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Original Article

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Association Between Persistent Treatment of Alzheimer's Dementia and Osteoporosis Using a Common Data Model

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ABSTRACT

Background and Purpose: As it becomes an aging society, interest in senile diseases is increasing. Alzheimer's dementia (AD) and osteoporosis are representative senile diseases. Various studies have reported that AD and osteoporosis share many risk factors that affect each other's incidence. This aimed to determine if active medication treatment of AD could affect the development of osteoporosis.
Methods: The Health Insurance Review and Assessment Service provided data consisting of diagnosis, demographics, prescription drug, procedures, medical materials, and healthcare resources. In this study, data of all AD patients in South Korea who were registered under the national health insurance system were obtained. The cohort underwent conversion to an Observational Medical Outcomes Partnership–Common Data Model version 5 format.
Results: This study included 11,355 individuals in the good persistent group and an equal number of 11,355 individuals in the poor persistent group from the National Health Claims database for AD drug treatment. In primary analysis, the risk of osteoporosis was significantly higher in the poor persistence group than in the good persistence group (hazard ratio, 1.20 [95% confidence interval, 1.09–1.32]; $p<0.001$).
Conclusions: We found that the good persistence group treated with anti-dementia drugs for AD was associated with a significant lower risk of osteoporosis in this nationwide study. Further studies are needed to clarify the pathophysiological link in patients with two chronic diseases.

Keywords: Alzheimer's Disease; Osteoporosis; Common Data Model

INTRODUCTION

Globally, the aging population is increasing rapidly, leading to a growing interest in geriatric diseases.[1] Alzheimer's disease (AD) accounts for 75% of dementia diseases. It is the most prevalent among neurodegenerative diseases. Its pathologic hallmarks are abnormal accumulation of beta-amyloid and tau protein leading to destruction of normal nerve cells. AD represents a significant health concern, given its high impact on quality of life.[2] Osteoporosis is also a highly prevalent disease among the elderly. It is characterized

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Jang JW, Hwang S; Data curation: Yu D, Baek H, Soung YG; Formal analysis: Jang JW, Hwang S; Investigation: Jang JW, Hwang S, Soung YG; Methodology: Jang JW, Hwang S, Yu D, Baek H, Soung YG, Kang SU; Software: Jang JW, Hwang S, Kang SU; Validation: Soung YG.

by increased risk of fracture and decreased bone density. Previous studies have suggested a potential common mechanism between these two diseases, with most epidemiological studies focusing on effects of osteoporosis on AD.[2]

Both AD and osteoporosis are common in the elderly. They share several risk factors such as aging, diabetes, and vitamin deficiency.[3] Based on past observational research, there is evidence suggesting that patients with osteoporosis experience a higher prevalence of AD compared to patients in a control group.[4] These studies support the notion that there is a pathophysiological link between the two diseases. Amyloid plaque deposition in the brain is the causal factor of AD. These pathological effects can extend to peripheral organs.[4] Furthermore, skeletal amyloid accumulation has been found to enhance osteoclast activity.[4] A recent study has demonstrated that the occurrence of AD in subjects with osteoporosis is 1.27 times higher than that of the control, supporting an increased risk of AD in patients with osteoporosis regardless of hyperlipidemia, hypertension, or blood glucose levels.[2] Another study has shown a 1.39-fold higher incidence of AD in osteoporosis patients than in the control group.[5] This study also found that the risk of AD was significantly reduced among subjects with osteoporosis treated with bisphosphonate or estrogen supplementation. Therefore, osteoporosis has emerged as a risk factor for AD.

In addition, it has been reported that the fracture incidence rate is 6.9 times higher in individuals with AD, and evidence concerning the relationship between these two diseases is continuously accumulating.[6] Both diseases are associated with genetic mutations in the *APOE4* gene as well as metabolic disturbances associated with reduced vitamin D levels and increased serum parathyroid hormone.[7] The coexistence of osteoporosis and AD is associated with amyloid hypothesis, which suggests an involvement of peripheral amyloid deposition.[4]

Through continuous efforts in AD medication development, disease-modifying drugs aducanumab and lecanemab have recently achieved conditional approval from the FDA. However, acetylcholinesterase inhibitors (AchEI) (such as donepezil, galantamine, rivastigmine) and NMDA receptor antagonists (such as memantine) currently represent available medical treatments in clinical practice.[8] These anti-dementia drugs have demonstrated short- to mid-term therapeutic efficacy and long-term cognitive and functional stabilization.[9] It is estimated that 30%–50% of patients exhibit poor adherence to prescribed medications for chronic diseases.[9] Non-sustained drug adherence has been shown to reduce therapeutic effects, resulting in prolonged disease progression, increase need of medical resources, and unnecessary prescriptions.[10] In particular, patients with AD and cognitive impairment tend to have lower abilities in drug management planning and task execution. Therefore, they have lower adherence rates compared to other patient groups. On top of that, AchEI use is associated with clinically important reduction in subjects with dementia.[11]

The purpose of the present study was to determine the incidence of osteoporosis based on the persistence of drug treatment in patients diagnosed with AD. Various previous studies have suggested an association between osteoporosis and AD. Therefore, this study aimed to determine whether persistent drug treatment for AD might affect the occurrence of osteoporosis. We hypothesized that persistent drug treatment for AD would lower the risk of developing osteoporosis. To ascertain this hypothesis, we examined the occurrence of osteoporosis by comparing a group of patients who took four anti-dementia drugs for more than 12 months with a group that took them for less than 3 months among patients diagnosed with AD for the first time.

METHODS

Data source

Data for this observational cohort study were sourced from a nationwide claims database in South Korea. There data were acquired from the Health Insurance Review and Assessment Service (HIRA). HIRA is a national institution responsible for providing comprehensive health insurance coverage to the entire South Korean population. HIRA claims data are generated through submission of healthcare service provider records for reimbursement purposes.[12] The dataset comprises a range of data elements, including demographic information, diagnosis records coded according to the International Classification of Disease (ICD), procedures conducted, prescription drug information classified by Anatomical Therapeutic Chemical codes, medical materials, and healthcare resource utilization.[13] Information regarding prescription drugs was extracted from pharmacy records that recorded dispensed prescriptions. In this study, data were obtained for the entire group of AD patients (n=22,710) who were enrolled in South Korea's national health insurance scheme.

Anonymized and standardized medical database format known as the Observational Medical Outcomes Partnership–Common Data Model (OMOP–CDM) version 5 was utilized to transform the cohort.[14] The OMOP-CDM serves as a standardized and unified data model, enabling integration of heterogeneous data sources into a common format. By utilizing CDM-based vocabulary, diverse data sources can be harmonized and consolidated, facilitating analysis of extensive datasets for a wide range of clinical research endeavors. The OHDSI consortium offers open-source solutions for using large-scale observational health data for diverse clinical studies.[14] Both OMOP-CDM and the OHDSI have gained recognition in pharmacoepidemiologic and pharmacovigilance research.[15,16] The Institutional Review Board (IRB) of Kangwon National University Hospital approved this study (IRB number: KNUH-2022-11-008), exempting the need for informed consent.

Study population and eligibility

Patients first diagnosed as AD (ICD 10th edition: F00 or G30) who initiated treatment with AD medication (donepezil, rivastigmine, galantamine or memantine) within 3 months of the diagnosis date were assigned into the AD cohort. The index date was set as the date of the initial diagnosis of AD with a prior observation duration of 180 days before the index date. During this prior observation period, subjects diagnosed with AD or osteoporosis (ICD 10th edition: M80-82) were excluded. Patients first diagnosed with AD were followed for a minimum of 18 months to observe the incidence of osteoporosis (**Fig. 1**). As sample data of HIRA-CDM dataset were available from January 2018 to April 2022, we enrolled subjects during 2019.

We divided patients into two groups in order to determine whether persistent use of AD medication was linked to a decline in the incidence of osteoporosis. The good persistence group consisted of patients who remained on medication for more than 365 days, while the poor persistence group comprised patients who discontinued medication within less than 90 days.

Outcomes

The outcome measure assessed in this study was the incidence of osteoporosis, specifically capturing only the first recorded instances utilizing diagnostic codes categorized within the SNOMED-CT classification.

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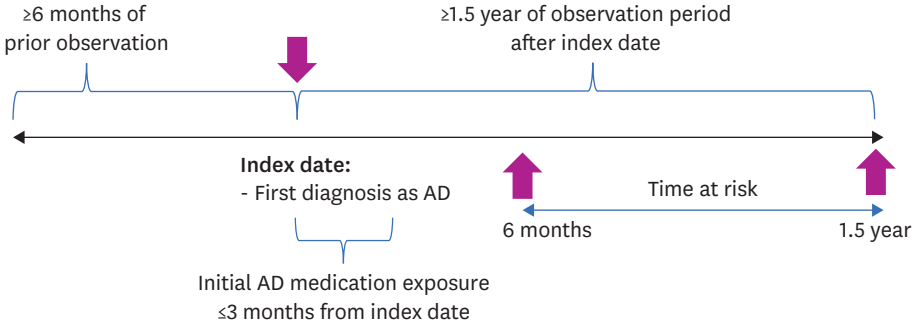

Fig. 1. The patients were divided into two groups to see if AD medication affected the decreased prevalence of osteoporosis. Good persistence group took drugs for more than 365 days, and poor persistence group took drugs for less than 90 days.
AD: Alzheimer's dementia.

Statistical analysis

The majority of analysis tools from OHDSI can be found within the ATLAS interactive analysis platform and the R package of the OHDSI Methods Library. The open-source software from OHDSI can be accessed from their GitHub repository (https://github.com/OHDSI/). We utilized ATLAS version 2.7 for this purpose and conducted an analysis on FEEDER-NET, a health data platform underpinned by OMOP-CDM. This ATLAS provides automatic analytic tools for cohort definition, propensity score matching, and survival analysis. The window of time-at-risk was between 6 months and 18 months after the index date to compare effects of treatment duration of AD between good and poor persistence groups simultaneously (**Fig. 1**). To balance baseline characteristics between good and poor persistence groups, propensity score matching was used with 1:1 nearest neighbor matching of subjects with the same scores. The balance of covariate distribution was assessed using the absolute standardized mean difference (aSMD) as a measure. Demographics of subjects (age and sex) and general medical disorders (cardiovascular disease, pulmonary disease, gastrointestinal disease, hematologic disease) were used to match covariates. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) of osteoporosis between good and poor persistence groups. Statistical significance was set at $p<0.05$.

RESULTS

For osteoporosis assessment, 22,710 patients receiving AD medication treatment were included in the study using data from the National Health Claims database. A total of 11,355 patients were assigned to the good persistence group. The poor persistence group also had 11,355 patients (**Fig. 2**). **Table 1** describes baseline characteristics of the primary analysis of osteoporosis.

All baseline characteristics between good persistence and poor persistence groups were balanced after propensity score matching (all aSMD <0.20; **Fig. 3**). In terms of baseline characteristics, there were no significant differences in any covariates between the two group.

Fig. 4 shows results of survival curve analysis after propensity score matching. The risk of osteoporosis was significantly higher in the poor persistence group than in the good persistence group in the analysis (HR, 1.20 [95% confidence interval, 1.09–1.32]; $p<0.001$) (**Table 2**).

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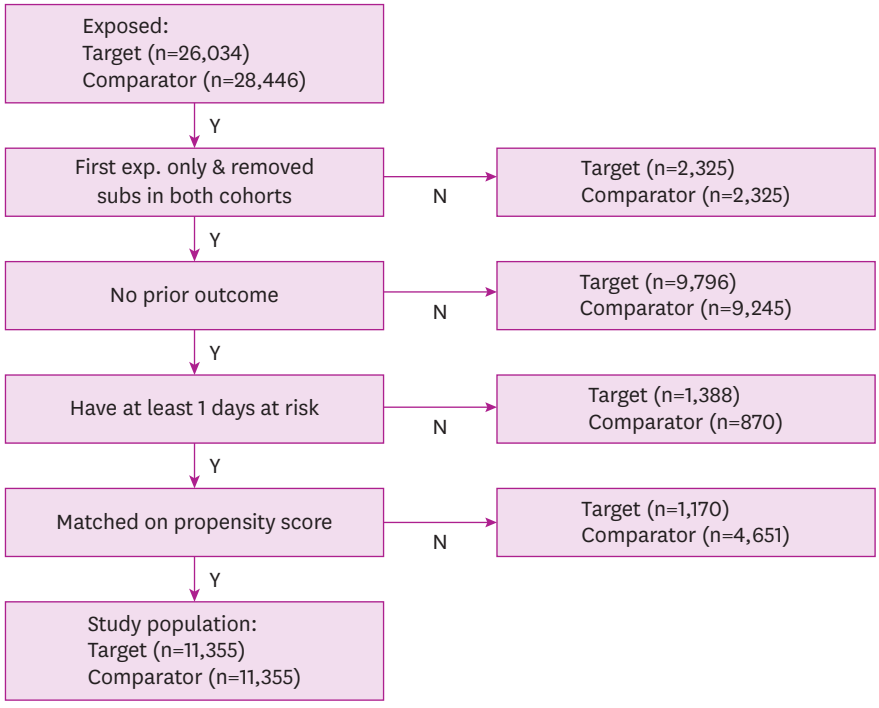

Fig. 2. Flow chart of the study population investigation of incidence of osteoporosis showing the number of subjects in the target (poor persistence group) and comparator (good persistence group).

Table 1. Baseline characteristics of the study population

Variables	Before matching		After matching	
	Poor persistent group (n=12,525)	Good persistent group (n=16,009)	Poor persistent group (n=11,355)	Good persistent group (n=11,355)
Female	6,776 (54.1%)	8,052 (50.3%)	6,040 (53.2%)	5,802 (51.1%)
Age <65	976 (6.3%)	789 (6.5%)	851 (7.6%)	976 (8.9%)
65–74	2,897 (18.1%)	2,267 (18.1%)	2,157 (19%)	2,055 (18.1%)
75–89	10,870 (67.9%)	8,491 (67.8%)	7,471 (65.8%)	7,255 (63.9%)
>90	1,248 (7.7%)	951.9 (7.6%)	862 (7.6%)	1,033 (9.1%)
Diabetes mellitus	4,347 (33.4%)	4,333 (34.6%)	3,610 (31.8%)	3,485 (30.7%)
Osteoarthritis	4,642 (29%)	4,422 (35.4%)	2,725 (24%)	2,679 (23.6%)
Rheumatoid arthritis	368 (2.3%)	363 (2.9%)	181 (1.6%)	158 (1.4%)
Schizophrenia	560 (3.5%)	275 (2.2%)	374 (3.3%)	329 (2.9%)
Hypertension	8,555 (68.3%)	11,158 (69.7%)	7,369 (64.9%)	7,358 (64.8%)
Dyslipidemia	7,315 (58.4%)	9,381 (58.6%)	5,893 (51.9%)	5,950 (52.4%)
Gastroesophageal reflux disease	4,421 (35.3%)	4,723 (29.5%)	2,896 (25.5%)	3,032 (26.7%)
Gastrointestinal hemorrhage	413 (3.3%)	496 (3.1%)	307 (2.7%)	307 (2.7%)
Atrial fibrillation	672 (4.2%)	513 (4.1%)	454 (4.0%)	442 (3.9%)
Cerebrovascular disease	3,553 (22.2%)	2,793 (22.3%)	2,350 (20.7%)	2,361 (20.8%)
Coronary artheriosclerosis	384 (2.4%)	288 (2.3%)	272 (2.4%)	249 (2.2%)
Heart disease	5,059 (31.6%)	4,033 (32.2%)	3,327 (29.3%)	3,224 (28.4%)
Heart failure	2,161 (13.5%)	1,803 (14.4%)	1,385 (12.2%)	1,442 (12.7%)
Ischemic heart diseases	2,737 (17.1%)	2,267 (18.1%)	1,850 (16.3%)	1,805 (15.9%)
Peripheral vascular disease	3,698 (23.1%)	3,381 (27.0%)	2,418 (21.3%)	2,384 (21.0%)
Venous thrombosis	208 (1.3%)	187 (1.5%)	124 (1.1%)	113 (1.0%)

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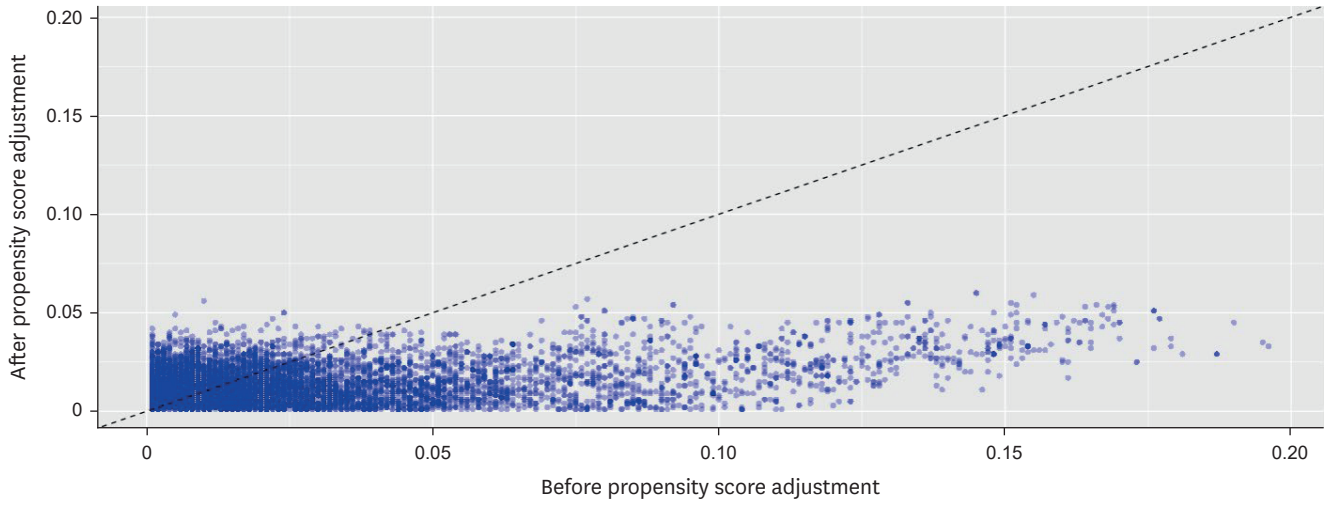
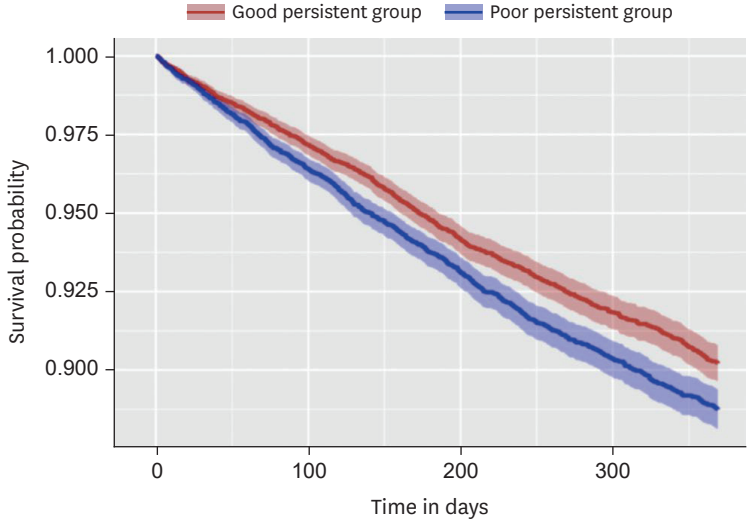


Fig. 3. Covariate balance before and after propensity score adjustment. Each dot represents the standardizes difference of means for a single covariate before and after propensity score adjustment on the propensity score.



No. at risk				
Poor persistent group	11,355	10,069	8,953	7,597
Good persistent group	11,355	10,527	9,661	8,265

Fig. 4. Kaplan-Meier survival curve investigating osteoporosis in the primary analysis.

Table 2. Cox's proportional hazards model for osteoporosis stratified by duration of AD medication treatment in AD patients

Outcome of interest	Good persistent group (IR/per 1,000 Pys)	Poor persistent group (IR/per 1,000 Pys)	Hazard ratio (95% CI)
Osteoporosis	102.63	120.45	1.20 (1.09–1.32)

AD: Alzheimer's dementia, IR: incidence ratio, Pys: person-year, CI: confidence interval.

DISCUSSION

Based on numerous previous studies on osteoporosis and AD, we hypothesized that active drug treatment for AD would affect the onset of osteoporosis. We derived results using HIRA

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data and the OMOP-CDM version 5 format. In terms of results, this study included a total of 11,355 individuals in the good persistent group and another 11,355 patients in the poor persistent group. These patients receiving AD drug treatment were included in this study using the National Health Claims database. Notably, osteoporosis risk showed a significant decrease in the good persistence group compared to that in the poor persistence group.

The association between disease and aging is a topic receiving increasing attention, with osteoporosis and AD serving as representative degenerative diseases that are currently being addressed in various studies.[3] Risk factors for both diseases include diabetes, obesity, aging, vitamin deficiency, chemotherapy, alcohol abuse, and interleukin-6 and/or apolipoprotein E ε4 gene mutations. These risk factors can affect glucose uptake.[3] Recent studies have provided evidence suggesting that diseases sharing biochemical pathways often manifest concurrently. This offers a plausible explanation for the link between osteoporosis and AD.[3] In addition, a recent study conducted in animals has reported an inhibitory effect of donepezil on bone mineral density reduction, showing that inhibiting AChE can reduce the formation of osteoclasts.[17] On the other hand, existing studies have addressed both effect of AD on onset of osteoporosis and impact of osteoporosis on onset of AD.[2,4] However, whether drug treatment for each disease can influence the occurrence of the other has not been reported yet, highlighting the need for such investigations.[5] Our study aimed to determine whether treatment for AD had an effect on the incidence of osteoporosis. Our findings confirmed that active drug treatment for AD significantly reduced the incidence of osteoporosis.

Compliance with anti-dementia drugs is crucial for their efficacy. It has been observed that, if treatment is resumed within three weeks of discontinuation, the previous effect persists. However, after six weeks, the effect of the previous drug treatment starts to decrease.[9] Therefore, continuous use of anti-dementia drugs is essential for treatment of AD. A clinical study has suggested that administration of donepezil commonly used in AD treatment can independently decrease the risk of hip fracture, proposing a direct impact on bone tissue.[17] Donepezil has been found to inhibit osteoclast function *in vitro* and inhibit resorption of bone *in vivo*, indicating its capability to lower the risk of fracture in patients with AD by preventing bone loss.[17] Subject with dementia is known to be associated with reduced physical activity[18] which is a risk factor of osteoporosis. Conversely, increased physical activity at any stage of life has a positive effect on bone health,[19-24] while reduced physical activity is a risk factor for osteoporosis, which may result in bone loss.[24-26] Thus, improvement of cognitive function through cognitive drug treatment can reduce the possibility of osteoporosis while preserving bone density through maintenance of daily life activities.

This study had several limitations. First, due to the de-identified nature of the CDM database, obtaining detailed clinical information through medical record review was not feasible in order to prioritize patient privacy. Consequently, our study lacked additional information regarding specific reasons for discontinuation of anti-dementia medications, such as follow-up failure, death, cessation due to side effects or drug switching. Second, the OMOP-CDM database did not encompass relevant factors such as cognitive status, educational level, or genetic information, although these factors are conventional and influential variables. Third, the conversion process of electronic medical records to CDM databases is susceptible to inherent data quality concerns, potentially leading to erroneous outcomes stemming from inadequately mapped codes in diagnosis, drug exposure, and outcomes. Lastly, although HIRA dataset provided long-term follow-up data, 'the HIRA-CDM data' was open from January of 2018 to April of 2022 that we could not elongate the follow-up duration for this

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version. The 2nd version of HIRA-CDM would be much longer. We will apply it with a long-term follow-up in our next research. Despite these limitations, our study successfully utilized large claim data to establish an association between drug persistence and osteoporosis based on the CDM framework.

In conclusion, we found that the good persistence group concerning anti-dementia drugs for AD was associated with a significantly lower risk of osteoporosis in a nationwide cohort study. Further studies are needed to clarify the pathophysiological link between these two chronic diseases.

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