Long-term use of proton-pump inhibitor on Alzheimer’s disease: a real-world distributed network analysis of six observational Korean databases using a Common Data Model

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Abstract
Background: Dementia has a crucial impact on the quality of life of elderly patients and their caregivers. Proton-pump inhibitors (PPIs) are the most frequently prescribed treatment, but they have been shown to be associated with dementia. The data are inconsistent, however.
Objective: To investigate the association between PPIs use and Alzheimer’s disease (AD) or all-cause dementia in six observational Korean databases using a Common Data Model (CDM) and to perform a distributed network analysis.
Methods: Subjects aged over 18 years between 1 January 2004 and 31 December 2020. Among 7,293,565 subjects from 6 cohorts, 41,670 patients met the eligibility criteria. A total of 2206 patients who were included in both cohorts or with a history of dementia were excluded. After propensity matching, 5699 propensity-matched pairs between the PPIs and histamine-2 receptor antagonist (H2RA) users were included in this study. The primary outcome was the incidence of AD at least 365 days after drug exposure. The secondary outcome was the incidence of all-cause dementia at least 365 days after drug exposure.
Results: In the 1:1 propensity score matching, the risk of AD or all-cause dementia was not significantly different between the PPIs and H2RA groups in all six databases. In the distributed network analysis, the long-term PPI users (≥365 days) were unassociated with AD [hazard ratio (HR) = 0.92, 95% confidence interval (CI) = 0.68–1.23; I² = 0%] and all-cause dementia (HR =1.04, 95% CI = 0.82–1.31; I² = 0%) compared with H2RA users.
Conclusion: In the distributed network analysis of six Korean hospital databases using Observational Medical Outcomes Partnership (OMOP)-CDM data, the long-term use of PPI was not associated with a statistically significantly increased risk of AD or all-cause dementia. Therefore, we suggest that physicians should not avoid these medications because of concern about dementia risk.

Keywords: Alzheimer disease, Common Data Model, dementia, H₂ receptor antagonist, proton-pump inhibitors

Introduction
Proton-pump inhibitors (PPIs) are the most frequently prescribed classes of drugs for the treatment of gastroesophageal reflux disease and peptic ulcers.¹ PPIs are preferred over histamine-2 receptor antagonists (H₂RAs) because PPIs have been shown to have superior efficacy at reducing gastric acid compared with H₂RAs.¹,² In
fact, PPI use rapidly increased from 0.2% in 1990 to 14.2% in 2018, whereas the usage of H$_2$RAs has remained relatively low (1.2%–3.4%) in the United Kingdom.\(^3\)

Presumed adverse events of PPIs, however, have been reported in the clinical field including *Clostridium difficile* infection,\(^4\) osteoporosis,\(^5\) chronic renal disease,\(^6\) and dementia.\(^7\) Among these factors, dementia has a crucial impact on the quality of life of elderly patients and their caregivers and is a healthcare-related socioeconomic burden.\(^8\) Vitamin B$_{12}$ deficiency, blocking acid secretion by binding to H$^+$/K$^+$-ATPase, and enhancing $\beta$-amyloid have been suggested to be associated with PPI-related cognitive decline.\(^9\) Nevertheless, because these studies have shown inconsistent results,\(^10,11\) the relationship between PPIs and dementia remains unclear. A recent meta-analysis of 10 studies suggested that the use of PPIs may not increase the risk of dementia.\(^12,13\) More recent studies, however, were not included in that meta-analysis,\(^14\) and most studies did not fully adjust for various confounding factors such as medications and combined diseases. Furthermore, it is important to consider the length of PPI exposure. The current lack of consensus on the long-term complications of PPIs related to dementia warrants further investigation using different study populations, statistical approaches, and time-at-risk (TAR) window.

Therefore, we investigated the association between PPIs use and Alzheimer’s disease (AD) or all-cause dementia in six observational Korean databases using a Common Data Model (CDM) and performed a distributed network analysis.

**Methods**

**Data source**

This study included patient-based retrospective cohort data from six medical centers including Ajou University Medical Center (AUMC, \(n = 3,109,677\)), Kangdong Sacred Heart Hospital, Hallym University College of Medicine (KDH, \(n = 1,689,604\)), Gangdong Kyung Hee University Hospital (KHNMC, \(n = 822,183\)), Kangwon National University Hospital (KWMC, \(n = 542,934\)), Pusan National University Hospital (PNUH, \(n = 1,753,001\)), and Wonkwang University Hospital (WKUH, \(n = 1,001,794\)) converted to the Observational Medical Outcomes Partnership (OMOP) CDM. OMOP-CDM contains standardized data with the same structure to generate network-wide results through distributed research networks using the same analysis program among collaborating organizations (Figure 1).

Observational Health Data Sciences and Informatics (OHDSI) is an international collaborative consortium aimed at facilitating the generation of high-quality evidence by generating and applying open-source data analysis solutions to a large network of health databases worldwide.\(^15\) Most Korean hospitals use electronic health record (EHR) systems; however, numerous Korean EHR data are not compatible with international coding systems. Since 2016, data from Ajou University and the Korean nationwide cohort database were successfully transformed into the OMOP-CDM model and validated.\(^16,17\) EHR data from each hospital were converted to the CDM version, which is potentially applicable for collaborating OHDSI networks worldwide. This study was approved by the Institutional Review Board of the study institution (Institutional Review Board number 2018-05-013) and conformed to the tenets of the Declaration of Helsinki.

**Study design and cohort definitions**

We conducted a retrospective, observational, comparative cohort study of all outpatient-based subjects aged over 18 years between 1 January 2004 and 31 December 2020. The study flowcharts of the included patients were shown in Figure 1 and Supplementary Figure 1, and diagram of study construction from six databases was depicted in Figure 2.

The index date of the target and comparative cohorts was defined as the first date of drug prescription. To avoid immortal time bias and duplication, both cohorts had continuous observation periods of 180 days before cohort entry as in our previous study.\(^18\) Both cohorts were censored or end of database at the time of the identification of dementia. PPI exposure was defined as prescription for more than 90, 180, or 365 days. In this study, TAR start was defined as the period from 1 day after the index date. We used TAR start of 180 days or 365 days from the cohort start date. Because the TAR end was set to 99,999 days, it means that the subject is followed up until the end of the observation (Figure 2).
Subjects who met at least one of the following criteria were excluded from the target and comparative cohorts: (1) history of dementia before cohort entry, (2) an observation period of less than 180 days, (3) history of drug use, and (4) aged <19 years. In the PPIs group, H2RAs users of 180 days before PPI exposure and all H2RAs users after PPI exposure were excluded.
and PPIs users of the same period were excluded from the H$_2$RAs group.

The target cohort was defined as new PPIs users who were prescribed PPIs for more than 90 consecutive days. In the subgroup analysis, the PPI group was further divided into subgroups by the duration of PPI exposure (≥180 or ≥365 days). All PPIs on the market in Korea were included in these analyses (esomeprazole, pantoprazole, lansoprazole, rabeprazole, omeprazole, ilaprazole, and dexlansoprazole). Continuous drug exposures were restricted by allowing less than 30-day gaps between the drug prescriptions. The comparative cohort was defined as subjects prescribed H$_2$RA for more than 90, 180, or 365 consecutive days. H$_2$RAs included ranitidine, nizatidine, cimetidine, famotidine, and lafutidine.

Outcomes

The primary analysis was performed to compare the risk of AD between PPIs and H$_2$RAs according to the duration of PPI exposure. The secondary analysis was performed to compare the risk of all-cause dementia including AD, Parkinson’s disease dementia, Lewy body dementia, frontotemporal dementia, and vascular dementia between PPIs and H$_2$RAs. Furthermore, we conducted the same analyses using another comparative cohort of non-PPIs users.

The primary outcome was the incidence of AD at least 365 days after drug exposure. AD was defined by the diagnosis codes F000 to F002 in the 10th version of the International Classification of Diseases codes (ICD-10). To clarify the diagnosis, patients with AD were required to have at least one antideementia medication among donepezil, rivastigmine, memantine, and galantamine. The secondary outcome was the incidence of all-cause dementia at least 365 days after drug exposure. Dementia was defined when documented with one of the following ICD-10 codes: G30, F00, F01, F05.1, G31.1, G31.82, and G31.9. We did not differentiate between dementia subtypes.

Covariates

We performed large-scale propensity score matching using the OMOP-CDM tool. The following covariates were used between the target and comparative cohorts: age, sex, all recorded comorbidities, prescribed drugs 365 days before the index date, and Charlson’s comorbidity index.

The distribution of preference scores between groups receiving PPIs and those receiving H$_2$RAs before and after matching and covariate balance was summarized with mean values for all baseline covariates in the target and comparator cohorts, with the associated standardized mean difference computed for each covariate. Standardized mean differences were lower than 0.1 after propensity score matching (Supplementary Figure 2).

Statistical analysis

Most OHDSI analysis tools are embedded in the ATLAS platform and the OHDSI Methods Library R packages. The open-source software in OHDSI is publicly available at the GitHub repository (https://github.com/OHDSI/). ATLAS ver. 2.7.3 was used herein, and we analyzed the platform of FEEDER-CDM, a health big-data platform based on OMOP-CDM supported by the Korean national project. We conducted the Cox regression analysis to examine the hazard ratio (HR) of two cohorts for AD and all-cause dementia. The Kaplan–Meier method was used to estimate the cumulative incidence rate (IR) of AD and all-cause dementia between the two groups. IRs were determined per 1000 person years by dividing the number of dementia events by the total number of person years at risk and multiplying the results by 1000. The cumulative incidence between the two groups was compared using the log-rank test. Two-sided $p$ values < 0.05 were considered statistically significant for all two-sided tests. We used 0.2 of the pooled standard deviation of the logit of the propensity score as caliper width for propensity score matching.

The assessment for statistical heterogeneity was calculated using the Chi-square and $I^2$ statistics. If heterogeneity ($p > 0.05; I^2 < 50\%$) did not exist, a fixed-effect model was used. Otherwise, a random-effect model was used.

Sensitivity analysis

To assess the robustness of the results, several sets of sensitivity analyses were performed using different definitions of TAR, propensity score matching, comparatives, and outcomes. First, in addition to 1:1 propensity score matching, 1:4 propensity score adjustments were performed. Second, two TAR periods (180 or 365 days) were applied. Third, we conducted this study using two control groups (H$_2$RA users or non-PPIs users). Fourth, we added logistic regression analyses.
Results
Among 7,293,565 subjects from 6 cohorts, 41,670 patients met the eligibility criteria. Because 2206 patients were included in both cohorts or had a history of dementia were excluded, 15,873 subjects who were PPIs users and 23,592 subjects who were H2RAs users were left. After propensity matching, 5699 propensity-matched pairs between the PPIs and H2RAs users were included in this study (Figure 1). The baseline characteristics are shown in Table 1.

The mean follow-up time was different from the six cohorts (AUMC = 1457 days, KDH = 1630 days, KHNMC = 1564 days, KWMC = 1758 days, PNUH = 1207 days, and WKUH = 1930 days). The number of subjects, follow-up time, number of outcome events, and event IR per 1000 patient years are presented in Table 2.

Association of PPIs and risk of AD and dementia compared with H2RAs
We conducted the Kaplan–Meier analyses for the risk of AD and all-cause dementia between PPIs and H2RAs groups after propensity score matching.

In the 1:1 propensity score matching, the risk of AD was not significantly different between the PPIs and H2RAs groups in all six databases [AUMC = 0.89 (95% confidence interval (CI) = 0.46–1.73), KDH = 0.80 (95% CI = 0.31–2.06), KHNMC = 1.00 (95% CI = 0.53–1.90), KWMC = 1.00 (95% CI = 0.54–1.84), PNUH = 0.67 (95% CI = 0.27–1.66), and WKUH = 1.00 (95% CI = 0.46–2.18)] (Figure 3).

In the 1:1 propensity score matching, the risk of all-cause dementia was not significantly different between the PPIs and H2RAs groups in all six databases [AUMC = 1.20 (95% CI = 0.60–2.40), KDH = 1.00 (95% CI = 0.47–2.12), KHNMC = 0.6 (95% CI = 0.31–1.14), KWMC = 1.18 (95% CI = 0.79–1.75), PNUH = 1.00 (95% CI = 0.43–2.34), and WKUH = 1.13 (95% CI = 0.69–1.84)] (Figure 4).

In the distributed network analysis with 1:1 propensity score matching, the long-term PPI users (≥365 days) were unassociated with AD [HR = 1.08, 95% CI = 0.59–1.99; F = 38.9%; I² = 38.9%; Figure 6(a)] and all-cause dementia [HR = 1.16, 95% CI = 0.81–1.67; F = 0%; I² = 0%; Figure 6(b)] compared with non-PPIs users. To assess the robustness of the results, in addition to 1:1 propensity score matching, 1:4 propensity score adjustment and 1:1 propensity score matching with an additional TAR period (365 days) were applied. No differences, however, were observed between PPI and non-PPIs users in all analyses (Table 3).

Sensitivity analysis
To support the robustness of the results, we also conducted the logistic regression analyses. In the distributed network analysis with 1:1 propensity score matching, the long-term PPI users (≥365 days) were unassociated with AD [odds ratio (OR) = 0.87, 95% CI = 0.72–1.06; F = 0%; I² = 0%] compared with H2RAs users (see the Supplementary Table). In the distributed network analysis with 1:1 propensity score matching, the long-term PPIs users (≥365 days) were unassociated with AD (OR = 1.14, 95% CI = 0.76–1.71; F = 0%) and all-cause dementia (OR = 0.84, 95% CI = 0.71–0.99; F = 0%) compared with H2RAs users (see the Supplementary Table). In addition, we performed sensitivity analysis to identify the influence of PPI duration on subjects with PPI use exceeding 90 and 180 days. Similar to the long-term PPI users (≥365 days), the risks of AD or all-cause dementia in these subgroups (PPI user ≥90 or ≥180 days) were unassociated with PPI use (Table 3).
Table 1. Distribution of baseline characteristics across six databases between the PPI $\geq$ 365 days group and the comparative group (H2RA) in the overall population before and after propensity score matching.

|                      | Before PS adjustment |          |          | After PS adjustment |          |          |
|----------------------|----------------------|----------|----------|---------------------|----------|----------|
|                      | PPIs     | H2RA    | SMD      | PPIs     | H2RA    | SMD      |
| **Dementia**         |          |          |          |          |          |          |
| Age group (years)    |          |          |          |          |          |          |
| 30–34                | 1.0      | 1.3      | −0.02    | 0.7      | 0.9      | −0.02    |
| 35–39                | 1.9      | 2.3      | −0.02    | 1.6      | 2.2      | −0.04    |
| 45–49                | 5.5      | 5.6      | 0.00     | 5.6      | 6.0      | −0.02    |
| 50–54                | 8.3      | 8.6      | −0.01    | 7.8      | 8.4      | −0.02    |
| 55–59                | 12.2     | 11.2     | 0.03     | 12.2     | 11.5     | 0.02     |
| 60–64                | 13.7     | 14.0     | −0.01    | 13.7     | 13.8     | 0.00     |
| 65–69                | 13.8     | 14.1     | −0.01    | 14.2     | 13.4     | 0.02     |
| 70–74                | 14.0     | 15.1     | −0.03    | 14.7     | 14.7     | 0.00     |
| 75–79                | 12.8     | 13.0     | −0.01    | 13.2     | 13.0     | 0.01     |
| 80–84                | 8.0      | 6.8      | 0.05     | 7.6      | 7.6      | 0.00     |
| 85–89                | 3.0      | 2.5      | 0.03     | 3.0      | 3.0      | 0.00     |
| Gender: female       | 54.9     | 51.9     | 0.06     | 53.3     | 53.0     | 0.01     |
| **Medical history: general** |          |          |          |          |          |          |
| Acute respiratory disease | 2.1      | 2.2      | −0.01    | 1.9      | 2.1      | −0.01    |
| Chronic obstructive lung disease | 3.4      | 4.5      | −0.05    | 3.5      | 3.0      | 0.03     |
| Depressive disorder  | 3.3      | 3.5      | −0.01    | 3.2      | 3.3      | 0.00     |
| Diabetes mellitus    | 11.9     | 12.0     | 0.00     | 11.7     | 12.1     | −0.01    |
| Gastroesophageal reflux disease | 13.4     | 3.2      | 0.38     | 5.4      | 6.6      | −0.05    |
| Hypertensive disorder | 28.8     | 30.2     | −0.03    | 29.4     | 30.0     | −0.01    |
| Lesion of liver      | 3.9      | 3.2      | 0.04     | 3.4      | 3.6      | −0.01    |
| Osteoarthritis       | 4.1      | 2.2      | 0.11     | 2.7      | 2.7      | 0.00     |
| Renal impairment     | 5.5      | 4.1      | 0.07     | 5.1      | 5.2      | 0.00     |
| Urinary tract infectious disease | 1.2      | 1.0      | 0.02     | 1.1      | 1.0      | 0.01     |
| Visual system disorder | 9.3      | 8.8      | 0.02     | 8.6      | 9.0      | −0.02    |
| **Medical history: cardiovascular disease** |          |          |          |          |          |          |
| Cerebrovascular disease | 6.3      | 9.9      | −0.13    | 7.6      | 7.1      | 0.02     |
| Heart disease        | 26.1     | 24.6     | 0.04     | 27.8     | 28.8     | −0.02    |
| Ischemic heart disease | 15.6     | 13.8     | 0.05     | 16.8     | 17.5     | −0.02    |

(Continued)
**Table 1.** (Continued)

| Dementia                                   | Before PS adjustment | After PS adjustment |
|--------------------------------------------|----------------------|---------------------|
|                                            | PPIs | H$_2$RA | SMD  | PPIs | H$_2$RA | SMD  |
| Peripheral vascular disease                | 2.4  | 1.9     | 0.04 |      | 1.9     | 2.0  | 0.00 |
| Pulmonary embolism                         | 0.5  | 0.3     | 0.03 | <0.1 | 0.0     | NaN  |

**Medication use**

| Agents acting on the renin–angiotensin system | 31.7 | 34.1 | −0.05 | 34.7 | 35.2 | −0.01 |
| Antibacterials for systemic use               | 27.9 | 30.9 | −0.07 | 25.3 | 25.7 | −0.01 |
| Antidepressants                               | 23.5 | 21.5 | 0.05  | 19.7 | 20.4 | −0.02 |
| Antiepileptics                               | 17.7 | 20.8 | −0.08 | 16.6 | 16.5 | 0.00  |
| Anti-inflammator and antirheumatic products  | 60.3 | 58.7 | 0.03  | 56.5 | 57.8 | −0.03 |
| Antineoplastic agents                        | 20.7 | 12.5 | 0.22  | 13.1 | 14.7 | −0.05 |
| Antipsoraticics                              | 1.5  | 1.6   | −0.02 | 1.0 | 1.1 | −0.01  |
| Antithrombotic agents                        | 47.7 | 53.4 | −0.11 | 52.5 | 52.5 | 0.00  |
| Beta blocking agents                         | 23.0 | 23.3 | −0.01 | 24.1 | 24.4 | −0.01 |
| Calcium channel blockers                     | 28.6 | 31.7 | −0.07 | 29.9 | 30.8 | −0.02 |
| Diuretics                                    | 23.1 | 24.1 | −0.02 | 23.3 | 23.6 | −0.01 |
| Drugs for acid-related disorders             | 36.4 | 47.4 | −0.22 | 33.9 | 33.8 | 0.00  |
| Drugs for obstructive airway diseases        | 21.0 | 22.3 | −0.03 | 17.1 | 17.1 | 0.00  |
| Drugs used in diabetes                       | 17.6 | 17.6 | 0.00  | 17.2 | 17.7 | −0.01 |
| Immunosuppressants                           | 12.2 | 7.7  | 0.15  | 8.5 | 8.8 | −0.01  |
| Lipid-modifying agents                       | 38.6 | 38.0 | 0.01  | 40.2 | 42.3 | −0.04 |
| Opioids                                      | 39.2 | 35.6 | 0.07  | 32.2 | 33.2 | −0.02 |
| Psycholeptics                                | 31.6 | 34.0 | −0.05 | 28.6 | 28.6 | 0.00  |

$H_2$RA, histamine-2 receptor antagonists; PPIs, proton-pump inhibitors; PS, propensity score; SMD, standardized mean difference; NaN, not a number.

Two propensity score adjustments (1:1 versus 1:4) and two different TAR factors (180 days and 365 days) were evaluated. These subgroup analyses results confirm the primary study outcomes.

**Discussion**

In the distributed network analysis of six Korean hospital databases using OMOP-CDM data, the long-term use of PPIs, compared with $H_2$RA or non-PPIs, was not associated with an increased risk of AD or all-cause dementia. There was no significant difference in the risk for AD or all-cause dementia according to the duration of PPI use. These results are consistent with other analyses using different propensity score matching and time windows. The findings are consistent with those of a recent meta-analysis of 10 studies involving 642,305 patients. To confirm a causal relationship, but not association, of the long-term complication of drugs, we should conduct well-designed randomized controlled trials (RCTs). This type of RCT, however,
Table 2. Incidence rates and risk of Alzheimer’s disease between long-term PPI users (\( \geq 365 \) days) and comparatives (H\(_2\)RA) in the six medical centers.

| Alzheimer’s disease | Number of subjects | Mean follow-up time (days) | Number of outcome events | Event incidence rate (IR) per 1000 patient years |
|---------------------|--------------------|----------------------------|--------------------------|-----------------------------------------------|
|                     | PPI users          | H\(_2\)RA users           | PPI users                | H\(_2\)RA users                             |
| 1:1 PS, time at risk 180 days |                    |                            |                          |                                               |
| AUMC                | 1507               | 1507                       | 1457                     | 1975                                         |
| KDH                 | 486                | 486                        | 1630                     | 1891                                         |
| KHNMC               | 669                | 669                        | 1564                     | 1845                                         |
| KWMC                | 772                | 772                        | 1758                     | 2126                                         |
| PNUH                | 1180               | 1180                       | 1207                     | 1373                                         |
| WKUH                | 874                | 874                        | 1930                     | 2458                                         |

AUMC, Ajou University Medical Center; H\(_2\)RA, histamine-2 receptor antagonists; KDH, Kangdong Sacred Heart Hospital, Hallym University College of Medicine; KHNMC, Gangdong Kyung Hee University Hospital; KWMC, Kangwon National University Hospital; PNUH, Pusan National University Hospital; PPIs, proton-pump inhibitors; WKUH, Wonkwang University Hospital.

Figure 3. Kaplan–Meier plots for the risks of Alzheimer’s disease on-treatment comparisons of proton-pump inhibitors versus histamine-2 receptor antagonists. (a) Ajou University Medical Center (AUMC), (b) Kangdong Sacred Heart Hospital, Hallym University College of Medicine (KDH), (c) Gangdong Kyung Hee University Hospital (KHNMC), (d) Kangwon National University Hospital (KWMC), (e) Pusan National University Hospital (PNUH), and (f) Wonkwang University Hospital (WKUH).
is very difficult to perform because of the long observation periods, huge cost, and ethical problems. Instead, causal inference from observational databases can be evaluated as a try to emulate a particular target trial. Thus, we can evaluate the causality of drug complications indirectly by satisfying the Hill criteria including strength of association, consistency, specificity, temporality, biological gradient, biological plausibility, coherence, experiment, and analogy. These study results should be reliable as the design of our research was based on a review of previous studies. First, regarding the strength of the association, the dementia risk of PPIs in previous reports had an HR of <2. This means that more clinical trials are needed to examine this connection because an HR <3 has a likelihood of potential bias, although it can also suggest biological plausibility. Second, this study showed consistent results in the extensive sensitivity and subgroup analyses. We conducted several sensitivity analyses using different drug exposure periods (≥90, ≥180, and ≥365 days), TAR windows (≥180 and ≥365 days), and propensity score matching (1:1 and 1:4). Third, regarding the specificity, because patients with dementia may have multiple comorbidities, there may be many drug–drug interactions. This study, however, was conducted using OMOP-CDM, which allowed large-scale propensity score matching including multiple drugs. Fourth, regarding the temporality, it is unknown how long dementia takes to develop. Dementia may be diagnosed at late stages or be undiagnosed. Therefore, to overcome this limitation, we used continuous observation periods of 180 days before cohort entry. After drug exposure, we used two different TAR windows (≥180 and ≥365 days) to clarify the drug effect on dementia occurrence. Fifth, regarding the biological gradient, although we conducted three different drug exposures (≥90, ≥180, and ≥365 days), we did not find a dose–response relationship in this study. Sixth, regarding analogy, a systematic review
reported that cognitive function was improved after bariatric surgery, which is a situation similar to vitamin B₁₂ deficiency.²³

The association between PPI use and dementia, however, is still vague. Regarding plausibility and experiments, some plausible mechanisms such as the increased production of β-amyloid (Aβ),²⁴ vitamin B₁₂ deficiency,¹⁰ and blocking acid secretion by binding to H⁺/K⁺-ATPase¹⁰ might be related. We cannot explain the exact mechanisms for the discrepancy between our findings and those of the prior studies. Given the widespread use of PPIs, however, these findings will be a significant step in better understanding the safety of long-term use of PPIs.

This study had some strengths. First, to define outcomes, other health claims data should depend on the medical code of diagnosis, and this always has a limitation of uncertainty. In Korea, however, physicians are required to demonstrate a clinical diagnosis of dementia from the medical history, as well as medical scores using the Mini-Mental State Examination, Clinical Dementia Ratings, or Global Deterioration Scale in order to prescribe the antidementia medications.²⁴ To improve the diagnostic accuracy of AD, we classified patients with AD when they had been prescribed antidementia medications with documented dementia codes. Second, this study was designed to focus on robustness and we performed various sensitivity analyses, which were consistent with our main analysis. Third, to clarify the impact of PPIs on AD or all-cause dementia, we compared PPI users and non-PPI users, as well as PPI uses and H₂RA users.

Despite these strengths, there were some limitations in this study. First, we could not determine the dementia status of patients or those with undiagnosed dementia. Physicians in South Korea, however, are required to provide strict diagnostic criteria before prescribing antidementia
Table 3. Risk of Alzheimer’s disease or all-cause dementia in the overall population between PPI users and comparatives (H₂RA or non-PPIs).

| Primary outcome: Alzheimer’s disease | PPIs | Subjects | Event | PPIs | Subjects | Event | HR | PPIs | Subjects | Event | HR |
|-------------------------------------|------|----------|-------|------|----------|-------|----|------|----------|-------|----|
| PPI ≥90 days                        |      |          |       |      |          |       |    |      |          |       |    |
| 1:1 PS, time at risk 180            | 15,638 | 279     | 15,638 | 344  | 1.00 [0.81–1.24] | 7553 | 97 | 7553 | 98      | 1.23 [0.83–1.82] |
| 1:1 PS, time at risk 365            | 13,585 | 257     | 13,585 | 271  | 1.15 [0.91–1.46] | 6477 | 87 | 6477 | 89      | 1.37 [0.88–2.13] |
| 1:4 PS, time at risk 180            | 15,638 | 279     | 28,840 | 629  | 1.07 [0.90–1.29] | 7553 | 97 | 21,076| 291     | 1.29 [0.96–1.73] |
| PPI ≥180 days                       |      |          |       |      |          |       |    |      |          |       |    |
| 1:1 PS, time at risk 180            | 10,120 | 231     | 10,120 | 233  | 0.99 [0.78–1.26] | 5877 | 87 | 5877 | 105     | 1.02 [0.68–1.52] |
| 1:1 PS, time at risk 365            | 8812  | 176     | 8812  | 172  | 1.09 [0.75–1.58] | 4972 | 76 | 4972 | 79      | 0.92 [0.54–1.56] |
| 1:4 PS, time at risk 180            | 10,120 | 231     | 18,561 | 431  | 1.04 [0.84–1.28] | 5877 | 87 | 16,747| 285     | 1.10 [0.82–1.48] |
| PPI ≥365 days                       |      |          |       |      |          |       |    |      |          |       |    |
| 1:1 PS, time at risk 180            | 5488  | 124     | 5488  | 148  | 0.92 [0.68–1.23] | 3461 | 55 | 3461 | 70      | 1.08 [0.59–1.99] |
| 1:1 PS, time at risk 365            | 5488  | 97      | 5488  | 123  | 1.03 [0.72–1.47] | 3442 | 46 | 3442 | 67      | 1.18 [0.55–2.50] |
| 1:4 PS, time at risk 180            | 5488  | 124     | 10,225| 300  | 0.93 [0.72–1.21] | 3461 | 55 | 10,249| 232     | 1.07 [0.64–1.78] |
| Secondary outcome: all-cause dementia|      |          |       |      |          |       |    |      |          |       |    |
| PPI ≥90 days                        |      |          |       |      |          |       |    |      |          |       |    |
| 1:1 PS, time at risk 180            | 16,008 | 513     | 16,008| 607   | 0.97 [0.74–1.28] | 6846 | 153 | 6846 | 151     | 1.16 [0.84–1.61] |
| 1:1 PS, time at risk 365            | 13,937 | 440     | 13,037| 483   | 1.12 [0.94–1.33] | 5839 | 130 | 5839 | 142     | 0.95 [0.68–1.32] |
| 1:4 PS, time at risk 180            | 16,008 | 513     | 29,529| 1111  | 1.06 [0.86–1.32] | 6846 | 153 | 19,267| 461     | 1.15 [0.91–1.46] |
| PPI ≥180 days                       |      |          |       |      |          |       |    |      |          |       |    |
| 1:1 PS, time at risk 180            | 10,456 | 373     | 10,456| 395   | 1.12 [0.77–1.62] | 5387 | 144 | 5387 | 143     | 1.40 [0.84–2.35] |
| 1:1 PS, time at risk 365            | 9073  | 343     | 9073  | 336   | 1.25 [1.02–1.53] | 4542 | 113 | 4542 | 130     | 1.08 [0.76–1.54] |
| 1:4 PS, time at risk 180            | 10,456 | 373     | 19,169| 787   | 1.13 [0.84–1.51] | 5387 | 144 | 15,545| 424     | 1.28 [0.96–1.71] |
| PPI ≥365 days                       |      |          |       |      |          |       |    |      |          |       |    |
| 1:1 PS, time at risk 180            | 5699  | 228     | 5699  | 274   | 1.04 [0.82–1.31] | 3194 | 101 | 3194 | 113     | 1.16 [0.81–1.67] |
| 1:1 PS, time at risk 365            | 5667  | 210     | 5667  | 237   | 1.19 [0.89–1.58] | 3179 | 76  | 3179 | 100     | 0.72 [0.47–1.11] |
| 1:4 PS, time at risk 180            | 5699  | 228     | 10,618| 525   | 1.08 [0.86–1.35] | 3194 | 101 | 9473 | 337     | 1.27 [0.97–1.66] |

H₂RA, histamine-2 receptor antagonists; HR, hazard ratio; PPIs, proton-pump inhibitors; PS, propensity score.
medications. Therefore, among all the diagnoses in the health claims data, the diagnosis of dementia is established relatively accurately. Second, we could not determine whether the prescribed dose was the actual dose taken. This, however, is a fundamental limitation of health claims data. Third, in the logistic regression analysis to evaluate the associations between PPI and all-cause dementia, some analyses showed marginal association differently from the main results. We suggest that because secondary outcome is all cause dementia including AD, Parkinson’s disease dementia, Lewy body dementia, fronto-temporal dementia, and vascular dementia, many confounding factors might affect this result. Despite that, our aim is to investigate the impact of PPI on AD and primary outcome analyses showed similar patterns consistent with the main analyses. Finally, the results of this study should not be generalized because this study included only six retrospective observational cohort databases from South Korea. However, we suggest that this study, which was well matched and showed consistent results through various statistical and multiple comparative analyses, is critical for the interpretation of the impact of PPIs on dementia.

**Conclusion**

In conclusion, long-term PPI use was not significantly associated with an increased risk of AD or all-cause dementia. These results are consistent with other analyses using different propensity score matching and time windows. Given some of the conflicting results, further research will be needed. However, we suggest that physicians should not avoid these medications because of concern about dementia risk.

**Declarations**

**Ethics approval and consent to participate**

The study protocol was approved by the institutional review board of Kangdong Sacred Heart Hospital, Seoul, Korea (IRB no. 2018-05-013).

**Consent for publication**

Not required.

**Author contributions**

Yerim Kim: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation;
Methodology; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing.

Seung In Seo: Methodology; Writing – review & editing.

Kyung Joo Lee: Data curation; Formal analysis; Methodology; Writing – review & editing.

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Availability of data and materials
Data are available upon reasonable request. The analytic R code is available from the corresponding author W.G.S. (e-mail: sgun9139@gmail.com).

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