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# Peptic ulcer does not increase the risk of dementia

## A nested case control study using a national sample cohort

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**Abstract**

Studies have shown that peptic ulcer disease (PUD) increases the risk of dementia via the mechanism of systemic inflammation. We examined the association between PUD and the risk of dementia using a population-based national sample cohort from South Korea.

Using the national cohort study from the Korean National Health Insurance Service, we extracted data for patients with dementia (n = 11,434) and for 1:4 matched control participants (n = 45,736) and then analyzed the previous histories of PUD from 2002 to 2013 using conditional logistic regression analyses. The controls were matched to the patients according to age, sex, income, region of residence, and past medical history. Subgroup analyses were performed based on age and sex.

There was no statistically significant difference in the incidence of PUD between the dementia and control groups (18.0% vs 17.4%, $P = .107$). The adjusted odds ratio (OR) for PUD was 0.92 (95% confidence interval [CI] = 0.88–0.97, $P = .002$). In the subgroup analysis based on age, the adjusted ORs for PUD were 0.93 (95% CI = 0.88–0.99) in the <80-year-old group and 0.90 (95% CI = 0.82–1.00) in the ≥80-year-old group (each $P < .05$). In the subgroup analysis based on sex, the adjusted ORs for PUD were 0.89 (95% CI = 0.81–0.97; $P < .05$) in men and 0.94 (95% CI = 0.89–1.00; $P = .06$) in women.

PUD does not increase the risk of dementia at any age or in either sex after adjusting for age and the history of hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, stroke, and depression.

**Abbreviations:** Aβ = amyloid beta, CI = confidence interval, DM = diabetes mellitus, HIRA-NSC = Health Insurance Review and Assessment Service-National Sample Cohort, HP = *Helicobacter pylori*, HPA = hypothalamus–pituitary–adrenal, HR = hazard ratio, ICD = international classification of diseases, IL = interleukins, NHIS = National Health Insurance Service, OR = odds ratio, PUD = peptic ulcer disease, TNF = tumor necrosis factor.

**Keywords:** cohort study, dementia, epidemiology, nested case-control study, peptic ulcer

## 1. Introduction

Peptic ulcer disease (PUD) is an inflammation of the stomach lining or the duodenum. PUD is a global problem with a lifetime risk of development ranging from 5% to 10% although there has been a decrease in the incidence of PUD due to improved hygiene and effective treatment.[1] *Helicobacter pylori* (HP) is a gram-negative, microaerophilic bacterium usually found in the stomach and constitutes one of the main risk factors for PUD.[2] HP infection causes an inflammatory response within the gastric mucosal layer, causes epithelial cell injury and has been associated with the development of not only different gastrointestinal diseases but also extragastric diseases, such as atherosclerosis, hypertension, and stroke via the mechanism of systemic inflammation.[3,4]

Dementia is a clinical syndrome characterized by persistent and progressive cognitive decline that interferes with the ability to socially and occupationally function.[5] The clinical characteristics of dementia include memory loss, communication and language impairment, agnosia, apraxia, and impaired executive function.[6] The main pathogenesis of dementia includes abnormal deposits of proteins such as of amyloid beta (Aβ)-peptides and tau protein that destroy neuronal cells and synapses in the areas of the brain that control memory and mental functions, and the narrowing and damaging of blood vessels in the brain such as vascular dementia.[7,8] The risk factors for dementia have been classified into unmodifiable risk factors, such as age, family

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history, and genetics and modifiable risk factors including depression, type 2 diabetes mellitus (DM), smoking, midlife hypertension, midlife obesity, and physical inactivity.[9] Chronic systemic inflammation has been observed during aging and age-related diseases, including hypertension, DM, atherosclerosis, cancer, and several neurodegenerative diseases.[10] In several studies, systemic inflammation has been linked with smaller brain volumes, poorer episodic memory, and progressive cognitive decline.[11,12]

Based on the above studies, several clinical studies have shown that PUD was associated with an increased risk of dementia. In a nationwide study of Taiwan, patients with HP infection were 1.60-fold (95% confidence interval [CI] = 1.32–1.95) more likely to develop dementia compared to patients without HP infection.[13] In another nationwide study of Taiwan, the incidence of PUD was higher in patients with dementia (hazard ratio [HR] = 1.27, 95% CI, 1.18–1.37).[14] However, since the number of these reported studies is limited and large studies have not been reported on the influence of PUD on the risk of dementia, it is important to assess the association between PUD and the risk of dementia with a large-scale population-based study.

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

## 2. Materials and methods

### 2.1. 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 these data was provided in our previous studies.[15,16]

### 2.2. Participant selection

Out of 1,125,691 cases with 114,369,638 medical claim codes, we included participants who were diagnosed with dementia (n = 13,102). Dementia was defined by the participants being diagnosed with Alzheimer's disease (G30) or dementia in Alzheimer's disease (F00). To enhance the accuracy of diagnosis, we selected the participants only if they were treated ≥2 times. We describe the reliability of the diagnosis of dementia in the supplementary material (S1). Peptic ulcer was defined using international classification of diseases (ICD)-10 codes K25 (gastric ulcer), K26 (duodenal ulcer), and K27 (peptic ulcer, site unspecified) in patients who underwent an endoscopy and were treated ≥2 times (n = 133,349).

The dementia participants were matched at a 1:4 ratio with patients (control group) in this cohort who had never been treated for dementia from 2002 through 2013 (Fig. 1). The control group was selected from the original population (n = 1,112,589). These subjects were matched for age, sex, income, region of residence, and past medical history (hypertension, DM, 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 of the list to the bottom. The matched control participants were assumed to be involved at the same time as each matched dementia participant (index date). Therefore, the control group subjects who died before the index date were excluded. Dementia participants for whom we could not identify enough matched participants were excluded (n = 1156). We also excluded participants aged <60 years (n = 512). Finally, 1:4 matching resulted in the inclusion of 11,434 dementia participants and 45,736 control participants. However, these participants were not matched for ischemic heart disease, stroke, and depression because strict matching increases the number of excluded study participants due to a lack of control participants. After matching, we analyzed the participants' previous histories of PUD in both the dementia and control groups.

### 2.3. Variables

The age groups were classified using 5-year intervals as follows: 60–64, 65–69, 70–74 . . . , and 85+ years old. A total of 6 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 re-categorized into 5 classes (class 1 [lowest income]—class 5 [highest income]). Region of residence was divided into 16 areas according to 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), DM (E10-E14), and dyslipidemia (E78) were assessed if the participants were treated ≥2 times. Ischemic heart disease (I24 and I25) and 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.

### 2.4. Statistical analyses

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

Conditional logistic regression analyses were used to analyze the OR for PUD associated with dementia. In this analysis, crude (simple) and adjusted (ischemic heart disease, stroke, and depression) models were used, and the 95% CIs were calculated. Data were stratified by age, sex, income, region of residence, hypertension, DM, and dyslipidemia.

For the subgroup analyses, we divided the participants by age (<80 years old and ≥80 years old) and sex (men and women).

Two-tailed analyses were conducted, and $P$ values <.05 were considered to indicate significance. The results were analyzed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

## 3. Results

The general characteristics (age, sex, income, region of residence, hypertension, DM, and dyslipidemia) of the participants were exactly the same due to matching ($P = 1.000$). The rates of ischemic heart disease, stroke, and depression were higher in the dementia group than in the control group (all $P < .05$). There was no statistically significant difference in the incidence of PUD

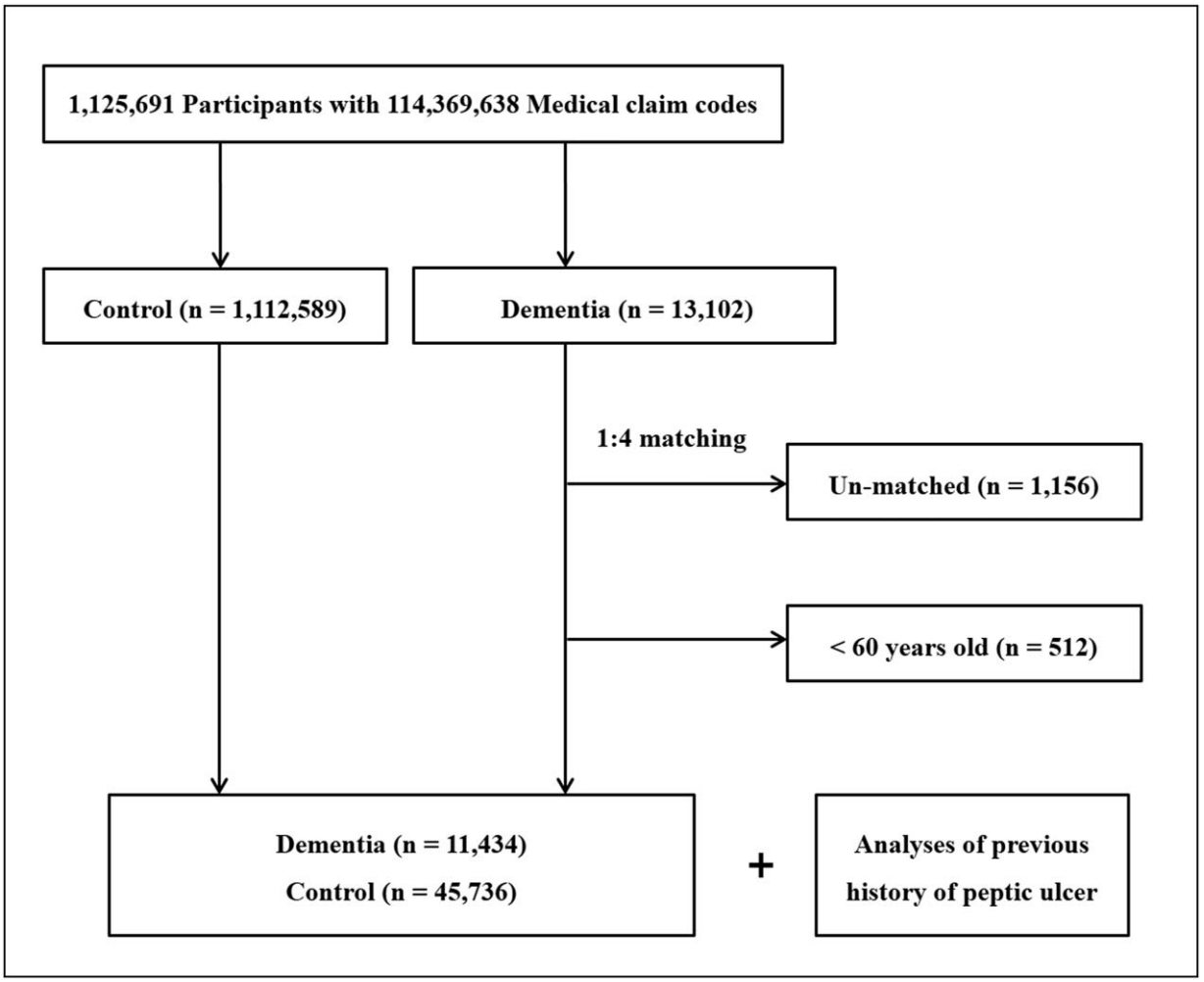


**Figure 1.** Schematic illustration of the participant selection process that was used in the present study. Of a total of 1,125,691 participants, 11,434 dementia participants were matched with 45,736 control participants with respect to age, group, sex, income, region of residence, and past medical history.

between the dementia and control groups (18.0% [2060/11,434] vs 17.4% [7947/45,736]; $P = .107$; Table 1).

The adjusted OR for PUD was 0.92 (95% CI = 0.88–0.97, $P = .002$) in the dementia group (Table 2).

According to the subgroup analysis by age, the adjusted ORs for PUD were 0.93 (95% CI = 0.88–0.99) in the <80-year-old group and 0.90 (95% CI = 0.82–1.00) in the ≥80-year-old group, (each $P < .05$, Table 3).

According to the subgroup analysis by sex, the adjusted ORs for PUD were 0.89 (95% CI = 0.81–0.97, $P = .008$) in men, and 0.94 (95% CI = 0.89–1.00, $P = .060$) in women (Table 3).

## 4. Discussion

In the present nationwide cohort study, we concluded that PUD does not increase the risk of dementia at any age after adjusting for age, hypertension, DM, dyslipidemia, and history of ischemic heart disease, stroke and depression.

Multiple medical diseases are common in patients with cognitive impairment disorders and several studies of the association between dementia and gastrointestinal disease have been conducted.[17–19]

Studies investigating the association between PUD and dementia were introduced in the 1990s. Early studies showed that patients regularly taking aluminum-containing antacid for treating PUD increased the risk of dementia.[20] In a recent nationwide study, dementia was associated with an increased risk of PUD independent of conventional risk factors (HR = 1.27, 95% CI = 1.18–1.37).[14] However, studies on the influence of PUD on the risk of dementia have not been reported in the previous literature.

Systemic inflammation is characterized by high circulating levels of active inflammatory cytokines, including C-reactive proteins, tumor necrosis factor-α (TNF-α) and interleukins (IL) 1β and 6, in addition to an increase in immune cell infiltration.[21] Increasing inflammatory cytokines and the resulting systemic inflammation affect unfavorable biomarkers of dementia by increasing burdens of Aβ-peptide and tau protein, and decreasing hippocampal volumes.[22]

The bacterial pathogen, *H pylori* (HP) commonly colonizes the human gastric mucosa and HP infection is the most common risk factor for gastritis, PUD, and gastric cancer.[4] Cytotoxins produced by HP infection induce inflammation by producing proinflammatory cytokines and downregulating immunity in

**Table 1**

**General characteristics of participants.**

| Characteristics | Total participants | | |
|---|---|---|---|
| | Dementia (n, %) | Control group (n, %) | *P* |
| Age (years old) | | | 1.000 |
| 60–64 | 580 (5.1) | 2320 (5.1) | |
| 65–69 | 1289 (11.3) | 5156 (11.3) | |
| 70–74 | 2325 (20.3) | 9300 (20.3) | |
| 75–79 | 2979 (26.1) | 11,916 (26.1) | |
| 80–84 | 2696 (23.6) | 10,784 (23.6) | |
| 85+ | 1565 (13.7) | 6260 (13.7) | |
| Sex | | | 1.000 |
| Male | 3657 (32.0) | 14,628 (32.0) | |
| Female | 7777 (68.0) | 31,108 (68.0) | |
| Income | | | 1.000 |
| 1 (lowest) | 2864 (25.0) | 11,456 (25.0) | |
| 2 | 1034 (9.0) | 4136 (9.0) | |
| 3 | 1379 (12.1) | 5516 (12.1) | |
| 4 | 1882 (16.5) | 7528 (16.5) | |
| 5 (highest) | 4275 (37.4) | 17,100 (37.4) | |
| Region of residence | | | 1.000 |
| Urban | 4623 (40.4) | 18,492 (40.4) | |
| Rural | 6811 (59.6) | 27,244 (59.6) | |
| Hypertension | 8309 (72.7) | 33,236 (72.7) | 1.000 |
| Diabetes | 4057 (35.5) | 16,228 (35.5) | 1.000 |
| Dyslipidemia | 3550 (31.0) | 14,200 (31.0) | 1.000 |
| Ischemic heart disease | 1706 (14.9) | 6050 (13.2) | <.001* |
| Stroke | 5522 (48.3) | 11,406 (24.9) | <.001* |
| Depression | 3233 (28.3) | 4726 (10.3) | <.001* |
| Peptic ulcer | 2060 (18.0) | 7947 (17.4) | .107 |

* Chi-square test or Fisher's exact test. Significance at $P < .05$.

**Table 2**

**Crude and adjusted odds ratio (95% confidence interval) for peptic ulcer disease.**

| Characteristics | Peptic ulcer | | | |
|---|---|---|---|---|
| | Crude | *P* | Adjusted† | *P* |
| Dementia | 1.04 (0.99–1.09) | .139 | 0.92 (0.88–0.97) | .002* |
| Control | 1.00 | | 1.00 | |

* Conditional logistic regression analyses stratified for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. Significance at $P < .05$.

† Adjusted model for ischemic heart disease, stroke, and depression histories.

gastric epithelial cells. Subsequently, HP infection becomes involved in the pathogenesis of extragastric diseases by inducing systemic inflammation.[23,24] HP infection was shown to induce neuroinflammation by inducing inflammatory mediators that disrupt the blood-brain barrier, prompt Aβ-peptide formation and increase the risk of dementia.[13,25–27]

In contrast to previous studies, our study showed that PUD did not increase the risk of dementia after adjusting for age, DM, hypertension, dyslipidemia and history of ischemic heart disease and stroke. In an experimental study in murine models, HP infection induced gastric inflammation compared to noninfected mice but did not induce brain neuroinflammation.[28] In a previous population-based study, HP infection did not increase the risk of dementia (HR = 1.04, 95% CI = 0.90–1.21).[29] Because the biological mechanisms of the association between PUD and dementia have not been fully identified in clinical studies, there is not enough evidence to prove that HP infection increases the risk of dementia.

The hippocampus plays a crucial role in learning and memory, and is one of the first regions of the brain to suffer damage in dementia.[30] Cortisol modulates hippocampal plasticity by binding to brain receptors involved with cognitive domains and a high level of cortisol has been observed in individuals with hippocampal atrophy and cognitive decline.[31,32] The hypothalamus-pituitary-adrenal (HPA) axis is activated by an individual's exposure to stress, and stress-induced cortisol has an effect on cognitive function.[33,34] Psychological stress is one of the risk factors for PUD by HPA axis dysfunction, which influences gastric blood flow and gastric acid secretion.[35,36] Because stress reactions can be a risk factor for both PUD and dementia by HPA axis dysregulation, PUD itself may not increase the risk of dementia.

Recent reviews have indicated that up to half of the dementia cases may be attributable to potentially modifiable risk factors, including smoking, physical inactivity, depression, midlife obesity, hypertension, and type 2 DM.[17,37] Some of these modifiable risk factors of dementia can increase the risk of PUD. Obesity increases the risk of PUD by causing alterations in the gut microbiome and decreasing gastric epithelial integrity.[38] The

**Table 3**

**Subgroup analysis of crude and adjusted odds ratios (95% confidence interval) for peptic ulcer disease according to age and sex.**

| Characteristics | Peptic ulcer | | | |
|---|---|---|---|---|
| | Crude | *P* | Adjusted† | *P* |
| Age <80 years old (n = 35,865) | | | | |
| Dementia | 1.05 (0.99–1.11) | .097 | 0.93 (0.88–0.99) | .019* |
| Control | 1.00 | | 1.00 | |
| Age ≥ 80 years old (n = 21,305) | | | | |
| Dementia | 1.00 (0.91–1.11) | .945 | 0.90 (0.82–1.00) | .044* |
| Control | 1.00 | | 1.00 | |
| Men (n = 18,285) | | | | |
| Dementia | 0.97 (0.89–1.05) | .458 | 0.89 (0.81–0.97) | .008* |
| Control | 1.00 | | 1.00 | |
| Women (n = 38,885) | | | | |
| Dementia | 1.08 (1.01–1.14) | .018* | 0.94 (0.89–1.00) | .060 |
| Control | 1.00 | | 1.00 | |

* Conditional logistic regression analyses stratified for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. Significance at $P < .05$.

† Adjusted model for ischemic heart disease, stroke, and depression histories.

gastric mucosa of patients with DM has increased vulnerability due to decreased gastric acid secretion and motility.[39] Depression had been proven to increase the risk of developing PUD in a population-based study of Taiwan.[40] We suggest that plausible risk factors for PUD tend to carry a higher risk of dementia than PUD itself.

This study has several limitations. First, dementia and PUD were diagnosed according to the ICD codes from the administrative claims data and were based on a count of the number of visits for dementia and PUD, which may not have been reflective of the actual number of dementia or PUD incidents experienced by the patients. Using ICD codes from a large claim code database could carry the possibility of misdiagnosis. However, medical claims are very important in Korea because the diagnosis affects the medical doctor and participants in various ways. Second, the severity of dementia could not be classified in this study. However, we defined dementia through the selection of participants only if they visited and were treated more than once to ensure an accurate diagnosis. Third, although we mentioned above that HP infection is a well-known etiology of PUD and is associated with confounders for dementia, our study cannot control for HP infection because HP infection was confirmed by clinical examinations, such as urea breath tests and upper endoscopy, after the diagnosis of PUD.[41] The incidence of HP infection in South Korea is approximately 50%, but only 5% to 10% of patients with HP infection develop PUD.[42,43] 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 have been low.

There were several strengths in this study. First, we used a population-based dataset consisting of one million subjects with a 12-year follow-up period to assess the risk of dementia in patients with PUD. Our study was the first to evaluate the association between PUD and dementia in a nationwide cohort study in South Korea. Second, the control group was matched with the dementia group not only for basic characteristics, including age, sex, income, and region of residence, but also for risk factors of dementia, such as hypertension, DM, dyslipidemia, and history of ischemic heart disease, stroke and depression. This detailed matching might provide valid evidence for the association between PUD and dementia.

## 5. Conclusion

Our study concluded that PUD is not associated with an increased risk of dementia after adjusting for age and history of hypertension, DM, dyslipidemia, ischemic heart disease, stroke, and depression regardless of age or sex.

## Author contributions

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**Project administration:** Jae Seung Soh, Jae Sung Lim.
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**Validation:** Song Yong Sim, Suk Woo Lee.
**Visualization:** Hyo Geun Choi.
**Writing – original draft:** Hyo Geun Choi, Suk Woo Lee.
**Writing – review & editing:** Suk Woo Lee.

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