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Depression, antidepressants, and the risk of coronary heart disease: A population-based cohort study

Chun-Jen Huang [a,b,c,1], Ming-Hsiung Hsieh [c,d,1], Wen-Hsuan Hou [e,f,1], Ju-Chi Liu [c,g,1], Chii Jeng [h,1], Pei-Shan Tsai [h,i,*,1]

[a] Department of Anesthesiology, Taipei Tzu Chi Hospital, The Buddhist Tzu Chi Medical Foundation, Taipei, Taiwan, ROC
[b] School of Medicine, Tzu Chi University, Hualien, Taiwan, ROC
[c] School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC
[d] Division of Cardiovascular Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, ROC
[e] Department of Physical Medicine and Rehabilitation, Taipei Medical University Hospital, Taipei, Taiwan, ROC
[f] School of Gerontology Health Management, College of Nursing, Taipei Medical University, Taipei, Taiwan, ROC
[g] Division of Cardiovascular Medicine, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan, ROC
[h] Graduate Institute of Nursing, College of Nursing, Taipei Medical University, Taipei, Taiwan, ROC
[i] Sleep Science Center, Taipei Medical University Hospital, Taipei, Taiwan, ROC

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ABSTRACT

Background: Evidence supporting a predictive role for depression in the pathgenesis of coronary heart disease (CHD) has mainly come from studies in Western countries. Conflicting data exist regarding the association between antidepressant use and the incidence of CHD. This population-based study tracked the risk of composite coronary events in a cohort with newly diagnosed depression compared to an age- and gender-matched cohort without depression. The association between antidepressant use and risk of coronary events in individuals with depression was also investigated.
Methods: In total, 39,685 individuals (7937 with depression and 31,748 without depression) aged 20–99 years selected from a random sample of 10^6 beneficiaries of the Taiwan National Health Insurance Program were followed up for up to 9 years with a median follow-up period of 8.76 years. Coronary events were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic and procedure codes. Antidepressant use was identified using Anatomical Therapeutic Chemical classification codes.
Results: The multivariable-adjusted hazard ratio (HR) for newly detected coronary events was 1.49 (95% confidence interval (CI) = 1.29–1.74, $p < 0.001$) for individuals with depression compared to age- and gender-matched individuals without depression. Use of selective serotonin reuptake inhibitors and tricyclic antidepressants did not significantly impact the risk of the composite coronary events among individuals with depression.
Conclusions: Depression is associated with an increased risk for CHD. No evidence supporting an association between antidepressants and coronary events was found.

1. Introduction

Coronary heart disease (CHD) is one of the leading causes of death worldwide [1]. Depression is a common comorbid condition in CHD patients. Depression is more prevalent in cardiac patients compared to the general population [2]. As projected by the Global Burden of Disease Study, depression and CHD will be the two leading causes of disability worldwide by 2020 [3]. Two meta-analyses aggregated results from prospective cohort studies and showed that depression increases the risk for the onset of CHD [4,5]. However, evidence supporting a predictive role of depression in the pathogenesis of CHD was from studies in European countries and the US. We thus took advantage of the Taiwan Longitudinal Health Insurance Database (LHID2000) that includes a nationally representative population and longitudinally tracked the risk of coronary events in a cohort with newly diagnosed depression, with a median follow-up period of 8.76 years, compared to an age- and gender-matched cohort without depression. We hypothesized that depression increases the risk of coronary events.

Previous studies exploring the association between antidepressant use and risk of myocardial infarction (MI)/CHD have had mixed results [6–13] with some supporting an increased risk of MI associated with tricyclic antidepressants (TCAs), some supporting a protective effect of selective serotonin reuptake inhibitors (SSRIs) on risk of MI, some arguing

* Corresponding author at: Graduate Institute of Nursing, College of Nursing, Taipei Medical University, 250 Wu-Hsing Street, Taipei 110, Taiwan, ROC. Tel.: +886 227338813; fax: +886 223772842.
E-mail address: ptsai@tmu.edu.tw (P.-S. Tsai).
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a lack of association between SSRIs and risk of MI, and some suggesting an increased risk of MI in SSRI users compared with nonusers. Most of these studies used a case-controlled study design [8–11], estimated the risk of MI that did not take into consideration "time to incident MI events" [8–11], or focused on a selected population [6,7,9,10]. Conflicting data also exist regarding the association between antidepressant use and the incidence of CHD in a handful of studies that estimated the hazard ratio (HR) of CHD based on a general population-based cohort design [12,13]. Poor adherence or discontinuation of antidepressants has been implicated to explain these conflicting results. For example, a recent retrospective cohort study demonstrated that continuous treatment with 12 or more weeks of antidepressant therapy was found to be associated with significantly reduced incident rates of myocardial infarction (MI) across different classes of antidepressants [14]. Mechanisms underlying the association between antidepressant use and CHD, if any, remain incompletely understood. Most importantly, potential effects of antidepressants might influence the association between depression and CHD. Previous studies examining the predictive power of depression for CHD rarely took the beneficial effects of antidepressants, if any, into consideration. In fact, prescriptions of antidepressant medications were even used as a proxy for severe depressive symptoms when examining whether depression predicts CHD [15]. We thus conducted this population-based retrospective cohort study to examine the respective effects of SSRIs and TCAs on the risk of coronary events in individuals newly diagnosed with depression.

2. Patients and methods

2.1. Study design and data sources

This study used a cohort study design and analyzed the LHID2000 released by the Taiwan National Health Research Institutes (NHRIs). The LHID2000 includes original claims data and registration files for 10^6 individuals randomly sampled from the 2000 Registry for Beneficiaries of the Taiwan National Health Insurance (NHI) program, which maintains the registration data of any individual who was once a beneficiary of the NHI program during the period of 1996–2000. There are approximately 23,720,000 individuals in this registry. The Taiwan NHRIs claimed that there were no statistically significant differences in gender distribution between the randomly sampled beneficiaries in the LHID2000 and all beneficiaries under the NHI program.

2.2. Study sample

Patients who had been diagnosed as having depression on at least two occasions between January 1, 2000 and December 31, 2007 were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (Supplementary Table 1). Between January 1, 2000 and December 31, 2007, 19,688 patients with a new diagnosis of depression were identified. Subjects aged <20 years of age, or who had an unidentified gender, a history of a depression diagnosis before January 1, 2000, or a history of antidepressant use, MI, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) before the first depression diagnosis were excluded, resulting in a total of 7937 newly detected subjects with depression.

The cohort without depression comprised subjects randomly selected from individuals without a depression diagnosis at a ratio of 1:4 (those with vs. without depression), with frequency matching by age and gender during the same period, and ultimately 31,748 subjects were included.

3. Cohorts treated and not treated with SSRIs

Among subjects with depression, we further identified subjects who had received SSRIs from the database of Anatomical Therapeutic Chemical (ATC) classification code, N06AB. NHI-covered SSRIs for treatment of depression in Taiwan are provided in Supplementary Table 2. Those patients who received SSRIs for a period of <4 months were excluded ($n = 4056$), and those who maintained the treatment for a period of ≥4 months were designated the SSRI-treated cohort ($n = 1102$). Those who received no SSRIs between 2000 and 2008 were designated the non-treated cohort ($n = 2779$).

4. Cohorts treated and not treated with TCAs

Subjects who received TCAs were also identified from the database by the ATC classification code, N06AA. NHI-covered TCAs for treating depression in Taiwan are provided in Supplementary Table 2. Those patients who received TCAs for a period of <4 months were excluded ($n = 1542$), and those who maintained treatment for a period of ≥4 months were designated the TCA-treated cohort ($n = 209$), whereas those who received no TCAs between 2000 and 2008 were designated the non-treated cohort ($n = 6186$).

5. Study endpoint and confounders

The primary endpoint was the composite of coronary events including MI, PCI, or CABG procedures (ICD-9-CM diagnostic and procedure codes are provided in Supplementary Table 1). PCI procedures included percutaneous transluminal coronary angioplasty (PTCA), PTCA with stenting, and coronary atherectomy. To allow for at least 1 year of follow-up, the depression and non-depression cohorts were both tracked from the date of selection until the end of 2008 or until loss to follow-up (i.e., withdrawing from the health insurance program) to identify MI events and PCI and CABG procedures.

For those who suffered from multiple episodes of MI, PCI, and CABG events, only the first event was included. The event survival time was defined as the period between the index date of selection and the first date when an event of interest was identified. To ascertain that all participants were free of the events of interest at the baseline, patients with a diagnosis of MI or who had a PCI or CABG procedure before the index date were excluded.

Baseline prognostic factors including the patient's age in years, gender, and comorbidities (diabetes mellitus [DM], hypertension, hyperlipidemia, alcohol-related illnesses, obesity, and chronic obstructive pulmonary disease [COPD]) (Supplementary Table 1) were extracted and adjusted in the regression model when necessary. Because the smoking status was unavailable, COPD was used as a proxy for smoking. TCA use for the SSRI-treated cohort and SSRI use for the TCA-treated cohort were also adjusted for in the models. Differences in health behaviors between subjects with and without depression could influence the association between depression and coronary events. We used influenza vaccination as a proxy of health behaviors. To assess whether there might be detection bias that could influence the association between depression and coronary events, we compared the mean number of visits to cardiology clinics between groups.

5.1. Ethics statement

This study used the anonymized LHID2000 data released by the Taiwan NHRIs, which is available to public access for research purposes. Information that could be used to identify patients, medical institutions and physicians, was scrambled before being sent to the NHRIs for database construction and was further scrambled before being released to researchers. Using the remaining health information to identify a person is deemed impossible. All researchers are required to sign a written consent asserting that they have no intention of attempting to obtain information that could potentially infringe patient information confidentiality before they can access the NHIRD.

6. Statistical analysis

The Statistical Package for the Social Sciences, version 16.0 (SPSS, Chicago, IL, USA) was used to perform the statistical analyses in this