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The association between the fluoxetine use and the occurrence of coronary heart disease: a nationwide retrospective cohort study

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Abstract

Background We explored if the administration of fluoxetine, recognized for its potential in adipocyte browning, entails a differential risk of coronary heart disease (CHD) in comparison to other SSRI medications.

Methods Using the National Health Insurance Research Database of Taiwan from 2000 to 2013, we conducted a retrospective cohort study. The exposure cohort comprised individuals prescribed fluoxetine for over 90 days ($n=2,228$). Conversely, those administered other SSRIs (excluding fluoxetine) for a duration surpassing 90 days were designated as the non-exposed cohort ($n=8,912$). CHD incidence served as our primary outcome measure, and we employed Cox proportional hazards models to scrutinize the relationship between fluoxetine exposure and CHD development rates.

Results Compared with the non-exposed cohort, the fluoxetine use had a significantly decreased 21% risk of developing CHD in the exposed cohort (adjusted hazard ratio: 0.79%, 95% confidence interval: 0.68–0.92). Noticeably, results indicated that there was an inverse association between the fluoxetine exposure and the risk of CHD, regardless of whether men, women or other age groups.

Conclusion Our findings suggest that clinical use of fluoxetine was associated with a 21% reduced risk of CHD relative to other SSRI prescriptions.

Keywords Cohort study, Fluoxetine, Selective serotonin reuptake inhibitor, Coronary heart disease

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Introduction

Depression, a universally acknowledged mental disorder, can profoundly impair an individual's functional capabilities. According to the Global Burden of Disease Study, both depression and coronary heart disease (CHD) were major contributors to the worldwide disease burden in 2020 [1]. Furthermore, compelling evidence suggests that depression acts as a significant predisposing factor for the development of CHD [2].

In the clinical management of depression, antidepressants are recognized as the standard pharmacological strategy, ranking among the most frequently prescribed medications worldwide [3]. A myriad of antidepressant drugs have been explored for depression treatment, with selective serotonin reuptake inhibitors (SSRIs) often chosen as first-line agents due to their pharmacological profile [4].

Fluoxetine, one of the earliest developed SSRIs, demonstrated a distinct efficacy and superior tolerability relative to other antidepressive agents [5]. In clinical discussions, the potential impact of antidepressant use, especially SSRIs, on CHD risk remains a topic of debate. Previous studies have alluded to a potential increased risk of CHD following SSRI administration [6–9]. Contrarily, some studies suggest that antidepressants might exert a protective effect against CHD risk [10, 11] while others found no discernible association with other antidepressive agents [12–16]. Meta-analyses have shown an association between antidepressant use and CHD risk in patients with pre-existing CHD at baseline [17], yet there has been limited focus on individuals without a history of CHD. Additionally, a definitive comparative risk of CHD between fluoxetine and other SSRIs remains elusive. Recent research in animal models indicates that fluoxetine promotes adipose browning [18, 19], phenomenon which has been linked to potential therapeutic effects against atherosclerosis [20, 21]. This novel perspective could herald an optimized clinical choice. Consequently, we embarked on this study to elucidate the comparative risk of CHD between fluoxetine and other SSRIs in individuals without prior CHD. This retrospective cohort study used population-representative data from the Taiwan National Health Insurance Research Database (NHIRD).

Materials and methods

Data sources

We use a nationwide database which called National Health Insurance Research Database (NHIRD) to complete this retrospective cohort study in Taiwan. NHIRD contained the majority of medical claims records from the National Health Insurance (NHI) Program. The NHI is a health insurance program that is state-funded, single-payer, applicable to all Taiwanese residents. We obtained the comprehensive medical records of insured individuals from the NHIRD, which including the demographic data, condition during the clinical visits, diagnostic codes for the disease, prescription, retrospectively [22]. The diagnoses in the database were encoded and recorded by the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM). Based on the good validity of the NHIRD, both in diseases diagnosis and prescription records, NHIRD had been applied to several high- quality epidemiological studies [23, 24]. We also extracted the data from the Longitudinal Health Insurance Database 2000 (LHID 2000) for this study, a subset of NHIRD. In the LHID 2000 dataset, there were one million beneficiaries randomly selected from the NHI in 2000. The content of LHID 2000 dataset included the details of historical ambulatory and inpatient care information. Among the beneficiaries, the distributions of demographic characteristics (age and gender) and medical care costs were not apparently different between the NHIRD and LHID 2000 [25]. Because all data used was encrypted and de-identified for scientific research, individual patient were not able to be tracked back and recognized in this study. This study was classified into the low-degree risk and free from the written-informed consent from the subjects. The protocol has been reviewed and permitted by the Institutional Review Board of Fu-Jen Catholic University (FJU-IRB No: C104014).

Study design and population

We included outpatient patients who have accepted SSRI fluoxetine or other SSRIs prescriptions for more than 90 days, a chronic prescription order period in the NHIRD. In this study, the exposure period was defined as the period between January 1, 2000 and December 31, 2005. During the exposure period, patients receiving fluoxetine were categorized as the exposed group and the non-exposed group was those receiving other SSRIs, including citalopram, paroxetine, sertraline, fluvoxamine, etoperidone, and escitalopram. In the present study, patients who received other SSRIs were defined as the non-exposed group for considerations of reducing potential confounding by indication [26]. The index date was marked as the date patients at the end of the 90 days of SSRI exposure. Patients in both exposed and non-exposed groups had no records of CHD diagnosis prior to the index date. The follow-up person-years were estimated for study participants from the index date to CHD diagnosisor until the end of December 31, 2013.Propensity score was calculated by the logistic regression model to adjust for potential confounders, including age, gender, index date, and comorbidities at the baseline, including diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272.4), hypertension (ICD-9-CM codes 401 to 405), cerebral vascular disease (ICD-9-CM codes

430 to 438), heart failure (ICD-9-CM code 428), chronic liver disease (ICD-9-CM codes 570 to 572), and chronic kidney disease (ICD-9-CM code 585). In addition, the use of co-medications were also concerned and collected by using the code of the Anatomic Therapeutic Chemical (ATC) classification system, which is a distinct identifier given to a medication based on the organ or system it targets and its mechanism of action. This classification system is managed by the World Health Organization (WHO). The contents of co-medications information involved beta blocking agents (ATC code C07), statins (ATC codes C10AA01, C10AA02, C10AA03, and C10AA04), clopidogrel (ATC code B01AC04), and aspirin (ATC code A01AD05). We excluded patients age under 20 years (n=1,750), those had a diagnosis of CHD before the index date (n=3,144) and patients with sex unknown (n=1), and patients who had been prescribed more than one type of SSRI or who switched between SSRIs in the study (n=3,772). Ultimately, there were 2,228 and 8,912 patients enrolled in the exposed cohort and the non-exposed cohort, respectively (Fig. 1). And there was no loss to follow-up in either the fluoxetine or comparison group during the follow-up period.

Clinical outcomes

Primary outcome of this cohort study was the new-onset of CHD between the two cohorts. Validity of CHD diagnosis was examined by the two conditions: patients in both cohorts had (1) more than two times outpatient diagnosis or (2) one inpatient diagnosis as one of CHDs as follows: acute myocardial infarction (ICD-9-CM code 410), other acute or subacute forms of ischemic heart disease (ICD-9-CM code 411), old myocardial infarction (ICD-9-CM code 412), angina pectoris (ICD-9-CM code 413) and other forms of chronic ischemic heart disease (ICD-9-CM code 414).

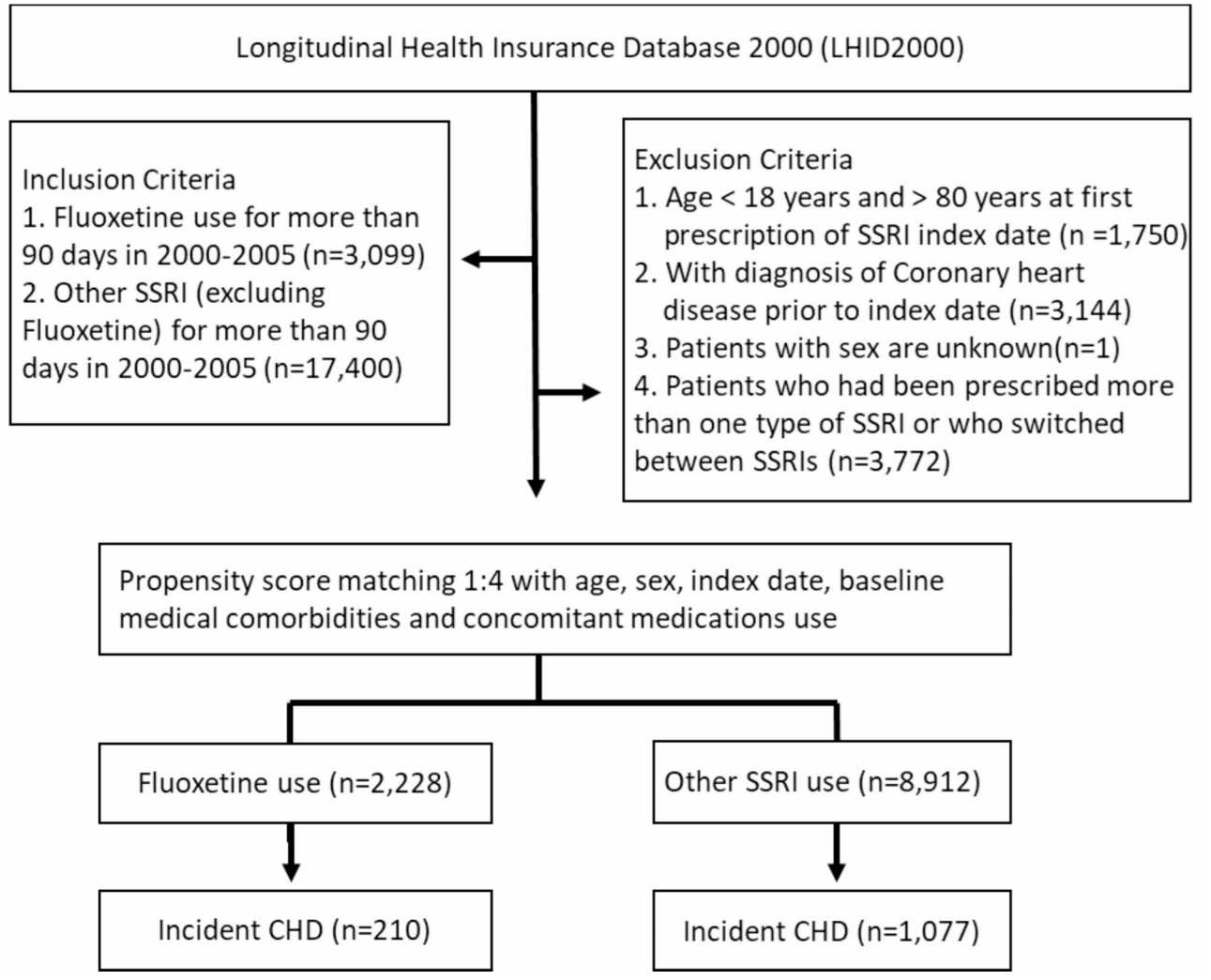

Fig. 1 Flow chart of participant selection. SSRI, selective serotonin receptor inhibitor

Table 1 Baseline characteristics of study cohorts

	Study cohorts		
Variable	**Other SSRIs**	**Fluoxetine**	**p value**
	(*n* = 8,912)	(*n* = 2,228)	
Age (mean ± SD)	42.62 ± 15.13	43.16 ± 15.63	0.131
Follow years	10.36 ± 2.72	10.17 ± 2.84	0.003
Gender (No., %)			0.079
Female	5481(61.5%)	1325(59.5%)	
Male	3431(38.5%)	903(40.5%)	
Comorbidities (No., %)			
Diabetes mellitus	1570(17.6%)	419(18.8%)	0.19
Hyperlipidemia	1273(14.3%)	321(14.4%)	0.882
Hypertension	2499(28.0%)	608(27.3%)	0.479
Cerebral vascular disease	1292(14.5%)	294(13.2%)	0.116
Heart failure	137(1.5%)	33(1.5%)	0.847
Chronic liver disease	1762(19.8%)	425(19.1%)	0.46
Chronic kidney disease	193(2.2%)	46(2.1%)	0.769
Concomitant medications			
Beta-blockade	5256(59.0%)	1314(59.0%)	1.000
Statins	1468(16.5%)	367(16.5%)	1.000
Clopidogrel	148(1.7%)	37(1.7%)	1.000
Aspirin	1674(18.8%)	400(18.0%)	0.368

SSRIs, selective serotonin reuptake inhibitors

Statistical analysis

Comparison of continuous and discrete variables between the two cohorts were assessed by using independent t test and Chi-square test. The cumulative risk of CHD for both cohorts was determined and compared by the Kaplan-Meier method with log-rank test. Finally, the Cox proportional hazards regression models were constructed to calculate hazard ratios (HRs) displayed with 95% confidence intervals (CIs) and investigate the correlation between prescriptions of fluoxetine versus other SSRIs and incident CHD after the adjustment of confounders. The log-minus-log plot of survival was undertook to verify inclusive variables met the proportionality assumption of the Cox regression mode [27]. Two-sided p value < 0.05 was considered the level of significant difference in the all tests. Study data were handled and managed by using the SAS 9.1 software (SAS Institute, Cary, NC).

Results

Table 1 illustrated characteristics of age, gender, existing comorbidities at baseline, and use of concomitant medications in the fluoxetine-exposed and control cohorts. Between the two cohorts, the mean of age years and the percentage of sex, comorbidities, and concomitant medications were not significantly different based on the propensity score matching scenario.

Shown in Table 2, in total, 210 new CHD cases occurred during the 22,662 person-years at the cohort group receiving fluoxetine; then it led to the incidence rate of 9.27 every 1,000 person-years. Corresponding to these patients with use of other SSRIs, there were 1,077 CHD cases happened in 92,344 person-years resulting in the incidence rate of 11.66 every 1,000 person-years. The cumulative incidence of CHD with exposure to other SSRIs was obviously higher than the comparison cohort with prescription of fluoxetine ($p < 0.001$). And the follow-up length was10.17 years in the fluoxetine cohort and 10.16 years in the comparison cohort. Figure 2 presents Kaplan-Meier curves illustrating the cumulative incidence of CHD across the two cohorts. The Schoenfeld test yielded a value of 0.939, consistent with the proportional hazards assumption. The fluoxetine-used cohort had an obviously reduced risk of CHD compared with another cohort (adjusted HR: 0.79, 95% CI: 0.68–0.92) illustrated in Table 2. Noticeably, the negative associations between the fluoxetine prescription and CHD occurrence were still observed even stratified by the gender and age subgroups (Table 3).

Discussion

This retrospective cohort study significantly identified an inverse association between fluoxetine use and CHD risk. After adjusting for potential confounders, our data highlighted a 21% reduction in CHD risk for the fluoxetine group compared to those using other SSRIs. Notably, this risk reduction associated with fluoxetine was consistent across both genders and all age groups.

Prior research has elucidated the intricate relationship between depression and CHD. Goldston & Baillie (2008) [28] emphasized the importance of both pharmacological and psychological interventions in reducing the risk associated with these conditions. A possible mechanism underlying the connection between depression and CHD

Table 2 Association between administration of fluoxetine and risk of coronary heart disease

Variable	No. of subjects	No. of CHD cases	Crude HR (95% CI)	Adjusted HR (95% CI)
Other SSRIs	8912	1077	1.00	1.00
Fluoxetine	2228	210	0.86 (0.49–0.98)	0.79 (0.68–0.92)

HR, hazard ratio; CI, confidence interval. SSRIs, selective serotonin reuptake inhibitors

Hazard ratios were adjusted for age, sex, index date, comorbidities, including diabetes mellitus, hyperlipidemia, hypertension, cerebral vascular disease, heart failure, chronic liver disease, and chronic kidney disease, as well as use of concomitant medications, including beta blocking agents, statins, clopidogrel and aspirin

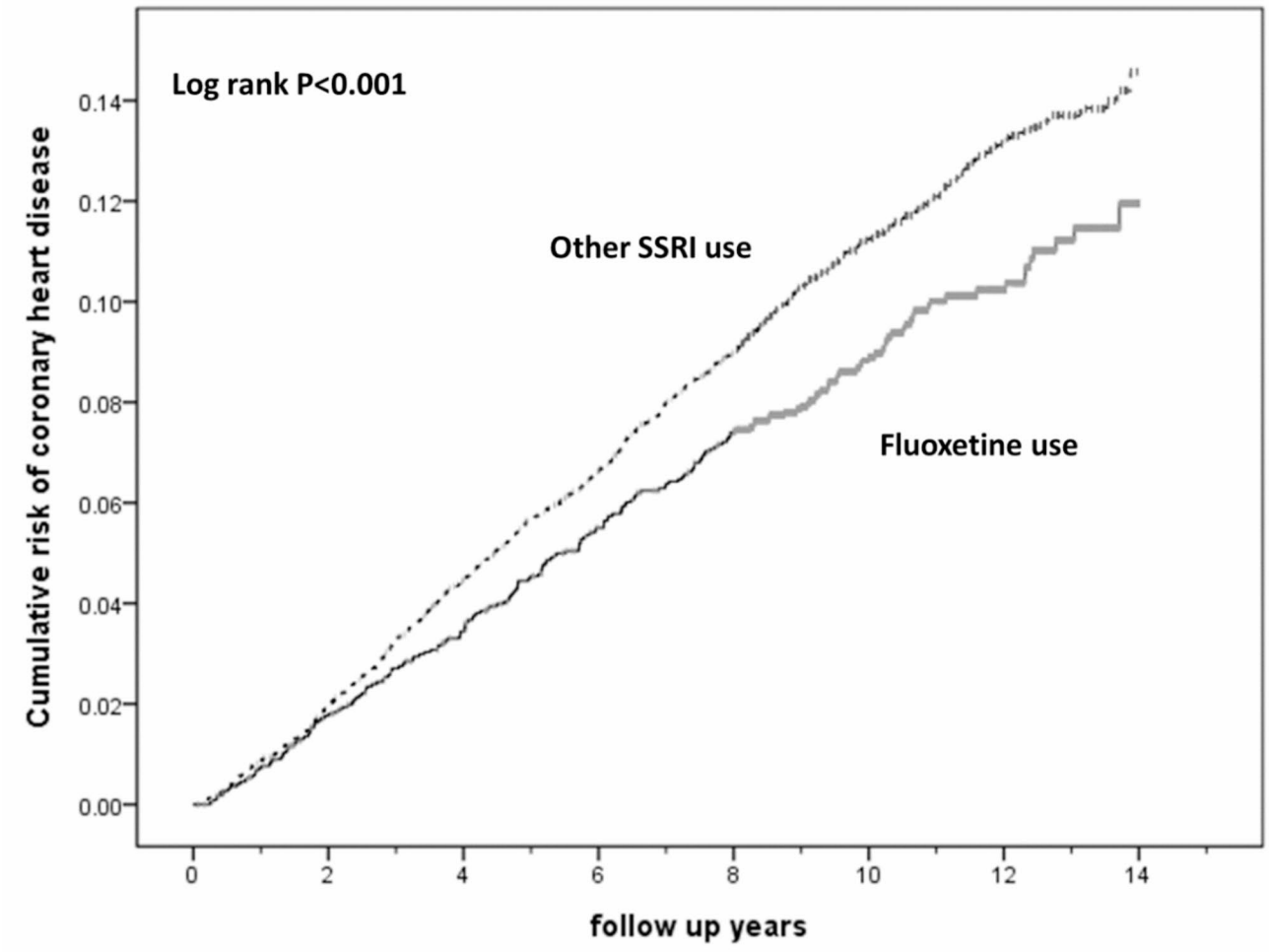

Fig. 2 Kaplan-Meier curves for the cumulative risk of coronary heart disease stratified by administration of fluoxetine and other SSRIs. SSRI, selective serotonin receptor inhibitor

pertains to the energy system, which is intricately modulated by various neuro-endocrine systems. Notably, serotonin is recognized as a pivotal neurotransmitter in this energy system [29]. Concurrently, the serotonin system plays a significant role in the pathogenesis of mental illnesses, including depression and anxiety-related disorders [30]. SSRIs, which inhibit serotonin reuptake to elevate brain serotonin levels, are essential in modulating mood, sleep, and eating behaviors. They are now primarily prescribed as antidepressants [31]. Given growing concerns about the frequent co-occurrence of metabolic diseases with mental illnesses, researchers have delved into the associations between SSRIs and lipid metabolism. Intriguingly, multiple studies have unveiled the potential of fluoxetine to modulate metabolic dysfunctions through adipocyte browning, a process that significantly burns fatty acids, subsequently reducing plasma triglyceride levels and hypercholesterolemia [32] Indeed, these investigations underscore a robust protective correlation between adipocyte activation and atherosclerosis [33, 34].

We considered the possibility that modifying the adipocyte browning process through SSRIs might help mitigate metabolic dysfunction and offer potential benefits. Adipocyte browning involves the conversion of energy-storing white adipose tissue (WAT) into more metabolically active brown adipose tissue, which burns energy in the form of heat, thereby increasing energy expenditure. Fluoxetine could inhibit the reuptake of serotonin at the synaptic level, increasing the availability of serotonin in the synaptic cleft. This elevated serotonin can regulate the expression of key genes involved in browning, such as UCP1, PRDM16, and PGC-1α, which are essential for the formation of brown adipocytes within white adipose tissue (WAT) [19, 35]. This process involves an increase in thermogenesis as well, resulting in higher energy expenditure and reduced fat mass. Additionally, consideration of fluoxetine's anti-inflammatory properties may also contribute to its metabolic benefits. Chronic

Table 3 Association between administration of fluoxetine and risk of coronary heart disease stratified by gender and age

Variable	No. of subjects	No. of CHD cases	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Gender						
Male						
Other SSRIs	3431	463	1.00		1.00	
Fluoxetine	903	89	0.74 (0.59–0.93)	0.009	0.77 (0.62–0.97)	0.027
Female						
Other SSRIs	5481	614	1.00		1.00	
Fluoxetine	1325	121	0.84 (0.69–1.02)	0.071	0.82 (0.67–0.99)	0.042
Age (years)						
≦49						
Other SSRIs	6173	406	1.00		1.00	
Fluoxetine	1540	70	0.71 (0.55–0.91)	0.008	0.68 (0.52–0.87)	0.003
50–64	1775	412	1.00		1.00	
Other SSRIs						
Fluoxetine	421	82	0.84 (0.66–1.06)	0.142	0.81 (0.64–1.03)	0.084
≧65	964	259	1.00		1.00	
Other SSRIs						
Fluoxetine	267	58	0.84 (0.63–1.12)	0.228	0.88 (0.66–1.17)	0.365

HR, hazard ratio; CI, confidence interval. SSRIs, selective serotonin reuptake inhibitors

Hazard ratios were adjusted for age, sex, index date, comorbidities, including diabetes mellitus, hyperlipidemia, hypertension, cerebral vascular disease, heart failure, chronic liver disease, and chronic kidney disease, as well as use of concomitant medications, including beta blocking agents, statins, clopidogrel and aspirin

inflammation is known to be closely associated with metabolic dysfunction, including insulin resistance and obesity [36]. By reducing inflammation [37], fluoxetine may further support adipocyte browning. Change and improve metabolic health. Animal model studies have shown that fluoxetine can induce adipocyte browning, leading to weight loss and improvement in metabolic parameters, even in the presence of a high-fat diet [32]. Although direct evidence in humans is limited, some studies suggest that fluoxetine can lead to weight loss and better metabolic outcomes, possibly due to enhanced thermogenesis [38]. In our study, we expanded those metabolic benefit into the possibility of decreasing the risk of CHD occurrence. And promising result showed a 21% decreasing risk of developing CHD in our cohort. However, there is no definitive evidence to suggest that fluoxetine's promotion of adipocyte browning is unique among SSRIs. It may simply be that fluoxetine has been the most extensively studied SSRI in this context. Further research is warranted to investigate the distinct mechanisms of browning induction across different SSRIs.

The strengths of this study included that compared to self-reported records, a comprehensive prescription database was selected to mostly minimized recall bias. Under this consideration, the NHIRD could be almost the representative sample of Taiwan population because its reimbursement policy is generalized and operated by a single-payer. This allowed us to conduct our analyses by using an unselected patient population in a real-life setting without leakage of personal information. However, there were also several methodological limitations on the interpretation of our findings in this work. In fact, the unavoidable bias that does exist is that information from medical claims databases often has limitation on the presentation of confounders [39]. We lacked of information of those possibly associated with CHD risk as potential confounders from claims dataset. We were not able to obtain the information about patients for the family history of CHD, lifestyle of smoking habits, how's the quality of physical activity, and obesity. Therefore, residual confounding was still not to be ruled out in the present study unfortunately. Second, in this study, we used the prescription database which was unable to confirm the actual condition, also, the records was anonymous, so direct patient contact for validation was not possible, leaving the possibility of treatment non-compliance. Furthermore, as this is a retrospective study, we were unable to conduct an on-treatment analysis to censor patients who discontinued treatment, due to the lack of detailed real-time prescription data. Despite these limitations, we believe the study results remain clinically meaningful.

Conclusion

Our findings suggest that fluoxetine administration was connected to a 21% reduced risk of CHD relative to other SSRI therapy. Then further studies to determine the clinical implications of the present study are still needed.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04280-5.

Supplementary Material 1

Supplementary Material 2

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Author contributions
Conceptualization, Fang-Ling Li, Yu-Tse Sheih, Ming-Hsun Lin and Chien-An Sun; Data curation, Yong-Chen Chen; Formal analysis, Yong-Chen Chen and Wen-Tung Wu; Investigation, Yu-Ching Chou; Methodology, Fang-Ling Li and Chien-An Sun; Project administration, Chien-An Sun; Supervision, Chien-An Sun; Validation, Fang-Ling Li, Yong-Chen Chen, Tsung-Kun Lin, Ming-Hsun Lin, Wen-Tung Wu, Yu-Ching Chou and Chien-An Sun; Writing – original draft, Fang-Ling Li, Yu-Tse Sheih, Ming-Hsun Lin and Chien-An Sun; Writing – review & editing, Chien-An Sun.

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Data availability
The data sets used in the present study are not available based on the policy of using nation-wide insurance claims datasets by the Ministry of Health and Welfare in Taiwan. Correspondence and requests for materials should be addressed to Chien-An Sun.

Declarations

Ethics approval and consent to participate
The Institutional Review Board (IRB) of Fu-Jen Catholic University approved the study and waived the need for informed consent because the identifcation of subjects in the National Health Insurance Research Database (NHIRD) had been de-identifed prior to their release for research in order to ensure confdentiality (FJU-IRB No: C104014). We conducted this study in accordance with the Code of Ethics of the World Medical Association Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Declaration of financial/other relationships
F-L Li, Y-T Shieh, M-H Lin, Y-C Chen, W-T Wu, T-K Lin, Y-C Chou and C-A Sun have disclosed that they have no relationships with or financial interests in any commercial companies related to this study or article.

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