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# Risk of Type 2 Diabetes in Patients With Nonapnea Sleep Disorders in Using Different Types of Hypnotics

## *A Population-Based Retrospective Cohort Study*

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**Abstract:** There has been insufficient evidence on whether exposure to hypnotics affects the risk of type 2 diabetes (T2DM). The aim of this study was to examine patients with nonapnea sleep disorders using zolpidem, benzodiazepines (BZDs), or a combination of both, and their risk of T2DM.

This was a population-based retrospective cohort study using data from 1997 to 2011. Data from the Taiwan National Health Insurance Research Database were employed for this study. A total of 45,602 patients with nonapnea sleep disorders and use of hypnotics were identified as the study cohort. The control cohort comprised 40,799 age- and sex-matched patients. We conducted a Cox proportional hazard regression analysis to estimate the effects of hypnotics on risk of T2DM.

The overall incidence of T2DM was 20.1 per 1000 person-years for patients using zolpidem, which was significantly higher than that of the control group (11.9 per 1000 person-years). Overall, patients with nonapnea sleep disorders using zolpidem had a higher risk of T2DM compared with patients not using zolpidem and the control cohort (adjusted hazard ratio [HR]=1.41, 95% confidence interval [CI]=1.35–1.48). We also observed a significantly higher risk of T2DM in patients with both zolpidem and BZD use (adjusted HR = 1.77, 95% CI = 1.64–1.91) than that of those without zolpidem use and BZD use.

Compared with patients not using hypnotics, patients using zolpidem had a higher risk of developing T2DM; the risk was particularly pronounced in those using both zolpidem and BZDs.

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**Abbreviations:** BZD = benzodiazepine, CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, NSD = nonapnea sleep disorders.

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## INTRODUCTION

Epidemiological studies have shown that the prevalence of sleep disorders is approximately 25% to 37% of the general adult population in Asia.<sup>1,2</sup> There is growing evidence that sleep plays a major role in the regulation of neuroendocrine function and metabolism in adults. Laboratory studies have found that sleep deprivation is related to glucose metabolism, which can reduce insulin sensitivity and increase insulin resistance or change the balance of orexins.<sup>3,4</sup> Prior studies have found associations between sleep problems and chronic diseases, including cardiovascular disease,<sup>5</sup> hypertension,<sup>6</sup> and type 2 diabetes (T2DM),<sup>7,8</sup> as well as an increased mortality from disease.<sup>9,10</sup>

Among sleep disorders, an increasing amount of study evidence suggests that sleep apnea syndrome or sleep-disordered breathing (SDB) is correlated with the prevalence and incidence of diabetes.<sup>11,12</sup> The effect of sleep apnea on metabolism regulation aspects has been extensively examined and supported, but research on the association between nonapnea sleep disorder (NSD) and T2DM has been relatively scant.<sup>8</sup>

Thus far, hypnotics have been employed as the mainline therapy for patients with NSDs.<sup>13</sup> They can be divided into benzodiazepines (BZDs) and nonbenzodiazepines (non-BZDs). Common adverse side effects include nausea, tiredness, weakness, dizziness, and confusion.<sup>14,15</sup> Previous studies have reported that patients using hypnotics are associated with an increased risk of dementia,<sup>16</sup> stroke,<sup>17</sup> and of cancer.<sup>18</sup>

Zolpidem is a widely used non-BZD hypnotic drug for treating insomnia. Prior studies have indicated correlations

**TABLE 1.** Comparison of Demographics and Comorbidity Between Nonapnea SD Patients and Controls

	Nonapnea SD								P-Value
	Nonzolpidem (N = 15,091)		Zolpidem (N = 30,511)		Total (N = 45,602)		Control (N = 40,799)		
	N	%	N	%	n	%	n	%	
Age, year									0.001
≤40	5232	34.7	7710	25.3	12,942	28.4	12,235	30.0	
41–65	6601	43.7	15,360	50.3	21,961	48.2	19,584	48.0	
>65	3258	21.6	7441	24.4	10,699	23.5	8980	22.0	
Mean (SD)*	48.7	17.8	51.8	16.0	50.8	16.7	49.6	16.9	0.001
Sex									0.57
Female	9052	60.0	19,999	65.6	29,051	63.7	25,916	63.5	
Male	6039	40.0	10,512	34.5	16,551	36.3	14,883	36.5	
Comorbidity									
Hypertension	6178	40.9	16,482	54.0	22,660	49.7	12,688	31.1	<0.001
Hyperlipidemia	3526	23.4	10,565	34.6	14,091	30.9	6418	15.7	<0.001
Stroke	2482	16.5	7411	24.3	9893	21.7	3968	9.73	<0.001
CAD	4724	31.3	13,026	42.7	17,750	38.9	7797	19.1	<0.001
Depression	1665	11.0	10,205	33.5	11,870	26.0	785	1.92	<0.001
Medication									
Benzodiazepines	2984	19.8	9929	32.5	12,913	28.3	1854	4.54	<0.001

Chi-square test compared to total nonapnea SD. CAD = coronary artery disease, SD = standard deviation.

\* Two sample *t*-test.

between the use of zolpidem and rising glucose concentrations, but the mechanism unclear.<sup>19</sup> Another study found that zolpidem caused sleep eating and a hyperglycemic state in patients with type 1 diabetes.<sup>20</sup> These findings are often restricted to specific sample sizes or case reports, limiting their possibilities for generalization. To date, few studies have explored the long-term effects of zolpidem on patients' glucose metabolism or risk of T2DM. Therefore, this study used the Taiwan National Health Insurance Research Database (NHIRD) to long-term track these characteristics. This study examined patients with NSDs using zolpidem as a treatment, and its correlation with an increased risk of diabetes; and patients with NSDs treated with a combination of different hypnotics (zolpidem and BZDs), and whether these have a synergistic effect on the risk of diabetes.

## METHODS

### Data Source

The Taiwanese government established a universal, single-payer health insurance program in 1995, providing insurance coverage for more than 99% of the country's population (<http://www.nhi.gov.tw/>). The National Health Research Institutes was mandated to establish and manage the NHIRD, which contains the annual original claims data for reimbursement. This retrospective cohort study used the Longitudinal Health Insurance Database (LHID), which consists of all the original claims data of 1 million beneficiaries randomly selected from the original 2000 registry for beneficiaries. To protect privacy, the identities of individuals included in the NHIRD were all encrypted. Diseases were identified in the NHIRD according to the International Classification of Diseases, 9th Revision, Clinical

Modification (ICD-9-CM). This study was exempted from full review by the institutional research ethics committee (CMU-REC-101-012).

### Sampled Participants

Patients aged 20 years or older diagnosed with NSDs between 1997 and 2001 were identified from the LHID (ICD-9-CM 307.4 and 780.5, except sleep apnea syndrome [ICD-9-CM 780.51, 780.53, and 780.57]). The NSD patients were divided into 2 groups, according to their zolpidem use: the zolpidem group included patients who had received zolpidem therapy, whereas the nonzolpidem group included patients who had not received zolpidem therapy during follow-up. We excluded patients with a history of type 1 or type 2 diabetes (ICD-9-CM 250), or with incomplete age or sex information. For the non-NSD control group, we randomly selected patients without a history of NSDs, sleep apnea syndrome, or zolpidem, and applied the same exclusion criteria as in the NSD group. The NSD and non-NSD patients were frequency matched by age (5-year spans), sex, and year of NSD diagnosis.

## OUTCOME

All study participants were followed up from the index date until the onset of T2DM (ICD-9-CM 250.×0 and 250.×2), withdrawal from the National Health Insurance (NHI) program, or the end of 2011.

### Comorbidities and Medications

Baseline comorbidities included hypertension (ICD-9-CM 401–405), hyperlipidemia (ICD-9-CM 272), stroke (ICD-9-CM

430–438), coronary artery disease (CAD) (ICD-9-CM 410–414), and depression (ICD-9-CM 296.2–296.3, 300.4, 311). The medication history of BZDs was also included.

### Statistical Analysis

Chi-squared and *t*-tests were used to evaluate the distributions of categorical and continuous variables between the NSD and non-NSD groups. The incidence densities of DM were calculated by sex, age, comorbidity, and BZD. Univariable and multivariable Cox proportional hazards regression models were used to determine the risk of developing DM, shown as a hazard ratio (HR) with a 95% confidence interval (CI). Multivariable analysis included the variables sex, age, comorbidity status, and medication with BZDs. For additional analyses the effect of the zolpidem medication cumulative duration and zolpidem medication cumulative dosage were also estimated. For zolpidem, the cumulative duration and cumulative dosage were divided into 3 levels on the basis of the dosage median and third quartile. All statistical analyses were performed using the SAS statistical package (Version 9.2 for Windows; SAS Institute, Inc., Cary, NC). A 2-tailed  $P < 0.05$  was considered significant.

### RESULTS

We identified 45,602 patients with NSDs (30,511 patients using zolpidem and 15,091 patients without zolpidem) and 40,799 patients in the non-NSD control group (Table 1). The majority of patients were aged 41 to 65 years (50.3%, 43.7%, and 48.0% in the zolpidem, nonzolpidem, and non-NSD groups, respectively). Females accounted for more than half of the patients in each group. Compared with those in the non-NSD group, the comorbidities of hypertension, hyperlipidemia, stroke, CAD, and depression, as well as BZD use were more prevalent in the NSD group. The average follow-up duration was 9.01 years for patients using zolpidem, 9.00 years for patients without zolpidem use, and 8.98 years for non-NSD patients (data not shown). Overall, the incidence of T2DM was higher in the zolpidem and nonzolpidem groups than in the non-NSD control group (20.1, 12.5, and 11.9 per 1000 person-year, respectively) (Table 2). Compared with the non-NSD control group, NSD patients using zolpidem (adjusted HR = 1.41, 95% CI = 1.35–1.48) were associated with a significantly higher risk of developing T2DM. The T2DM incidence was greater in males than in females and increased with age in all the zolpidem, nonzolpidem, and non-NSD control groups. Male NSD patients in the non-zolpidem group (adjusted HR = 1.11, 95% CI = 1.02–1.22) were associated with a higher risk of developing T2DM compared with the non-NSD male controls. The risk of T2DM in NSD patients using zolpidem was higher than in non-NSD patients for all age groups. NSD patients using zolpidem also had a higher risk than non-NSD patients, whether with or without comorbidity. The BZD-specific-zolpidem group to control group adjusted HR of T2DM was significant for both patients without BZD use (adjusted HR = 1.41, 95% CI = 1.34–1.48) and patients with BZD use (adjusted HR = 1.52, 95% CI = 1.34–1.72).

Table 3 shows that the overall risk of T2DM was 1.45 times higher in NSD patients using zolpidem than in NSD patients without zolpidem use (adjusted HR = 1.45, 95% CI = 1.38–1.54). The sex-specific relative risk of T2DM in NSD patients using zolpidem versus nonzolpidem NSD patients was significantly higher for both females and males. The risk of T2DM in NSD patients using zolpidem was higher than in nonzolpidem NSD patients regardless of age group, comorbidity status, or BZD use.

Table 4 shows the interaction of zolpidem use, comorbidity, and BZD use on the risk of T2DM. Compared with nonzolpidem patients without comorbidities, the patients using zolpidem with comorbidity had an adjusted HR that increased to 2.98 (95% CI = 2.64, 3.35). In addition, we observed a significantly higher risk of T2DM in patients with both zolpidem and BZD use (adjusted HR = 1.77, 95% CI = 1.64–1.91) compared with those without Zolpidem use and BZD use. Patients with comorbidity and BZD use had a higher risk of T2DM compared with patients without comorbidity and BZD use (adjusted HR = 1.92, 95% CI = 1.71–2.14).

Furthermore, we estimated the risk of T2DM according to the cumulative duration and cumulative dosage of zolpidem use (Table 5). Compared with NSD patients without zolpidem use, NSD patients administered zolpidem for less than 60 days (adjusted HR = 2.33, 95% CI, 2.20–2.47) had a higher T2DM risk. However, compared with NSD patients without zolpidem use, both NSD patient groups with 60 to 350 days and >350 days of zolpidem use had significantly lower risks of T2DM (adjusted HR = 0.78, 95% CI = 0.72–0.85; adjusted HR = 0.51, 95% CI = 0.46–0.56, respectively). Similar results were observed for the cumulative dosage of zolpidem use.

### DISCUSSION

The results of this study show that after adjustment for potential confounders (age, sex, comorbidities, and hypnotics), NSD patients using zolpidem have a 45% and 41% higher risk of T2DM compared with NSD patients without zolpidem use and patients with neither NSDs nor the use of hypnotics, respectively (Tables 2 and 3). The present study found that a strong correlation exists between the use of zolpidem and an increased risk of T2DM. In addition, in Table 4, the NSD groups that used only zolpidem or only BZDs had a 48% and 26% higher risk of T2DM, respectively, compared with the reference group (patients without zolpidem or BZD use); moreover, when both zolpidem and BZDs are used together, there is a 77% increased risk of T2DM. This indicates that the use of both zolpidem and BZDs by NSD patients reflects an increased risk of T2DM; furthermore, the concomitant use of zolpidem with BZDs exhibits a joint effect on the patients' risk of T2DM. Based on our research, this is the first longitudinal population-based study on the risk of T2DM associated with the use of zolpidem and different hypnotics in patients with NSDs.

Zolpidem is a frequently prescribed non-BZD hypnotic drug that enhances the effect of the gamma-aminobutyric acid neurotransmitter, whose receptor binds selectively onto the omega-1 receptor subtype.<sup>13</sup> Zolpidem therefore has a sedative hypnotic effect that lowers sleep latency and increases overall sleep time.<sup>21</sup> There is growing evidence that exposure to hypnotics could contribute to the development of different diseases such as dementia, stroke, and cancer.<sup>16–18</sup> However, research on the association between hypnotics and T2DM has been relatively scant. A previous study indicated that zolpidem use is related to the risk of acute pancreatitis;<sup>22</sup> patients who receive at least one prescription of zolpidem in 7 days have a 7-fold increased odds ratio for experiencing acute pancreatitis. The presenting or subtle pancreas damage could be a possible mechanism for zolpidem users developing diabetes.

In addition, a previous report on patients' intake of zolpidem and the occurrence of nocturnal sleep-related eating disorder (NSRED) and hyperglycemia revealed a chronological relationship.<sup>23</sup> Furthermore, another study found that NSRED led to a glucose-renewed state in patients using zolpidem; yet

**TABLE 2.** Comparison of Incidence Densities and Hazard Ratio of Type 2 Diabetes in Study Subjects

	Control (N = 40,799)			Nonzolidem (N = 15,091)			Zolpidem (N = 30,511)		
	Case	Rate <sup>†</sup>	Rate <sup>†</sup>	Case	Rate <sup>†</sup>	Rate <sup>†</sup>	Case	Rate <sup>†</sup>	Rate <sup>†</sup>
All	4368	11.9	12.5	1718	12.5	12.5	5523	20.1	20.1
Gender									
Female	2762	11.6	11.6	991	11.6	11.6	3584	19.5	19.5
Men	1606	12.5	13.9	727	13.9	13.9	1939	21.4	21.4
Age									
≤40	286	2.41	3.39	183	3.39	3.39	482	6.18	6.18
41–65	2707	14.6	16.4	1006	16.4	16.4	3299	23.6	23.6
>65	1375	22.0	24.1	529	24.1	24.1	1742	30.5	30.5
Comorbidity <sup>  </sup>									
No	1334	5.84	4.85	305	4.85	4.85	577	9.87	9.87
Yes	3034	21.9	19.0	1413	19.0	19.0	4946	22.9	22.9
Benzodiazepines									
No	4080	11.6	10.7	1221	10.7	10.7	3262	17.0	17.0
Yes	288	21.6	21.6	497	21.6	21.6	2261	27.2	27.2

CI = confidence interval, CAD = coronary artery disease, HR = hazard ratio.

<sup>†</sup> Incidence rate, per 1000 person-years.

<sup>‡</sup> Relative hazard ratio.

<sup>§</sup> Hazard ratio mutually adjusted for age, sex, comorbidities of hypertension, hyperlipidemia, stroke, CAD, depression and medication of benzodiazepines; \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ .

<sup>||</sup> Patients with any one of the comorbidities (including hypertension, hyperlipidemia, stroke, CAD, and depression) were classified as the comorbidity group.

**TABLE 3.** Comparison of Hazard Ratio of Type 2 Diabetes in Nonapnea SD Patients With and Without Zolpidem Treatment by Demographic Characteristics

	Zolpidem Treatment	
	No Adjusted HR <sup>†</sup> (95% CI)	Yes Adjusted HR <sup>†</sup> (95% CI)
All	1 (Reference)	1.45 (1.38, 1.54)***
Gender		
Women	1 (Reference)	1.51 (1.41, 1.63)***
Men	1 (Reference)	1.39 (1.28, 1.52)***
Age		
≤40	1 (Reference)	1.67 (1.40, 2.00)***
41–65	1 (Reference)	1.44 (1.34, 1.55)***
>65	1 (Reference)	1.35 (1.22, 1.49)***
Comorbidity		
No	1 (Reference)	1.81 (1.57, 2.08)***
Yes	1 (Reference)	1.22 (1.15, 1.29)***
Benzodiazepines		
No	1 (Reference)	1.47 (1.38, 1.58)***
Yes	1 (Reference)	1.38 (1.25, 1.52)***

CI = confidence interval, CAD = coronary artery disease, HR = hazard ratio, SD = standard deviation.  
<sup>†</sup>Hazard ratio mutually adjusted for age, sex, comorbidities of hypertension, hyperlipidemia, stroke, CAD, depression, and medication of benzodiazepines; \**P* < 0.05, \*\**P* < 0.01, \*\*\**P* < 0.001.

halting the use of zolpidem brought blood sugar levels back to normal.<sup>20</sup> These case reports showed that NSRED often followed after the use of zolpidem. Patients with NSRED are in a state of unconsciousness while preparing or eating a large amount of food; they have no memory of the night’s activity upon waking. This results in weight gain or blood sugar instability, though the physiological mechanisms remain unknown.<sup>23,24</sup> NSRED is considered a complex sleep behavior (CSB). Nonetheless, the use of high doses of zolpidem (>10 mg/day) is considered to increase the probability and the occurrence of CSBs.<sup>25</sup> Based on previous studies,<sup>26</sup> the prevalence of zolpidem inducing NSRED is considered to be 1%, and only a low number of patients develop it. Therefore, NSRED may be a risk factor associated with T2DM, but not the major cause of T2DM development in patients with zolpidem use.

As shown in Tables 2 and 3, our study found that the use of BZDs or zolpidem is correlated with a significantly increased risk of diabetes, and that zolpidem users have a higher risk of developing diabetes than BZD users do. Although the main mechanism remains unclear for these results, we inferred potential mechanism from previous studies may provide some explanation. First, a previous study found that the use of BZDs (in particular, clonazepam) was related to changes in insulin secretion and sensitivity.<sup>27</sup> Another experimental study found that 15 days of zolpidem use followed by 15 days of consecutive BZD use resulted in a decrease in insulin sensitivity by 12% and 4%, respectively.<sup>19</sup> In addition, we understand that a conventional dose of any BZDs typically decreases the hypothalamic–pituitary–adrenocortical cortex (HPA) axis activity. However, higher doses of BZDs could stimulate basal circulating corticosterone levels.<sup>28</sup> Second, zolpidem was reported to produce an exceptionally high increase in plasma adrenocorticotrophic hormone and corticosterone concentrations compared with BZDs.<sup>29</sup> These biological theories could support the current findings that zolpidem users had a higher risk of developing

**TABLE 4.** Cox Proportional Model Measured Hazard Ratios in Nonapnea SD Patients With Zolpidem Treatment-Associated Type 2 Diabetes With Interaction of Comorbidity and Benzodiazepines

Variables	Event	PY	Rate <sup>†</sup>	Adjusted HR <sup>†</sup> (95% CI)	<i>P</i> -Value <sup>‡</sup>
Zolpidem	Comorbidity <sup>‡</sup>				<0.001
–	–	305	62,909	4.85	1 (Reference)
–	+	1413	74,552	19.0	2.39 (2.11, 2.72)***
+	–	577	58,441	9.87	1.89 (1.65, 2.17)***
+	+	4946	216,314	22.9	2.98 (2.64, 3.35)***
Zolpidem	Benzodiazepines				<0.001
–	–	1221	114,394	10.7	1 (Reference)
–	+	497	23,067	21.6	1.26 (1.14, 1.41)***
+	–	3262	191,660	17.0	1.48 (1.38, 1.58)***
+	+	2261	83,096	27.2	1.77 (1.64, 1.91)***
Comorbidity <sup>‡</sup>	Benzodiazepines				<0.001
–	–	751	11,1516	6.73	1 (Reference)
–	+	131	9833	13.3	1.64 (1.37, 1.98)***
+	–	3732	194,537	19.2	1.58 (1.43, 1.74)***
+	+	2627	96,329	27.3	1.92 (1.71, 2.14)***

CI = confidence interval, CAD = coronary artery disease, HR = hazard ratio, PY = person-years.  
<sup>†</sup>Hazard ratio mutually adjusted for age, sex, comorbidities of hypertension, hyperlipidemia, stroke, CAD, depression and medication of benzodiazepines; \**P* < 0.05, \*\**P* < 0.01, \*\*\**P* < 0.001.  
<sup>‡</sup>Patients with any one of the comorbidities (including hypertension, hyperlipidemia, stroke, CAD, and depression) were classified as the comorbidity group.

**TABLE 5.** Incidence and Adjusted Hazard Ratio of Type 2 Diabetes and Duration of Zolpidem Therapy in Patients With Nonapnea SD

Zolpidem exposed	N	Case	Rate <sup>†</sup>	Adjusted HR <sup>§</sup> (95% CI)
Nonzolpidem	15,091	1718	12.5	1.00
Duration on zolpidem				
≤60 days	15,001	4009	32.6	2.33 (2.20, 2.47) <sup>***</sup>
60–350	8116	912	11.8	0.78 (0.72, 0.85) <sup>***</sup>
>350 days	7394	602	8.06	0.51 (0.46, 0.56) <sup>***</sup>
Cumulative dose of zolpidem				
≤540 mg	15,209	4039	32.3	2.29 (2.16, 2.42) <sup>***</sup>
541–2890 mg	7669	840	11.5	0.77 (0.71, 0.84) <sup>***</sup>
>2890 mg	7633	644	8.39	0.53 (0.49, 0.59) <sup>***</sup>

CI = confidence interval, CAD = coronary artery disease, HR = hazard ratio.

<sup>†</sup> Incidence rate, per 1000 person-years.

<sup>§</sup> Hazard ratio mutually adjusted for age, sex, comorbidities of hypertension, hyperlipidemia, stroke, CAD, depression and medication of benzodiazepines; \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

diabetes than do BZD users because of an increase of HPA axis activity in patients taking drugs for an NSD.

Our study found that among NSD patients with zolpidem use, females and young adults ( $\leq 40$  years) predominantly have a T2DM risk (Table 3). We could not confirm the exact mechanism in these results. However, previous studies have indicated that a pharmacokinetic property of zolpidem is greatly affected by sex and age differences; for example, the zolpidem clearance rate has been lower in women than in men, which may contribute to the observed increased incidence of adverse drug reactions in women.<sup>30,31</sup> Furthermore, a potential explanation that we could not rule out is that young adults tend to have fewer comorbidities and are more affected by zolpidem or NSDs. A previous study also found that among NSD patients, those younger than 40 years were more prone to have a T2DM risk than other age groups.<sup>8</sup> These findings regarding young adults require more attention, because previous studies have suggested that increased incidences of chronic diseases in young adults are associated with elevated mortality rates resulting from subsequent diseases.<sup>32</sup>

As shown in Table 4, when both zolpidem and BZDs are used together would have a higher risk for the users to develop diabetes than only zolpidem or only BZDs users. Therefore, the joint effect of zolpidem and BZD use is worthy of attention. In clinical treatments, over 50% of patients with NSD adopt a combined use of different types of hypnotics.<sup>33</sup> Previous studies have suggested that the combined use of hypnotics may increase the occurrence of adverse effects such as falling, bone fractures, and car accidents;<sup>21,34</sup> however, no study has assessed the risks associated with diabetes. This study is the first to propose that the concomitant use of hypnotics results in an increased risk of diabetes. Although previous studies reported that BZDs or zolpidem are associated with increased blood sugar levels, the results have been limited to the observation of the short-term use of 2 types of hypnotics on glucose metabolism.<sup>19</sup> It remains unclear whether the concomitant use of hypnotics poses a long-term impact on changes in glucose metabolism. Furthermore, we understand that the common side effects of hypnotic drugs, including muscle relaxation, drowsiness, and residual daytime effects,<sup>14</sup> may lead to a poor mental state and tiredness,

which in turn reduce the willingness to perform daily activities.<sup>35</sup> Therefore, we could not rule out lower activity levels having a subsequent effect on the development of T2DM.

Table 5 shows that extremely long-term zolpidem use, more than 60 days or more than 540 mg in cumulative dosage, paradoxically decreases the risk of developing diabetes. There are some possible explanations for this dramatic situation. First, generally, in patients with long-term use zolpidem, the severity of NSDs may be alleviated, and the adverse effects of NSDs decrease for diabetes risk. Second, a previous study found that patients with continuous zolpidem exposure were associated with adaptive changes in GABA-A receptors and were prone to develop tolerance.<sup>36</sup> However, in our study, we could not confirm the possible mechanism; because of the tolerance effects in the HPA axis, the specifically higher risk of diabetes would be eliminated if zolpidem is used for more than 60 days.

The cohort study design's strength is to use general population-based database (the NHIRD) including a very big sample-size under the Taiwan government's policy and operation. In addition, the health claims reimbursement is universal by only 1 buyer. Therefore, every insurance claim should be checked by the peer review of the medical specialists. However, there are still certain study limitations which remain possibly unmeasured or unknown confounding factors and are noteworthy potential biases that may compromise the results: no individual data such as lifestyles-habits, body weight-length, physical-exercise activity, socioeconomic conditions, and family histories in the NHIRD; level of evidence a retrospective cohort study is generally lower than a prospective cohort or randomized-controlled study to evaluate the relationship between zolpidem use and T2DM; the data in the NHIRD are primarily used to bill and are not validated to scientific researches; we could not confirm whether the patients prescribed with hypnotics had the truly drug intake behaviors.

To summarize, this is the first population-based retrospective cohort study using the Taiwan NHIRD to track patients with NSDs using zolpidem or BZDs and their relative risk of diabetes. The results show that the use of zolpidem or BZDs

increases the risk of diabetes, and that zolpidem users have a higher risk of developing diabetes than BZD users do. Moreover, the combined use of zolpidem and BZDs reveals a synergistic effect on the risk of diabetes in patients with NSDs. The results of this study will help clinical practitioners cautiously assess the T2DM risk of a hypnotic's user.

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### REFERENCES

- Wong WS, Fielding R. Prevalence of insomnia among Chinese adults in Hong Kong: a population-based study. *J Sleep Res.* 2011;20:117–126.
- Kao CC, Huang CJ, Wang MY, et al. Insomnia: prevalence and its impact on excessive daytime sleepiness and psychological well-being in the adult Taiwanese population. *Qual Life Res.* 2008;17:1073–1080.
- Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med.* 2004;141:846–850.
- Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet.* 1999;354:1435–1439.
- Chien KL, Chen PC, Hsu HC, et al. Habitual sleep duration and insomnia and the risk of cardiovascular events and all-cause death: report from a community-based cohort. *Sleep.* 2010;33:177–184.
- Fernandez-Mendoza J, Vgontzas AN, Liao D, et al. Insomnia with objective short sleep duration and incident hypertension The Penn State Cohort. *Hypertension.* 2012;60:929–935.
- Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Sleep duration as a risk factor for diabetes incidence in a large US sample. *Sleep.* 2007;30:1667–1673.
- Lai YJ, Lin CL, Lin MC, et al. Population-based cohort study on the increase in the risk for type 2 diabetes mellitus development from nonapnea sleep disorders. *Sleep Med.* 2013;14:913–918.
- Ferrie JE, Kumari M, Salo P, et al. Sleep epidemiology – a rapidly growing field. *Int J Epidemiol.* 2011;40:1431–1437.
- Ferrie JE, Shipley MJ, Cappuccio FP, et al. A prospective study of change in sleep duration: associations with mortality in the Whitehall II cohort. *Sleep.* 2007;30:1659–1666.
- Aurora RN, Punjabi NM. Obstructive sleep apnoea and type 2 diabetes mellitus: a bidirectional association. *Lancet Respir Med.* 2013;1:329–338.
- Pandey A, Demede M, Zizi F, et al. Sleep apnea and diabetes: insights into the emerging epidemic. *Curr Diab Rep.* 2011;11:35–40.
- Dang A, Garg A, Rataboli PV. Role of zolpidem in the management of insomnia. *CNS Neurosci Ther.* 2011;17:387–397.
- Holbrook AM, Crowther R, Lotter A, et al. Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ.* 2000;162:225–233.
- Sithampanathan K, Sadera A, Leung L. Adverse effects of benzodiazepine use in elderly people: a meta-analysis. *Asian J Gerontol Geriatr.* 2012;7:2012.
- Chen PL, Lee WJ, Sun WZ, et al. Risk of dementia in patients with insomnia and long-term use of hypnotics: a population-based retrospective cohort study. *PLoS One.* 2012;7:e49113.
- Huang WS, Tsai CH, Lin CC, et al. Relationship between zolpidem use and stroke risk: a Taiwanese population-based case-control study. *J Clin Psychiatry.* 2013;74:e433–e438.
- Kao CH, Sun LM, Liang JA, et al. Relationship of zolpidem and cancer risk: a Taiwanese population-based cohort study. *Mayo Clin Proc.* 2012;87:430–436.
- Gramaglia E, Ramella Gliardi V, Olivetti I, et al. Impact of short-term treatment with benzodiazepines and imidazopyridines on glucose metabolism in healthy subjects. *J Endocrinol Invest.* 2014;37:203–206.
- Zisser H, Rivera SC, Lane J. Zolpidem-induced sleep-eating resulting in significant hyperglycemia in a subject with type 1 diabetes discovered via continuous glucose monitoring. *Clin Diabetes.* 2013;31:133–135.
- Greenblatt DJ, Roth T. Zolpidem for insomnia. *Expert Opin Pharmacother.* 2012;13:879–893.
- Lai SW, Lin CL, Liao KF. Increased relative risk of acute pancreatitis in zolpidem users. *Psychopharmacology (Berl).* 2015;232:2043–2048.
- Najjar M. Zolpidem and amnesic sleep related eating disorder. *J Clin Sleep Med.* 2007;3:637–638.
- Dang A, Garg G, Rataboli PV. Zolpidem induced nocturnal sleep-related eating disorder (NSRED) in a male patient. *Int J Eat Disord.* 2009;42:385–386.
- Hwang TJ, Ni HC, Chen HC, et al. Risk predictors for hypnosedative-related complex sleep behaviors: a retrospective, cross-sectional pilot study. *J Clin Psychiatry.* 2010;71:1331–1335.
- Valiensi SM, Cristiano E, Martínez OA, et al. Sleep related eating disorders as a side effect of zolpidem. *Medicina (B Aires).* 2010;70:223–226.
- Chevassus H, Mourand I, Molinier N, et al. Assessment of single-dose benzodiazepines on insulin secretion, insulin sensitivity and glucose effectiveness in healthy volunteers: a double-blind, placebo-controlled, randomized cross-over trial [ISRCTN08745124]. *BMC Clin Pharmacol.* 2004;4:3.
- Mikkelsen JD, Söderman A, Kiss A, et al. Effects of benzodiazepines receptor agonists on the hypothalamic-pituitary-adrenocortical axis. *Eur J Pharmacol.* 2005;519:223–230.
- Mikkelsen JD, Bundzikova J, Larsen MH, et al. GABA regulates the rat hypothalamic-pituitary-adrenocortical axis via different GABA-A receptor alpha-subtypes. *Ann N Y Acad Sci.* 2008;1148:384–392.
- Greenblatt DJ, Harmatz JS, von Moltke LL, et al. Comparative kinetics and response to the benzodiazepine agonists triazolam and zolpidem: evaluation of sex-dependent differences. *J Pharmacol Exp Ther.* 2000;293:435–443.
- Olubodun JO, Ochs HR, von Moltke LL, et al. Pharmacokinetic properties of zolpidem in elderly and young adults: possible modulation by testosterone in men. *Br J Clin Pharmacol.* 2003;56:297–304.
- Miura K, Daviglius ML, Dyer AR, et al. Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men: the Chicago Heart Association Detection Project in Industry. *Arch Intern Med.* 2001;161:1501–1508.

33. Bourgeois J, Elseviers MM, Azermai M, et al. Benzodiazepine use in Belgian nursing homes: a closer look into indications and dosages. *Eur J Clin Pharmacol*. 2012;68:833–844.
34. Lin FY, Chen PC, Liao CH, et al. Retrospective population cohort study on hip fracture risk associated with zolpidem medication. *Sleep*. 2014;37:673–679.
35. Kang DY, Park S, Rhee CW, et al. Zolpidem use and risk of fracture in elderly insomnia patients. *J Prev Med Public Health*. 2012;45:219–226.
36. Vlainić J, Jembrek MJ, Vlainić T, et al. Differential effects of short- and long-term zolpidem treatment on recombinant (1/2)α subtype of GABA(A) receptors in vitro. *Acta Pharmacol Sin*. 2012;33:1469–1476.