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The risk of Alzheimer's disease associated with benzodiazepines and related drugs: a nested case–control study

Tapiainen V, Taipale H, Tanskanen A, Tiihonen J, Hartikainen S, Tolppanen A-M. The risk of Alzheimer's disease associated with benzodiazepines and related drugs: a nested case–control study.

Objective: To assess the association between benzodiazepine and related drug (BZDR) use and risk of Alzheimer's disease (AD) with cumulative consumption and duration of use based models.
Method: A nationwide nested case–control study of all Finnish community-dwelling persons who received clinically verified AD diagnosis in 2005–2011 (N = 70 719) and their matched controls (N = 282 862). AD diagnosis was based on DSM-IV and NINCDS-ADRDA criteria. BZDR purchases were extracted from the Prescription Register since 1995. The association between BZDR use and AD was assessed using conditional logistic regression with 5-year lag time between exposure and outcome.
Results: Benzodiazepine and related drug use was associated with modestly increased risk of AD (adjusted OR 1.06, 95% CI 1.04–1.08). A dose–response relationship was observed with both cumulative consumption and duration. Adjustment for other psychotropics removed the cumulative dose–response relationship by attenuating the ORs in the highest dose category.
Conclusion: Benzodiazepine and related drug use in general was associated with modestly increased risk of AD. No major differences were observed between different subcategories of BZDRs (i.e. benzodiazepines, Z drugs, short-/medium-acting or long-acting BZDRs). As dose–response relationship abolished after adjustment for other psychotropics, it is possible that the association may partially be due to antidepressants and/or antipsychotics, or concomitant use of these medications.

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Significant outcomes

- Benzodiazepine and related drug (BZDR) use in general was associated with modestly increased risk of Alzheimer's disease. Cumulative dose–response relationship was abolished after adjustment for other psychotropics, indicating that the association may partially be due to these medications, or reasons for their concomitant use.
- Even though the association between BZDR use and Alzheimer's disease was small in this study, BZDRs should be avoided when possible and threshold for prescribing should be high enough due to their overall adverse effect profile.

Limitations

- Only reimbursed drug purchases could be extracted from the Prescription Register, and therefore, BZDR use may be underestimated in our study. This is likely nondifferential misclassification.
- Information of drug use in hospitals was not available from the Prescription Register which may have caused some misclassification of exposure.

Introduction

The prevalence of benzodiazepine (BZD) and related drug (Z drug) use, that is benzodiazepine and related drug (BZDR) use, among older people varies between 9–32% in developed countries (1–5). Their adverse effects and events include drowsiness, higher risk of falls and hip fractures and mobility problems (6). Despite the recommendations (7), BZDRs are commonly used long term (8). Short-term negative effects on memory and cognition are well known (9–12.) Thus, their long-term use has been hypothesized to hasten cognitive decline and increase dementia risk.

Alzheimer's disease (AD) accounts for 60–80% of dementia cases (13). BZDRs are used to treat prodromal or neuropsychiatric symptoms of dementia/AD such as anxiety and insomnia (14–16). Because AD has long latency period, prodromal symptoms can arise years before diagnosis of AD. Thus, protopathic bias must be taken into account using sufficient time lag between BZDR use and AD. In most of the studies, the time lag in main analyses has been 1–2 years (17–20), and in one study 5 years (21). These studies have been inconsistent, with some claiming that BZDRs and BZDs are AD/dementia risk factors (18, 21, 22) and others reporting no association (20). One, without any time lag reported that BZDs were associated with decreased risk of AD (23). A recent meta-analysis (22) concluded about 50% increased dementia risk among BZDRs users.

Studies on dose–response relationship of BZDs have been equally heterogeneous, with two studies showing a dose–response effect (18, 21), one reporting an increased risk with smaller cumulative doses only (17), and one reporting null results (20). We are aware on only one study that assessed association between Z drugs and AD or vascular dementia, concluding with null results (20).

The impact of elimination time has also been debated. Three previous studies found higher dementia risk for those who used long-acting BZDRs compared to those who used short-acting BZDRs (18, 19, 21). One study (19) found the risk only for long-acting but not for short-acting BZDRs and one study (20) found no associations.

Aims of the study

We assessed the association between benzodiazepine and related drug use and risk of Alzheimer's disease in a nationwide nested case–control study of all clinically verified Alzheimer's disease cases diagnosed in Finland in 2005–2011. The effect of dose, half-life, cumulative consumption and duration, as well as the individual associations of benzodiazepines and Z drugs, were examined.

Material and methods

Study population

Cases of the study were from the nationwide MEDALZ (Medication use and Alzheimer's disease) cohort that includes all Finnish community-dwelling persons who received a clinically verified AD diagnosis in 2005–2011 (N = 70 719, age range 34–105 years, 65.2% women) (24). To conduct a nested case–control study of the population of Finland, 1–4 age, sex and region of residence matched controls were identified for each case (N = 282 862).

Data sources

Data were extracted from the Special Reimbursement Register (since 1972), the Prescription Register (since 1995), the Hospital Discharge Register (since 1972) and the population censuses maintained by Statistics Finland since 1970. All data sources have nationwide coverage.

Register data were retrieved using personal identity numbers (25). All data were de-identified before submission to the research team, and therefore, ethics committee approval was not required according to Finnish legislation. Permissions for data use were received from register maintainers. Registers and linkage process have been previously described in detail (24).

Identification of AD cases

The AD cases were identified from the Special Reimbursement Register. The diagnostic criteria of AD were based on NINCDS-ADRDA (26) and DSM-IV (27). All AD cases had to fulfil the requirements for the reimbursement of anti-AD drugs which are as follows: (i) symptoms consistent with AD; (ii) a decrease in social capacity over a period of at least 3 months; (iii) received a computed tomography/magnetic resonance imaging scan; (iv) had possible alternative diagnoses excluded; and (v) received confirmation of the diagnosis by a registered neurologist or geriatrician (28).

Identification of controls

The matched controls were identified from nationwide registers of the Social Insurance Institution of Finland (SII) including all residents with the

following criteria: (i) alive and community-dwelling during the last day of the month when case was diagnosed with AD (index date); (ii) no special reimbursement for AD medication or acetylcholinesterase inhibitor or memantine purchases (N06D) before index date and within 12 months after it.

BZDR use

Benzodiazepine and related drugs are categorized according to World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system (29). BZDRs were defined as benzodiazepines (ATC-classes N05BA and N05CD and clonazepam N03AE01) and benzodiazepine-related drugs, so called Z drugs (ATC class N05CF). Various combination products including a BZD component, such as combination of diazepam with glycopyrronium, were identified as being on market and used by the study cohort during the follow-up, and these also were included in analysis. Use of combination products was recoded to the use of the corresponding BZD substance (diazepam-glycopyrronium recoded as diazepam use) to retrieve total duration of use and cumulative consumption for each drug substance (Table S1).

Benzodiazepine and related drugs were classified into short-/medium- and long-acting BZDRs according to Gomm et al. (18), with the exception of alprazolam that was classified as long-acting, because of its increased half-life in old adults (30). The following substances were categorized as short-/medium-acting BZDRs: oxazepam (N05BA04), lorazepam (N05BA06), temazepam (N05CD07), zopiclone (N05CF01), zolpidem (N05CF02), triazolam (N05CD05) and midazolam (N05CD08); and long-acting BZDRs: diazepam (N05BA01) chlordiazepoxide (N05BA02), alprazolam (N05BA12), nitrazepam (N05CD02), clobazam (N05BA09), clorazebate (N05BA05) and clonazepam (N03AE01).

Benzodiazepine and related drug use was calculated since 1995 until 5 years before the index date (date of AD diagnosis of the index case). BZDR use was defined as any BZDR use during the follow-up.

Benzodiazepine and related drug use periods, that is when continuous drug use started and ended, were calculated using validated PRE2DUP-method from prescription register data (31, 32). The method is based on mathematical modelling and calculation of sliding averages of Defined Daily Dose (DDD) (33) for each ATC code. Each drug substance was modelled separately and then overlapping use periods combined to retrieve 'any BZDR use'. Individuals could change the BZDR substance during the 'any BZDR' use period. BZD, Z drug, long-acting and short-/medium-acting BZDR use periods were constructed similarly.

To study the impact of exposure duration, BZDR use was categorized into four groups according to the cumulative duration of BZDR use: 1 day–1 month, 1 month–1 year, 1–5 years and over 5 years. Same cut-offs were used for BZDs, Z drugs, short-/medium-acting BZDRs and long-acting BZDRs.

To study the effect of cumulative BZDR consumption in DDDs, cumulative amount of DDDs were calculated from drug purchase data. Cumulative sum of DDDs was categorized to three groups according to tertiles of cumulative consumption: 1–102 DDD, 103–779 DDD, 780–32 298 DDD for BZDR use. Respectively for BZDs, 1–61 DDD, 62–451 DDD, 452–26 037 DDD and for Z drugs 1–123 DDD, 124–750 DDD, 751–23 990 DDD.

Cumulative BZDR consumption in DDDs was converted to total standardized doses (TSDs) based on minimum effective daily dose according to Gray et al. (34) and Ashton Manual (35) to examine whether results differ if TSDs are used instead of DDDs (Table S2). Cumulative sum of TSDs was categorized to three groups according to tertiles of cumulative consumption: 1–415.8 TSD, 415.8–5000 TSD, 5001.3–513 349 TSD for BZDR use. Respectively for BZDs, 10–250 TSD, 250.5–2720 TSD, 2721–512 672.3 TSD and for Z drugs 11.7–373.3 TSD, 373.3–4083.3 TSD, 4083.3–177 676.7 TSD.

For dose-dependency analyses, cumulative purchased amount in DDDs was divided by duration of use for each person to define the average BZDR dose. The average BZDR dose was categorized to low (>0 to <0.5 DDD/day), medium (≥0.5 to <1 DDD/day) and high (≥1 DDD/day). Doses were categorized similarly for BZDs and Z drugs.

Confounders

The following comorbidities were used for adjustment: asthma/COPD, any cardiovascular disease (arrhythmia, hypertension, coronary disease or heart failure) and diabetes from the Special Reimbursement Register and mental and behavioural disorders (any of ICD-10 F-codes, excluding F00-F03 dementia diagnoses, and corresponding ICD-9 and -8 codes) from the Hospital Discharge register from 1972 onwards.

A composition variable indicating substance abuse was derived from the Hospital Discharge Register data using mental and behavioural disorders due to psychoactive substance use (ICD-10

codes F10–F19), alcohol-induced chronic pancreatitis (ICD-10 codes K86.00, K86.01 and K86.08) and hospitalizations due to substance abuse.

Antipsychotic use (purchased or not antipsychotics class N05A excluding lithium (N05AN)) and similarly antidepressant use (all antidepressants (N06A) excluding 'Monoamine oxidase inhibitors, non-selective' (N06AF) as they were not on market in Finland during the study period) was extracted from the Prescription register since 1995.

Socioeconomic position, defined as the highest occupational social class, was obtained from the censuses maintained by Statistics Finland. The data were collected on 5-year intervals between 1970 and 1990, on 1993, 1995, 2000, and annually from 2004 onwards. An ordinal variable with the following categories was derived 'managerial/professional', 'office worker', 'farming/forestry', 'sales/industry/cleaning', 'unknown' and 'did not respond'.

All confounders were extracted until 5 years before the AD diagnosis of the index case.

Statistical analysis

All analyses were conducted using Stata, version 13.1. All continuous variables were compared with Wilcoxon rank-sum test due to skewed distributions. All categorical variables were compared with conditional logistic regression.

The associations between BZDR exposure and AD were assessed with conditional logistic regression. To account for reverse causality, only drug use that occurred at least 5 years before AD diagnosis was considered in the analysis. Those persons who were exposed only during the lag time were not included in the analyses. Persons who did not use any BZDRs during follow-up (1995–2011) were used as reference group (N = 190 924). Similar 5-year time lag was applied to confounders. To calculate the attributable proportion among the exposed (i.e. the proportion of disease in the exposed group that can be attributed to the exposure), the following formula was used: $\mathrm{AR}\% = \frac{(\mathrm{OR}-1)}{\mathrm{OR}}$.

Results

Characteristics of study population

History of diabetes, mental disorders as well as antidepressant and antipsychotic use were more common among AD cases. (Table 1). There were no major differences in socioeconomic position.

Use of any BZDR was more common among cases (40.2%) than controls (37.0%) due to more common use of BZDs (Table 2). Cases were also more likely to have used both BZDs and Z drugs, or short-/medium- and long-acting BZDRs.

Table 1. Characteristics of study population at 5 years before the index date

	Total (N = 353 581)		AD cases (N = 70 719)		Controls (N = 282 862)		
	N	%	*N*	%	*N*	%	*P*
Comorbidities							
Asthma/COPD	26 711	7.6	5392	7.6	21 319	7.5	0.427
Cardiovascular disease†	152 347	43.1	31 726	44.9	120 621	42.6	<0.001
Diabetes	28 297	8.0	6904	9.8	21 393	7.6	<0.001
Any mental disorder	25 251	7.1	5655	8.0	19 596	6.9	<0.001
Substance abuse	5329	1.5	1247	1.8	4082	1.4	<0.001
Socioeconomical position							
Managerial/ professional	75 061	21.2	14 680	20.8	60 381	21.3	<0.001
Office	29 576	8.4	5974	8.4	23 602	8.3	<0.001
Farming, forestry	68 965	19.5	13 443	19.0	55 522	19.6	<0.001
Sales, industrial, cleaning	141 080	39.9	30 150	42.6	110 930	39.2	<0.001
Unknown	29 227	8.3	5932	8.4	23 295	8.2	<0.001
Did not reply	9672	2.7	540	0.8	9132	3.2	<0.001
Non-BZDR drug use							
Antipsychotic use	23 693	6.7	5505	7.8	18 188	6.4	<0.001
Antidepressant use	56 263	15.9	13 524	19.1	42 739	15.1	<0.001

Index date: date of AD diagnosis for each case and the corresponding matching date for controls.
AD, Alzheimer's disease; BZDR, Benzodiazepine and related drug.
†Cardiovascular disease: arrhythmia, hypertension, coronary disease or heart failure.

Total cumulative consumption of BZDRs and BZDs in DDDs during the follow-up was higher in cases, and duration of use was longer than in controls (Table S3). Similar, although smaller differences were observed with Z drug consumption. Cases also used both short-/medium-acting and long-acting BZDRs for longer periods. There were no significant differences in average BZDR doses (DDD/day). Assessment of BZDR use duration according to dose categories showed that highest doses were used shorter time and total consumption of BZDRs was smaller in the highest dose group (Table S4).

Average time for exposure assessment (the 5-year time lag not included in the exposure assessment time) was 8.7 years (SD 2.0). The exposure assessment time ranged from 5.0 years to 11.9 years.

Association between any BZDR use and AD

Any BZDR use was associated with an increased risk of AD (OR 1.19, 95% CI 1.17–1.21) compared

Table 2. Association between benzodiazepine and related drug use and Alzheimer's disease with 5-year lag time between exposure and outcome

	AD cases (*N* = 70 719)		Controls (*N* = 282 862)		Unadjusted OR (95% CI)	Adjusted 1† OR (95% CI)	Adjusted 2‡ OR (95% CI)
	N	%	*N*	%			
No BZDR use	35 627	50.4	155 297	54.9	1.00 (Reference in all analyses)		
Drug class							
Any BZDR use	28 462	40.2	104 746	37.0	1.19 (1.17–1.21)	1.13 (1.11–1.15)	1.06 (1.04–1.08)
Only BZD	15 148	21.4	56 628	20.0	1.17 (1.15–1.20)	1.12 (1.09–1.14)	1.05 (1.03–1.08)
Only Z drug	5390	7.6	20 750	7.3	1.14 (1.10–1.18)	1.09 (1.05–1.12)	1.05 (1.01–1.08)
Both BZD & Z drug	7924	11.2	27 368	9.7	1.27 (1.24–1.31)	1.20 (1.17–1.24)	1.09 (1.05–1.12)
Elimination half-life							
Only short-/medium-acting	12 904	18.2	48 711	17.2	1.16 (1.14–1.19)	1.11 (1.08–1.13)	1.05 (1.03–1.08)
Only long-acting	6621	9.4	25 146	8.9	1.15 (1.12–1.19)	1.10 (1.07–1.14)	1.06 (1.03–1.09)
Both short-/medium- and long-acting	8937	12.6	30 889	10.9	1.27 (1.24–1.31)	1.20 (1.17–1.23)	1.08 (1.05–1.11)

AD, Alzheimer's disease; BZDR, Benzodiazepine and related drug; BZD, Benzodiazepine.

†Adjusted for any mental disorder, substance abuse, asthma/COPD, cardiovascular disease (arrhythmia, hypertension, coronary disease or heart failure), diabetes and socioeconomic position.

‡Adjusted for antidepressant use, antipsychotic use, any mental disorder, substance abuse, asthma/COPD, cardiovascular disease (arrhythmia, hypertension, coronary disease or heart failure), diabetes and socioeconomic position.

Table 3. Association between benzodiazepine and related drug average dose and Alzheimer's disease with 5-year lag time between exposure and outcome

	AD cases (*N* = 70 719)		Controls (*N* = 282 862)		Unadjusted OR (95% CI)	Adjusted 1† OR (95% CI)	Adjusted 2‡ OR (95% CI)
	N	%	*N*	%			
No BZDR use	35 627	50.4	155 297	54.9	1.00 (Reference in all analyses)		
BZDR							
>0 to <0.5 DDD/day	8180	11.6	29 383	10.4	1.22 (1.19–1.26)	1.16 (1.13–1.20)	1.10 (1.07–1.13)
≥0.5 to <1 DDD/day	11 996	17.0	44 129	15.6	1.19 (1.17–1.22)	1.13 (1.10–1.16)	1.06 (1.03–1.08)
≥1 DDD/day	8286	11.7	31 234	11.0	1.16 (1.13–1.19)	1.10 (1.07–1.13)	1.02 (0.99–1.05)
BZD							
>0 to <0.5 DDD/day	10 472	14.8	37 685	13.3	1.22 (1.19–1.25)	1.16 (1.13–1.19)	1.09 (1.06–1.12)
≥0.5 to <1 DDD/day	8220	11.6	29 907	10.6	1.21 (1.18–1.24)	1.14 (1.11–1.17)	1.06 (1.03–1.09)
≥1 DDD/day	4380	6.2	16 404	5.8	1.17 (1.13–1.21)	1.10 (1.06–1.14)	1.02 (0.98–1.05)
Z drug							
>0 to <0.5 DDD/day	74	0.1	312	0.1	1.05 (0.81–1.35)	1.00 (0.77–1.29)	0.95 (0.74–1.23)
≥0.5 to <1 DDD/day	6264	8.9	22 208	7.9	1.24 (1.20–1.28)	1.17 (1.14–1.21)	1.09 (1.06–1.13)
≥1 DDD/day	6976	9.9	25 598	9.0	1.20 (1.16–1.23)	1.14 (1.10–1.17)	1.06 (1.03–1.09)

AD, Alzheimer's disease; BZDR, Benzodiazepine and related drug; DDD, Defined Daily Dose (33); BZD, Benzodiazepine.

†Adjusted for any mental disorder, substance abuse, asthma/COPD, cardiovascular disease (arrhythmia, hypertension, coronary disease or heart failure), diabetes and socioeconomic position.

‡Adjusted for antidepressant use, antipsychotic use, any mental disorder, substance abuse, asthma/COPD, cardiovascular disease (arrhythmia, hypertension, coronary disease or heart failure), diabetes and socioeconomic position.

with no use (Table 2). The association was attenuated after adjustment for comorbidities, socioeconomic position and use of other psychotropics (OR 1.06, 95% CI 1.04–1.08) The attributable proportion among the exposed was 0.057. Similar associations were observed with the use of BZD or Z drug alone. The same pattern was observed with short-/medium- and long-acting BZDRs.

Average BZDR dose and the risk of AD

In average dose analysis among BZDR users, unadjusted ORs were slightly higher in persons with lower average dose compared to higher doses (Table 3). The same was evident among BZD users. Z drug use was not associated with AD in low dose group, and the highest risk was observed in the medium dose group. In general, the differences were small and the 95% CIs were overlapping. Adjustments for comorbidities, socioeconomic position and other psychotropics slightly lowered ORs and removed the associations in high-dose groups among BZDR users and BZD users but did not change previously mentioned order of risks.

Duration of BZDR use and AD risk

The risks in all drug categories were the highest in the two longest duration of use groups (1–5 years

Table 4. Association between duration of benzodiazepine and related drugs use and Alzheimer's disease with 5-year lag time between exposure and outcome

	AD cases (*N* = 70 719)		Controls (*N* = 282 862)				
	N	%	*N*	%	Unadjusted OR (95% CI)	Adjusted 1† OR (95% CI)	Adjusted 2‡ OR (95% CI)
No BZDR use	35 627	50.4	155 297	54.9	1.00 (Reference in all analyses)		
BZDR							
1 day–1 month	2901	4.1	11 521	4.1	1.10 (1.06–1.15)	1.06 (1.02–1.11)	1.03 (0.98–1.07)
1 month–1 year	9473	13.4	35 804	12.7	1.16 (1.13–1.19)	1.11 (1.08–1.14)	1.06 (1.03–1.09)
1–5 years	8505	12.0	30 391	10.7	1.23 (1.20–1.26)	1.17 (1.13–1.20)	1.08 (1.05–1.12)
Over 5 years	7583	10.7	27 030	9.6	1.23 (1.20–1.27)	1.16 (1.12–1.19)	1.05 (1.01–1.08)
BZD							
1 day–1 month	2832	4.0	11 086	3.9	1.12 (1.07–1.17)	1.07 (1.03–1.12)	1.03 (0.99–1.07)
1 month–1 year	8685	12.3	32 098	11.3	1.19 (1.16–1.22)	1.13 (1.10–1.17)	1.07 (1.04–1.10)
1–5 years	6366	9.0	22 344	7.9	1.25 (1.22–1.29)	1.18 (1.15–1.22)	1.09 (1.06–1.13)
Over 5 years	5189	7.3	18 468	6.5	1.24 (1.20–1.28)	1.16 (1.12–1.20)	1.05 (1.01–1.09)
Z drug							
1 day–1 month	1763	2.5	6656	2.4	1.16 (1.10–1.22)	1.11 (1.06–1.18)	1.06 (1.00–1.12)
1 month–1 year	4758	6.7	17 353	6.1	1.20 (1.16–1.25)	1.15 (1.11–1.19)	1.08 (1.04–1.12)
1–5 years	4403	6.2	15 469	5.5	1.25 (1.21–1.30)	1.19 (1.14–1.23)	1.09 (1.06–1.14)
Over 5 years	2390	3.4	8640	3.1	1.22 (1.16–1.28)	1.14 (1.09–1.19)	1.04 (0.99–1.09)
Short-/medium-acting							
1 day–1 month	2249	3.2	8795	3.1	1.12 (1.07–1.17)	1.07 (1.02–1.13)	1.03 (0.98–1.08)
1 month–1 year	6414	9.1	24 044	8.5	1.17 (1.14–1.21)	1.12 (1.09–1.15)	1.06 (1.03–1.10)
1–5 years	6755	9.6	24 167	8.5	1.23 (1.19–1.27)	1.16 (1.13–1.20)	1.08 (1.05–1.11)
Over 5 years	6423	9.1	22 594	8.0	1.25 (1.21–1.29)	1.17 (1.13–1.21)	1.06 (1.02–1.09)
Long-acting							
1 day–1 month	1822	2.6	7171	2.5	1.11 (1.06–1.17)	1.07 (1.01–1.13)	1.03 (0.97–1.08)
1 month–1 year	5691	8.0	20 895	7.4	1.19 (1.16–1.23)	1.14 (1.11–1.18)	1.08 (1.05–1.12)
1–5 years	4060	5.7	13 931	4.9	1.28 (1.23–1.33)	1.21 (1.17–1.26)	1.12 (1.07–1.16)
Over 5 years	3985	5.6	14 038	5.0	1.25 (1.20–1.30)	1.17 (1.13–1.22)	1.05 (1.01–1.09)

AD, Alzheimer's disease; BZDR, Benzodiazepine and related drug; BZD, Benzodiazepine.

†Adjusted for any mental disorder, substance abuse, asthma/COPD, cardiovascular disease (arrhythmia, hypertension, coronary disease or heart failure), diabetes and socioeconomic position.

‡Adjusted for antidepressant use, antipsychotic use, any mental disorder, substance abuse, asthma/COPD, cardiovascular disease (arrhythmia, hypertension, coronary disease or heart failure), diabetes and socioeconomic position.

and >5 years), and the risks slightly lowered in shorter use compared to nonusers of each drugs (Table 4). In the fully adjusted model, no risks were observed in the shortest use (1 day–1 month) and the risks increased until the second longest (1–5 years) duration of use group. No significant differences in risks between BZDs and Z drugs, or short-/medium- and long-acting BZDRs were observed.

Cumulative BZDR consumption and risk of AD

In unadjusted analyses, a dose–response relationship was evident in the DDD analyses and less clear in the equivalent dose analyses where the ORs for the highest category were similar to the lowest category for BZDRs and Z drugs (Table 5). In the fully adjusted model, the differences between the highest and lowest category disappeared and the highest ORs were seen in the second tertiles of each drug category. Similar results were observed with equivalent doses.

Discussion

Our study showed that the past use of BZDRs was associated with modestly increased risk of AD (adjusted OR 1.06, 95% CI 1.04–1.08). The attributable proportion among the exposed was 0.057, meaning that assuming there was no uncontrolled bias or confounding, 5.7% of AD cases occurring among BZDR users were attributable to exposure. This is worrying because BZDRs are commonly used among old persons (1–5), and despite recommendations (7), the use is often long term (8). This is the first study on this topic that also included BZD combination products. Adjustment for other psychotropics removed the dose–response relationship by attenuating the ORs in the highest cumulative consumption category.

Comparison with other studies

All drug categories (BZDRs, BZDs, Z drugs, short-/medium-acting and long-acting BZDRs) were associated with higher risk of AD. No major

Table 5. Association between cumulative benzodiazepine and related drug consumption and Alzheimer's disease with 5-year lag time between exposure and outcome

	AD cases (*N* = 70 719)		Controls (*N* = 282 862)		Unadjusted	Adjusted 1†	Adjusted 2‡
	N	%	*N*	%	OR (95% CI)	OR (95% CI)	OR (95% CI)
No BZDR use	35 627	50.4	155 297	54.9	1.00 (Reference in all analyses)		
Consumption in DDDs							
BZDR							
1–102	9268	13.1	35 430	12.5	1.15 (1.12–1.18)	1.10 (1.07–1.13)	1.06 (1.03–1.08)
103–779	9476	13.4	34 636	12.2	1.20 (1.17–1.23)	1.14 (1.11–1.17)	1.08 (1.05–1.10)
780–32 298	9718	13.7	34 680	12.3	1.23 (1.20–1.26)	1.15 (1.12–1.19)	1.05 (1.02–1.08)
BZD			198 866	70.3			
1–61	7507	10.6	28 405	10.0	1.16 (1.13–1.19)	1.11 (1.08–1.14)	1.06 (1.03–1.09)
62–451	7777	11.0	27 728	9.8	1.23 (1.20–1.27)	1.17 (1.14–1.21)	1.10 (1.06–1.13)
452–26 037	7788	11.0	27 863	9.9	1.23 (1.20–1.26)	1.15 (1.12–1.19)	1.04 (1.01–1.08)
Z drug							
1–123	4330	6.1	16 161	5.7	1.18 (1.13–1.22)	1.12 (1.08–1.17)	1.06 (1.03–1.10)
124–750	4499	6.4	15 974	5.6	1.24 (1.19–1.28)	1.18 (1.14–1.22)	1.10 (1.06–1.14)
751–23 990	4485	6.3	15 983	5.7	1.23 (1.19–1.28)	1.16 (1.12–1.20)	1.06 (1.02–1.10)
Consumption in TSDs							
BZDR							
1–415.8	9168	13.0	35 236	12.5	1.14 (1.11–1.17)	1.09 (1.06–1.12)	1.05 (1.02–1.08)
415.8–5000	9807	13.9	34 599	12.2	1.24 (1.21–1.28)	1.18 (1.15–1.22)	1.11 (1.08–1.14)
5001.3–513 349	9487	13.4	34 911	12.3	1.19 (1.16–1.23)	1.12 (1.09–1.15)	1.01 (0.98–1.04)
BZD							
10–250	7536	10.7	28 661	10.1	1.15 (1.12–1.19)	1.10 (1.07–1.14)	1.06 (1.03–1.09)
250.5–2720	7700	10.9	27 493	9.7	1.23 (1.20–1.27)	1.17 (1.14–1.20)	1.09 (1.06–1.12)
2721–512 672.3	7836	11.1	27 842	9.8	1.24 (1.20–1.27)	1.16 (1.13–1.19)	1.05 (1.02–1.08)
Z drug							
11.7–373.3	4323	6.1	16 229	5.7	1.17 (1.13–1.21)	1.12 (1.08–1.16)	1.06 (1.02–1.09)
373.3–4083.3	4684	6.6	15 720	5.6	1.31 (1.26–1.36)	1.25 (1.20–1.29)	1.16 (1.12–1.20)
4083.3–177 676.7	4307	6.1	16 169	5.7	1.17 (1.13–1.21)	1.10 (1.06–1.14)	1.01 (0.97–1.05)

AD, Alzheimer's disease; DDD, Defined Daily Dose (33); BZDR, Benzodiazepine and related drug; BZD, Benzodiazepine; TSD, Total Standardized Dose based on minimum effective daily dose according to Gray et al. (34) and Ashton Manual (35).

†Adjusted for any mental disorder, substance abuse, asthma/COPD, cardiovascular disease (arrhythmia, hypertension, coronary disease or heart failure), diabetes and socioeconomic position.

‡Adjusted for antidepressant use, antipsychotic use, any mental disorder, substance abuse, asthma/COPD, cardiovascular disease (arrhythmia, hypertension, coronary disease or heart failure), diabetes and socioeconomic position.

differences between these categories were observed. The overall risk of past BZDR use we found was smaller than in most previous studies (18, 21, 22). One previous study found no association (20). It was also only previous study that investigated Z drugs separately and did not find association between Z drugs or BZDs and AD. Some (18, 19, 21) but not all (20) studies have found higher risk of dementia for long-acting BZDR use compared to short-/medium-acting use. Classifications into short-/medium-acting and long-acting BZDRs varied in previous studies, and therefore, their results are not directly compared to ours.

Lower (≥0 to <0.5 DDD/day) average doses of BZDRs increased the risk more than the higher doses (≥0.5 DDD/day). One explanation for this is that highest doses were used shorter time and total consumption of BZDRs was smaller in the highest dose group. In addition, high and low doses might have been used for different indications. Our result is contrary to previous study (18) where average dose -dependent association was found. However, the differences between average dose categories in our results were small.

Similar to a previous study (21), a dose–response relationship between cumulative BZDR consumption and AD was observed when other psychotropics were not taken into account. In our study, adjustment for psychotropics removed the dose–response relationship, suggesting that the association was at least partially explained by more frequent use of other psychotropics among high-dose users. This result is in line with one previous study (17), which found risk for dementia with two lowest cumulative consumption categories but not with the highest consumption category. In that study, an increased risk for dementia was observed with 1- and 2-year lag time, but none with a 5-year lag time which is contrary to our findings. Another study with 2-year lag time also concluded with null results (20). It might be that these null results are due to lack of power as both these studies had considerably smaller study samples, low number of AD cases and persons in subcategories.

Strengths and weaknesses of the study

Our study is a nationwide nested case–control study of all community-dwelling AD cases who received a clinically verified AD diagnosis in 2005–2011. The diagnoses were confirmed according to a standardized protocol, and the positive predictive value of diagnoses is high (PPV 97.1%) (36). To our knowledge, our study is the largest one in this topic and this enabled us to perform more detailed analyses according to the duration, dose and type of BZDRs. In addition, due to the long exposure assessment, we were able to use a 5-year time lag between exposure and outcome, which is longer than in main analyses of most of the previous studies (17–20) and accounts at least partially for the reverse causality. The 5-year time lag is justified by our previous studies in the same population, showing that a steep increase in the use of antidepressants (37) and antipsychotics (38) occurs in this time window.

A further strength is the exposure ascertainment. We used data on purchased prescriptions, which were modelled to actual use periods with a validated PRE2DUP modelling method (32). This enabled us to assess duration of use and dose (intensity of use) issues properly, which offer additional information on the associations between different drug use patterns. Further, including combination BZDs as exposures reduces indication bias as combinations are indicated for a larger variety of symptoms (such as gastrointestinal cramps, dizziness and muscle tension) than traditional BZDs. This also reduces the possibility of protopathic bias.

Our study is limited in the sense that only reimbursed BZDR purchases were included. It is likely that nonreimbursed small size packages were equally often purchased by cases and controls. This would dilute our estimates by increasing the confidence intervals, but not cause systematic bias. Thus, our results may be an underestimation. In addition, Prescription Register does not include information on drug use in hospital. This might have caused some misclassification of exposure. However, as we restricted the analyses to time preceding AD diagnosis by at least 5 years, it is likely that the amount of possibly misclassified exposure time was similar between cases and controls.

In conclusion, BZDR use in general was associated with modestly increased AD risk, with no major differences between BZDR subcategories (i.e. BZD, Z drug, short-/medium-acting or long-acting). Due to frequent use of BZDRs among older people, even small increases in absolute risk may be important on a population level. A dose–response relationship between BZDR use and AD was observed, but adjustment for other psychotropics removed this relationship suggesting that the association was at least partially explained by more frequent use of antidepressants and/or antipsychotics, or reasons for concomitant use of these medications. Even though association between BZDR use and AD was modest in this study, BZDRs should be avoided if possible and threshold for prescribing should be high enough due to overall adverse effect profile of the BZDRs.

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Declaration of Interest

VT, AMT and SH report no competing interests. HT, JT and AT have participated in research projects funded by Janssen and Eli Lilly with grants paid to the institution where they were employed. AT is a member of advisory board of Janssen. JT has served as a consultant to the Finnish Medicines Agency (Fimea) and European Medicines Agency (EMA), has received lecture fees from Eli Lilly, Janssen-Cilag, Lundbeck, and Otsuka; and grants from the Stanley Foundation and Sigrid Jusélius Foundation.

Authors' contributions

AMT, HT, SH and VT planned the study. VT performed statistical analyses, drafted the first version of the manuscript and acts as a guarantor. AT and HT preprocessed and modelled prescription data. All authors contributed to the interpretation of the data, revised the manuscript, and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Combination products including benzodiazepines and related drugs and how they were recoded in this study.

Table S2. Conversion of benzodiazepine and related drug consumption in Defined Daily Doses to standardised doses.

Table S3. Use of benzodiazepine and related drugs at 5 years before the index date.

Table S4. Cumulative consumption and use periods of benzodiazepine and related drugs by dose categories.