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Benzodiazepine Use and Long-Term Mortality in South Korean Adult Population: A Cohort Study

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Purpose: Studies have reported mixed results on the association between benzodiazepine use and mortality. Here, we investigated whether benzodiazepine use is associated with a higher risk of 5-year all-cause mortality, and examined the association between benzodiazepine use and 5-year disease-specific mortality.

Materials and Methods: In this population-based cohort study, a nationally representative sample cohort in South Korea was examined. In 2010, benzodiazepine users were defined as individuals prescribed benzodiazepine continuously over 30 days for regular administration, and all other subjects were included in the control group. The primary endpoint was 5-year all-cause mortality, evaluated from 2011 to 2015. Propensity score (PS) matching and time-dependent Cox regression were performed for statistical analysis, which included benzodiazepine use during 2011–2015 as a time-dependent variable.

Results: A total of 822414 adult individuals were included in the final analysis, and the all-cause 5-year mortality was recorded in 20991 individuals (2.7%). The benzodiazepine group included 30837 patients and the control group comprised 791377 patients. After PS matching, 61672 individuals (30836 in each group) were included in the final analysis. After PS matching, the 5-year all-cause mortality in the benzodiazepine group was 10.0% (3082/30836), whereas that in the control group was 9.4% (2893/30836). In time-dependent Cox regression analysis of the PS-matched cohort, the benzodiazepine group showed 1.15-fold higher 5-year all-cause mortality (hazard ratio: 1.15, 95% confidence interval: 1.09–1.22; $p<0.001$) compared to the control group.

Conclusion: Benzodiazepine use was associated with increased 5-year all-cause mortality in the South Korean adult population. Further studies are needed to confirm these findings.

Key Words: Benzodiazepine, mortality, population

INTRODUCTION

Benzodiazepine is a commonly prescribed psychoactive drug for the treatment of anxiety and sleep disorders.[1] It has been reported that 7.8% of the Dutch population aged 55–64 years and 5.2% of the United States (US) population aged 18–80 years use benzodiazepine.[2] In addition, the number of benzodiazepine prescriptions in the US increased from 1996 to 2013.[3] As long-term benzodiazepine use causes dependence and addiction,[4] benzodiazepine prescription presents public health burden and concern.[5]

Cohort studies before 2009 have reported mixed results on the association between benzodiazepine use and mortality.[6] More recent epidemiological studies have reported that the risk of all-cause mortality in adult benzodiazepine users is higher than that in non-users, even when used for less than 1 month.[7,8] In addition, several studies conducted in adult populations have not provided evidence for an increased risk of all-cause mortality with benzodiazepine use; however, the results have suggested associations with a wide range of causes of death, such as cancer,[7,9,10] cardiovascular disease,[9,11-13] respiratory diseases,[11] and suicide.[9,10,12] In 2017, Patorno, et al.[14] reported that there was no increase or a minor increase in the risk of all-cause mortality among benzodiazepine users compared to that in non-users in the US. However, information regarding the long-

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term all-cause mortality and disease-specific mortality based on exposure to benzodiazepine is still lacking, necessitating more studies.

Therefore, the present study aimed to investigate whether benzodiazepine use is associated with a higher risk of 5-year all-cause mortality in the adult population in South Korea. Additionally, we examined the association between benzodiazepine use and 5-year disease-specific mortality.

MATERIALS AND METHODS

Design and ethical concerns

The present population-based cohort study was conducted in accordance with the Reporting of Observational Studies in Epidemiology guidelines. The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (X-1905-541-903) and Health Insurance Review and Assessment Service. The requirement for informed consent was waived due to the retrospective nature of the study, which involved the use of anonymized data extracted from the South Korean National Health Insurance Service (NHIS) database.

Data source: NHIS sample cohort

The sample cohort of the NHIS database was developed to provide health-related data for medical research in the South Korean population. The database was created from a random stratified sample of approximately one million people registered under the NHIS in 2002, and was designed to be demographically and socioeconomically representative of the national population of South Korea. The cohort was dynamic and was followed up until the end of 2015. Additional cohort data, including those of infants, were analyzed to allow for attrition due to death and follow-up loss. Using stratified extraction methods, individuals were added to the cohort annually to replace those who had died or emigrated in the previous year. This was performed to ensure that the cohort continued to represent the national population in terms of demographic and socioeconomic status of the South Korean population. The sample cohort database included information on individuals' demographic characteristics, socioeconomic status, healthcare use, medical history, and cause of death.[15]

Study population

We included all adult patients (age ≥18 years) in the 2010 NHIS sample cohort. We then excluded individuals who died in 2010 and those who moved out of the country between 2011 and 2015, as benzodiazepine prescription information was no longer available after emigration.

Exposure variable: benzodiazepine use

The prescription data of medication during 2010–2015 were extracted for this study. Using the prescription data of benzodiazepine in 2010, benzodiazepine users were defined as individuals who were prescribed benzodiazepine continuously over 30 days for regular intake. All other subjects were included in the control group; for example, individuals who had never been prescribed benzodiazepine and those who had been prescribed benzodiazepine for <30 days were included in the control group. Benzodiazepines included alprazolam, clobazam, clonazepam, chlordiazepoxide, diazepam, lorazepam, and triazolam in the present study.

Study endpoint

The primary endpoint was the 5-year all-cause mortality. As we excluded individuals who died in 2010 from the analytic cohort, survival time and mortality were assessed from January 1, 2011 to December 31, 2015. In addition, we evaluated the 5-year disease-specific mortality, which was classified based on the main diseases causing death according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes. In particular, we considered 5-year cancer (C00-D48), cardiovascular disease (I00-I99), respiratory diseases (J00-J99), digestive diseases (K00-K93), infectious and parasitic diseases (A00-B99), endocrine and metabolic diseases (E00-E90), nervous system diseases (G00-G99), musculoskeletal disease-related mortality (M00-M99), and injury- and poisoning-related mortality (S00-T98).

Confounders

Data on the following variables were collected as confounders: 1) demographic information (age and sex); 2) socioeconomic information [income level in five groups, and place of residence in 2010 (Seoul, metropolitan cities, or others)]; 3) Charlson comorbidity index, which was calculated using the registered ICD-10 diagnostic codes between 2009 and 2010 in the NHIS database (Supplementary Table 1, only online); and 4) the number of outpatient clinic visits in 2010 (day). Data on the number of outpatient clinic visits were collected in the study to reflect frailty in individuals, and were divided into four groups (0–7, 8–30, 31–90, and >90 days).

Statistical analysis

The demographic and clinical characteristics of all individuals are presented as mean with standard deviation for continuous variables and number with percentage for categorical variables. First, we performed 1:1 propensity score (PS) matching between the benzodiazepine and control groups to reduce the possibility of bias in observational study.[16] For PS matching, the nearest neighbor method was used without replacement with a caliper of 0.25. All covariates were included in PS modeling, and logistic regression was used to calculate PS in the PS model. The absolute value of the standardized mean difference (ASD) was used to evaluate the balance between groups before and after PS matching. The ASD was set at <0.1 to

confirm adequate balance between the groups. After confirming the adequate balance between groups through PS matching, we performed time-dependent Cox regression analysis,[17] as our study focused on time-dependent exposure to benzodiazepine use in the 2010 cohort between 2011 and 2015. To confirm whether benzodiazepine exposure varied during 2011–2015, we investigated the proportion of benzodiazepine users who discontinued benzodiazepine therapy or commenced it during the evaluation period, that is, 2011–2015. The results revealed that exposure to benzodiazepine therapy varied between the benzodiazepine users and controls throughout the evaluation period (Supplementary Table 2, only online). Therefore, exposure to benzodiazepine prescription was considered a time-dependent variable, and all-cause death from January 1, 2011 to December 31, 2015 was set as the event in the time-dependent Cox model of the PS-matched cohort. Next, we constructed nine time-dependent Cox regression models to investigate whether benzodiazepine use was associated with specific disease-related 5-year mortality in the PS-matched cohort. The nine disease-specific 5-year mortalities were used as endpoints in each model. Correction for multiple comparisons was not performed to reduce the chances of missing important associations. In addition, 1:1 PS matching identification was not included in the models as a random intercept in this study.

For sensitivity analysis, in addition to analyses of the PS-matched cohort, we fit a multivariable time-dependent Cox regression model for 5-year all-cause mortality in the entire cohort to determine whether the results obtained from the PS-matched cohort were generalizable to the entire cohort. In the multivariable time-dependent Cox regression model, benzodiazepine exposure from 2011 to 2015 was included as a time-dependent variable, while all other covariates were included in the model as time-fixed covariates. Finally, we performed subgroup analyses according to age to examine whether similar hazard ratios (HRs) were estimated for each age group (<40, 40–60, and >60 years). Multivariable time-dependent Cox regression modeling was used for the subgroup analyses. The results of the Cox regression models are presented as HR with 95% confidence interval (CI). All multivariable models of the entire cohort were confirmed to have no multicollinearity (variance inflation factor <2.0). All statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Results with p-values <0.05 were considered statistically significant.

RESULTS

The 2010 NHIS sample cohort comprised 826909 adult individuals. We excluded 4487 individuals who died in 2010 and 208 who moved out of South Korea between 2011 and 2015. As a result, 822414 adult individuals were included in the final

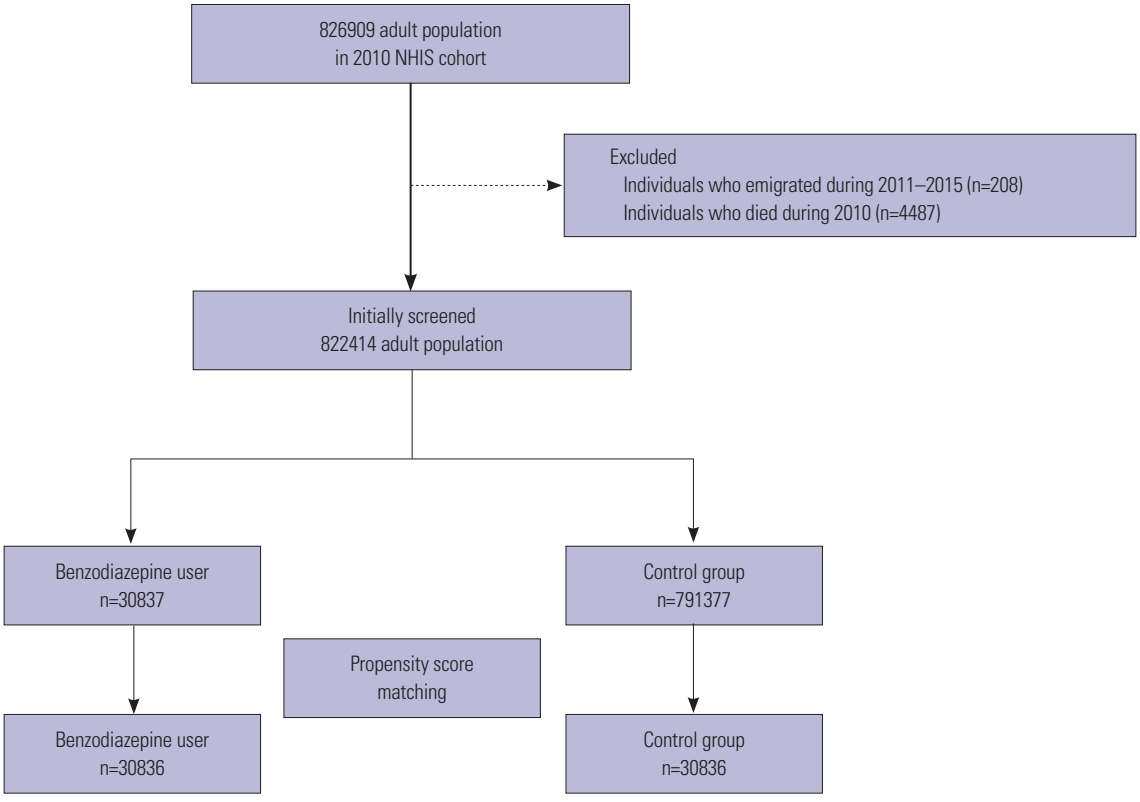

Fig. 1. Flow chart of participant selection.

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Table 1. Comparison of Baseline Characteristics between Benzodiazepine Users and Controls Before and After PS Matching

Variable	Before PS matching		ASD	After PS matching		ASD
	Benzodiazepine users n=30837	Controls n=791377		Benzodiazepine users n=30836	Controls n=30836	
Age, yr	60.6 (14.5)	43.9 (15.9)	0.271	60.6 (14.5)	60.0 (15.6)	0.026
Sex, male	11408 (37.0)	396379 (50.1)	1.154	11408 (37.0)	11795 (38.3)	0.038
Annual income level in 2020						
1st (lowest income level)	4133 (13.4)	109392 (13.8)		4133 (13.4)	4049 (13.1)	
2nd	3843 (12.5)	128945 (16.3)	0.116	3843 (12.5)	3872 (12.6)	0.003
3rd	7367 (23.9)	175795 (22.2)	0.039	7367 (23.9)	7321 (23.7)	0.004
4th	6340 (20.6)	171731 (21.7)	0.028	6339 (20.6)	6386 (20.7)	0.004
5th (highest income level)	9154 (29.7)	205514 (26.0)	0.081	9154 (29.7)	9208 (29.9)	0.004
Residence at 2010						
Capital city (Seoul)	5486 (17.8)	169387 (21.4)		5486 (17.8)	5422 (17.6)	
Metropolitan city	7813 (25.3)	201943 (25.5)	0.004	7812 (25.3)	7900 (25.6)	0.007
Others	17538 (56.9)	420047 (53.1)	0.077	17538 (56.9)	17514 (56.8)	0.002
Charlson comorbidity index	3.1 (2.4)	1.1 (1.6)	0.833	3.1 (2.4)	3.0 (2.5)	0.057
Hypertension	16413 (53.2)	131316 (16.6)	0.734	16412 (53.2)	16073 (52.1)	0.022
Myocardial infarction	1122 (3.6)	5982 (0.8)	0.154	1121 (3.6)	1038 (3.4)	0.014
Congestive heart failure	2930 (9.5)	13510 (1.7)	0.266	2929 (9.5)	2588 (8.4)	0.038
Peripheral vascular disease	8529 (27.7)	55881 (7.1)	0.461	8528 (27.7)	8111 (26.3)	0.030
Cerebrovascular disease	7985 (25.9)	36235 (4.6)	0.487	7984 (25.9)	7357 (23.9)	0.046
Peptic ulcer disease	16971 (55.0)	178236 (22.5)	0.654	16970 (55.0)	16444 (53.3)	0.034
DM without chronic complication	9294 (30.1)	75382 (9.5)	0.449	9293 (30.1)	9007 (29.2)	0.020
DM with chronic complication	4129 (13.4)	29532 (3.7)	0.284	4128 (13.4)	3857 (12.5)	0.026
Renal disease	624 (2.0)	5136 (0.6)	0.098	624 (2.0)	570 (1.8)	0.012
Dementia	406 (1.3)	1458 (0.2)	0.099	406 (1.3)	353 (1.1)	0.015
Hemiplegia or paraplegia	800 (2.6)	4415 (0.6)	0.128	799 (2.6)	748 (2.4)	0.010
Rheumatic disease	2845 (9.2)	22277 (2.8)	0.222	2844 (9.2)	2707 (8.8)	0.015
Mild liver disease	11673 (37.9)	123414 (15.6)	0.459	11672 (37.9)	11370 (36.9)	0.020
Moderate to severe liver disease	533 (1.7)	5395 (0.7)	0.080	533 (1.7)	502 (1.6)	0.008
Chronic pulmonary disease	13998 (45.4)	188136 (23.8)	0.434	13997 (45.4)	13632 (44.2)	0.024
Any cancer	3092 (10.0)	27745 (3.5)	0.217	3091 (10.0)	2965 (9.6)	0.014
Metastatic solid tumor	324 (1.1)	3370 (0.4)	0.061	324 (1.1)	316 (1.0)	0.003
Outpatient clinic visit in 2010, day						
0–7	3708 (12.0)	501749 (63.4)		3708 (12.0)	3924 (12.7)	
8–30	19793 (64.2)	261473 (33.0)	0.650	19793 (64.2)	20142 (65.3)	0.024
31–90	7168 (23.2)	27662 (3.5)	0.468	7167 (23.2)	6636 (21.5)	0.041
>90	168 (0.5)	493 (0.1)	0.066	168 (0.5)	134 (0.4)	0.015

PS, propensity score; ASD, absolute value of standardized mean difference; DM, diabetes mellitus.
Presented as mean value with standard deviation or number with percentage.

analysis, and the all-cause 5-year mortality was observed in 20991 (2.7%) individuals. The benzodiazepine group comprised 30837 (3.8%) individuals and the control group comprised 791377 (96.2%) individuals. After PS matching, 61672 individuals (30836 in each group) were included in the final analysis (Fig. 1). The results of the comparison of demographic and clinical characteristics between the benzodiazepine and control groups before and after PS matching are presented in Table 1. After PS matching, all ASDs between the groups were below 0.1, suggesting adequate balance through PS matching.

Main analysis after PS matching

Table 2 shows the results of survival analyses before and after PS matching. After PS matching, the 5-year all-cause mortality in the benzodiazepine group was 10.0% (3082/30836), whereas that in the control group was 9.4% (2893/30836). In the time-dependent Cox regression model of the PS-matched cohort, the benzodiazepine group showed 1.15-fold higher 5-year all-cause mortality (HR: 1.15, 95% CI: 1.09–1.22; $p<0.001$) compared to the control group. The analysis results of the disease-specific time-dependent Cox regression models of the PS-

Table 2. Five-Year All-Cause Mortality Before and After PS Matching

Five-year mortality	Event (%)	HR (95% CI)
Before PS matching		
Control group	22290/791377 (2.8)	1
Benzodiazepine users	3082/30837 (10.0)	3.00 (2.86, 3.14)
After PS matching		
Control group	2893/30836 (9.4)	1
Benzodiazepine users	3082/30836 (10.0)	1.15 (1.09, 1.22)

PS, propensity score; HR, hazard ratio; CI, confidence interval.

Table 3. HR of Disease-Specific 5-Year Mortality in the PS-Matched Cohort

Five-year mortality (benzodiazepine users)	HR (95% CI)
Cancer (C00-D48, n=7579)	1.04 (0.93, 1.16)
Cardiovascular disease (I00-I99, n=5470)	1.14 (1.02, 1.27)
Respiratory disease (J00-J99, n=2137)	1.06 (0.89, 1.25)
Digestive disease (K00-K93, n=1130)	1.53 (1.17, 2.00)
Infectious and parasitic disease (A00-B99, n=668)	0.88 (0.63, 1.22)
Endocrine, and metabolic disease (E00-E90, n=1134)	1.23 (0.97, 1.56)
Nervous system disease (G00-G99, n=790)	2.09 (1.55, 2.81)
Musculoskeletal disease (M00-M99, n=136)	0.99 (0.53, 1.84)
Injury, and poisoning (S00-T98, n=2993)	1.42 (1.17, 1.73)

PS, propensity score; HR, hazard ratio; CI, confidence interval.

matched cohort are presented in Table 3. The 5-year nervous system disease-related mortality in the benzodiazepine group was the highest (HR: 2.09, 95% CI: 1.55–2.81; $p<0.001$), compared to that in the control group. The risks of 5-year digestive disease mortality and injury- and poisoning-related mortality in the benzodiazepine group were 1.53-fold (HR: 1.53, 95% CI: 1.17–2.00; $p=0.002$) and 1.42-fold higher than those in the control group (HR: 1.42, 95% CI: 1.17–1.73; $p<0.001$), respectively. The 5-year mortalities due to cancer ($p=0.511$), respiratory diseases ($p=0.524$), endocrine and metabolic diseases ($p=0.083$), infectious and/or parasitic diseases ($p=0.434$), and musculoskeletal diseases ($p=0.962$) were not associated with benzodiazepine use.

Sensitivity and subgroup analyses in the entire cohort

Table 4 shows the analysis results of the multivariable time-dependent Cox regression model for 5-year all-cause mortality in the entire cohort. In the model, the benzodiazepine group showed 1.22-fold higher 5-year all-cause mortality compared to the control group (HR: 1.22, 95% CI: 1.17–1.28; $p<0.001$). Table 5 shows the results of subgroup analyses according to age using the multivariable time-dependent Cox regression model. In the subgroup analyses, the benzodiazepine group showed the highest HR for 5-year all-cause mortality in the <40 year group (HR: 2.00, 95% CI: 1.39–2.87; $p<0.001$), followed by the 40–60 year group (HR: 1.45, 95% CI: 1.28–1.63; $p<0.001$) and >60 year group (HR: 1.23, 95% CI: 1.17–1.28; $p<0.001$).

Table 4. HR of 5-Year All-Cause Mortality in the Entire Cohort

Five-year mortality	HR (95% CI)
Benzodiazepine users (vs. controls)	1.22 (1.17, 1.28)
Age, yr	1.10 (1.10, 1.10)
Sex, male	1.85 (1.80, 1.89)
Income level	
1st (lowest income level)	1
2nd	0.99 (0.94, 1.04)
3rd	1.08 (1.04, 1.13)
4th	0.84 (0.81, 0.88)
5th (highest income level)	0.74 (0.71, 0.77)
Residence	
Capital city (Seoul)	1
Metropolitan city	1.20 (1.15, 1.25)
Other area	1.16 (1.12, 1.20)
Charlson comorbidity index	1.22 (1.22, 1.23)
Hypertension	1.05 (1.02, 1.08)
Congestive heart failure	1.48 (1.42, 1.54)
Chronic pulmonary disease	1.12 (1.09, 1.15)
Cerebrovascular disease	1.36 (1.31, 1.40)
Dementia	1.59 (1.47, 1.73)
DM with chronic complication	1.26 (1.22, 1.31)
DM without chronic complication	1.24 (1.21, 1.28)
Hemi- or Paraplegia	2.10 (1.99, 2.22)
Myocardial infarction	1.24 (1.17, 1.32)
Mild liver disease	1.12 (1.09, 1.15)
Severe liver disease	1.98 (1.84, 2.13)
Peptic ulcer disease	0.98 (0.95, 1.01)
Peripheral vascular disease	0.93 (0.90, 0.96)
Renal disease	1.95 (1.84, 2.07)
Rheumatic disease	0.98 (0.93, 1.03)
Any cancer	1.60 (1.54, 1.66)
Metastatic cancer	3.60 (3.37, 3.85)
Outpatient clinic visit in 2010, day	
0–7	1
8–30	0.68 (0.66, 0.70)
31–90	0.61 (0.58, 0.64)
>90	0.76 (0.63, 0.91)

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus.

Table 5. Subgroup Analyses according to Age

Five-year mortality [benzodiazepine users (vs. controls)]	HR (95% CI)
<40 yr (n=343058)	2.00 (1.39, 2.87)
40–60 yr (n=332496)	1.45 (1.28, 1.63)
>60 yr (n=146660)	1.23 (1.17, 1.28)

HR, hazard ratio; CI, confidence interval.

DISCUSSION

This population-based cohort study showed that benzodiazepine use was associated with a higher risk of 5-year all-cause mortality in the South Korean adult population. Among disease-

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specific mortalities, benzodiazepine use exhibited the highest risk for nervous system disease-related mortality. Additionally, benzodiazepine use was not associated with mortality due to cancer, infectious and/or parasitic diseases, respiratory diseases, endocrine and metabolic diseases, or musculoskeletal diseases. In addition, our subgroup analyses showed that the association between benzodiazepine use and increased 5-year all-cause mortality was most evident in the younger population, that is, those <40 years old.

A previous study reported that benzodiazepine users had a higher risk for all-cause mortality than non-users in two large cohort studies in France and the UK.[18] The study focused on the risk for all-cause mortality for up to 12 months,[18] whereas our study examined the 5-year all-cause mortality. Another retrospective longitudinal study reported that benzodiazepine use was associated with an increase in all-cause mortality based on a time-dependent Cox model.[19] The study analyzed patients with schizophrenia,[19] whereas we focused on the general adult population in South Korea. Conversely, a recent large retrospective cohort study in the US reported that the initiation of benzodiazepine prescription was not associated with mortality over an observation period of up to 6 months.[14] However, in a sensitivity analysis with a follow-up period of 48 months, the mortality was increased by 4% in benzodiazepine users compared to that in non-users (HR: 1.04, 95% CI: 1.02–1.07),[14] suggesting that benzodiazepine exposure can influence the relative long-term all-cause mortality, as observed in our study. Therefore, recent evidence suggests that the all-cause and long-term mortality might be increased in benzodiazepine-users compared to those in non-users.

In the disease-specific Cox proportional hazard models, the 5-year mortality due to nervous system diseases was most closely associated with benzodiazepine use in the present study. It might be influenced by the indication of benzodiazepine prescription, as benzodiazepines have been prescribed for various indications such as anxiety, insomnia, and epilepsy.[20] Such diseases, which are indications for benzodiazepine, are closely related to disorders in the central nervous system.[21] Therefore, benzodiazepine users could have suffered from neurological disorders in the present study, and this could have led to the increased 5-year nervous system disease-related mortality in our study. In this regard, a previous study reported that a higher mortality rate was associated with benzodiazepine use in individuals with Alzheimer's disease.[22]

Previous studies have suggested an association between benzodiazepine use and a wide range of causes of death, such as cancer[7,9,10] and cardiovascular disease.[9,11-13] While our study showed that benzodiazepine use was associated with a higher risk of cardiovascular disease, the 5-year cancer mortality was not associated with benzodiazepine use. The issue regarding the association between cancer risk and benzodiazepine exposure has been controversial.[23-25] Although recent meta-analyses have suggested a positive association between benzodiazepine exposure and cancer risk,[23,24] the most recently published meta-analysis reported that the use of lower dose hypnotics and shorter durations of exposure to benzodiazepines do not seem to be associated with an increased risk of cancer.[25] Additionally, a dose-response relationship between benzodiazepine exposure and cancer risk has been suggested.[25] Since we did not evaluate the effect of the dosage of benzodiazepine, the result regarding 5-year cancer mortality should be interpreted with caution, and additional studies should be performed.

The results of the subgroup analyses according to age were significant in this study. Previous studies have reported that benzodiazepine use is associated with a higher risk of mortality among older adults.[26-28] However, information regarding the relationship between benzodiazepine use and mortality among young adults is still lacking. In the US, benzodiazepine dependence and misuse among young adults are important social and public health issues.[29] Another previous study reported that the misuse rate of benzodiazepine was the highest in young adults and the lowest in older individuals in the US.[30] The misuse or abuse of benzodiazepine is known to be associated with a higher risk of both mortality[31] and suicide.[32] In our study, the misuse of benzodiazepine in young adults might have affected the results. However, information regarding this issue is still lacking, and more research is needed to confirm the relationship between benzodiazepine use and mortality risk among young adults.

This study had some limitations. First, some important physiologic variables, such as body mass index, were not included in the analysis since relevant data were not available in the NHIS database. Furthermore, we used the ICD-10 codes registered in the NHIS database to calculate the Charlson comorbidity indices. However, some of the underlying diseases specified using the codes might not reflect the actual underlying diseases. Lastly, we used PS modeling or multivariable time-dependent Cox regression modeling to adjust for confounders in the present study; however, there might be residual and unmeasured confounders, which might have affected the results of the present study.

In conclusion, benzodiazepine use was associated with increased 5-year all-cause mortality in the South Korean adult population. This association was most evident in the young adult population aged <40 years. In addition, benzodiazepine use was associated with the 5-year nervous system disease-related mortality. Further studies are needed to confirm these findings.

AUTHOR CONTRIBUTIONS

Conceptualization: Tak Kyu Oh and In-Ae Song. Data curation: Hye Youn Park. Formal analysis: Tak Kyu Oh. Investigation: Tak Kyu Oh and In-Ae Song. Methodology: Tak Kyu Oh and In-Ae Song. Project administration: In-Ae Song. Supervision: Tak Kyu Oh and In-Ae Song. Writing—original draft: Tak Kyu Oh. Writing—review & editing: Hye Youn Park and In-Ae Song. Approval of final manuscript: all authors.

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