

Z-Drug Use and All-Cause Mortality: A Meta-Analysis of Observational Cohort Studies

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Introduction: Non-benzodiazepine hypnotic drugs known as z-drugs (including zolpidem, eszopiclone, zopiclone, zaleplon) are commonly prescribed for insomnia patients worldwide. Z-drugs have been thought to be safer than benzodiazepines; however, several studies have raised controversy over the side effects of z-drug. This meta-analysis was conducted to evaluate the association between z-drugs and all-cause mortality.

Methods: To evaluate the association between z-drugs and all-cause mortality, we conducted a meta-analysis of observational cohort studies identified through PubMed, Embase, and Scopus up to 14 March 2025. The study populations included clinical patients. The pooled hazard ratio of all-cause mortality was calculated using a random-effects model with corresponding 95% confidence of intervals (CI). Sensitivity analysis and subgroup analyses were also performed.

Results: Nine cohort studies involving 2,018,397 participants were included for the meta-analysis. Z-drug use was significantly associated with an increased risk of overall mortality (HR = 1.600; 95% CI 1.027–2.491; $P = 0.038$), with evidence of substantial heterogeneity ($I^2 = 99.642\%$, $P < 0.001$). Sensitivity analysis confirmed result stability (HRs 1.440–1.761; all $p < 0.05$). Subgroup analyses showed a consistent positive trend across regions, follow-up durations, and study quality (HRs 1.120–1.780), though not all were statistically significant.

Discussion: This meta-analysis showed a positive association between z-drug use and all-cause mortality; however, the substantial between-study heterogeneity ($I^2 = 99.6\%$) warrants cautious interpretation of these findings. Clinicians should exercise caution when prescribing z-drugs to high-risk patients.

Keywords: non-benzodiazepine hypnotics, zolpidem, zopiclone, eszopiclone, zaleplon

Introduction

Insomnia is one of the most common symptoms that lead people to hospital. In the United States, more than 5 million people visit hospitals each year for insomnia management.¹ Estimates of the prevalence of insomnia vary from 10% to 40%, depending on how insomnia is defined.^{2–7} In the results of a 2002 Korean study on the prevalence of insomnia, the prevalence according to the criteria for complaining of insomnia symptoms 3 or more times a week was 17%, and the prevalence according to DSM-IV insomnia disorder was 5%. As in North America and European countries, insomnia is widespread in Korea.⁸ In addition, the prevalence of insomnia has recently been increasing worldwide.^{9–12}

Treatment options for chronic insomnia include cognitive behavioral therapy (CBT) and pharmacotherapy. Medications approved for insomnia disorder are the following: benzodiazepine receptor agonists, dual orexin receptor agonists, histamine receptor antagonists, melatonin receptor agonist. Among the medications, zolpidem, zopiclone, eszopiclone, and zaleplon are the non-benzodiazepine benzodiazepine receptor agonist, and they are also known as z-drugs. Z-drugs selectively bind to the α -1 subunit of the GABA_A receptor and have a shorter half-life than benzodiazepines (BZDs).¹³ For these reasons, z-drugs were considered to be safer than BZDs because they were less likely to cause drug dependence, abuse, withdrawal symptoms, and other side effects. However, adverse effects of z-drugs are

gradually being reported. The adverse effects of z-drugs include not only the adverse effects of BZDs but also decreased cognitive and memory abilities, falls, fractures, traffic accidents, and infections. Furthermore, a few studies have begun to discuss that its use may increase mortality.^{14,15}

As such, there is controversy about the various adverse effects of z-drugs; however, studies have reported inconsistent results to date on whether z-drug use increases mortality. Previous meta-analyses^{16,17} assessed z-drugs only as part of subgroup analyses, providing limited evidence on their independent effect. Therefore, a focused evaluation of mortality risk specifically associated with z-drug use remains needed. Thus, this meta-analysis aimed to investigate the relations between z-drug use and all-cause mortality.

Methods

Search Strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.¹⁸ Three databases, including Pubmed, Embase, and SCOPUS, were searched through 14 March, 2025. We searched for observational studies analyzing the association between z-drug use and all-cause mortality using the keywords “z-drug” OR “zolpidem” OR “zopiclone” OR “eszopiclone” OR “zaleplon” AND “mortality” (Appendix 1). All authors independently reviewed the retrieved articles. Only observational studies in humans written in English were included. Duplicated studies, *in-vitro* or *in-vivo* studies, and animal studies were excluded. Randomized controlled trials were also excluded because they generally lack the long-term real-world exposure needed to evaluate mortality risk, which was the primary focus of this study. We have registered the method at INPLASY and is also available on (<https://inplasy.com/wp-content/uploads/2025/03/INPLASY-Protocol-7587.pdf>).

Selection Criteria

The inclusion criteria were as follows: (1) human studies; (2) observational cohort studies; (3) studies reporting the association between z-drug use and mortality; (4) studies providing calculable data and effects estimates such as odds ratios (ORs), hazard ratios (HRs) with 95% confidence intervals (CIs), or p-values; and (5) studies written in English.

The exclusion criteria were as follows: (1) duplicated studies; (2) randomized controlled studies; (3) *in-vitro*, *in-vivo*, and animal studies; (4) reviews, conference abstracts, posters, notes; (5) studies with inadequate available data.

Data Extraction and Quality Assessment

Relevant data were extracted from selected articles, including age, sex, z-drug exposure, mortality outcome (including HR and 95% CI), and details about the study (study design, location, follow-up periods, number of participants, and study populations).

The quality of the study was assessed using the Newcastle-Ottawa Scale (NOS).¹⁹ The NOS is a tool to evaluate the quality of case-control studies and cohort studies. In this meta-analysis, only cohort studies were included, and the cohort study quality rating scale was used. A cohort study can be evaluated with a total of 8 items for cohort selection, comparability, and outcome evaluation. For each item, a star is given if the evidence is of high quality (except for the comparability item, a maximum of two stars can be given), resulting in a total of 0–9 stars. The average NOS value of the included studies was 7.3. If the NOS of each study was higher than 7.3, it was classified as high-quality, and conversely, when it was low, it was classified as low-quality. Because the NOS has no universally accepted cutoff and the included studies showed a narrow distribution of scores, we used the mean NOS score (7.33) as a data-driven threshold to classify studies into high- and low-quality groups.

Data Synthesis and Analysis

Statistical analyses were performed using the Comprehensive Meta-Analysis ver.2.2.064 software (Biostat Inc., Englewood, NJ, USA), with statistical significance set as $p < 0.05$. Hazard ratios (HRs) were used as the sole effect measure because all included studies reported HRs. We calculated pooled hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) to summarize the results of studies on whether z-drug use increases all-cause mortality using

the Dersimonian and Laird random effects model.²⁰ We assessed the degree of heterogeneity among the selected studies by the χ^2 -based Cochrane Q test and Inconsistency score (I^2). A p-value less than 0.10 from the χ^2 -based Cochrane Q test indicates a significant heterogeneity. Because heterogeneity was substantial, we conducted leave-one-out sensitivity analyses and subgroup analyses by region, follow-up duration, and study quality to further assess variability.

A series of sensitivity analysis and subgroup analysis were also performed. Sensitivity analysis was done by excluding each included study one by one, and the pooled hazard ratios after removing each study were compared. In addition, subgroup analyzes were performed according to Western or Eastern countries, study duration of more than or less than 5 years, and low or high study quality. Funnel plot, Begg and Mazumdar's rank correlation test, and Egger's regression test were used for evaluating potential publication bias.²¹ We observed the asymmetry of the funnel plot and calculated its degree. When $p < 0.05$, it was considered that there was a significant publication bias. Results of individual studies and pooled estimates were visually presented using forest plots. Study characteristics and quality assessments were summarized in tables.

Results

Study Selection

A total of 510 studies were retrieved from three databases: Pubmed, SCOPUS, and Embase. Excluding 129 duplicated studies, full-text review was performed on the remaining 30 studies after screening through title and abstract.

Excluding 129 duplicated studies, screening was done based on the title and abstract, and then full-text review was performed on the remaining 30 articles. Four studies did not meet the inclusion criteria, five studies did not have suitable results for analysis, 11 studies corresponded to review, conference abstract, poster, note, and short survey, respectively, and the full text of 1 study could not be found. As a result, nine studies were used for meta-analysis, excluding 21 studies. The detailed process of study selection is shown in Figure 1.

All included studies were, incidentally, cohort studies, of which three were prospective cohort studies^{16,22,23} and six were retrospective cohort studies.^{24–29} Three studies were conducted in the United States,^{16,22,23} three in the United Kingdom,^{24,28,29} one in Korea,²⁵ one in Sweden,²⁶ and one in Taiwan.²⁷ A total of 2,018,397 subjects from the nine studies were included, with an average age of 47.25 years, and the average follow-up period varied from 2.5 to 14 years. The detailed characteristics of the 9 articles used in the meta-analysis are shown in Table 1.

Z- Drug Use and the All-Cause Mortality

The pooled HR derived from the meta-analysis using the random-effects model was 1.600 (Figure 2). The 95% confidence interval was in the statistically significant range of 1.027 to 2.491, suggesting that there is a significant positive correlation between z-drug use and all-cause mortality. That is, z-drug use is associated with significantly increased all-cause mortality. However, substantial heterogeneity was apparent with an I^2 of 99.642% and a p-value of less than 0.001.

Sensitivity Analysis

Sensitivity analysis was performed to check if there is a specific study that has a significant effect on research effectiveness and heterogeneity. Each study included in the meta-analysis was excluded one by one to calculate the hazard ratio. There was no significant change in HRs (Table 2), so it was confirmed that there was no study that significantly biased the results.

Subgroup Analysis

A subgroup analysis was performed to check whether there are any characteristics that affect heterogeneity. Results were analyzed according to Western-Eastern countries, study periods over or under 5 years, and low or high study quality (Table 3).

Pooled analysis of the seven studies performed in three Western countries (the United States, the United Kingdom, Sweden) showed HR 1.780 (95% CI: 0.564–2.223), and pooled analysis of the 2 studies performed in two Asian

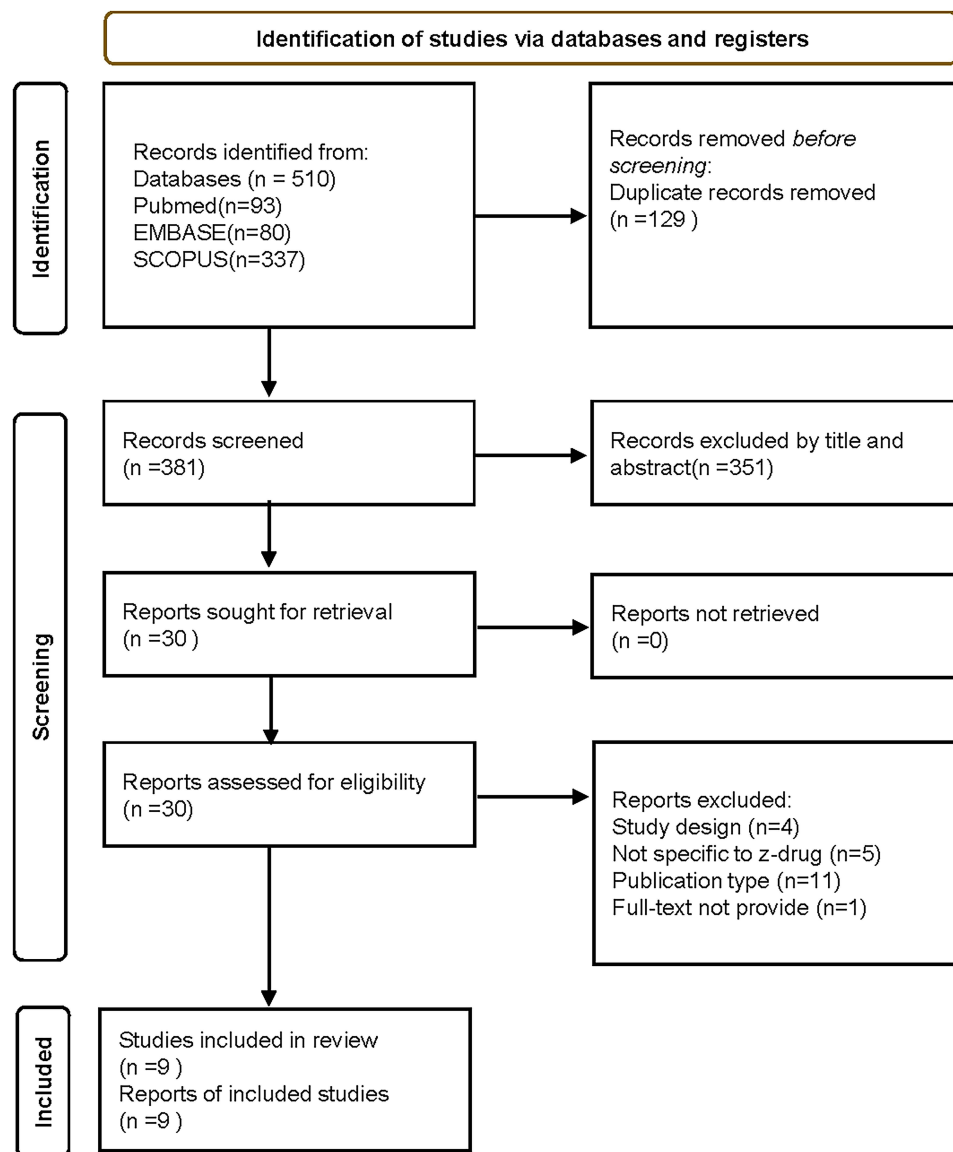


Figure 1 Flow diagram of the literature search and selection of studies for the meta-analysis.

countries (Korea, Taiwan) showed HR 1.120 (95% CI: 0.564–2.223). Both groups demonstrated a positive association between z-drug use and all-cause mortality, but it was statistically significant only in the Western group.

According to the follow-up period of each study, the follow-up period was shorter (<5 years) in five studies, and it was longer (>5 years) in four studies. The association between z-drug use and all-cause mortality was not statistically significant in both groups with shorter follow-up period (HR 1.653; 95% CI 0.796–3.432) and longer follow-up period (HR 1.533; 95% CI: 0.809–2.905).

We also conducted a subgroup analysis by quality of study. The mean quality of study calculated by Newcastle Ottawa Scale (NOS) was 7.3 among the included studies ([Supplementary Table 1](#)). Studies with NOS of 7.3 or higher were considered high quality, whereas those with NOS of less than 7.3 were considered low quality. Four high quality studies did not show statistically significant result (HR 1.533; 95% CI: 0.809–2.905), and five low quality studies also showed non-statistically significant result (HR 1.653; 95% CI: 0.796–3.432).

Table 1 Characteristics of Included Studies

Author (Year)	Nation	Study Design	Study Population	Total Participants (Female %)	Age	Mean Follow-Up (years)	Adjusted Variables	Quality Assessment (NOS)
Haines, A. ²² (2021)	USA	Prospective cohort	Aged 50–79 postmenopausal women from the Women's Health Initiative study	40728(100)	NA	14.0±6.3	Age, race, education, smoking, alcohol, physical activity, hormone use, high cholesterol, systolic blood pressure, DM, CVD, or cancer, sleep disturbances (WHIIRS), hours of sleep, propensity to be on any hypnotic at baseline of follow-up	8
Macleod, J. ²⁴ (2019)	UK	Retrospective cohort	Aged 15–64 years patients prescribed opioid agonist treatment between 1998–2014 from the Clinical Practice Research Datalink	12118(32.7)	38.8±10.4	3.4	Age, sex, comorbidity, region, OAT type, OAT period	7
Choi, J.W. ²⁵ (2018)	Korea	Retrospective cohort	Aged 40 years and older patients from 5% of the National Health Insurance Service beneficiaries	500959(44.8)	54.7±10.6	10.98	Age, sex, insurance premium, CCI score, anxiety, depression, insomnia, psychotic disorders	9
Abrahamsson, T. ²⁶ (2017)	Sweden	Retrospective cohort	All aged patients who were prescribed methadone or buprenorphine for opioid maintenance treatment between 2005–07-01 and 2012–12-31	4501 (26.2)	34.4 (28.7–42.1)	4.76	Age, sex, previous non-fatal overdose, previous psychiatric in-patient treatment, previous suicide attempt, OMT status	6
Lan, T.Y. ²⁷ (2015)	Taiwan	Retrospective cohort	Aged 16 years and older patients in the National Health Insurance Research Database	1313147(NA)	NA	9.66±1.40	Age, sex, level of main medical facility, area of residence, and Elixhauser comorbidities	9
Weich, S. ²⁸ (2014)	UK	Retrospective cohort	Aged 16 years and older in the General Practice Research Database	104145(59.0)	55.4	7.6	Age, sex, physical health problems, prescriptions for non-study drugs	9
Obiora, E. ²⁹ (2013)	UK	Retrospective cohort	All aged patients in the Health Improvement Network database with a diagnosis of pneumonia between 2001–07-01 and 2002–07-01	4964(53.59)	NA	2.8	Age, sex, Townsend deprivation score, current smoking, alcohol, CCI score, depression and psychosis	6
Kripke, D.F. ¹⁶ (2012)	USA	Prospective cohort	Aged 18 years and older patients from 41 country areas of Pennsylvania served by the Geisinger Health System	34205(63.1)	NA	2.5	Age, sex, ethnicity, marital status, BMI, alcohol, smoking, diagnosis in 12 classes of comorbidity	7
Winkelmayer, W.C. ²³ (2007)	USA	Prospective cohort	Patients from the national cohort of Dialysis Morbidity and Mortality study wave 2 conducted in 1996–1997	3630(46.3)	58.6	3.05	NA	5

Abbreviations: NOS, Newcastle–Ottawa scale; DM, diabetes mellitus; CVD, cerebrovascular disease; OAT, opioid agonist treatment; CCI, Charlson comorbidity index; OMT, opioid maintenance treatment; BMI, body mass index; NA, not applicable.

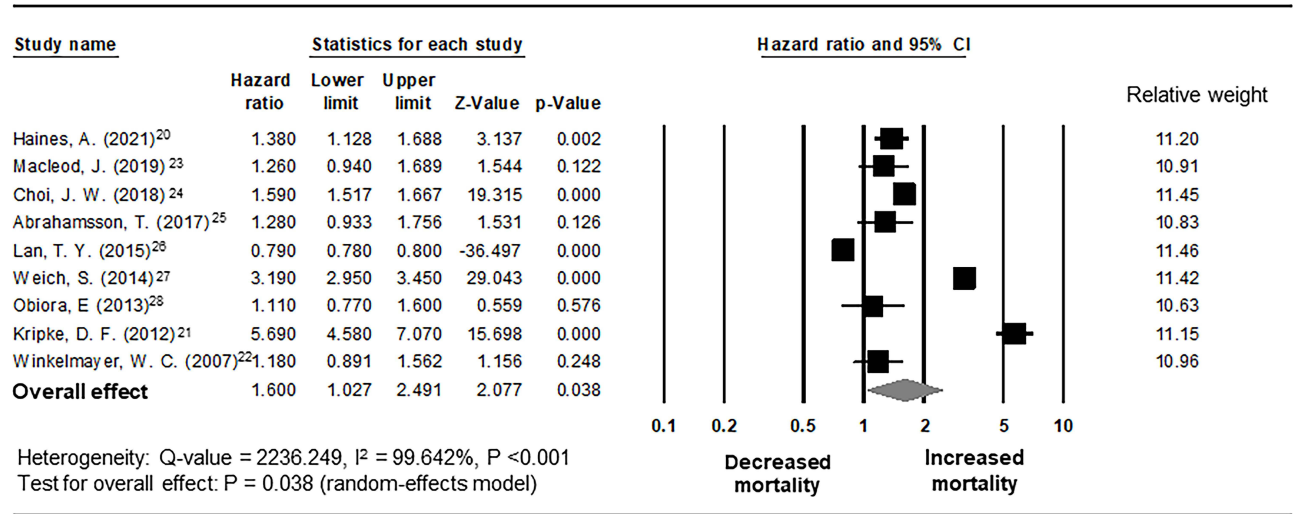


Figure 2 Forest plot of the association of z-drug use and the all-cause mortality.

Although most results were not statistically significant, a consistent trend was observed for an increase in all-cause mortality with z-drug use, regardless of country, study duration, or study quality.

Publication Bias

Funnel plot, Egger’s test for a regression intercept, and Begg and Mazumdar’s rank correlation test were performed to find out publication bias. As shown in Figure 3, no significant asymmetry was observed in the funnel plot. Also, both the Egger’s test and Begg’s test showed insignificant results (Egger’s test: p-value=0.072; Begg’s test: p-value=0.251), confirming that there was no significant publication bias.

Table 2 Sensitivity Analysis by Excluding Each Study One-by-One

Excluded Study (Author, Year)	Observed HR	Effect Size and 95% Confidence Interval			Test of Null (Two-Tailed)	
		Mean HR without This Study	Lower Limit	Upper Limit	z-Value	p-value
Haines, A., 2021 ²²	1.38	1.718	1.237	2.386	3.230	0.001
Macleod, J., 2019 ²⁴	1.26	1.735	1.254	2.399	3.328	0.001
Choi, J. W., 2018 ²⁵	1.59	1.679	1.047	2.692	2.149	0.032
Abrahamsson, T., 2017 ²⁶	1.28	1.730	1.252	2.392	3.320	0.001
Lan, T. Y., 2015 ²⁷	0.79	1.761	1.233	2.517	3.108	0.002
Weich, S., 2014 ²⁸	3.19	1.545	1.217	1.960	3.576	0.000
Obiora, E., 2013 ²⁹	1.11	1.756	1.272	2.424	3.424	0.001
Kripke, D. F., 2012 ¹⁶	5.69	1.440	1.073	1.933	2.431	0.015
Winkelmayer, W.C., 2007 ²³	1.18	1.749	0.264	2.420	3.375	0.001

Table 3 Subgroup Analysis According to Country, Follow-Up Periods, Quality of Study

Subgroups	Number of Studies	Effect Size and 95% Confidence Interval			Test of Null (Two-Tailed)	
		HR	Lower Limit	Upper Limit	z-Value	p-value
Countries						
Asia	2	1.120	0.564	2.223	0.325	0.745
Western	7	1.780	1.116	2.840	2.421	0.015
Follow-up periods						
<5 years	5	1.653	0.796	3.432	1.347	0.178
≥5 years	4	1.533	0.809	2.905	1.311	0.190
Quality of Study						
High (NOS≥7.3)	4	1.533	0.809	2.905	1.311	0.190
Low (NOS<7.3)	5	1.653	0.796	3.432	1.347	0.178

Discussion

This study is a meta-analysis evaluating the association between z-drug use and all-cause mortality. When a total of 9 studies and 2,018,397 subjects were analyzed, z-drug use significantly increased all-cause mortality. The association remained even in the sensitivity analysis in which included studies were removed one by one, and in the subgroup

Funnel Plot of Standard Error by Log hazard ratio

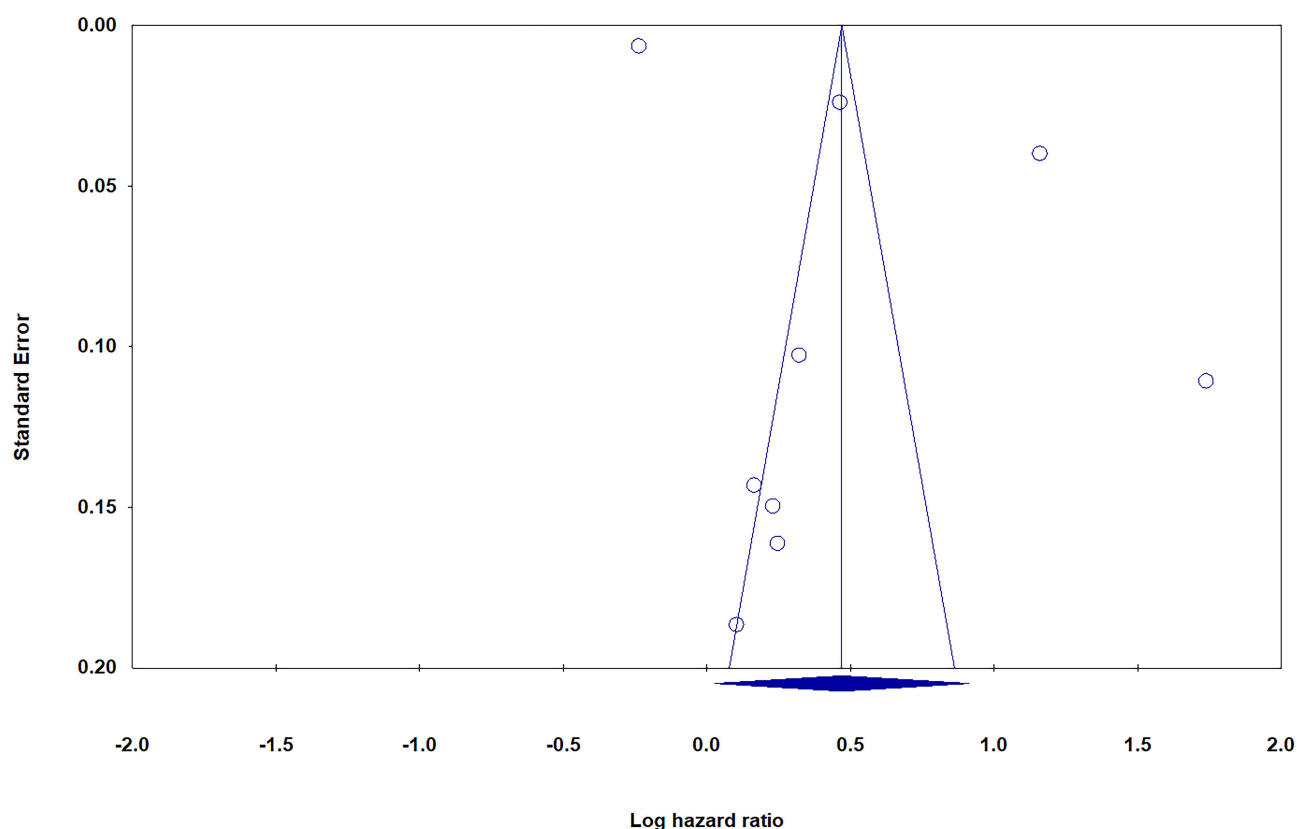


Figure 3 Funnel plot for publication bias.

analysis conducted according to country, study period, and study quality. Thus, our findings indicate that z-drug use is associated with an increased risk of all-cause mortality.

Notably, although the heterogeneity among studies was substantial ($I^2 = 99.642\%$), the leave-one-out sensitivity analysis revealed no single study that disproportionately influenced the pooled hazard ratio. This suggests that the heterogeneity may stem from the accumulation of moderate between-study differences—such as variations in study populations, exposure definitions, or analytical adjustments—rather than the presence of an extreme outlier. Moreover, individual study findings were not entirely consistent, with some reporting higher and others lower mortality risks, likely reflecting differences in population characteristics, baseline risk profiles, and the extent of confounder adjustment. This pattern of dispersed heterogeneity is not uncommon in meta-analyses of observational studies and may reflect the real-world variability in clinical settings. Nevertheless, the consistent direction of effect across sensitivity and subgroup analyses supports the robustness of our findings.

Differences in baseline prevalence of suicidal behavior may have contributed to the unexplained heterogeneity. Given its association with both z-drug use and mortality, residual confounding related to unmeasured psychiatric comorbidities and polypharmacy likely remains. Some degree of confounding by indication is possible, as underlying insomnia and psychiatric conditions are themselves associated with mortality and were not uniformly adjusted across studies. Thus, while an association was observed, cautious interpretation is warranted. As most studies lacked detailed psychiatric data, further analysis was not feasible. Future research should incorporate mental health variables to better clarify this relationship.

In this study, the relationship between z-drug use and all-cause mortality showed a significant positive correlation with HR 1.600. This is similar to a previous study reporting HR 1.73 (95% CI: 0.95–3.16), which was a meta-analysis of hypnotic use and mortality published in 2016.¹⁷ Although the HR was similar to our study, the previous study did not show a statistically significant association between z-drug use and all-cause mortality. The previous study included only five studies, and the result was the pooled effect of mortality risk associated with z-drug use performed as a sub-analysis. To our knowledge, this study provides the most up-to-date and focused synthesis on z-drug use and all-cause mortality.

The mechanism by which z-drug use causes higher mortality is not yet fully understood, but some possible explanations include: First, z-drug use is associated with increased risk for falls, fractures, and accidents.^{30–32} Falls can lead to upper extremity and hip fractures, which are strongly associated with disability, morbidity and mortality.³³ The association can be mainly explained by the residual effect of z-drug that may cause drowsiness, delayed reaction time, and impaired balance.^{34,35} Complex sleep behaviors, including sleep-driving and sleep-walking, can be another possible explanation.³⁶ The complex sleep behavior may be due to the fact that z-drugs have less muscle-relaxing and anticonvulsant effects than BZDs because of the selective binding to the GABA_A α -1 subunit.³⁷ Consequently, z-drug use can increase the risk of death through these events. Second, z-drug use may be less risky than BZDs,³⁸ but can increase the risk of obstructive sleep apnea (OSA) through pharyngeal muscle relaxation, increased duration of apnea, and hypoxia.³⁹ In recent years, evidence has been reported that z-drugs do not increase the risk of OSA by increasing the respiratory arousal threshold and increasing genioglossus muscle responsiveness.^{40,41} However, uncertainty remains about its effect on severe OSA. OSA is known to be an important risk factor for cardiovascular disease based on experimental and population-based data results and is associated with increased cardiovascular morbidity and mortality.^{42–46} Moreover, in a cohort study that identified the risk of cardiovascular disease and all-cause mortality in elderly women with sleep disturbance,²² the use of z-drug was associated with an increased risk of CVD and all-cause mortality. Third, previous studies have identified an increased risk of infection and cancer associated with z-drug use.^{16,29,47,48} Among z-drugs, zopiclone and zaleplon are clastogenic, and clastogen can cause mutations by disruption or breakage of chromosomes.⁴⁹ In addition, z-drug use may also alter immune surveillance. In a mouse study by Sanders et al,⁵⁰ expression of GABA_A receptors in macrophages and monocytes was confirmed, and GABA_A receptor activation inhibited the release of inflammatory cytokines such as TNF- α and IL-6. The increase in infection, inflammation, and mutation due to these actions may eventually lead to cancer development and progression, which may increase the mortality rate. Fourth, z-drug use may increase the risk of psychiatric disorders such as depression, which in turn may increase the risk of suicide.^{51–53} Given these potential pathways, it is essential to consider safety and mortality risks when

prescribing sedative–hypnotic agents, particularly in patients with chronic insomnia or comorbid psychiatric conditions. More research is needed in the future to understand the clearer mechanism.

The limitations of this study are as follows: First, this meta-analysis included only observational cohort studies. Further randomized controlled trials are needed. Second, there was a significant heterogeneity. However, the use of a random-effects model, along with rigorous sensitivity and subgroup analyses, helped account for this variability and reinforce the stability of the observed association. Third, an intrinsic limitation of meta-analysis is that the possibility of selection and recall bias in the collected studies cannot be excluded. In addition, further high-quality studies are needed to confirm and refine these findings. Fourth, drug-specific and dose–response analyses could not be performed because the included studies did not consistently report stratified mortality outcomes by individual z-drugs or provide harmonized quantitative dose information.

Nevertheless, this study has certain strengths. It provides a timely and focused synthesis of the current evidence on z-drug use and all-cause mortality. Sensitivity and subgroup analyses supported the consistency of the observed association, and no substantial publication bias was detected.

Conclusion

This study is to evaluate the association between z-drug use and all-cause mortality, and found that z-drug use was associated with approximately a 60% higher risk of mortality compared to non-users. Although z-drugs are often considered safer than benzodiazepines, the findings suggest that they may not represent a safer option for the treatment of insomnia. Therefore, healthcare providers should be cautious when prescribing z-drugs to high-risk patients.

Disclosure

The author(s) report no conflicts of interest in this work and received no financial support for the research.

References

1. Ford ES, Wheaton AG, Cunningham TJ, Giles WH, Chapman DP, Croft JB. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: findings from the national ambulatory medical care survey 1999–2010. *Sleep*. 2014;37(8):1283–1293. doi:10.5665/sleep.3914
2. Ancoli-Israel S, Roth T. Characteristics of insomnia in the united states: results of the 1991 national sleep foundation survey. I. *Sleep*. 1999;22(Suppl 2):S347–353.
3. Bixler EO, Kales A, Soldatos CR, Kales JD, Healey S. Prevalence of sleep disorders in the Los Angeles metropolitan area. *Am J Psychiatry*. 1979;136(10):1257–1262.
4. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA*. 1989;262(11):1479–1484. doi:10.1001/jama.1989.03430110069030
5. Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment. Prevalence and correlates. *Arch Gen Psychiatry*. 1985;42(3):225–232. doi:10.1001/archpsyc.1985.01790260019002
6. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev*. 2002;6(2):97–111. doi:10.1053/smr.2002.0186
7. Simon GE, VonKorff M. Prevalence, burden, and treatment of insomnia in primary care. *Am J Psychiatry*. 1997;154(10):1417–1423.
8. Ohayon MM, Hong S-C. Prevalence of insomnia and associated factors in South Korea. *J Psychosom Res*. 2002;53(1):593–600. doi:10.1016/S0022-3999(02)00449-X
9. Albrecht JS, Wickwire EM, Vadlamani A, Scharf SM, Tom SE. Trends in insomnia diagnosis and treatment among medicare beneficiaries, 2006–2013. *Am J Geriatr Psychiatry*. 2019;27(3):301–309. doi:10.1016/j.jagp.2018.10.017
10. Calem M, Bisla J, Begum A, et al. Increased prevalence of insomnia and changes in hypnotics use in England over 15 years: analysis of the 1993, 2000, and 2007 national psychiatric morbidity surveys. *Sleep*. 2012;35(3):377–384. doi:10.5665/sleep.1700
11. Chaput JP, Yau J, Rao DP, Morin CM. Prevalence of insomnia for Canadians aged 6 to 79. *Health Rep*. 2018;29(12):16–20.
12. Pallesen S, Sivertsen B, Nordhus IH, Bjorvatn B. A 10-year trend of insomnia prevalence in the adult Norwegian population. *Sleep Med*. 2014;15(2):173–179. doi:10.1016/j.sleep.2013.10.009
13. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnotics: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet*. 2004;43(4):227–238. doi:10.2165/00003088-200443040-00002
14. Gunja N. The clinical and forensic toxicology of Z-drugs. *J Med Toxicol*. 2013;9(2):155–162. doi:10.1007/s13181-013-0292-0
15. Gunja N. In the Zzz zone: the effects of Z-drugs on human performance and driving. *J Med Toxicol*. 2013;9(2):163–171. doi:10.1007/s13181-013-0294-y
16. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open*. 2012;2(1):e000850. doi:10.1136/bmjopen-2012-000850
17. Parsaik AK, Mascarenhas SS, Khosh-Chashm D, et al. Mortality associated with anxiolytic and hypnotic drugs-A systematic review and meta-analysis. *Aust N Z J Psychiatry*. 2016;50(6):520–533. doi:10.1177/0004867415616695
18. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1. doi:10.1186/2046-4053-4-1

19. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* **2010**;25(9):603–605. doi:10.1007/s10654-010-9491-z
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* **1986**;7(3):177–188. doi:10.1016/0197-2456(86)90046-2
21. Sterne JAC, Harbord RM. Funnel plots in meta-analysis. *Stata J.* **2004**;4(2):127–141. doi:10.1177/1536867X0400400204
22. Haines A, Shadyab AH, Saquib N, Kamensky V, Stone K, Wassertheil-Smoller S. The association of hypnotics with incident cardiovascular disease and mortality in older women with sleep disturbances. *Sleep Med.* **2021**;83:304–310. doi:10.1016/j.sleep.2021.04.032
23. Winkelmayer WC, Mehta J, Wang PS. Benzodiazepine use and mortality of incident dialysis patients in the United States. *Kidney Int.* **2007**;72(11):1388–1393. doi:10.1038/sj.ki.5002548
24. Macleod J, Steer C, Tilling K, et al. Prescription of benzodiazepines, z-drugs, and gabapentinoids and mortality risk in people receiving opioid agonist treatment: observational study based on the UK Clinical practice research datalink and office for national statistics death records. *PLoS Med.* **2019**;16(11):e1002965. doi:10.1371/journal.pmed.1002965
25. Choi JW, Lee J, Jung SJ, Shin A, Lee YJ. Use of sedative-hypnotics and mortality: a population-based retrospective cohort study. *J Clin Sleep Med.* **2018**;14(10):1669–1677. doi:10.5664/jcsm.7370
26. Abrahamsson T, Berge J, Öjehagen A, Håkansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment—A nation-wide register-based open cohort study. *Drug Alcohol Depend.* **2017**;174:58–64. doi:10.1016/j.drugalcdep.2017.01.013
27. Lan TY, Zeng YF, Tang GJ, et al. The use of hypnotics and mortality - A population-based retrospective cohort study. *PLoS One.* **2015**;10(12):e0145271. doi:10.1371/journal.pone.0145271
28. Weich S, Pearce HL, Croft P, et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study. *BMJ.* **2014**;348.
29. Obiora E, Hubbard R, Sanders RD, Myles PR. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. *Thorax.* **2013**;68(2):163–170. doi:10.1136/thoraxjnl-2012-202374
30. Treves N, Perlman A, Kolenberg Geron L, Asaly A, Matok I. Z-drugs and risk for falls and fractures in older adults—a systematic review and meta-analysis. *Age Ageing.* **2018**;47(2):201–208. doi:10.1093/ageing/afx167
31. Diem SJ, Ewing SK, Stone KL, Ancoli-Israel S, Redline S, Ensrud KE. Use of non-benzodiazepine sedative hypnotics and risk of falls in older men. *J Gerontol Geriatr Res.* **2014**;3(3):158. doi:10.4172/2167-7182.1000158
32. Rudisill TM, Zhu M, Kelley GA, Pilkerton C, Rudisill BR. Medication use and the risk of motor vehicle collisions among licensed drivers: a systematic review. *Accid Anal Prev.* **2016**;96:255–270. doi:10.1016/j.aap.2016.08.001
33. Morley JE. A fall is a major event in the life of an older person. *J Gerontol a Biol Sci Med Sci.* **2002**;57(8):M492–495. doi:10.1093/gerona/57.8.M492
34. Leufkens TR, Vermeeren A. Zopiclone's residual effects on actual driving performance in a standardized test: a pooled analysis of age and sex effects in 4 placebo-controlled studies. *Clin Ther.* **2014**;36(1):141–150. doi:10.1016/j.clinthera.2013.11.005
35. Bocca ML, Marie S, Lelong-Boulouard V, et al. Zolpidem and zopiclone impair similarly monotonous driving performance after a single nighttime intake in aged subjects. *Psychopharmacology.* **2011**;214(3):699–706. doi:10.1007/s00213-010-2075-5
36. Yang BR, Kim YJ, Kim MS, et al. Prescription of zolpidem and the risk of fatal motor vehicle collisions: a population-based, case-crossover study from South Korea. *CNS Drugs.* **2018**;32(6):593–600. doi:10.1007/s40263-018-0520-x
37. Harbourn K, Nevo ON, Zhang R, Chan V, Croteau D. Association of eszopiclone, zaleplon, or zolpidem with complex sleep behaviors resulting in serious injuries, including death. *Pharmacoepidemiol Drug Saf.* **2020**;29(6):684–691. doi:10.1002/pds.5004
38. Hsu T-W, Chen HM, Chen TY, Chu CS, Pan CC. The association between use of benzodiazepine receptor agonists and the risk of obstructive sleep apnea: a nationwide population-based nested case-control study. *Int J Environ Res Public Health.* **2021**;18(18):9720. doi:10.3390/ijerph18189720
39. Carberry JC, Grunstein RR, Eckert DJ. The effects of zolpidem in obstructive sleep apnea – an open-label pilot study. *J. Sleep Re.* **2019**;28(6):e12853. doi:10.1111/jsr.12853
40. Carter SG, Berger MS, Carberry JC, et al. Zopiclone Increases the arousal threshold without impairing genioglossus activity in obstructive sleep apnea. *Sleep.* **2016**;39(4):757–766. doi:10.5665/sleep.5622
41. Carberry JC, Fisher LP, Grunstein RR, et al. Role of common hypnotics on the phenotypic causes of obstructive sleep apnoea: paradoxical effects of zolpidem. *Eur Respir J.* **2017**;50(6):1701344. doi:10.1183/13993003.01344-2017
42. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med.* **2000**;342(19):1378–1384. doi:10.1056/NEJM200005113421901
43. Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med.* **2009**;6(8):e1000132. doi:10.1371/journal.pmed.1000132
44. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation.* **2010**;122(4):352–360. doi:10.1161/CIRCULATIONAHA.109.901801
45. Cadby G, McArdle N, Briffa T, et al. Severity of OSA is an independent predictor of incident atrial fibrillation hospitalization in a large sleep-clinic cohort. *Chest.* **2015**;148(4):945–952. doi:10.1378/chest.15-0229
46. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med.* **2010**;182(2):269–277. doi:10.1164/rccm.200911-1746OC
47. Kripke DF. Possibility that certain hypnotics might cause cancer in skin. *J. Sleep Re.* **2008**;17(3):245–250. doi:10.1111/j.1365-2869.2008.00685.x
48. Joya FL, Kripke DF, Loving RT, Dawson A, Kline LE. Meta-analyses of hypnotics and infections: eszopiclone, ramelteon, zaleplon, and zolpidem. *J Clin Sleep Med.* **2009**;05(04):377–383. doi:10.5664/jcsm.27552
49. Kripke DF. Hypnotic drug risks of mortality, infection, depression, and cancer: but lack of benefit. *F1000Res.* **2016**;5:918. doi:10.12688/f1000research.8729.1
50. Sanders RD, Godlee A, Fujimori T, et al. Benzodiazepine augmented γ -amino-butyric acid signaling increases mortality from pneumonia in mice. *Crit Care Med.* **2013**;41(7):1627–1636. doi:10.1097/CCM.0b013e31827c0c8d
51. Kripke DF. Greater incidence of depression with hypnotic use than with placebo. *BMC Psychiatry.* **2007**;7:42. doi:10.1186/1471-244X-7-42
52. Sun Y, Lin CC, Lu CJ, Hsu CY, Kao CH. Association between zolpidem and suicide: a nationwide population-based case-control study. *Mayo Clin Proc.* **2016**;91(3):308–315. doi:10.1016/j.mayocp.2015.10.022
53. Tubbs AS, Fernandez F-X, Ghani SB, et al. Prescription medications for insomnia are associated with suicidal thoughts and behaviors in two nationally representative samples. *J Clin Sleep Med.* **2021**;17(5):1025–1030. doi:10.5664/jcsm.9096

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