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Risk of major adverse cardiovascular events among traditional Chinese medicine users: a cohort study with a subgroup analysis of male patients with sexual dysfunction

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Abstract

Background: The association between traditional Chinese medicine (TCM) use and major adverse cardiovascular events (MACEs) in males with sexual dysfunction (SD) remains underexplored. **Methods**: This retrospective cohort study analyzed data from Taiwan's National Health Insurance Research Database (2001–2018), including 2 million randomly selected individuals. A propensity score-matched cohort of TCM users (n = 144,114) and non-TCM users (n = 144,114) was followed for an average of 9.49 years. The primary analysis examined the risk of MACEs in the overall matched cohort using Cox proportional hazards models and Kaplan-Meier methods. A secondary analysis focused on 4959 males with SD. **Results**: Among the overall matched cohort, the incidence of MACEs was higher in TCM users than in non-TCM users (9.93 *vs.* 9.08 per 1000 person-years; adjusted hazard ratio (aHR) 1.07, 95% confidence interval (CI) (1.04, 1.09), $p < 0.001$). The risk was notably higher among older TCM users ($\geq$50 years) and those with pre-existing comorbidities. In the SD subgroup, TCM users exhibited a 1.23-fold increased risk of MACEs compared to non-TCM users (aHR 1.23, 95% CI (1.05, 1.43), $p = 0.009$). Further analysis by SD type showed that this increased risk was primarily observed in patients with organic SD (aHR 1.24, 95% CI (1.06, 1.45), $p = 0.006$). In contrast, no statistically significant difference was found among those with non-organic SD (aHR 0.58, 95% CI (0.19, 1.82), $p = 0.353$). **Conclusions**: TCM users with SD had a higher incidence of MACEs than non-TCM users, even after adjustment for confounders. While this association remained significant, residual confounding due to underlying comorbidities and differences in health-seeking behaviors remains a potential limitation. Further prospective studies are needed to investigate the long-term cardiovascular effects of TCM and optimize risk-based treatment strategies, particularly for high-risk SD patients with comorbidities.

Keywords

Chinese herbal drugs; Major adverse cardiac events; Physiological sexual dysfunction; Psychosexual dysfunctions; Traditional Chinese medicine

Riesgo de eventos cardiovasculares adversos mayores entre los usuarios de medicina tradicional china: un estudio de cohortes con un análisis de subgrupos en pacientes varones con disfunción sexual

Resumen

Antecedentes: La asociación entre el uso de la medicina tradicional china (MTC) y los eventos cardiovasculares adversos mayores (ECAM) en varones con disfunción sexual (DS) sigue siendo poco explorada. **Métodos**: Este estudio de cohorte retrospectivo analizó datos de la Base de Datos de Investigación del Seguro Nacional de Salud de Taiwán (2001–2018), que incluyó a 2 millones de individuos seleccionados aleatoriamente. Se identificó una cohorte emparejada por puntuación de propensión compuesta por usuarios de MTC (n = 144,114) y no usuarios de MTC (n = 144,114), con un seguimiento promedio de 9.49 años. El análisis primario examinó el riesgo de ECAM en la cohorte emparejada global mediante modelos de riesgos proporcionales de Cox y métodos de Kaplan-Meier. Un análisis secundario se centró en 4959 hombres con DS. **Resultados**: En la cohorte emparejada global, la incidencia de ECAM fue mayor en los usuarios de MTC que en los no usuarios (9.93 frente a 9.08 por cada 1000 personas-año; razón de riesgo ajustada (aHR) 1.07, intervalo de confianza del 95% (IC) (1.04–1.09), $p < 0.001$). El riesgo fue notablemente mayor entre los usuarios de MTC de edad avanzada (≥50 años) y aquellos con comorbilidades preexistentes. En el subgrupo de DS, los usuarios de MTC presentaron un riesgo 1.23 veces mayor de ECAM en comparación con los no usuarios de MTC (aHR 1.23, IC del 95% (1.05–1.43), $p = 0.009$). Un análisis adicional según el tipo de DS mostró que este mayor riesgo se observó principalmente en pacientes con DS orgánica (aHR 1.24, IC del 95% (1.06–1.45), $p = 0.006$), mientras que no se encontró una diferencia estadísticamente significativa entre aquellos con DS no orgánica (aHR 0.58, IC del 95% (0.19–1.82), $p = 0.353$). **Conclusiones**: Los usuarios de MTC con DS presentaron una mayor incidencia de ECAM en comparación con los no usuarios de MTC, incluso después del ajuste por factores de confusión. Si bien esta asociación se mantuvo significativa, la confusión residual derivada de comorbilidades subyacentes y diferencias en los comportamientos de búsqueda de atención médica sigue siendo una posible limitación. Se requieren estudios prospectivos adicionales para investigar los efectos cardiovasculares a largo plazo de la MTC y optimizar estrategias de tratamiento basadas en el riesgo, particularmente para pacientes con DS de alto riesgo y comorbilidades.

Palabras Clave

Medicina tradicional china; Eventos cardiovasculares adversos mayores; Disfunción sexual fisiológica; Disfunciones psicosexuales; Medicamentos herbales chinos

1. Introduction

Erectile dysfunction (ED) and premature ejaculation (PE) are common conditions among males, arising from both organic and non-organic causes [1]. Organic causes include vascular, neurological, endocrine, cavernous, urogenital, and drug-induced factors [2]. Vascular factors include atherosclerosis, diabetes, hypertension, hyperlipidemia and coronary artery disease, with endothelial dysfunction specifically associated with an increased risk of cardiac events [3]. Urogenital factors, including prostate diseases, can further contribute to ED [4]. Neurogenic ED may arise from conditions such as spinal cord injury, Parkinson's disease, dementia, multiple sclerosis, stroke, pelvic trauma and cancer surgery [5, 6]. Endocrine-related ED is frequently associated with hypogonadism, while cavernous ED often involves conditions such as Peyronie's disease [7, 8]. Drug-induced ED may occur with the use of antipsychotics, selective serotonin reuptake inhibitors (SSRIs), and illicit substances such as marijuana, opium and cocaine [9, 10]. Non-organic factors, including psychological and lifestyle-related causes such as anxiety, depression, smoking, alcohol use and obesity, also significantly contribute to sexual dysfunction (SD) [11].

The common treatment for ED is the use of oral phosphodiesterase 5 inhibitors (PDE5Is) [12]. However, combining PDE5Is with nitrates is contraindicated because of the risk of a dangerous drop in blood pressure [13, 14]. For PE, treatment typically involves SSRIs, which delay ejaculation, as well as amide-based local anesthetics such as lidocaine [15]. In Asia, a significant number of male patients with SD seek supplementary therapy with traditional Chinese medicine (TCM), and some combine both Western medication and Chinese herbal medicine (CHM) [16]. TCM is frequently used for managing chronic conditions, including metabolic and cardiovascular diseases, as well as SD. Many male patients with SD opt for TCM as an alternative or complementary treatment, particularly when concerned with the side effects or limited efficacy associated with Western medicine.

In Taiwan, TCM is widely integrated into the healthcare system, with a substantial proportion of the population regularly utilizing its services. According to the National Health Insurance Annual Report, approximately 26.7% of the population sought TCM treatment between 2001 and 2018 [17]. More recent data from 2023 indicate that TCM outpatient utilization has increased further, reaching 30.5% of the population, highlighting its sustained role in healthcare [18]. For male genital disorders classified under the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM), codes N41–N53 (excluding benign prostatic hyperplasia, N40, the outpatient consultation rate was 148 per 100,000 males. In contrast, the overall TCM outpatient visit rate among males was significantly higher at 24,113 per 100,000 [18]. These data suggest that, despite male genital disorders representing a relatively small proportion of outpatient consultations,

TCM remains extensively utilized by the male population in Taiwan. However, although patients with SD frequently seek TCM, large-scale epidemiological studies quantifying the precise proportion of SD patients utilizing TCM remain limited.

According to TCM theory, the "kidney" health is related to various systems, and male sexual dysfunction (MSD) is attributed to "kidney essence deficiency". TCM practitioners often use CHM to "tonify the kidneys" when treating MSD [19, 20]. Nevertheless, the cardiovascular risks associated with TCM use in male patients with SD remain inadequately explored. Therefore, this study aimed to investigate the associations between TCM use in male patients with SD and their risk of experiencing major adverse cardiovascular events (MACEs).

2. Materials and methods

2.1 Data source

This retrospective cohort study utilized data from Taiwan's National Health Insurance Research Database (NHIRD), which has provided de-identified, comprehensive healthcare data for nearly the entire Taiwanese population since 1995. The NHIRD encompasses both TCM and Western medicine, allowing for detailed analyses of integrative healthcare utilization. In this study, TCM specifically refers to CHM and does not include other TCM modalities such as acupuncture or manual therapy. In 2016, the database transitioned from the ICD-9-CM to the ICD-10-CM diagnosis codes. This study was approved by the Ethics Committee of China Medical University Hospital, Taiwan (approval number: CMUH109-REC2-031). Due to privacy regulations, all personal data within the NHIRD is encrypted, thus obviating the need for informed consent.

2.2 Study design

Between 2001 and 2018, 2 million Taiwanese individuals were randomly selected from the NHIRD and categorized into TCM users and non-TCM users. TCM users were defined as patients who received TCM for more than 30 days, whereas individuals treated for less than 30 days were classified as non-TCM users. The index date was defined as the first recorded instance of TCM use for the TCM group, while it was randomly assigned for the non-TCM group.

To ensure comparability between groups, a stepwise selection process was applied. Patients who did not meet the inclusion criteria were excluded before conducting propensity score matching (PSM). After exclusion, 1:1 PSM was performed based on age, comorbidities (such as hypertension, diabetes, hyperlipidemia, coronary artery disease, and chronic kidney disease), medication use (including PD5EIs, SSRIs and nitrates) and index year. This matching process resulted in a balanced cohort of male TCM users (n = 144,114) and male non-TCM users (n = 144,114), effectively minimizing potential confounding factors.

From this matched cohort, male patients diagnosed with SD were identified for a subgroup analysis to assess whether the cardiovascular risks observed in SD patients were specific to their condition or reflected a general trend among male TCM users (Fig. 1).

2.2.1 Exclusion criteria

Patients were excluded from the study based on the following criteria: records dates outside the 2001–2018 period; female patients; ages younger than 20 or older than 70 years at the index date; pre-existing SD or MACEs; discontinuation of TCM after SD diagnosis; missing data; and specific comorbidities including cancer [21], spinal cord injury, pelvic fracture, multiple sclerosis, Parkinson's disease, dementia, schizophrenia [22], or Peyronie's disease. For the SD subgroup analysis, patients simultaneously diagnosed with both organic and non-organic SD were excluded to ensure clear classification. After applying these exclusion criteria, the resulting cohort was used to identify the SD subgroup for further analysis.

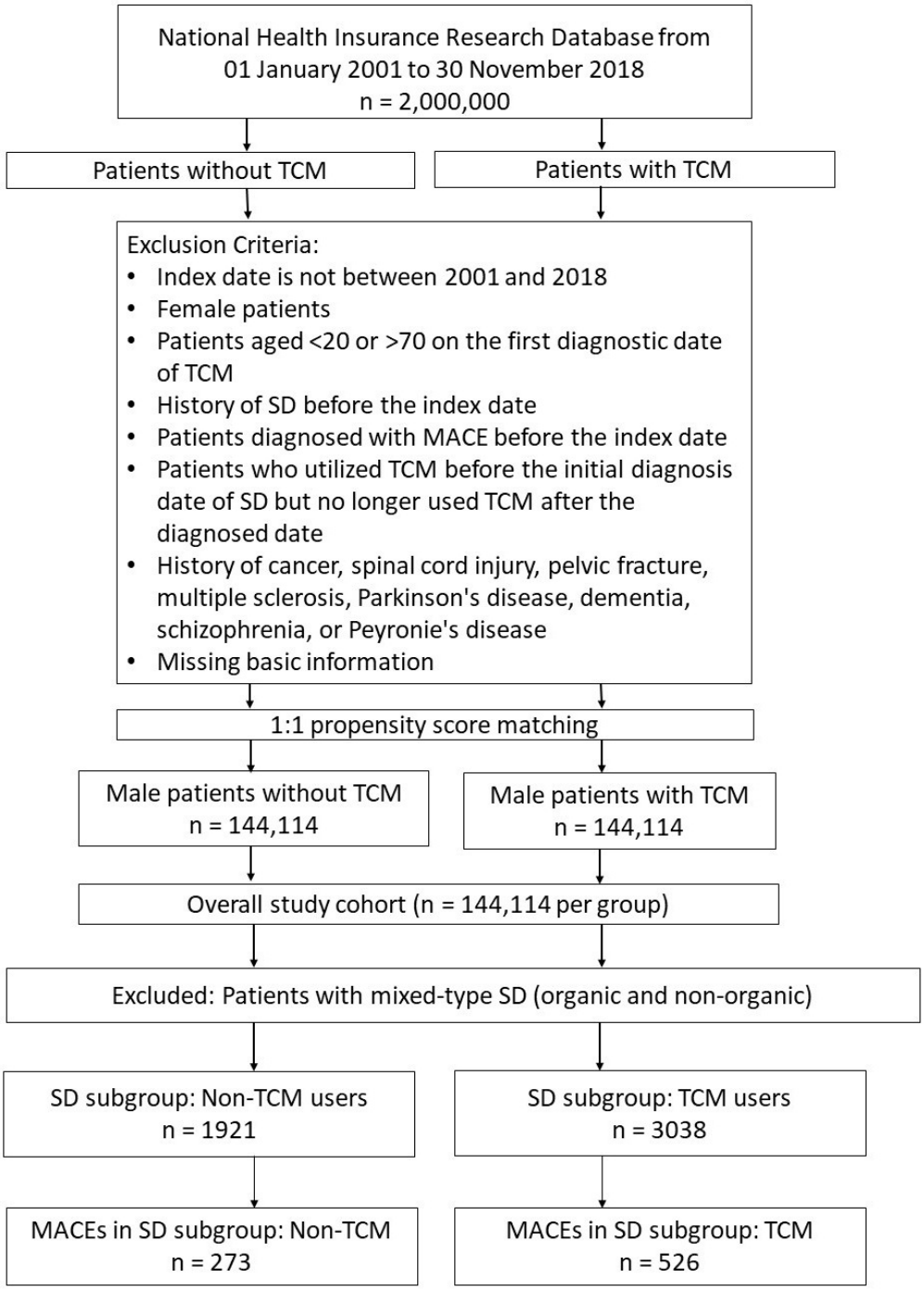
2.2.2 Inclusion criteria

Male patients aged 20–70 years with newly diagnosed SD were included in the study. From the matched study cohort (n = 144,114 per group), SD cases were identified and classified as either organic SD or non-organic SD, based on diagnostic codes from both ICD-9-CM and ICD-10-CM (**Supplementary Table 1**). Organic SD was defined as SD primarily caused by physiological or anatomical abnormalities, such as vascular disease, endocrine disorders, or neurological damage [2]. In contrast, non-organic SD was associated with psychological or behavioral factors, including anxiety, stress, or depression [11]. After applying the above described exclusion criteria, the final SD subgroup consisted of 1921 non-TCM users and 3038 TCM users. These patients were subsequently analyzed to determine the cardiovascular risk associated with TCM use.

2.2.3 Study cohort and follow-up

This study utilized data from the Taiwan's NHIRD covering the period from January 2001 to November 2018. Patients were classified into TCM and non-TCM groups according to the predefined criteria in Section 2.2. Since the NHIRD included claims data up to December 2018, the latest possible inclusion in the TCM group consisted of patients who initiated TCM treatment in November 2018 and completed at least 30 days of treatment. Patients who started TCM treatment in December 2018 were excluded from the TCM group since they could not fulfill the required 30-day treatment period before the study endpoint.

Both the overall matched cohort (n = 144,114 per group) and the SD subgroup were followed from their respective index dates until the first occurrence of MACEs (the primary outcome), withdrawal from the NHIRD, death, loss to follow-up, or the study endpoint on December 31, 2018. Given the enrollment period (2001–2018), follow-up durations varied accordingly. The mean follow-up time was 9.27 ± 5.21 years for TCM users and 9.71 ± 5.22 years for non-TCM users. Although most patients had follow-up durations within this range, individual follow-up periods varied considerably, ranging from several months for patients enrolled in 2018 up to a maximum of 17 years for those enrolled in 2001.



F I G U R E 1. Flowchart illustrating the recruitment of patients with MSD receiving TCM or non-TCM treatment from the NHIRD in Taiwan from 2001–2018. MACEs: major adverse cardiovascular events; MSD: male sexual dysfunction; NHIRD: National Health Insurance Research Database; SD: sexual dysfunction; TCM: traditional Chinese medicine.

2.3 Primary outcomes and confounders

The primary outcome was the incidence of MACEs, including ischemic stroke, hemorrhagic stroke, acute coronary syndrome, heart failure, and malignant arrhythmia after the index date [23]. Primary outcomes and baseline comorbidities were identified via disease codes, requiring documentation from at least two outpatient visits or one hospitalization. Potential confounders included comorbidities such as hypertension, diabetes, coronary artery disease, atherosclerosis, prostate diseases, alcohol-related illnesses, obesity, depression, anxiety, hyperlipidemia, chronic kidney disease, illicit drug dependence or abuse and nicotine dependence [24]. Comparisons of medication use included PDE5Is, amide drugs, SSRIs and nitrates. The detailed disease and Anatomical Therapeutic Chemical (ATC) codes are provided in **Supplementary Table 1**.

2.4 Statistical analysis

Propensity scores were estimated using logistic regression, using TCM as the dependent variable and baseline characteristics

as independent variables, to create balanced cohorts of TCM and non-TCM users. Covariate balance was assessed post-matching. Baseline demographics and comorbidities were compared using Chi-square tests, with continuous variables presented as means ± standard deviations and categorical variables presented as counts and percentages. Differences between groups were evaluated via unpaired *t*-tests and standardized mean differences (SMD), with SMD values <0.1 indicating no significant difference [25]. Hazard ratio (HR) and 95% confidence interval (CI) were calculated via Cox proportional hazards regression, adjusting for age, comorbidities and medication use. Sensitivity analyses were performed to examine the consistency of results across patient subgroups stratified by age, comorbidities and SD status, aiming to determine whether the observed associations remained robust under different conditions. The Kaplan-Meier method was used to estimate the cumulative incidence of MACEs, with survival curves generated using R software. All other statistical analyses were conducted using Statistical Analysis System (SAS) software, version 9.4 (SAS Institute Inc., Cary, NC, USA), with statistical significance set at $p < 0.05$.

3. Results

3.1 Comparison of baseline characteristics between non-TCM and TCM cohorts, including the SD subgroup

The baseline demographics and comorbidities of the matched cohorts (144,114 TCM users and 144,114 non-TCM users) are summarized in Table 1. The mean age was similar between the groups: 41.40 ± 12.82 years for non-TCM users and 41.08 ± 12.81 years for TCM users. The follow-up periods were also comparable, with 9.27 ± 5.21 years for non-TCM users and 9.71 ± 5.22 years for TCM users. Within this matched cohort, 4959 participants were diagnosed with SD, comprising 1921 non-TCM users and 3038 TCM users. Across both the overall cohort and the SD subgroup, no significant differences were observed between the groups in terms of comorbidities or medication use between the groups (all SMD values <0.1).

3.2 HR and 95% CI for MACEs in the overall cohort, including patients with and without SD

Table 2 presents the HR and incidence rates of MACEs in the overall cohort, which includes both patients with and without SD. After adjusting for age, comorbidities and medication use, the incidence rates of MACEs were 9.93 and 9.08 per 1000 person-years in the TCM and non-TCM groups, respectively. Compared with non-TCM users, the TCM users presented a higher risk of MACEs (adjusted hazard ratio (aHR) 1.07, 95% CI (1.04, 1.09), $p < 0.001$), along with a 1.24-fold in risk of ischemic stroke (aHR 1.24, 95% CI (1.20, 1.28), $p < 0.001$). Conversely, TCM users, compared to non-TCM users, had significantly lower risks of hemorrhagic stroke (aHR 0.80, 95% CI (0.76, 0.85), $p < 0.001$), along with lower risks for acute coronary syndrome (aHR 0.93, 95% CI (0.88, 0.98), $p = 0.007$) and malignant arrhythmia (aHR 0.91, 95% CI (0.83, 0.99), $p = 0.031$). No significant difference was observed for heart failure (aHR 0.95, 95% CI (0.91, 1.00), $p = 0.048$). Fig. 2 illustrates the cumulative incidence of MACEs and specific cardiovascular events in the overall cohort, comparing TCM and non-TCM users. The Kaplan-Meier analysis showed a significantly higher cumulative incidence of MACEs (Fig. 2A) and ischemic stroke (Fig. 2B) in TCM users (log-rank test, $p < 0.001$), but a lowerer incidence (log-rank test, $p < 0.001$) for hemorrhagic stroke (Fig. 2C). No significant differences were found for acute coronary syndrome (Fig. 2D), heart failure (Fig. 2E), or malignant arrhythmia (Fig. 2F).

3.3 Stratification analysis of MACEs associated with TCM use

Supplementary Table 2 represents the stratified analysis, and demonstrates that TCM users had a significantly greater risk of MACEs compared to non-TCM users among the individual aged 50–59 years (aHR 1.09, 95% CI (1.04, 1.13), $p < 0.001$) and 60–69 years (aHR 1.09, 95% CI (1.04, 1.14), $p < 0.001$). Similarly, an increased risk was noted among patients with hypertension (aHR 1.14, 95% CI (1.07, 1.22), $p < 0.001$) and hyperlipidemia (aHR 1.23, 95% CI (1.12, 1.35), $p < 0.001$). Conversely, patients with chronic kidney disease exhibited a significantly reduced risk of MACEs (aHR 0.84, 95% CI (0.72, 0.98), $p = 0.026$). Additionally, a slightly elevated risk of MACEs was observed in TCM users concurrently taking SSRIs (aHR 1.24, 95% CI (1.02, 1.50), $p = 0.028$). No significant associations were found with PDE5Is, amide drugs, illicit drug dependence or nicotine dependence.

3.4 HR and incidence rates for MACEs among male patients with different types of SD (subgroup analysis)

Table 3 presents the HR and incidence rates for MACEs among male patients with different types of SD. In the subgroup of 4959 male patients with SD, TCM users had a significantly higher risk of MACEs than non-TCM users (aHR 1.23, 95% CI (1.05, 1.43), $p = 0.009$). Further analysis by SD type showed that this increased risk was primarily observed in patients with organic SD (aHR 1.24, 95% CI (1.06, 1.45), $p = 0.006$). In contrast, no significant difference was found among those with non-organic SD (aHR 0.58, 95% CI (0.19, 1.82), $p = 0.353$).

4. Discussion

4.1 Association between TCM use and MACEs: main findings and subgroup analysis

This study is the first large-scale retrospective cohort study to examine the association between TCM use and MACEs. In the overall cohort, the aHR for MACEs was 1.07 among TCM users compared with non-TCM users, even after adjusting for age, comorbidities and medication use. While this association remained statistically significant, the relatively small effect size suggests that minor residual differences in baseline characteristics or unmeasured confounders may have influenced the result.

TABLE 1. Comparison of baseline characteristics between non-TCM and TCM cohorts.

Variable	Non-TCM (N = 144,114)		TCM (N = 144,114)		SMD
	n	%	n	%	
Age, yr					
20–29	31,486	21.85	32,163	22.32	0.011
30–39	35,550	24.67	36,731	25.49	0.019
40–49	35,842	24.87	35,202	24.43	0.010
50–59	26,926	18.68	25,923	17.99	0.018
60–69	14,310	9.93	14,095	9.78	0.005
Mean (SD)[a]	41.40	12.82	41.08	12.81	0.025
Comorbidities					
Hypertension	11,305	7.84	10,967	7.61	0.009
Diabetes mellitus	6291	4.37	5966	4.14	0.011
Coronary artery disease	2752	1.91	2701	1.87	0.003
Atherosclerosis	358	0.25	348	0.24	0.001
Prostate diseases	5716	3.97	5501	3.82	0.008
Alcohol-related illnesses	2621	1.82	2645	1.84	0.001
Obesity	352	0.24	338	0.23	0.002
Depression	2726	1.89	2748	1.91	0.001
Anxiety	5845	4.06	5772	4.01	0.003
Hyperlipidemia	9171	6.36	8737	6.06	0.012
Chronic kidney disease	1100	0.76	1062	0.74	0.003
Illicit drug dependence or abuse	327	0.23	336	0.23	0.001
Nicotine dependence	1980	1.37	1972	1.37	<0.001
Medication					
PDE5Is	37	0.03	28	0.02	0.004
Amides	46	0.03	42	0.03	0.002
SSRIs	2821	1.96	2806	1.95	0.001
Nitrates	8565	5.94	8364	5.80	0.006
Mean follow-up time (SD)[a], yr					
MACEs	9.27	5.21	9.71	5.22	0.083
Ischemic stroke	9.43	5.21	9.90	5.21	0.091
Hemorrhagic stroke	9.59	5.19	10.21	5.18	0.120
Acute coronary syndrome	9.57	5.19	10.19	5.18	0.119
Heart failure	9.56	5.19	10.16	5.18	0.116
Malignant arrhythmia	9.63	5.19	10.26	5.18	0.120
Sexual dysfunction					
Without sexual dysfunction	142,193	98.67	141,076	97.89	0.060
With sexual dysfunction	1921	1.33	3038	2.11	
Non-organic sexual dysfunction	84	0.06	225	0.16	0.030
Organic sexual dysfunction	1837	1.27	2813	1.95	0.054

[a] *t-test, Chi-square test. MACEs: major adverse cardiovascular events; PDE5Is: phosphodiesterase 5 inhibitors; SD: standard deviation; SMD: standardized mean difference (≤0.1 indicates a negligible difference); SSRIs: selective serotonin reuptake inhibitors; TCM: traditional Chinese medicine; yr: year. Blank SMD cells indicate that comparison was not performed.*

TABLE 2. HR and 95% CI for MACEs in all patients regardless of SD status.

Outcome	Non-TCM			TCM			cHR	95% CI	*p*-value	aHR	95% CI	*p*-value
	Event	PY	IR	Event	PY	IR						
MACEs	12,133	1,336,411.71	9.08	13,900	1,399,118.03	9.93	1.09	(1.07, 1.12)***	<0.001	1.07	(1.04, 1.09)***	<0.001
Ischemic stroke	6254	1,358,292.81	4.60	8412	1,426,503.83	5.90	1.28	(1.24, 1.32)***	<0.001	1.24	(1.20, 1.28)***	<0.001
Hemorrhagic stroke	2728	1,381,634.24	1.97	2460	1,471,459.72	1.67	0.84	(0.80, 0.89)***	<0.001	0.80	(0.76, 0.85)***	<0.001
Acute coronary syndrome	2638	1,379,668.69	1.91	2748	1,468,392.67	1.87	0.97	(0.92, 1.02)	0.216	0.93	(0.88, 0.98)**	0.007
Heart failure	3494	1,377,327.19	2.54	3786	1,463,755.23	2.59	1.01	(0.96, 1.06)	0.681	0.95	(0.91, 1.00)*	0.048
Malignant arrhythmia	998	1,388,344.57	0.72	1032	1,478,135.74	0.70	0.96	(0.88, 1.04)	0.307	0.91	(0.83, 0.99)*	0.031

*aHR: adjusted hazard ratio (adjusted for age, comorbidities and medication); cHR: crude hazard ratio; CI: confidence interval; SD: sexual dysfunction; IR: incidence rate; MACEs: major adverse cardiovascular events; PY: person-years; TCM: traditional Chinese medicine. *p < 0.05; **p < 0.01; ***p < 0.001.*

TABLE 3. HR and incidence rates for MACEs among male patients with different types of SD (subgroup analysis).

Variable	Non-TCM			TCM			cHR	95% CI	*p*-value	aHR	95% CI	*p*-value
	Event	PY	IR	Event	PY	IR						
Without SD	11,860	1,318,197.03	9.00	133,74	1,364,109.19	9.80	1.09	(1.06, 1.12)***	<0.001	1.06	(1.03, 1.09)***	<0.001
With SD	273	18,214.68	14.99	526	35,008.84	15.02	0.99	(0.86, 1.15)	0.908	1.23	(1.05, 1.43)**	0.009
Non-organic SD	5	822.33	6.08	9	2117.34	4.25	0.72	(0.24, 2.14)	0.550	0.58	(0.19, 1.82)	0.353
Organic SD	268	17,392.35	15.41	517	32,891.50	15.72	1.01	(0.87, 1.17)	0.897	1.24	(1.06, 1.45)**	0.006

*aHR: adjusted hazard ratio (adjusted for age, comorbidities and medication); cHR: crude hazard ratio; CI: confidence interval; IR: incidence rate; MACEs: major adverse cardiovascular events; PY: person-years; SD: sexual dysfunction; TCM: traditional Chinese medicine. **p < 0.01; ***p < 0.001.*

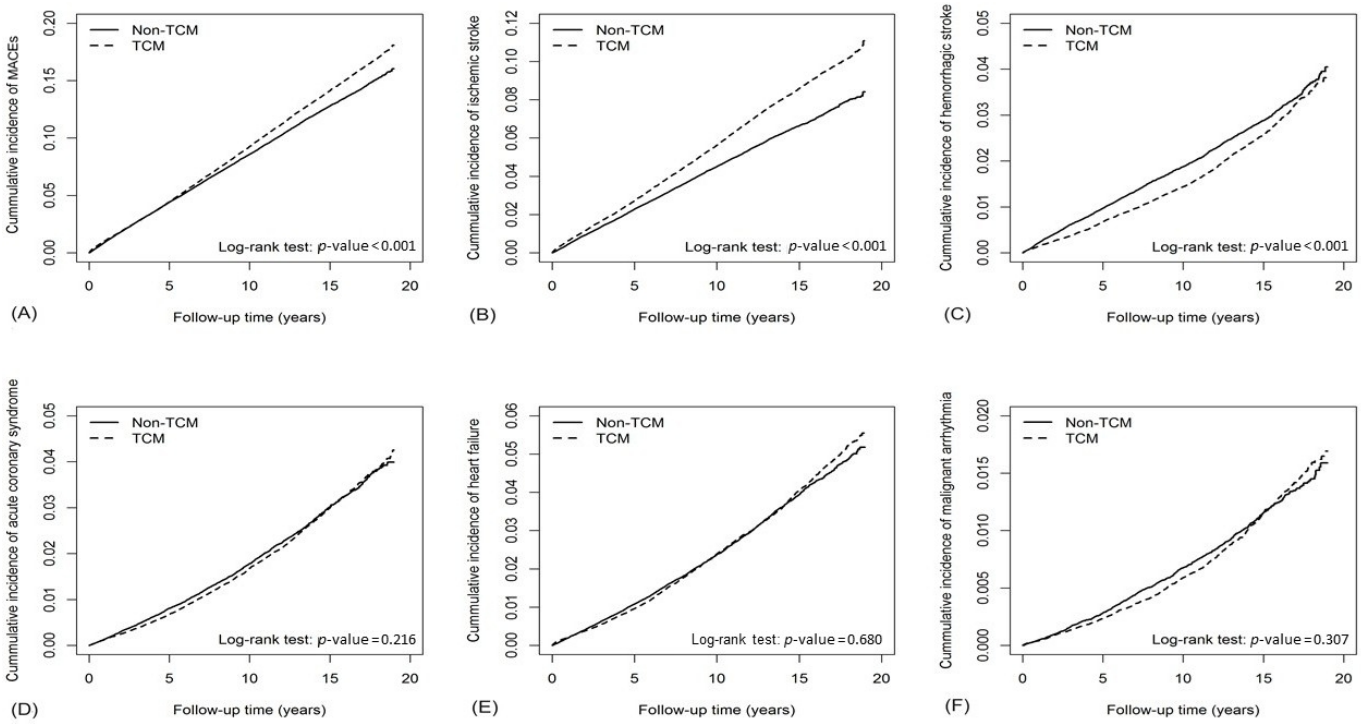


FIGURE 2. Cumulative incidence curves of cardiovascular outcomes among TCM and non-TCM users. (A) major adverse cardiovascular events (MACEs). (B) ischemic stroke. (C) hemorrhagic stroke. (D) acute coronary syndrome. (E) heart failure. (F) malignant arrhythmia. The analysis includes all patients, encompassing both those with and without SD. SD: sexual dysfunction; TCM: traditional Chinese medicine.

Selection bias may have contributed to this association. Some TCM users may have sought treatment for conditions unrelated to cardiovascular or SD, reflecting differences in baseline health status, undiagnosed comorbidities and healthcare-seeking behaviors. These differences could independently influence cardiovascular risk, indicating that the observed association may partly reflect baseline health disparities rather than a direct causal effect of TCM use. Although our statistical adjustments aimed to minimize these biases, residual confounding cannot be entirely excluded.

However, selection bias alone may not fully explain the observed association. Our subgroup analysis revealed that the increased risk of MACEs was particularly pronounced among patients with SD who used TCM (aHR 1.23), especially in those with organic SD (aHR 1.24). Given that SD itself is an early marker of vascular dysfunction and cardiovascular disease [3], these findings suggest that the increased cardiovascular risk may not solely result from baseline health differences, but could also involve potential biological effects associated with TCM.

Although our study cannot establish causality, it highlights the need for further investigation into the interplay between TCM use, SD severity and cardiovascular health. To minimize confounding, we employed PSM and multivariate Cox regression models to account for major cardiovascular risk factors, such as hypertension and hyperlipidemia. Despite these adjustments, the risk of MACEs remained higher in the TCM group compared with the non-TCM group, suggesting that additional factors, including potential pharmacological effects of CHMs, may contribute to this association.

Further research incorporating clinical biomarkers, pharmacodynamic assessments, and prospective study designs is needed to clarify whether the observed association represents a clinically meaningful difference or is partially attributable to inherent limitations in observational data.

4.2 Potential biological explanations for the observed association

Several hypotheses may explain this association. One possibility is that certain kidney-yang tonifying herbs commonly used for SD treatment may influence cardiovascular function. Herbs, such as Epimedium Leaf (Yin-Yang-Huo, *Epimedii folium*), Morinda Root (Ba-Ji-Tian, *Morindae officinalis radix*), Desert-living Cistanche (Rou-Cong-Rong, *Cistanchis herba*) and Songaria Cynomorium Herb (Suo-Yang, *Cynpomorii herba*), are frequently prescribed in TCM to enhance kidney-yang and sexual function [26–31]. These herbs are traditionally described as having warming and energizing properties, which may enhance metabolic activity and stimulate adrenergic responses. Some studies suggest that they may also modulate vascular function, potentially affecting blood pressure regulation and sympathetic nervous system activity [19, 32–34].

Additionally, some kidney-yang tonics may exert androgenic effects, resembling testosterone, which is known to influence cardiovascular function [30, 35, 36]. These androgenic effects could lead to increased blood pressure and vasoconstriction [37, 38], aligning with our findings that patients with hypertension or hyperlipidemia using TCM faced a greater risk of MACEs. Certain CHMs, such as Ginseng Root (Ren-Shen,

Ginseng radix et rhizome), have been reported to cause a temporary increase in blood pressure and palpitations when used as aphrodisiacs [33, 36, 39]. These short-term hemodynamic changes suggest a possible mechanism through which kidney-yang tonics could influence cardiovascular outcomes, particularly in individuals with pre-existing cardiovascular conditions. However, the long-term cardiovascular impact of these herbs remains uncertain, highlighting the need for further research to elucidate their potential effects on vascular health.

4.3 Other cardiovascular considerations associated with TCM use

Beyond the increased risk of MACEs, other cardiovascular considerations related to TCM use warrant further discussion. One particularly notable finding was the potential interaction between SSRIs and kidney-tonifying Chinese herbs concerning cardiovascular outcomes. Our analysis showed that TCM users concurrently taking SSRIs exhibited a slightly elevated risk of MACEs (aHR 1.24, 95% CI (1.02, 1.50), $p = 0.028$). Although this association reached statistical significance, the lower boundary of the 95% CI was close to 1, suggesting the possibility of a limited clinical effect. SSRIs have previously been reported to be associated with alterations in vascular function and changes in coagulation pathways; however, their potential contribution to cardiovascular risk in combination with TCM use remains uncertain [40–42]. Further studies are therefore necessary to confirm this relationship and clarify potential biological mechanisms.

Additionally, several observed associations had CI values near 1, warranting cautious interpretation. TCM users with chronic kidney disease showed a modestly reduced risk of MACEs (aHR 0.84, 95% CI (0.72, 0.98), $p = 0.026$), while slight reductions were noted for acute coronary syndrome (aHR 0.93, 95% CI (0.88, 0.98), $p = 0.007$) and malignant arrhythmia (aHR 0.91, 95% CI (0.83, 0.99), $p = 0.031$). These findings may reflect differences in healthcare-seeking behaviors, patient characteristics, or unmeasured confounding rather than the true protective effects of TCM. To clarify their clinical significance, additional research incorporating clinical biomarkers and detailed medication use patterns is required.

4.4 Strengths of the study

This study has several notable strengths, particularly in its methodology and data source. By utilizing Taiwan's NHIRD, a large and nationally representative database, our study achieves high external validity. The application of PSM and multivariate Cox regression models effectively minimized selection bias by balancing baseline cardiovascular risk factors between TCM users and non-TCM users. Additionally, performing stratified analyses across key subgroups, such as different age groups and patients with or without pre-existing cardiovascular conditions, provided a more nuanced understanding of how TCM use may differentially impact cardiovascular risk.

Furthermore, restricting the study population to males aged 20–70 years ensured greater relevance to the demographic most susceptible to SD, while also reducing potential confounding from extreme age groups [43]. Although this selection approach improved internal comparability, future research should explore whether these findings extend to other demographic groups. Moreover, by excluding patients with mixed organic and non-organic SD, we improved the precision of our analysis in differentiating cardiovascular risks associated with organic versus non-organic SD. This refinement enhances the interpretability of our findings and reduces potential misclassification bias. Collectively, these methodological strengths reinforce the reliability of our findings and enhance the robustness of our conclusions regarding the association between TCM use and cardiovascular risk in male patients with SD.

4.5 Limitations of the study

Despite these strengths, this study has several notable limitations.

First, although we applied PSM and multivariate Cox regression to balance baseline cardiovascular risk factors, residual confounding from unmeasured variables cannot be fully excluded. Taiwan's NHIRD does not include certain lifestyle factors, such as illegal substance use, nicotine dependence, or out-of-pocket purchases of medications like PDE5Is and amide sprays, which may influence cardiovascular outcomes.

Second, selection bias remains a potential concern. Some TCM users may have had different healthcare-seeking behaviors or underlying health conditions that were not fully captured in our matching process. In particular, some patients may have turned to TCM due to dissatisfaction with conventional treatments, potentially indicating a higher baseline cardiovascular risk among TCM users. Although this scenario could have contributed to the observed association, it is unlikely to fully explain the increased risk of MACEs, given that our subgroup analysis showed a stronger association in patients with SD, particularly organic SD. We adjusted for major cardiovascular risk factors and performed stratification analyses across different age groups (20–29, 30–39, 40–49, 50–59 and 60–69 years). However, differences in comorbidity burden within each age stratum could still exist and partly influence the observed association between TCM use and MACEs incidence. Although we attempted to mitigate this concern by adjusting for individual cardiovascular risk factors, residual confounding from unmeasured comorbidities cannot be entirely ruled out.

Third, the classification of patients into the TCM group was based on an initial exposure criterion of at least 30 days of TCM treatment, rather than the cumulative exposure over the entire study period. This threshold was selected to ensure a meaningful level of engagement with TCM, rather than incidental or sporadic use, and aligns with prior research and pharmacoepidemiological studies in Taiwan, where a 30-day exposure threshold has been commonly applied to evaluate TCM-related risks [44, 45]. Applying an initial treatment period to define exposure is a well-established approach in observational studies, particularly within causal inference frameworks, as it provides a structured method for estimating associations with health outcomes [46]. However, this classification does not distinguish between patients who continued TCM use beyond 30 days and those who discontinued after meeting the minimum criterion. Since our study assessed the association

between initial TCM exposure and MACEs in patients with SD, we defined TCM users based on their early treatment status rather than cumulative exposure over time.

The Kaplan-Meier curves illustrate the long-term risk trajectory of patients who initially met the TCM exposure criteria, regardless of ongoing treatment adherence. While this method enables the assessment of long-term cardiovascular risk in individuals with early TCM exposure, its interpretation should consider the limitations of exposure classification in distinguishing short-term from long-term users.

Fourth, although this study specifically defined TCM as CHM, variations in herbal compositions and dosages among individual TCM users do likely introduce heterogeneity. Our study primarily focused on kidney-yang tonifying CHMs commonly used for SD treatment. However, the variability in specific herbal formulations could lead to differences in cardiovascular effects. Although some kidney-yang tonifying CHMs have been suggested to influence cardiovascular function, clinical evidence remains inconclusive. These uncertainties highlight the need for further pharmacological and biomarker-based studies to clarify the cardiovascular safety profile of specific TCM treatments, particularly in high-risk populations.

Fifth, the NHIRD lacks detailed laboratory and clinical data, including testosterone levels, International Index of Erectile Function-5 (IIEF-5) scores and biomarker-based cardiovascular risk assessments [47]. This limitation prevents us from directly assessing SD severity and its cardiovascular implications. However, the NHIRD has been validated for accurately identifying cardiovascular outcomes, reducing the likelihood of misclassification bias [48, 49].

Sixth, the use of TCM could be influenced by underlying health conditions beyond cardiovascular or SD. Although our study focused on TCM use in patients with SD, it is possible that individuals sought TCM treatment for other medical conditions that were not captured in our database. This potential selection bias may have influenced the observed association between TCM use and the risk of MACEs. Future studies should explore the specific clinical indications for TCM prescriptions to better understand their role in cardiovascular outcomes.

Finally, as an observational study, establishing causal relationships between TCM use and cardiovascular risk remains challenging due to the possibility of unmeasured confounding variables. Future studies should incorporate prospective designs, clinical biomarkers, and pharmacokinetic assessments to distinguish between the confounding effects of pre-existing conditions and the potential pharmacological interactions of CHMs.

5. Conclusions

Our analysis of a large Taiwanese cohort identified an association between TCM use and an increased risk of major adverse cardiovascular events compared with non-TCM users in male patients with SD, particularly among those with organic SD. To particularly minimize potential confounding, we applied PSM and multivariate analyses to balance baseline cardiovascular risk factors. While the observed association remained significant, causality cannot be established, and unmeasured confounders, including potential selection bias related to health-seeking behaviors and differences in comorbidity burden, may have contributed to the observed risk. Although baseline health differences may partly explain this association, direct biological effects of TCM remain plausible. Further prospective studies are needed to clarify the potential underlying mechanisms, assess the long-term cardiovascular safety of specific TCM formulations, and develop personalized, risk-based treatment strategies, particularly for SD patients with high cardiovascular risk or multiple comorbidities.

ABBREVIATIONS

aHR, adjusted hazard ratio; ATC, Anatomical Therapeutic Chemical; CHM, Chinese herbal medicine; cHR, crude hazard ratio; CI, confidence interval; ED, erectile dysfunction; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; IIEF-5, International Index of Erectile Function-5; IR, incidence rate; MACEs, major adverse cardiovascular events; MSD, male sexual dysfunction; NHIRD, National Health Insurance Research Database; PDE5Is, phosphodiesterase 5 inhibitors; PE, premature ejaculation; PSM, propensity score matching; PY, person-years; SAS, Statistical Analysis System; SD, sexual dysfunction; SMD, standardized mean difference; SSRIs, selective serotonin reuptake inhibitors; TCM, traditional Chinese medicine; yr, year.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

WCY—conceptualization, project administration, supervision, writing-original draft, review and editing. HJL—data curation, formal analysis, software, visualization. Both authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Review Committee of China Medical University Hospital, Taiwan (approval number: CMUH109-REC2-031) on 20 October 2020. Given that this is a retrospective study using de-identified data from the Taiwan's NHIRD, the requirement for informed consent was waived by the ethics committee.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://files.intandro.com/files/article/1972593400501682176/attachment/Supplementary%20material.docx.

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