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REVIEW

Use of Drugs Affecting $GABA_A$ Receptors and the Risk of Developing Alzheimer's Disease and Dementia: a Meta-Analysis and Literature Review

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Abstract
The gamma-aminobutyric acid (GABA) system is known for its role in cognitive functions and memory processes. However, the activity of $GABA_A$ receptors and their associated pathways influence the accumulation of β-amyloid peptide (Aβ), a key hallmark in the development and prognosis of research examining the relationship between the use of drugs affecting $GABA_A$ receptors and the risk of developing Alzheimer's disease (AD) and dementia. This study aimed to examine the association between GABAA receptor-affecting drugs and the risk of AD and dementia, focusing on benzodiazepines, zolpidem, and anesthetics. This meta-analysis included all English articles on AD, dementia, and $GABA_A$ receptor agonist medications published before May 2024. The articles were identified through searches conducted on PubMed and Scopus databases. The extracted data were analyzed using STATA software (version 14.2). *Q* statistics and the I^2 index were used to evaluate heterogeneity, while Egger's test and funnel plot were utilized to detect publication bias. A total of 19 articles (10 case–control and 9 cohort articles) were eligible for the analysis, involving 2,953,980 patients. The use of GABA agonists was found to have a statistically significant relationship with the development of dementia ($RR = 1.15$, 95% CI: 1.02–1.29, $I^2 = 87.6\%$) and AD ($RR = 1.21$, 95% CI: 1.04–1.40, $I^2 = 97.6\%$). In the drug-based subgroup, we observed that zolpidem consumption was associated with an increased incidence of AD and dementia ($RR = 1.28$, 95% CI: 1.08–1.52, $I^2 = 24.3\%$), similar to the effects of benzodiazepines (BZDs; $RR = 1.11$, 95% CI: 1.04–1.18, $I^2 = 87.2\%$). Meta-regression analysis showed that the duration of follow-up, which ranged from 5 to 11 years across the studies, was significantly associated with heterogeneity ($P = 0.036$). Our findings indicate that the use of zolpidem and BZD is associated with an increased risk of dementia and AD.

Keywords Alzheimer's disease · GABA-A receptor · Prognosis

Introduction

Dementia is a neurodegenerative clinical syndrome characterized by a progressive decline in mental functions, including cognition, memory, and emotional processing. It is a major cause of disability in aging societies [1]. The annual prevalence of dementia is estimated to be approximately 7.5 cases per 1000 people worldwide, and it is expected to double every 20 years in aging populations [2]. The most common cause of dementia is Alzheimer's disease (AD), which is responsible for 60–80% of cases of age-related dementia [3]. AD is a progressive neurodegenerative disorder marked by widespread neuronal dysfunction, resulting in cognitive decline and impairments in learning and memory [4].

The main features of AD pathogenesis involve the accumulation of β-amyloid peptide (Aβ) and abnormal buildup of proteins within neurons, leading to the formation of neurofibrillary tangles consisting of hyperphosphorylated tau proteins [5–7]. These pathological processes cause reduced synaptic strength of neurotransmitters, impairing signaling pathways, causing neurodegeneration, and giving rise to neuronal death [8, 9]. The degeneration of neurofibrillary structures in the basal forebrain ultimately results in

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a widespread loss of cholinergic neuron function, which is necessary for short-term memory and cognitive processes [10].

The GABA system is linked to learning and memory in the human brain. The GABAergic neurons originate from the medial septal nucleus, and the diagonal band of the nucleus extends throughout the hippocampal region, participating in the glutamate pathways of the nervous system [11, 12]. The function of GABAergic neurons, which are distributed in the cortex and hippocampus, is significantly impacted by the pathogenesis of AD and is believed to contribute to memory impairment [13, 14]. Therefore, this system has become a target for understanding the pathophysiology of AD and for developing effective treatments [15]. Recent studies have demonstrated that stimulating the $GABA_A$ receptor neurotransmission and using GABA-mimetic drugs are associated with significant neuroprotection against Aβ aggregation and neurotoxicity [16–18]. These findings suggest that selective pharmacological modulation of $GABA_A$ receptors may provide symptom relief and disease-modifying effects in AD. Moreover, stimulating $GABA_A$ receptors with certain medications could represent a potential treatment for patients with AD [19].

Benzodiazepines (BZDs), like other sedative-hypnotic medications, remain among the most commonly prescribed psychoactive drugs with depressant effects on the central nervous system in older individuals [20]. BZDs act as $GABA_A$ receptor agonists by enhancing GABAergic neurotransmission, increasing the affinity of receptors, and mediating sedative effects [21]. Their adverse events include drowsiness, dizziness, hip fractures, and delirium, as well as an increased risk of falls [22, 23]. Thus, older populations exposed to BZDs may be at a higher risk of drug-induced cognitive disturbances or may exhibit clinical presentations similar to dementia. Research has shown that the use of BZDs is associated with an increased risk of delirium and acute cognitive impairment. Furthermore, the long-term use of these medications may be connected with an increased risk of dementia or gradual cognitive decline [24–29].

Zolpidem, a non-BZD hypnotic agent, functions as an agonist of the $GABA_A$ receptor complex and is commonly prescribed for patients, including older adults, particularly those who suffer from insomnia and sleep disturbances [30]. Although zolpidem is linked to fewer adverse effects compared to BZDs, its use may still pose an increased risk of cognitive and psychomotor decline in older populations, potentially leading to long-term memory loss and a heightened risk of developing probable AD [31].

Surgery and anesthesia have a relationship with postoperative cognitive disturbance and increased risk of developing AD in the future [32]. Anesthesia alone can accelerate the production [33, 34] and aggregation [35, 36] of Aβ by synergistically enhancing Aβ oligomerization, as well as tau protein phosphorylation and aggregation [37]. Volatile anesthetics have been shown to elevate Aβ and phosphorylated tau levels [38–41] and may impact the neurochemical pathways involved in AD [38]. Several studies have indicated that commonly used inhalational anesthetics, such as isoflurane and sevoflurane, can enhance Aβ accumulation and neuroinflammation in cultured cells, neurons, and animal models [33–41]. These studies suggest that using anesthetics during surgery may influence the neurochemical pathways relevant to the pathogenesis of AD. The present systematic review and meta-analysis investigated the association between drugs that affect $GABA_A$ receptors with the likelihood of developing AD and dementia, specifically assessing the effects of three drug groups: BZDs, zolpidem, and anesthetics.

Methods

Search Strategy

A web search was conducted to identify observational studies (cohort, cross-sectional, case–control, and case report) published until May 8, 2024, in the PubMed and Scopus databases. To enhance the accuracy, two authors performed the search independently. The keywords used in the search entailed "Alzheimer Disease," "GABA-A Receptor," "GABA-A Receptor Agonists," "GABA-A Receptor Antagonists," "Benzodiazepines," "Alprazolam," "Chlordiazpoxide," "Medazepam," "Midazolam," "Olanzapin," "Triazolam," "Benzodiazepinones," "Anthramycin," "Bromazepam," "Clonazepam," "Devazepide," "Diazepam," "Flumazenil," "Flunitrazepam," "Flurazepam," "Lorazepam," "Nitrazepam," "Oxazepam," "Pirenzepine," "Prazepam," "Temazepam," "Barbiturates," "Amobarbital," "Hexobarbital," "Mephobarbital," "Methohexital," "Murexide," "Phentobarbital," "Phenobarbital," "Primidone," "Secobarbital," "Thiobarbiturates," "Thiamylal," "Thiopental," "Barbital," "Neurosteroids," "General Anesthetics," "Inhalation Anesthetics," "Intravenous Anesthetics," "Dissociative Anesthetics," "Alfentanil," "Chloralose," "Etomidate," "Fentanyl," "Ketamine," "Propanidid," "Propofol," "Sodium Oxybate," "Sufentanil," "Tiletamine," "Urethane," "2-(3-methoxyphenyl)−2-(ethylamino)cyclohexanone" OR "2-Oxo-PCE," "Muscimol," "THIP," "Thujone," "Picrotoxin," "Bicuculline," "Gabazine" OR "Cicutoxin," "Oenanthotoxin," "Sinomenine," "Thiocolchicoside," "Tutin," "Pitrazepine," "Hydrastine," "Gabamide," "Gaboxadol," "Ibotenic Acid," "Isoguvacine,""Isonipecotic Acid," "Picamilon," "Progabide," "Quisqualamine," "SL 75102," "Thiomuscimol," "Zaleplon," "Z drugs," "zolpidem," "Eszopiclone." The initial selection of eligible studies was based on the titles of articles. To identify relevant publications, the

reference lists of all related reviews (narrative and systematic) were examined.

Study Selection

The review process involved two reviewers who independently evaluated the titles and abstracts of each study and subsequently assessed the full texts of the eligible articles. Any disagreements were resolved through discussion or consultation with the senior investigator.

Inclusion and Exclusion Criteria

The included criteria were (1) studies investigating individuals consuming drugs that affect $GABA_A$ receptors, (2) interventions involving drugs that influence $GABA_A$ receptors, specifically BZDs, zolpidem, and anesthetics, (3) comparisons made either with individuals not using these drugs or those different classes of medications, and (4) studies reporting outcomes related to the risk of developing AD and dementia (Table 1). Non-human research, systematic reviews, meta-analyses, reviews, editorials, case reports, non-English publications, and duplicate studies were excluded from the analysis.

Data Extraction

A standard form in Microsoft Excel Office 2016 was used to extract the data. Two authors independently gathered the relevant data from the eligible studies. The following details were extracted from each study: author, research design, publication year, follow-up duration, sample size, disease, comparator groups, outcome measures, estimates, age, and location.

Quality Assessment

Based on the Ottawa checklist, the Newcastle–Ottawa Scale (NOS) was employed to assess the quality of each study in three areas: selection, comparability, and outcome. According to the NOS score standards, studies were classified into three categories: high (scores of 7 or higher), moderate (scores of 5–6), and low (scores of 0–4) quality studies.

Statistical Analysis

Hazard ratios were utilized to estimate the occurrence of dementia and AD among users of $GABA_A$ antagonists (including BZDs, zolpidem, and anesthetics) compared to a control group. The variance was evaluated using the binomial distribution. Each study was assigned an average weight value to synthesize the results from multiple studies. Q statistics and the I^2 index were employed to evaluate the heterogeneity, with a significance threshold of less than 10%. A random-effect model was applied to heterogeneous studies when the I^2 value exceeded 60%. The Metaprop command in STATA was utilized to ensure variance stability after calculating the Freeman-Tukey Double Arcsine Transformation for pooled proportion estimates. Additionally, the Metaprop command in STATA was used for sensitivity analysis. Data analysis was conducted using STATA version 14.2 software. The Egger's test and funnel plot were employed to identify publication bias graphically. The funnel plot compared the estimated study effect sizes of studies to their sample sizes using a scatter plot with two variables (x and y). Publication bias was assessed through linear regression analysis, including both the intercept and slope parameters.

Results

Study Selection

Following the database search, 1285 studies were identified. After eliminating duplicate records, 779 records remained. Of these, 651 were deemed irrelevant during abstract screening, and 52 were removed before full-text appraisal. After screening 76 full-text records, 19 studies were included, representing research published between 2010 and 2021 (Fig. 1).

Study Characteristics

Ten studies were case–control studies, and nine were cohort studies with follow-up periods ranging from 60 to

Table 1 Study population, intervention, comparison, and outcomes (PICO) criteria

Domain	Criteria selection
Participants	Patients who consume drugs affecting GABA-A receptors
Intervention group	Drugs that affect GABA-A receptors, including benzodiazepines, zolpidem, and anesthetics
Comparison group	Individuals not using drugs that impact GABA-A receptors
Outcomes	Outcomes regarding the risk of developing AD and dementia

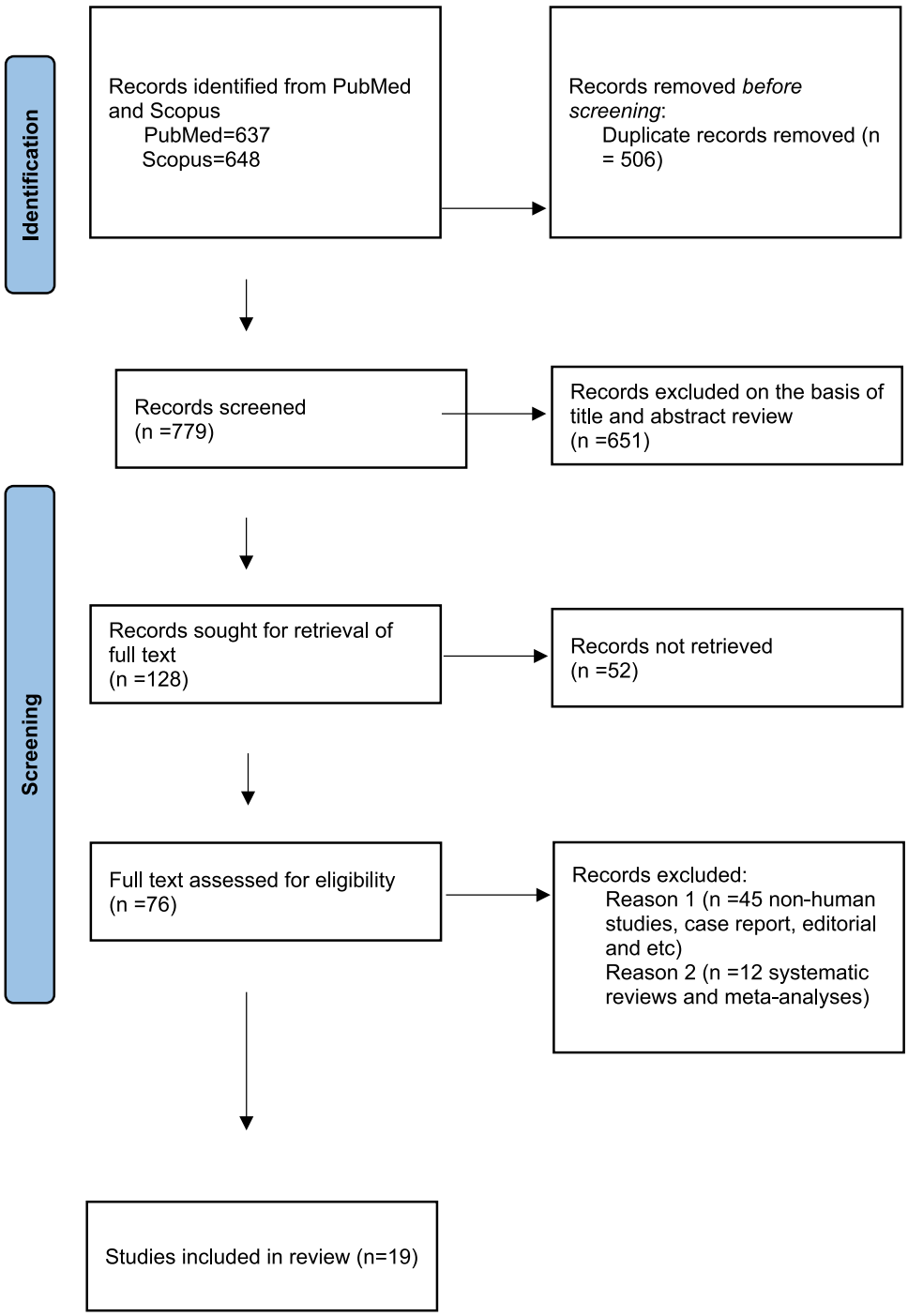


Fig. 1 PRISMA 2020 flow diagram for new systematic reviews, including searches of databases only

188 months. The studies collectively involved a total of 2,953,980 participants. The methodological quality assessment was determined using the NOS criteria. Most of the research studies received high-quality ratings, achieving a final score of six or more. Additionally, the majority of the studies made adjustments for age, sex, comorbidities, socioeconomic variables, and lifestyle factors. Table 2 presents detailed information about the included studies.

Subgroup Based on Disease

Among 19 studies eligible for inclusion in this analysis, seven examined the use of BZD and other medications, such as zolpidem and anesthetics, concerning the risk of developing dementia (*RR* [relative risk] = 1.15, 95% CI: 1.02–1.29, $I^2 = 87.6\%$). The remaining studies specifically focused on the association between the use of BZDs and other drugs and

Table 2 Baseline characteristics of included studies

Study (Ref.)	Country	Study design	Drug	Disease	Follow-up	Sample size	Mean age (SD)	*N* female (%)	Diagnostic criteria	*N* case	*N* control	*N* outcome	*N* no_outcome	HTN (*n*)	DM (*n*)	HR (95% CI)	OR (95% CI)	Main findings
Torres-Bondia et al. 2021 [42]	Spain	Cohort	Benzodiazepines and z-drugs	Dementia	13	167,790	67.86 (14.44)	97,085 (58)	ICD-10	5856	161,934			74,098	30,274	1.01 (0.94–1.08)		The incidence of dementia was not higher among all BZDR users
Joyce et al. 2022 [43]	US	Case–control	Benzodiazepines	AD and related dementias	14	1,750,383	NA	NA	ICD-9-CM, ICD-10-M	437,662	1,312,721			1,567,676	696,686		1.73 (0.968–1.19)	Little evidence regarding a causal relation between BZD use and dementia risk was found
Tournier et al. 2021 [44]	France	Case–control	Benzodiazepines	Dementia	8	3026	82.76 (7.68)	2238	ICD-10	618	2408						Benzodiazepine, short half-life: 1.20 (0.99–1.44) benzodiazepine, long half-life: 1.10 (0.92–1.32)	Exposure to benzodiazepines of short half-life tended to be associated with an increase in the risk of dementia broadly defined
Tournier et al. 2021 [44]	France	Case–control	Benzodiazepines	AD	7.9	1878	82.22 (7.56)	1435	ICD-10	381	1497						Benzodiazepine, short half-life: 2.96 (2.23–3.95) benzodiazepine, long half-life: 2.41 (1.82–3.20)	The risk of AD was strongly associated with benzodiazepines

Table 2 (continued)

Study (Ref.)	Country	Study design	Drug	Disease	Follow-up	Sample size	Mean age (SD)	*N* female (%)	Diagnostic criteria	*N* case	*N* control	*N* outcome	*N* no_outcome	HTN (*n*)	DM (*n*)	HR (95% CI)	OR (95% CI)	Main findings
Chan et al. 2017 [45]	China	Case–control	BZD	Dementia	9.8	273	87 (4)	213 (78)	Diagnostic and statistical manual of mental disorders, 5th edition	91	182			218	85		1.71 (1.02–2.89)	High-dose benzodiazepine use may be associated with dementia in the Chinese population
Shih et al. 2015 [46]	Taiwan	Case–control	Zolpidem	Dementia		25,218		13,329 (53)	ICD-9-CM	8406	16,812			19,071	6762		1.33 (1.24–1.41)	Zolpidem usage might be associated with an increased risk for dementia in older adults
Cheng et al. 2017 [47]	Taiwan	Cohort	Zolpidem	AD	10	6922	72	4351 (63)	ICD-9-CM			75	3386	3970	1450	1.35 (0.85–2.13)		The high cumulative dose of zolpidem was associated with an increased risk of Alzheimer's disease in older adults

Table 2 (continued)

Study (Ref.)	Country	Study design	Drug	Disease	Follow-up	Sample size	Mean age (SD)	*N* female (%)	Diagnostic criteria	*N* case	*N* control	*N* outcome	*N* no_outcome	HTN (*n*)	DM (*n*)	HR (95% CI)	OR (95% CI)	Main findings
Burke et al. 2019 [48]	US	Cohort	Zolpidem	AD	9.28	6782	72 (10)	5516 (81)	An insidious onset of symptoms definitively reported or observed cognitive decline and either amnestic or non-amnestic cognitive deficit manifestation							3.56 (0.71–17.8)		Sleep disturbance was significantly associated with eventual AD development. (zolpidem increased hazard of probable AD)
Lee et al. 2018 [49]	Korea	Cohort	Both	AD	5	268,170	61 (9)	121,507 (45)	ICD-10			27,925	240,245	122,410	52,715	1.75 (1.67–1.82)		The risk of Alzheimer's dementia was elevated when exposed to sedative-hypnotics regardless of the drug
De Gage et al. 2014 [50]	Canada	Case–control	BZD	AD	7.19	8980		6015 (67)	ICD-9 331.0	1796	7184			5663	1635		1.51 (1.36–1.69)	Benzodiazepine use was associated with an increased risk of AD

Table 2 (continued)

Study (Ref.)	Country	Study design	Drug	Disease	Follow-up	Sample size	Mean age (SD)	*N* female (%)	Diagnostic criteria	*N* case	*N* control	*N* outcome	*N* no_outcome	HTN (*n*)	DM (*n*)	HR (95% CI)	OR (95% CI)	Main findings
Gray et al. 2016 [51]	US	Cohort	BZD	Dementia	7.3	3434	74 (3)	2047 (60)	CASI			793	2637	1662	272	1.25 (1.03–1.51)		The risk of dementia was slightly higher in people with minimal exposure to benzodiazepines
Nafti et al. 2019 [52]	Canada	Cohort	BZD	AD	10	5281	75 (7)	3220 (61)	3MS			5015	266	1851	499	0.84 (0.63–1.12)		Benzodiazepine use is not implicated in the pathogenesis of dementia or AD
Tapiainen et al. 2018 [53]	Finland	Case–control	BZD	AD		353,581			NINCDS-ADRDA and DSM-IV	70,719	282,862						1.06 (1.04–1.08)	Benzodiazepine and related drug use were associated with an increased risk of AD
Jeong et al. 2021 [54]	South Korea	Cohort	BZD	AD	11	234,634		128,311 (55)	ICD-10			15,038	219,596	26,525	8466	1.03 (0.98–1.09)		Individuals who used short-acting hypnotics (BDZ) were found to have a higher risk of Alzheimer's disease than non-users

Table 2 (continued)

Study (Ref.)	Country	Study design	Drug	Disease	Follow-up	Sample size	Mean age (SD)	*N* female (%)	Diagnostic criteria	*N* case	*N* control	*N* outcome	*N* no_outcome	HTN (*n*)	DM (*n*)	HR (95% CI)	OR (95% CI)	Main findings
Jeong et al. 2021 [54]	South Korea	Cohort	BZD	AD	11	234,634		128,311 (55)	ICD-10			15,038	219,596	26,525	8466	1.28 (1.09–1.51)		Individuals who used long-acting hypnotics (BDZ) were found to have a higher risk of Alzheimer's disease than non-users
Bie´try et al. 2017 [55]	Switzerland	Case–control	BZD	AD		2876		1850 (64)	Recorded first-time use of acetylcholinesterase inhibitors or the N-methyl-D-aspartate receptor antagonist memantine using anatomic therapeutic chemical classification (ATC) codes N06DA02 for donepezil, N06DA03 for rivastigmine, N06DA04 for galantamine, or N06DX01 for memantine	1438	1438						0.82 (0.70–0.97)	Benzodiazepine use was not associated with an increased risk of developing AD (possible protopathic bias present)

Table 2 (continued)

Study (Ref.)	Country	Study design	Drug	Disease	Follow-up	Sample size	Mean age (SD)	*N* female (%)	Diagnostic criteria	*N* case	*N* control	*N* outcome	*N* no_outcome	HTN (*n*)	DM (*n*)	HR (95% CI)	OR (95% CI)	Main findings
Bié try et al. 2017 [55]	Switzerland	Case–control	Zolpidem	AD		2876		1850 (64)	The same as above	1438	1438						0.99 (0.69–1.42)	Benzodiazepine use was not associated with an increased risk of developing AD (possible protopathic bias present)
Grossi et al. 2019 [56]	UK	Cohort	BZD	Dementia	10	3045	75 (9)	1838 (60)	AGECAT			220	2825			1.06 (0.72–1.60)		Benzodiazepine medications were not associated with dementia
Imfeld et al. 2015 [27]	UK	Case–control	BZD	AD		33,646		23,012 (68)	An algorithm based on recordings of specific dementia tests (e.g. MMSE, CDT, or 7-min screen), referrals to specialists, brain imaging, or dementia symptoms	16,823	16,823			15,733	3496		0.95 (0.90–1.00)	Benzodiazepine use was not associated with an increased risk of developing AD
Aldaz et al. 2020 [57]	Spain	Case–control	BZD	Dementia		77,609	81 (6)	54,372 (70)	ICPC 2	15,212	62,397			37,728	16,628		1.05 (1.01–1.10)	Weak association between benzodiazepine use and the development of dementia

Table 2 (continued)

Study (Ref.)	Country	Study design	Drug	Disease	Follow-up	Sample size	Mean age (SD)	*N* female (%)	Diagnostic criteria	*N* case	*N* control	*N* outcome	*N* no_outcome	HTN (*n*)	DM (*n*)	HR (95% CI)	OR (95% CI)	Main findings
Richardson et al. 2020 [58]	UK	Cohort	BZD	AD		265			GMS-AGECAT diagnostic algorithm			118	147				1.69 (0.75–3.80)	There is no evidence that benzodiazepine drug use was associated with typical pathological features of AD
Zuo et al. 2010 [59]	US	Case–control	Anesthetics	AD		187	60	100 (53)	ICD-9-CM	26	161						1.26 (0.52–3.09)	Anesthesia/surgery may not be independent factors for AD development

AD (*RR* = 1.21, 95% CI: 1.04–1.40, I^2 = 97.6%). Pooling the RR estimates showed a statistically significant association between BZD use and the occurrence of AD or dementia, with substantial heterogeneity observed among the studies (*RR* = 1.19, 95% CI: 1.07–1.31, I^2 = 96.6%; Fig. 2).

Subgroup Based on Drug

This analysis was conducted to determine the effect of three groups of drugs—BZDs, zolpidem, and anesthetics—on users and the associated risk of developing AD and dementia. Only one study was included for anesthetics, which indicated no significant difference between the groups (*RR* = 1.26, 95% CI: 0.52–3.09). A statistically significant association was found between zolpidem use and the risk of developing AD and dementia (*RR* = 1.28, 95% CI: 1.08–1.52, I^2 = 24.3%). Also, the use of BZDs demonstrated a similar association (*RR* = 1.11, 95% CI: 1.04–1.18, I^2 = 87.2%). Furthermore, a single study evaluated cases of concurrent zolpidem or BZD use, revealing a significant risk as well (*RR* = 1.75, 95% CI: 1.67–1.82; Fig. 3).

Subgroup Based on the Continents and Study Design

There was a statistically significant relationship between living in Asia and developing AD and dementia secondary to exposure to GABA-modifying drugs (*RR* = 1.36, 95% CI: 1.07–1.74, I^2 = 97.9%). However, studies from Europe (*RR* = 1.05, 95% CI: 0.98–1.13, I^2 = 84.9%) and America (*RR* = 1.19, 95% CI = 0.96–1.48, I^2 = 82.7%) did not show any significant relationship (Fig. 4).

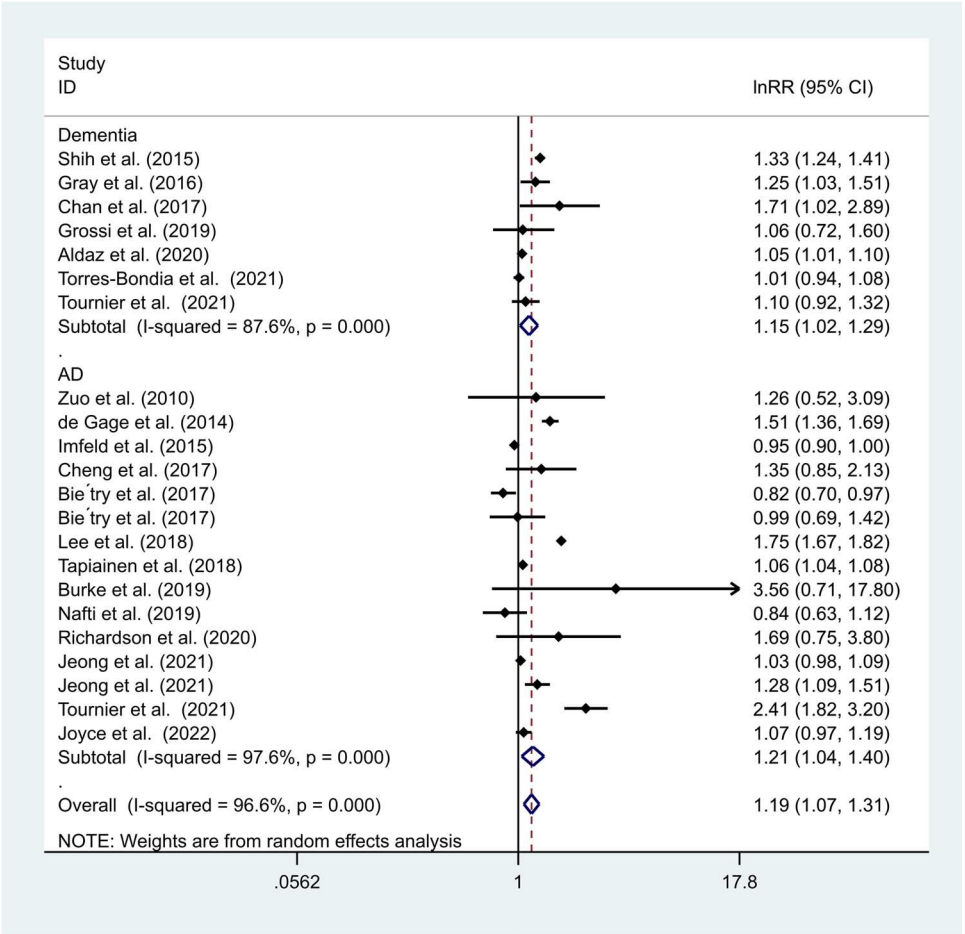


Fig. 2 Forest plot of the RR subgroup analysis based on disease. Each square shows effect estimates of individual studies with their 95% CI. The size of the squares is proportional to the weight of each study in the meta-analysis. This plot shows studies in the order of publication date and first author's names (based on a random effect model)

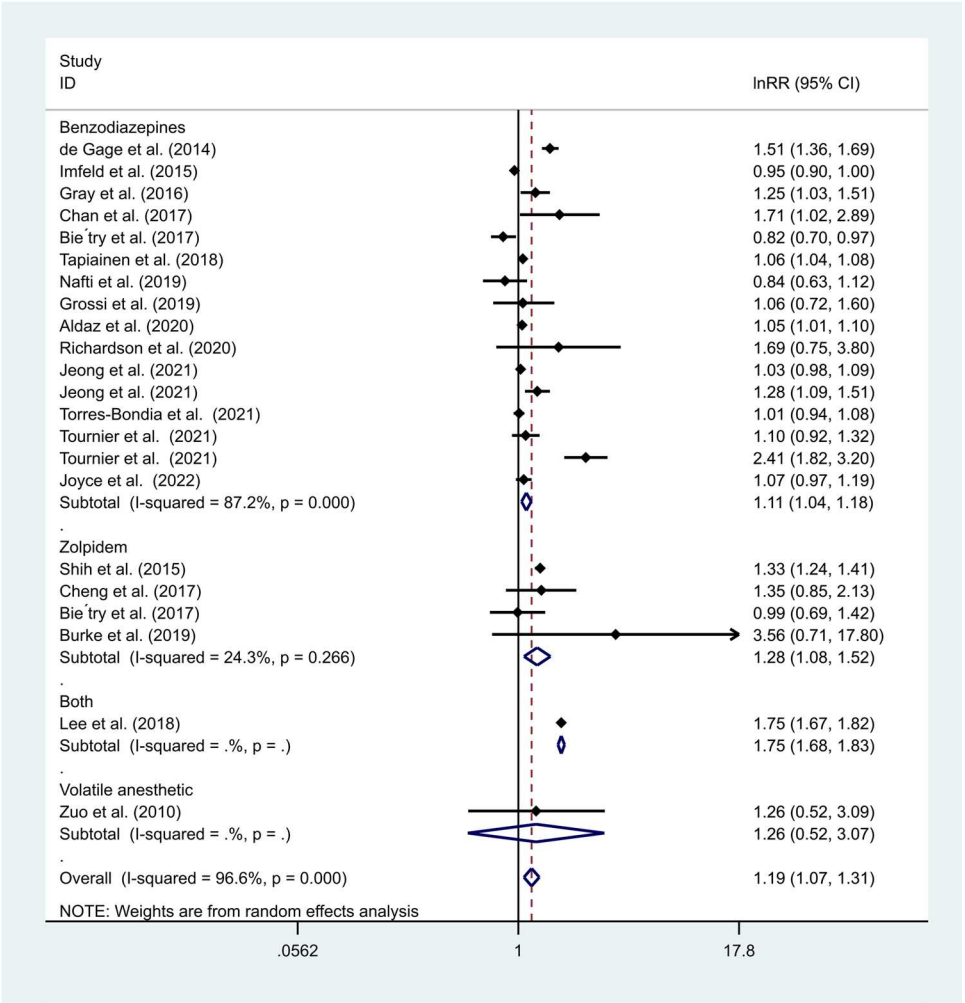


Fig. 3 Forest plot of the RR subgroup analysis based on the drug. Each square shows the effect estimates of individual studies, accompanied by 95% CI. The size of each square is proportional to the weight of each study in the meta-analysis. This plot displays the studies in the order of publication date and name of the first author (based on a random effects model)

Stratifying by study design, statistically significant associations were observed between medication use and AD/dementia in the case–control ($RR = 1.16$, 95% CI: 1.06–1.26, $I^2 = 92.6\%$, $P < 0.01$) but not in the cohort ($RR = 1.22$, 95% CI = 0.97–1.53, $I^2 = 97.2\%$, $P = 0.088$) studies (Fig. 5). Table 3 summarizes all the results of the meta-analysis.

Meta-Regression

Using a univariate meta-regression analysis, we identified variables that may contribute to the heterogeneity observed among studies. The meta-regression analysis revealed that comorbidities, including hypertension, neuropsychiatric diseases, diabetes mellitus, and cardiovascular diseases, did not significantly influence heterogeneity between the studies ($P = 0.673$, $P = 0.444$, $P = 0.676$, and $P = 0.544$, respectively). Similarly, meta-regression analysis based on age did not indicate any statistically significant effect on the heterogeneity of risk estimates for GABA agonist drug use concerning the risk of developing AD or dementia ($P = 0.929$). However, the duration of follow-up, which ranged from 5 to 11 years across the studies, was significantly associated with heterogeneity ($P = 0.036$; Fig. 6).

Sensitivity Analysis

We conducted a comprehensive sensitivity analysis to ensure the robustness and reliability of our meta-analysis results. This process involved systematically omitting each study from the analysis to assess the potential impact on the overall findings. Our results indicated that excluding any single study did not significantly alter the overall effect estimates or the conclusions of the meta-analysis (Fig. 7).

Publication Bias

Figure 8 depicts a funnel plot for studies examining the risk of AD and dementia in users of BZD. According to the results of Egger's test, there was no evidence of publication bias among the included papers ($P = 0.449$). Furthermore,

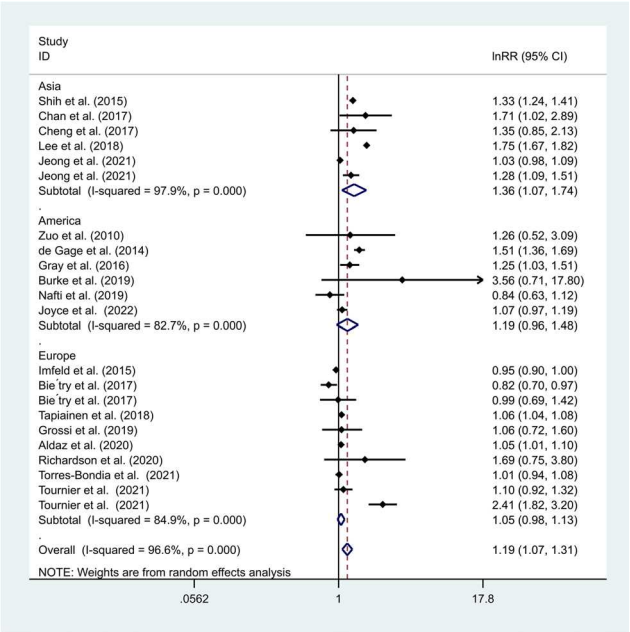


Fig. 4 Forest plot of the RR subgroup analysis based on the continent. Each square shows effect estimates of individual studies with their 95% CI. The size of the squares is proportional to the weight of each study in the meta-analysis. This plot shows studies in the order of publication date and first author's names (based on a random effect model)

this finding demonstrated that both positive and negative results have been published in the literature.

Discussion

GABA, the primary inhibitory neurotransmitter in the central nervous system of vertebrates, activates both ionotropic and metabotropic receptors in adults. $GABA_A$ receptors are ligand-gated, heteropentameric ion channels that respond to this key neurotransmitter in the basal ganglia and facilitate the influx of chloride ions. This process leads to neuronal hyperpolarization and inhibition of neuronal signaling [22]. Research has demonstrated that disruptions in GABAergic transmission contribute to cognitive impairments. Notably, significant reductions in GABA levels have been observed in the brains of individuals with AD, which may underlie some of the psychological and behavioral symptoms associated with severe cases of dementia [60, 61]. Several studies have shown that the pathophysiology of AD is associated with the accumulation of Aβ deposits [62, 63]. It is believed that the long-term use of GABA-mimetic drugs, such as BZDs and anesthetics, may result in a reduced cognitive reserve, decreased GABA receptor activity, and an impaired ability to utilize alternative neural networks due to lower levels of brain activation [52, 54, 64].

Several experiments conducted in both mice and patients with AD have demonstrated that the accumulation of misfolded Aβ disrupts the function of GABAergic interneurons, giving rise to a decline in synaptic communication and neural network activity. This disruption ultimately results in impaired cognitive function [65–68]. Biochemical research has shown that GABA neurotransmitter levels in the cerebrospinal fluid and temporal cortex of individuals with AD are significantly reduced, indicating that synaptic activity and neuronal transmission are compromised [69–72]. Moreover, in mice with AD, stimulating $GABA_A$ receptors with baicalein (a positive allosteric modulator of the BZD site of the $GABA_A$ receptors) for 8 weeks resulted in a substantial decrease in Aβ production, noticeable improvements in cognitive function, and a reduction in pathological characteristics [73]. Considering all these findings, targeting $GABA_A$ receptors appears to hold promise as a potential therapeutic approach for the treatment of AD [74].

In this study, we collated data from available literature on the RR of AD for users of three groups of GABA mimetic drugs: BZD, zolpidem, and anesthetics. We conducted meta-analyses to calculate pooled estimates based on the existing evidence. Although some studies have shown a weak association between BZD use and dementia [75], previous research indicates that individuals who use BDZ are at a higher risk of developing AD compared to non-users [54]. Several studies have also provided evidence of a significant association between a high cumulative dose of zolpidem and an increased risk of AD [47, 48]. Our analyses exhibit that the RR of developing AD for zolpidem users is 28% greater than that of non-users. This observation suggests that zolpidem, as a non-BZD sedative, may be associated with an increased risk of eventual AD development, especially among the elderly population [76]. A study by Zuo et al. found that anesthetics and surgeries performed under general anesthesia may not be independent risk factors for AD [59]. Given that AD is one of the major causes of disability in aging societies, the use of GABA-mimetic drugs presents a significant concern for this demographic.

The studies included in our meta-analysis demonstrated a 21% increased risk of dementia among BZD users [45, 76], providing evidence of a significant effect of BZDs on the progressive decline of cognitive function. Furthermore, we found that this risk was similarly elevated when focusing specifically on examining between BZD and AD, the most prevalent cause of dementia [48, 77]. Similarly, Zhong et al. conducted a meta-analysis to quantify the association between BZD use and the risk of dementia. They found that the pooled adjusted RRs for dementia in individuals who

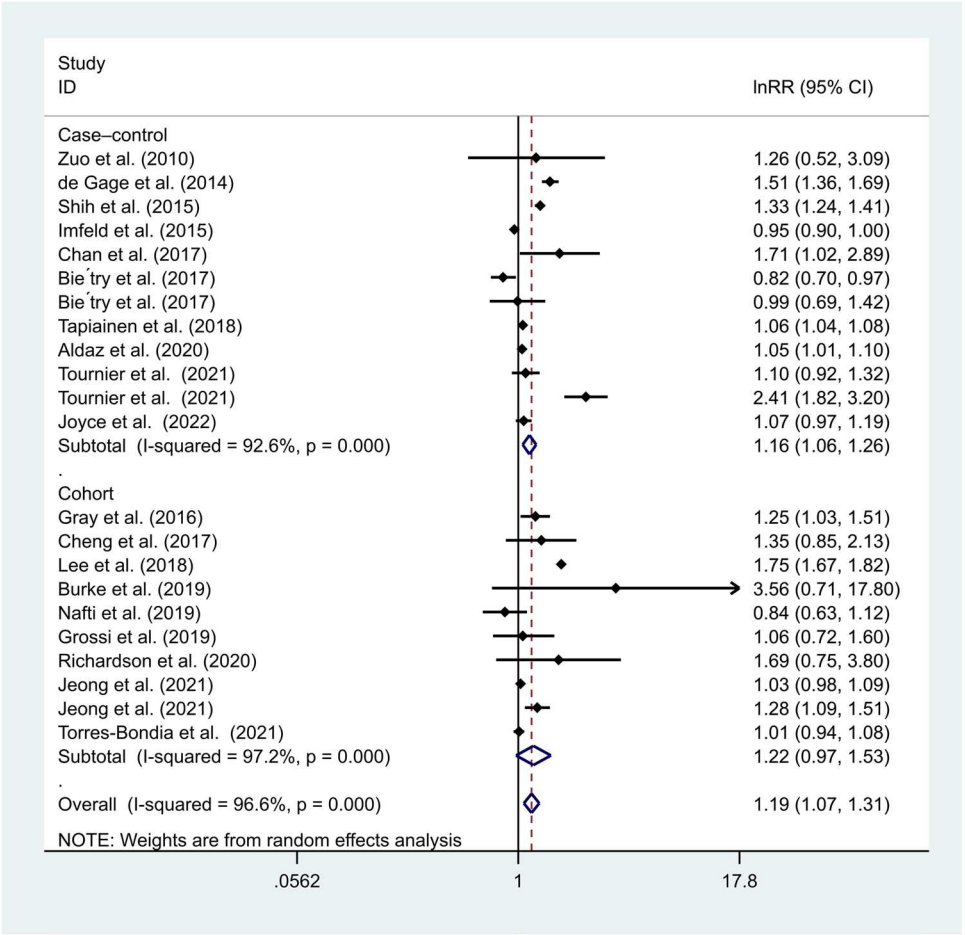


Fig. 5 Forest plot of the RR subgroup analysis is based on the study design. Each square shows the effect estimates of individual studies with their 95% CI. The size of the squares is proportional to the weight of each study in the meta-analysis. This plot indicates studies in the order of publication date and first author's names (based on a random effect model)

had used these drugs in the past, recently, or at any time, compared to those who had never used them, were 1.55 (95% CI: 1.17–2.03), 1.55 (95% CI: 1.31–1.83), and 1.49 (95% CI: 1.30–1.72), respectively. They noted that the risk of developing dementia increased by 22% for every additional 20 defined daily doses taken annually ($RR = 1.22$; 95% CI: 1.18–1.25) compared to individuals who do not take these drugs [29]. Likewise, AlDawsari et al. conducted a meta-analysis to explore the association between the use of sedative-hypnotic medications and the risk of dementia and found an increased risk of dementia associated with the use of BZDs; however, they highlighted that their findings might have been confounded by indication and protopathic bias [78]. Another meta-analysis conducted by Islam et al. disclosed that individuals who used BZDs had 78% higher odds of developing dementia compared to those who did not use these medications ($OR = 1.78$; 95% CI: 1.33–2.38). The authors also highlighted that observational studies from Asia showed a stronger association ($OR = 2.40$; 95% CI: 1.66–3.47), while studies from North America and Europe indicated a moderate association ($OR = 1.49$; 95% CI: 1.34–1.65 and $OR = 1.43$; 95% CI: 1.16–1.75) [79]. Moreover, our analysis revealed that the continent where the studies were conducted significantly influenced the risk of AD among GABA-mimetic users. The studies included in our analysis investigated three continents: Asia, Europe, and America. Notably, although residing in either Europe or America and being exposed to GABA-mimetic agents did not significantly impact the development of AD, there was a substantial relationship between living in Asia, exposure to GABA-mimetic agents, and an increased risk of dementia.

The study design appears to be a crucial factor. Cohort studies have explored that GABA-mimetic drugs are not associated with an increased risk of AD, despite their significant impact on AD risk in certain case–control study designs. The use of GABA-mimetic drugs, such as BZDs and zolpidem, in the region where individuals reside is associated with an increased risk of AD and dementia. The risk of developing AD is significantly higher in GABA-mimetic agents compared to non-users, and it is notably higher for individuals in Asia than for those in Europe or America. We also conducted meta-regression analyses

Table 3 Results of meta-analysis

Data	Variable	Number of studies	Sub-group	ES	I^2 (%)	*P*-value
Demographic data	Mean age (SD)	6	Dementia	77.89 (6.91)		
		6	AD	70.27 (8.44)		
	% Female [95% CI]	7	Dementia	64.71 [58.55–70.63]	99.87	
		11	AD	63.55 [57.36–69.53]	99.98	
Risk factors	% HTN [95% CI]	4	Dementia	59.70 [48.55–70.37]	99.96	
		7	AD	44.38 [13.60–77.82]	100	
	% DM [95% CI]	4	Dementia	19.91 [16.29–23.79]	99.75	
		7	AD	14.11 [3.75–29.60]	100	
Relative risk [95% CI]						
Based on drug		14	BZD	1.11 [0.04–1.18]	87.2	< 0.001
		4	Zolpidem	1.28 [1.08–1.52]	24.3	0.005
		1	Both	1.75 [1.67–1.82]		
		1	Anesthetics	1.26 [0.52–3.09]		
Based on disease		7	Dementia	1.15 [1.03–1.29]	87.6	0.018
		13	AD	1.21 [1.05–1.40]	97.6	0.011
Based on continent		5	Asia	1.36 [1.07–1.74]	97.9	0.013
		6	America	1.19 [0.96–1.48]	82.7	0.109
		8	Europe	1.05 [0.98–1.13]	89.9	0.178
Based on the study design		10	Case–control	1.16 [1.06–1.26]	92.6	< 0.001
		9	Cohort	1.22 [0.97–1.53]	97.2	0.008
Overall		19		1.19 [1.07–1.31]	96.6	< 0.001

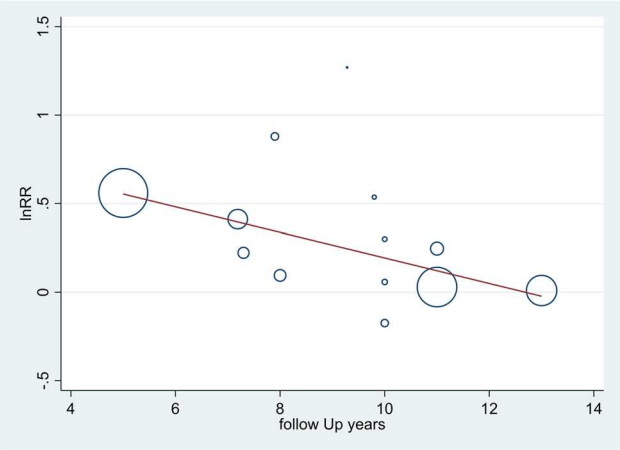
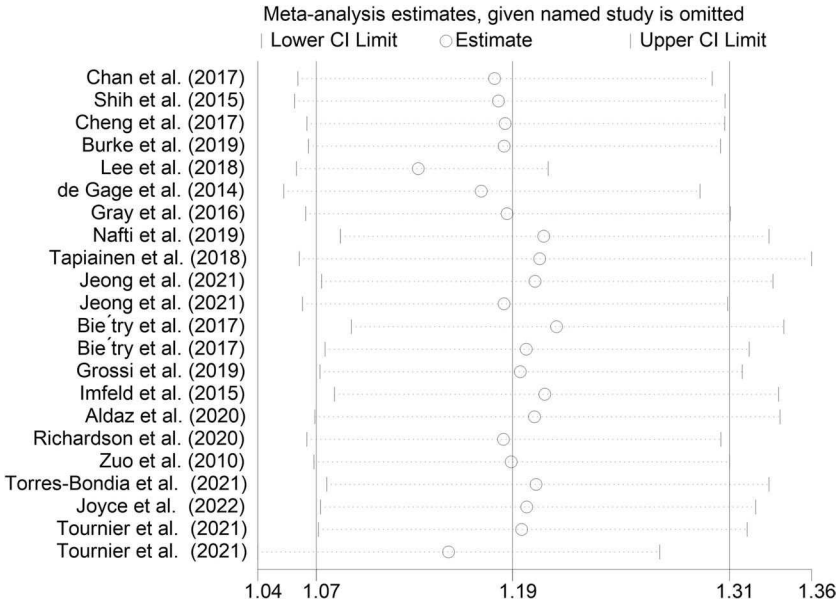


Fig. 6 Meta-regression analysis of lnRR with years of follow-up

focusing on comorbidities, including hypertension, neuropsychiatric disease, diabetes mellitus, and cardiovascular disease. Despite being a risk factor for morbidity and mortality, especially in aging populations, these comorbidities did not significantly impact the observed associations between GABA agonist use and the development of AD or dementia. Furthermore, the meta-regression analysis based on the age and gender of the individuals did not appear to influence the estimated risk of GABA agonist use concerning the development of AD and dementia.

As we discussed earlier, several studies have demonstrated that despite the protective role of the GABAergic system against AD, prolonged use of GABA agonists, such as BZDs, can increase the risk of dementia or progressive mental decline, particularly in older adults. Microglia may serve as a potential mechanism responsible for the cognitive impairments associated with BZDs. BZDs can bind to the translocator proteins on the surface of microglial cell organelles, thereby activating these brain immune cells. This activation can lead to degradation recycling, resulting in progressive cognitive decline among long-term users of GABA-mimetic drugs [80].

Our study has several limitations, including the language of publication, limited data availability in the studies we included, and heterogeneity among the studies. Likewise, we were unable to consider factors related to exposure intensity, such as medication dosage or duration. Despite these limitations, we conducted a meta-analysis that combined results from multiple studies and settings to produce meaningful findings.



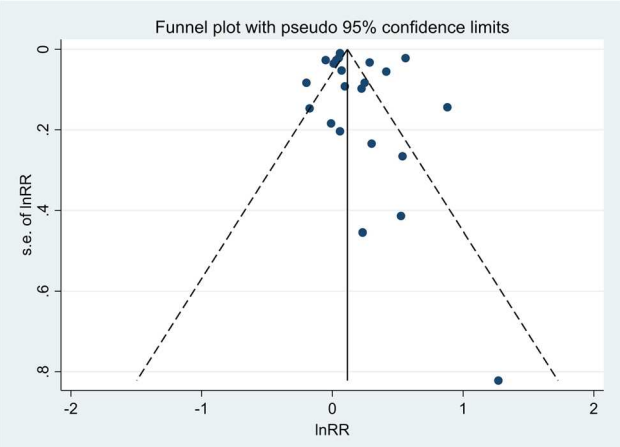


Fig. 7 Sensitivity analysis

Fig. 8 Funnel plot for publication bias

Conclusions

Notwithstanding the variability of the findings of the included studies, the use of BZDs and zolpidem has been associated with an increased risk of AD and dementia. Given that these two classes of medications are commonly prescribed, especially to middle-aged individuals who are at a heightened risk for AD and dementia, these findings may offer valuable insights into the prevention and treatment of dementia. The results of our meta-analysis suggest a need for caution when prescribing these medications, especially for long-term use. Clinicians should weigh these risks carefully when considering treatment options for patients, particularly those who are predisposed to cognitive decline. Furthermore, the study underscores the importance of monitoring cognitive health in patients taking these drugs. However, prospective cohort studies with larger sample sizes and extended follow-up periods are necessary to determine whether this relationship is accurate or influenced by methodological biases or reverse causation. Additionally, randomized controlled trials with substantial sample sizes and prolonged follow-up durations should be conducted, focusing specifically on the impact of BZD usage on the likelihood of developing dementia, to either support or challenge the findings of our meta-analysis.

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Author Contributions The study was conceived and designed by F.S., K.E. and K.V.. S.A. and M.K., performed the literature search and identified the relevant studies. A.Z., A.D., and H.Gh. assessed the included studies' quality and risk of bias. S.N. and M.J. prepared the tables and figures to present the results. A.Z., A.E., K.E., and A.S. drafted the manuscript and wrote the scientific content. RE updated the search and data extraction sheet, and revised the manuscript. MM, MJE, and AT reviewed and critically revised the draft. K.V. supervised the study and provided guidance and feedback. All other authors reviewed and approved the final version of the manuscript.

Data Availability The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author at reasonable request.

Declarations

Ethics Approval The current study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (ethical code: IR.SBMU.RETECH.REC.1400.3260).

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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