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ORIGINAL ARTICLE

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Use of α1-adrenoceptor antagonists tamsulosin and alfuzosin and the risk of Alzheimer's disease

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Abstract

Purpose: Tamsulosin has been associated with dementia, but the results have been inconsistent. Concerns have been raised about using exposure assessment time too close to the outcome. We investigated the association between use of α1-adrenoceptor antagonists indicated for benign prostate hyperplasia and risk of Alzheimer's disease (AD) using different exposure windows.

Methods: The study (24 602 cases and 98 397 matched controls) included men from the Finnish nationwide nested case–control study on Medication and Alzheimer's disease (MEDALZ). Cases received clinically verified AD diagnosis during 2005–2011 and were community-dwelling at the time of diagnosis. Use of tamsulosin and alfuzosin in 1995–2011 was identified from the Prescription Register and categorized based on whether it had occurred within 3 years before AD diagnosis (lag time) or before that. Dose–response analysis using defined daily doses of drug (DDDs) was conducted. Associations were investigated with conditional logistic regression, adjusted for confounders and mediators.

Results: The use of α1-adrenoceptor antagonists before lag time associated with an increased risk of AD (OR 1.24 [1.20–1.27]). After adjustment for comorbidities and concomitant drug use throughout the assessment time (confounders) and healthcare contacts within the lag period (mediators), the association weakened (aOR 1.10 [1.06–1.14]). We found no evidence of dose–response-relationship when comparing the users of higher than median DDDs to the users of lower than median DDDs.

Conclusion: Our findings, especially the lack of dose–response-relationship and attenuation after mediator adjustment, do not provide strong support for the previous hypothesis on α1-adrenoceptor antagonists as a risk factor for dementia.

KEYWORDS
alfuzosin, Alzheimer's disease, benign prostatic hyperplasia, dementia, tamsulosin, α1-adrenoceptor antagonist

An abstract of this work has been submitted to the 17th meeting of the European Union of Geriatric Medicine Society (13–17/10/2021) and AD/PD2022 meeting (15–20/3/2022).

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Key Points

- α1-adrenoceptor antagonists tamsulosin and alfuzosin were associated with an increased risk of Alzheimer's disease in Finnish men, also when the analyses were restricted to use that had occurred at least 3 years before AD diagnosis.
- The association reduced substantially when adjusted for confounders and mediators, indicating that the association may be explained by these factors.
- Similar risk between tamsulosin and alfuzosin users can also imply that the results merely reflect the association between benign prostate hyperplasia and AD.
- We found no evidence of dose–response relationship as the risk of AD was comparable between those with higher and lower exposure levels.

Plain Language Summary

α1-adrenoceptor antagonists tamsulosin and alfuzosin are used to treat benign prostate hyperplasia, a condition which is common among older men. Earlier studies have linked tamsulosin to higher risk of dementia but concerns have been raised about using exposure assessment time too close to the outcome. In this study, tamsulosin associated with an increased risk of Alzheimer's disease in Finnish men, also when medication use that had occurred at least 3 years before Alzheimer's disease diagnosis was considered. However, the association reduced substantially when adjusted for comorbidities, and healthcare contact within 3 years before AD diagnosis, indicating that the association with higher risk may be explained by these factors. Similar risk between tamsulosin and alfuzosin users can also imply that the association of these drugs merely reflects the previously reported association between benign prostate hyperplasia and Alzheimer's disease, not that these medications themselves increase the risk. No evidence of dose–response relationship was observed, as the risk of Alzheimer's disease was comparable between those with higher and lower use of these medications. Taken together, our findings do not provide strong support on the previous hypothesis on these medications as a risk factor for dementia.

1 | BACKGROUND

Tamsulosin, an α1-adrenoceptor antagonist, was recently linked to a higher risk of dementia, but the results have been inconsistent.[1–3] Concerns have been raised about the timing of the exposure in one[1] of the earlier studies.[4,5] The progression of cognitive disorders is slow,[6] which should be taken into account in risk factor studies. Further, the prodromal symptoms can lead to increased health care contacts, and thus changes in drug use, including the initiation of new drugs, are more likely to happen during this time. The median follow-up in the study by Duan et al.[1] was less than 2 years, which has been criticized as being too short to cause dementia.[4,5] In addition, in two studies[1,2] the assessment of drug exposure was continued until the diagnosis of cognitive disorder. Hence, the results may be explained by reverse causality.

$\alpha 1_a$-receptor blockade in brain has been suggested as an explanation for the possible association between tamsulosin and dementia, but further studies are needed to demonstrate whether these putative effects of tamsulosin have clinical relevance. Exploration of the safety of α1-adrenoceptor antagonists is motivated by the large number of users. These drugs are widely used as a first-line choice to treat lower urinary tract symptoms (LUTS) in benign prostatic hyperplasia (BPH).[7] Additionally, they are commonly used in management of LUTS due to causes not related to the prostate, such as neurological disorders. As LUTS become more frequent with age, majority of the users are older men.

Due to the global ageing, cognitive disorders, including Alzheimer's disease (AD), are a significant health issue.[6] Therefore, identification of modifiable risk factors is relevant, particularly when no curative treatment is available. Even a small risk reduction could be significant on a population level.

We investigated the association between α1-adrenoceptor antagonists (tamsulosin and alfuzosin) and the risk of AD in a nested case–control study of Finnish men with 16 years' exposure assessment, using different exposure assessment windows.

2 | METHODS

2.1 | Study population

This study was restricted to men (24 602 AD cases and 98 397 controls) from the Finnish nationwide MEDALZ study (Medication use

and AD) that includes community-dwelling Finnish residents who received clinically verified AD diagnosis during 2005–2011. Detailed information of the MEDALZ study has been published earlier.[8] For AD case, 1–4 comparison persons matched by age, sex and region of residence on the date of AD diagnosis (index date) were obtained using incidence density sampling. Linkage across registers was done using personal identification numbers by the register maintainers.

2.2 | AD diagnosis

AD cases were identified from the Special Reimbursement Register. All the AD diagnoses were clinically verified by specialists in NINCDS-ADRDA and DSM-IV criteria.[9,10] In Finland, anti-dementia drugs are recommended to all patients with AD by Current Care guidelines for cognitive disorders.[11] During the observation period the Social Insurance Institution granted the special reimbursement for anti-dementia drug purchases to patients in mild or moderate state of AD, and for that a clinically verified diagnosis was required.

2.3 | Drug exposure

α1-adrenoceptor antagonist purchases were identified from the Prescription register from 1995 onwards (Table S1) using Anatomical Therapeutic Chemical (ATC) classification system[12] code G04CA, and included the following drugs: G04CA01 (alfuzosin), G04CA02 (tamsulosin), and G04CA52 (the combination of tamsulosin and dutasteride). The few users of tamsulosin and dutasteride combination were included as tamsulosin users. These were the only BPH-indicated α1-adrenoceptor antagonists used by our study population.

To avoid reverse causality we considered drug exposure that had occurred at least 3 years before the index date as "true" exposure. Exposure that had occurred within the 3-year lag time before the index date was included as its own category. To investigate dose–response relationship, we calculated the cumulative exposure from DDDs and generated drug- and time window-specific exposure categories (higher vs. lower exposure based on median exposure within each drug and time window stratum).

To compare the risk between different α1-adrenoceptor antagonists, we categorized those who had purchased these drugs before lag time into three categories depending on purchase history: alfuzosin use only, tamsulosin use only and purchases of both alfuzosin and tamsulosin.

2.4 | Confounders and mediators

The data on comorbidities and drug use were identified from the national registers as described in Table S1. The data on occupational social classes were from the Statistics Finland.

To control for confounding, following covariates were ascertained from the beginning of applied data source until 3 years before the index date: Cardiovascular diseases, stroke, diabetes, asthma or COPD, acute cancer, cataract, inpatient care with psychiatric diagnoses, history of substance abuse, and the use of benzodiazepines and related drugs (BZDR), antidepressants and antipsychotics and 5-alpha reductase inhibitors (5-ARI). The number of different ATC-codes in the first year of exposure assessment (1995) was categorized as follows: none, 1–2, 3–4, 5–7, and 8 or more, and used as a crude proxy of number of different drugs at the beginning of exposure assessment.

To evaluate whether the increased health care contacts within the 3 years before index date explained the results, we adjusted for the following mediators: number of hospital admissions (categorized as 0, 1, 2, 3, 4–5, and 6 or more), outpatient visits in specialized healthcare (categorized as 0, 1–2, 3–4, 5–6, 7–11, and 12 or more) and the number of different purchased prescription drugs excluding the α1-adrenoceptor antagonists (categorized as 0, 1, 2–3, 4–6, and 7 or more). These mediators were measured in the lag time window only (and occurred between the main exposure assessment and outcome, that is, were part of the hypothesized "causal" pathway). These analyses evaluate whether the possibly increased risk of AD among the exposed is explained by higher likelihood of being diagnosed with AD due to increased contact with healthcare professionals among them. Because the mediation analysis is conceptually correct only for the main exposure assessment, it was not performed for exposure in lag time only. The results for total exposure in DDDs were adjusted for the mediators, but the partially overlapping assessment period for exposure and mediators should be borne in mind when interpreting those results.

2.5 | Statistical analysis

The differences between cases and controls and users and non-users were compared by using the two-sample *T* test for continuous variables and Pearson's chi-squared test for categorical variables. The association between drug exposure and AD were assessed by using the conditional logistic regression and adjusted for confounders and mediators. The results are presented as odds ratios (OR) and adjusted odds ratios (aOR) with 95% confidence intervals. Analyses were performed using Stata MP14.0.

First, we investigated the risk of AD between users and non-users of α1-adrenoceptor antagonists, and for all tamsulosin and alfuzosin users separately. Second, the risk was investigated according to type of α1-adrenoceptor antagonist use. In addition, we evaluated the risk separately based on timing of exposure (before lag time, lag time only, or both). In the dose–response analyses risk of AD was compared between those with higher than median cumulative DDDs and lower than median cumulative DDDs within each time window and drug-specific stratum.

3 | RESULTS

3.1 | Characteristics

The mean age of the study population was 78.7 years (Table 1). The mean age at the first α1-adrenoceptor antagonist purchase was

TABLE 1 Characteristics of the study population including cases with Alzheimer's disease (AD) and controls without AD, assessed to 3 years before AD diagnosis (the index date)

	AD cases $N = 24\,602$	Controls $N = 98\,397$	*p* Value
Age at index date, mean, (95% CI)	78.7 (78.7–78.8)	78.7 (78.7–78.7)	matched
Age at first α1-adrenoceptor antagonist purchase, mean, (95% CI)	73.2 (73.1–73.3)	73.2 (73.1–73.2)	0.628
Highest occupational social class before AD, *n*, (%)			<0.001
Managerial/professional	6613 (26.9)	26 755 (27.2)	
Office	775 (3.2)	2825 (2.9)	
Farming, forestry	5470 (22.2)	22 686 (23.1)	
Sales, industrial, cleaning	11 214 (45.6)	41 389 (42.1)	
Unknown	530 (2.2)	4742 (4.8)	
Cardiovascular disease, *n*, (%)	11 950 (48.6)	45 439 (46.2)	<0.001
Stroke, *n*, (%)	2418 (9.8)	7932 (8.1)	<0.001
Diabetes, *n*, (%)	3306 (13.4)	9693 (9.9)	<0.001
Asthma/COPD, *n*, (%)	2303 (9.4)	8892 (9.0)	0.114
Cataract, *n*, (%)	4068 (16.5)	14 571 (14.8)	<0.001
Acute cancer, *n*, (%)	2109 (8.6)	8205 (8.3)	0.237
Inpatient care with psychiatric diagnoses, *n*, (%)	1279 (5.2)	4261 (4.3)	<0.001
Substance abuse, *n*, (%)	1643 (6.7)	5602 (5.7)	<0.001
Benzodiazepine and related drug use, *n*, (%)	7298 (29.7)	26 118 (26.5)	<0.001
Antidepressant use, *n*, (%)	4176 (17.0)	12 485 (12.7)	<0.001
Antipsychotic drug use, *n*, (%)	1385 (5.6)	3927 (4.0)	<0.001
5-ARI drug use, *n*, (%)	634 (2.6)	2179 (2.2)	0.001
Use of any α1-adrenoceptor antagonist[a], *n*, (%)	10 531 (42.8)	35 932 (36.5)	<0.001
Sum of prescribed ATC-codes[b], median (IQR)	2 (0–4)	2 (0–4)	<0.001
Categorized drug sum[b], *n*, (%)			<0.001
None	7052 (28.7)	32 896 (33.4)	
1–2	6738 (27.4)	26 233 (26.7)	
3–4	4840 (19.7)	18 375 (18.7)	
5–7	3788 (15.4)	13 590 (13.8)	
8 or more	2184 (8.9)	7303 (7.4)	
Hospital admissions during lag time, *n*, (%)			<0.001
0	8256 (33.6)	46 539 (47.3)	
1	4797 (19.5)	18 864 (19.2)	
2	3465 (14.1)	11 439 (11.6)	
3	2303 (9.4)	6921 (7.0)	
4–5	2739 (11.1)	7318 (7.4)	
6–or more	3042 (12.4)	7316 (7.4)	
Outpatient visits during lag time, *n*, (%)			<0.001
0	3965 (16.1)	28 294 (28.8)	
1–2	5268 (21.4)	19 497 (19.8)	
3–4	3990 (16.2)	14 153 (14.4)	
5–6	2941 (12.0)	9874 (10.0)	
7–11	4458 (18.1)	13 759 (14.0)	
12 or more	3980 (16.2)	12 820 (13.0)	
New drugs[c] during lag time, *n*, (%)			
0	2049 (8.3)	13 620 (13.8)	
1	2480 (10.1)	11 516 (11.7)	

TABLE 1 (Continued)

	AD cases $N = 24\,602$	Controls $N = 98\,397$	p Value
2–3	5843 (23,8)	23 652 (24.0)	
4–6	7065 (28.7)	25 911 (26.3)	
7 or more	7165 (29.1)	23 698 (24.1)	

[a]Assessment to the index date.
[b]In year 1995.
[c]Excluding α1-adrenoceptor antagonists.

73.2 years in cases and controls. Comorbidities, especially cardiovascular diseases and diabetes were more common in AD cases than in controls. The use of drugs was more common in cases, both when indicated by specific categories such as psychotropic drugs, or number of different ATC codes purchased during the first year of exposure assessment. The cases also had more health care contacts including hospital admissions, outpatient visits and new drug purchases in the 3-year time window before the index date.

The characteristics of users of different α1-adrenoceptor antagonists and non-users are shown in Table 2. The mean age at the index date was higher in the user groups than in the non-users. Comorbidities and concomitant drug use before the lag time were more common in user groups, and the median number of drugs in use in the beginning of the exposure was higher. The prevalence of cardiovascular diseases and use of BZDRs were higher in only tamsulosin users than in only alfuzosin users. The users with purchases of both

TABLE 2 Characteristics of α1-adrenoceptor antagonist users by type of exposure before lag time (exposure at least 3 years before the index date), including individuals with and without AD

	No use $N = 87\,546$	Only alfuzosin use $N = 3869$	Only tamsulosin use $N = 27\,717$	Purchases of both alfuzosin and tamsulosin $N = 3867$
Age at index date mean, (95% CI)	78.1 (64.4–88.9)	79.6 (68.8–89.3)	80.4 (70.3–89.4)	80.5 (70.3–89.4)
Age at first α1-adrenoceptor antagonist purchase, mean, (95% CI)		73.2 (73.0–73.4)	72.1 (72.0–72.29)	71.0 (70.8–71.2)
Highest occupational class before AD, *n*, (%)				
Managerial/professional	23 132 (26.4)	1148 (29.7)	7831 (28.3)	1257 (32.5)
Office	2605 (3.0)	111 (2.9)	773 (2.8)	111 (2.9)
Farming, forestry	19 843 (22.7)	857 (22.2)	6647 (24.0)	809 (20.9)
Sales, industrial, cleaning	37 455 (42.8)	1687 (43.6)	11 848 (42.8)	1613 (41.7)
Unknown	4511 (5.2)	66 (1.7)	618 (2.2)	77 (2.0)
Cardiovascular disease, *n*, (%)	38 792 (44.3)	1867 (48.3)	14 679 (53.0)	2051 (53.0)
Stroke, *n*, (%)	6627 (7.6)	342 (8.8)	2923 (10.6)	458 (11.8)
Diabetes, *n*, (%)	8747 (10.0)	449 (11.6)	3335 (12.0)	468 (12.1)
Asthma/COPD, *i*, (%)	7034 (8.0)	401 (10.4)	3287 (11.9)	473 (12.2)
Cataract, *n*, (%)	11 734 (13.4)	722 (18.7)	5346 (19.3)	837 (21.6)
Acute cancer, *n*, (%)	6168 (7.1)	393 (10.2)	3308 (11.9)	445 (11.5)
Inpatient care with psychiatric diagnoses, *n*, (%)	3648 (4.2)	204 (5.3)	1455 (5.3)	233 (6.0)
Substance abuse, *n*, (%)	4902 (5.6)	232 (6.0)	1827 (6.6)	284 (7.34)
Benzodiazepine & related drug use, *n*, (%)	19 961 (22.8)	1314 (34.0)	10 415 (37.6)	1726 (44.6)
Antidepressant use, *n*, (%)	9743 (11.1)	690 (17.8)	5234 (18.9)	994 (25.7)
Antipsychotic use, *n*, (%)	3300 (3.8)	185 (4.8)	1556 (5.6)	271 (7.0)
5-ARI drug use, *n*, (%)	1279 (1.5)	104 (2.7)	1212 (4.4)	218 (5.6)
Sum of purchased ATC-codes[a], median (IQR)	1 (0–4)	2 (0–5)	3 (1–5)	3 (1–6)
Categorized drug sum[a], *n*, (%)				
None	32 056 (36.3)	1053 (27.2)	6122 (22.1)	717 (18.5)

(Continues)

TABLE 2 (Continued)

	No use $N = 87\,546$	Only alfuzosin use $N = 3869$	Only tamsulosin use $N = 27\,717$	Purchases of both alfuzosin and tamsulosin $N = 3867$
1–2	23 702 (27.1)	1027 (26.5)	7291 (26.3)	951 (24.6)
3–4	15 667 (17.9)	810 (20.9)	5942 (21.4)	796 (20.6)
5–7	10 908 (12.5)	624 (16.1)	5048 (18.2)	798 (20.6)
8 or more	5213 (6.0)	355 (9.2)	3314 (12.0)	605 (15.7)
Hospital admissions during lag time, *n*, (%)				
0	42 246 (48.3)	1494 (38.6)	9853 (35.6)	1202 (31.1)
1	16 550 (18.9)	808 (20.9)	5539 (20.0)	764 (19.8)
2	10 060 (11.5)	513 (13.3)	3771 (13.6)	560 (14.5)
3	6025 (6.9)	338 (8.7)	2477 (8.9)	384 (9.9)
4–5	6430 (7.3)	354 (9.2)	2.849 (10.3)	424 (11.0)
6 or more	6235 (7.1)	362 (9.4)	3228 (11.7)	533 (13.8)
Outpatient visits during lag time, *n*, (%)				
0	26 483 (30.3)	669 (17.3)	4654 (16.8)	453 (11.7)
1–2	18 096 (20.7)	747 (19.3)	5278 (19.0)	644 (16.7)
3–4	12 685 (14.5)	610 (15.8)	4306 (15.5)	542 (14.0)
5–6	8439 (9.6)	480 (12.4)	3421 (12.3)	475 (12.3)
7–11	11 642 (13.3)	707 (18.3)	5075 (18.3)	793 (20.5)
12 or more	10 201 (11.7)	656 (17.0)	4983 (18.0)	960 (24.8)
New drugs[b] during lag time, *n*, (%)				
0	13 727 (15.7)	224 (5.8)	1581 (5.7)	137 (3.5)
1	10 862 (12.4)	365 (9.4)	2543 (9.2)	226 (5.8)
2–3	21 711 (24.8)	896 (23.2)	6161 (22.2)	727 (18.8)
4–6	22 346 (25.5)	1188 (30.7)	8321 (30.0)	1121 (29.0)
7 or more	18 900 (21.6)	1196 (30.9)	9111 (32.9)	1656 (42.8)

[a]In year 1995.
[b]Excluding α1-adrenoceptor antagonists.

tamsulosin and alfuzosin used substantially more often antidepressants and BZRDs than users in other groups or non-users. Regardless of the type of exposure, the users had more health care contacts within the 3 years before the index date than the non-users.

3.2 | Association between use of α1-adrenoceptor antagonists and AD

The use of α1-adrenoceptor antagonists before the index date was more prevalent in cases than controls (Table 3). Before lag time 32.3% (7938) of cases and 28.0% (27515) of controls had used α1-adrenoceptor antagonists. Tamsulosin use was more common (28.8%, $n = 7090$ in cases and 24.9%, $n = 24\,494$ in controls) than alfuzosin use (7.3%, $n = 1799$ of cases and 6.0%, $n = 5937$ of controls).

α1-adrenoceptor antagonist use that had occurred at least 3 years before the index date was associated with increased risk of AD (OR 1.24 [1.20–1.27], Table 3). Adjustment for confounders slightly weakened the association, and additional adjustment for mediators further decreased it, but the association was still evident (aOR 1.10 [1.07–1.14]). Comparable results were obtained in separate analyses for tamsulosin and alfuzosin. Mediator adjustment had the largest effect on the OR, but the association with increased risk was observed also after this adjustment (aOR 1.10 [1.06–1.14] and aOR 1.12 [1.06–1.18] for tamsulosin and alfuzosin, respectively).

In the analyses based on time of exposure for a specific α1-adrenoceptor antagonist, stronger associations were observed with drug use during the lag time than use before lag time, especially for tamsulosin (Table 3). Smaller differences between time categories were observed for alfuzosin. These associations were also partially explained by confounders, and adjustment for mediators decreased the association, albeit it was still observed after adjusting for confounders and mediators.

In the comparative analysis of type of α1-adrenoceptor antagonist used before the lag time, stronger association in comparison to nonusers was observed for those with purchases of both tamsulosin

TABLE 3 Characteristics of AD cases and controls and associations between AD and α1-adrenoceptor antagonist use categorized by timing of exposure, compared with non-use

	AD cases $N = 24\,602$	Controls $N = 98\,397$	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	Adjusted OR (95% CI)[b]
α1-adrenoceptor antagonist use before lag time					
Any	7938 (32.3)	27 515 (28.0)	1.24 (1.20–1.27)	1.16 (1.12–1.19)	1.10 (1.07–1.14)
Tamsulosin	7090 (28.8)	24 494 (24.9)	1.23 (1.19–1.27)	1.15 (1.11–1.19)	1.10 (1.06–1.14)
Alfuzosin	1799 (7.3)	5937 (6.0)	1.23 (1.17–1.30)	1.16 (1.10–1.23)	1.12 (1.06–1.18)
Categorized α1-adrenoceptor antagonist use, *n*, (%)					
No use	14 071 (57.2)	62 465 (63.5)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Lag time only	2593 (10.5)	8417 (8.6)	1.37 (1.31–1.44)	1.32 (1.25–1.38)	Not applicable
Before lag time	3282 (13.3)	11 627 (11.8)	1.26 (1.21–1.32)	1.19 (1.14–1.24)	1.14 (1.09–1.20)
Before & at lag time	4656 (18.9)	15 888 (16.2)	1.31 (1.26–1.36)	1.22 (1.17–1.26)	1.12 (1.08–1.17)
Categorized tamsulosin use, *n*, (%)					
No use	15 390 (62.6)	67 128 (68.2)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Lag time only	2122 (8.6)	6775 (6.9)	1.37 (1.30–1.44)	1.32 (1.25–1.39)	Not applicable
Before lag time	3382 (13.8)	11 802 (12.0)	1.26 (1.20–1.31)	1.18 (1.13–1.23)	1.14 (1.09–1.19)
Before & at lag time	3708 (15.1)	12 692 (12.9)	1.28 (1.23–1.34)	1.19 (1.14–1.24)	1.11 (1.06–1.16)
Categorized alfuzosin use, *n*, (%)					
No use	21 641 (88.0)	88 614 (90.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Lag time only	1162 (4.7)	3846 (3.9)	1.24 (1.16–1.32)	1.20 (1.12–1.28)	Not applicable
Before lag time	1028 (4.2)	3455 (3.5)	1.22 (1.14–1.32)	1.16 (1.07–1.24)	1.12 (1.04–1.20)
Before & at lag time	771 (3.1)	2482 (2.5)	1.28 (1.18–1.39)	1.20 (1.11–1.31)	1.13 (1.04–1.23)
Type of exposure before lag time, *n*, (%)					
None	16 664 (67.7)	70 882 (72.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Only tamsulosin	6139 (25.0)	21 578 (21.9)	1.22 (1.18–1.26)	1.14 (1.10–1.18)	1.09 (1.06–1.13)
Only alfuzosin	848 (3.5)	3021 (3.1)	1.21 (1.11–1.30)	1.14 (1.06–1.24)	1.09 (1.01–1.18)
Purchases of both alfuzosin and tamsulosin	951 (3.9)	2916 (3.0)	1.40 (1.30–1.51)	1.29 (1.19–1.39)	1.21 (1.12–1.31)

Note: Lag time refers to 0–3 years before the index date.
[a]Adjusted for highest occupational class, cardiovascular disease, stroke, diabetes, asthma or COPD, cataract, acute cancer, inpatient care with psychiatric diagnoses, substance abuse, use of benzodiazepines and related drugs, antidepressants, antipsychotics and 5-alpha reductase inhibitors, and categorized sum of purchased drugs in 1995.
[b]Adjusted for abovementioned confounders and mediators (categorized sum of hospital admissions, outpatient visits and new drugs [excluding α1-adrenoceptor antagonists] during the lag time).

and alfuzosin, than for use on just one α1-adrenoceptor antagonist (Table 3). Tamsulosin and alfuzosin use had similar associations, and the impact of adjustment for confounders and mediators was identical to the other analyses.

3.3 | Dose–response analysis

We found no evidence of a dose–response relationship in analyses comparing high and low exposure categories during the entire exposure period or exposure that had occurred at least 3 years before the analysis. When cumulative exposure in lag time was compared, there was no difference in alfuzosin exposure categories, while those with higher exposure to tamsulosin had lower risk of AD than the low exposure category (Table 4).

4 | DISCUSSION

Use of tamsulosin and alfuzosin were associated with an increased risk of AD in Finnish men, also when the analyses were restricted to drug exposure that had occurred at least 3 years before AD diagnosis. This 3-year lag time was used to minimize the impact of protopathic bias. This has been previously demonstrated to be essential for the outcomes with long latency period, including AD.[13] The association reduced substantially after adjusting for comorbidities and concomitant drug use throughout the assessment time (confounders) and healthcare contacts within the lag period (mediators), indicating that the association may be explained by these factors. Furthermore, we found no evidence of dose–response relationship. Therefore, our results do not strongly support the earlier finding[1] on these drugs as risk factor for dementia.

TABLE 4 Dose–response analysis of associations between the α1-adrenoceptor antagonist use, and AD

	Median group of cumulative DDD	AD cases $N = 24\,602$	Controls $N = 98\,397$	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[b] OR (95% CI)
Tamsulosin use[c]						
Lag time only	First (30–540 DDD)	3197 (54.8)	9884 (50.8)	1.00 (reference)	1.00 (reference)	Not applicable
	Second (546–2700 DDD)	2633 (45.2)	9583 (49.2)	0.86 (0.78–0.94)	0.85 (0.78–0.93)	Not applicable
Before lag time	First (30–270 DDD)	3684 (52.0)	12 741 (52.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Second (300–4350 DDD)	3406 (48.0)	11 753 (48.0)	1.00 (0.93–1.08)	0.99 (0.92–1.06)	0.98 (0.91–1.06)
Any exposure	First (30–360 DDD)	4717 (51.2)	15 959 (51.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Second (370–5670 DDD)	4495 (48.8)	15 310 (49.0)	0.99 (0.93–1.05)	0.98 (0.92–1.04)	0.98 (0.92–1.04)
Alfuzosin use						
Lag time only	First (20–360 DDD)	1023 (52.9)	3360 (53.1)	1.00 (reference)	1.00 (reference)	Not applicable
	Second (362.67–3040 DDD)	910 (47.1)	2968 (46.9)	1.15 (0.90–1.46)	1.13 (0.88–1.46)	Not applicable
Before lag time	First (20–160 DDD)	949 (52.8)	3197 (53.9)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Second (180–4560 DDD)	850 (47.3)	2740 (46.2)	1.03 (0.81–1.31)	1.04 (0.81–1.33)	1.00 (0.77–1.29)
Any exposure	First (20–200 DDD)	1435 (48.5)	4979 (50.9)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Second (209–7040 DDD)	1526 (51.5)	4804 (49.1)	1.14 (0.97–1.34)	1.12 (0.95–1.32)	1.10 (0.93–1.31)

Note: Users of more than median DDDs are compared to users of less than median DDDs in different time categories. Lag time refers to 0–3 years before the index date. Any exposure is the combined exposure during actual exposure assessment period (before lag time) and during the lag time.

[a]Adjusted for highest occupational class, cardiovascular disease, stroke, diabetes, asthma or COPD, cataract, acute cancer, inpatient care with psychiatric diagnoses, substance abuse, use of benzodiazepines and related drugs, antidepressants, antipsychotics and 5-alpha reductase inhibitors, and categorized sum of purchased drugs in 1995.

[b]Adjusted for abovementioned confounders and mediators (categorized sum of hospital admissions, outpatient visits and new drugs [excluding α1-adrenoceptor antagonists] during the lag time).

[c]Including the use of tamsulosin and dutasteride combination.

On the grounds of the baseline characteristics and our sensitivity analysis, the α1-adrenoceptor antagonist users had more comorbidities, which are also known risk factors for AD, such as diabetes, stroke and cardiovascular diseases.[14–16] Psychiatric diagnoses and the use of antipsychotics, antidepressants and BZDRs before the lag time were also more common among the users than non-users. The association between use of anticholinergic antipsychotics, BZDRs and antidepressants and cognitive disorders have previously been demonstrated,[17–19] and these drugs may be used to treat prodromal symptoms of AD.[20] After adjustment for these confounders, the strength of the associations notably reduced for both tamsulosin and alfuzosin. Taken together, the observation that morbidities and concomitant drugs were more common among the exposed indicate that they had higher initial risk of AD per se regardless of α1-adrenoceptor antagonist exposure.

Interestingly, men with BPH were recently shown to have higher risk of AD.[21] The relative risk estimates for AD among men with BPH from that Danish cohort study were in the same range as those observed for α1-adrenoceptor antagonist use occurring at least 3 years before outcome assessment in our study. The authors proposed that nocturia, leading to fragmented sleep, sleep deprivation and disruptions in glymphatic flow as the reason for their findings.[21] Supportive of the hypothesis of BPH itself being the risk factor, the ORs for alfuzosin and tamsulosin were of similar magnitude in our study. If one of these drugs was a risk factor, one would expect to observe different ORs for tamsulosin and alfuzosin in comparison to nonusers. In addition, the highest ORs were observed among men who had used both tamsulosin and alfuzosin. It is possible that these switches from one drug to another indicate poorer control and more severe symptoms of BPH, ultimately leading to more severe disruptions in glymphatic system and increased risk of AD as proposed by Norgaard et al.[21]

The users of α1-adrenoceptor antagonists had more contacts to specialized health care during the lag time. This is in line with previous observation on steep increase in the hospital and total medical care costs, starting 6 months before AD diagnosis.[22] Furthermore, based on the initiations of new drug therapies, it seems that the users also had more contacts with primary health care during the lag time. These findings indicate that due to the more frequent contacts with doctors or examinations of other conditions, the users of α1-adrenoceptor antagonists may have also been more likely to be diagnosed with AD. The additional adjustment for these mediators weakened the associations substantially, which supports the effects of comorbidities. It should be noted that using the number of initiated new drug therapies as an indicator for primary health care contacts may underestimate the real number of contacts. Therefore, we were unable to fully address the mediation via increased healthcare contacts and in reality this indirect association may be even larger than observed in our study.

The association between tamsulosin use during lag time and increased risk of AD more likely reflects reversal causality than true risk factor. In the dose–response analysis the majority of α1-adrenoceptor antagonist purchases were made during the lag time, which possibly reflects frequent health care contacts and initiations of new drug therapies due to oncoming dementia diagnosis. Because of the investigation of prodromal symptoms of AD, the LUTS have also become more likely to be diagnosed and treated.

The incoherence of the dose–response was observed especially for tamsulosin. To strengthen the causal nature of association between tamsulosin use and AD, an increased risk would have been expected in users with higher compared to lower exposure during the lag time. Instead, we found a decreased risk. These results were contrary to the previous findings of Duan et al.[1] and do not support the causal nature of the association.

The biological explanation for the possible association between cognitive decline and α1-adrenoceptors is still uncertain. Tamsulosin and alfuzosin both cause similar α1-adrenoceptor inhibition, and therefore it is logical that the results in our study were quite parallel to both drugs. The hypothesis proposed by Duan et al.[1] suggests, that tamsulosin inhibits the α1A-adrenoceptors in the central nervous system and therefore has higher risk of cognitive adverse effects than other α1-adrenoceptor antagonists. Based on animal studies tamsulosin should not pass the blood brain barrier[23,24] but there are also opposite observations.[25] However, aging and especially neurodegenerative processes such as AD are known to increase the permeability of the blood brain barrier,[26,27] so the α1-adrenoceptor antagonists might affect brains.

The strength of our study was the long-term exposure assessment, enabled by comprehensive registers, and the use of lag time in analysis, that ensured the reliable assessment of drug exposure. The nationwide cohort, which covers Finnish citizens with the clinically verified diagnoses of AD, ensured the reliable definition of the outcome. The MEDALZ study also includes mixed dementia cases having symptoms mainly due to AD. We used an unexposed comparison group, because this indirectly enables the assessment of indication for drug use as a risk factor, but also the comparison of different exposure categories. Use of an active comparison typically requires exclusion of persons with multiple types of drug exposure (e.g., tamsulosin and alfuzosin), while our design retains the information also from this exposure group. Use of 5-ARI was very low in our study, and therefore it was not used as a comparison group. Further, many users of 5-ARI were exposed to tamsulosin and/or alfuzosin, meaning that differentiating the risk estimates for individual drugs would likely not have been possible.

Our study has its limitations relating to restricted information about the register-based data. The data on primary care visits were not available in our study and the data on lifestyle confounders were absent. The Prescription Register does not cover data on non-reimbursed drugs. This does not impact the drug exposure assessment, but may have a minor effect on the drug-based confounder and mediator data as, for example, benzodiazepines, that are also prescribed for small package sizes.

In conclusion, our findings do not provide strong support on the previous hypotheses on α1-adrenoceptor antagonists as a risk factor for dementia, or higher risk of AD in tamsulosin users compared to alfuzosin users. The association between these drugs and AD is partly

explained by increased health care contacts 3 years before diagnosis, and the lack of meaningful dose–response relationship does not support the causality.

AUTHOR CONTRIBUTIONS

Laura Latvala participated in designing and conceptualization of the study, performed statistical analyses, interpreted the results, wrote the first draft of the manuscript, revised the draft with input from all authors. Miia Tiihonen designed and conceptualized the study, interpreted the results, revised the manuscript for important intellectual content. Teemu J. Murtola interpreted the results, revised the manuscript for important intellectual content. Sirpa Hartikainen designed and conceptualized the study, interpreted the results, revised the manuscript for important intellectual content. Anna-Maija Tolppanen designed and conceptualized the study, planned and supervised the statistical analyses, interpreted the results, revised the manuscript for important intellectual content.

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CONFLICT OF INTEREST

L.L., A.M.T., S.H., M.T. report no conflicts of interest. T.J.M. reports consultation fees from Novartis, Astellas and Janssen and lecture fees from Ferring, Novartis, Janssen, Sanofi, Bayer, Roche and Pfizer.

ETHICS STATEMENT

According to the Finnish legislation no formal ethical approval was required for this register-based study. The data were de-identified and the study participants were not contacted nor interfered for any treatment. The data were used with the permission of the register maintainers.

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REFERENCES

1. Duan Y, Grady JJ, Albertsen PC, Helen WZ. Tamsulosin and the risk of dementia in older men with benign prostatic hyperplasia. *Pharmacoepidemiol Drug Saf*. 2018;27(3):340-348. doi:10.1002/pds.4361
2. Tae BS, Jeon BJ, Choi H, Cheon J, Park JY, Bae JH. α-Blocker and risk of dementia in patients with benign prostatic hyperplasia: a nationwide population based study using the National Health Insurance Service database. *J Urol*. 2019;202(2):362-368. doi:10.1097/JU.0000000000000209
3. Sohn J, Lee S, Kwon Y, Kim J, Kim Y, Lee JJ. The impact of tamsulosin on cognition in Alzheimer disease with benign prostate hyperplasia: a study using the Hallym Smart Clinical Data Warehouse. *Medicine (Baltimore)*. 2020;99(22):e20240. doi:10.1097/MD.0000000000020240
4. Andrade C. How to read a research paper: an exercise in critical thinking in the context of an epidemiologic study on Tamsulosin and the risk of dementia. *J Clin Psychiatry*. 2018;79(6). doi:10.4088/JCP.18f12660
5. Madersbacher S, Michel MC. Re: Tamsulosin and the risk of dementia in older men with benign prostatic hyperplasia. *Eur Urol*. 2018;74(4):522-523. doi:10.1016/j.eururo.2018.07.013
6. Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines. World Health Organization, 2019. Accessed May 6, 2021. http://www.ncbi.nlm.nih.gov/books/NBK542796/.
7. Management of Benign Prostatic Hyperplasia: American Urological Association Guidelines Statement. Accessed May 6, 2021. Updated 2014. https://www.auanet.org/guidelines/.
8. Tolppanen A, Taipale H, Koponen M, et al. Cohort profile: the Finnish Medication and Alzheimer's disease (MEDALZ) study. *BMJ Open*. 2016;6(7):e012100. doi:10.1136/bmjopen-2016-012100
9. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*. 1984;34(7):939-944. doi:10.1212/wnl.34.7.939
10. American Psychiatric Association, ed. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. 4th ed. American Psychiatric Association; 1994.
11. *Memory Disorders*. Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim, Societas Gerontologica Fennica, the Finnish Geriatrics Association, the Neurological Association of Finland, the Psychogeriatric Association of Finland and the General Practice Association of Finland. Helsinki: The Finnish Medical Society Duodecim (Updated 2020). Accessed March 19, 2021. www.kaypahoito.fi.
12. WHO Collaborating Centre for Drug Statistics Methodology. *The Anatomical Therapeutic Chemical Classification System. Structure and Principles*. Accessed April 30, 2021. http://www.whocc.no/atc/structure_and_principles/.
13. Tapiainen V, Hartikainen S, Taipale H, Tiihonen J, Tolppanen A. Hospital-treated mental and behavioral disorders and risk of Alzheimer's disease: a nationwide nested case-control study. *Eur Psychiatry*. 2017;43:92-98.
14. Zhang J, Chen C, Hua S, et al. An updated meta-analysis of cohort studies: diabetes and risk of Alzheimer's disease. *Diabetes Res Clin Pract*. 2017;124:41-47.
15. Honig LS, Tang M, Albert S, et al. Stroke and the risk of Alzheimer disease. *Arch Neurol*. 2003;60(12):1707-1712.
16. Newman AB, Fitzpatrick AL, Lopez O, et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the cardiovascular health study cohort. *J Am Geriatr Soc*. 2005;53(7):1101-1107. 10.1111/j.1532-5415.2005.53360.x
17. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med*. 2015;175(3):401-407. doi:10.1001/jamainternmed.2014.7663
18. Islam MM, Iqbal U, Walther B, et al. Benzodiazepine use and risk of dementia in the elderly population: a systematic review and meta-analysis. *Neuroepidemiology*. 2016;47(3–4):181-191. doi:10.1159/000454881
19. Wang Y, Tai P, Poly TN, et al. Increased risk of dementia in patients with antidepressants: a meta-analysis of observational studies. *Behav Neurol*. 2018;2018. doi:10.1155/2018/5315098
20. Saarelainen L, Taipale H, Koponen M, et al. The incidence of benzodiazepine and related drug use in persons with and without Alzheimer's disease. *J Alzheimers Dis*. 2016;49(3):809-818. doi:10.3233/JAD-150630
21. Nørgaard M, Horváth-Puhó E, Corraini P, Sørensen HT, Henderson VW. Sleep disruption and Alzheimer's disease risk: inferences from men with benign prostatic hyperplasia. *EClinicalMedicine*. 2021;32(3):100740. doi:10.1016/j.eclinm.2021.100740
22. Taipale H, Purhonen M, Tolppanen A, Tanskanen A, Tiihonen J, Hartikainen S. Hospital care and drug costs from five years before until two years after the diagnosis of Alzheimer's disease in a Finnish nationwide cohort. *Scand J Public Health*. 2016;44(2):150-158. doi:10.1177/1403494815614705
23. Franco-Salinas G, de la Rosette JJMCH, Michel MC. Pharmacokinetics and pharmacodynamics of tamsulosin in its modified-release and oral

controlled absorption system formulations. *Clin Pharmacokinet*. 2010; 49(3):177-188. doi:10.2165/11317580-000000000-00000
24. Yamada S, Ohkura T, Deguchi Y, Kimura R. In vivo measurement by [3H]Tamsulosin of alpha1 adrenoceptors in rat tissues in relation to the pharmacokinetics. *J Pharmacol Exp Ther*. 1999;289(3):1575-1583.
25. Giuliano F. Impact of medical treatments for benign prostatic hyperplasia on sexual function. *BJU Int*. 2006;97(Suppl 2):34-45. doi:10.1111/j.1464-410X.2006.06104.x
26. Erdő F, Denes L, de Lange E. Age-associated physiological and pathological changes at the blood-brain barrier: a review. *J Cereb Blood Flow Metab*. 2017;37(1):4-24. doi:10.1177/0271678X16679420
27. Bowman GL, Dayon L, Kirkland R, et al. Blood-brain barrier breakdown, neuroinflammation, and cognitive decline in older adults. *Alzheimers Dement*. 2018;14(12):1640-1650. doi:10.1016/j.jalz.2018.06.2857

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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