Association between the use of hypnotics and risk of Alzheimer's Disease

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INTRODUCTION

- As widely prescribed hypnotics, benzodiazepines and related drugs are commonly used among the elderly to treat anxiety and insomnia, despite the known risks. In South Korea, benzodiazepine was the most frequently prescribed hypnotics and the number of prescription of benzodiazepine is on the rise. Owing to the high prescription rate not only in Korea but worldwide, the use of hypnotics including benzodiazepines is an emerging issue due to the health outcomes. As the risk and safety of hypnotics increased, interest in the side effects of hypnotics which influence dementia, also increased.
- Dementia is a rapidly growing public health problem affecting around 50 million people globally, in ageing societies. The World Health Organization (WHO) cites that there are nearly 10 million new cases every year and this will triple by 2050. Likewise, the number of dementia patients have increased rapidly in Korea. Nearly 6.9% of the elderly over 65 years have dementia, that is expected to affect around 2.71 million people by 2050. Dementia also has a huge economic impact; medical costs due to dementia have been increasing 20% every year and the social costs have been about 12 trillion won (1% of the GDP) in Korea. People with dementia often live for many years after their symptoms begin, requiring long-term care and support; dementia could be a matter of concern not only for those who suffer from it, but also for their caregivers and families. Therefore, support in dementia is important for both, the economic as well as caregiver issues.
- Drugs administration in the elderly requires caution; however, drugs prescription for the elderly is extensive and often inappropriate. It is important to detect dementia early, and prevent it from worsening by implementing a drug that relieves symptoms. Therefore, it is necessary to investigate the association between the use of hypnotics divided into long- and short-acting, and the risk of Alzheimer's disease, to prevent the development of dementia. As pathophysiology of dementia differed by type, we focused on Alzheimer's disease as the effect of the hypnotics on the brain was more likely in Alzheimer's disease than the others. Consequently, the current study examined the association between the use of hypnotics and dementia while focusing on Alzheimer's disease among the South Korean population.

METHODS

- Data for this study were obtained from 2002 to 2013 Korean National Health Insurance Service National Sample Cohort (NHIS-NSC). As Alzheimer's disease is an age dependent disease, we only included individuals over 50 years old. The risk of Alzheimer's disease (ICD-10: F00) is the dependent variable of this study. The primary independent variable was the use of hypnotics. We selected 25 commonly used benzodiazepines. These benzodiazepines were divided into two groups based on the duration of their action, known as the half-life. Drugs that have a longer half-life($t_{1/2} \geq 20$ h) were considered long-acting, while those with a shorter half-life ($t_{1/2} < 20$ h) were considered to be short-acting. Participants were divided into three categories: long-acting hypnotics, short-acting hypnotics, or non-users.
- Chi-square test was conducted to investigate the general characteristics of the study population. Cox proportional hazards model with time-dependent covariates was used to examine factors associated with the risk of Alzheimer's disease37,38. The Kaplan-Meier survival curves were used to compare survival rates between groups. Differences were considered statistically significant with a p-value < 0.05. All data analyses used SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

Table 1. General characteristics of the study population

Variables	Total		Risk of Alzheimer's Disease				*P*-value
			Yes		No		
Total	292,810	(100.0)	17,308	(5.9)	275,502	(94.1)	
Hypnotics							<0.0001
Long-acting	8,404	(2.9)	603	(7.2)	7,801	(92.8)	
Short-acting	69,728	(23.8)	4,297	(6.2)	65,431	(93.8)	
No	214,678	(73.3)	12,408	(5.8)	202,270	(94.2)	
Sex							<0.0001
Male	115,376	(39.4)	5,729	(5.0)	109,647	(95.0)	
Female	177,434	(60.6)	11,579	(6.5)	165,855	(93.5)	
Age							<0.0001
50-59	81,303	(27.8)	379	(0.5)	80,924	(99.5)	
60-65	38,464	(13.1)	770	(2.0)	37,694	(98.0)	
65-70	45,399	(15.5)	2,139	(4.7)	43,260	(95.3)	
70-75	51,272	(17.5)	4,417	(8.6)	46,855	(91.4)	
75-80	41,232	(14.1)	4,808	(11.7)	36,424	(88.3)	
≥80	35,140	(12.0)	4,795	(13.6)	30,345	(86.4)	
Social Security							<0.0001
Health Insurance	103,402	(35.3)	4,859	(4.7)	98,543	(95.3)	
Medical Aid	189,408	(64.7)	12,449	(6.6)	176,959	(93.4)	
Region							<0.0001
Metropolitan	119,875	(40.9)	6,095	(5.1)	113,780	(94.9)	
City	78,035	(26.7)	4,775	(6.1)	73,260	(93.9)	
Rural	94,900	(32.4)	6,438	(6.8)	88,462	(93.2)	
Disability							<0.0001
Yes	45,502	(15.5)	3,224	(7.1)	42,278	(92.9)	
No	247,308	(84.5)	14,084	(5.7)	233,224	(94.3)	
Income							0.0048
Low	59,227	(20.2)	3,348	(5.7)	55,879	(94.3)	
Middle	103,450	(35.3)	6,258	(6.0)	97,192	(94.0)	
High	130,133	(44.4)	7,702	(5.9)	122,431	(94.1)	
Charlson Comorbidity Index (CCI)							<0.0001
0-2	55,120	(18.8)	727	(1.3)	54,393	(98.7)	
3-4	108,159	(36.9)	3,220	(3.0)	104,939	(97.0)	
≥5	129,531	(44.2)	13,361	(10.3)	116,170	(89.7)	
Diabetes							<0.0001
Yes	6,650	(2.3)	546	(8.2)	6,104	(91.8)	
No	286,160	(97.7)	16,762	(5.9)	269,398	(94.1)	
Hypertension							0.0344
Yes	32,823	(11.2)	1,855	(5.7)	30,968	(94.3)	
No	259,987	(88.8)	15,453	(5.9)	244,534	(94.1)	
Depression							0.151
Yes	11,393	(3.9)	638	(5.6)	10,755	(94.4)	
No	281,417	(96.1)	16,670	(5.9)	264,747	(94.1)	

Table 2 Results of association between use of hypnotics and the risk of Alzheimer's diseases

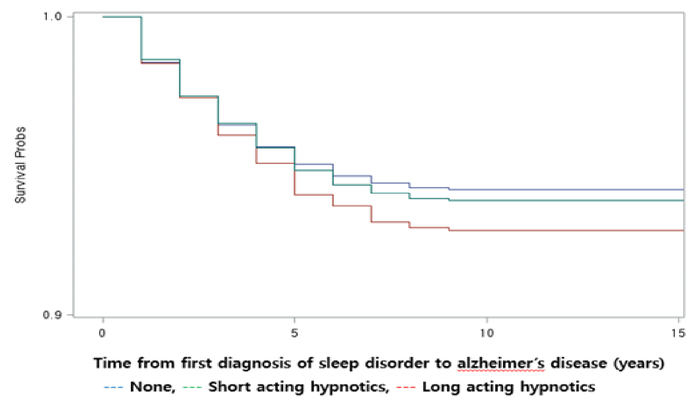
Variables	Alzheimer's Disease					
	Model 1[a]		Model 2[b]		Model 3[c]	
	HR	95% CI	HR	95% CI	HR	95% CI
Hypnotics						
Long-acting	1.25	(1.15 - 1.35)	1.26	(1.16 - 1.37)	1.18	(1.09 - 1.28)
Short-acting	1.07	(1.03 - 1.10)	1.04	(1.00 - 1.07)	1.06	(1.02 - 1.09)
No	1.00		1.00		1.00	
Sex						
Male			1.00		1.00	
Female			1.45	(1.41 - 1.50)	1.57	(1.52 - 1.62)
Age						
50-59			0.23	(0.20 - 0.26)	0.27	(0.24 - 0.30)
60-65			1.00		1.00	
65-70			2.46	(2.27 - 2.67)	2.26	(2.09 - 2.46)
70-75			4.61	(4.27 - 4.98)	4.11	(3.80 - 4.43)
75-80			6.42	(5.95 - 6.93)	5.74	(5.32 - 6.19)
≥80			7.54	(6.98 - 8.14)	6.99	(6.48 - 7.55)
Social Security						
Health Insurance			1.00		1.00	
Medical Aid			1.01	(0.97 - 1.05)	0.99	(0.95 - 1.02)
Region						
Metropolitan			1.00		1.00	
City			1.26	(1.22 - 1.31)	1.29	(1.25 - 1.34)
Rural			1.25	(1.21 - 1.30)	1.23	(1.19 - 1.28)
Disability						
Yes			1.08	(1.04 - 1.12)	0.99	(0.95 - 1.02)
No			1.00		1.00	
Income						
Low			1.00		1.00	
Middle			1.29	(1.24 - 1.35)	1.20	(1.15 - 1.25)
High			0.99	(0.95 - 1.04)	0.94	(0.90 - 0.98)
Charlson Comorbidity Index (CCI)						
0-2					1.00	
3-4					2.05	(1.90 - 2.23)
≥5					6.08	(5.64 - 6.55)
Diabetes						
Yes					1.13	(1.04 - 1.23)
No					1.00	
Hypertension						
Yes					1.00	(0.95 - 1.05)
No					1.00	
Depression						
Yes					1.19	(1.10 - 1.28)
No					1.00	

[a] Adjusted only hypnotics
[b] Adjusted for hypnotics, age, sex, social security, region, disability, and income
[c] Adjusted for hypnotics, age, sex, social security, disability, income, CCI, diabetes, hypertension, and depression

Table 3 Subgroup Analysis of the Association between risk of Alzheimer's Disease and covariates, according to use of hypnotics

	Hypnotics						
	Long Acting			Short Acting			No
	Adjusted HR	95% CI		Adjusted HR	95% CI		Adjusted HR
		Lower	Upper		Lower	Upper	
Sex							
Male	1.10	(0.95 - 1.26)		1.10	(1.03 - 1.17)		1.00
Female	1.24	(1.12 - 1.37)		1.03	(0.99 - 1.08)		1.00
Income							
Low	1.65	(1.40 - 1.94)		1.00	(0.92 - 1.09)		1.00
Middle	1.03	(0.90 - 1.19)		1.06	(1.00 - 1.13)		1.00
High	1.10	(0.97 - 1.25)		1.07	(1.01 - 1.12)		1.00
Diabetes							
Yes	2.01	(1.17 - 3.46)		1.63	(1.36 - 1.95)		1.00
No	1.16	(1.07 - 1.27)		1.04	(1.00 - 1.08)		1.00
Hypertension							
Yes	1.32	(1.02 - 1.71)		1.05	(0.94 - 1.17)		1.00
No	1.17	(1.07 - 1.27)		1.05	(1.02 - 1.09)		1.00

Figure 1. Kaplan-Meier survival curves results comparing the survival rate between the use of hypnotics and risk of Alzheimer's disease



Adjusted for age, sex, social security, disability, income, CCI, diabetes, hypertension, and depression

DISCUSSION

- For an ageing society, it has become more important to prevent or manage dementia by alleviating the symptoms. Benzodiazepines could lower the brain activity which could affect limited cognitive functions. Moreover, there are studies that shows the association between hypnotics and cognitive decline. Some previous studies have shown that insomnia is associated with the early manifestation of Alzheimer's disease. Our study results support this by showing that the use of hypnotics is associated with Alzheimer's disease. Moreover, long-acting benzodiazepines have been considered potentially inappropriate medications especially for the elderly. As long-acting benzodiazepines could accumulate in the blood for the elderly more easily, the risk of dementia increased when they use long-acting benzodiazepines. Therefore, more cautious use in older adults is needed.
- Those who have chronic diseases are more likely to have Alzheimer's disease when they use hypnotics. It is known that hypertensive elderly patients were highly associated with poor cognitive functions. Previous research shows that white matter medullary arterioles are vulnerable to hypertension, which could cause microvascular dysfunction and narrowing, which can lead to cerebral hypo perfusion and poor cognitive functions. This study could provide evidence that chronic diseases such as hypertension or diabetes is associated with Alzheimer's disease in long or short-acting hypnotics users than non-users. This further demonstrates that the use of hypnotics is associated with an increased risk of Alzheimer's disease in individuals suffering from chronic diseases.
- It should be noted that the current study has several limitations. First, we used the data from the prescription of the drugs, there could be limitations such as some buying hypnotics without prescription, which we could not adjust. Second, as we used only benzodiazepines in the study, we could not find out the effect of other hypnotics. Therefore, further studies including non-benzodiazepines is needed. Third, we could not find out the reason for using hypnotics. Lastly, due to our large sample study, the result should be interpreted carefully. For strength of the study, despite the limitations, this study has used the national sampling cohort data to assess the association between the use of hypnotics and the risk of Alzheimer's disease; this data represents almost the entire South Korean population of affected individuals, thereby providing evidence for the implementation of policies to prevent inappropriate use of hypnotics. Moreover, this study includes data over a period of nearly 10 years, and considering that dementia takes a long time to develop, it could demonstrate the association better.

CONCLUSION

- The current study has identified an association between the use of hypnotics and the risk of Alzheimer's disease among the South Korean middle-aged and elderly people. Our findings suggest that people using hypnotics especially the long-acting hypnotics, had a higher risk of Alzheimer's disease. These results imply that paying attention to those who use hypnotics is important to prevent them from suffering from Alzheimer's disease, especially the elderly. This implies that caution should be exerted while prescribing long-acting hypnotics, especially for the elderly. Our study also suggests future interventions to alleviate the risk of suffering from Alzheimer's disease associated with the use of hypnotics.