Use of bladder antimuscarinics is associated with an increased risk of dementia: a retrospective population-based case–control study

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The association between bladder antimuscarinic use and dementia development is unclear. We used data from the Taiwan National Health Insurance Research Database to determine the association between the exposure dose and duration of bladder antimuscarinics and the subsequent dementia risk. We enrolled participants aged 55 years or more and defined a dementia cohort (International Classification of Diseases, Ninth Revision, Clinical Modification codes 290, 294.1, and 331.0). We used a propensity score matching method, and randomly enrolled two controls without dementia. We evaluated dementia risk with respect to the exposure dose and duration of treatment with seven bladder antimuscarinics (oxybutynin, propiverine, tolterodine, solifenacin, trospium, darifenacin, and fesoterodine) used for at least 1 year before the index date, after adjusting for age, sex, comorbidities, and medications. The dementia risk was 2.46-fold (95% confidence interval: 2.22–2.73) higher in Taiwanese patients who used bladder antimuscarinics for ≥ 1 year than in those who were not exposed to this treatment. The risk proportionally increased with increasing doses of antimuscarinics for less than 4 years. Taiwanese patients aged 55 years or more on bladder antimuscarinics exhibited a higher risk of dementia. Additional studies in other countries are required to determine whether this result is valid worldwide.

Dementia is a common neurological degenerative disorder, the prevalence of which increases with age. Dementia is currently one of the leading causes of disability and death in older adults, and there are no reliable treatments to reverse the development and progression of dementia. However, some evidence suggests that changing the lifestyle and environment of patients may help reduce dementia development¹². Consequently, dementia is usually under diagnosed globally³⁴; early identification and reducing exposure to risk factors are important strategies to prevent dementia in the general population⁵.

Anticholinergic (AC) agents can block the acetylcholine (Ach) activity in both central and peripheral nervous systems⁶. The most commonly used ACs are tricyclic antidepressants, first-generation antihistamines, and bladder antimuscarinics⁷. Several studies in western countries have suggested that ACs might affect cognition, thereby increasing the risk of dementia among users⁸–⁹. Therefore, ACs are recommended to be avoided in frail and older adults. However, most of these studies showed limited correlation between the use of ACs for the central nervous system and dementia development. It is unclear whether the increased risk of dementia observed in these studies was caused by ACs specifically or with interaction of other medications used for co-existing brain disorders. Moreover, antimuscarinics may affect bladder function at the efferent or afferent axis. They serve as antagonists of the muscarinic AC receptor and operate on the post-junctional excitatory receptors in detrusor muscles¹⁰.
There are considerable differences in brain penetration between the bladder antimuscarinics and ACs used for the central nervous system disorders. It is uncertain whether the urogenital use of antimuscarinic ACs would increase the risk of developing dementia due to the apparent pharmacodynamic differences between urogenital and central nervous ACs. For further investigation, we aimed to study the correlation between the exposure of bladder antimuscarinics and the risk of developing subsequent dementia. We used data from a nationwide, population-based database in Taiwan to analyze their possible relationships.

Methods

Data resource. The dataset used in this study was derived from the National Health Insurance Research Database (NHIRD) in Taiwan, which covers approximately 99% of the entire population of 23 million people in Taiwan. The Longitudinal Health Insurance Database (LHID) includes all original claims data and registration files from 2000 to 2013 for one million individuals randomly sampled from the Registry for Beneficiaries of the NHIRD program in 2000 in Taiwan. This database has been validated by several studies, to prove the correct coding of different diseases. This study was approved by the Institutional Review Board of China Medical University and the Hospital Research Ethics Committee (IRB permit number: CMUH-104-REC2-115) and is in compliance with institutional guidelines. Written informed consent from patients was waived due to low risk, and the study was approved by the institutional IRB of China Medical University and the Hospital Research Ethics Committee.

Study subjects. In this case–control study, we aimed to examine the effects of bladder antimuscarinics on the development of dementia. Study subjects comprised patients with dementia coded with ICD-9-CM 290, 294.1, and 331.0, and diagnosed by a neurologist or a general physician in the medical care system of Taiwan during 2000–2013. The first diagnosed date of dementia was defined as the index date. Disease diagnosis in the LHID was defined according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The controls were subjects without dementia during 2000–2013 and were randomly selected from the LHID.

We excluded individuals younger than 55 years and individuals with missing data of age and sex. Considering that such a short-term exposure to antimuscarinics was less likely to cause dementia, subjects who used antimuscarinics for less than 1 year were excluded. For each dementia case, we used a propensity score matching method and randomly selected two controls from the non-dementia group. The controls were assigned the same index year as their matched cases with respect to age, sex, comorbidities, and medications mentioned below.

Exposure assessment and covariates. The use of bladder antimuscarinics was evaluated before the index date. For those who used ACs for at least 1 year before the index date, we obtained data of seven types of bladder antimuscarinics (oxybutynin, G04BD04; propiverine, G04BD06; tolterodine, G04BD07; solifenacin, G04BD08; trosiptum, G04BD09; darifenacin, G04BD10; fesoterodine, G04BD11) based on World Health Organization ATC codes. Patients without any prescription of ACs during the study period were classified as AC non-users. The duration of AC use was categorized as medium (1–3 years), long (4–7 years), and prolonged (>7 years) durations. The cumulative dose of AC use during the study period was quantified for each patient using the World Health Organization Defined Daily Dose (DDD) and graded as follows: non-use, low-dose (<207), medium-dose (207–3271), and high-dose (>3271) users.

Several modifiable risk factors are shared among patients with dementia, and we additionally adjusted for the effects of occurrence of various cardiovascular diseases to predispose dementia among the subjects. Therefore, we adjusted pre-existing comorbidities including hypertension (ICD-9-CM code 401–405, A260, and A269), stroke (ICD-9-CM code 430–437, and A29), transient ischemic attack (ICD-9-CM code 435.9), subarachnoid hemorrhage (ICD-9-CM code 852.0), coronary heart disease (ICD-9-CM code 414.00, 414.05, 414.8, and 414.9), heart failure (ICD-9-CM code 428.0), atrial fibrillation (ICD-9-CM code 427.9), hyperlipidemia (ICD-9-CM code 272.0–272.4), and diabetes mellitus (ICD-9-CM code 250 and A181). Moreover, anxiety (ICD-9-CM code 300.0), depression (ICD-9-CM code 296.2, 296.3, 296.82, 300.4, 309.0, 309.1, and 311), bipolar disorder (ICD-9-CM code 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8, and 296.89), schizophrenia (ICD-9-CM code 295 and A211), severe learning difficulties (ICD-9-CM code 319), cognitive decline (ICD-9-CM code 311), asthma (ICD-9-CM code 493), chronic obstructive pulmonary disease (ICD-9-CM code 490–496), and renal disease (ICD-9-CM code 403.01, 403.11, 403.91, 404.02, 404.03, 404.13, 404.92, 404.93, V42.0, V45.1, V56.x, and 790) were included and adjusted.

Furthermore, we adjusted for the potentially confounding effects of other drugs, including aspirin, non-steroidal anti-inflammatory drugs, antihypertensives, statins, anxiolytics, hypnotics, antidepressants, and anti-Parkinson’s disease and antipsychotic medications. Treatment with these drugs before the index date was evaluated as a part of the analysis.

Statistical analysis. Propensity score matching was used to optimize comparability between the dementia and non-dementia groups using a non-parsimonious multivariable logistic regression model, with dementia as the dependent variable. Age, sex, comorbidities, medications, and index year were used as independent variables to match cases between the two groups. Descriptive statistics for the cases of dementia and non-dementia groups were reported, including demographic characteristics, comorbid disease, and medications. The standardized difference of was used to test the differences in continuous and categorical matching variables. A standardized mean difference of ≤0.10 indicates a negligible difference between the groups.

We used conditional logistic regression to assess the risk of dementia associated with bladder antimuscarinics. The odds ratio (OR) and 95% confidence interval (CI) for dementia were calculated and subsequently adjusted
for covariates including age, sex, comorbidities, and medications. The covariates adjusted for in the analytical models were listed as adjusted OR (aOR). To assess the dose–effect relationship, we analyzed the risks of dementia according to the cumulative DDD of bladder antimuscarinics (≤ 207 DDD, 207–3271 DDD, and > 3271 DDD) relative to non-users and stratified by 1–3, 4–7, and > 7 exposure years. We used SAS statistical software (Version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA) for data analysis. Results with a P-value of less than 0.05 were considered to be statistically significant.

**Results**

Table 1 shows the demographic and clinical characteristics of the study population. A total of 20,246 patients with dementia and 40,394 patients without dementia were enrolled in this study between January 1, 2000 and December 31, 2013 in the propensity score-matched population. The mean (SD) age was 77.3 (8.54) and 77.3 (10.3) years in the dementia and non-dementia groups, respectively. Among the subjects, females aged 75 to 84 years were dominant (Table 1). After propensity score matching, distribution of age, sex, comorbidities, and medications did not significantly differ between the groups. The detailed flow chart for the identification of the study subjects is shown in Fig. 1.

Table 2 presents the association between bladder antimuscarinics and the risk of developing dementia. After adjusting for potential confounders, antimuscarinic users exhibited a 2.46-fold increased risk of dementia compared with that in non-users (95% CI = 2.22–2.73). With respect to comorbidities, subjects with hypertension (aOR = 0.93, 95% CI = 0.89–0.98), asthma (aOR = 0.91, 95% CI = 0.89–0.97), and COPD (aOR = 0.86, 95% CI = 0.82–0.90) exhibited a lower risk of developing dementia. As for medication use, patients using aspirin, nonsteroidal anti-inflammatory drugs, statin, anxiolytics, and hypnotics exhibited a lower risk of developing dementia. On the contrary, those using anti-depressants drug, anti-Parkinson’s disease drug, and anti-psychotic drug showed a higher risk of developing dementia (Table 2).

Table 3 presents the association between the cumulative DDD of bladder antimuscarinics and the risk of developing dementia by stratification according to the exposure to antimuscarinics. In patients who had been taking antimuscarinics for less than 4 years before the index date, an increased DDD was proportionally associated with the increased risk of developing dementia (aOR = 2.23, 95% CI = 1.12–4.44 for ≤ 207 DDD; aOR = 2.35, 95% CI = 0.87–6.32 for 207–3271 DDD; aOR = 12.8, 95% CI = 5.15–32.1 for > 3271 DDD) compared with that in the controls. In individuals exposed for 4–7 years, those who used ≤ 207 DDD (aOR = 2.82, 95% CI = 1.68–4.75), 207–3271 DDD (aOR = 2.23, 95% CI = 1.10–4.53), and > 3271 DDD (aOR = 1.90, 95% CI = 0.94–3.81) of antimuscarinics did not exhibit the trend of proportional increase in the risk of developing dementia. In patients with an exposure duration greater than 7 years, only those taking antimuscarinics at 207–3271 DDD (aOR = 1.19, 95% CI = 1.00–1.41) presented an equal risk of developing dementia compared with that in the controls (Table 3).

Table 4 presents the duration (years) of dementia identified in the dementia group and presents the year of study entry in the non-dementia group. We calculated the duration of exposure in both groups. The mean (SD) duration of exposure was 5.87 (3.96) and 5.93 (3.47) years in the dementia and non-dementia groups (Table 4).

**Discussion**

In this retrospective nation-wide population-based case–control study, we noted that the risk of dementia increased 2.46-fold in Taiwanese patients aged 55 years or older who had been previously using bladder antimuscarinics for 1 year or more. Specifically, the risk proportionally increased with increasing dosage in patients taking antimuscarinics for less than 4 years. Richardson et al. reported that dementia development might be associated with an increasing dose of antimuscarinics for less than 4 years before the index date, an increased DDD was proportionally associated with the increased risk of developing dementia (aOR = 2.23, 95% CI = 1.12–4.44 for ≤ 207 DDD; aOR = 2.35, 95% CI = 0.87–6.32 for 207–3271 DDD; aOR = 12.8, 95% CI = 5.15–32.1 for > 3271 DDD) compared with that in the controls. In individuals exposed for 4–7 years, those who used ≤ 207 DDD (aOR = 2.82, 95% CI = 1.68–4.75), 207–3271 DDD (aOR = 2.23, 95% CI = 1.10–4.53), and > 3271 DDD (aOR = 1.90, 95% CI = 0.94–3.81) of antimuscarinics did not exhibit the trend of proportional increase in the risk of developing dementia. In patients with an exposure duration greater than 7 years, only those taking antimuscarinics at 207–3271 DDD (aOR = 1.19, 95% CI = 1.00–1.41) presented an equal risk of developing dementia compared with that in the controls (Table 3).

In this study, we analyzed the correlations between seven bladder antimuscarinics (oxybutynin, propiverine, tolterodine, solifenacin, trospium, darifenacin, and fesoterodine) and the subsequent dementia development. There are five subtypes (M1–M5) of muscarinic ACs receptors, and the M2 and M3 muscarinic Ach receptors are the major receptors that mediate smooth muscle contraction, proliferation, and remodeling of the bladder17,18. In contrast, evidence from recent postmortem human brain studies have implicated the involvement of the
Table 1. Characteristics of patients with and without dementia and comparison between baseline and during follow-up. PS propensity score, COPD chronic obstructive pulmonary disease. a All comorbidities and medications before ps matching. b All comorbidities and medication were after ps matching. *P-value using chi-square for the comparisons between with and without fetal adverse. † Average age using Wilcoxon rank-sum test for verification. § A standardized mean difference of ≤ 0.10 indicates a negligible difference between the cohorts.

| Characteristic | Original population\(^a\), no. (%) | PS matched population\(^b\), no. (%) |
|---------------|-----------------------------------|------------------------------------|
|               | Dementia cohort (n = 20,690) | Non dementia cohort (n = 194,980) | Dementia cohort (n = 20,246) | Non dementia cohort (n = 40,394) |
| Sex           |                                   |                                    |                               |                             |
| Female        | 10,849 (52.4)                     | 93,169 (47.8)                     | 10,625 (52.5)                  | 20,626 (51.1)                |
| Male          | 9841 (47.6)                       | 101,808 (52.2)                    | 9621 (47.5)                    | 19,768 (48.9)                |
| Age at diagnosis of dementia |                                   |                                    |                               |                             |
| 55–64         | 1898 (9.17)                       | 86,719 (44.5)                     | 1869 (9.23)                    | 5388 (13.3)                  |
| 65–74         | 5672 (27.4)                       | 55,493 (28.4)                     | 5566 (27.5)                    | 11,030 (27.3)                |
| 75–84         | 9280 (44.8)                       | 35,567 (18.2)                     | 9055 (44.7)                    | 14,533 (36.0)                |
| ≥ 95          | 231 (1.12)                        | 3159 (1.62)                       | 223 (1.10)                     | 1722 (4.26)                  |
| Age at diagnosis of dementia (mean, SD)\(^†\) | 77.3 (8.53)                       | 68.8 (10.5)                       | 77.3 (8.54)                    | 77.3 (10.3)                  |
| Comorbidity   |                                   |                                    |                               |                             |
| Hypertension  | 10,007 (48.4)                     | 58,313 (29.9)                     | 9781 (48.3)                    | 20,635 (51.1)                |
| Stroke        | 4858 (23.5)                       | 26,496 (13.6)                     | 4750 (23.5)                    | 9983 (24.7)                  |
| Transient ischemic attack | 417 (2.02)                       | 1830 (0.94)                       | 407 (2.01)                     | 808 (2.00)                   |
| Subarachnoid hemorrhage | 130 (0.63)                       | 510 (0.26)                        | 129 (0.64)                     | 251 (0.62)                   |
| Coronary heart disease | 1675 (8.10)                      | 7950 (4.0)                        | 1639 (8.10)                    | 3139 (8.22)                  |
| Heart failure | 1765 (8.53)                       | 7794 (4.0)                        | 1721 (8.50)                    | 3395 (8.40)                  |
| Atrial fibrillation | 35 (0.17)                        | 148 (0.08)                        | 35 (0.17)                      | 67 (0.17)                    |
| Hyperlipidemia | 6476 (31.3)                      | 35,008 (17.9)                     | 6326 (31.2)                    | 13,099 (32.4)                |
| Diabetes      | 6992 (33.8)                       | 39,287 (20.1)                     | 6827 (33.7)                    | 14,271 (35.3)                |
| Anxiety       | 4093 (19.7)                       | 21,192 (10.8)                     | 4000 (19.7)                    | 8285 (20.5)                  |
| Depression    | 3418 (16.5)                       | 16,673 (8.55)                     | 3337 (16.5)                    | 6913 (17.1)                  |
| Bipolar disorder | 488 (2.36)                       | 2240 (1.15)                       | 475 (2.35)                     | 970 (2.40)                   |
| Schizophrenia | 735 (3.55)                        | 3564 (1.83)                       | 717 (3.54)                     | 1476 (3.65)                  |
| Severe learning difficulties | 142 (0.69)                       | 711 (0.36)                        | 140 (0.69)                     | 290 (0.72)                   |
| Cognitive decline | 906 (4.38)                       | 3939 (2.02)                       | 882 (4.36)                     | 1755 (4.34)                  |
| Asthma        | 5525 (26.7)                       | 29,949 (15.3)                     | 5394 (26.6)                    | 11,518 (28.5)                |
| COPD          | 10,404 (50.3)                     | 61,864 (31.7)                     | 10,177 (50.3)                  | 21,551 (53.3)                |
| Renal disease | 2211 (10.7)                       | 10,814 (5.55)                     | 2161 (10.7)                    | 4498 (11.1)                  |
| Medication    |                                   |                                    |                               |                             |
| Aspirin       | 16,415 (79.3)                     | 109,091 (55.9)                    | 16,049 (79.2)                  | 32,063 (79.4)                |
| Nonsteroidal anti-inflamatory drugs | 20,322 (98.2)                   | 177,372 (90.9)                    | 19,884 (98.2)                  | 39,606 (98.1)                |
| Antihypertensives | 19,244 (93.0)                   | 141,644 (72.6)                    | 18,823 (92.9)                  | 37,731 (93.4)                |
| Statin        | 5839 (28.2)                       | 33,062 (16.9)                     | 5704 (28.2)                    | 11,265 (27.9)                |
| Anxiolytic    | 19,226 (92.9)                     | 151,847 (77.8)                    | 18,798 (92.8)                  | 37,251 (92.2)                |
| Hypnotic      | 10,175 (49.1)                     | 55,308 (28.3)                     | 9960 (49.2)                    | 19,701 (48.8)                |
| Anti-depressants drug | 9721 (46.9)                   | 25,319 (13.0)                     | 8231 (40.7)                    | 11,460 (28.4)                |
| Anti-Parkinson’s disease drug | 4177 (20.2)                        | 22,563 (11.6)                     | 3767 (18.6)                     | 3400 (8.42)                  |
| Anti-psychotic drug | 12,885 (62.3)                  | 76,063 (39.0)                     | 12,616 (62.3)                  | 21,428 (53.0)                |
M₁ muscarinic Ach receptors in various psychiatric disorders. Some studies have further demonstrated the dominant functional distribution of the M₁ muscarinic receptors for ACh uptake in the human brain. Our study results implied that bladder antimuscarinics might possibly produce subtle effects on M₁ activity, in addition to their known antagonistic effects on the M₂ and M₃ receptors. Because of the potential effect of bladder antimuscarinics on the M₁ muscarinic receptor, bladder antimuscarinics has been supposed to cause dementia development. Furthermore, we cannot completely rule out the role of other subtypes of muscarinic receptors besides the M₁ receptor that exhibits less expressed in the brain, and the brain penetration of various bladder antimuscarinics might be different. More laboratory studies could help clarify the detailed mechanism of different antimuscarinics and expression of different ACh subtypes in dementia development.

Globally, approximately 47 million people suffer from dementia with an estimated global cost of 818 billion US dollar in 2015, and the patient number would triple by 2050. Older adults who develop dementia are less likely to return to their ordinary lives than those who do not. The mechanisms of dementia development are too complicated to be fully understood in older adults with co-existing chronic disorders. First, older adults with bladder disorders might have sedentary lifestyles with poor sleep and personal hygiene or even with alcohol abuse and drug addiction. Sedentary lifestyles would potentially increase the risk of dementia development. Second, bladder disorders often exist with local or systemic inflammation to associate with an increased risk of dementia development. It is difficult to design a study that can distinguish the effects of inflammatory disorders from that of antimuscarinics on dementia development. However, the relationship between the risk of dementia and the dose of bladder antimuscarinics provides supports our hypothesis. These results indicate that bladder antimuscarinics increase predisposition to dementia development.

The major limitation of this study was that dementia cases diagnosed using the ICD-9-CM coding system are often underestimated. Although the NHIC program covers nearly 99% of Taiwanese citizens and guarantees equality of access to medical services for everyone throughout the country, some dementia cases might be outside the scope of our study. With a higher rate of dementia diagnosis in older adults with bladder disorders, there might be some patients who did not receive bladder antimuscarinics before the incident dementia diagnosis. Second, we could not directly contact the patients because their identities were anonymized in the accessible LHD. Therefore, we could not analyze all confounding factors for dementia development within the patients’ families or the psychological burden on patients. Third, the poor adherence to bladder antimuscarinics in patients was another potential limitation of this study. However, our study demonstrates a statistically significant increase in the risk of dementia development in patients using bladder antimuscarinics. These results highlight the need to further explore bladder antimuscarinics as a predisposing factor for dementia development.

**Conclusions**

Taiwanese patients aged 55 years or more undergoing treatment with bladder antimuscarinics exhibited a higher risk for dementia development. Additional studies in other countries are required to determine whether this result is valid worldwide.

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**Figure 1.** Flow chart for establishing antimuscarinic use and comparison cohorts using the National Health Insurance Research Database (NHI RD).
| Variable                        | N     | Dementia | Crude OR (95%CI) | P-value | Adjusted OR (95%CI)* | P-value |
|--------------------------------|-------|----------|------------------|---------|----------------------|---------|
| **Bladder antimuscarinic drugs** |       |          |                  |         |                      |         |
| Non-use                        | 57,833| 19,212   | 1 (reference)    |         | 1 (reference)        |         |
| Use                            | 2807  | 1034     | 1.17 (1.08–1.26) | <0.0001 | 2.46 (2.22–2.73)     | <0.0001 |
| **Comorbidity**                |       |          |                  |         |                      |         |
| **Hypertension**               |       |          |                  |         |                      |         |
| No                             | 30,224| 10,465   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 30,416| 9,781    | 0.89 (0.86–0.92) | <0.0001 | 0.93 (0.89–0.98)     | 0.0064  |
| **Stroke**                     |       |          |                  |         |                      |         |
| No                             | 45,907| 15,496   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 14,733| 4,750    | 0.93 (0.89–0.97) | 0.0007  | 1.00 (0.94–1.06)     | 0.99    |
| **Transient ischemic attack**  |       |          |                  |         |                      |         |
| No                             | 59,425| 19,839   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 1215  | 407      | 1.00 (0.89–1.13) | 0.93    | 1.05 (0.88–1.25)     | 0.57    |
| **Subarachnoid hemorrhage**    |       |          |                  |         |                      |         |
| No                             | 60,260| 20,117   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 380   | 129      | 1.02 (0.82–1.26) | 0.81    | 1.03 (0.76–1.38)     | 0.82    |
| **Coronary heart disease**     |       |          |                  |         |                      |         |
| No                             | 55,682| 18,607   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 4958  | 1639     | 0.98 (0.92–1.04) | 0.6     | 1.00 (0.91–1.09)     | 0.98    |
| **Heart failure**              |       |          |                  |         |                      |         |
| No                             | 55,524| 18,525   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 5116  | 1721     | 1.01 (0.95–1.07) | 0.68    | 1.07 (0.98–1.17)     | 0.11    |
| **Atrial fibrillation**        |       |          |                  |         |                      |         |
| No                             | 60,538| 20,211   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 102   | 35       | 1.04 (0.69–1.57) | 0.84    | 1.11 (0.70–1.76)     | 0.62    |
| **Hyperlipidemia**             |       |          |                  |         |                      |         |
| No                             | 41,215| 13,920   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 19,425| 6,326    | 0.94 (0.91–0.98) | 0.003   | 1.02 (0.97–1.08)     | 0.27    |
| **Diabetes**                   |       |          |                  |         |                      |         |
| No                             | 39,542| 13,419   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 21,098| 6,827    | 0.93 (0.89–0.96) | <0.0001 | 0.99 (0.95–1.04)     | 0.95    |
| **Anxiety**                    |       |          |                  |         |                      |         |
| No                             | 48,355| 16,246   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 12,285| 4,000    | 0.95 (0.91–0.99) | 0.03    | 1.03 (0.97–1.10)     | 0.31    |
| **Depression**                 |       |          |                  |         |                      |         |
| No                             | 50,380| 16,909   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 10,250| 3,357    | 0.95 (0.91–1.00) | 0.05    | 1.00 (0.94–1.07)     | 0.83    |
| **Bipolar disorder**           |       |          |                  |         |                      |         |
| No                             | 59,195| 19,771   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 1445  | 475      | 0.97 (0.87–1.09) | 0.67    | 0.95 (0.81–1.13)     | 0.62    |
| **Schizophrenia**              |       |          |                  |         |                      |         |
| No                             | 58,447| 19,529   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 2193  | 717      | 0.96 (0.88–1.06) | 0.48    | 0.96 (0.83–1.11)     | 0.62    |
| **Severe learning difficulties**|      |          |                  |         |                      |         |
| No                             | 60,210| 20,106   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 430   | 140      | 0.96 (0.78–1.17) | 0.71    | 0.94 (0.70–1.25)     | 0.67    |
| **Cognitive decline**          |       |          |                  |         |                      |         |
| No                             | 58,003| 19,364   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 2637  | 882      | 1.00 (0.92–1.08) | 0.94    | 1.03 (0.92–1.15)     | 0.53    |
| **Asthma**                     |       |          |                  |         |                      |         |
| No                             | 43,728| 14,852   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 16,912| 5,394    | 0.91 (0.87–0.94) | <0.0001 | 0.91 (0.86–0.97)     | 0.004   |
| **COPD**                       |       |          |                  |         |                      |         |
| No                             | 28,912| 10,069   | 1 (reference)    |         | 1 (reference)        |         |
| Yes                            | 31,728| 10,177   | 0.88 (0.85–0.91) | <0.0001 | 0.86 (0.82–0.90)     | <0.0001 |
Table 2. Risk of dementia with prior use of bladder antimuscarinic drugs, other medications, and comorbidities. OR odds ratio. *Adjusted for age, sex, all comorbidities, all medications, other anticholinergic drugs.

| Variable                | N     | Dementia | Crude OR (95%CI) | P-value | Adjusted OR (95%CI)* | P-value |
|-------------------------|-------|----------|------------------|---------|----------------------|---------|
| Medication              |       |          |                  |         |                      |         |
| Aspirin                 |       |          |                  |         |                      |         |
| Non-use                 | 12,528| 4197     | 1 (reference)    |         | 1 (reference)        |         |
| Use                     | 48,112| 16,049   | 0.99 (0.95–1.03) | 0.76    | 0.88 (0.84–0.92)     | < 0.0001|
| Nonsteroidal anti-inflammatory drugs |   |          |                  |         |                      |         |
| Non-use                 | 1150  | 362      | 1 (reference)    |         | 1 (reference)        |         |
| Use                     | 59,490| 19,884   | 1.09 (0.96–1.23) | 0.16    | 0.82 (0.72–0.95)     | 0.008   |
| Antihypertensives       |       |          |                  |         |                      |         |
| Non-use                 | 4086  | 1423     | 1 (reference)    |         | 1 (reference)        |         |
| Use                     | 56,554| 18,823   | 0.93 (0.87–0.99) | 0.04    | 0.81 (0.75–0.87)     | < 0.0001|
| Statin                  |       |          |                  |         |                      |         |
| Non-use                 | 43,671| 14,542   | 1 (reference)    |         | 1 (reference)        |         |
| Use                     | 16,969| 5704     | 1.01 (0.97–1.05) | 0.45    | 0.96 (0.92–1.00)     | 0.04    |
| Anxiolytic              |       |          |                  |         |                      |         |
| Non-use                 | 4591  | 1448     | 1 (reference)    |         | 1 (reference)        |         |
| Use                     | 56,049| 18,798   | 1.09 (1.02–1.16) | 0.005   | 0.84 (0.78–0.90)     | < 0.0001|
| Hypnotic                |       |          |                  |         |                      |         |
| Non-use                 | 30,979| 10,286   | 1 (reference)    |         | 1 (reference)        |         |
| Use                     | 29,661| 9960     | 1.01 (0.98–1.05) | 0.32    | 0.83 (0.80–0.86)     | < 0.0001|
| Anti-depressants drug   |       |          |                  |         |                      |         |
| Non-use                 | 40,949| 12,015   | 1 (reference)    |         | 1 (reference)        |         |
| Use                     | 19,691| 8231     | 1.73 (1.66–1.79) | < 0.0001| 1.60 (1.54–1.67)     | < 0.0001|
| Anti-Parkinson's disease drug | |          |                  |         |                      |         |
| Non-use                 | 53,473| 16,479   | 1 (reference)    |         | 1 (reference)        |         |
| Use                     | 7167  | 3767     | 2.48 (2.36–2.61) | < 0.0001| 2.22 (2.11–2.34)     | < 0.0001|
| Anti-psychotic drug     |       |          |                  |         |                      |         |
| Non-use                 | 26,596| 7630     | 1 (reference)    |         | 1 (reference)        |         |
| Use                     | 34,044| 12,616   | 1.46 (1.41–1.51) | < 0.0001| 1.29 (1.24–1.34)     | < 0.0001|
Table 3. Risk of dementia associated with cumulative use of bladder antimuscarinic drugs among study patients. OR odds ratio. *Adjusted for age, sex, all comorbidities, all medications, and other anticholinergic drugs.

| Exposure category | Study patients, no (%) | OR (95% CI) | P-value | Adjusted P-value |
|-------------------|------------------------|-------------|---------|-----------------|
| **Cumulative use (TSDDs)** | | | | |
| Exposure in the 1 to 3 years before index date | | | | |
| Patients, no. | 1085 | 9493 | NA | NA |
| Non-use | 1062 (97.8) | 9334 (98.3) | 1 (reference) | 1 (reference) |
| ≤ 207 | 10 (0.92) | 96 (1.01) | 0.91 (0.47–1.76) | 0.79 | 2.23 (1.12–4.44) | 0.02 |
| 207–3271 | 5 (0.46) | 45 (0.47) | 0.97 (0.38–2.46) | 0.96 | 2.35 (0.87–6.32) | 0.09 |
| > 3271 | 8 (0.74) | 18 (0.19) | 3.90 (1.69–9.00) | 0.001 | 12.8 (5.15–32.1) | < 0.0001 |
| Exposure in the 4 to 7 years before the index date | | | | |
| Patients, no. | 1766 | 3980 | NA | NA |
| Non-use | 1706 (96.6) | 3883 (97.6) | 1 (reference) | 1 (reference) |
| ≤ 207 | 31 (1.76) | 43 (1.08) | 1.64 (1.03–2.61) | 0.03 | 2.82 (1.68–4.75) | < 0.001 |
| 207–3271 | 15 (0.85) | 25 (0.63) | 1.36 (0.71–2.59) | 0.34 | 2.23 (1.10–4.53) | 0.02 |
| > 3271 | 14 (0.79) | 29 (0.73) | 1.09 (0.57–2.08) | 0.77 | 1.90 (0.94–3.81) | 0.07 |
| Exposure for more than 7 years before the index date | | | | |
| Patients, no. | 17,395 | 26,921 | NA | NA |
| Non-use | 16,490 (94.8) | 25,496 (94.7) | 1 (reference) | 1 (reference) |
| ≤ 207 | 256 (1.47) | 444 (1.65) | 0.89 (0.76–1.04) | 0.14 | 1.07 (0.89–1.29) | 0.42 |
| 207–3271 | 325 (1.87) | 466 (1.73) | 1.07 (0.93–1.24) | 0.3 | 1.19 (1.00–1.41) | 0.04 |
| > 3271 | 324 (1.86) | 515 (1.91) | 0.97 (0.84–1.11) | 0.69 | 1.03 (0.87–1.23) | 0.66 |

Table 4. Number of patients identified and duration of exposure.
Data availability
The original data are available at NHI, and we are not allowed to release despite reasonable application.

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T.H.: data interpretation, manuscript preparation; Y.C.Y., L.T.C.: data analysis, manuscript preparation; J.H.W.: study design; S.Z.L.: study design; D.C.D.: study concepts, design and manuscript preparation, and revision.

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Competing interests
The authors declare no competing interests.

Additional information
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