, 8]. Increases in inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor-α (TNF-α), as a result of HP infection-induced systemic inflammation may be involved in the regulation of bone turnover [9]. Low calcium intake and decreased calcium absorption are important risk factors for osteoporosis, and gastric and duodenal mucosal inflammation as well as consumption of alkaline substances may significantly decrease calcium absorption [10]. Several gastrointestinal diseases, including Crohn's disease, ulcerative colitis, celiac disease, can influence bone metabolism, as can a history of gastrectomy and the use of proton-pump inhibitors (PPIs) [11].

A growing amount of evidence from several clinical studies has indicated that PUD is associated with an increased risk of osteoporosis. In a case-control study of 263 postmenopausal women, PUD was found to be an independent risk factor for osteoporosis. A Taiwanese study reported a 1.12-fold higher risk of osteoporosis in patients with PUD [12, 13]. However, only a few large-scale studies have been reported, and the mechanism of osteoporosis by PUD has not yet been elucidated. It is important to reaffirm the association between PUD and the risk of osteoporosis with a large-scale population-based study.

The aim of this study was to investigate the risk of osteoporosis in PUD in South Korea using a nationwide, population-based dataset obtained from the Korean National Health Insurance Service (NHIS).

Materials and 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). The detailed description of these data was described in our previous studies [14, 15].

Participant selection

Out of 1,125,691 cases with 114,369,638 medical claim codes, we included participants who were diagnosed with peptic ulcers. Peptic ulcers were defined using International Classification of Disease, Tenth Revision (ICD-10) codes from K25 (gastric ulcer), K26 (duodenal ulcer), and K27 (peptic ulcer, site unspecified) patients underwent an endoscopy and visited a hospital or clinic ≥ 2 times (n = 133,349).

Osteoporosis was defined using the ICD-10 codes M80 (osteoporosis with pathological fracture), M81 (osteoporosis without pathological fracture), and M82 (osteoporosis in diseases classified elsewhere) from 2002 through 2013. Among the patients diagnosed with osteoporosis, we selected those who were treated for osteoporosis ≥ 2 times or had been diagnosed with osteoporosis by dual-energy X-ray absorptiometry (DEXA) or computed tomography (CT) (claim codes: E7001-E7004). Because the Korean NHIS defines an osteoporosis diagnosis as a T-score ≤ − 2.5 at the lumbar spine or femoral neck based upon bone mineral density (BMD) by DEXA, all participants underwent a DEXA (n = 94,912).

The PUD participants in this cohort were matched at a 1:1 ratio of patients:controls and had never been treated for osteoporosis from 2002 through 2013. The control group was selected from the original population without PUD (n = 992,342). These subjects were matched for age, group, sex, income, region of residence, and past medical history (hypertension, diabetes, and dyslipidemia). To prevent a selection bias when selecting the matched participants, the control group participants were sorted using a random number order, and they were then selected from the top to the bottom on the list. The matched control participants were assumed to be involved at the same time as each matched PUD participant (index date). Therefore, the control group subjects who died before the index date were excluded. Additionally, participants who had a history of osteoporosis before the index date were excluded from the PUD and control groups. In the PUD group, 8249 participants were excluded due to a previous diagnosis of osteoporosis. PUD participants for whom we could not identify enough matched participants were excluded (n = 10). We also excluded participants aged less than 50 years (n = 75,088). Instead, we conducted a separate analysis of the association between PUD and osteoporosis before age 50. Finally, 1:1 matching resulted in the inclusion of 50,002 PUD participants and 50,002 control participants (Fig. 1). The mean follow-up time from the index date to the final date (December 31, 2013) or death date was similar for both the PUD group (96.8 months, standard deviation [SD] = 40.3) and the control group (95.5 months, SD = 40.7). However, the participants were not matched for ischemic heart disease, cerebral stroke, chronic obstructive pulmonary disease (COPD), or depression because strict matching increased the number of excluded study participants due to a lack of control participants. After matching, we analyzed the occurrence of osteoporosis in both the PUD and control groups.

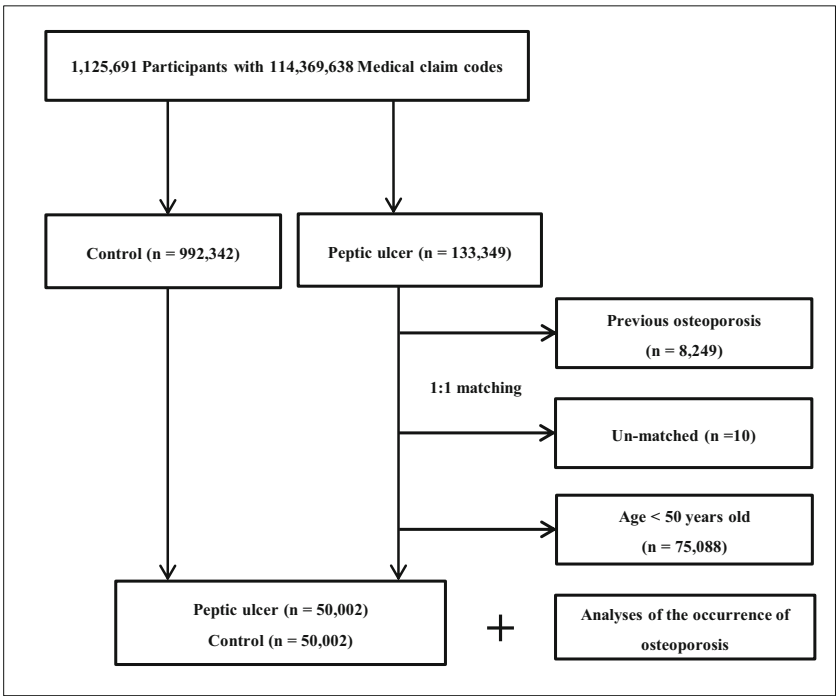

Fig. 1 Schematic illustration of the participant selection process that was used in the present study. Of a total of 1,125,691 participants, 50,002 peptic ulcer participants were matched with 50,002 control participants with respect to age, group, sex, income, region of residence, and past medical history

Variables

The age groups were classified using 5-year intervals as follows: 50–54, 55–59, 60–64…, and 80+ years old. A total of 7 age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employed health insurance classes, and 20 employed health insurance classes). These groups were recategorized into 5 classes (class 1 [lowest income]–class 5 [highest income]). The region of residence was divided into 16 areas according to the administrative district. 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. For the accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were assessed if the participants were treated ≥ 2 times. Ischemic heart disease (I24 and I25) and cerebral stroke (I60-I66) were assessed if the participants were treated ≥ 1 time. Depression was defined using ICD-10 codes F31 (bipolar affective disorder) through F39 (unspecified mood disorder) recorded by a psychiatrist ≥ 2 times. Chronic obstructive pulmonary disease (COPD) was determined by ICD-10 codes J43 (emphysema) through J44 (other chronic obstructive pulmonary disease) if the participants were treated with short-acting beta agonists, short-acting muscarinic antagonists, and long-acting antimuscarinics or inhaled corticosteroids. The duration of PPI prescriptions was measured. Gastric cancer was defined by ICD-10 code C16 if the patients were treated more than once. Anemia was defined ICD-10 codes D60 through D64 if the patients were treated more than once.

Statistical analyses

Chi-square tests were used to compare the general characteristics between the PUD and control groups.

To analyze the hazard ratio (HR) of PUD for osteoporosis, a stratified Cox proportional hazard model was used. In this analysis, crude (simple) and adjusted (ischemic heart disease, cerebral stroke, COPD, depression, gastric cancer, anemia, and PPI prescription dates) models were used, and 95% confidence intervals (CIs) were calculated. In both models, age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia were stratified. Kaplan-Meier analysis was used to estimate cumulative incidence, and the differences between the curves were tested using the log-rank test. Survival was calculated until the occurrence of hospitalization, an ambulatory visit for osteoporosis, or the end of the study period (December 31, 2013). Whichever occurred first.

For the subgroup analyses, we divided the participants by age and sex (< 65 years old, and ≥ 65 years; men and women) to confirm these associations in the different age and sex categories.

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

Results

The time durations from the index date to osteoporosis were 49.2 months (SD = 35.6) in the PUD group and 51.3 months (SD = 36.9) in the control group. The rate of osteoporosis was higher in the PUD group (27.3% [13,662/50,002]) than in the control group (20.9% [10,440/50,002], $P < 0.001$, Table 1). The general characteristics (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia) of the participants were exactly the same due to matching ($P = 1.000$). The rates of ischemic heart disease, stroke, COPD, gastric cancer, anemia, and depression were higher in the PUD group than in the control group (all $P < 0.05$).

Table 1 General participant characteristics

Characteristic	Total participants		*P* value
	Peptic ulcer (*n*, %)	Control (*n*, %)	
Age (years old)			1.000
50–54	13,756 (27.5)	13,756 (27.5)	
55–59	11,167 (22.3)	11,167 (22.3)	
60–64	10,208 (20.4)	10,208 (20.4)	
65–69	7631 (15.3)	7631 (15.3)	
70–74	4345 (8.7)	4345 (8.7)	
75–79	1974 (4.0)	1974 (4.0)	
80+	921 (1.8)	921 (1.8)	
Sex			1.000
Male	26,750 (53.5)	26,750 (53.5)	
Female	23,252 (46.5)	23,252 (46.5)	
Income			1.000
1 (lowest)	8139 (16.3)	8139 (16.3)	
2	7396 (14.8)	7396 (14.8)	
3	8546 (17.1)	8546 (17.1)	
4	11,042 (22.1)	11,042 (22.1)	
5 (highest)	14,879 (29.8)	14,879 (29.8)	
Region of residence			1.000
Urban	21,990 (44.0)	21,990 (44.0)	
Rural	28,012 (56.0)	28,012 (56.0)	
Hypertension	28,845 (57.7)	28,845 (57.7)	1.000
Diabetes	15,808 (31.6)	15,808 (31.6)	1.000
Dyslipidemia	20,726 (41.5)	20,726 (41.5)	1.000
Ischemic heart disease	6058 (12.1)	4871 (9.7)	< 0.001*
Stroke	9498 (19.0)	8717 (17.4)	< 0.001*
Depression	7247 (14.5)	4426 (8.9)	< 0.001*
COPD	13,662 (27.3)	10,440 (20.9)	< 0.001*
Gastric cancer	2890 (5.8)	786 (1.6)	< 0.001*
Anemia	1906 (3.8)	1254 (2.5)	< 0.001*
Osteoporosis	13,662 (27.3)	10,440 (20.9)	< 0.001*

*Chi-square test; significance at $P < 0.05$

COPD, chronic obstruction pulmonary disease

Table 2 Crude and adjusted HRs (95% CI) of peptic ulcer for osteoporosis

Characteristic	Hazard ratio (95% CI)			
	Crude†	*P* value	Adjusted†‡	*P* value
Peptic ulcer		< 0.001*		< 0.001*
Yes	1.45 (1.42–1.49)		1.36 (1.33–1.40)	
No	1.00		1.00	

*Cox proportional hazard regression model; significance at $P < 0.05$

†Stratified by age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories

‡Adjusted model for ischemic heart disease, cerebral stroke, depression, COPD, gastric cancer, anemia histories, and dates of PPI intake

HR, hazard ratio; *CI*, confidence interval; *COPD*, chronic obstruction pulmonary disease; *PPI*, proton-pump inhibitor

The adjusted HR for osteoporosis was 1.36 (95% CI = 1.33–1.40) in the PUD group ($P < 0.001$, Table 2). Kaplan-Meier analysis showed similar results ($P < 0.001$, Fig. 2).

In the subgroup analyses, all of the adjusted HRs for osteoporosis were higher in the PUD group than in the control group (each $P < 0.001$, Table 3). The adjusted HRs were 1.33 (95% CI = 1.21–1.47) in men < 65 years old, 1.34 (95% CI = 1.29–1.39) in women < 65 years old, 1.42 (95% CI = 1.30–1.56) in men ≥ 65 years old, and 1.40 (95% CI = 1.33–1.47) in women ≥ 65 years old.

In the analysis of subjects under 50 years old, the adjusted HR for osteoporosis was 1.50 (95% CI = 1.43–1.58) in the PUD group ($P < 0.001$, Supplemental Table 1).

Discussion

In the present nationwide cohort study, we found that PUD is associated with an increased risk of osteoporosis in people regardless of sex.

Osteoporosis may occur as a result of a number of systemic diseases or a variety of gastrointestinal diseases including gastrectomy, irritable bowel syndrome, celiac disease, ulcerative colitis, and Crohn's disease, all of which are known to be associated with osteopenia or osteoporosis [11].

Recently, several cohort studies of the association between the risk of PUD and osteoporosis were conducted. Although the subjects were limited to postmenopausal women, the bone mineral densities in the lumbar spine and femoral bone were lower in the group of women with PUD than in the comparison group without PUD [12]. In a population-based study in the USA, the incidence of hip fractures was 25% with a relative risk (RR) of 2.5 (95% confidence interval [CI], 1.9–3.3), and the incidence of vertebral fractures was 41% with an RR of 4.7 (95% CI, 3.8–5.7) in patients who had undergone gastrectomy for

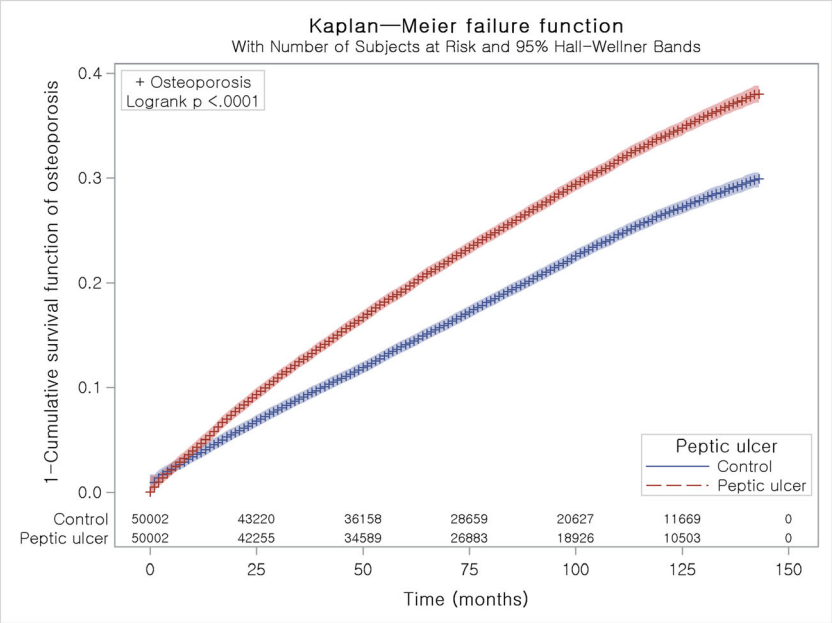

Fig. 2 Cumulative incidence of osteoporosis for patients with peptic ulcer and the general population control cohort

PUD [16]. In a nationwide study in Taiwan, the osteoporosis risk was 1.85 times greater in the PUD group than in the non-PUD group (13.88 vs 5.80 per 1000 person-years, respectively) after adjusting for covariates [13].

Table 3 Crude and adjusted HRs (95% CI) of peptic ulcer for osteoporosis according to age and sex

Characteristics	Osteoporosis			
	Crude†	*P* value	Adjusted† ‡	*P* value
Age < 65 years old, men (*n* = 37,694)				
Peptic ulcer	1.47 (1.34–1.61)	< 0.001*	1.33 (1.21–1.47)	< 0.001*
Control	1.00		1.00	
Age < 65 years old, women (*n* = 32,568)				
Peptic ulcer	1.43 (1.38–1.48)	< 0.001*	1.34 (1.29–1.39)	< 0.001*
Control	1.00		1.00	
Age ≥ 65 years old, men (*n* = 15,806)				
Peptic ulcer	1.54 (1.41–1.68)	< 0.001*	1.42 (1.30–1.56)	< 0.001*
Control	1.00		1.00	
Age ≥ 65 years old, women (*n* = 13,936)				
Peptic ulcer	1.46 (1.39–1.53)	< 0.001*	1.40 (1.33–1.47)	< 0.001*
Control	1.00		1.00	

*Cox proportional hazard regression model; significance at $P < 0.05$

†Stratified by age, income, region of residence, hypertension, diabetes, and dyslipidemia histories

‡Adjusted model for ischemic heart disease, cerebral stroke, depression, COPD, gastric cancer, anemia histories, and dates of PPI intake

HR, hazard ratio; *CI*, confidence interval; *COPD*, chronic obstruction pulmonary disease; *PPI*, proton-pump inhibitor

Several investigations have determined that there is an increased risk of osteoporosis in patients with PUD. First, calcium plays an important role in bone mineral accretion and bone development, and two of the most important risk factors for osteoporosis are low dietary calcium intake and decreased calcium absorption caused by upper gastrointestinal tract disease [17–19]. Hypochlorhydric or achlorhydric conditions induced by gastrectomy, gastric infection, or the use of antacids are associated with a decreased level of calcium absorption, and gastric infection-induced elevated intragastric pH increases the risk for PUD [20–23]. Inflammatory changes in gastric and duodenal mucosa may significantly decrease calcium absorption and lead to negative effects on the metabolism of bone tissue [24].

Second, HP infection causes PUD by inducing a localized and systemic inflammatory response that may increase the levels of several cytokines including TNF-α, IL-1, and IL-6 [25]. Chronic inflammatory processes are crucial for osteoclastogenesis without coupling to new bone formation, and these cytokines stimulate osteoclast development and, therefore, the process of bone resorption [26, 27]. The cytotoxin-associated gene A toxin (CagA) of HP has a stronger systemic pro-inflammatory reaction, and a higher prevalence of the CagA HP strain was observed in men and women with osteoporosis than in people without osteoporosis [9]. Atrophic gastritis, which is more prevalent in the elderly and is associated with HP infections, is associated with an increased likelihood of osteoporosis [28].

Third, psychological stress is a common risk factor for PUD. Although HP infection, NSAIDs, and smoking are the main risk factors for PUD, the incidence of idiopathic PUD is 5–20%, and this incidence is increasing [29]. The mechanism for the development of PUD due to psychological stress has

been suggested to be through increases in the secretion of pepsin and gastric acid and the subsequent gastric mucosal injury; in addition, PUD may be caused by neurological dysfunction influencing the sympathetic activity, the hypothalamic-pituitary-adrenal axis and the subsequently increased cortisol levels [30, 31]. These neurological changes induced by chronic psychological stress decrease bone mass and the deterioration of bone quality [32]. Several clinical studies have shown that chronic psychological stress is a risk factor for osteoporosis [33, 34].

Because estrogen deficiency plays an important role in osteoporosis development, an intrinsic sex difference plays a role in the incidence of osteoporosis. Despite the higher risk of osteoporosis in women than in men, 25% of men experience an osteoporosis-related fracture and the majority of male osteoporosis cases have at least one secondary cause [35, 36]. Sex-steroid hormones, such as estrogen, progesterone, and testosterone have major roles in regulating bone metabolism in adulthood, and the effect of estrogen on BMD is very strong compared with those of any other factors [37, 38]. The development of gastric ulceration is linked to the changes that occur within hormonal changes, especially those related to the secretion of sex hormones. Testosterone delayed oral and gastric ulcer healing by raising gastric acid secretion and plasma IL-1β and TNF-α [39]. In contrast, estrogen was proven to prevent peptic ulcers by enhancing gastric ulcers and regulating duodenal bicarbonate secretion [40, 41]. Although the maintenance of optimal testosterone levels is associated with preserving bone health, testosterone-mediated increases in pro-inflammatory cytokines, such as IL-1β and TNF-α and gastrointestinal ulceration can have a negative effect on the maintenance of bone mass in men. Although the incidence of osteoporosis is higher in women than in men and is influenced by estrogen, our study shows that the odds ratio of osteoporosis on PUD is similar in men and women. This fact implies that PUD may be a risk factor for osteoporosis.

The study has several limitations. First, osteoporosis and PUD were diagnosed according to the ICD codes from the administrative claims data and the numbers of visits for osteoporosis or PUD were counted, which may not have been reflective of the actual number of osteoporosis or PUD incidents experienced by the patients. Using ICD codes in the large claim code could carry the possibility of misdiagnosis. Second, the patient information, including smoking, dietary factors, and BMI, all of which may contribute to osteoporosis and PUD, was unavailable in the administrative dataset. Thus, the association between PUD and osteoporosis may be partially explained by the absence of these confounding factors. The prevalence of smoking in Korea was 30.8% among adult men and 6.3% among adult women in the Korean National Health and Nutrition Examination Survey [42]. The association between PUD and osteoporosis may be partially explained by the absence of these confounding factors. Because the most important causative factor for COPD is smoking, we considered COPD instead of cigarette smoking to increase control of the effect of smoking on osteoporosis to some extent [43]. Third, the NHIS lacks clinical information and therefore did not allow us to differentiate among PUD patients by severity or disease activity. Fourth, a potential confounder that our study did not control was HP infection. The incidence of HP infection in South Korea is approximately 50%, but only 5–10% of patients with HP infection develop PUD [44, 45]. The control group was generated using a random selection process, and the likelihood of considerably different HP infection rates between the PUD and control groups may be low.

Our study also had several strengths. First, we used a population-based dataset consisting of one million subjects with up to a 12-year follow-up period to assess the risk of osteoporosis in patients with PUD. Our study was the first to evaluate the association between PUD and osteoporosis in a nationwide cohort study in South Korea. Second, the control group was matched with the PUD group for basic characteristics, including age, sex, income, and region of residence and for medical history. This detailed matching might provide valid evidence for the effect of PUD on osteoporosis.

Conclusion

In the current nationwide cohort study, we found that PUD is associated with an increased risk of osteoporosis regardless of sex.

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Compliance with ethical standards The ethics committee of Hallym University (2017–I102) approved the use of these data. A written informed consent was exempted by the Institutional Review Board.

Conflicts of interest None.

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