

# No association between proton pump inhibitor use and dementia risk: data mining of US Food and Drug Administration adverse event reporting system

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## Research Article

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# Abstract

Proton pump inhibitors (PPIs) were widely used around the world. Studies suggested conflicting results between PPIs treatment and the risk of dementia. This study examined the association between six PPIs and dementia risk by mining the US FDA Adverse Event Reporting System (FAERS) database from 2004 to 2019. We employed reporting odds ratio (ROR) and proportional reporting ratio (PRR) to detect the signals of dementia relevant to PPIs. We also analyzed characteristics of PPI reports, compared dementia events between short- and long- duration PPIs treatment. Finally, we identified 2104 dementia cases with PPIs treatment. We did not detect significant signals between PPIs and dementia, ROR = 0.99, 95%CI 0.94–1.03, PRR = 0.99, 95%CI 0.95–1.03, even in gastroesophageal reflux disease cases ROR = 0.65, 95%CI 0.58–0.73, PRR = 0.67, 95%CI 0.60–0.74. No significant differences of dementia events were detected between short- and long- duration groups, the OR (95%CI) of the 6 months, 1 year, 3 years and 5 years comparison were 0.85 (0.68–1.06), 0.92 (0.71–1.18), 0.81 (0.57–1.15) and 0.79 (0.52–1.22), respectively. Based on the current FAERS data mining, we discovered no association between PPIs use and the risk of dementia.

## Introduction

Proton pump inhibitors (PPIs) were commonly used worldwide, to treat peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), *Helicobacter pylori* infection, or prevent side effects of glucocorticoids or non-steroidal anti-inflammatory drugs (NSAIDs) [1]. However, PPIs were also overused by off label indication, excessive dosage and long-term treatment [2, 3].

With the widespread use of PPIs, numerous studies concerned the safety of PPIs treatment [4–7]. The association between PPIs therapy and dementia was a hot issue. PPIs were reported to increase  $\beta$ -amyloid ( $A\beta$ ) levels in the mouse brain by affecting the  $\beta$ - and  $\gamma$ -secretase enzymes [8], and to lead to vitamin B12 deficiency which was associated with cognitive impairment [9]. Some studies reported PPIs use could increase the risk of dementia [10–16]. More recent studies found no significant association between PPIs treatment and dementia [17–21]. Professor Lai expounded, to test the risk of dementia, the potentially offending agent should be taken for a long time, such as PPIs in GERD treatment [22]. However, the association between long-term PPIs treatment and risk of dementia was also conflicting [23, 24].

Adverse event reporting system (AERS) data was an outstanding source for pharmacovigilance analysis and post-marketing drug safety monitoring. The United States Food and Drug Administration AERS (FAERS) is one of the largest databases open to the public [25]. To the end of 2019, FAERS had gathered more than ten million of adverse cases reported by both health professionals and non-health professionals. The FAERS data could be used to detect signals of drug-associated adverse events by data mining methods [26, 27]. To the best of our knowledge, there was no research concerning the association between PPIs use and dementia risk based on FAERS database. The objective of present study was to detect the association between PPIs treatment and the potential risk of dementia by systematically assessing spontaneous reports submitted to the FAERS database.

## Results

# Characteristics Analysis

After data cleaning, we retrieved a total of 11450529 cases from January 2004 to December 2019, 5414695 of which were reported by health professionals. We screened 35251 PPIs-associated adverse event cases and 326943 dementia cases reported by health professionals (Figure 1). We further identified 2104 PPI users with dementia events reported by health professionals (Table 1). No case was identified for dexrabeprazole.

**Table 1.** Characteristics of dementia cases with PPIs treatment reported by health professionals in FAERS. PPIs: proton pump inhibitors; FAERS: FDA adverse events reporting system.

Characteristics	Subgroups	Dementia cases		All cases /N
		cases /n	proportion /%	
Drug	All PPIs	2104	100.00	35251
	Omeprazole	746	35.46	10299
	Pantoprazole	556	26.43	8963
	Esomeprazole	389	18.49	7273
	Lansoprazole	288	13.69	6093
	Rabeprazole	91	4.33	1439
	Dexlansoprazole	34	1.62	1184
	Age	≤65 years	859	40.83
	65 to 85 years	712	33.84	10659
	≥85 years	229	10.88	2196
	Unknown	304	14.45	8601
Sex	Female	1138	54.09	17241
	Male	807	38.36	13273
	Unknown	159	7.56	4737
Reporter	Physician	746	35.46	13713
	Pharmacist	275	13.07	4743
	Other health professional	1083	51.47	16795
Country (top 5)	Great Britain	573	27.23	5075
	France	341	16.21	6083
	United States	336	15.97	10954
	Italy	164	7.79	1488
	Canada	136	6.46	1252

Among cases reported with age, the proportion of PPI users with dementia events was larger in below-65-year group than other age groups. Female cases were reported more than male, the ratio of female proportion versus male proportion were 1.41.

Other health professional (51.47%) reported the most cases, followed by physician (35.46%) and pharmacist (13.07%). Great Britain (27.23%) reported the most cases, followed by France (16.21%) and

United States (15.9%). The number of PPI users with dementia events was almost increasing year by year (Figure 2).

## Signal Detection

We first conducted signal detection based on all PPIs indications, detected no significant signals between PPIs use and dementia events, ROR = 0.99, 95%CI 0.94 - 1.03, PRR = 0.99, 95%CI 0.95 - 1.03. We then conducted signal detection in individual PPI regimens, detected no significant signals in all the six PPIs as well (Table 2).

We further conducted signal detection based on cases with the indication of GERD, 303 dementia cases were gathered out of 7537 PPI users with GERD indication reported by health professionals in FAERS. However, no significant signal between each PPIs treatment and dementia events was detected, ROR = 0.65, 95%CI 0.58 - 0.73, PRR = 0.67, 95%CI 0.60 - 0.74 (Table 2).

**Table 2.** Signal detection for PPIs associated dementia reported by health professionals in FAERS. PPIs: proton pump inhibitors; FAERS: FDA adverse events reporting system; AE: adverse event; ROR: reporting odds ratio; PRR: proportional reporting ratio; 95%CI: 95% confidence interval; GERD: gastroesophageal reflux disease.

PPIs indication	Drugs	Dementia cases /n	All AE cases /N	Proportion /%	ROR	95%CI for ROR	PRR	95%CI for PRR
ALL indications	All PPIs	2104	35251	5.97	0.99	0.94 - 1.03	0.99	0.95 - 1.03
	Omeprazole	746	10299	7.24	1.22	1.13 - 1.31	1.20	1.12 - 1.29
	Pantoprazole	556	8963	6.20	1.03	0.94 - 1.12	1.03	0.95 - 1.11
	Esomeprazole	389	7273	5.35	0.88	0.79 - 0.97	0.89	0.80 - 0.98
	Lansoprazole	288	6093	4.73	0.77	0.69 - 0.87	0.78	0.70 - 0.88
	Rabeprazole	91	1439	6.32	1.05	0.85 - 1.30	1.05	0.86 - 1.28
	Dexlansoprazole	34	1184	2.87	0.46	0.33 - 0.65	0.48	0.34 - 0.66
	GERD	All PPIs	303	7537	4.02	0.65	0.58 - 0.73	0.67
	Omeprazole	86	1821	4.72	0.77	0.62 - 0.96	0.78	0.64 - 0.96
	Esomeprazole	66	1282	5.15	0.84	0.66 - 1.08	0.85	0.67 - 1.08
	Pantoprazole	66	1828	3.61	0.58	0.46 - 0.75	0.60	0.47 - 0.76
	Lansoprazole	48	1685	2.85	0.46	0.34 - 0.61	0.47	0.36 - 0.62
	Rabeprazole	20	303	6.60	1.10	0.70 - 1.73	1.09	0.72 - 1.67
	Dexlansoprazole	17	618	2.75	0.44	0.27 - 0.71	0.46	0.29 - 0.73

## Time Event Comparison

We estimated the time interval from PPIs use to adverse events onset, comparing dementia event between short- and long- time interval groups. 457 dementia cases were identified out of 8848 PPI users with time interval data reported by health professionals in FAERS. We divided different short- and long- time interval with 6 months, 1 year, 3years and 5 year. However, no significant difference was found between each short- and long- time interval groups (Table 3). The OR value (95%CI) of the 6 months, 1 year, 3 years and 5 years comparison were 0.85 (0.68 - 1.06), 0.92 (0.71 - 1.18), 0.81 (0.57 - 1.15) and 0.79 (0.52 - 1.22), respectively.

**Table 3.** Comparison of dementia events between short-term and long-term proton pump inhibitors treatment cases. AE: adverse event; OR: odds ratio; 95%CI: 95% confidence interval.

Groups	Time interval	Dementia cases		All AE cases /N	OR		Chi-square test	
		case /n	proportion /%		value	95%CI	$\chi^2$	P value
Groups1	≈6 months	103	4.58	2251	0.85	0.68 - 1.06	2.140	0.143
	≤6 months	354	5.37	6597				
Groups2	≈1 year	78	4.82	1618	0.92	0.71 - 1.18	0.479	0.489
	≤1 year	379	5.24	7230				
Groups3	≈3 years	36	4.31	836	0.81	0.57 - 1.15	1.390	0.238
	≤3 years	421	5.25	8012				
Groups4	≈5 years	23	4.19	549	0.79	0.52 - 1.22	1.137	0.286
	≤5 years	434	5.23	8299				

## Discussion

The current study investigated the association between six PPI agents and the risk of dementia, compared different time interval of PPIs treatment and dementia events. The results indicated no association between dementia events and PPI agents, including dexlansoprazole, lansoprazole, pantoprazole, omeprazole, esomeprazole and rabeprazole. To the best of our knowledge, this was the first study concerned the association between PPIs use and dementia risk based on FAERS database.

With the widespread use of PPI agents, PPIs-associated adverse events had caught health professionals' attention, as well as the public and the media. In FAERS database, nearly three quarter of the PPIs AE cases were reported by non-health professionals. To reduce the influence of non-health professionals, we only included cases reported by health professionals. However, the number of dementia cases treated by PPIs were increasing by years in FAERS, the risk of stimulated reporting could not be complete ruled out.

Based on the  $\beta$ -amyloid enhancement [8], vitamin B12 deficiency phenomena [9] and the widespread PPIs use, the risk of dementia and PPIs use had become a hot topic. Professor Akter first revealed five different PPI agents had varying degrees of influence on different cognitive domains associated with dementia based on the Cambridge Neuropsychological Test Automated Battery (CANTAB) software test [10]. Professor Haenisch conducted the first epidemiological investigation, indicated PPIs might have an impact on dementia risk based on the German Study on Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe) [11]. Then, professor Gomm conducted the first prospective cohort study, revealed regular PPIs

treatment had a significantly increased risk of dementia using data derived from the largest German statutory health insurer, Allgemeine Ortskrankenkassen (AOK) [12], which had been hotly commented.

However, conflicting results had been gradually published. Professor Lochhead conducted a nationwide prospective cohort study and divided PPI users into four groups based on duration of PPIs treatment, revealed a modest association between duration of PPIs use and cognitive function, however, Lochhead stated that the results could not support PPIs use increases dementia risk [28]. Professor Taipale finished a nationwide nested case–control study which set a lag window of different duration, found PPIs use was not associated with risk of Alzheimer's disease with a 3-year lag window [29]. Professor Gray reported a prospective cohort study and found no association between PPIs exposure and dementia risk after a mean follow-up of 7.5 years [20]. Professor Cooksey conducted a large population-based study based on electronic health-data from the Secure Anonymised Information Linkage (SAIL) Databank from 1999 to 2015, could not confirm an association between PPIs use and an increased risk of dementia [17]. The current study based the FAERS big data, indicated no significant signal between PPIs use and the risk of dementia. Even compared in different time duration, no significant difference of dementia events was found between short- and long- time interval groups.

Our study revealed no association between dementia risk and PPIs treatment based on the FAERS real world big data, however, certain limitations existed. FAERS is a spontaneous reporting system, voluntary and opened to health professional as well as the public, so under-reporting, over-reporting or missing data was inevitable [30]. The time event comparison only included limited cases with time data reported. Although non-health professionals' reports excluded, the risk of stimulated reporting could not be eliminated.

In summary, the current study revealed no association between six PPI agents and the risk of dementia based on the FAERS data. Our findings suggested that dementia events might not be considered as a factor in discontinuing PPIs treatment.

## **Materials And Methods**

### **Data Source**

We downloaded FAERS data from January 2004 to December 2019 in the FAERS Quarterly Data Extract Files website [31]. FAERS data was processed anonymously, so no ethical review was required.

The FAERS datasets consisted of seven data tables as follow: "DEMO" table for patient demographic and administrative information, "DRUG" table for the drug information, "REAC" table for adverse events information, "OUTC" table for patient outcomes information, "RPSR" table for report sources information, "THER" table for drug therapy start and end dates information and "INDI" table for the indications for drug use. We managed FAERS data in local by Microsoft SQL server 2017 software.

We first removed duplicated cases from the original data as the FDA recommended. We removed the same records from “DEMO” table and left one, then deleted the earliest FDA\_DT when the CASEIDs were the same and removed the lower PRIMARYID when the CASEID and FDA\_DT were the same. In the current study, we only included cases reported by health professionals, including physicians, pharmacists and other health professionals.

## PPI Regimens Identification

In “DRUG” table, drugs could be documented in various forms, such as generic names, brand names, synonymous names or their abbreviations. We used the MedEx software (MedEx UIMA 1.3.7, Vanderbilt university, US) to standardize different names of the same drug into the “generic name” [32, 33].

We tried to identify seven single component PPI regimens with the WHO Anatomical Therapeutic Chemical (ATC) code of A02BC from local FAERS database. The seven PPI regimens (ATC code) included omeprazole (A02BC01), pantoprazole (A02BC02), lansoprazole (A02BC03), rabeprazole (A02BC04), esomeprazole (A02BC05), dexlansoprazole (A02BC06) and dexrabeprazole (A02BC07). We restricted the drug role as Primary Suspected (PS) drug.

## Dementia Events Identification

According to Medical Dictionary for Regularly Activities (MedDRA) and Standardised MedDRA Queries (SMQs) version 23.1. We identified dementia cases in “REAC” table using SMQ (code: 20000097) broad searching, including 99 Preferred Terms (PTs). For cases reported more than one PTs of the same SMQ, we removed duplicate records and kept one. The PTs details could be found in Supplementary Table S1.

## Data Mining

We gathered the characteristics of dementia cases with PPIs treatment, including cases attributed to different PPIs, age and sex, reporter and report country, annual case reported, as well as indications.

We employed reporting odds ratio (ROR) and proportional reporting ratio (PRR) to detect signals of dementia event relevant to PPIs. The calculation method of ROR, PRR and their 95% confidence interval (95% CI) were shown in Supplementary Table S2. A significant signal was defined as both ROR and PRR signal detected. The ROR signal criteria was cases  $\geq 3$  and the lower limit of 95% CI exceed one[34]. The PRR signal criteria was cases  $\geq 3$ , PRR  $\geq 2$  and  $\chi^2 \geq 4$  [35].

We further calculated signals between PPIs use and dementia event in GERD cases who might receive long-term PPIs treatment.

## Statistical Analysis

We estimated the time interval from PPIs use to adverse events reported in all PPIs (PS) cases reported by health professionals in FAERS. We unified the time format as yyyy-mm-dd. The time interval was calculated using event date (EVENT\_DT) minus drug start date (START\_DT). To make the calculation more accurately, we excluded cases not in the period of 2004 to 2019, cases without year, month or day data in either EVENT\_DT or START\_DT field, and cases with earlier event date than drug start date. We compared dementia event between short- and long- duration using Pearson's chi-squared test. *P* value less than 0.05 indicated significant difference.

The statistical analyses were conducted by SPSS version 20.0 (IBM corporation, Armonk, New York, USA) and GraphPad prism version 8.0.2 (GraphPad Software, San Diego, California, USA).

## Declarations

## Authors Contributions

Bin Wu and Ting Xu designed the research.

Bin Wu, Fangyuan Tian, Qiaozhi Hu, Fengbo Wu, Yuwen Li and Ting Xu wrote the article.

Bin Wu and Fangyuan Tian collected the data.

Bin Wu and Qiaozhi Hu performed data analysis.

Bin Wu, Fengbo Wu, Yuwen Li and Ting Xu contributed to data interpretation and intellectual content.

## Conflicts of Interest

The authors have no conflicts.

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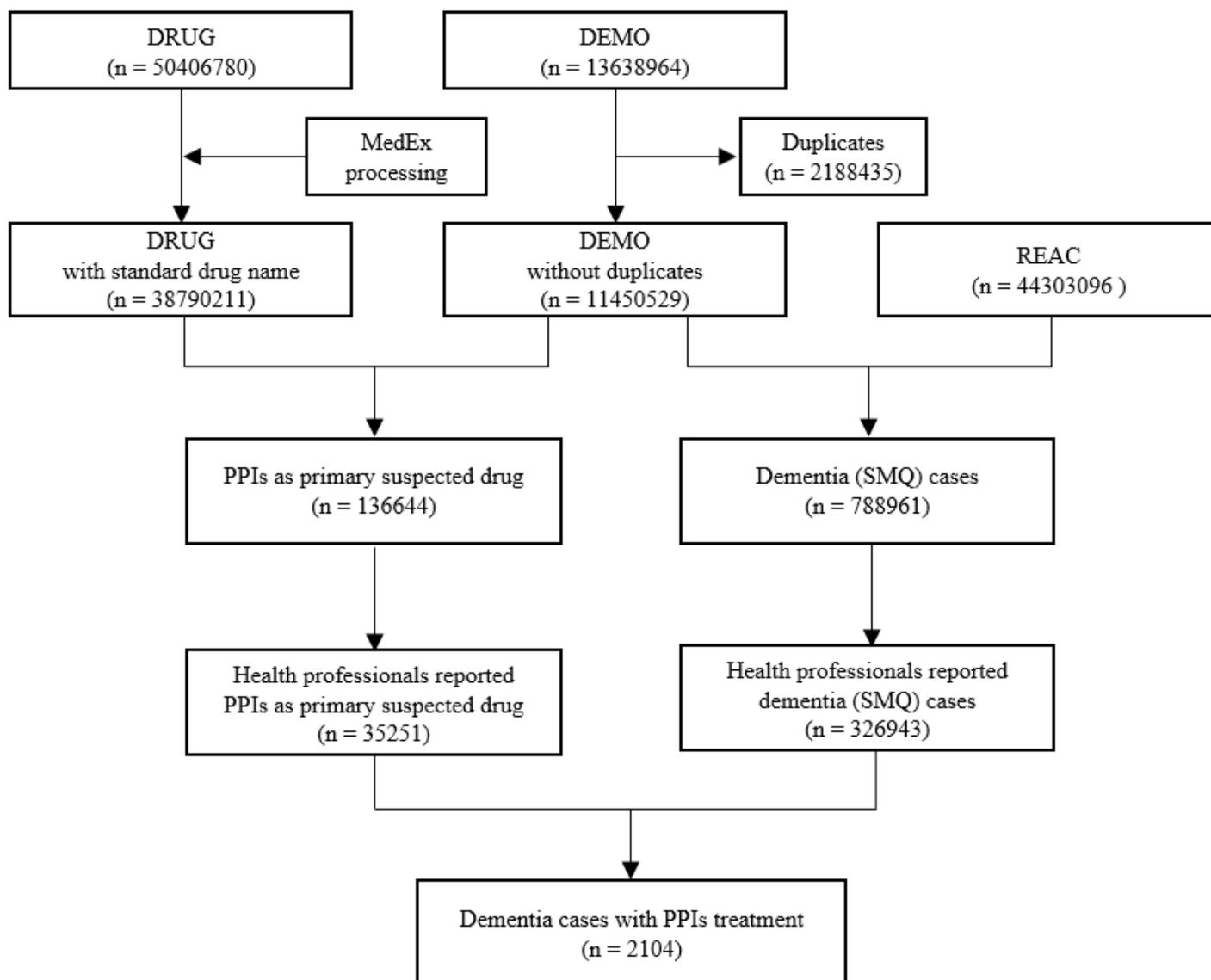
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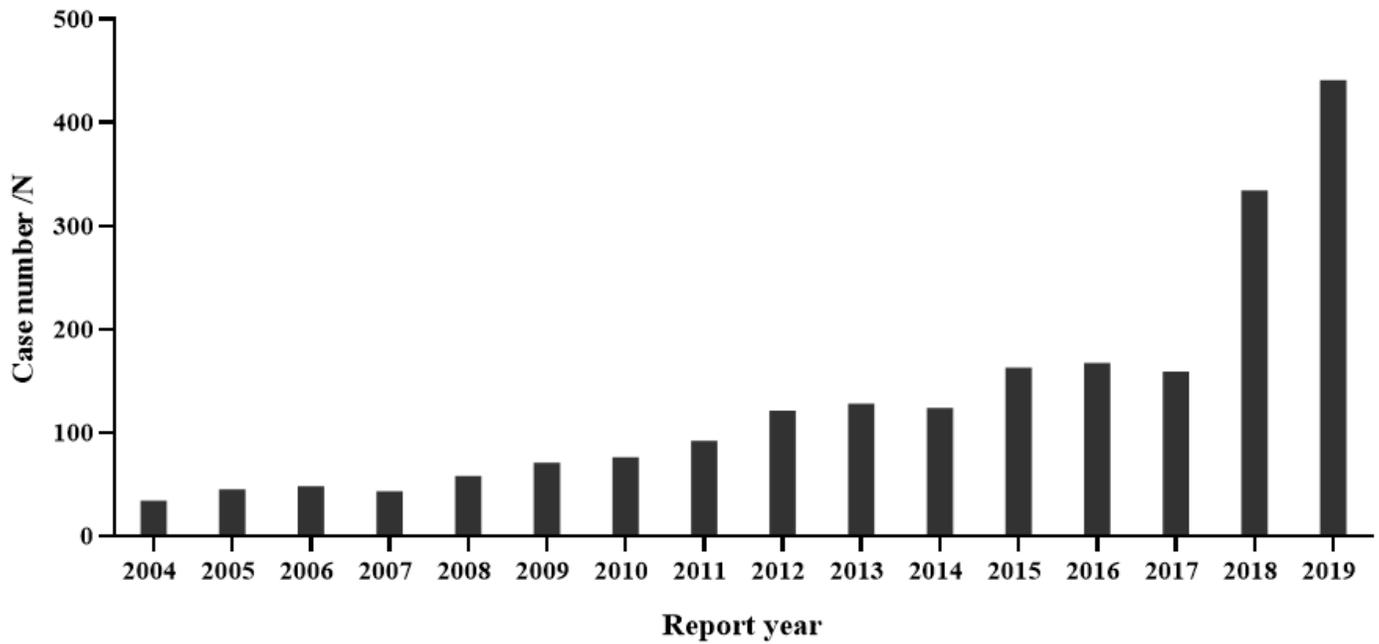
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## Figures



**Figure 1**

Flow chart of identifying dementia cases with PPIs treatment reported by health professionals from FAERS database. PPIs: proton pump inhibitors; FAERS: FDA adverse events reporting system; SMQ: Standardised MedDRA Queries.



**Figure 2**

Annual reports of dementia cases with PPIs treatment by health professionals in FAERS. PPIs: proton pump inhibitors; FAERS: FDA adverse events reporting system.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTables.docx](#)