Non-alcoholic fatty liver disease among patients with sleep disorders: a Nationwide study of Taiwan

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases. Studies have shown that sleep apnea is associated with NAFLD. However, studies on the association between sleep disorders in general and NAFLD are limited. We conducted a nationwide population-based longitudinal study to evaluate this potential association.

Methods: We identified patients diagnosed with sleep disorders in the years 2000 through 2005 in Taiwan using the National Health Insurance Research Database and selected an equal number of patients without sleep disorders from the same database as the comparison cohort. The patients were followed from the index date to the diagnosis of NAFLD or the end of 2013. We used Cox proportional hazards models to estimate the risk of NAFLD associated with sleep disorders.

Results: A total of 33,045 patients with sleep disorders were identified. The incidence of NAFLD was 14.0 per 10,000 person-year in patients with sleep disorders and 6.2 per 10,000 person-year in the comparison cohort. The adjusted hazard ratio (AHR) of NAFLD associated with sleep disorders was 1.78 (95% confidence interval [95%CI]: 1.46–2.16), and other independent risk factors included male sex (AHR = 1.31, 95%CI: 1.12–1.54), age 40–59 years (AHR = 1.49, 95%CI: 1.21–1.82), and dyslipidemia (AHR = 2.51, 95%CI: 2.08–3.04). In the subgroup analyses, both patients with (AHR = 2.24, 95%CI: 1.05–4.77) and without (AHR = 1.77, 95%CI: 1.46–2.15) sleep apnea had an increased risk of NAFLD.

Conclusions: Sleep disorders are associated with NAFLD, even in patients without sleep apnea. Further studies are warranted to explore the mechanisms of the association.

Keywords: Epidemiology, Sleep disorders, Nonalcoholic fatty liver disease, Population-based cohort study

Background

Nonalcoholic fatty liver disease (NAFLD) is a rapidly growing public health threat globally. NAFLD is believed to be a hepatic border of metabolic syndrome and is associated with many metabolic changes such as insulin resistance. The proposed mechanisms of NAFLD include predisposition and intake of higher energy, which result in liver damages ranging from steatosis to nonalcoholic steatohepatitis, advanced fibrosis, and eventually, cirrhosis [1, 2]. The prevalence of NAFLD in the general population is 20 to 30% in the Western world [3], and 5 to 40% across the Asia-Pacific region [4–6]. NAFLD is also an emerging liver disease in Taiwan, with prevalence ranging from 11.4 to 41% [7].

Sleep apnea is a kind of sleep disorders (SD). It refers to momentary, often cyclical, cessations in breathing rhythm, sufficient to cause significant arterial hypoxemia and hypercapnia [8]. Many studies have been conducted on the association between sleep apnea and NAFLD, and the pooled odds ratios were approximately 2 to 3 in
meta-analyses [9, 10]. However, sleep apnea constitutes only a portion of sleep disturbance. SD, including short sleep duration, poor sleep quality, etc. [11, 12], are common in the general population [13, 14]. For example, more than 25% of the Taiwanese adults suffer from insomnia [15]. Patients with SD are at increased risks of obesity, insulin resistance, dyslipidemia, hypertension, diabetes mellitus [16], and cardiovascular disease [17], which have all been reported to be associated with NAFLD [18, 19]. Studies on the risk of NAFLD associated with SD are limited. Using “sleep disorder” and “non-alcoholic fatty liver disease” as the keywords to search the literature indexed in the PubMed, we found that most of the previous studies were focused on sleep apnea, and all the limited studies on NAFLD associated with SD in general were cross-sectional studies, which may fall prey to the problem of “inverse causation,” i.e. NAFLD being a cause instead of an outcome of SD. Therefore, we conducted a longitudinal study to evaluate the association between SD, including sleep apnea, and NAFLD.

Methods

We conducted a retrospective population-based cohort study in Taiwan using the National Health Insurance system established by the Taiwanese government in 1995, which covers nearly all Taiwanese citizens. The National Health Insurance Research Database 2000 (NHIRD 2000) contains medical claim data from one million beneficiaries who were randomly selected in 2000. The cohort members have been followed up since the construction of the database, which included the registry of beneficiaries, disease registry profile, drug prescriptions, and other medical services. The disease registry profile recorded the disease history for each insured individual according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The database underwent de-identification before it was released for research use.

The target cohort are those who had SD (defined by having ICD-9-CM 307.4 or 780.5 among the diagnoses on the claims) for at least three consecutive months from 2000 to 2005. The index date of an SD patient was defined as the first diagnosis date. The same number of beneficiaries as those in the SD cohort were randomly selected from those who did not have SD from the same database as the comparison cohort. We excluded candidates who were under 20 years of age and who had a history of NAFLD (ICD-9-CM 571.8), liver cirrhosis (ICD-9-CM 571.2, 571.5, or 571.6), hepatitis B (ICD-9-CM V02.61, 070.20, 070.22, 070.30, or 070.32), hepatitis C (ICD-9-CM V02.62, 070.41, 070.44, 070.51, or 070.54), organic sleep disorders (ICD-9-CM 327), or narcolepsy (ICD-9-CM 347) before the index date. Both cohorts were followed up from the index date to the date when NAFLD was diagnosed or the end of 2013.

To control potential confounding factors, we collected data on diabetes (ICD-9-CM 250), dyslipidemia (ICD-9-CM 272), hypertension (ICD-9-CM 401–405), ischemic heart disease (IHD; ICD-9-CM 410–414), depression (ICD-9-CM 296.2, 296.3, 300.4, or 311), and anxiety (ICD-9-CM 300).

We present continuous variables as mean ± standard deviation and categorical variables as number (percentage). Differences in categorical variables between groups were evaluated using Pearson’s chi-square tests, and Student’s t-tests were used to evaluate differences in continuous variables. The incidence rate (IR) of NAFLD was calculated as the number of events divided by the person-year observed. We further plotted the cumulative incidence curves for the SD and compared the two cohorts using the Kaplan-Meier method. The log-rank test was used to evaluate the difference.

We used Cox proportional hazards regression models to obtain the hazard ratios (HRs) associated with SD. Univariate analyses were followed by multivariate analyses adjusting for sex, age, and comorbidities, including diabetes mellitus, dyslipidemia, hypertension, ischemic heart disease (IHD), depression, and anxiety. Furthermore, we divided the SD cohort into two subgroups, the sleep apnea group (ICD-9-CM 780.51, 780.53, or 780.57) and the non-apnea group (ICD-9-CM 307.4, 780.50, 780.52, 780.54, 780.55, 780.56, or 780.59), and conducted analyses separately.

In all statistical tests, the significant level was set at 0.05 (two-tailed). All statistical analyses were performed using the SAS 9.4 software (SAS Institute, Cary, NC, USA) or the R software. Our study protocol was reviewed and approved by the Ethics Review Board of the China Medical University Hospital (CMUH104-REC2–115).

Results

A total of 33,045 patients were included in the SD cohort, and therefore the comparison cohort also had 33,045 members. The proportion of men was 39.7% in the SD cohort and 57.6% in the comparison cohort (p < 0.001) (Table 1). The mean age of the SD cohort was 12.3 years older than that of the comparison cohort (53.6 vs. 41.3 years, p < 0.001). The prevalence rates of the comorbidities of diabetes mellitus, dyslipidemia, hypertension, IHD, depression, and anxiety were all significantly higher in the SD cohort than those in the comparison cohort (all p < 0.001).

The IR of NAFLD was 14.0 per 10,000 person-year in the SD cohort and was only 6.2 per 10,000 person-year in the comparison cohort. The HR was 2.26 (95% confidence interval [95% CI]: 1.92–2.67) in the SD cohort.
with the comparison cohort as the reference (Table 2). After adjusting for age, sex, and comorbidities (diabetes, dyslipidemia, hypertension, IHD, depression, and anxiety), we found that patients with SD had an increased risk of developing NAFLD, with an adjusted HR (AHR) of 1.78 (95% CI: 1.46–2.15). In addition, there were significant higher risks associated with male sex (AHR = 1.31, 95% CI: 1.12–1.54), age 40–59 years (AHR = 1.49, 95% CI: 1.21–1.82), and dyslipidemia (AHR = 2.51, 95% CI: 2.08–3.04). However, the AHRs associated with diabetes (AHR = 1.04, 95% CI: 0.82–1.33) and hypertension (AHR = 1.02, 95% CI: 0.84–1.25) did not reach statistical significance in the multi-variate Cox proportional hazards regression analyses. The cumulative incidence of NAFLD in the SD cohort was significantly higher than that in the comparison cohort (p < 0.001) (Fig. 1).

In the stratified analyses (Table 3), the AHR in women was 1.82 (95% CI: 1.35–2.46), similar to that in men (AHR = 1.79, 95% CI: 1.38–2.32). At the age of 20–39, 40–59 and ≥60 years, the AHR was 1.71 (95% CI: 1.18–2.48), 1.89 (95% CI: 1.44–2.47) and 1.23 (95% CI: 0.79–1.91), respectively. All the AHRs in the groups without the comorbidity were significantly higher than those in the groups with the comorbidity. Specifically, the AHR was 1.84 (95% CI: 1.50–2.26) in patients without diabetes, 2.10 (95% CI: 1.67–2.65) in patients without dyslipidemia, 2.03 (95% CI: 1.61–2.57) in patients without hypertension, 1.88 (95% CI: 1.53–2.31) in patients without IHD, 1.81 (95% CI: 1.48–2.20) in patients without depression, and 1.82 (95% CI: 1.48–2.24) in patients without anxiety. None of the AHRs in the subgroups with those comorbidities reached statistical significance.

Amongst the SD cohort, the sleep apnea group had an increased risk of NAFLD, with an AHR of 2.24 (95% CI: 1.05–4.77) after adjustment for age, sex, and the comorbidities (Table 4). Nonetheless, the non-apnea group also had an increased risk of NAFLD, with an AHR of 1.77 (95% CI: 1.46–2.15).

**Discussion**

This nationwide retrospective population-based cohort study found that patients with SD had a significantly higher risk of developing NAFLD. The increased risk of NAFLD was observed not only in the subgroups of SD patients with sleep apnea, but also in SD patients without sleep apnea. Previous studies on the association between SD and NAFLD were mostly on sleep apnea. Using “sleep disorder” and “non-alcoholic fatty liver disease” as the key words to search the literature indexed in the PubMed, we found five studies on the association between NAFLD and SD in general. The National Health and Nutrition Examination Survey (NHANES) in 2005 to 2010 in the U.S. found that SD was associated with a 1.4 times higher risk of NAFLD [20]. A study of 69,463 middle-aged Korean workers and their spouses found that short sleep duration and poor sleep quality were associated with the risk of NAFLD in all participants. However, a study of 46 patients with biopsy-proven NAFLD and 22 healthy controls also found that in the NAFLD patients, sleep duration was shortened, sleep...
onset was delayed, and sleep quality was poor [22]. A study of 2172 people in Japan found that the prevalence of NAFLD tended to decrease as sleep duration increased in men, but in women, and that it was lowest in the group with a sleep duration of 6 to \(\leq 7\) h and highest in the groups with sleep durations of \(\leq 6\) and > 8 h [23]. In younger populations, a study of 708 non-diabetic youngsters found that sleep shortage was associated with the presence of NAFLD [24]. In general, findings in those studies are compatible with our finding of an association between SD and NAFLD.

We observed an AHR of 2.24 for developing NAFLD in the SD patients with sleep apnea, which is consistent with the pooled odds ratios (between 2 and 3) obtained in meta-analyses [9, 10]. Chronic intermittent hypoxia [25, 26], which has been shown to induce liver steatosis [27], is generally considered as a major mechanism through which sleep apnea leads to NAFLD. Nonetheless, we also observed an increased risk of NAFLD in SD patients without sleep apnea. There should be mechanisms other than chronic intermittent hypoxia through which SD may cause NAFLD. Epidemiologic studies have shown that sleep insufficiency may lead to alternation of glucose homeostasis [28], insulin resistance [29, 30], weight gain [31], obesity [32], metabolic syndrome [33, 34], and diabetes mellitus [35, 36], which are all associated with NAFLD [16, 37–39]. In experimental studies, sleep disturbance was found to induce some inflammatory cytokines such as tumor necrosis factor-alpha,

| Characteristics          | N   | Event | Person-year | Incidence Rate (/10,000 person-year) | Hazard Ratio (95% Confidence Interval) |
|--------------------------|-----|-------|-------------|-------------------------------------|---------------------------------------|
|                          |     |       |             |                                     | Univariate p-value | Multivariate a p-value |
| Sleep disorders          |     |       |             |                                     | Reference                | Reference               |
| No                       | 33,045 | 206 | 333,121 | 6.2                                | Reference                | Reference               |
| Yes                      | 33,045 | 441 | 314,627 | 14.0                               | 2.26 (1.92–2.67)         | < 0.001                 | 1.78 (1.46–2.16)         | < 0.001                 |
| Sex                      |     |       |             |                                     | Reference                | Reference               |
| Women                    | 33,939 | 325 | 337,279 | 9.6                                | Reference                | Reference               |
| Men                      | 32,151 | 322 | 310,470 | 10.4                               | 1.08 (0.92–1.26)         | 0.35                    | 1.31 (1.12–1.54)         | < 0.001                 |
| Age (year)               |     |       |             |                                     | Reference                | Reference               |
| 20–39                    | 25,278 | 166 | 260,647 | 6.4                                | Reference                | Reference               |
| 40–59                    | 24,088 | 337 | 245,204 | 13.7                               | 2.16 (1.79–2.60)         | < 0.001                 | 1.49 (1.21–1.82)         | < 0.001                 |
| \(\geq 60\)              | 16,724 | 144 | 141,898 | 10.2                               | 1.59 (1.27–1.99)         | < 0.001                 | 0.86 (0.66–1.13)         | 0.28                    |
| Comorbidities            |     |       |             |                                     | Reference                | Reference               |
| Diabetes                 |     |       |             |                                     | Reference                | Reference               |
| No                       | 59,745 | 556 | 592,827 | 9.4                                | Reference                | Reference               |
| Yes                      | 6345  | 91   | 54,922  | 16.6                               | 1.77 (1.41–2.20)         | < 0.001                 | 1.04 (0.82–1.33)         | 0.73                    |
| Dyslipidemia             |     |       |             |                                     | Reference                | Reference               |
| No                       | 55,165 | 411 | 544,066 | 7.6                                | Reference                | Reference               |
| Yes                      | 10,925 | 236 | 103,683 | 22.8                               | 3.01 (2.56–3.53)         | < 0.001                 | 2.51 (2.08–3.04)         | < 0.001                 |
| Hypertension             |     |       |             |                                     | Reference                | Reference               |
| No                       | 47,383 | 407 | 479,123 | 8.5                                | Reference                | Reference               |
| Yes                      | 18,707 | 240 | 168,625 | 14.2                               | 1.68 (1.43–1.97)         | < 0.001                 | 1.02 (0.84–1.25)         | 0.83                    |
| Ischemic Heart Disease   |     |       |             |                                     | Reference                | Reference               |
| No                       | 56,255 | 529 | 560,892 | 9.4                                | Reference                | Reference               |
| Yes                      | 9835  | 118 | 86,856  | 13.6                               | 1.44 (1.18–1.76)         | < 0.001                 | 0.86 (0.68–1.08)         | 0.19                    |
| Depression               |     |       |             |                                     | Reference                | Reference               |
| No                       | 61,761 | 574 | 606,799 | 9.5                                | Reference                | Reference               |
| Yes                      | 4329  | 73  | 40,950  | 17.8                               | 1.88 (1.47–2.40)         | < 0.001                 | 1.23 (0.94–1.62)         | 0.14                    |
| Anxiety                  |     |       |             |                                     | Reference                | Reference               |
| No                       | 52,100 | 437 | 514,026 | 8.5                                | Reference                | Reference               |
| Yes                      | 13,990 | 210 | 133,722 | 15.7                               | 1.84 (1.56–2.17)         | < 0.001                 | 1.16 (0.95–1.42)         | 0.15                    |

*Adjusted for sex, age (categorical), diabetes, dyslipidemia, hypertension, depression, anxiety, and ischemic heart disease in Cox proportional hazards regressions
interleukin-1 beta, and interleukin-6 [40–42], which play important roles in the pathogenesis of NAFLD [43–45]. Also, sleep loss elevates the level of ghrelin and reduces the level of leptin [46, 47], which increase appetite and further cause obesity. Moreover, chronic insomnia activates the hypothalamo–pituitary–adrenal axis [48], increases stress hormone, worsens insulin resistance, and facilitates the progression of NAFLD [49].

We performed stratified analyses according to most of the generally recognized risk factors for NAFLD, including diabetes mellitus, hypertension, dyslipidemia, depression, and anxiety [19, 50, 51]. The results showed that the effects of SD on the development of NAFLD were significant in patients without these factors, but not in those with these factors. This provided insights that SD may lead to NAFLD through pathways different from those associated with these risk factors and that SD may be a major risk factor for NAFLD in relatively healthy people.

All five of the previous studies on the association between SD and NAFLD that we identified in the literature review adopted cross-sectional study designs. With a longitudinal study design, our study has the advantage of providing stronger evidence of causation in terms of temporal relationship. In addition, most of the previous studies used questionnaires to define SD, and the diagnosis of NAFLD was not confirmed by a physician in all the cases. In the NHANES study [20], for example, the diagnosis of SD was established by questionnaires, and NAFLD was defined as elevated liver enzymes without chronic hepatitis B, chronic hepatitis C, or alcoholic liver disease. In our study, all the diagnoses of SD and NAFLD were made by physicians and subject to routine audits by specialists hired by the National Health Insurance. Furthermore, our study also has the advantage of controlling most of the major potential confounders, including sex, age, and comorbidities of diabetes, hypertension, dyslipidemia, IHD, depression, and anxiety at the same time, which had not been achieved in previous studies. As a result, in addition to SD, we identified male sex, age between 40 and 59 years old, and dyslipidemia as independent risk factors for NAFLD. Because SD and NAFLD are exceedingly common in the general population, we suggest screening programs for NAFLD in patients of SD with above factors.

Our study also has some limitations. First, our study included SD patients who chose to seek medical aid, and therefore the results may not be generalized to the patients who do not seek medical aid. A common reason why SD patients do not seek medical aid is that the illness is not severe. However, studying only the patients who were diagnosed by physicians ensured the accuracy of diagnoses, which is regarded as a strength of our study. Second, although obesity is a well-established risk factor for NAFLD, we were unable to evaluate its effects because the number of patients coded with ICD-9-CM 278 in the NHIRD2000 was small. Again, this was due to the fact that not all patients of obesity would seek medical aids. Nonetheless, we included diabetes, hypertension, and IHD in the analyses, and these conditions are major outcomes of obesity. In other words, the effects of obesity were adjusted indirectly to a certain degree in our analyses. Third, NHIRD2000 does not contain information on sleep pattern, duration, and quality. Therefore, we were unable to study the effects of SD in greater details.

Conclusions
In this nationwide population-based cohort study, patients with SD had a higher risk of developing NAFLD, including those SD patients who did not have sleep apnea. The association was observed in the subgroups without comorbidities of diabetes, dyslipidemia, hypertension, IHD, depression, or anxiety, but was not observed in the patients who had these comorbidities. This finding indicates that SD may lead to NAFLD through pathways that do not involve these previously recognized risk factors. Further studies are warranted to explore these pathways.
### Table 3 Incidence rates and hazard ratios of non-alcoholic fatty liver disease according to sleep disorder status

| Characteristics | Comparison Cohort | Sleep Disorder Cohort | Compared to the Comparison Cohort |
|-----------------|-------------------|-----------------------|----------------------------------|
|                 | Event  | Person-year | IR   | Event | Person-year | IR   | Crude | p-value | Adjusted | p-value | Crude | p-value | Adjusted | p-value |
| Women           | 186    | 320,194     | 5.8  | 370   | 272,633     | 13.6 | 2.34 (1.96–2.79) | < 0.001 | 1.81 (1.50–2.16) | < 0.001 |
| Men             | 20     | 12,927      | 15.5 | 71    | 41,995      | 16.9 | 1.11 (0.68–1.82) | 0.68    | 1.17 (0.68–1.99) | 0.57    |
| Age (year)      |        |             |      |       |             |      |       |         |          |         |
| 20–39           | 88     | 183,841     | 4.8  | 78    | 76,805      | 10.2 | 2.11 (1.55–2.86) | < 0.001 | 1.71 (1.18–2.48) | 0.004   |
| 40–59           | 89     | 111,058     | 8.0  | 248   | 134,146     | 18.5 | 2.31 (1.81–2.94) | < 0.001 | 1.89 (1.44–2.47) | < 0.001 |
| ≥ 60            | 29     | 38,222      | 7.6  | 115   | 103,676     | 11.1 | 1.46 (0.97–2.20) | 0.07    | 1.23 (0.79–1.91) | 0.35    |
| Comorbidities   |        |             |      |       |             |      |       |         |          |         |
| Diabetes        |        |             |      |       |             |      |       |         |          |         |
| No              | 153    | 309,909     | 4.9  | 258   | 234,156     | 11.0 | 2.24 (1.83–2.73) | < 0.001 | 2.10 (1.67–2.65) | < 0.001 |
| Yes             | 53     | 23,212      | 22.8 | 183   | 80,471      | 22.7 | 0.99 (0.74–1.36) | 0.99    | 1.03 (0.74–1.44) | 0.85    |
| Hypertension    |        |             |      |       |             |      |       |         |          |         |
| No              | 157    | 295,681     | 5.3  | 250   | 183,442     | 13.6 | 2.56 (2.10–3.13) | < 0.001 | 2.03 (1.61–2.57) | < 0.001 |
| Yes             | 49     | 37,440      | 13.1 | 191   | 131,186     | 14.6 | 1.12 (0.82–1.53) | 0.49    | 1.09 (0.78–1.52) | 0.61    |
| Ischemic heart disease |  |     | | | | | | | |
| No              | 190    | 319,112     | 6.0  | 339   | 241,780     | 14.0 | 2.35 (1.97–2.81) | < 0.001 | 1.88 (1.53–2.31) | < 0.001 |
| Yes             | 16     | 14,009      | 11.4 | 102   | 72,847      | 14.0 | 1.23 (0.73–2.09) | 0.44    | 1.04 (0.60–1.82) | 0.88    |
| Depression      |        |             |      |       |             |      |       |         |          |         |
| No              | 203    | 331,189     | 6.1  | 371   | 275,610.    | 13.5 | 2.19 (1.85–2.60) | < 0.001 | 1.81 (1.48–2.20) | < 0.001 |
| Yes             | 3      | 1932        | 15.5 | 70    | 39,017      | 17.9 | 1.16 (0.37–3.68) | 0.80    | 0.99 (0.31–3.17) | 0.98    |
| Anxiety         |        |             |      |       |             |      |       |         |          |         |
| No              | 191    | 322,595     | 5.9  | 246   | 191,432     | 12.9 | 2.17 (1.79–2.62) | < 0.001 | 1.82 (1.48–2.24) | < 0.001 |
| Yes             | 15     | 10,526      | 14.3 | 195   | 123,196     | 15.8 | 1.11 (0.66–1.88) | 0.69    | 1.04 (0.61–1.77) | 0.88    |

IR Incidence rate per 10,000 person-year

*Model mutually adjusted for sex, age (categorical), diabetes, dyslipidemia, hypertension, depression, anxiety, and ischemic heart disease

### Table 4 Incidence rates and hazard ratios of non-alcoholic fatty liver disease in different subgroups

| Subgroup                | N   | Event | Person-year | Incidence Rate (/10,000 person-year) | Hazard Ratio (95% Confidence Interval) |
|-------------------------|-----|-------|-------------|--------------------------------------|---------------------------------------|
|                         |     |       |             |                                      | Crude | p-value | Adjusted | p-value |
| Comparison Cohort       | 33,045 | 206  | 333,121     | 6.2                                  | Reference | Reference |
| Sleep Disorder Cohort   |       |       |             |                                      |         |         |          |         |
| Apnea Group             | 388 | 7     | 3751        | 18.7                                 | 3.01 (1.42–6.39) | 0.004 | 2.24 (1.05–4.77) | 0.04 |
| Non-apnea Group         | 32,657 | 434  | 310,877     | 14.0                                 | 2.25 (1.91–2.66) | < 0.001 | 1.77 (1.46–2.15) | < 0.001 |

*Model adjusted for sex, age (categorical), diabetes, dyslipidemia, hypertension, depression, anxiety, and ischemic heart disease
Ethics approval and consent to participate

Researchers can apply for the data via HWDC, Department of Health, which has been transferred to the Health and Welfare Data Science Center (HWDC). The data is from the National Health Insurance Research Database (NHIRD), Department of Health, Ministry of Health and Welfare, and in writing the manuscript.

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Authors’ contributions

The contributions of the authors of this paper are as following: Y-TW, P-YL, C-YL, J-SW, Y-FC, and H-RG conceived the study; Y-TW, P-YL, and C-LW designed the study; and H-JC and C-CL performed statistical analysis. Y-TW, P-YL, C-LW, and H-RG drafted the manuscript, and all authors read and approved the final manuscript.

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Availability of data and materials

The data is from the National Health Insurance Research Database (NHIRD), which has been transferred to the Health and Welfare Data Science Center (HWDC). Researchers can apply for the data via HWDC, Department of Statistics, Ministry of Health and Welfare, Taiwan (http://dep.mohw.gov.tw/DOS/np-2497-113.html).

Ethics approval and consent to participate

Our study protocol was reviewed and approved by the Ethics Review Board of the China Medical University Hospital (CMUH104-REC2-115) in 2015.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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