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Use of Sedative-Hypnotic Medications and Risk of Dementia: A Systematic Review and Meta-Analysis

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Abstract

Aim: Growing evidence suggest an association between the use of sedative-hypnotic medications and risk of dementia. The aim of this study is to examine this association using a meta-analysis approach.

Methods: MEDLINE (PubMed) and SCOPUS were systematically searched for studies published in English only. Studies' quality was evaluated using the Newcastle-Ottawa scale, and an overall odds ratio was pooled using the random-effects model.

Results: 35 articles were included. Pooled odds ratios (ORs) for dementia from all records were (O1.33, 95%CI 1.19-1.49) for benzodiazepines (BZDs) combined use (Subgroup-1), (OR:1.46, 95%CI 1.23-1.73) for short-acting BZDs use (Subgroup-2), (OR:1.72, 95%CI 1.48-1.99) for long-acting BZDs use (Subgroup-3), (OR:1.13, 95%CI 0.97-1.32) for BZDs without specification of duration of action (Subgroup-4), (OR:1.64, 95%CI 1.13-2.38) for the combined BZDs and Z-drugs, (OR: 1.43, 95%CI 1.17-1.74) for Z-drugs only, (OR:1.14, 95%CI 0.88-1.46) for antidepressants use, (OR:0.97, 95%CI 0.68-1.39) for antipsychotics use and (OR: 0.98, 95%CI 0.85-1.13) for anticonvulsants use. When sensitivity-analysis was performed, association between overall use of BZDs and short-acting BZDs with the increased risk of dementia disappeared after exclusion of studies that were not adjusted for age covariate (OR:1.2, 95%CI 1.0-1.44) and (OR:1.22, 95%CI 0.75-2.01), respectively. Adjustment for protopathic bias by introduction of a lag-period showed no evidence of increased risk of dementia with the use of BZDs (Subgroup-1) (OR:1.14, 95%CI 0.82-1.58), Z-drugs (OR:1.29, 95%CI 0.78-2.13), and combined BZDs and Z-drugs use (OR:1.51, 95%CI 0.91-2.53). Combined use of BZDs and Z-drugs showed more positive association when only studies of non-user design were analysed (OR:2.75, 95%CI 2.23-3.39).

Conclusions: All the investigated sedative-hypnotics showed no association with increased risk of dementia except for BZDs. However, the observed association with BZDs did not persist after exclusion of studies with potential reverse causation and confounding by indication. Therefore, this association needs to be assessed carefully in future research.

Keywords: Dementia, Sedative-hypnotics, Benzodiazepines, Antidepressants, Antipsychotics.

Introduction

Sleep disturbances are common in older adults and often unrelated to any medical condition. However, there has been growing interest in the relationship between sleep disturbances and the development of adverse health consequences (1–3). It has been suggested that sleep disorders such as poor sleep quality, insomnia, or obstructive sleep apnea may not only be a feature of the ageing brain and part of the natural progression of dementia disease but also a risk factor for neurodegenerative diseases, including dementia (4,5). Moreover, several studies have suggested that improving sleep quality may be of future interest in the primary prevention of dementia (6,7).

Many medications with sedative and hypnotic properties are used for the treatment of insomnia and other sleep disturbances in patients with or without dementia, including benzodiazepines (BZDs), non-benzodiazepines (Z-drugs), antidepressants, antipsychotics, antihistamines, and less frequently, barbiturates (8). Although these drugs are used to treat insomnia and other sleep disturbances, their effectiveness is still arguable and they have in turn been linked with negative clinical outcomes such as increased risk of cognitive decline, dementia, hospital admission and falls (4,9). Over the past few years, an increasing number of population-based studies have been conducted on sedative-hypnotics users to investigate the risk of dementia. Some revealed an increased risk of dementia with hypnotics use (10,11), whereas others reported no association (12,13). Furthermore, two previous meta-analyses were conducted to assess the risk of dementia with BZDs only, but their findings were limited by potential unmeasured confounding variables and reverse causation (14,15). Owing to limitations related to the design of studies (e.g. uncontrolled confounders) and the variation in exposure and outcome measures between them, it is difficult to draw conclusions on the consistency of this association. Moreover, the possibility of protopathic bias cannot be eliminated, meaning that insomnia and depression could be prodromal symptoms of dementia, and cognitive impairment and memory loss could have appeared as a natural progression of the disease (16).

In light of these contradictions between studies on the risk of dementia with sedative-hypnotic medications use, a meta-analysis is particularly useful for synthesizing available evidence, studying the effect of other sedative-hypnotics and addressing any methodological limitations in order to fill the gap and potentially resolve current contradictions.

Methodology

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(17). A written protocol was published on PROSPERO website in July 2020 (Registration ID: CRD42020186701).

Search strategy and study selection

The search was conducted for published literature on MEDLINE (PubMed) and SCOPUS from the inception to May 2020, and on EMBASE from May 2010 to May 2020. Further search was conducted by checking references lists manually and contacting authors of relevant articles. Studies were identified using the search terms "(sedative-hypnotics OR benzodiazepines OR z-drugs OR barbiturates OR antidepressants OR antipsychotics OR antihistamines OR melatonin) AND (dementia OR alzheimer's OR cognitive impairment)". The search was restricted to human studies and articles published in English. Studies were included if they were randomised controlled trials (RCT) or observational studies. Studies were excluded if they reported the effects of sedative-hypnotics in participants already known to have dementia, reported the prevalence of use rather than studying sedative-hypnotics as a risk factor, were case reports, abstracts or reviews.

Data extraction

Following the implementation of the search strategy, all citations were exported to Covidence® for deduplication and screening (18). One investigator (AA) screened the titles and abstracts of all of the initially identified studies to determine if they fulfil the selection criteria, while two other investigators – (SA) and (NA) – randomly selected 20% of the studies and evaluated them independently for inclusion eligibility. All potentially eligible studies were reviewed in full for inclusion in the systematic review following the same approach. Any uncertainty, discrepancy or doubt about eligibility was resolved through consultation with a third reviewer (AK) acting as a referee. Data were first extracted on the 8th of June 2020. Data were extracted using a standardised data extraction form that included information on the study design, setting, country, number of participants, population characteristics, type of sedative-hypnotics, exposure definition, description of the comparator, outcome of interest, outcome measure, outcome assessment, measure of effect, covariates adjusted for, main study results, induction of lag period between exposure and outcome, and quality level. Data were extracted by one investigator (AA), and any uncertainties and discrepancies were identified and resolved through discussion with a second investigator (AK) acting as a referee.

Assessment of methodological quality

Since no RCTs were found to meet the inclusion criteria, the methodological quality of the included observational studies was assessed using the Newcastle-Ottawa Scale (NOS) (19), and was independently assessed by another reviewer (SA). The Newcastle-Ottawa scale consists of eight items with a maximum score of nine. Studies were classified as high, moderate and low quality based on a total score of ≥7, 5-6, and ≤ 4, respectively (20). Discrepancies were resolved through discussion with a third reviewer (AK) acting as a referee.

Statistical analysis

STATA software (version16.0, Stata Corp, College Station, TX) was used to perform data synthesis and analysis. The statistical heterogeneity across studies was evaluated using I-squared statistic (21). A cut-off value of 50% was then used as an accepted measure to define high heterogeneity. The odds ratio was pooled to summarise the relationship between use of sedative-hypnotics and risk of dementia, with 95% CI as the measure of association using the random effect model.

Given the heterogeneity and differences in the mode of actions of the different sedative-hypnotic medication classes, the pooled estimate was stratified by each class of sedative-hypnotic separately. The sedative-hypnotic medication classes included BZDs, Z-drugs, Z-drugs, and BZDs combined use, antidepressants (Tricyclic antidepressants (TCAs), Selective serotonin reuptake inhibitor (SSRIs) and Serotonin antagonist and reuptake inhibitors (SARIs)), antipsychotics (i.e. lithium vs. other antipsychotics), and anticonvulsants.

Regarding BZDs, some studies have assessed only long or short-acting BZDs and some did evaluated BZDs as a whole without specifying the duration of action; therefore, the analysis of all BZDs studies(sub-group 1)was further stratified by their duration of actions into three sub-groups: short-acting BZDs studies only (sub-group 2), long-acting BZDs studies only (sub-group 3), and studies that evaluated BZDs without specification of the duration of action (sub-group 4).

Forest plots were generated for each exposure-outcome comparison. To identify potential sources of heterogeneity, a subgroup analysis was conducted to investigate the impact of the study design, the quality of the study, and geographic region. Sensitivity analysis was performed by excluding studies that were not adjusted for age to assess the impact of adjustment for the most important covariate, studies that did not introduce a lag-period between exposure and outcome (i.e. studies that did not control for protopathic bias- without having any prior criteria about what constituted a sufficiently long lag period but rather we only considered whether a study accounted for a lag-period or not), and studies that used an active comparator as a control group to assess the presence of potential confounding by indication. Finally, funnel plots and Egger's test were used to test the presence of potential publication bias within this meta-analysis.

Results

Literature search and study characteristics

A sum of 6,371 records was identified through the initial database search. After removing duplicates, 5,749 relevant records remained for title and abstract screening, after which 75 articles were selected for full-text screening; based on the inclusion and exclusion criteria, 35 articles were eligible for inclusion (Figure 1) all of which were observational studies. The characteristics of included studies are presented in Table 1. The 35 eligible studies included 4,257,670 participants from four different continents: 15 studies (43%) from Europe (10,13,22–34), 12 studies (34%) from Asia (11,35–45), seven studies (20%) from North America (12,46–51) and one study (3%) from Australia (52). The sedative-hypnotics that were studied: BZDs alone were evaluated in 11 studies (12,13,22,24,26,29,30,36,45,46,49), BZDs and Z-drugs (separate or in combination) in other 11 studies (11,25,28,33,37,39–44), antidepressants alone in five studies (23,31,35,47,48), antidepressants and BZDs in two studies (27,51), antidepressants and antipsychotics in two studies (32,38), antipsychotics and anticonvulsants in two studies (34,50), BZDs and psychotropic medications in one study (10), antipsychotics alone in one study (52) and antihistamines in one study (37). The extent of the introduction of a lag-period between exposure and outcome and adjustment for age and other potential covariates including medications and comorbidities varied between studies (Table 1). For the quality assessment, the mean NOS score for the 35 studies assessed was 7.17 (Table 1).

Pooled estimates of the associations between the various sedative-hypnotic medications and dementia

1. Benzodiazepines (BZDs)

Overall, 20 different studies measured the association between use of BZDs and risk of dementia (sub-group 1) (10–13,22,24,26–30,33,36,37,39,44–46,49,51). Seven studies assessed the risk associated with short and long-acting BZDs (10,11,22,36,37,44,49) (sub-group 2, 3), and 17 studies measured the association between use of BZDs as a class without specification of the duration of action (sub-group 4) (10,12,13,22,24,26–30,33,37,39,45,46,49,51).

The following four types of estimates were calculated: the overall pooled estimate for sub-group 1 revealed an increased risk of dementia (OR: 1.33, 95%CI 1.19-1.49) (Figure 2A). Upon the sub-group analysis based on BZDs duration of action, pooled estimates from seven studies showed a significant increased risk of dementia with short-acting BZDs use (sub-group 2) (OR:1.46, 95%CI 1.23-1.73) (Figure 2B) and long-acting BZDs use (sub-group 3) (OR:1.72, 95% CI 1.48-1.99) (Figure 2C) (10,11,22,36,37,44,49). On the other hand, the pooled estimate from the 17 studies that

evaluated the use of BZDs as a class without specification of the duration of action (sub-group 4), indicated lack of association between dementia and BZDs use (OR:1.13, 95% CI 0.97-1.32) (Figure 2D). Potential causes of high heterogeneity were investigated using subgroup analysis (Table 2).

2. Combined use of BZDs and Z-drugs

Eight studies involving 794,666 participants showed that combined use of BZDs and Z-drugs (Zolpidem, Zopiclone, Zaleplon and Eszopilcone) is associated with a 1.64 folds increase in dementia risk (95% CI 1.13-2.38) (Figure 2E) (13,25,28,33,39,42–44).

3. Use of Z-drugs

Eight studies involving 954,852 participants investigated the association between Z-drugs use and risk of dementia (11,13,28,33,37,40,41,44); the pooled estimate showed that there is a significant increased risk of dementia (OR:1.43, 95% CI 1.17-1.74) (Figure 2F).

4. Use of antidepressants

Eleven studies measured the association between the use of antidepressants and risk of dementia (11,23,27,31,32,34,35,38,47,48,51), out of which two had the same population but with a different study design and different exposures (SSRIs vs. antidepressants) (23,34). One study had four estimates of association between dementia and four classes of antidepressants (paroxetine, non-paroxetine SSRIs, SARIs and TCAs) (47). Another study had three effect sizes for three exposures (TCAs, SSRIs and new-generation antidepressants) (35). When the odds ratios from all records were pooled, no association was detected between use of antidepressants and risk of dementia (OR: 1.14, 95% CI 0.88-1.46) (Figure 2G). When subgroup analysis was conducted according to exposure sub-classes, no evidence of association was found: antidepressants (OR: 1.07, 95% CI 0.78 – 1.47), paroxetine (OR:1.07, 95% CI 0.76-1.52), other SSRIs (OR:0.82, 95% CI 0.42-1.6) and TCAs (OR:1.03, 95% CI 0.91-1.17).

5. Use of antipsychotics

Five different studies reported four estimates of the association between antipsychotics and risk of dementia, and two estimates of the association between lithium and risk of dementia (32,34,38,50,52). The pooled odds ratio of all records failed to find an association (overall OR: 0.97, 95%CI 0.68-1.39) (Figure 2H). Subgroup analysis of type of exposure also failed to find an association: (antipsychotics OR: 1.18, 95%CI 0.84-1.65; lithium OR: 0.63, 95%CI 0.38-1.07).

6. Use of anticonvulsants

Two studies with 46,787 participants failed to find an association between anticonvulsants use and risk of dementia (OR: 0.98, 95%CI 0.85-1.13) (Figure 2I) (34,50).

Narrative summary

Histamine antagonists were investigated for their sedative and anticholinergic properties and risk of dementia in one case-control study that was conducted in Korea involving 11,124 participants (37). The study found a positive correlation between H2-receptor antagonist use and risk of dementia (OR: 1.66, 95% CI 1.52–1.80). Furthermore, a prospective cohort study that took place in France reported a positive association between psychotropics use (antipsychotics, anxiolytics, hypnotics, sedatives, antidepressants, psychostimulants and nootropics) and risk of dementia (adjusted HR:1.47, 95%CI 1.16–1.86) (10).

Sensitivity analysis

The results of sensitivity analysis for all exposures are shown in Figures 3-10.

1. Effect of adjustment for age covariate

When records that did not adjust for age were excluded, all aforementioned associations persisted for all exposures except for BZDs combined use (sub-group 1)and short-acting BZDs (sub-group 2), with the association moving towards null hypothesis: (OR:1.2, 95%CI 1.0-1.44) and (OR:1.22, 95%CI 0.75-2.01), respectively (Figure 3A) (Figure 5A). For antidepressants, the exclusion of records that did not adjust for age resulted in a positive association (OR: 1.23, 95%CI 1.06-1.42) instead of a lack of association (Figure 9A).

2. Effect of introduction of lag-period (control for protopathic bias)

The introduction of a lag-period between exposure and outcome has been used in many observational studies to reduce the influence of protopathic bias on the results. Exclusion of studies that did not introduce a lag-period produced a lack of association between BZDs combined use (sub-group 1) and risk of dementia (OR:1.14, 95%CI 0.82-1.58) (Figure 3B), BZDs and Z-drugs combined use and risk of dementia (OR:1.51, 95%CI 0.91-2.52) (Figure 7B), and between Z-drugs use and risk of dementia (OR:1.29, 95%CI 0.78-2.13) (Figure 8B).

3. Effect of non-user design (potential confounding by indication)

Only one study used an active-comparator, which means that the exposure of interest was compared against another comparator (48), after excluding this study the level of association moved from a lack of association between antidepressants use and risk of dementia (OR:1.14, 95%CI 0.88-1.46) to a positive association (OR:1.24, 95%CI 1.05-1.47) (Figure 9C). After exclusion

of studies that did not specify the type of comparator (i.e. active-comparator or non-user design), the pooled estimate of remaining studies (i.e. studies that used non-user design) produced a more positive association between combined use of BZDs and Z-drugs and risk of dementia (OR:2.75, 95%CI 2.23-3.39) instead of a less positive one (OR:1.64, 95%CI 1.13-2.38) (Figure 7C). In contrast, short-acting BZDs (sub-group 2) showed a lack of association when studies of non-user design only were analysed (OR:1.22, 95%CI 0.75- 2.01) instead of a positive association (OR:1.46, 95%CI 1.23-1.73) (Figure 5C).

A summary of the Pooled estimates of the associations between the various sedative-hypnotic medications and dementia is presented in Table 3.

Publication bias

There was no evidence of publication bias through the funnel plots and Egger's test in the BZDs records (p=0.7122), BZDs and Z-drugs records (p=0.5247), Z-drugs record (p=0.3660), antidepressants records (p=0.0757) or antipsychotics records (p=0.4404). On the other hand, there was a highly significant publication bias in short and long-acting BZDs records (p=0.0006).

Discussion

The association between sleep and the risk of dementia has generated considerable interest and hence sedative-hypnotics use has become an area of debate. This meta-analysis of different exposures showed an increased risk of dementia associated with the use of BZDs (BZDs only use, Z-drugs only use, and combined use of BZDs and Z-drugs). However, when sensitivity analysis was performed, some of these associations changed or disappeared: association between use of BZDs combined (sub-group 1) and short-acting BZDs (sub-group 2) with the increased risk of dementia has disappeared after exclusion of studies that were not adjusted for age covariate. When adjustment for protopathic bias was accounted for by introduction of a lag-period, no evidence of increased risk of dementia was found with the use of BZDs combined (sub-group 1), Z-drugs, and combined use BZDs and Z-drugs. Combined use of BZDs and Z-drugs showed more positive association when studies of non-user design only were analysed. In contrast, no evidence of association was found with the risk of dementia and use of antidepressants, antipsychotics and anticonvulsants, although antidepressants use shifted to a positive association with the risk of dementia after exclusion of the only study that used an active-comparator design.

Our findings regarding BZDs use and association with an increased risk of dementia are further supported by two recent meta-analyses which found that long-term users of BZDs had 1.5- to 2-folds increased risk of developing dementia (14,15). In contrast, other studies have explained the

association by protopathic bias, reverse causality and confounding by indication, meaning that insomnia and depression are independent risk factors associated with both the exposure (sedative-hypnotics use) and the outcome (dementia) which could have resulted in an incorrect estimate of the association (13,53). This hypothesis raises concerns about potential reverse causation and protopathic bias causing the observed association. In this meta-analysis, this hypothesis was supported by the changes observed in the associations when sensitivity analysis was performed. In pharmacoepidemiological studies, when users are compared with non-users, confounding by indication becomes a great concern (54). In this meta-analysis, potential confounding by indication was tested; after excluding the only study that used an active-comparator the level of association moved from a lack to a positive association between antidepressants use and risk of dementia. Furthermore, when only studies of non-user design were pooled, a greater positive association between combined BZDs and Z-drugs use and risk of dementia was observed, suggesting potential confounding by indication. Future research should therefore consider using an active comparator to avoid confounding by indication in observational studies.

One physiological hypothesis supporting the association is that hypnotics potentiate GABA transmission by acting on $GABA_A$ receptors, lowering neuronal activity within the hippocampus, resulting in impaired cognitive function and inability to compensate for memory loss (55,56). Another hypothesis opposing the association is that sleep disturbances are associated with an increased level of amyloid beta (Aβ), which is crucially involved in the pathogenesis of Alzheimer's disease (3), and that sleep has a physiological role in the clearance of the amyloid beta (Aβ) and the microtubule-associated protein tau through the glymphatic system (1,2). Thus, it is logically assumed that improving or maintaining sleep, and in particular slow wave sleep through use of pharmacological or non-pharmacological approaches may offer some protection against Alzheimer's disease (1). Generally, due to controversial effectiveness and possible serious outcomes it is recommended to closely evaluate sedative-hypnotics use for sleep disorders (4). Further experiments using relevant animal models would be useful for evaluating the molecular mechanism of action of these drugs in relation to sleep and the progression of pathology.

Strengths and limitations

This meta-analysis possesses several strengths. First, it studied the risk of dementia associated with several types of sedative-hypnotics besides BZDs and assessed the effect of BZDs according to the duration of action. Second, it included a large number of studies with substantial populations, which it is anticipated will increase the generalizability of the findings. Third, we performed sensitivity analysis to strengthen the findings and address any potential methodological limitations. Moreover, the majority of included studies were adjusted for psychiatric disorders such as depression and anxiety, which are risk factors for dementia and

potential confounders. Additionally, sub-group analysis was conducted to evaluate the impact of geographical area, study design and quality level of included records on the pooled estimates.

Nevertheless, this review has several limitations. First, high heterogeneity raises concerns about the reliability of pooled results; although attempts were taken to identify sources of heterogeneity, any conclusions drawn must be accepted with caution. Second, the study results were based on the analysis of observational studies; therefore, the pooled results might be subject to uncontrolled or residual confounding. Third, despite the fact that sensitivity analysis was undertaken to exclude any potential source of bias, the duration of "lag-periods", in the studies that included one, varied substantially from one year to five years, which makes it possible that lag period in some of the studies was too short to be effective in removing bias. It is very challenging to address protopathic bias especially in our current study as we were restricted by what has been reported and performed in the eligible studies, however, we hope that by conducting a primary research, where we have the control over the study design, method and analysis, such as prospective cohort studies with long follow-up time, this issue of protopathic bias could be addressed. Moreover, variation of the length of follow-up periods between studies could have resulted in under- or overestimation of the results, thus a longer follow-up period is encouraged in future research to measure more precisely the risk of long-term use of sedative-hypnotics and better evaluate the role of sleep disturbances, anxiety and depression in the pathogenesis of dementia. Furthermore, there was inconsistency in defining exposures (e.g. some studies used elimination half-life, defined daily dose, ever-use vs. past use). Using a unified measure of exposure in future research might result in a pooled estimate with a lower level of heterogeneity and greater statistical reliability. We have not considered performing a network meta-analysis in our current study because the focus was to evaluate the association of sedative-hypnotics medications with dementia rather than comparing the effect of sedative-hypnotics medications to each other in terms of their association with dementia. However, we are planning to perform a network meta-analysis in our future study. Finally, 17 out of the 35 records did not mention polypharmacy among the confounding variables adjusted for, which increases the chance of pooled estimates being subject to uncontrolled confounding.

Conclusion

Based on pooled estimates, this research indicates that the use of antidepressants, antipsychotics and anticonvulsants is not associated with an increased risk of dementia. At the same time, BZDs appear to be associated with an increased risk of dementia, but this association is potentially confounded by indication and protopathic bias. Therefore, larger prospective cohort studies with

a longer follow-up period are needed to confirm whether the association is true or influenced by reverse causation and methodological biases.

Declaration of Interest

None

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Supporting information

- PRISMA checklist (docx.)
- The data that support the findings of this study are available on request from the corresponding author, *AsmaAlDawsari*.

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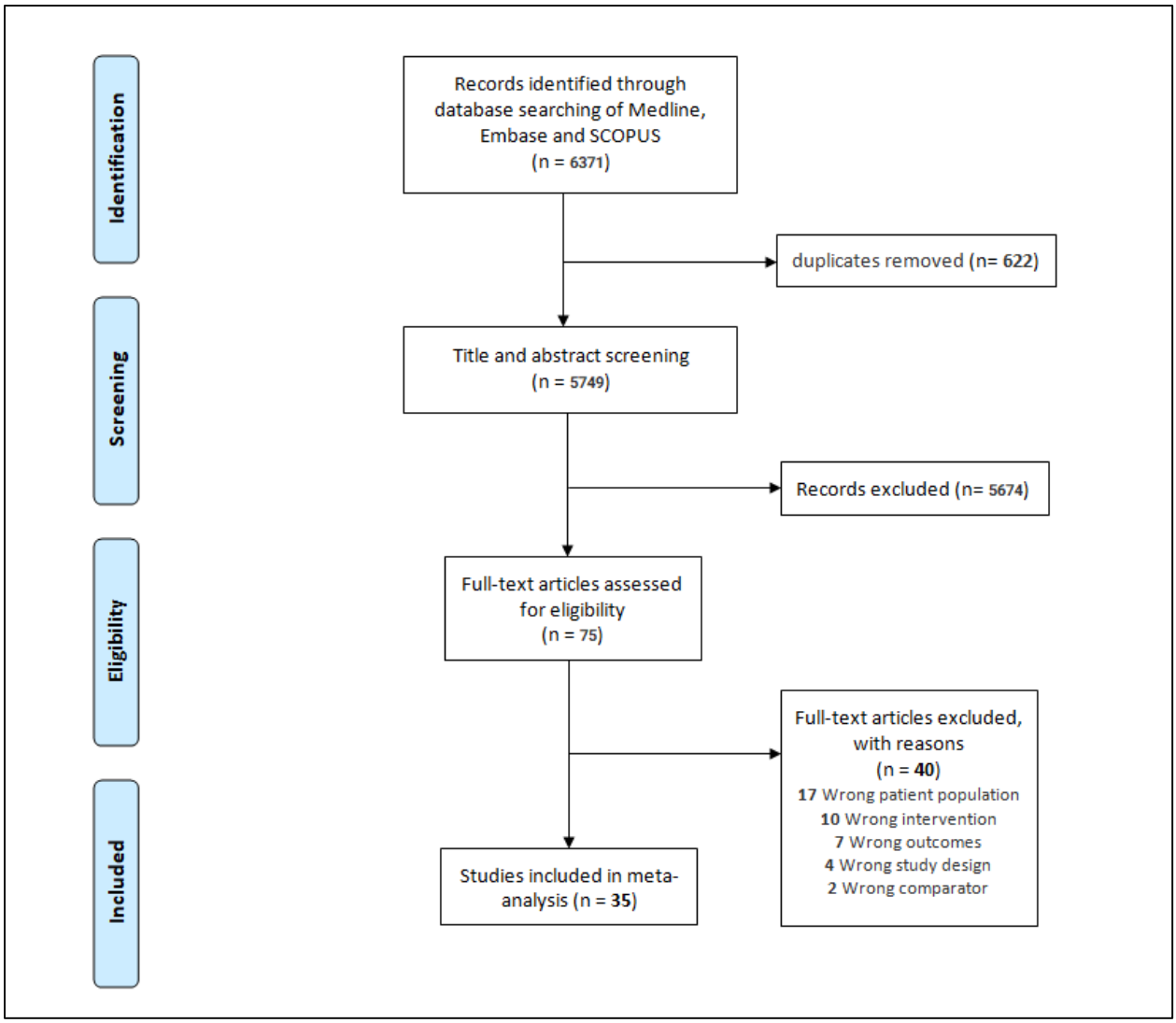
(Figure1). PRISMA flowchart of identification of studies.



(Table 1).Characteristics of the 35 included studies regarding sedative-hypnotics use and risk of dementia.

Authors/ study location	Study cohort	Exposure of interest	Definition of exposure	Exposure assessment	Outcome assessment	Adjusted factors	Introduction of lag-period	Quality score
Nafti M et al., 2020 Canada(46)	5281	BZDs	BZDs use	Face-to-face interview or self-reported in a questionnaire	Clinical diagnosis	Age, sex, education, smoking, alcohol intake, physical activity, depression, MI, HTN, stroke, diabetes and NSAIDs use.	No	9
Richardson K et al., 2019 UK(29)	324703	BZDs	BZDs use	Recorded prescriptions	Claim records	Sex, age, deprivation, smoking status, cardiovascular risk factors, depression, insomnia, sleep disturbance, antidepressants and antipsychotics use and physicians consultation.	Yes (4 years)	7
Hafdi M et al., 2019 Netherlands(22)	3526	BZDs	BZDs use and elimination half-life: short and long-acting	Self-report and recorded prescriptions	Clinical diagnosis	Sex, age, MMSE score, depressive symptoms at baseline and level of education.	No	7
Chan T et al., 2017 China(45)	273	BZDs	BZDs Prescribed daily dose (PDD): the total doses in milligrams divided by the total duration of use in days by all subjects in the cohort.	Recorded prescriptions	Clinical diagnosis	Depression and stroke/TIA	No	4
Gray Sh et al., 2016 USA(12)	3434	BZDs	Total standardized daily dose (TSDD): was calculated by multiplying the	Recorded prescriptions	Clinical diagnosis	Age, sex, educational level, BMI, current smoking, regular exercise, self-rated health, HTN, diabetes mellitus, stroke, coronary heart disease and history of high depressive symptoms.	Yes (5 years)	8

Authors/ study location	Study cohort	Exposure of interest	Definition of exposure	Exposure assessment	Outcome assessment	Adjusted factors	Introduction of lag-period	Quality score
			drug strength and the number					

Authors/ study location	Study cohort	Exposure of interest	Definition of exposure	Exposure assessment	Outcome assessment	Adjusted factors	Introduction of lag-period	Quality score
			of tablets dispensed.					
Takada M et al., 2016 Japan(36)	FAERS: 1,051,372 Canada: 77,041	BZDs	BZDs use	Online reporting database of adverse reactions	Claim records	-	No	5
Imfeld P et al., 2015 UK(13)	26459	BZDs Z-drugs BZDs and Z-drugs	BZDs use Z-drugs use BZDs and Z-drugs use	Recorded prescriptions	Clinical diagnosis	BMI, smoking status and depression.	No	8
Billioti de et al., 2014 Canada(49)	8980	BZDs	BZDs use and elimination half-life: short and long-acting	Face-to-face interview	Clinical diagnosis	HTN, MI, stroke, platelet inhibitors or oral anticoagulant use, diabetes mellitus, hypercholesterolaemia, anxiety, depression and insomnia.	No	5
Lagnaouia R et al., 2002 France(30)	3654	BZDs	BZDs use	Face-to-face interview	Clinical diagnosis	Age, gender, education, living alone, depression, history of psychiatric diseases and wine consumption.	No	7
Grossi C et al., 2019 UK(27)	3045	BZDs Antidepressants	BZDs use Antidepressants use	Face-to-face interview	Clinical diagnosis	Sex, age, education, social class, recruitment centre, study arm, stroke, PD, epilepsy, sleep problems, anxiety, depression and disability.	No	9
Tseng L et al., 2019 Taiwan(44)	260502	BZDs Z-drugs BZDs and Z-drugs	BZDs elimination half-life Z-drug use BZDs and Z-drug use	Recorded prescriptions	Clinical diagnosis	Age, sex, comorbidity Index, and anticholinergic cognitive burden (ACB) score.	Yes (1 year)	9

Authors/ study location	Study cohort	Exposure of interest	Definition of exposure	Exposure assessment	Outcome assessment	Adjusted factors	Introduction of lag-period	Quality score
Lee J et al., 2018 Korea(11)	268170	BZDs Z-drugs Antidepressants	BZDs elimination half-life Z-drug use Antidepressants use	Recorded prescriptions	Clinical diagnosis	Sex, diabetes mellitus, HTN, hyperlipidaemia, CVDs, anxiety, insomnia, depression and psychotic disorder.	Yes (5 years)	8
Tapiainen V et al., 2018 Finland(33)	353581	BZDs Z-drugs BZDs and Z-drugs	BZDs use Z-drug use BZDs and Z-drug use	Recorded prescriptions	Claim records	Antidepressant use, antipsychotic use, any mental disorder, substance abuse, asthma/COPD, CVDs, diabetes and socioeconomic position.	Yes (5 years)	6
Bietry F et al., 2017 Switzerland(28)	2876	BZDs Z-drugs BZDs and Z-drugs	BZDs, Z-drugs, BZDs and Z-drugs use and duration of use (number of prescriptions)	Recorded prescriptions	Claim records	Age, sex, home location and antidepressants use.	Yes (2 years)	8
Park H et al., 2017 Korea(37)	11124	BZDs Z-drugs H2-receptor antagonists	BZDs use and elimination half-life Z-drugs use H2-receptor antagonists use	Recorded prescriptions	Claim records	Comorbidities and Potentially inappropriate medication (PIM) use.	No	8
Gomm W et al., 2016 Germany(25)	105725	BZDs and Z-drugs	BZDs and Z-drugs use	Recorded prescriptions	Claim records	Polypharmacy and comorbidities.	Yes (2 years)	7
Brodrick J et al., 2016 USA(50)	74	BZDs Antidepressants	BZDs use Antidepressants use	Recorded prescriptions	Clinical diagnosis	-	No	5
Chiu H et al., 2015 Taiwan(43)	5960	BZDs and Z-drugs	BZDs and Z-drugs use	Recorded prescriptions	Clinical diagnosis	Propensity score (the propensity to receive treatment that was conditional on the baseline characteristics).	No	7
Shash D et al.,	8240	BZDs	BZDs use and	Face-to-face	Clinical	Age, sex, BMI, living status,	No	7

Authors/ study location	Study cohort	Exposure of interest	Definition of exposure	Exposure assessment	Outcome assessment	Adjusted factors	Introduction of lag-period	Quality score
2015 France(10)		Psychotropic medication	elimination half-life Psychotropics use	interview	diagnosis	education, self-perceived health, alcohol consumption, smoking, diabetes, history of cardiovascular or cerebrovascular disease, hypercholesterolemia, cognitive status, centre, cranial trauma, depressive symptoms, anxiety and insomnia.		
Chen PL et al., 2012 Taiwan(42)	34158	BZDs and Z-drugs	BZDs and Z-drugs use and elimination half-life	Recorded prescriptions	Clinical diagnosis	HTN, type 2 diabetes mellitus, hyperlipidemia and stroke.	No	6
Gallacher J et al., 2011 UK(26)	1134	BZDs	BZDs use	Assessment of medication history	Clinical diagnosis	Age, social class, smoking, alcohol intake, education, BMI, angina, IHD, MMSE at baseline, anxiety and daytime sleepiness.	No	5
Wu Ch et al., 2009 Taiwan(39)	5405	BZDs BZDs and Z-drugs	BZDs, BZDs and Z-drugs use, duration of use and cumulative dose	Recorded prescriptions	Claim records	Mood disorder, anxiety disorder, alcoholism, psychotic-related disorder, HTN, diabetes, CVDs, and dyslipidemia.	No	7
Cheng H et al., 2017 Taiwan(41)	6922	Z-drugs	Z-drugs use	Recorded prescriptions	Claim records	Age, sex, HTN, stroke, MI, diabetes, anxiety, depression, hypercholesterolemia, psychotic-related disorder, alcohol-related disorder, sleep disorder, PD, head injury and polypharmacy.	No	9

Authors/ study location	Study cohort	Exposure of interest	Definition of exposure	Exposure assessment	Outcome assessment	Adjusted factors	Introduction of lag-period	Quality score
Shih HI et al., 2015	25218	Z-drugs	Z-drugs use	Recorded prescriptions	Claim records	Age, sex, CAD, diabetes, anti-hypertension drugs,	No	8

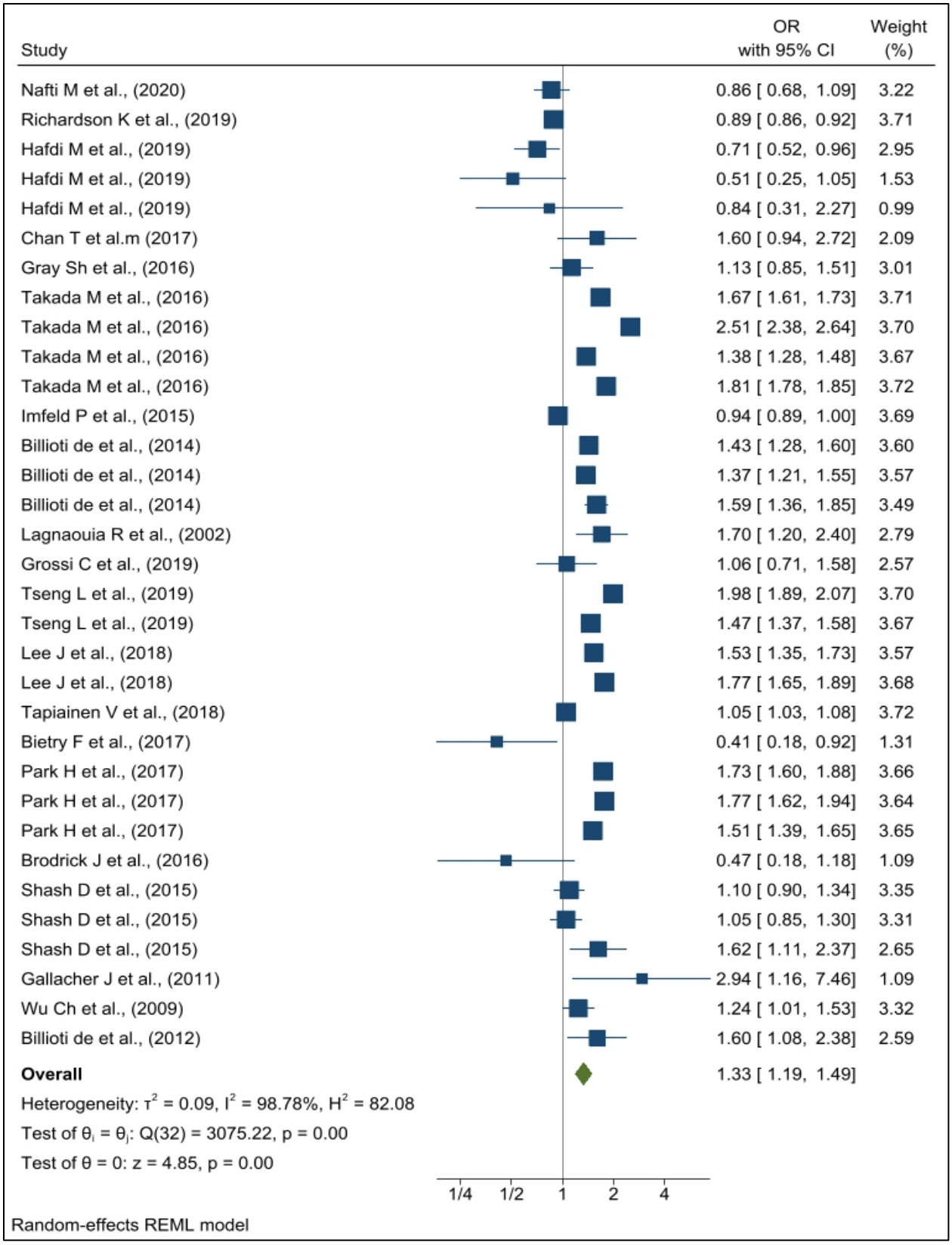
Authors/ study location	Study cohort	Exposure of interest	Definition of exposure	Exposure assessment	Outcome assessment	Adjusted factors	Introduction of lag-period	Quality score
Taiwan(40)						stroke, statin, depression, anxiety and BZD use.		
Liu Y et al., 2020-07-13 Taiwan(38)	790240	Antidepressants Antipsychotics	Antidepressants use Antipsychotic use	Recorded prescriptions	Claim records	Sex, age group, geographical area of residence, urbanization level, monthly income and comorbidities.	No	8
Richardson K et al., 2018 UK(32)	324703	Antidepressants Antipsychotics	Antidepressants use Antipsychotic use	Recorded prescriptions	Health records	Age, region, falls, fractures, number of doctor consultations, number of prescriptions for the following drugs: BZD, Z-drugs, antinausea, antivertigo, antiepileptics, and antiparkinson drugs.	No	8
Roughead E et al., 2017 Australia(52)	15612	Antipsychotics	Antipsychotic use	Recorded prescriptions	Claim records	Socioeconomic status, HTN, diabetes mellitus, CVDs, cancer, clinical depression, substance abuse, alcohol,tobacco and BZD use.	No	7
Brauer R et al., 2019 UK(31)	424996	Trazodone	Trazodone use	Recorded prescriptions	Health records	Patients characteristics including age, lifestyle variables and risk factors for dementia.	No	9
Heath L et al., 2018 USA(47)	3059	Paroxetine Non-paroxetine SSRIs TCAs SARIs	Total standardized daily doses (TSDDs)	Recorded prescriptions	Health records	Age, sex, race, education, depression , and baseline covariates including Cognitive Abilities Screening Instrument score, hypertension, diabetes, heart disease CVDs, BMI, exercise, and history of smoking.	Yes (2 years)	7

Authors/ study location	Study cohort	Exposure of interest	Definition of exposure	Exposure assessment	Outcome assessment	Adjusted factors	Introduction of lag-period	Quality score
Bali V et al.,	23748	Paroxetine	Paroxetine use	Recorded	Claim	Sex, endocarditis, IHD, MI,	No	5

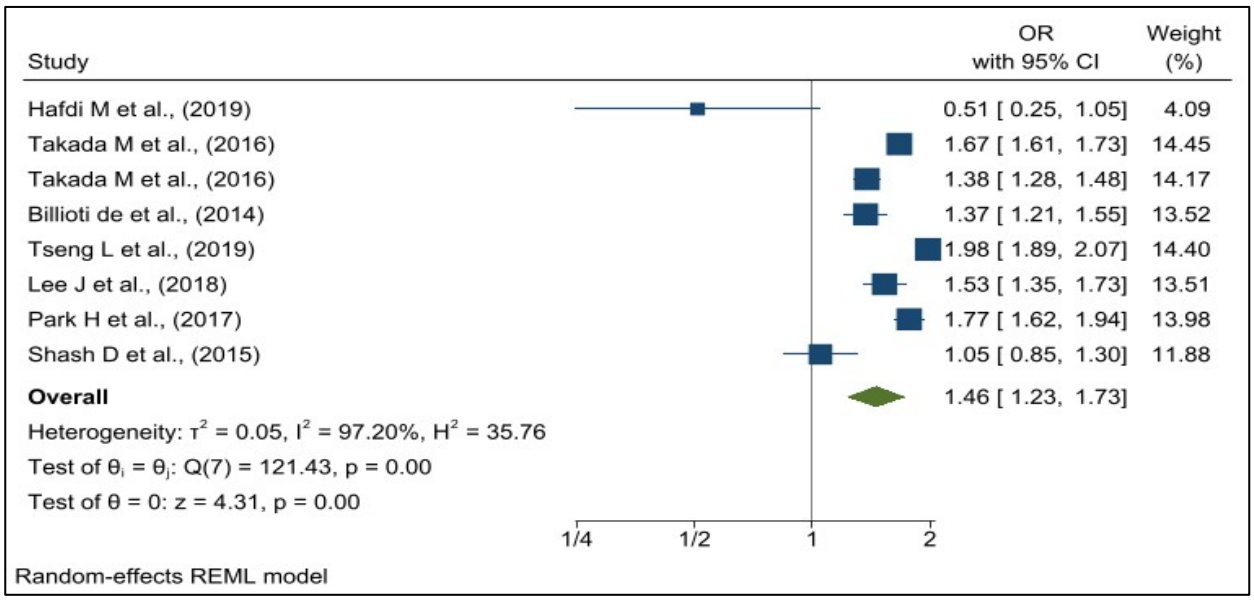
Authors/ study location	Study cohort	Exposure of interest	Definition of exposure	Exposure assessment	Outcome assessment	Adjusted factors	Introduction of lag-period	Quality score
2015 USA(48)				prescriptions	records	arrhythmia, mood disorder, antihyperlipidemic drugs and hematological agents.		
Lee CWS et al., 2017 Taiwan(35)	3548	SSRIs TCAs	SSRIs use TCAs use	Recorded prescriptions	Health records	Propensity score and other groups of antidepressants.	No	8
Gerhard T et al., 2015 USA(50)	41 931	Lithium Anticonvulsants	Lithium and anticonvulsants continuous use	Recorded prescriptions	Claim records	Gender, ethnicity, age, medical eligibility, long-term care residency, depression, anxiety, alcohol-related disorders, drug-related disorders, CVD, diabetes, PD, antidepressant, antipsychotic and anti-anxiety medications use.	No	8
Kessing L et al., 2010 Denmark(34)	4856	Lithium Anticonvulsants Antipsychotics Antidepressants	Number of prescriptions (duration of use)	Recorded prescriptions	Clinical diagnosis	Any purchase of anticonvulsants, antidepressants or antipsychotics.	No	7
Kessing L et al., 2010 Denmark(23)	4856	SSRIs	Number of prescriptions (duration of use)	Recorded prescriptions	Clinical diagnosis	Any purchase of anticonvulsants, antidepressants or antipsychotics.	No	8
Billioti de et al., 2012 France(24)	1063	BZDs	New use of BZDs	Face-to-face interview	Clinical diagnosis	Age, sex, education, singleness, wine consumption, polypharmacyandMMSE between inclusion (T0) and three year follow-up visit (T3).	No	9

Abbreviations: BZD, benzodiazepine; MI, Myocardial infarction; HTN, hypertension; NSAIDs, nonsteroidal inflammatory drugs; MMSE, Mini-Mental State Examination; FAERS, Food and Drug Administration Adverse Event Reporting System; TIA, transient ischaemic attack; BMI, body mass index; CVDs, cerebrovascular diseases; ,IHD, ischemic heart disease; PD, Parkinson's disease.

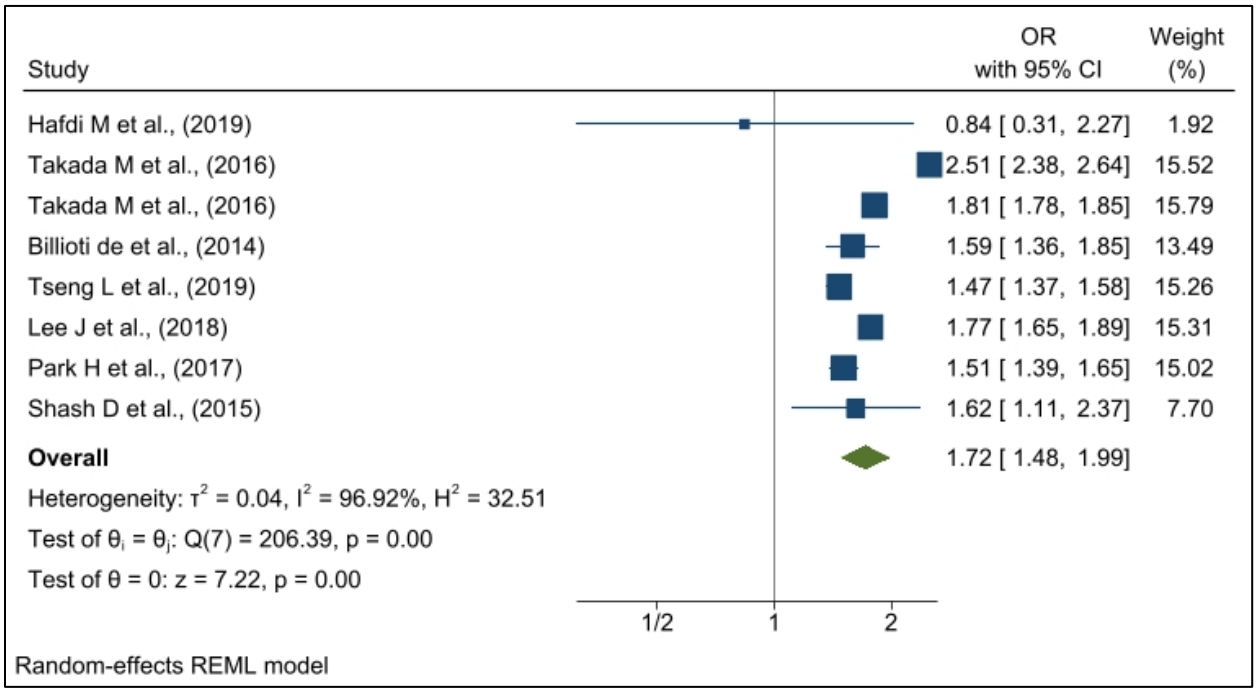
(Figure 2). Meta-analysis on sedative-hypnotics use and risk of dementia.



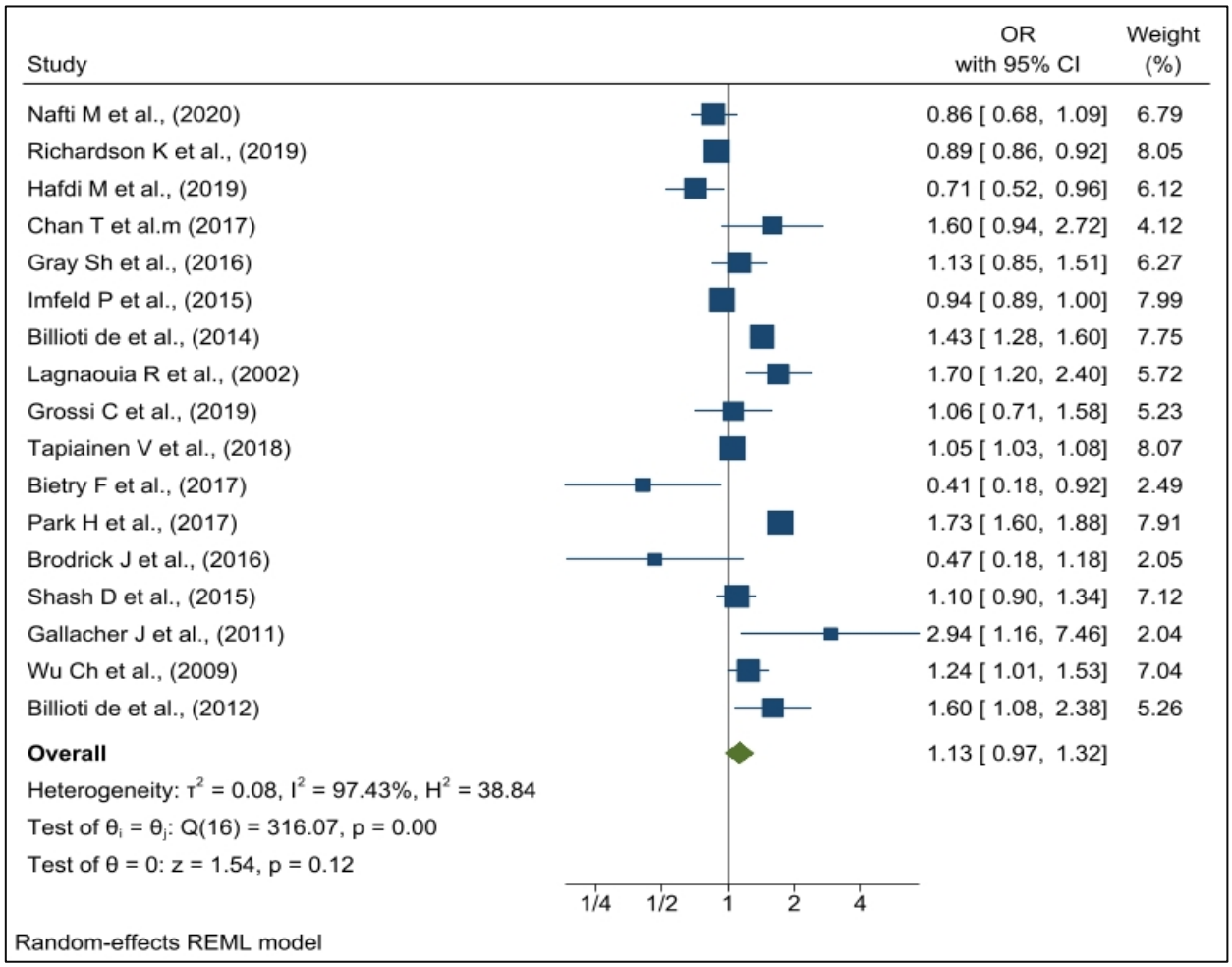
(Figure 2A). Meta-analysis on BZDs combined use and risk of dementia (Subgroup-1).



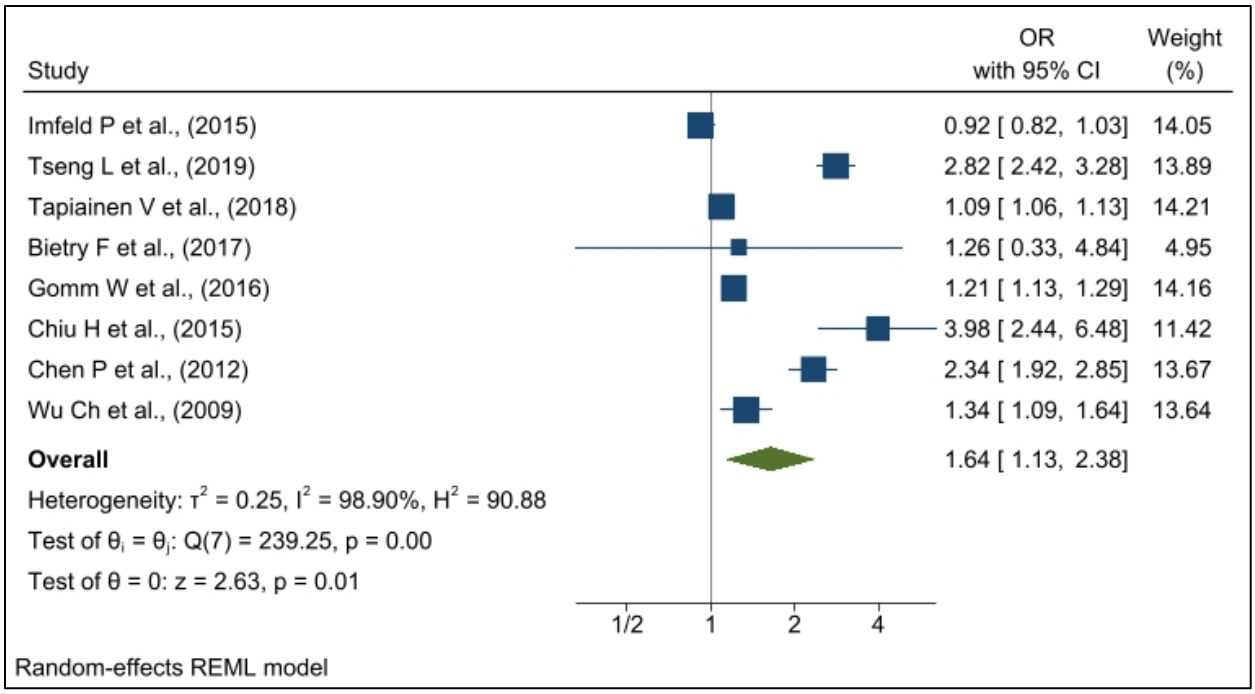
(Figure 2B). Meta-analysis on short-acting BZDs and risk of dementia (Subgroup-2).



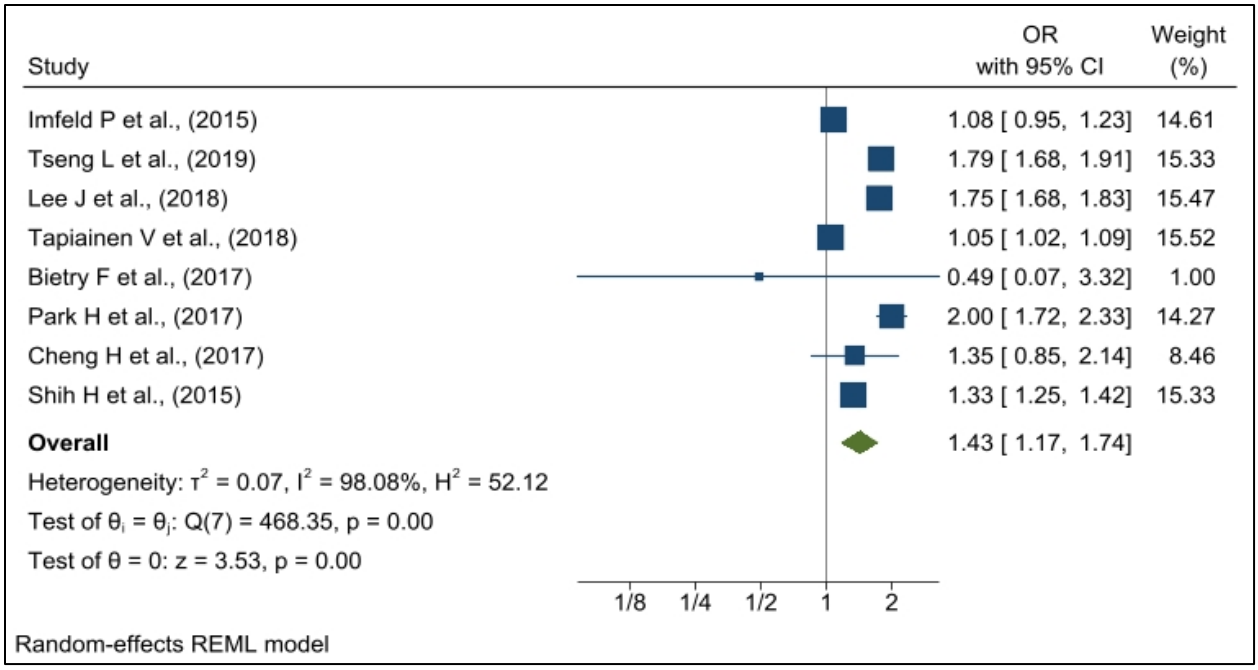
(Figure 2C). Meta-analysis on long-acting BZDs use and risk of dementia (Subgroup-3).



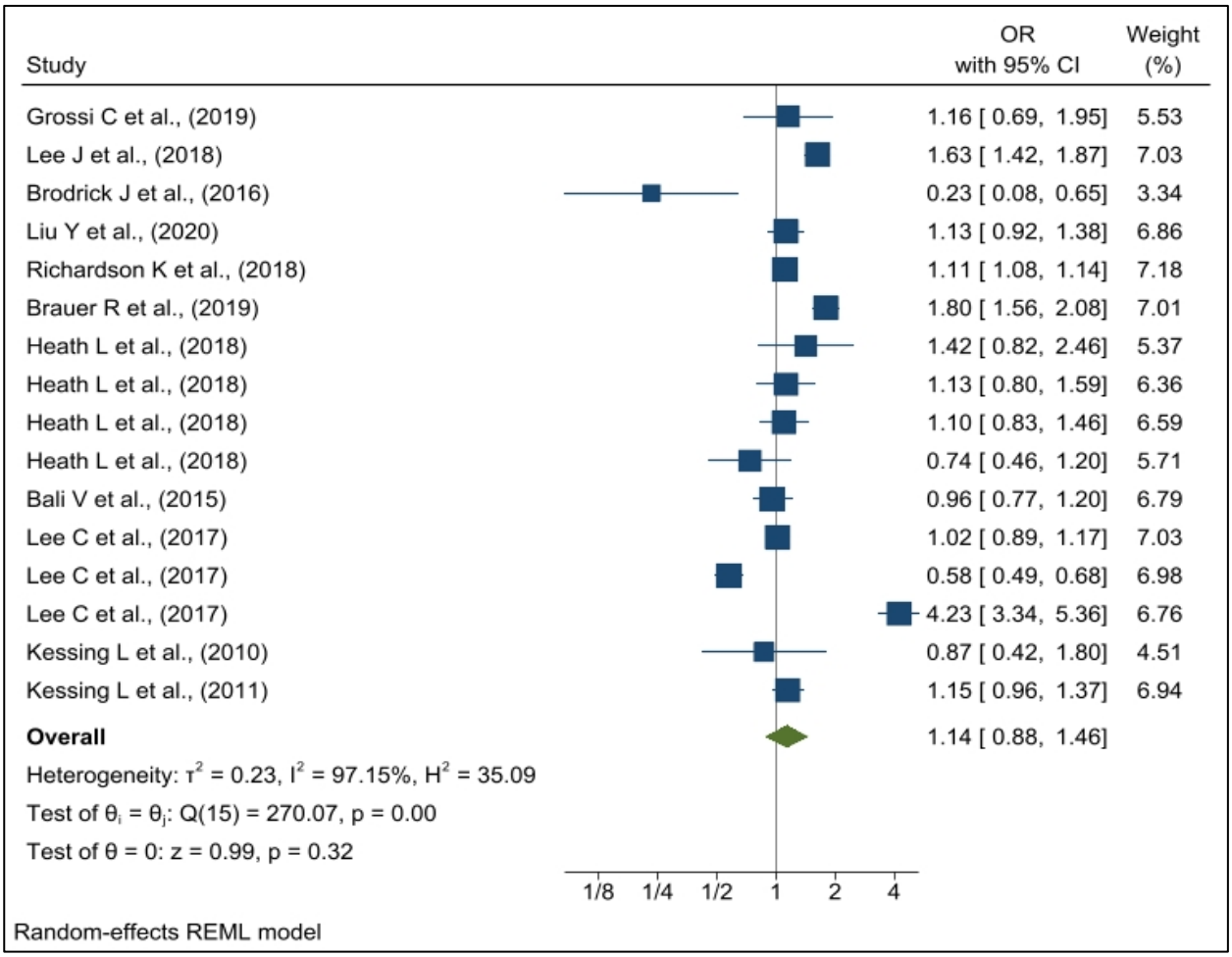
(Figure 2D). Meta-analysis on BZDs use as a whole without specification of duration of action and risk of dementia (Subgroup-4).



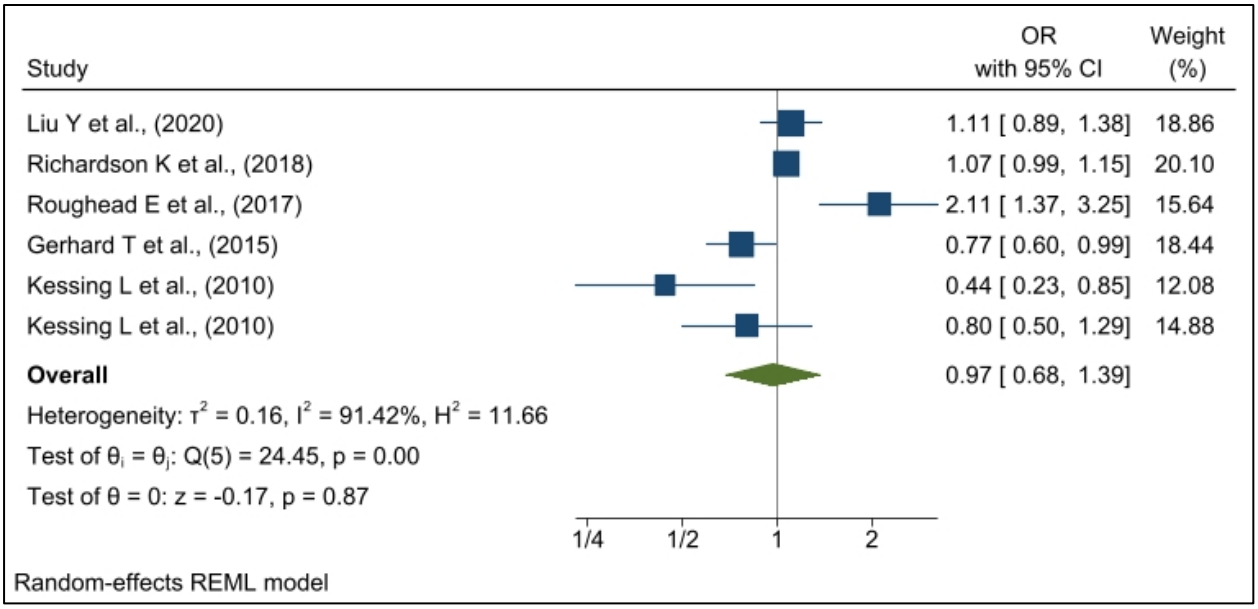
(Figure 2E). Meta-analysis on BZDs and Z-drugs combined use and risk of dementia.



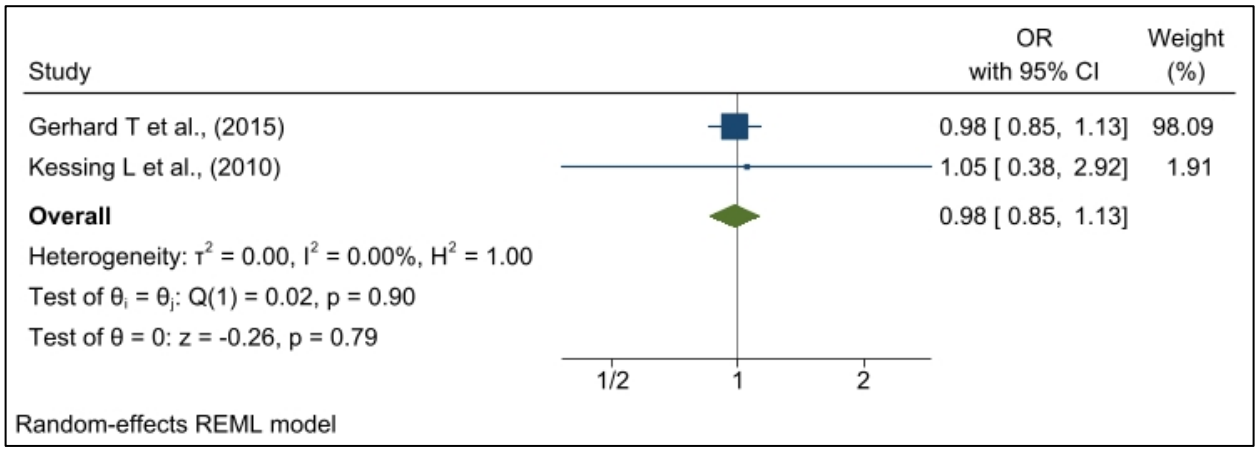
(Figure 2F). Meta-analysis on Z-drugs use and risk of dementia.



(Figure 2G). Meta-analysis on antidepressants use and risk of dementia.



(Figure 2H). Meta-analysis on antipsychotics use and risk of dementia.



(Figure 2I). Meta-analysis on anticonvulsants use and risk of dementia.

The squares represent the OR for each individual study, with the area reflecting the weight assigned to the study. The horizontal line across each square represents the 95% confidence interval. The diamond represents the pooled estimate (OR), with the width representing 95% confidence interval.

(Table 2). Subgroup analyses of sedative-hypnotics use and risk of dementia.

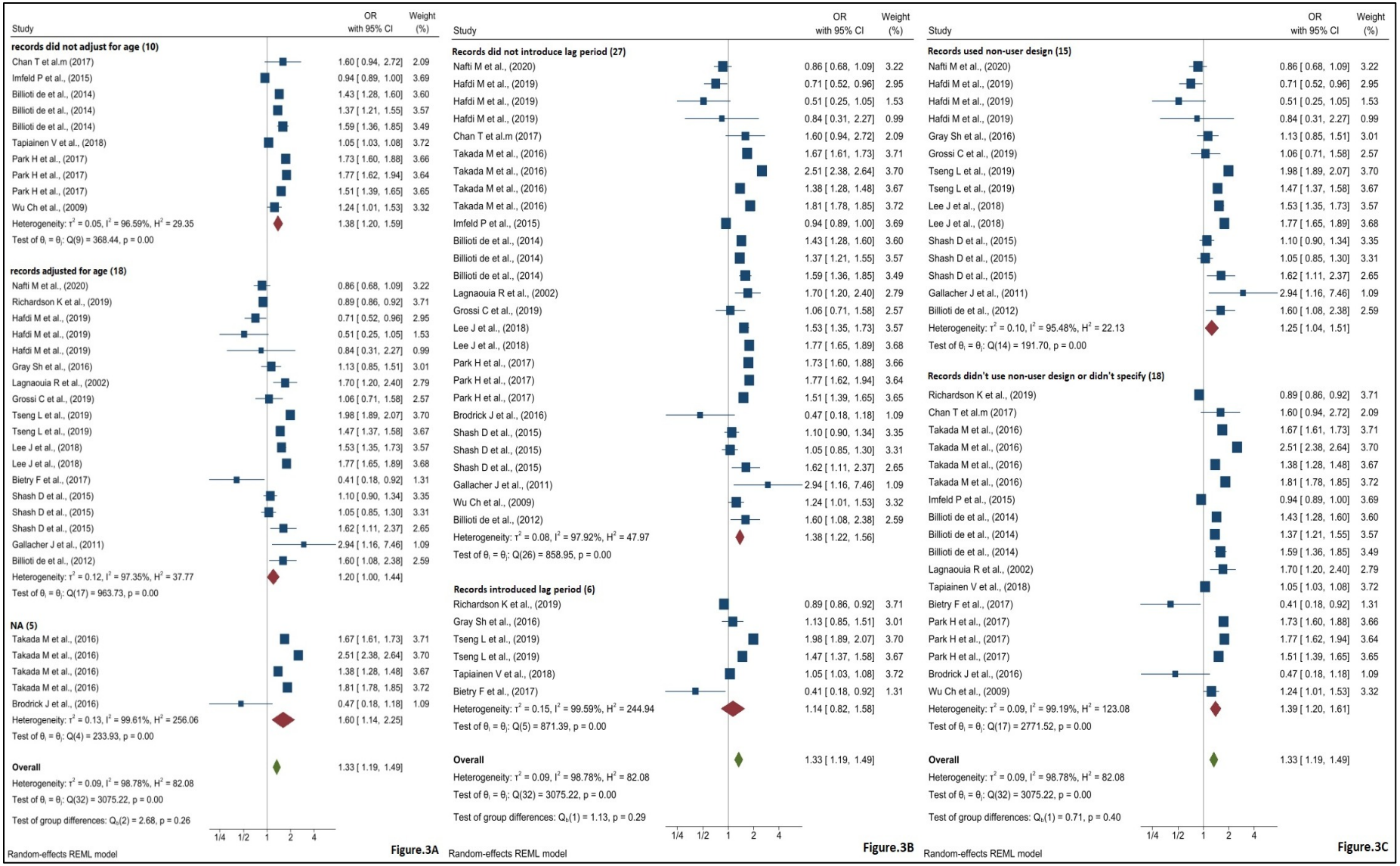
Country of study				Study Design				Level of Quality			
BZDs use – without specification of the duration of action (Subgroup-4) - (17 Records)											
Group[a]	**n**	**OR(95% CI)**	**I^2 (%)**	**Group[a]**	**n**	**OR(95% CI)**	**I^2 (%)**	**Group[a, b]**	**n**	**OR(95% CI)**	**I^2 (%)**
Canada	2	1.12 (0.68,1.09)	93	Prospective Cohort	7	1.08 (0.86-1.35)	70	High	12	1.09(0.91, 1.3)	96
France	3	1.39 (1.03, 1.87)	64	Retrospective Cohort	-	-	-	Moderate	3	1.21 (0.72,2.03)	98
UK	4	0.92 (0.87, 0.97)	40	Case-control	10	1.15 (0.92, 1.42)	99	Low	1	-	-
USA	2	0.81(0.35, 1.88)	69								
short-acting BZDs (Subgroup-2) (8 Records)											
Group[a]	**n**	**OR(95% CI)**	**I^2 (%)**	**Group[a]**	**n**	**OR(95% CI)**	**I^2 (%)**	**Group[a, b]**	**n**	**OR(95% CI)**	**I^2 (%)**
Japan	2	1.52 (1.26, 1.83)	95	Prospective Cohort	3	1.09 (0.53, 2.26)	97	High	5	1.35 (0.93, 1.97)	98
Korea	2	1.66 (1.44, 1.91)	72	Case-control	4	1.54 (1.36, 1.75)	92	Moderate	3	1.48 (1.29, 1.69)	90
long-acting BZDs (Subgroup-3) (8 Records)											
Group[a]	**n**	**OR(95% CI)**	**I^2 (%)**	**Group[a]**	**n**	**OR(95% CI)**	**I^2 (%)**	**Group[a, b]**	**n**	**OR(95% CI)**	**I^2 (%)**
Japan	2	2.13 (1.55, 2.93)	99	Prospective Cohort	3	1.47 (1.37, 1.58)	0	High	5	1.57 (1.41, 1.75)	74
Korea	2	1.64 (1.4, 1.91)	88	Retrospective Cohort	1	-	-	Moderate	3	1.94 (1.49, 2.53)	99
				Case-control	4	1.83 (1.46, 2.29)	98.3				
BZDs and Z-drugs combination (8 Records)											
Group[a]	**n**	**OR(95% CI)**	**I^2 (%)**	**Group[a]**	**n**	**OR(95% CI)**	**I^2 (%)**	**Group[a, b]**	**n**	**OR(95% CI)**	**I^2 (%)**
Taiwan	4	2.37 (1.54, 3.64)	93	Prospective Cohort	2	3.09 (2.29, 4.16)	43	High	6	1.67 (1.04, 2.69)	98
				Retrospective Cohort	1	-	-	Moderate	2	1.59 (0.75, 3.35)	98
				Case-control	5	1.12 (0.97, 1.29)	90				
Z-drugs (8 Records)											
Group[a]	**n**	**OR(95% CI)**	**I^2 (%)**	**Group[a]**	**n**	**OR(95% CI)**	**I^2 (%)**	**Group[a, b]**	**n**	**OR(95% CI)**	**I^2 (%)**
Korea	2	1.83 (1.62, 2.08)	63.6	Prospective Cohort	1	-	-	High	7	1.52 (1.25, 1.84)	96
Taiwan	3	1.51 (1.2, 1.9)	93.6	Retrospective Cohort	2	1.71 (1.47, 1.98)	18	Moderate	1	-	-
				Case-control	5	1.29 (0.97, 1.71)	97.7				
Antidepressants (11 Records)											
Group[a]	**n**	**OR(95% CI)**	**I^2 (%)**	**Group[a]**	**n**	**OR(95% CI)**	**I^2 (%)**	**Group[a, b]**	**n**	**OR(95% CI)**	**I^2 (%)**
Taiwan	2	1.29 (0.57, 2.94)	99	Prospective Cohort	3	1.10 (0.97, 1.26)	0	High	9	1.22 (0.95, 1.57)	97

UK	3	1.35 (0.96, 1.89)	93	Retrospective Cohort	5	1.30 (0.99, 1.71)	89	Moderate	2	0.52 (0.13, 2.05)	86
USA	3	1.0 (0.87, 1.15)	0	Case-control	3	0.97 (0.4, 2.34)	99.5				

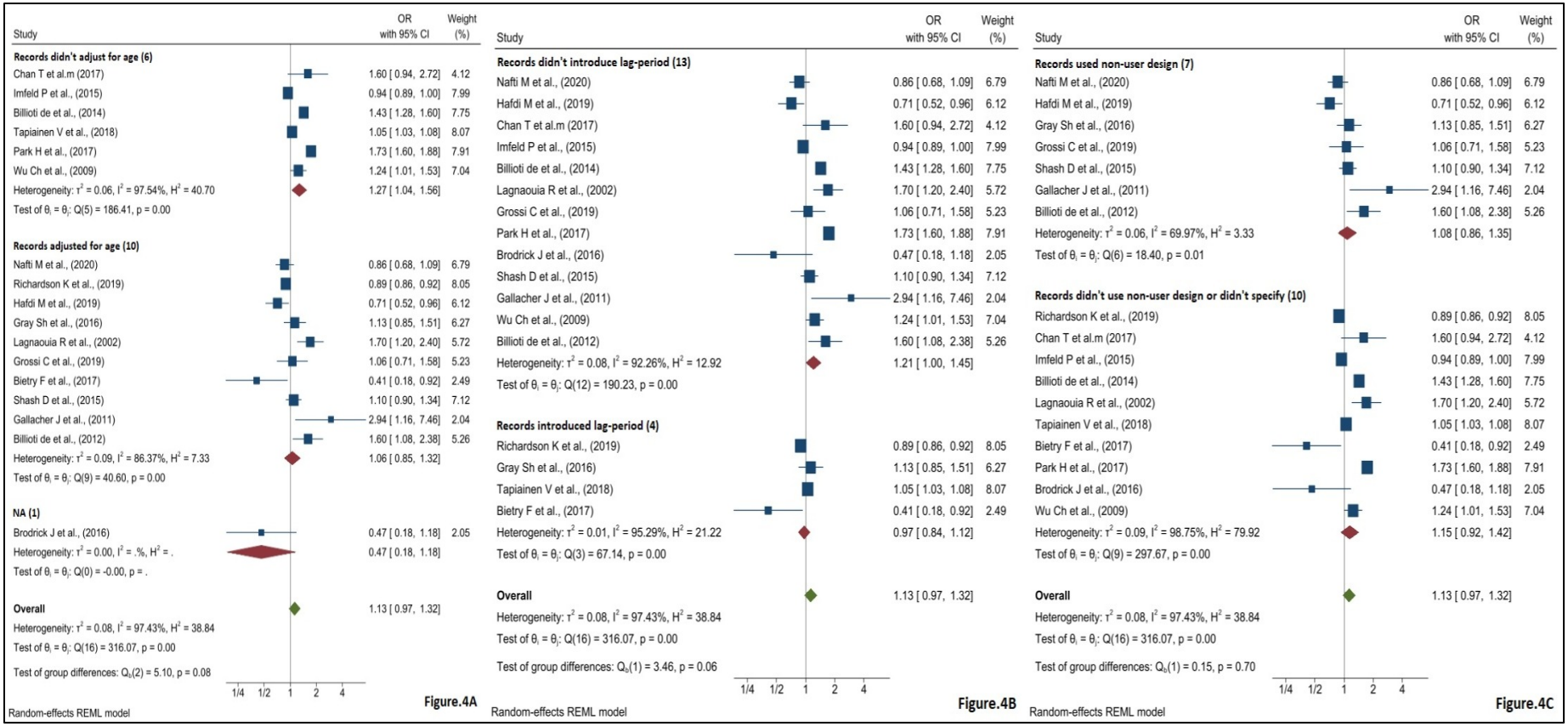
a: Groups of one study only were not mentioned as they have I^2=0%

b: High quality (NOS score of ≥7), moderate quality (NOS score of 5-6), low quality (NOS score of ≤4)

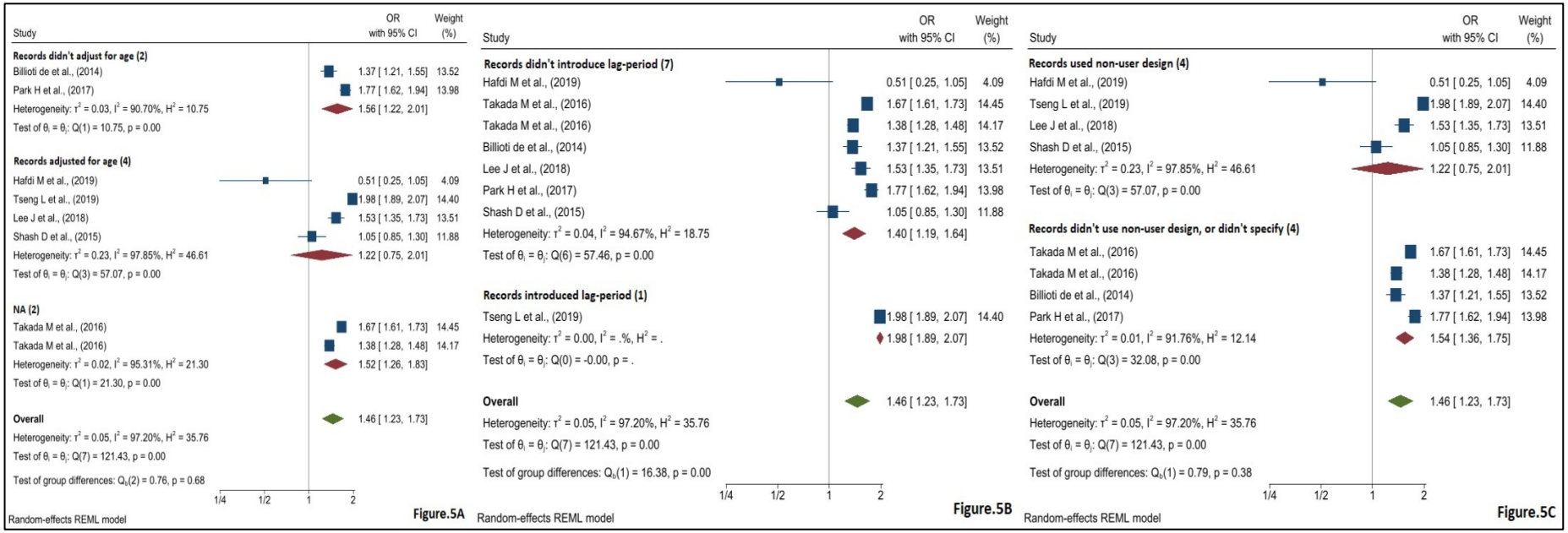
(Figure 3) Sensitivity analysis of BZDs combined use (Subgroup-1): **(Figure 3A)** sensitivity analysis for adjusting for age covariate. **(Figure 3B)** sensitivity analysis for introducing lag-period.**(Figure 3C)** sensitivity analysis for using non-user design.



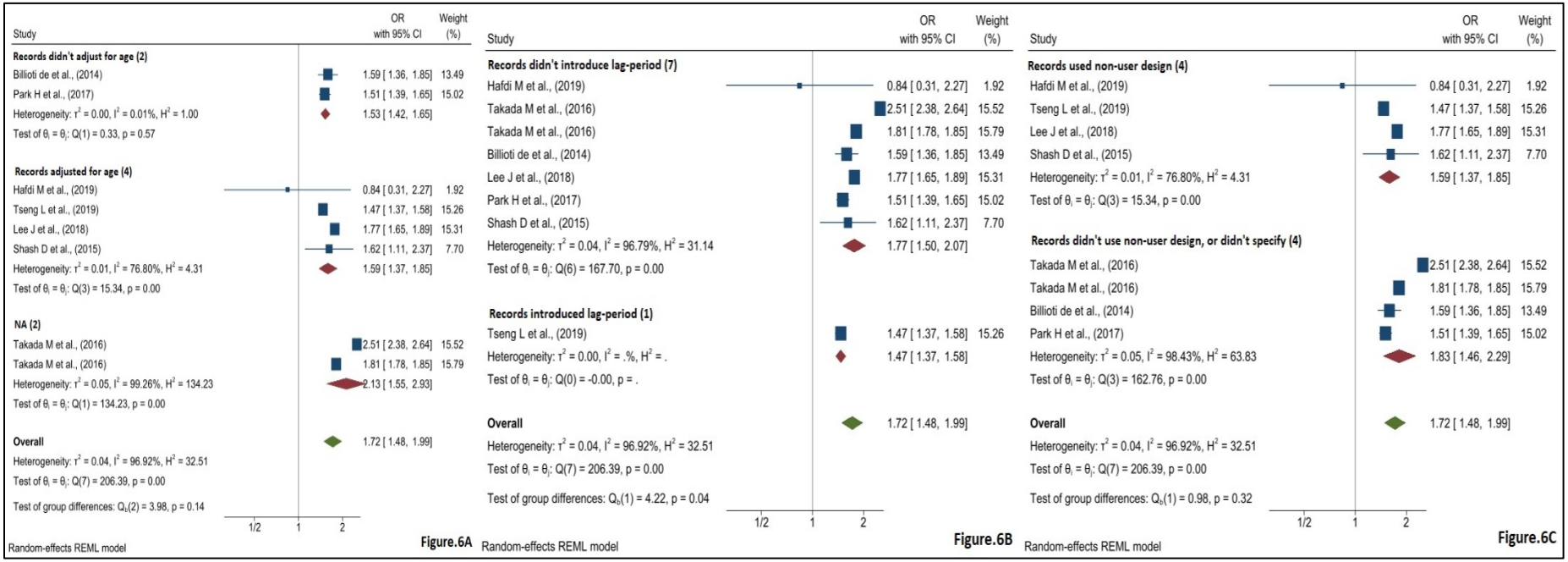
(Figure 4) Sensitivity analysis of BZDs use without specification of the duration of action (Subgroup-4):**(Figure 4A)** sensitivity analysis for adjusting for age covariate. **(Figure 4B)** sensitivity analysis for introducing lag-period.**(Figure 4C)** sensitivity analysis for using non-user design.



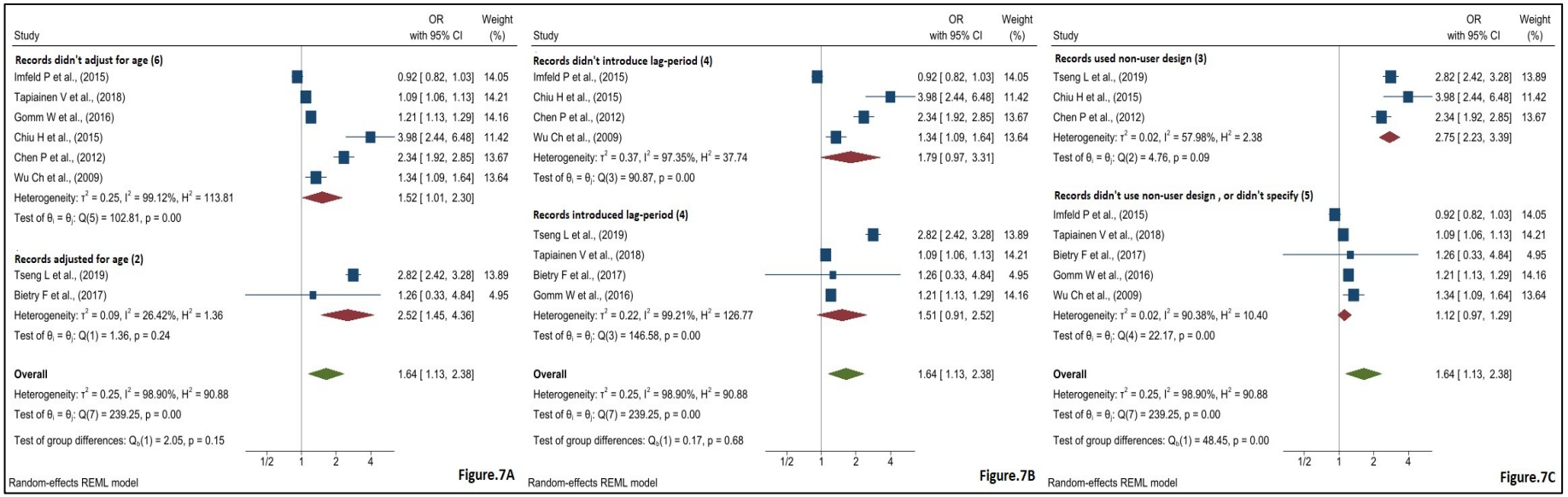
(Figure 5) Sensitivity analysis for short-acting BZDs use (Subgroup-2):**(Figure 5A)** sensitivity analysis for adjusting for age covariate. **(Figure 5B)** sensitivity analysis for introducing lag-period.**(Figure 5C)** sensitivity analysis for using non-user design.



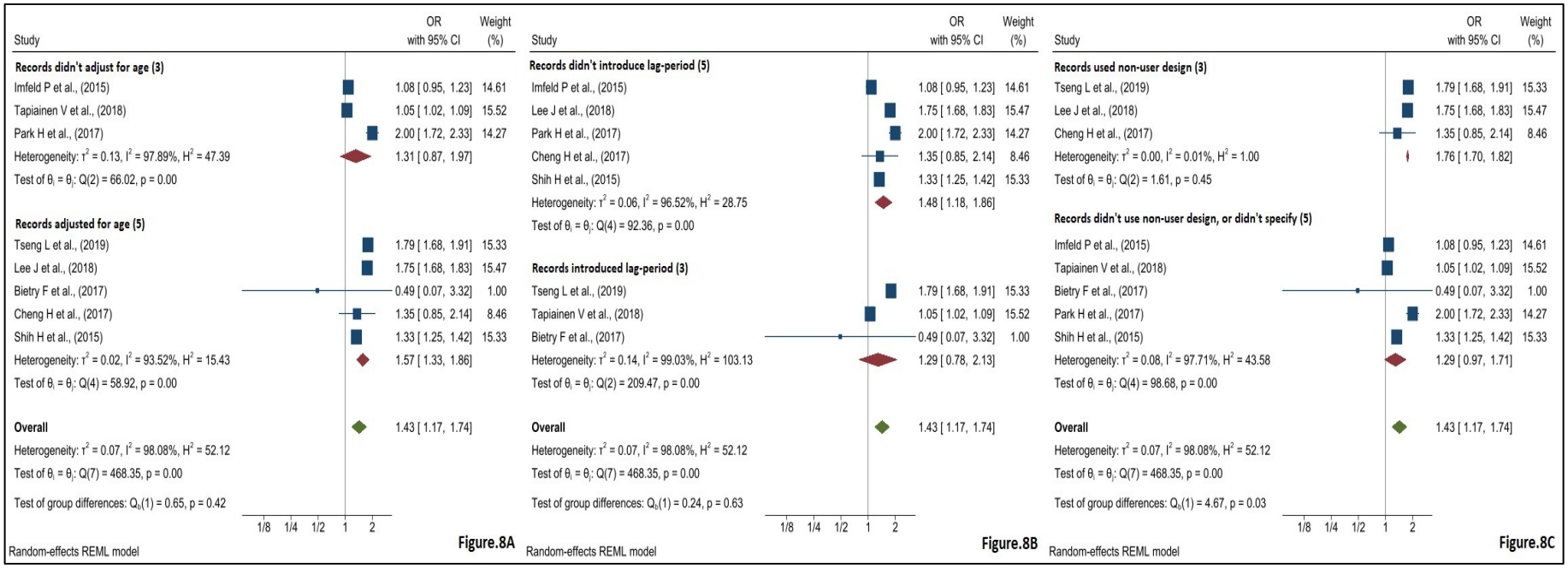
(Figure6) Sensitivity analysis for long-acting BZDs use (Subgroup-3): **(Figure 6A)** sensitivity analysis for adjusting for age covariate. **(Figure 6B)** sensitivity analysis for introducing lag-period.**(Figure 6C)** sensitivity analysis for using non-user design.



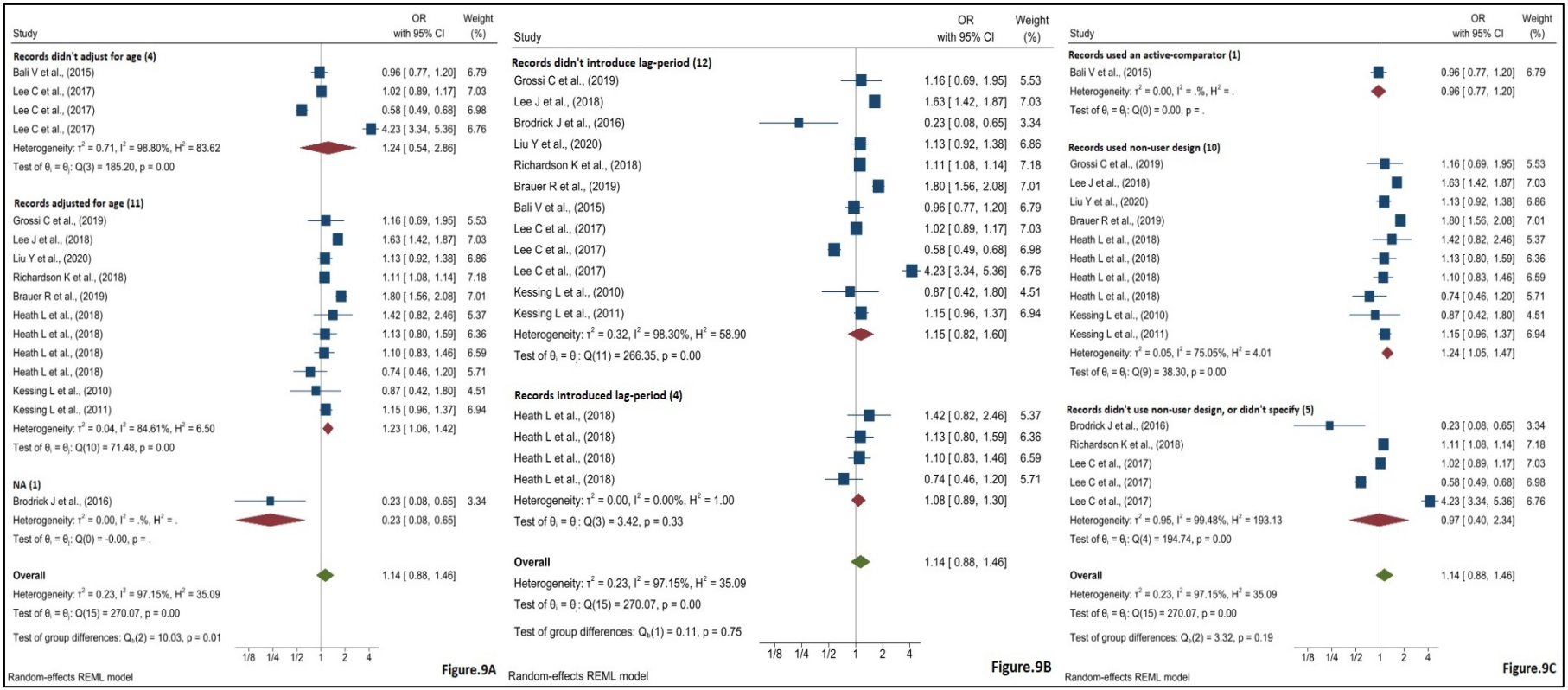
(Figure 7) Sensitivity analysis for BZDs and Z-drugs combined use: **(Figure 7A)** sensitivity analysis for adjusting for age covariate. **(Figure 7B)** sensitivity analysis for introducing lag-period.**(Figure 7C)** sensitivity analysis for using non-user design.



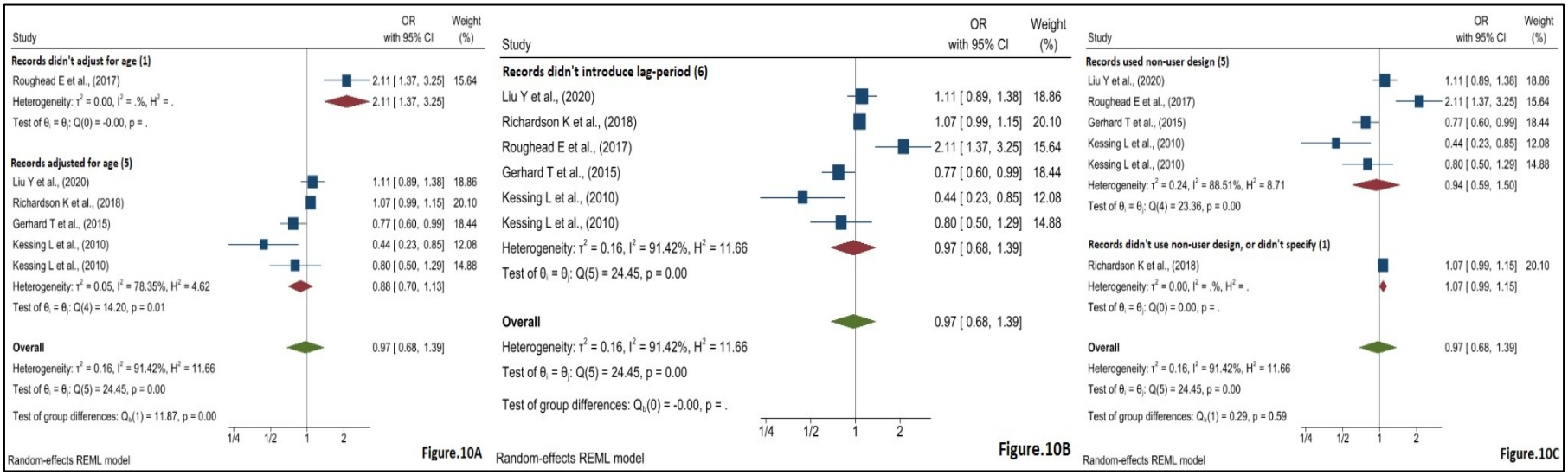
(Figure 8) Sensitivity analysis for Z-drugs use: **(Figure 8A)** sensitivity analysis for adjusting for age covariate. **(Figure 8B)** sensitivity analysis for introducing lag-period.**(Figure 8C)** sensitivity analysis for using non-user design.



(Figure 9) Sensitivity analysis for antidepressants use: **(Figure 9A)** sensitivity analysis for adjusting for age covariate. **(Figure 9B)** sensitivity analysis for introducing lag-period.**(Figure 9C)** sensitivity analysis for using non-user design.



(Figure 10) Sensitivity analysis for antipsychotics use: **(Figure 10A)** sensitivity analysis for adjusting for age covariate. **(Figure 10B)** sensitivity analysis for introducing lag-period.**(Figure 10C)** sensitivity analysis for using non-user design.



(Table 3). Summary of the Pooled estimates of the associations between the various sedative-hypnotic medications and dementia.

Sedative-Hypnotics	**Overall Pooled estimates (OR)**	**Effect of adjustment for age covariate**		**Effect of introduction of lag-period (control for protopathic bias)**		**Effect of non-user design (potential confounding by indication)**	
		Records didn't adjust for age	**Records Adjusted for age**	**Records didn't introduce lag-period**	**Records introduced lag-period**	**Records used non-user design**	**Records didn't use non-user design or didn't specify**
BZDs from all records (sub-group 1)	(OR:1.33, 95%CI 1.19-1.49)	(OR:1.38, 95%CI 1.20-1.59)	(OR:1.20, 95%CI 1.00-1.44)	(OR:1.38, 95%CI 1.22-1.56)	(OR:1.14, 95%CI 0.82-1.58)	(OR:1.25, 95%CI 1.04-1.51)	(OR:1.39, 95%CI 1.20-1.61)
Short-acting BZDs (sub-group 2)	(OR:1.46, 95%CI 1.23-1.73)	(OR:1.56, 95%CI 1.22-2.01)	(OR:1.22, 95%CI 0.75-2.01)	(OR:1.40, 95%CI 1.19-1.64)	(OR:1.98, 95%CI 1.89-2.07)	(OR:1.22, 95%CI 0.75-2.01)	(OR:1.54, 95%CI 1.36-1.75)
Long-acting BZDs use (sub-group 3)	(OR:1.72, 95% CI 1.48-1.99)	(OR:1.53, 95%CI 1.42-1.65)	(OR:1.59, 95%CI 1.37-1.85)	(OR:1.77, 95%CI 1.50-2.07)	(OR:1.47, 95%CI 1.37-1.58)	(OR:1.59, 95%CI 1.37-1.85)	(OR:1.83, 95%CI 1.46-2.29)
BZDs without specification of the duration of action (sub-group 4)	(OR:1.13, 95% CI 0.97-1.32)	(OR:1.27, 95%CI 1.04-1.56)	(OR:1.06, 95%CI 0.85-1.32)	(OR:1.21, 95%CI 1.00-1.45)	(OR:0.97, 95%CI 0.84-1.12)	(OR:1.08, 95%CI 0.86-1.35)	(OR:1.15, 95%CI 0.92-1.42)
BZDs and Z-drugs combined use	(OR:1.64, 95% CI 1.13-2.38)	(OR:1.52, 95%CI 1.01-2.30)	(OR:2.52, 95%CI 1.45-4.36)	(OR:1.79, 95%CI 0.97-3.31)	(OR:1.51, 95%CI 0.91-2.52)	(OR:2.75, 95%CI 2.23-3.39)	(OR:1.12, 95%CI 0.97-1.29)
Z-drugs	(OR:1.43, 95% CI 1.17-1.74)	(OR:1.31, 95%CI 0.87-1.97)	(OR:1.57, 95%CI 1.33-1.86)	(OR:1.48, 95%CI 1.18-1.86)	(OR:1.29, 95%CI 0.78-2.13)	(OR:1.76, 95%CI 1.70-1.82)	(OR:1.29, 95%CI 0.97-1.71)
Antidepressants	(OR:1.14, 95% CI 0.88-1.46)	(OR:1.24, 95%CI 0.54-2.86)	(OR:1.23, 95%CI 1.06-1.42)	(OR:1.15, 95%CI 0.82-1.60)	(OR:1.08, 95%CI 0.89-1.30)	(OR:0.96, 95%CI 0.77-1.20)	(OR:1.24, 95%CI 1.05-1.47)
Antipsychotics	(OR:0.97, 95%CI 0.68-1.39)	(OR:2.11, 95%CI 1.37-3.25)	(OR:0.88, 95%CI 0.70-1.13)	(OR:0.97, 95%CI 0.68-1.39)	-	(OR:0.94, 95%CI 0.59-1.50)	(OR:1.07, 95%CI 0.99-1.15)
Anticonvulsants	(OR: 0.98, 95%CI 0.85-1.13)	-	-	-	-	-	-