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Original Research

Relationships of Hypnotics with Incident Dementia and Alzheimer's Disease: A Longitudinal Study and Meta-Analysis

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1. Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China; 2. Jining Medical University, Jining, China; # The cohort data used in preparation for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Abstract

BACKGROUND: Evidence describing the association between hypnotics use and dementia risk is conflicting. It is unknown if the controversy is related to the type or dose of hypnotics or if hypnotics affect different populations.

OBJECTIVES: We sought to derive lessons learned and future projections based on evidence from longitudinal studies.

MEASUREMENTS: In the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, 1,543 older adults without dementia (mean age = 73.3 years, female = 45%) were followed for four years. The association between hypnotics and the risk of Alzheimer's disease (AD) was investigated using Cox proportional hazards regressions. Next, electronic databases were searched until March 2022 to conduct the evidence synthesis of the associations of hypnotics with incident risk of dementia.

RESULTS: In the ADNI cohort, ever use of hypnotics was associated with an increased risk of AD (hazard ratio = 1.96, 95% confidence intervals = 1.23-3.11, $p < 0.01$). This association was significant for benzodiazepines and Z-drugs but not for melatonin. The association was stronger in long-term (more than one year) users and those with high cumulative doses. A meta-analysis of 26 longitudinal studies with 3,942,018 participants revealed a correlation between the use of hypnotics and the risk of dementia (relative risk = 1.23, 95% confidence intervals = 1.13-1.33, $p < 0.001$, median risk difference = 4%). It is a linear dose-response relationship, if a person takes the daily recommended dose for 100 days, their risk of developing dementia increases by 5% relative to non-users. According to subgroup analyses, neither association was significant among patients with a history of insomnia.

CONCLUSIONS: Individuals who use hypnotics, especially high-dose or long-term users, are at a higher risk of dementia and AD. The main issue with conclusion credibility is heterogeneity.

Key words: Hypnotics, Alzheimer's disease, dementia, longitudinal, meta-analysis.

Abbreviations: AD: Alzheimer's disease; ACD: all-cause dementia; ADNI: Alzheimer's Disease Neuroimaging Initiative; Aβ: Amyloid β; BZDs: Benzodiazepines; BMI: Body mass index; CI: Confidence interval; CNS: Central nervous system; DDD: defined daily dose; CDDD: Cumulative defined daily dose; CBT: Cognitive behavioral therapy; GABA: Gamma-aminobutyric acid; HR: Hazard ratio; MCI: Mild cognitive impairment; NOS: Newcastle-Ottawa Quality Assessment Scale; NC: Normal cognition; OR: Odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines; PI: Prediction interval; RR: Relative risk; VD: vascular dementia.

Introduction

According to estimates, the number of people with dementia worldwide will rise from 57.4 million in 2019 to 152.8 million in 2050 (1, 2). Dementia lowers patients' quality of life and burdens society and families significantly. Early prevention is crucial because there are no effective treatments available. Our previous research has shown that insomnia is detrimentally associated with dementia and its pathological marker (3, 4). Therefore, clinicians frequently use hypnotics, such as benzodiazepines (BZDs), to improve sleep quality. Additionally, BZDs and other hypnotics are used to treat depression, anxiety, agitation, seizures, muscle spasms, and premedication for anesthesia (5, 6). Around 9–12% of older adults have used hypnotics to treat various sleep or mood disorders (7). Interestingly, epidemiological evidence showed that there was still much controversy as to whether hypnotics were associated with a higher risk of dementia (8, 9). The debate may be attributable to differences in the definition of hypnotics, reasons for hypnotic prescription, and accompanying conditions (such as insomnia or depression) of the studied population. For instance, some studies found that BZDs or Z-drugs were associated with an increased risk of cognitive impairment or dementia (10). In contrast, others found no causal association (11) and found that long-term Z-drug users had a lower incidence of dementia (12). As both sleep and hypnotics are research hotspots (13), researchers have paid increased attention to i) whether the associations between hypnotics and dementia risk vary with the type or dosage

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of hypnotics; ii) whether, given the close relationship between insomnia and dementia (4), hypnotics are also associated with a higher risk of dementia among insomnia patients; and iii) the limitations of the current evidence and what can be anticipated from future research.

As a result, we followed a three-step procedure. First, the role of hypnotics in predicting Alzheimer's disease (AD) was analyzed in an independent, multi-center cohort of participants grouped by hypnotic exposure and population characteristics. The strength of the evidence was then assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) principle in a thorough meta-analysis. Finally, a dose-response analysis was conducted to illuminate the causal relationship.

Methods

Alzheimer's Disease Neuroimaging Initiative cohort

Participants

Data used in this study were obtained from participants in the ADNI cohort (www.adni-info.org.), designed to develop biochemical, genetic, imaging, and clinical biomarkers for the early detection and tracking of AD. ADNI is a large, multicenter, longitudinal neuroimaging study initiated in 2004 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations. Participants aged 55-90 were recruited from 59 United States and Canada sites. The studied population herein were non-demented participants at baseline. Participants underwent standardized neuropsychological assessments, in-person interviews for detailed medical history, and cognitive evaluation at study entry and follow-up. The study was approved by the institutional review boards at all participating centers, and written informed consent was obtained from every participant (14).

Use of Hypnotics

Information on hypnotics at baseline was collected based on the medication log file and self-reports during the initial clinical interview. In the present study, hypnotics comprised three main types: BZDs, Z-drugs, and melatonin. Exposure duration is the cumulative time from the first dose to the last follow-up. Hypnotic users were firstly categorically classified as i) ever users: who had at least one record of hypnotic use, ii) past users: who had ended the use before the index date, and iii) current users: who had hypnotic use reported at the index date. Next, the defined daily dose (DDD), recommended by the World Health Organization, is the assumed average maintenance dose per day of a drug, and the daily dose of each type of hypnotic was based on the international standard DDD (anatomical therapeutic chemical / DDD Index 2020. http://www.whocc.no/atc_ddd_index/). Cumulative defined daily dose (CDDD), the sum of DDDs of any hypnotics, serves as the index of the cumulative dosage of the hypnotics. CDDD were calculated using the following formula: the sum of (frequency × sub-dose × drug duration) / (DDD of the drug). The cutoff of half-life time was according to the definition proposed by the French National Agency for Drug Safety; hypnotics with half-life >20 hours belong to long-acting hypnotics or otherwise short-acting hypnotics.

AD diagnosis

AD dementia was diagnosed based on the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria (15). The neurologist made the diagnosis according to brain structure scans, cognitive score, and independent living ability.

Covariate measurements

The covariates included in the basic models were age, gender, years of education (continuous variable), cognitive status (mild cognitive impairment [MCI] versus normal cognition [NC]), and APOE ε4 status. rs7412 and rs429358 were genotyped separately by an APOE ε4 genotyping kit to define the APOE ε2/ ε3/ ε4 isoforms (16). Furthermore, other confounders were confirmed by screening the medical history, including hyperlipidemia (yes or no), hypertension (yes or no), diabetes (yes or no), stroke history (yes or no), insomnia (yes or no), depression (yes or no), anxiety (yes or no), and current smoking status (yes or no). Obesity was defined as body mass index (BMI) $\geq 28\ kg/m^2$.

Meta-analysis

Search Strategy and selection criteria

Our meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines (PRISMA) statement (17). A review protocol was registered in the PROSPERO database (registration number: CRD42020220841). A literature search was carried out in PubMed, Cochrane, Web of Science, and EMBASE to obtain longitudinal studies (updated till March 2022), using the following search terms: Alzheimer, Alzheimer's disease, dementia, and hypnotics (for the detailed search terms see Supplementary File). To avoid

omission, we also searched published systematic reviews and bibliographies of relevant original studies.

Studies were included if they simultaneously met the following criteria: i) the study explored the association between hypnotic use and the risk of dementia; ii) the study was a population-based longitudinal cohort; iii) the study provided risk estimates or the available data that could be used to calculate risk estimates; iiii) participants were adults without dementia at baseline. There were no restrictions on language. If the same cohort was repeatedly reported, we included the study with the most extended follow-up or largest sample size. Two independent reviewers (H-JH and T-CC) performed the literature search and screening. Any discrepancy was resolved by discussion with the third reviewer (XW).

Data extraction

Two experienced investigators (H-JH and T-CC) independently extracted data using pre-designed templates, including general items (first author, publication year, cohort name, and country), study design, sample source, participation rate at baseline (generalizability), mean age, female percentage, baseline cognitive status, sample size, incident cases, type and measurement of hypnotics, outcome, diagnostic criteria, follow-up duration, attrition rate, adjusted confounders, and the multivariable-adjusted risk estimates. Any disagreement was addressed by negotiation with the third reviewer (XW).

Grading study quality, meta-analysis credibility, and strength of recommendations

A revised version of the Newcastle-Ottawa Quality Assessment Scale (NOS) developed by Xu et al. (3, 18) was used to assess the quality of eligible studies. NOS consists of eight items with a maximum score of nine. Scores for these items evaluated the risk of bias in three domains: sample selection, confounding bias, and outcome (Appendix 1). The total score of NOS was considered an indicator of the overall risk of bias for every study. Studies with high, moderate, and low quality were defined as having a total score of ≥ 7, 4 to 7, and ≤ 4, respectively. The credibility of the meta-analysis was assessed according to GRADE criteria, including five domains: inconsistency, publication bias, imprecision, risk of bias, and indirectness (https://gdt.gradepro.org/) (Appendix 2). Two experienced investigators (H-JH and T-CC) independently performed the above assessments.

Statistical analyses

In the ADNI cohort, inter-group differences were tested using chi-square and non-parametric analyses. We tested the proportional hazards assumption, the cumulative incidence curve for each cohort was measured using the Kaplan–Meier method, the curve difference was calculated using the log-rank test (Appendix 3), and the time-dependent Cox proportional hazards regression models were used to assess whether baseline hypnotic use increased the risk of incident AD. Individuals who were lost to follow-up were censored during their last evaluation. Risk estimates were expressed as hazard ratios (HR) and 95% confidence intervals (CI). Three models were employed: 1) model 1: a model without adjustment for covariates; 2) model 2: a model adjusted for age, gender, years of education, APOE ε4 status, and cognitive status; 3) model 3: a model adjusted for those covariates in model 2 plus additional covariates, including diabetes mellitus type 2, depression, anxiety, obesity, hypertension, hyperlipidemia, insomnia history, stroke history, and current smoking status. Stratified analyses were performed according to type and dosage of hypnotics, gender, age (< 65 years: middle-age; ≥ 65: old-age), and history of insomnia, depression, or anxiety. In order to reduce protopathic bias due to the inclusion of those in the prodromal stage of AD, sensitivity analyses were performed by excluding those who progressed to AD within one year of follow-up (1-year lag time). And we also did a nested case-control study based on this cohort. The R program performed the Propensity score matching process; Briefly, for each hypnotic user, we randomly selected four comparison subjects who did not use hypnotics and were matched with hypnotic users by age, gender, years of education, and APOE ε4 status. The "survival," "survminer," "ggpubr," "ggplot2," "survival", and "magrittr" packages in R version 3.4.3 software were used to conduct the above analyses.

In meta-analyses, the effect estimates and 95% CIs were log-transformed and pooled by random models (DerSimonian-Laird method) (19). Some studies reported odds ratios (OR) but not relative risks (20) or HRs. Given that ORs tend to over-estimate the effect sizes compared to RRs/HRs, especially when the incidence is high, we used the following algorithm to transform OR into RR (21): RR adjusted = OR adjusted / [(1 - P0) + (P0 × OR adjusted]. P0 indicates the incidence of endpoint in the non-exposed group of cohorts. When P0 is not available, the incidence rate of the total sample was used as a proxy (21). A 95% prediction interval (PI) was calculated better to evaluate the result's precision (22). Risk difference (RD) was also calculated to aid the clinical decision better.

The I2 metric quantified the heterogeneity. The source of heterogeneity was explored via subgroup analyses, sensitivity analyses, and meta-regression (if the number of studies ≥ 10). Subgroup analyses were performed according to type, dosage, and half-life of hypnotics, hypnotic use status, outcome, NOS quality score, sample size, follow-up duration, region, study design, the presence or absence of insomnia, type of effect estimates and whether the confounders (insomnia, anxiety, and depression) were adjusted. Sensitivity analyses excluded studies with a higher risk of bias

Table 1. Characteristics of hypnotic users compared with nonusers in the ADNI cohort

Characteristics	Hypnotics users	Nonusers	P-value
Number	94	1,449	
Follow-up duration (mean years)	1.92 ± 1.00	2.81 ± 1.24	< 0.01
Age (mean years)	72.83 ± 7.30	73.32 ± 7.06	0.56
Female (n, %)	55 (68.51%)	642 (44.31%)	0.01
Education level (mean years)	16.59 ± 2.86	16.13 ± 2.74	0.09
APOE ε4 carriers (n, %)	40 (42.55%)	622 (42.93%)	0.94
Insomnia (n, %)	30 (31.91%)	80 (5.52%)	< 0.01
Depression (n, %)	34 (36.17%)	277 (19.12%)	< 0.01
Anxiety (n, %)	17 (18.09%)	82 (5.66%)	< 0.01
Diabetes mellitus type 2 (n, %)	5 (5.32%)	123 (8.49%)	0.31
Hypertension (n, %)	43 (45.74%)	650 (44.86%)	0.67
Hyperlipidemia (n, %)	51 (54.26%)	680 (46.93%)	0.09
Stroke history (n, %)	3 (3.19%)	53 (3.66%)	0.85
Smoking status (n, %)	14 (14.89%)	217 (14.98%)	0.92
Obesity (n, %)	24 (25.43%)	517 (35.68%)	0.07

and additionally included the ADNI cohort study to examine the robustness of the results. Publication bias was assessed as follows: (1) Egger method was carried out to test the symmetry of the funnel plot. (2) After the trim-fill method, the contour-enhanced funnel plot was used to determine if any asymmetry was due to publication bias.

The dose-response relationship between CDDD of hypnotics and dementia risk was examined by Robust Error Integrated-Regression Model (23, 24). We defined the average level of the midpoint of the upper and lower boundaries in CDDD of hypnotics. We multiplied or divided the reported boundary by 1.25 for studies with an open-ended boundary. The "metagen", "metabias", and "trimfill" packages in R 3.4.3 software and Stata version 12.0 (StataCorp LP, College Station, Texas, USA) were used to conduct all the above analyses.

Results

ADNI cohort

Baseline characteristics of the study population in the ADNI cohort

A total of 1,543 non-demented participants (mean age = 73.3 years, female proportion = 45%) were followed up for four years (mean = 2.75 years), among whom 94 participants (6%) had at least one record of hypnotic use (30 non-insomniacs used hypnotics to treat anxiety or depression), and 323 participants (21%) developed AD. Follow-up duration, female proportion, and medical history (insomnia, depression, and anxiety) showed significant inter-group differences, whereas no significant differences in age, years of education, APOE ε4 status, lifestyle, and vascular risk factors were identified between hypnotic users and non-users (Table 1).

Association between the Use of Hypnotics and AD Risk

In model 1, the use of any category of hypnotics included in our study was significantly associated with a higher risk of developing AD (HR = 1.70, 95% CI = 1.09-2.66, p = 0.02). The significance remained unchanged in models 2 and 3 (Table 2). Stratified analyses according to type and half-life of hypnotics showed that the association remained significant in BZDs, Z-drugs, and short-acting hypnotics (BZDs: HR = 1.88, 95% CI = 1.03–3.44, p = 0.04; Z-drugs: HR = 3.05, 95% CI = 1.24–7.52, p = 0.02; short-acting hypnotics: HR = 1.91, 95% CI = 1.18–3.09, p < 0.01) rather than melatonin or long-acting hypnotics. Moreover, the association of hypnotics with dementia risk was dose-dependent, and it was more significant in long-term users (1-5 years duration: HR = 1.97, 95% CI = 1.03–3.74, p = 0.04; ≥ 5 years exposure duration: HR = 2.26, 95% CI = 1.10–4.66, p = 0.03) and in those with increased dosage of hypnotics (≥ 365 CDDD: HR = 3.30, 95% CI = 1.73–6.30, p < 0.01). Subgroup analyses according to study characteristics showed that the association was significant in past users (HR = 3.44, 95% CI = 1.67–7.07, p < 0.01), older people (HR = 2.14, 95% CI = 1.33–3.43, p < 0.01), females (HR = 2.43, 95% CI = 1.32–4.46, p < 0.01), and individuals without insomnia (HR = 1.86, 95% CI = 1.12–3.08, p = 0.02) or anxiety (HR = 2.18, 95% CI = 1.33–3.57, p < 0.01) history. We performed two sensitivity analyses to explore the robustness of our results. First, A sensitivity analysis excluding participants who progressed to AD in the first

Table 2. Hazard ratios with corresponding 95% confidence intervals for the association of the use of hypnotics and AD in the whole cohort

Exposure	n / N	Model 1		Model 2		Model 3	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Any type*	94/1449	1.70 (1.09, 2.66)	0.02	1.64 (1.05, 2.58)	0.03	1.96 (1.23, 3.11)	<0.01
Hypnotics type*							
BZDs	55/1449	1.51 (0.84, 2.69)	0.17	1.57 (0.88, 2.81)	0.12	1.88 (1.03, 3.44)	0.04
Z-drugs	19/1449	2.22 (0.91, 5.38)	0.08	2.45 (1.00, 6.01)	0.05	3.05 (1.24, 7.52)	0.02
Melatonin	26/1449	1.51 (0.56, 4.06)	0.42	1.13 (0.42, 3.04)	0.82	1.33 (0.49, 3.61)	0.58
Half-time*							
Long-acting hypnotics	6/1449	2.14 (0.53, 8.60)	0.28	1.85 (0.46, 7.53)	0.39	2.64 (0.63, 11.00)	0.18
Short-acting hypnotics	88/1449	1.66 (1.04, 2.65)	0.03	1.62 (1.01, 2.60)	0.04	1.91 (1.18, 3.09)	<0.01
Use status							
Current use	65/1449	1.45 (0.83, 2.53)	0.19	1.25 (0.71, 2.20)	0.43	1.54 (0.87, 2.74)	0.14
Past use	29/1449	2.37 (1.17, 4.79)	0.02	3.31 (1.63, 6.75)	<0.01	3.44 (1.67, 7.07)	<0.01
Exposure duration*							
<1 year	27/1449	1.01 (0.32, 3.15)	0.99	1.22 (0.39, 3.85)	0.73	1.43 (0.45, 4.52)	0.55
1-5 years	35/1449	1.88 (1.00, 3.54)	0.05	1.68 (0.90, 3.18)	0.11	1.97 (1.03, 3.74)	0.04
≥5 years	32/1449	1.96 (0.97, 3.97)	0.06	1.81 (0.89, 3.68)	0.10	2.26 (1.10, 4.66)	0.03
CDDD*							
<365 CDDD	21/1449	1.66 (0.68, 4.02)	0.26	1.50 (0.62, 3.66)	0.37	1.44 (0.58, 3.54)	0.43
≥365 CDDD	31/1449	2.80 (1.48, 5.27)	<0.01	2.82 (1.49, 5.35)	<0.01	3.30 (1.73, 6.30)	<0.01
Insomnia history*							
With	30/80	2.31 (0.64, 8.26)	0.20	2.02 (0.54, 7.58)	0.38	2.66 (0.44, 16.19)	0.29
Without	60/1350	2.07 (1.26, 3.38)	<0.01	1.89 (1.15, 3.11)	0.01	1.86 (1.12, 3.08)	0.02
Depression history*							
With	34/277	1.65 (0.87, 3.13)	0.12	2.05 (1.08, 3.91)	0.03	2.38 (1.18, 4.83)	0.02
Without	56/1153	1.51 (0.80, 2.86)	0.21	1.33 (0.70, 2.53)	0.39	1.55 (0.81, 2.96)	0.19
Anxiety history*							
With	17/82	0.82 (0.24, 2.77)	0.75	1.12 (0.30, 4.11)	0.87	0.78 (0.18, 3.33)	0.73
Without	73/1348	1.92 (1.19, 3.11)	<0.01	1.70 (1.05, 2.76)	0.03	2.18 (1.33, 3.57)	<0.01
Gender*							
Male	39/807	1.43 (0.70, 2.91)	0.33	1.21 (0.59, 2.48)	0.61	1.34 (0.63, 2.85)	0.44
Female	55/642	2.08 (1.16, 3.71)	0.01	2.11 (1.17, 3.78)	0.01	2.43 (1.32, 4.46)	<0.01
Age*							
Middle age	12/160	0.63 (0.09, 4.52)	0.65	0.47 (0.07, 3.40)	0.45	0.73 (0.10, 5.34)	0.76
Old age	82/1289	1.86 (1.18, 2.93)	<0.01	1.88 (1.18, 2.99)	<0.01	2.14 (1.33, 3.43)	<0.01

Abbreviations: *, ever use of hypnotics; BZDs, Benzodiazepines; AD, Alzheimer's disease; HR, hazard ratios; CI, confidence intervals; CDDD, cumulative defined daily dose. n, hypnotic users; N, nonusers. Model 1: crude HR with no covariates adjusted; Model 2: HR adjusted for age, gender, education, APOE ε4 status, and diagnosis; Model 3: HR adjusted for model 1 + depression, anxiety, diabetes mellitus type 2, hypertension, hyperlipidemia, stroke history, insomnia, smoking status, and obesity.

year showed the results barely changed (Appendix 4). Besides, no stratification effect was found in use status, half-time, and gender. Second, to reduce sample sizes differences, for each hypnotic user (N=94), we randomly selected four comparison subjects (N=376) who did not use hypnotics and were matched with hypnotic users by age, gender, years of education, and APOE ε4 status, as is shown in Figure 1, the primary results were barely changed.

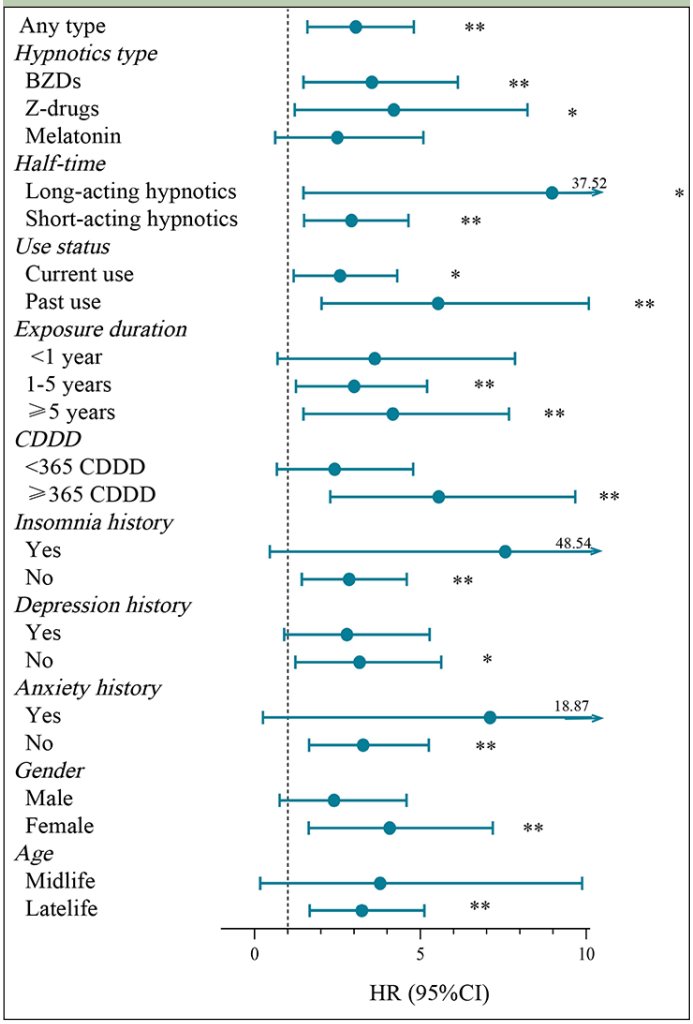
Meta-analysis

Searching Results and study characteristics

Figure 2A exhibits the flow diagram of the study selection process. The search yielded 20,235 articles after de-duplication. After scanning the titles and abstracts, 69 articles were considered potentially eligible. After reviewing the full texts and integrating them with 2

additional papers searched by citations, a total of 26 longitudinal studies (13 cohort studies and 13 nested case-control studies) were finally included. Compared with a previous meta-analysis (25), our meta-analysis additionally included 8 cohort studies and 9 nested case-control studies, which were published recently, and the differences between the two meta-analyses were shown in Appendix 5. As shown in Figure 2B, nineteen (73%) studies (11, 12, 26-42) analyzed the associations of BZDs with all-cause dementia (ACD, 84%), AD (26%), or vascular dementia (VD, 5%). Five (19%) studies (10, 12, 27, 34, 43) investigated the relationship of Z-drugs with ACD (60%) or AD (40%). Nine (35%) studies (12, 27, 34, 35, 44-48) reported the association of any hypnotics (unspecified) with ACD (78%), AD (33%), or VD (11%). The detailed characteristics of the studies were summarized in Table 3 and Appendix 6, among which the mean age of the population ranged from 61 to 87 years (median = 74.2 years), and the mean follow-up varied from 2 to 24 years (median = 10 years).

Figure 1. Hazard ratios with corresponding 95% confidence intervals for the association of the use of hypnotics and AD in the nested case-control studies



Abbreviations: HR, Hazard ratio; CI, Confidence interval; BZDs, Benzodiazepines; CDDD, Cumulative defined daily dose; *, 0.01 > p ≥0.05; **, p < 0.01

Association between the use of hypnotics with dementia risk

As shown in Appendix 7, the use of hypnotics was associated with a 23% higher risk of dementia (RR = 1.23, 95% CI = 1.13-1.33, I^2 = 98.0%) after pooling 26 longitudinal studies with 3942,018 participants and 213,895 incident cases. Appendix 8 showed the incidence rates of eligible cohorts (median RD = 4%, range = 1% to 14%). The risk of dementia ranged from 15% to 30% in the studies for any hypnotics (unspecified) (RR = 1.30, 95% CI = 1.12-1.52, I^2 = 98.9%), BZDs (RR = 1.15, 95% CI = 1.07-1.24, I^2 = 97.4%), and Z-drugs (RR = 1.20, 95% CI = 0.99-1.47, I^2 = 98.6%). As for the subtypes of dementia, the relationship remained significant for ACD (RR = 1.21, 95% CI = 1.11-1.32, I^2 = 97.3%); a borderline significant relationship was revealed for AD (RR = 1.22, 95% CI = 0.96-1.55, I^2 = 98.8%); and there was no association for VD (RR = 1.69, 95% CI = 0.74-3.82, I^2 = 60.8%).

Sensitivity analysis by dropping one study each time or dropping studies with poor generality, inadequate follow-up, or high attrition rates barely changed the primary result; we could not identify which studies might have contributed to high heterogeneity (Appendix 9). And additional inclusion of the ADNI cohort study made the results more significant (Appendix 10). Meta-regression revealed that sample size, female proportion, NOS quality score, and follow-up duration could not explain the heterogeneity (Appendix 11). As shown in Figure 3, the association showed high-level stability within multiple subgroups. Interestingly, no significant association was revealed between hypnotic use and dementia risk in participants with insomnia (RR = 1.35, 95% CI = 0.88-2.06). No publication bias was revealed (Egger's p = 0.11, Appendix 12).

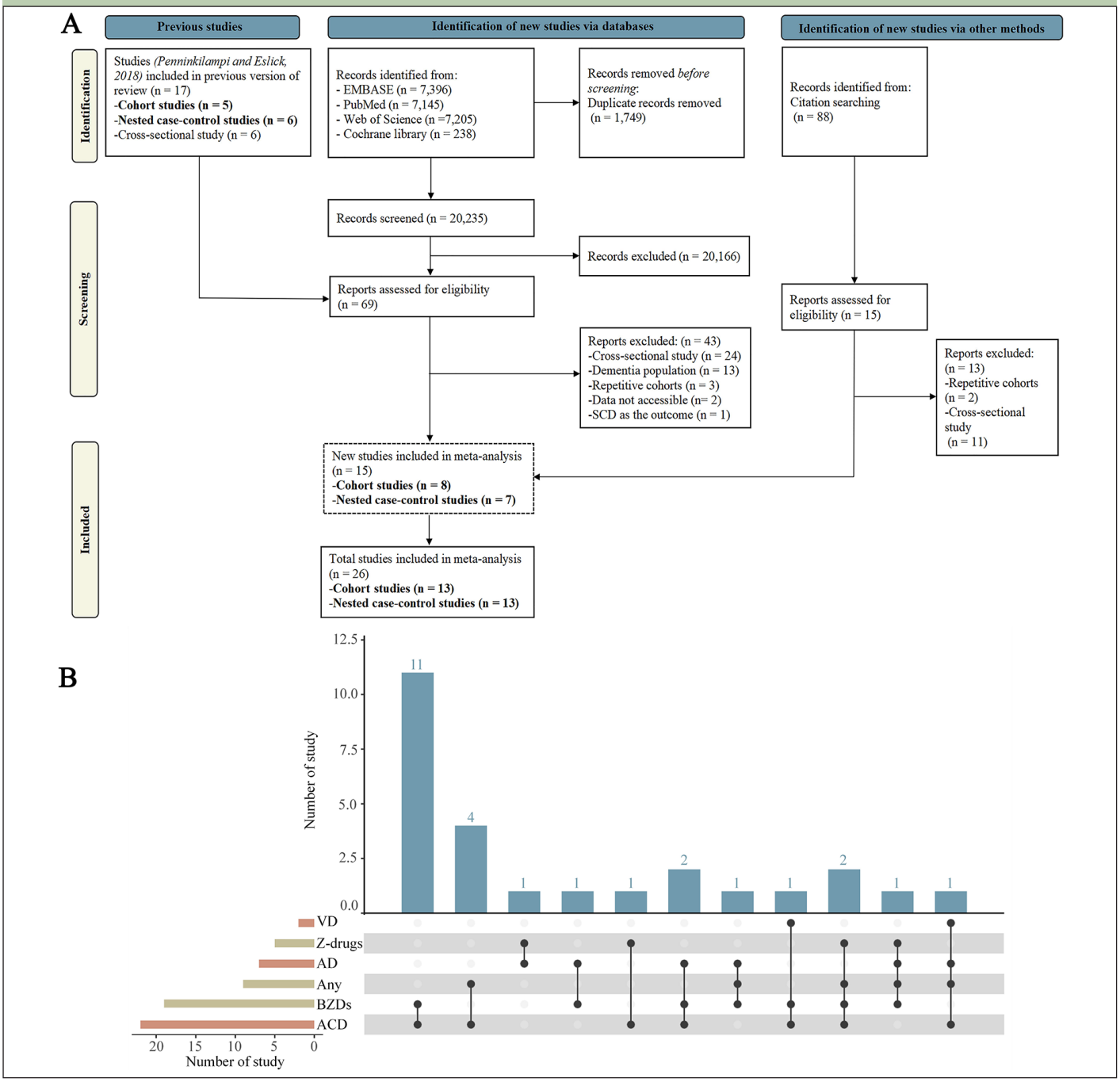
Dose-response analysis

A total of 5 longitudinal studies investigated the association between CDDD and dementia risk. The mean age ranged from 61.1 to 75.6 years old, and the mean follow-up duration varied from 5 to 16 years. The dose-response analysis uncovered a significant linear association between CDDD and dementia risk, such that if a person takes one recommended daily dose for 100 days, the risk of developing dementia increases by 5% compared to non-users (p=0.002). (Appendix 13)

Summary of evidence credibility

The average quality of evidence for included studies is moderate (median score = 6.42). As shown in Figures 4A and 4B, the overall evidence levels were rated as "very low" due to the large heterogeneities. Accordingly, several primary recommendations for clinical practices and future research were proposed in Table 4.

Figure 2. Search flowchart and summary characteristics of included studies



The search yielded 20,235 articles after de-duplication. After scanning the titles and abstracts, 69 articles were considered potentially eligible. After reviewing the full texts and integrating them with 2 additional papers searched by citations, a total of 26 longitudinal studies were finally included. (2A); 19 studies analyzed the effect of BZDs on all-cause dementia, AD, or VD. 5 studies investigated the relationship of Z-drugs with ACD or AD, and 9 studies reported the connection of any hypnotics with ACD, AD, or VD. (2B); Abbreviations: AD, Alzheimer's disease; VD, vascular dementia; ACD, all-cause dementia; SCD, subjective cognitive decline; BZDs, Benzodiazepines.

Discussion

In the current study, we discovered that: i) the use of BZDs and Z-drugs was associated with increased risks of dementia and AD; ii) the effects were dose-dependent, such that the effects of hypnotics on dementia risk could be pronounced among those long-term or high dose users; iii) stratified analyses revealed no significant association between hypnotic use and dementia risk in insomnia patients; and iiii) heterogeneity limited the current evidence level and more homogenous studies are warranted in the future.

This study proposes several primary recommendations for clinicians. The first-line treatment should be cognitive-behavioral therapy (CBT), which has high efficacy and almost no side effects (49-51). Patients who wish to withdraw from BZDs and Z-drugs can receive CBT support (52). If withdrawal fails, BZDs or Z-drugs should

Table 3. Characteristics of 26 studies included in the meta-analysis

N	First author; Publication year	Cohort name; Country; Study design	Incident cases/ Sample size	Follow-up Duration (years)	Female (%)	Age (Mean or range years)	Type and measurement of hypnotics	Outcome and diagnostic criteria	Quality scores
1	Cavaillès C; 2022	Three-City study; France; Co	695/6,851 (D) 470/6,626 (A) 139/6,295 (V)	12 (max); 8.9 (mean)	60	73.7	Any; Self-report	D (DSM-IV) A (NINDS) V (NINDS)	6
2	Gerlach LB; 2021	VHA; USA; Co	34,766/528,066	15 (max)	2.3	77	B; Prescription	D (ICD-9-CM)	5.5
3	Torres-Bondia F; 2021	CatSalut Spain; Co	5856/167,790	5 (min) 13 (max)	57.9	67.9	Any, B (L & S), Z; Prescription	D (ICD-10)	7
4	Rebecca Robbins; 2021	NHATS; US; Co	NA/6,373	8 (max)	59	65+	Any; Questionnaire	D (AD8)	7
5	Pablo Aldaz; 2021	AEMPS; Spain; N	15,212/1,310,416	6.3 (mean)	70	81	B (L & S); Prescription	D (ICPC 2)	7
6	Li-Yen Tseng; 2020	NHIRD (2003-2012); China; Co	23,919/260,502	9 (max)	51	73.24	Z; Self-report	D (ICD-9-CM)	7
7	Merete Osler; 2020	DNPR; Denmark; N	9,776/48,880	2 (max)	61	73.2	Any, B, Z, and L & S of both; Prescription	D (ICD-8/ICD-10)	6
8	Mohamed Nafti; 2020	CSHA; Canada; Co	830/5,28 (D) 564/5,015 (A)	11.4 (max); 5.4 (mean)	61	74.1	B; Prescription & Self-report	D (DSM-III-R) A (NINCDS-ADRDA)	6.5
9	Ching-EnLin; 2020	NHIRD (2002-2015); China; N	951/8,712	15.99 (max); 9.33 (mean)	48	65.83	Any; Prescription	D (ICD-9-CM)	6
10	Melanie Hafdi; 2020	preDIVA; Netherlands; Co	233/3454	8 (max); 6.7 (mean)	54	74.33	B (L & S); Self-report	D (DSM-IV)	8.5
11	Yeon-Hee Baek BA; 2020	NHIS (2002-2016); Korea; N	4,167/616,256	7 (max); 5.5 (mean)	35	NA	B (L & S); Prescription	D (NA)	6
12	Kathryn Richardson; 2019	CPRD; UK; N	40,770/60,027	20 (max);7.1 (mean)	63	83	B; Prescription	D (NA)	7
13	Carlota M Grossi; 2019	CFAS; UK; Co	220/8,216	10 (max)	59	65+	B; Self-report	D (AGECAT)	6.5
14	Tapiainen V; 2018	MEDALZ; Finnish; N	70,719/353,581	11.9 (max); 8.7 (mean)	65	34–105	Any, B (L & S), and Z; Prescription	A (DSM-IV & NINCDS-ADRDA)	6
15	Joonki Lee; 2018	NHIS (2002-2015); Korea; Co	27,925/268,170	12 (max); 10.97 (mean)	45	61.12	Any, B (L & S); Prescription	A (ICD-10)	6
16	Hui-Ting Cheng; 2017	NHIRD (2001-2011); China; N	75/6,922	6 (max);5.97 (mean)	63	72.1	Z; Prescription	A (NA)	4.5
17	Francis Mawanda; 2017	VHA; US; Co	25,639/417,172	9.03 (mean)	2	67.7	Any; Prescription	D (ICD-9)	7
18	Chan TT; 2017	HA; China; N	91/273	14 (max); 9.8 (mean)	78	87	B; Prescription	D (DSM-5)	6
19	Dalia Shash; 2016	The three-City study; France; Co	647/7,130	11 (max); 8 (mean)	59	73.6	B (L & S); Prescription	D (DSM-IV)	7
20	Shelly L Gray; 2016	The Adult Changes in Thought study; US; Co	797/3,434 (D) 637/3,434 (A)	10 (max); 7.3 (mean)	60	74.4	B; Prescription	D and A (NA)	8
21	Gomm W; 2016	AOK; Germany; N	21,145/105,725	7 (max); 4.7 (mean)	54	75.2	Any (L & S); Prescription	D (ICD-10)	7
22	Hsiao-Yean Chiu; 2015	LHID 2000; China; N	88/5,960	9 (max)	49	20+	Any; Prescription	D (ICD-9-CM)	6
23	Billioti de Gage; 2014	RAMQ; Canada; N	1,796/8,980	10 (max)	67	79.2	B (L & S); Prescription	A (ICD-9-CM)	6
24	John Gallacher; 2012	Caerphilly; UK; Co	93/1,134 (D) 44/1,134 (V)	24 (max) 22 (mean)	0	61	B; Self-report	D (DSM-IV) V (NINCDS-AIREN)	6.5
25	Chi-Shin; 2009	NHIRD (1997-2004); China; N	779/5,405	5 (max); 4.6 (mean)	50	75.6	B; Prescription	D (ICD-9-CM)	5
26	Lagnaoui R; 2002	PAQUID; France; N	150/3,669	8 (max);3 (mean)	65	74.1	B; Self-report	D (DSM-III-R)	6

Abbreviations: Co, Cohort studies; N, Nested case-control studies; B, Benzodiazepines; Z, Z-drugs; M, Melatonin; Any, Any hypnotics; L, Long-acting hypnotics; S, Short-acting hypnotics; A, Alzheimer's disease; V, Vascular dementia; NA, Not available; ICD, International Statistical Classification of Diseases and Related Health Problems; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICPC 2, International Classification of Primary Care; AD8, An 8-item informant screener for dementia; NINDS, National Institute of Neurological Disorders and Stroke; AGECAT, Automated Geriatric Examination for Computer Assisted Taxonomy; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria; &, and.

Table 4. The potential benefits and risks of taking hypnotics to prevent dementia

Risks	Benefits
√ The risk of dementia was significantly elevated by 15% to 30%, though the risk difference is limited. √ The effect might be enlarged for long-term or high-dose users. √ Potential side-effects of hypnotics include addiction, daytime dysfunction, drowsiness, etc.	√ Improving sleep quality or mood might be favorable for lowering the risk of dementia, considering that no significant effects were revealed for insomnia patients.
Clinical Recommendations	
> Particular attention should be paid to screening for cognitive impairments among individuals taking hypnotics. > When hypnotics were inevitably used to treat insomnia, the elevated risk of developing dementia might be limited for those small-dose, short-term, or intermittent users.	
Research Recommendations	
> The associations of melatonin with dementia risk warrant more investigations. > For serving precise prevention strategy, the effects of hypnotic use on dementia risk deserve more investigation for patients with insomnia or mood disorders. > Heterogeneity is a major source of concern to weaken evidence credibility. Future studies should consider the pharmacological properties of different types of hypnotics, clarify whether sleep/mood problems are a risk factor or a consequence of dementia, and exclude confounding effects caused by the co-occurrence of sleep and mood disorders. > As for individuals who continue to have insomnia symptoms after taking hypnotics, the effects of hypnotics should be further explored. > Given the unfavorable effects of both sleep and hypnotics on cognitive function, the roles of non-pharmacological treatments for insomnia in preventing dementia should be explored.	

be prescribed on a short-term, intermittent basis, or melatonin could be prescribed as an alternative because it inhibits expressions of β-AP and S100β proteins in the hippocampal (53) and attenuates amyloid β (Aβ) pathology (54) and has not been found to increase the risk of dementia. However, regularly monitoring the cognitive function of BZD or Z-drug users is reasonable, especially for long-term or high-dose users.

Stratified effects may impact the association between hypnotic use and dementia risk. BZDs and other hypnotics are used to treat insomnia, acute situational anxiety, chronic anxiety disorders, depression, alcohol withdrawal syndrome, catatonia, muscle spasms, hypomania, and delirium; people without a history of insomnia can also take hypnotics (55, 56). And hypnotics do not increase the risk of dementia in patients with insomnia. However, the effects may have been confounded by the type and dosage of hypnotics. The associations were more prominent in females and elderly individuals, which may be explained by the fact that older adults and females are more sensitive to the side effects of hypnotics due to age-related changes in pharmacodynamics and pharmacokinetics (57), as well as a lower elimination rate in females (58). More evidence is required for precise prevention, and clinicians should avoid prescription abuse when treating sleep disturbance and mood disorders.

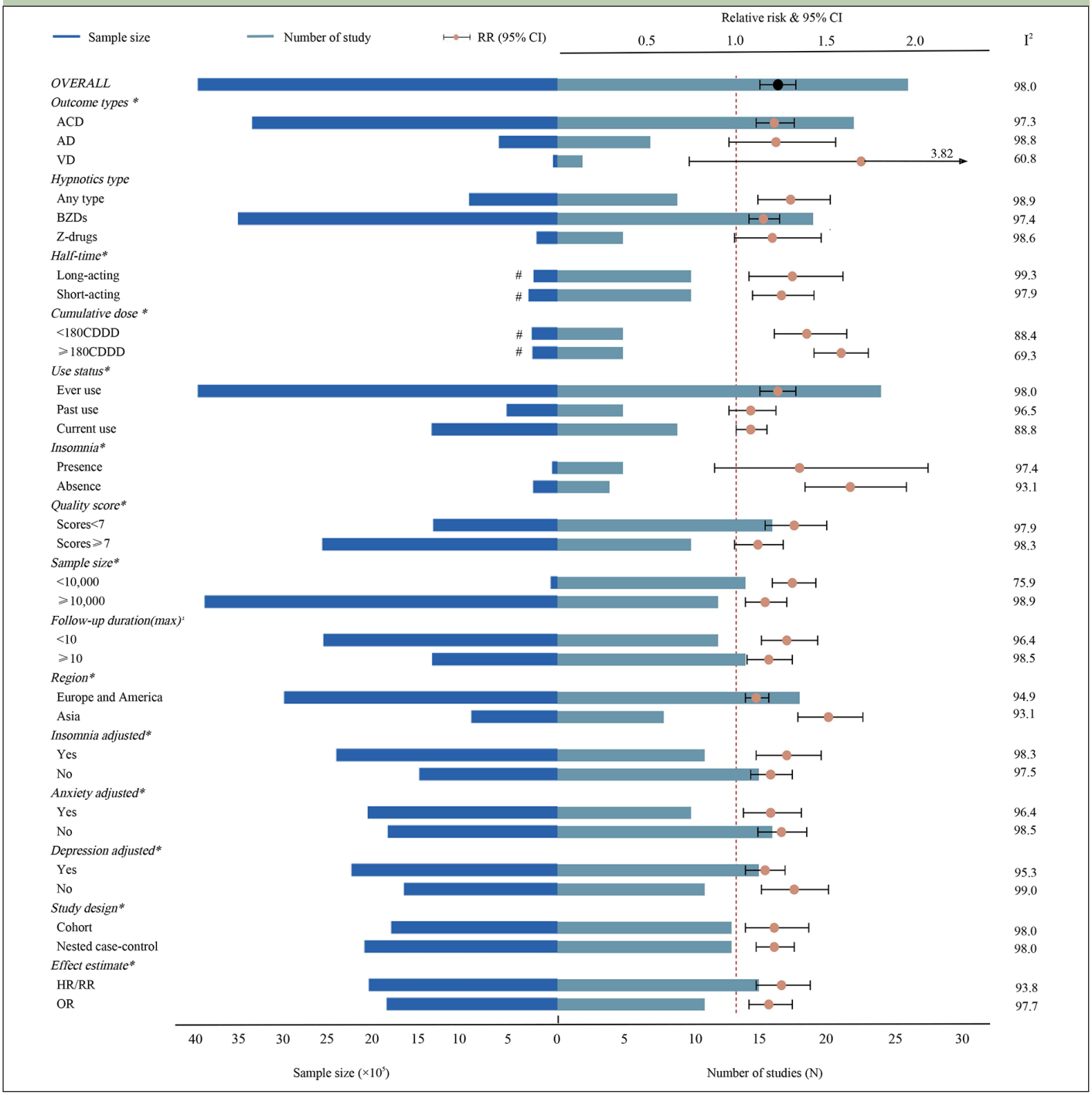
The causal link between hypnotics and dementia risk was supported by mounting evidence. First, based on longitudinal studies, the significant linear dose-response relationship supported the causal association between hypnotic use and dementia risk. Second, experiments on animals showed that the Aβ40 and Aβ42 levels were elevated in older mice treated with BZDs compared to the controls (59). Finally, a randomized controlled trial demonstrated that BZDs impair memory by decreasing the extent and magnitude of activation in the hippocampal, fusiform, and inferior prefrontal regions of interest (60).

Several mechanisms may explain how hypnotics affect dementia. First, both BZDs and Z-drugs are gamma-aminobutyric acid (GABA) agonists that function as positive allosteric modulators of GABAA receptors to increase chloride conductance and the efficacy of GABA at GABAA receptors (61), resulting in synaptic inhibition in the central nervous system (CNS) and dementia (38, 62). Second, BZDs and Z-drugs cause decreased hippocampal neuronal activity and dementia through the alpha1 and alpha5 subunits (63-65). In addition, chronic use of BZDs increased the accumulation of Aβ plaques between nerve cells, which inhibited neuronal function and eventually led to the progression of AD (59).

High heterogeneity is a significant issue that reduces the robustness of the evidence (25, 66). Therefore, future researchers are encouraged to: i) separately analyze different types of hypnotics due to their distinct pharmacological properties; ii) analyze the interactive effects of hypnotics and insomnia on dementia risk (65); iii) consider the reverse causal effects of sleep disturbance and mood disorders, as these conditions may be early manifestations of dementia or neurodegeneration (67, 68); and iiii) avoid the confounding effects of insomnia and mood disorders, which frequently coexist (43, 69).

The current study has several benefits. 1) To investigate causality, we used longitudinal cohorts and dose-response analyses. 2) We separately analyzed the association according to hypnotic type, dosage, and use status. 3) Our study was the first to examine the association between

Figure 3. Association of hypnotics with risk of dementia in subgroup analyses

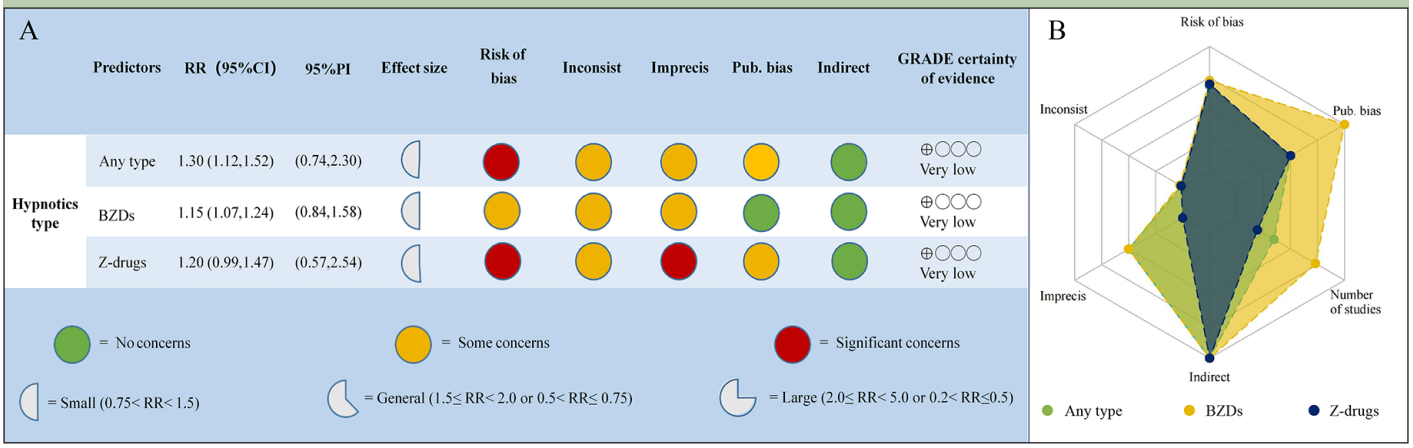


*, any hypnotics group; #, including study without sample size data. Abbreviations: AD, Alzheimer's disease; VD, vascular dementia; ACD, all-cause dementia; HR, Hazard ratio; OR, Odds ratio; RR, Relative risk; CI, Confidence interval; BZDs, Benzodiazepines;

hypnotics and dementia risk using a subgroup analysis stratified by the presence or absence of insomnia. 4) We assessed the reliability of the evidence and outlined the lessons learned and future projections.

However, several limitations should be noted. 1) Longitudinal observational findings do not equate to causal relationships. 2) Due to insufficient evidence, no further stratified meta-analyses could be conducted. 3) Due to a lack of evidence, an analysis of melatonin was limited. 4) The heterogeneity was high, and the conclusion's robustness was low. 5) We did not consider the bias caused by antipsychotics and antidepressants occasionally used to treat insomnia. 6) Participants in the meta-analyses cannot be homogeneous, even if multiple subgroup analyses were conducted. 7) The large differences in sample sizes of the ADNI cohort may cause an unreliable hazard ratio estimated, even if we did a nested case-control analysis based on this cohort.

Figure 4. The credibility of meta-analyses results



The overall evidence levels were rated as "very low", and heterogeneity is a major source of concern. Abbreviations: HR, hazard ratio; Inconsist, inconsistency; Imprecis, imprecision; Indirect, indirectness; Pub.bias, publication bias.

In conclusion, using hypnotics was associated with an increased risk of dementia. The association was dose-dependent and may be affected by age, gender, and the presence or absence of insomnia. More research is required to investigate the potential stratified effects of dementia prevention.

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