Decreased Risk of Stroke in People Using Red Yeast Rice Prescriptions (LipoCol Forte®): a Total Population-Based Retrospective Cohort Study

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The influence of red yeast rice (RYR) on the risk of incident stroke remains underexplored. We aimed to compare the risk of stroke between people with and without use of RYR prescriptions. We used research data from the National Health Insurance Program in Taiwan and identified 34,723 adults (aged ≥ 20 years) who first received the RYR prescription from 2010 to 2014. To select the appropriate control group, we used frequency matching by age and sex (case-control ratio = 1 : 1) and identified a non-RYR cohort that included 34,723 adults who first received lovastatin. Events of an incident stroke that occurred during the follow-up period of 2010–2017 were identified from medical claims. The adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of stroke risk associated with RYR prescription were calculated in the multiple Cox proportional hazard model. Compared with the non-RYR cohort, patients who received RYR prescriptions had a decreased risk of stroke (HR 0.65, 95% CI 0.59–0.71), including hemorrhagic stroke (HR 0.60, 95% CI 0.44–0.83), ischemic stroke (HR 0.49, 95% CI 0.43–0.57), and other types of strokes (HR 0.53, 95% CI 0.42–0.67). The association between RYR prescription and stroke risk was significant in both sexes and in people aged more than 40 years, as well as in those individuals with various medical conditions. The frequency of RYR prescription (HR 0.57, 95% CI 0.50–0.64) was associated with a decreased risk of stroke with a dose-response relationship (p for trend<0.0001). This study showed a potentially positive effect of RYR on the risk of stroke. However, compliance with medication use should be cautioned. The findings of this study require future studies to validate the beneficial effects of RYR prescription on stroke risk.

1. Introduction

Stroke remains as one of the leading causes of death and disability due to the fact that it was estimated that nearly 13.7 million people experienced new strokes and that 5.5 million people died from stroke in 2016 throughout the world [1–4]. Almost 5% of all disability-adjusted life years and 10% of all deaths throughout the world are due to stroke [2]. According to statistics from the American Heart Association, the economic costs of stroke treatment and poststroke care can...
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2.1. Source of Data. The epidemiology, prevention, and treatment of stroke have been well established, and hypercholesterolemia is known for being a major risk factor for stroke. Although statins have been proven to effectively control the levels of total cholesterol and are also widely used throughout the world, the risk of diabetes after treatment with statins has also attracted attention [5, 6].

Red yeast rice (RYR), which is also known as Monascus purpureus Went rice, is an herbal medicine that has been frequently used among patients with hypercholesterolemia in the Chinese population, and its therapeutic effects have been previously investigated [7–10]. Scientifically processed RYR prescriptions (such as Xuezhikang®, HypoCol®, and Lip-oCol Forte®) that contain monacolin K (lovastatin) have been proven to effectively reduce the levels of total cholesterol and low-density lipoprotein cholesterol [11–13]. In addition, a recent study found that people who used RYR had a lower risk of diabetes than people who used statins [14]. However, more assessments of the potential side effects of RYR are needed, although the tolerance and safety of the RYR use has been previously reviewed and studied [9, 15, 16].

A systematic review and meta-analysis evaluated seven clinical trials and suggested that RYR was associated with improved cardiovascular outcomes and lipid profiles in myocardial infarction patients with borderline hypercholesterolemia [17]. Nevertheless, limited information is available on the comparison of the risk of incident stroke between people who did and did not use RYR. By using reimbursement claim data from the National Health Insurance Program in Taiwan, we conducted a retrospective cohort study with a real-world database to evaluate the effects of RYR prescriptions on the risk of incident stroke.

2. Methods

2.1. Source of Data. We conducted this study by using research data from the National Health Insurance in Taiwan. This insurance program was initiated in 1995 and currently covers almost all population (approximately, 23 million people). The research data of Taiwan’s National Health Insurance Program constitute a real-world database that has been previously evaluated and the related research articles have been accepted in the journals throughout the world [13, 14, 18–20]. For the protection of personal privacy, patient identification was decoded and scrambled in this study, which was also reviewed and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB-201905042; TMU-JIRB-201902053) and E-DA Hospital (EDA-JIRB-2019001).

2.2. Study Design. In this real-world database that included a retrospective cohort of 23 million insured individuals, we identified 47235 patients (aged 20 years and older) who first used RYR prescriptions between 2010 and 2014 and who were without a history of stroke before the date of RYR use and categorized them as the RYR cohort. During the same index period, 50,886 patients used lovastatin (aged 20 years and older) who did not use RYR prescriptions were identified. Both groups were matched by age and sex (with a case-control ratio = 1 : 1), and they had no history of stroke before the index date; thus, there were 34,723 patients with RYR prescriptions and 34,723 patients without RYR prescriptions for comparison. Patients with any physicians’ diagnoses (including primary and secondary diagnoses during inpatient and outpatient care) of stroke before the use of RYR prescriptions or the index date were excluded, in order to ensure that all of the study participants were free of stroke at the start of both cohorts. The follow-up started from the time of the use of RYR prescriptions or the index date and lasted until the occurrence of stroke events, censoring due to death, or loss to follow-up by December 31, 2017. Therefore, no immortal time bias existed in this study. We sought to evaluate the risk of incident stroke between the RYR cohort and the comparison cohort during the follow-up period.

2.3. Definitions and Criteria. The use of RYR was defined as people who visited clinics of traditional Chinese medicine and who received a physician’s prescription for RYR (Lip-oCol Forte®) under the coverage of Taiwan’s National Health Insurance Program. The prescription of RYR is an all-natural RYR extract that has been scientifically processed and the related details were described in the previous studies [13, 14].

The main outcome of incident stroke (430–437) and medical conditions was identified by using physicians’ diagnoses and the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We defined stroke cases as people who had the first occurrence of stroke and who received inpatient care by neurologists and/or neurosurgeons during stroke hospitalization and during the follow-up period. Coexisting medical conditions were determined from medical claims and included hypertension (401–405), mental disorders (290–319), diabetes (250), chronic obstructive pulmonary disease (490, 491, 496), ischemic heart disease (410–414), liver cirrhosis (571.2, 571.5, 571.6), heart failure (428), and renal dialysis (administration codes, D8 and D9). The Charlson comorbidity index, emergency visits, and number of hospitalizations were also considered to be indicators of personal medical conditions in this study. The low income statuses of patients were identified by the definition of the Ministry of Health and Welfare, Taiwan.

2.4. Statistical Analysis. We used Chi-square tests to compare the baseline characteristics between people with and without the use of RYR prescriptions. Using multivariate Cox proportional hazard regressions, we conducted different adjusted models of the covariates (age, sex, low income, hypertension, mental disorders, diabetes, chronic obstructive pulmonary disease, ischemic heart disease, liver cirrhosis, heart failure, and renal dialysis) to calculate the corresponding adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of incident stroke that were associated with the use of RYR prescriptions. The
risk of incident stroke between people who did and did not use RYR prescriptions was also calculated in the subgroup analyses by age, sex, number of medical conditions, emergency visits, hospitalizations, and the Charlson comorbidity index. In addition, we performed sensitivity analyses and excluded incident cases of stroke within the initial one-, two-, and three-month follow-up periods.

3. Results

The characteristics of people with and without the use of RYR prescriptions are shown in Table 1. Under frequency matching by age and sex, compared to the non-RYR group, the RYR cohort had lower proportions of low income (< 0.0001) and medical conditions, including hypertension (p < 0.0001), diabetes (p < 0.0001), chronic obstructive pulmonary disease (p < 0.0001), liver cirrhosis (p < 0.0001), heart failure (p < 0.0001), renal dialysis (p < 0.0001), and the Charlson comorbidity index scores ≥3 (p < 0.0001). The proportions of hospitalizations ≥3 times (p < 0.0001), emergency visits ≥3 (p < 0.0001), the use of anti-hypertension drugs (p < 0.0001), and the use of anticoagulant drugs (p < 0.0001) were lower in people who had RYR than in those individuals without RYR. The unmatched characteristics of people with and without the use of RYR prescriptions are shown in Table S1.

In Table 2, compared with those individuals who did not use RYR, people who used RYR prescriptions had a lower risk of stroke during the follow-up period (HR 0.65, 95% CI 0.59–0.71). The use of RYR prescriptions was also associated with a decreased risk of hemorrhagic stroke (HR 0.60, 95% CI 0.44–0.83), ischemic stroke (HR 0.49, 95% CI 0.43–0.57), and other types of strokes (HR 0.53, 95% CI 0.42–0.67). After excluding incident stroke cases during the initial one month (HR 0.66, 95% CI 0.60–0.73), two months (HR 0.67, 95% CI 0.61–0.74), and three months (HR 0.68, 95% CI 0.61–0.75) of the follow-up period, the use of RYR prescriptions was also associated with a decreased stroke risk.

The stratified analysis (Table 3) revealed that the association between the use of RYR prescriptions and a decreased risk of stroke was significant in women (HR 0.66; 95% CI 0.58–0.77), men (HR 0.63; 95% CI 0.55–0.72), and those people aged more than 20 years. The adjusted HRs of stroke risk that were associated with RYR prescription use among people with 0, 1, 2, and ≥3 medical conditions were 0.39 (95% CI 0.31–0.50), 0.58 (95% CI 0.50–0.68), 0.68 (95% CI 0.57–0.81), and 0.74 (95% CI 0.60–0.92), respectively. The association between the use of RYR prescriptions was associated with a decreased risk of stroke in people with the Charlson comorbidity index scores of 0 (HR 0.56, 95% CI 0.46–0.68), 1 (HR 0.70, 95% CI 0.59–0.84), 2 (HR 0.71, 95% CI 0.56–0.90), and ≥3 (HR 0.66, 95% CI 0.55–0.79). The use of RYR prescriptions was associated with the decreased stroke risk among people with emergency visits and hospitalizations. In Table 4, there was a potential dose-response relationship between the frequencies of RYR use and decreased stroke risk with an HR of 0.57 (95% CI 0.50–0.64).

| Table 1: Baseline characteristics of people with and without use of RYR prescription. |
|---------------------------------|---------------------------------|-----------------|-----------------|
|                                 | No RYR*                         | RYR prescription  |
|                                 | N = 34723                      | N = 34723        |
| **Sex**                        |                                |                 | **p value**     |
| Female                         | 19279 (55.5)                   | 19279 (55.5)    | 1.0000          |
| Male                           | 15444 (44.5)                   | 15444 (44.5)    |                 |
| **Age, years**                 |                                |                 |                 |
| 20–29                          | 503 (1.5)                      | 503 (1.5)       |                 |
| 30–39                          | 2115 (6.1)                     | 2115 (6.1)      |                 |
| 40–49                          | 6814 (19.6)                    | 6814 (19.6)     |                 |
| 50–59                          | 14476 (41.7)                   | 14476 (41.7)    |                 |
| 60–69                          | 7768 (22.4)                    | 7768 (22.4)     |                 |
| 70–79                          | 2563 (7.4)                     | 2563 (7.4)      |                 |
| ≥80                            | 484 (1.4)                      | 484 (1.4)       |                 |
| **Low income**                 |                                |                 |                 |
| No                             | 33397 (96.2)                   | 33397 (97.7)    |                 |
| Yes                            | 1326 (3.8)                     | 786 (2.3)       |                 |
| **Medical conditions**         |                                |                 |                 |
| Hypertension                   | 17302 (49.8)                   | 13568 (39.1)    | <0.0001         |
| Mental disorders               | 10753 (31.0)                   | 10816 (31.2)    | 0.6054          |
| Diabetes                       | 14608 (42.1)                   | 7296 (21.0)     | <0.0001         |
| Heart failure                  | 1187 (3.4)                     | 697 (2.0)       | <0.0001         |
| Renal dialysis                 | 700 (2.0)                      | 188 (0.5)       | <0.0001         |
| Ischemic heart disease         | 6347 (18.3)                    | 5338 (15.4)     | <0.0001         |
| COPD                           | 5267 (15.2)                    | 4622 (13.3)     | <0.0001         |
| Liver cirrhosis                | 2347 (6.8)                     | 1845 (5.3)      | <0.0001         |
| **CCI, score**                 |                                |                 |                 |
| 0                              | 6565 (18.9)                    | 10019 (28.9)    | <0.0001         |
| 1                              | 9086 (26.2)                    | 8181 (23.6)     |                 |
| 2                              | 6118 (17.6)                    | 6138 (17.7)     |                 |
| ≥3                             | 12954 (37.3)                   | 10385 (29.9)    |                 |
| **Number of hospitalizations** |                                |                 | <0.0001         |
| 0                              | 19271 (55.5)                   | 23189 (66.8)    |                 |
| 1                              | 6829 (19.7)                    | 6306 (18.2)     |                 |
| 2                              | 3304 (9.5)                     | 2483 (7.2)      |                 |
| ≥3                             | 5319 (15.3)                    | 2745 (7.9)      |                 |
| **Number of emergency visits** |                                |                 | <0.0001         |
| 0                              | 13454 (38.8)                   | 16545 (47.7)    |                 |
| 1                              | 7718 (22.2)                    | 8140 (23.4)     |                 |
| 2                              | 4514 (13.0)                    | 3974 (11.4)     |                 |
| ≥3                             | 9037 (26.0)                    | 6064 (17.5)     |                 |
| **Use of antihypertensive drug**|                                |                 | <0.0001         |
| Use of anticoagulant drug       | 1415 (4.1)                     | 786 (2.3)       |                 |

4. Discussion

This was the first study to compare the risk of incident stroke between people who did and did not use RYR prescriptions. We found a decreased risk of incident stroke in people who used RYR prescriptions, with significant findings observed regardless of age, gender, or medical conditions. Decreased risks of hemorrhagic stroke and ischemic stroke associated with the use of RYR prescriptions were also found in this study.
Table 2: Risk of incident stroke between RYR cohort and non-RYR group during the follow-up period.

<table>
<thead>
<tr>
<th>Incident stroke</th>
<th>RYR</th>
<th>No RYR</th>
<th>n</th>
<th>PYs</th>
<th>Events</th>
<th>Incidence*</th>
<th>HR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke</td>
<td>RYR</td>
<td></td>
<td>34723</td>
<td>212022</td>
<td>1482</td>
<td>6.99</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>RYR</td>
<td></td>
<td>34723</td>
<td>215445</td>
<td>267</td>
<td>7.24</td>
<td>0.87</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>RYR</td>
<td></td>
<td>34723</td>
<td>183391</td>
<td>160</td>
<td>3.87</td>
<td>0.65 (0.59–0.71)</td>
</tr>
<tr>
<td>Other stroke</td>
<td>RYR</td>
<td></td>
<td>34723</td>
<td>214373</td>
<td>421</td>
<td>1.96</td>
<td>1.00 (Reference)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; PYs, person-years; RYR, red yeast rice. *Per 1000 person-years. †Adjusted for all covariates listed in Table 1.

Sensitivity analysis: after excluding the incident stroke cases during initial one month, two months, and three months, the risks of stroke associated RYR were 0.66 (95% CI 0.60–0.73), 0.67 (95% CI 0.61–0.74), and 0.68 (95% CI 0.61–0.75), respectively.

Table 3: Stratified analysis for the association between risk of stroke and RYR prescription.

<table>
<thead>
<tr>
<th>Incident stroke</th>
<th>RYR</th>
<th>No RYR</th>
<th>n</th>
<th>PYs</th>
<th>Events</th>
<th>Incidence*</th>
<th>HR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>RYR</td>
<td></td>
<td>19279</td>
<td>118911</td>
<td>708</td>
<td>5.95</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Men</td>
<td>RYR</td>
<td></td>
<td>15444</td>
<td>93111</td>
<td>774</td>
<td>8.31</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Age, 20–39 years</td>
<td>RYR</td>
<td></td>
<td>2618</td>
<td>16407</td>
<td>33</td>
<td>2.01</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Age, 40–49 years</td>
<td>RYR</td>
<td></td>
<td>6814</td>
<td>42595</td>
<td>196</td>
<td>4.60</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Age, 50–59 years</td>
<td>RYR</td>
<td></td>
<td>14476</td>
<td>89266</td>
<td>513</td>
<td>5.75</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Age, 60–69 years</td>
<td>RYR</td>
<td></td>
<td>7768</td>
<td>46372</td>
<td>248</td>
<td>3.23</td>
<td>0.65 (0.55–0.77)</td>
</tr>
<tr>
<td>Medical conditions, 0</td>
<td>RYR</td>
<td></td>
<td>4817</td>
<td>28186</td>
<td>192</td>
<td>6.81</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Medical conditions, 1</td>
<td>RYR</td>
<td></td>
<td>12363</td>
<td>73476</td>
<td>548</td>
<td>7.46</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Medical conditions, 2</td>
<td>RYR</td>
<td></td>
<td>9916</td>
<td>61299</td>
<td>428</td>
<td>6.98</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Medical conditions, ≥3</td>
<td>RYR</td>
<td></td>
<td>7627</td>
<td>49061</td>
<td>314</td>
<td>6.40</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>CCI score, 0</td>
<td>RYR</td>
<td></td>
<td>6565</td>
<td>38085</td>
<td>332</td>
<td>8.72</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>CCI score, 1</td>
<td>RYR</td>
<td></td>
<td>10019</td>
<td>50253</td>
<td>195</td>
<td>3.88</td>
<td>0.56</td>
</tr>
<tr>
<td>CCI score, 2</td>
<td>RYR</td>
<td></td>
<td>9086</td>
<td>54107</td>
<td>435</td>
<td>8.04</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>CCI score, ≥3</td>
<td>RYR</td>
<td></td>
<td>8181</td>
<td>42426</td>
<td>205</td>
<td>4.83</td>
<td>0.70</td>
</tr>
<tr>
<td>Emergency visit, 0</td>
<td>RYR</td>
<td></td>
<td>6118</td>
<td>37765</td>
<td>251</td>
<td>6.65</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Emergency visits, 1</td>
<td>RYR</td>
<td></td>
<td>6138</td>
<td>32766</td>
<td>131</td>
<td>4.00</td>
<td>0.71</td>
</tr>
<tr>
<td>Emergency visits, ≥2</td>
<td>RYR</td>
<td></td>
<td>12954</td>
<td>82065</td>
<td>464</td>
<td>5.65</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Hospitalizations, 0</td>
<td>RYR</td>
<td></td>
<td>10385</td>
<td>56970</td>
<td>193</td>
<td>3.39</td>
<td>0.66</td>
</tr>
<tr>
<td>Hospitalizations, 1</td>
<td>RYR</td>
<td></td>
<td>13454</td>
<td>79028</td>
<td>589</td>
<td>7.45</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Hospitalizations, ≥2</td>
<td>RYR</td>
<td></td>
<td>16545</td>
<td>84041</td>
<td>255</td>
<td>3.03</td>
<td>0.48</td>
</tr>
</tbody>
</table>

CCI, the Charlson comorbidity index; CI, confidence interval; HR, hazard ratio; PYs, person-years; RYR, red yeast rice. *Per 100 person-years. †Adjusted for all covariates listed in Table 1.
We propose several reasons to explain the reduction in the stroke risk in patients using RYR prescriptions in this study. First, a meta-analysis of randomized trials of statins (including six trials involving lovastatin) demonstrated large reductions in cholesterol and clear evidence of benefits regarding stroke [21]. The herbal medicine RYR contains monacolin K (lovastatin); thus, the mechanism regarding the lowering of the level of total cholesterol in patients who used RYR is clearly obvious [7, 9, 10, 21]. Undoubtedly, the reduction of the high level of total cholesterol to a normal range is one of the key points of reducing carotid atherosclerosis and subsequent stroke risk [22].

Second, in addition to conventional medicine (also known as biochemical medicine or Western medicine), traditional Chinese medicine is the second most common medical choice in Taiwan, Korea, Japan, and China. People with hyperlipidemia who choose second opinions and receive therapy with RYR prescriptions (as prescribed by physicians with specialties in traditional Chinese medicine) may have better knowledge, attitudes, and practices regarding disease prevention and health promotion [23]; therefore, these factors may also contribute to the decreased incidence of stroke.

Third, an animal study suggested that RYR was effective in combatting obesity-related inflammation, insulin resistance, and nonalcoholic fatty liver diseases in mice, irrespective of monacolin K levels [24]. Our previous analyses also provided some potential evidence to support the hypothesis that a decreased risk of incident diabetes was found in people who used RYR prescriptions [14]. It is believed that the reduction of the risk of diabetes is helpful for the prevention of stroke [25]. However, the results of the current study could not be fully explained by the previously described reasons. In addition to monacolin K, RYR prescriptions contain gamma-aminobutyric acid and various monacolins, phytosterols, and isoflavones [7, 26], and very little is known about the effects of these constituents on atherosclerosis or stroke. We suggest that future studies should evaluate the effects of other components of RYR on inflammation, hyperlipidemia, atherosclerosis, and stroke.

Despite the beneficial effects of RYR on hypercholesterol, as well as the fact that some studies have suggested that RYR is relatively safe [7, 11, 12, 15], the potential side effects of RYR should be considered, such as muscle symptoms, central nervous system complaints, and diabetes, with these effects being partially similar to the effects of statins [27]. Some studies and case reports have indicated that dietary supplements containing red yeast rice may be related to hepatotoxicity [28–30], symptomatic myopathy [28, 30, 31], and erectile dysfunction [32]. Therefore, the uncertain safety of the dietary intake of RYR was indicated by the European Food Safety Authority (EFSA) and other studies [9, 10, 33]. However, the side effects of RYR could not be independently investigated because several clinical trials combined RYR use with other dietary supplements [26, 34, 35]. Unlike dietary supplements, it was suggested that the content of RYR prescriptions with good manufacturing practices were relatively stable and safe, such as Xuezhikang®, HypoCol®, and LipoCol Forte® [7, 11, 12]. Thus, we suggest that the continuous surveillance of adverse reactions from RYR use should become a priority of future trials.

In this study, we used statistical methods and procedures to analyze a real-world database for evaluating the risk of incident stroke in patients using RYR prescriptions. To reduce confounding biases, we used four models of multivariate Cox proportional hazard regressions to adjust for sociodemographic factors, medical conditions, the Charlson comorbidity index, and the use of medical care as potential confounders. To avoid immortal time biases, we calculated the person years in the RYR cohort, beginning from the date of medication intake until the end of the study during the follow-up period. To validate new-onset stroke cases, we conducted sensitivity analyses in three models, which excluded stroke cases within the initial one-, two-, and three-month follow-up periods. To test the reliability, we performed stratified analyses to present the use of RYR associated with decreased stroke risk in various subgroups by age, sex, medical conditions, and use of medical care. To demonstrate the potential dose-response relationship, we calculated the cumulative use of RYR prescriptions and the decreased stroke risk.

The main limitation of our study was the unavailable information concerning patients’ compliance with RYR use. Thus, we did not understand whether the study subjects took all of their RYR prescriptions. Second, detailed information on socioeconomic status, lifestyle habits (such as smoking and drinking of alcohol), physical activity, eating habits, biochemical measures (such as fasting sugar and lipid levels), and the severity of comorbid disease was not.
available from the insurance database. Third, the incident stroke and coexisting medical conditions were identified according to the physician’s diagnosis during patient visits for medical care. Therefore, we could not exclude the small possibility that very few people with very minor strokes did not seek medical care; thus, we could not identify these stroke cases. Fourth, the unavailable data concerning knowledge, attitudes, and practices regarding disease prevention and family care are also limitations. In addition, we could not evaluate whether more than half of the participants were older than 60-years-old and which individuals may need to take more than one medication, as well as the fact that these medications may influence the control of medical condition and stroke occurrence. Another study limitation involves the possibility that we could not consider all medication use of the participants in this study. In addition, our study was an observational retrospective cohort study that could not provide causal inferences or concrete evidence between the use of RYR prescriptions and stroke risk. Finally, healthy worker effects in the RYR cohort and residual confounding biases were also possible in this study.

In conclusion, we indicated the possibility that people who used RYR prescriptions may have a lower risk of incident stroke, compared to non-RYR users, in this observational study. The decreased risk of incident stroke varied within people with levels of cumulative consumption of RYR prescriptions. However, the outcomes after stroke were not associated with the use of RYR prescriptions. Some limitations need to be cautiously considered when interpreting our findings. We suggest that large multicenter trials be conducted to provide further safety assessments and concrete evidence to demonstrate the relationship between RYR prescriptions and the incident risk of stroke.

Abbreviations

ICD-9-CM: International Classification of Diseases, 9th revision, clinical modification
CI: Confidence interval
RYR: Red yeast rice
HR: Hazard ratio.

Data Availability

The data underlying this study is from the Health and Welfare Data Science Center. Interested researchers can obtain the data through formal application to the Health and Welfare Data Science Center, Department of Statistics, Ministry of Health and Welfare, Taiwan (https://dep.mohw.gov.tw/dos/lp-2506-113.html). Under the regulations from the Health and Welfare Data Science Center, we have made the formal application (including application documents, study proposals, and ethics approval of the institutional review board) of the current insurance data from in 2019. The authors of the present study had no special access privileges in accessing the data which other interested researchers would not have.

Disclosure

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Ta-Liang Chen has equal contribution with the first author. Conceptualization was done by Chuen-Chau Chang, Mao-Feng Sun, Yi-Chun Chou, Chun-Chieh Yeh, Chaur-Jong Hu, Yih-Giun Cherng, Ta-Liang Chen, and Chien-Chang Liao. Formal analysis was carried out by Chien-Chang Liao. Investigation was conducted by Chuen-Chau Chang, Mao-Feng Sun, Yi-Chun Chou, Chun-Chieh Yeh, Chaur-Jong Hu, Yih-Giun Cherng, Ta-Liang Chen, and Chien-Chang Liao. Methodology was done by Chuen-Chau Chang, Mao-Feng Sun, Yi-Chun Chou, Chun-Chieh Yeh, Chaur-Jong Hu, Yih-Giun Cherng, Ta-Liang Chen, and Chien-Chang Liao. Validation was performed by Chuen-Chau Chang, Mao-Feng Sun, Yi-Chun Chou, Chun-Chieh Yeh, Chaur-Jong Hu, Yih-Giun Cherng, Ta-Liang Chen, and Chien-Chang Liao. Visualization was carried out by Chuen-Chau Chang, Mao-Feng Sun, Yi-Chun Chou, Chun-Chieh Yeh, Chaur-Jong Hu, Yih-Giun Cherng, Ta-Liang Chen, and Chien-Chang Liao. Chuen-Chau Chang and Chien-Chang Liao wrote the original draft. Review and editing was done by Mao-Feng Sun, Yi-Chun Chou, Chun-Chieh Yeh, Chaur-Jong Hu, Yih-Giun Cherng, Ta-Liang Chen, and Chien-Chang Liao.

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Supplementary Materials

Supplementary Description Table 1 Characteristics of patients with use of RYR prescription and lovastatin before matching by propensity score. (Supplementary Materials)

References

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