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# Does depression increase the risk of stroke in patients with rheumatoid arthritis? A population-based cohort study

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## ABSTRACT

**Objectives:** Comorbid depression is common and undertreated in patients with rheumatoid arthritis (RA). It remains uncertain whether comorbid depression provoked the risk of poor clinical outcome, stroke in particular, among RA patients. This work aimed to determine if depression onset during the treatment process increases stroke risk for patients with RA as compared to those with (a) neither RA nor depression, (b) RA only, and (c) depression only.

**Design:** A nationwide, population-based cohort study.

**Setting:** Taiwan's Longitudinal Health Insurance Database.

**Participants:** We identified 8,045 subjects with a newly diagnosed RA between 1997 and 2010, together with 32,600 subjects without RA matched by age, gender and index date. All subjects were further divided into four groups based on whether they were diagnosed with comorbid depression during the follow-up period.

**Main outcome measure:** The incidence rate and hazard ratio for incident stroke were estimated by the end of 2012 using Cox proportional-hazard regression.

**Results:** We discovered that RA patients with the comorbid depression exhibited the highest risk of stroke, with an adjusted hazard ratios (HRs) of 2.18 (95% confidence interval = 1.87-2.54). Those with RA only or those with depression only still had the higher risk of stroke by 43% and 57% as compared with subjects without either condition. Multivariate analysis showed RA subjects who were male or older, incurred the onset of depression, or had comorbidities such as hypertension, diabetes as well as heart disease had a greater risk of stroke.

**Conclusions:** This study cleared up the significant association between RA and the subsequent risk of stroke, and further highlighted that the onset of depression within the treatment process may increase stroke risk for RA subjects. Findings could assist healthcare providers to pinpoint RA individuals with a higher predisposition of stroke, which could

facilitate the provision of appropriate rehabilitation.

**Keywords**：rheumatoid arthritis, depression, stroke, cohort study

**Strengths and limitations of this study**

- The main outcome measures employed in this work are validated due to the application of population-based cohort study, based on a nationwide claim database, thus decreasing recall and selection bias.
- This is the first report to clarify the effect of comorbid depression on the stroke risk among RA subjects, which was beneficial for healthcare providers in guiding more effective treatment strategies to improve the clinical outcomes for them.
- Misclassification of diseases may occur when using an administrative database.

## INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease manifested as long-term joint damage, chronic debilitating pain, and premature mortality. This disease often affects people 30 to 50 years of age and results in disability and inability to work, thus posing a heavy burden on patients with RA, their families and the healthcare system.[1] A review of the financial burdens of RA in the United States showed that the annual direct medical costs of RA reached about $9 billion, and the total societal costs (the sum of direct and indirect costs) was estimated to exceed $39 billion.[2]

Despite improvements in the diagnosis and treatment of RA, patients with RA still have a lower life expectancy (6-7 years) when compared with the general population.[3] This increased mortality is due primarily to cardiovascular diseases such as myocardial infarction (MI) or stroke.[4-6] Nevertheless, unlike the studies of RA predicting the onset of MI,[4 7 8] evidence for an association between RA and the development of stroke remains conflicting. A meta-analysis of 15 articles indicated that individuals with RA had a 63% higher risk for MI, but not for stroke [odds ratio (OR)= 1.14, 95% confidence interval(CI) = 0.86-1.51] when compared to the general population.[4] On the other hand, a recent Danish study involving 18,247 patients with RA, who were followed for a median of 4.8 years, indicated that those with RA had a 30% higher risk of stroke than a non-RA group.[9] Another meta-analysis of 17 studies reported that patients with RA had a higher predisposition to develop stroke than did non-RA subjects, with a pool risk of 1.91.[8]

One cause for concern is that the former studies did not consider the effect of accompanying psychological factors on the risk of stroke; depression, in particular, which is often underdiagnosed and undertreated.[10] Depression, a well-documented comorbidity among people with chronic diseases, including arthritis, may exacerbate functional disabilities, affect adherence to treatment, and be a barrier to self-care and self-management behaviors.[11] A

recent meta-analysis estimated that the prevalence of depression among patients with RA ranges from 14.8 to 38.8%,[12] and findings from our previous study indicated that RA patients were nearly twice as likely to experience depression as the general population.[13] Indeed, once patients with RA suffered from concomitant depression, they had a 7.2% increase in medical costs ($12,225 vs. $11,404),[14] and their likelihood of mortality more than doubled.[11] Therefore, information as to whether symptoms of depression increase the risk of stroke in patients with RA would be of utmost importance in laying the groundwork for the implementation of more effective therapeutic interventions to achieve more favorable prognoses, thus serving to extend the life expectancy of patients with RA.

Given the alarming rate of depression in patients with RA, and the link between depression and increased cardiovascular events, it becomes imperative to investigate if comorbid depression is related to poor clinical outcomes, stroke in particular, among RA patients. However, to date, no clinical observations or empirical data have documented this concern, and evidence from prospective studies is still lacking. The aim of this cohort study, therefore, was to determine if RA patients with the comorbid depression were at an increased risk for stroke as compared to those with (a) neither RA nor depression, (b) RA only, and (c) depression only, using claims data from the National Health Insurance (NHI) of Taiwan.

## METHODS

### Data sources

The data analyzed in this cohort study were retrieved from the Longitudinal Health Insurance Database (LHID), maintained by the Bureau of NHI (BNHI) and provided to scientists in Taiwan for research purposes. Taiwan launched a single-payer NHI Program in 1995 in order to remove financial barriers to medical care for all legal residents. At the end of 2010, more than 99% of Taiwan's population had enrolled in this program.[15] The LHID is a subset of the

NHI database, and contains comprehensive utilization and enrollment information for one million randomly selected NHI beneficiaries, representing 5% of all enrollees in Taiwan in 2000. Because a multistage stratified systematic sampling method was used for this study, there were no statistically significant differences regarding gender or age between the sampled group and the total number of enrollees.[15] This study complied with the guidelines of the Declaration of Helsinki and was approved by the local institutional review board and ethics committee of Buddhist Dalin Tzu Chi Hospital, Taiwan (No. B10004021-1). As the LHID data files contained only de-identified secondary data, the need for informed consent from individual patient consent was waived by the institutional review board.

**Study subjects**

Diagnoses in the insurance claims data were coded according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM). The LHID records were used to identify patients with RA in the age bracket 20-to-90 years of age, and newly diagnosed patients between 1997 and 2010. Those who were diagnosed with an ICD-9-CM code of 714.0 comprised the RA cohort. To improve the diagnostic accuracy, we selected only those who had at least three outpatient visits for RA treatment or those patients who were admitted to the hospital with a primary diagnosis of RA during the study period.[13] The year when a patient was newly diagnosed with RA was defined as the index year.

For each case of RA, we randomly selected, from the remaining insured population without RA, four control subjects who were frequency matched to the RA case in terms of gender, age and index year. After the exclusion of subjects with a diagnosis of depression (ICD-9-CM 296.2, 296.3, 300.4 or 311) or stroke (ICD-9-CM 430-438) before the index date, a total of 8045 RA patients and 32600 non-RA subjects were included in the data analysis. Occurrence of stroke or depression was defined based on the subject who had at least 3

outpatient service claims, or at least 1 inpatient hospitalization claim since 1996, when the computerized claims from the LHID were available, until the date of cohort entry. Thereafter, all subjects were followed up until the end of 2012 to measure the incidence of stroke. Only verified strokes that occurred one year following the first diagnosis of RA were included in order to render the temporal link between RA and stroke more plausible. We further stratified the RA cohort into two groups based on whether they were diagnosed with comorbid depression between the index date and the follow-up period. In accordance with the same rationale, the non-RA cohort was divided into two groups based on the existence (or no existence) of depression. Follow-up person-years (PYs) were calculated as the time interval from the entry date to the earliest occurrence of one of the following: a diagnosis of stroke, the date of withdrawal from insurance, or December 31, 2012, whichever came first.

**Demographic characteristics and comorbid conditions**

Demographic characteristics analyzed in this study included age, gender, monthly income, and level of urbanization of the subject's employment or residential area. Monthly income was grouped into 3 levels: ≤ 17,880 New Taiwan Dollars (NTD)$, 17,881-43,900 NTD$, and ≥ 43,901NTD$. All 316 cities and townships in Taiwan were classified into 7 ordered levels of urbanization based on various indicators including population density, proportion of residents with college or higher education, percentage of elderly (> 65 years of age) people, proportion of the workforce in agriculture, and number of physicians per $10^5$ people.[16] Level 1 refers to the “most urbanized” and level 7 refers to the “least urbanized” areas. The level of urbanization was further divided into 3 strata: urban (levels 1-2), suburban (levels 3-4), and rural (levels 5-7) areas. Baseline comorbid conditions for each subject included hypertension (ICD-9-CM 401-405), diabetes (ICD-9-CM 250), heart disease (ICD-9-CM 410-429), chronic kidney disease (ICD-9-CM 585), tobacco use (ICD-9-CM 305.1), alcohol

dependence syndrome (ICD-9-CM 303), and cancer (ICD-9-CM 140-208). The frequency of ambulatory care visits within the study period for each subject was considered to correct for surveillance bias.

**Statistical analysis**

Intergroup differences were evaluated using the independent-sample t-test or nonparametric Kolmogorov-Smirnov test for continuous variables, and the $\chi^2$ test or Fisher exact test for categorical variables. The incidence rate of stroke in the four groups is presented as the number of cases per 1,000 PYs. To assess the risk of developing stroke across the four groups, Cox proportional hazards regression model was applied to compute the crude and adjusted hazard ratios (HRs) and the 95% confidence intervals (CI) for stroke among them. A multivariate Cox proportional hazards regression model was then used to identify risk factors that might be related to the incident of stroke and their adjusted HRs within RA cohorts. All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA), and $p < 0.05$ was considered statistically significant.

**RESULTS**

Table 1 shows the distribution of demographic data and comorbid medical disorders for the RA and non-RA cohorts. The RA cohorts were more likely to have a lower monthly income ($p = 0.001$), reside in a rural area ($p < 0.001$), have more visits seeking medical care ($p < 0.001$), and suffer comorbid conditions including hypertension, diabetes, heart disease, chronic kidney disease or alcohol dependence syndrome (all $p < 0.01$).

Of the total sample of 40,645 patients, 4550 had an incident stroke during the follow-up period. The crude and adjusted HRs for stroke in patients with depression only, RA only, and both, as a group, are shown in Table 2. Overall, after adjustment for potential confounders,

relative to those with neither RA nor depression, subjects with RA and depression exhibited the highest risk of developing a stroke, with an adjusted HRs of 2.18 (95% CI = 1.87-2.54), followed by those with depression (adjusted HRs = 1.57, 95% CI = 1.41-1.75), and those with RA only (adjusted HRs = 1.43, 95% CI = 1.12-1.55).

Table 3 presents Cox regression model of factors related to the onset of stroke among individuals with RA. Compared to those without depression, those with depression were significantly more likely to develop a stroke (adjusted HRs = 1.63, 95% CI = 1.37-1.92) after adjustment for confounding factors. Results also showed that age was related to the risk of stroke. There was a 5% increase in the risk of stroke for each 1-year increment (95% CI = 1.03-1.08). Compared with females, males had an adjusted HRs of 1.17 for stroke (95% CI = 1.03-1.28). Additionally, some comorbid conditions including hypertension, heart disease and diabetes increased the risk of stoke with adjusted HRs of 1.51 (95% CI = 1.40-1.84), 1.48 (95% CI = 1.31-1.73) and 1.34 (95% CI = 1.16-1.56), respectively.

## DISCUSSION

Previous studies of the association between RA and the risk of stroke using hospital/community-based populations yielded mixed findings.[4 8 9 17] It is noteworthy that these studies essentially ignored the effect of accompanying depressive symptoms, a common psychological problem among RA patients, on the relationship between the two diseases. To the best of our knowledge, this was the first population-based, nationwide study which attempted to determine if depression modified the association between RA and stroke, and could therefore help to facilitate the provision of more appropriate interventions to successfully manage rheumatological disorders and prevent the subsequent risk of cardiovascular diseases.

This 15-year follow-up study found that individuals with RA had a 43% greater-adjusted risk of stroke when compared with the general population. These findings are in agreement

with the results of prior studies conducted in Western populations.[8 9] It has been argued that rheumatological disorders are an overlapping group of conditions that are characterized by chronic inflammation involving connective tissues and organs.[1 6 18] Once inflammation occurs in the body, the vascular endothelial cells secrete proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) or interleukin (IL)-6, which activate and attract massive numbers of white blood cells to the damaged region within the lumen of the vessel. Following infiltration into the tunica media, white blood cells absorb oxidized LDL-C and become foam cells, consequently accelerating the risk of thromboembolism.[19] In addition, a growing body of evidence has shown that inflammatory cytokines stimulate the production of matrix metalloproteinases (MMPs) as well, and this may cause further injury to the blood-brain barrier, thereby provoking a greater susceptibility to stroke.[20 21]

A noteworthy feature of the current study herein was that once patients with RA were diagnosed with comorbid depression during the treatment process, they exhibited more than double the likelihood of stroke than the general population. We speculate that there are several potential reasons as to why depression exacerbate the risk of stroke in these patients. First, the presence of symptoms of depression is likely linked to treatment nonadherence and an increase in unhealthy lifestyles, such as poor nutrition and physical inactivity, and these may contribute to the development of a stroke.[22] Second, symptoms of depression can cause systematic inflammation that worsens the manifestations of RA. Recent studies have demonstrated that depressed individuals with RA had higher circulating levels of inflammatory markers such as IL-6, TNF-α and C-reactive protein (CRP)[10]; all of which play important roles in the pathogenesis of cardiovascular events.[19] It is also noteworthy that only one in five patients with depression is estimated to have been treated and referred to appropriate psychiatric services after the onset of RA.[23] The implementation of a standardized psychosocial assessment, and of patient care procedures, as part of routine care

may therefore help in the early referral of high-risk patients for further therapeutic interventions.

This study also indicated that males were at a 1.17-fold greater risk of stroke than females in the RA cohorts. No previous study has examined gender differences in the risk of stroke among patients with RA, which renders a comparison of results impossible. Nevertheless, this is consistent with the observation that males have a higher risk of stroke than females among the general population.[24] There are several possible explanations for this result. First, women appear to have greater health consciousness with regard to stroke prevention than men, and immediately seek medical therapy at the slightest irregularity in well-being, so the onset of chronic diseases may be expected to be lower in women than in men.[25] Second, lifetime exposure to ovarian estrogens may protect against the risk of stroke for females. Extensive animal experiments and human studies have supported the function of estrogens as neuroprotectants against neurodegenerative diseases, particularly stroke, through enhancing basal release of Nitric Oxide (NO) to curb coronary thrombosis and atherosclerosis.[24 26] Recently, estrogenic agents have been suggested as a novel therapeutic approach to treat the neuronal damages associated with global ischemia.[24 27]

Consistent with the findings of prior studies conducted in the general population,[18 24] age was positively correlated with the risk of stroke among patients with RA. We speculate that with aging, blood vessels gradually lose elasticity and gain resistance, slowing the flow of blood. Moreover, with poor circulation, fat is prone to accumulate in the abdomen and release free fatty acids into the serum, leading to higher insulin resistance, elevated serum triglycerides, and increased levels of LDL-C,[28] thereby resulting in the greater risk of stroke.

Findings of this study indicate that patients with RA and several comorbid conditions such as hypertension, diabetes or heart disease had a significantly greater risk for stroke. Those with chronic kidney disease and cancer showed a tendency for stroke, but the association

failed to reach statistical significance. Despite the lack of comparative studies on the effects of comorbid conditions on stroke among patients with RA, our findings are consistent with past arguments made in the literature.[6] The elevated risk of stroke may be attributed to several causes. For example, insulin resistance and hypertension are common cardiovascular risk factors among individuals with RA.[29] Moreover, the functional impairment induced by comorbid conditions may lead to limited physical activity which could, very likely, trigger additional risk of stroke. Finally, the immunosuppresive therapies used for patients with RA have been found to have deleterious effects. Some review articles indicated that the use of corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) may be related to the risk of cardiovascular events.[6 19] Before prescribing these drugs, rheumatologists should carefully appraise the inherent cerebrovascular or cardiovascular risk among patients with RA.

Several limitations of this study should be considered when interpreting these results. First, we could not account for some potential confounding factors such as social networks, coping modes, or educational level because these data were unavailable in the LHID. Future research controlling for those untested variables is needed to better determine if the present findings are replica across diverse groups of individuals. Second, the identification of exposure and outcome were based on the ICD-9-CM, and misclassification is inevitable. However, as the approach to coding and the availability of data were similar regardless of case/control status, we believe this bias is rather inconsequential. Additionally, we selected only those cases with RA, depression or stroke after they were recorded as having either at least three outpatient visits reporting consistent diagnoses, or one inpatient admission. Therefore, the approach adopted is likely to minimize this error. It should also be noted that the NHI of Taiwan randomly samples claims from hospitals, interviews patients, and reviews medical charts to verify the accuracy of medical records. Third, since data regarding the severity of RA were unavailable in this database, failure to adjust for the level of disability might lead to bias in

subject selection. Nonetheless, the multivariate analysis applied in this study considered the impact of several comorbid conditions including hypertension, diabetes, heart disease, chronic kidney disease, tobacco use, alcohol dependence syndrome and cancer. Furthermore, we performed a sensitivity analysis focusing on those RA subjects without comorbid conditions to test the robustness of our findings. This showed that depressed RA subjects with no known comorbid condition still had a higher risk of stroke when compared to those without RA and depression, with adjusted HRs of 1.65 (95% CI = 1.23-2.03). Fourth, evidence derived from any observational cohort study is generally less robust than that obtained from randomized control trials since cohort studies are subject to various biases related to confounding effects. Despite our careful efforts to maintain adequate control of confounding factors, unpredictable biases could still remain if they stem from unmeasured or unknown confounders. Notwithstanding these limitations, the strengths of this study must also be acknowledged and these include the immediate availability of data, the comprehensiveness of the database, and the statistical power derived from the samples' large sizes. In addition, this retrospective 15-year cohort study allowed us to clearly determine if the symptoms of depression exacerbated the risk of stroke for those with RA, and the corresponding findings could serve as a reference for future treatment strategies.

In conclusion, this study demonstrated that patients with RA and comorbid depression were more than twice as likely to have a stroke than were those of the healthy controls. We further found that the factors contributing to the high risk of stroke included being male, older, as well as having depression and a comorbid condition such as hypertension, diabetes or heart disease. Healthcare providers may, therefore, be able to better recognize those demographic and diseases characteristics that contribute to the risk of stroke among patients with RA from this population-based study. The need to routinely screen RA patients for depression and institute culturally appropriate interventions should be emphasized. Healthcare providers

would benefit from being cognizant of the possible occurrence of depression among patients with RA, discuss this often underreported issue with them, and strive to achieve better clinical outcomes.

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**Contributors** All the authors approved the contents of the submitted article. Conceived and designed the experiments: TTY CSY. Analyzed the data: TTY GHR. Contributed reagents/materials/analysis tools: TTY LNS LMC GHR. Wrote the paper: TTY LH GHR. Final approval of manuscript: TTY LNS LH CSY LMC GHR.

**Competing interests** The authors declare no competing financial interests.

**Ethics approval** This study was approved by the Research Ethics Committee of Dalin Tzuchi Hospital (No. No. B10004021-1).

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**Table 1 Demographic data and comorbidity comparison of the study subjects.**

| Variables | Non-RA cohort N = 32600 (%) | RA cohort N = 8045(%) | p |
|---|---|---|---|
| Age (years) | | | 0.85 |
| <=40 | 5378(16.5) | 1331(16.5) | |
| 41-60 | 15569(47.8) | 3814(47.4) | |
| $60^{+}$ | 11653(35.7) | 2900(36.0) | |
| Mean ± Standard Deviation (SD) | 55.00±14.63 | 55.01±14.65 | 0.94 |
| Gender | | | 0.95 |
| Female | 22461(68.9) | 5540(68.9) | |
| Male | 10139(31.1) | 2505(31.1) | |
| Monthly income | | | <0.001 |
| Low | 15218(46.7) | 3513(43.7) | |
| Median | 15985(49.0) | 4213(52.4) | |
| High | 1397(4.3) | 319(4.0) | |
| Level of urbanization | | | <0.001 |
| Urban | 18839(57.8) | 4485(55.7) | |
| Suburban | 5311(16.3) | 1258(15.6) | |
| Rural | 8450(25.9) | 2302(28.6) | |
| Comorbidity | | | |
| Hypertension | 5965(21.2) | 2216(27.6) | <0.001 |
| Diabetes | 2717(9.6) | 1046(13.0) | <0.001 |
| Heart disease | 3054(10.8) | 1273(15.8) | <0.001 |
| Chronic kidney disease | 264(0.9) | 123(1.5) | <0.001 |
| Cancer | 959(3.4) | 268(3.3) | 0.75 |
| Alcohol dependence syndrome | 30(0.1) | 18(0.2) | 0.002 |
| Tobacco use | 36(0.1) | 10(0.1) | 0.74 |
| Visits seeking medical care | | | |
| Mean ± SD (median, $25^{th}$-$75^{th}$ percentile) | 234.55 ± 194.08 (185, 97-319) | 159.90 ±155.87 (114, 52-219) | <0.001 |

**Table 2 Crude and adjusted HRs of stroke for those with RA and comorbid depression,**

**those with RA only, those with depression only as compared to those with neither RA nor depression.**

| Patient group | Event | PY | Incidence | Crude HRs (95% CI) | Adjusted HRs * (95% CI) |
|---|---|---|---|---|---|
| **Non-RA cohort** | | | | | |
| Neither RA nor depression | 3063 | 245086.81 | 12.50 | 1.00 | 1.00 |
| Depression only | 377 | 24540.32 | 15.36 | 1.23 (1.11-1.37) | 1.57 (1.41-1.75) |
| **RA cohort** | | | | | |
| RA only | 929 | 55223.83 | 16.82 | 1.35 (1.25-1.45) | 1.43 (1.12-1.55) |
| RA and depression | 181 | 9901.31 | 18.28 | 1.48 (1.26-1.71) | 2.18 (1.87-2.54) |

per 1,000 person-years for incidence rate.

*Adjusted for age, gender, level of urbanization, income, visits seeking medical care, and comorbidity

**Table 3 Multivariate analysis of factors for the incidence of stroke among patients with RA.**

| Variables | Cox regression model (n=8045) | |
|---|---|---|
| | Adjusted HRs* | 95% CI |
| Depression | | |
| No | 1 | |
| Yes | 1.63 | 1.37-1.92 |
| Age | 1.05 | 1.03-1.08 |
| Gender | | |
| Female | 1 | |
| Male | 1.17 | 1.03-1.28 |
| Monthly income | | |
| Low | 1 | |
| Median | 0.97 | 0.85-1.10 |
| High | 0.85 | 0.58-1.26 |
| Level of urbanization | | |
| Urban | 1 | |
| Suburban | 1.10 | 0.92-1.30 |
| Rural | 1.06 | 0.92-1.22 |
| Comorbidity | | |
| Hypertension | | |
| No | 1 | |
| Yes | 1.51 | 1.40-1.84 |
| Diabetes | | |
| No | 1 | |
| Yes | 1.34 | 1.16-1.56 |
| Heart disease | | |
| No | 1 | |
| Yes | 1.48 | 1.31-1.73 |
| Chronic kidney disease | | |
| No | 1 | |
| Yes | 1.02 | 0.76-1.30 |
| Cancer | | |
| No | 1 | |
| Yes | 1.12 | 0.84-1.47 |
| Visits seeking medical care | 0.99 | 0.98-1.01 |

Adjusted for all variables in the model.

## STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | P1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | P 3-P4 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | P5 - P6 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | P6 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | P 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | P6 - P7 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | P8 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | P7 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | P7-P8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | P8-P9 |
| Bias | 9 | Describe any efforts to address potential sources of bias | P9 |
| Study size | 10 | Explain how the study size was arrived at | P7. |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | P7-P9 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | P9. |
| | | (*b*) Describe any methods used to examine subgroups and interactions | P9 |
| | | (*c*) Explain how missing data were addressed | NA |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | P8 |
| | | (*e*) Describe any sensitivity analyses | P14 |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | P9-P10 |
| | | (b) Give reasons for non-participation at each stage | NA |
| | | (c) Consider use of a flow diagram | NA |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | P9 |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA |
| | | (c) Summarise follow-up time (eg, average and total amount) | P20 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | P9. P20 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | P10, P20 |
| | | (*b*) Report category boundaries when continuous variables were categorized | P20 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | P20 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | P10 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | P13-P14 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | P14-P15 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | P16 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Does depression increase the risk of stroke in patients with rheumatoid arthritis? A population-based cohort study

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| | |

# Does depression increase the risk of stroke in patients with rheumatoid arthritis? A population-based cohort study

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## ABSTRACT

**Objectives:** Comorbid depression is common and undertreated in patients with rheumatoid arthritis (RA). It remains uncertain whether comorbid depression provoked the risk of poor clinical outcome, stroke in particular, among RA patients. This work aimed to determine if depression onset during the treatment process increases stroke risk for patients with RA as compared to those with (a) neither RA nor depression, (b) RA only, and (c) depression only.

**Design:** A nationwide, population-based cohort study.

**Setting:** Taiwan's Longitudinal Health Insurance Database.

**Participants:** We identified 8,045 subjects with a newly diagnosed RA between 1997 and 2010, together with 32,600 subjects without RA matched by age, gender and index date. All subjects were further divided into four groups based on whether they were diagnosed with comorbid depression during the follow-up period.

**Main outcome measure:** The incidence rate and hazard ratio for incident stroke were estimated by the end of 2012 using Cox proportional-hazard regression.

**Results:** We discovered that RA patients with the comorbid depression exhibited the highest risk of stroke, with an adjusted hazard ratios (HRs) of 2.18 (95% confidence interval = 1.87-2.54). Those with RA only or those with depression only still had the higher risk of stroke by 43% and 57% as compared with subjects without either condition. Multivariate analysis showed RA subjects who were male or older, incurred the onset of depression, or had comorbidities such as hypertension, diabetes as well as heart disease had a greater risk of stroke.

**Conclusions:** This study cleared up the significant association between RA and the subsequent risk of stroke, and further highlighted that the onset of depression within the treatment process may increase stroke risk for RA subjects. Findings could assist healthcare providers to pinpoint RA individuals with a higher predisposition of stroke, which could

facilitate the provision of appropriate rehabilitation.

**Keywords**：rheumatoid arthritis, depression, stroke, cohort study

**Strengths and limitations of this study**

- The main outcome measures employed in this work are validated due to the application of population-based cohort study, based on a nationwide claim database, thus decreasing recall and selection bias.
- This is the first report to clarify the effect of comorbid depression on the stroke risk among RA subjects, which was beneficial for healthcare providers in guiding more effective treatment strategies to improve the clinical outcomes for them.
- Misclassification of diseases and failure to adjust for disease severity might lead to somewhat skewed findings

## INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease manifested as long-term joint damage, chronic debilitating pain, and premature mortality. This disease often affects people 30 to 50 years of age and results in disability and inability to work, thus posing a heavy burden on patients with RA, their families and the healthcare system.[1] A review of the financial burdens of RA in the United States showed that the annual direct medical costs of RA reached about $9 billion, and the total societal costs (the sum of direct and indirect costs) was estimated to exceed $39 billion.[2]

Despite improvements in the diagnosis and treatment of RA, patients with RA still have a lower life expectancy (6-7 years) when compared with the general population.[3] This increased mortality is due primarily to cardiovascular diseases such as myocardial infarction (MI) or stroke.[4-6] Nevertheless, unlike the studies of RA predicting the onset of MI,[4 7 8] evidence for an association between RA and the development of stroke remains conflicting. A meta-analysis of 15 articles indicated that individuals with RA had a 63% higher risk for MI, but not for stroke [odds ratio (OR)= 1.14, 95% confidence interval (CI) = 0.86-1.51] when compared to the general population.[4] On the other hand, a recent Danish study involving 18,247 patients with RA, who were followed for a median of 4.8 years, indicated that those with RA had a 30% higher risk of stroke than a non-RA group.[9] Another meta-analysis of 17 studies reported that patients with RA had a higher predisposition to develop stroke than did non-RA subjects, with a pool risk of 1.91.[8]

One cause for concern is that the former studies did not consider the effect of accompanying psychological factors on the risk of stroke; depression, in particular, which is often underdiagnosed and undertreated.[10] Depression, a well-documented comorbidity among people with chronic diseases, specifically arthritis, may exacerbate functional disabilities, affect adherence to treatment, and be a barrier to self-care and self-management behaviors.[11]

A recent meta-analysis estimated that the prevalence of depression among patients with RA ranges from 14.8 to 38.8%,[12] and findings from our previous study indicated that RA patients were nearly twice as likely to experience depression as the general population.[13] Indeed, once patients with RA suffered from concomitant depression, they had a 7.2% increase in medical costs ($12,225 vs. $11,404),[14] and their likelihood of mortality more than doubled.[11] Given the alarming rate of depression and the corresponding physical burden on patients with RA, it is imperative to implement effective therapeutic interventions to achieve more favorable therapeutic outcomes, thus serving to extend the life expectancy of patients with RA. Notably, based on former research, the activation of innate inflammatory mechanisms that accompany depressive mood was assumed to affect the susceptibility to development of cardiovascular diseases in addition to the influence of behavioral factors, [15-18] implying that the causative role of depression should not be neglected as determining the association of RA with stroke.

With this growing evidence on the association between RA and subsequent risk of stroke, and the limited information on whether depression serves as a potential factor that affects the relationship between these two conditions, findings from a long-term population-based nationwide study could be useful in allocating medical resources and in instituting fact-based policymaking. Nevertheless, to date, no clinical observations or empirical data have documented this concern. The aim of this cohort study, therefore, was to determine if RA patients with the comorbid depression were at an increased risk for stroke as compared to those with (a) neither RA nor depression, (b) RA only, and (c) depression only, using claims data from the National Health Insurance (NHI) of Taiwan.

## METHODS

### Data sources

The data analyzed in this cohort study were retrieved from the Longitudinal Health Insurance

Database (LHID), maintained by the Bureau of NHI (BNHI) and provided to scientists in Taiwan for research purposes. Taiwan launched a single-payer NHI Program in 1995 in order to remove financial barriers to medical care for all legal residents. At the end of 2010, more than 99% of Taiwan's population had enrolled in this program.[19] The LHID is a subset of the NHI database, and contains comprehensive utilization and enrollment information for one million randomly selected NHI beneficiaries, representing 5% of all enrollees in Taiwan in 2000. Because a multistage stratified systematic sampling method was used for this study, there were no statistically significant differences regarding gender or age between the sampled group and the total number of enrollees.[19] This study complied with the guidelines of the Declaration of Helsinki and was approved by the local institutional review board and ethics committee of Buddhist Dalin Tzu Chi Hospital, Taiwan (No. B10004021-1). As the LHID data files contained only de-identified secondary data, the need for informed consent from individual patient consent was waived by the institutional review board.

**Study subjects**

Diagnoses in the insurance claims data were coded according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM). The LHID records were used to identify patients with RA in the age bracket 20-to-90 years of age, and newly diagnosed patients between 1997 and 2010. Those who were diagnosed with an ICD-9-CM code of 714.0 comprised the RA cohort. To improve the diagnostic accuracy, we selected only those who had at least three outpatient visits for RA treatment or those patients who were admitted to the hospital with a primary diagnosis of RA during the study period.[13] The year when a patient was newly diagnosed with RA was defined as the index year.

For each case of RA, we randomly selected, from the remaining insured population without RA, four control subjects who were frequency matched to the RA case in terms of

gender, age and index year. After the exclusion of subjects with a diagnosis of depression (ICD-9-CM 296.2, 296.3, 300.4 or 311) or stroke (ICD-9-CM 430-438) before the index date, a total of 8045 RA patients and 32600 non-RA subjects were included in the data analysis. Occurrence of stroke or depression was defined based on a criterion that indicated at least 3 outpatient service claims, or at least 1 inpatient hospitalization claim, since 1996, when the computerized claims from the LHID became available, until the date of cohort entry. Thereafter, all subjects were followed up until the end of 2012 to measure the incidence of stroke. Only verified strokes that occurred one year following the first diagnosis of RA were included in order to render the temporal link between RA and stroke more plausible. We further stratified the RA cohort into two groups based on whether they were diagnosed with comorbid depression between the index date and the follow-up period. In accordance with the same rationale, the non-RA cohort was divided into two groups based on the existence (or no existence) of depression. Follow-up person-years (PYs) were calculated as the time interval from the entry date to the earliest occurrence of one of the following: a diagnosis of stroke, the date of withdrawal from insurance, or December 31, 2012, whichever came first.

**Demographic characteristics and comorbid conditions**

Demographic characteristics analyzed in this study included age, gender, monthly income, and level of urbanization of the subject's employment or residential area. Monthly income was grouped into 3 levels: ≤ 17,880 New Taiwan Dollars (NTD)$, 17,881-43,900 NTD$, and ≥ 43,901NTD$. All 316 cities and townships in Taiwan were classified into 7 ordered levels of urbanization based on various indicators including population density, proportion of residents with college or higher education, percentage of elderly (> 65 years of age) people, proportion of the workforce in agriculture, and number of physicians per $10^5$ people.[20] Level 1 refers to the “most urbanized” and level 7 refers to the “least urbanized” areas. The level of

urbanization was further divided into 3 strata: urban (levels 1-2), suburban (levels 3-4), and rural (levels 5-7) areas. Baseline comorbid conditions for each subject included hypertension (ICD-9-CM 401-405), diabetes (ICD-9-CM 250), heart disease (ICD-9-CM 410-429), chronic kidney disease (ICD-9-CM 585), tobacco use (ICD-9-CM 305.1), alcohol dependence syndrome (ICD-9-CM 303), and cancer (ICD-9-CM 140-208). The frequency of ambulatory care visits within the study period for each subject was considered to correct for surveillance bias.

**Statistical analysis**

Intergroup differences were evaluated using the independent-sample t-test or nonparametric Kolmogorov-Smirnov test for continuous variables, and the $\chi^2$ test or Fisher exact test for categorical variables. The incidence rate of stroke in the four groups is presented as the number of cases per 1,000 PYs. To assess the risk of developing stroke across the four groups, Cox proportional hazards regression model was applied to compute the crude and adjusted hazard ratios (HRs) and the 95% confidence intervals (CI) for stroke among them. We also performed a sensitivity analysis to test the robustness of the findings using asthma, a disease not related to stroke, to replace depression. Finally, a multivariate Cox proportional hazards regression model was then used to identify risk factors that might be related to the incident of stroke and their adjusted HRs within RA cohorts. All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA), and $p < 0.05$ was considered statistically significant.

**RESULTS**

Table 1 shows the distribution of demographic data and comorbid medical disorders for the RA and non-RA cohorts. The RA cohorts were more likely to have a lower monthly income

(p = 0.001), reside in a rural area (p < 0.001), have more visits seeking medical care (p < 0.001), and suffer comorbid conditions including hypertension, diabetes, heart disease, chronic kidney disease or alcohol dependence syndrome (all p < 0.01).

Of the total sample of 40,645 patients, 4550 had an incident stroke during the follow-up period. The crude and adjusted HRs for stroke in patients with depression only, RA only, and both, as a group, are shown in Table 2. Overall, after adjustment for potential confounders, relative to those with neither RA nor depression, subjects with RA and depression exhibited the highest risk of developing a stroke, with an adjusted HRs of 2.18 (95% CI = 1.87-2.54), followed by those with depression (adjusted HRs = 1.57, 95% CI = 1.41-1.75), and those with RA only (adjusted HRs = 1.43, 95% CI = 1.12-1.55).

Table 3 presents Cox regression model of factors related to the onset of stroke among individuals with RA. Compared to those without depression, those with depression were significantly more likely to develop a stroke (adjusted HRs = 1.63, 95% CI = 1.37-1.92) after adjustment for confounding factors. Results also showed that age was related to the risk of stroke. There was a 5% increase in the risk of stroke for each 1-year increment (95% CI = 1.03-1.08). Compared with females, males had an adjusted HRs of 1.17 for stroke (95% CI = 1.03-1.28). Additionally, some comorbid conditions including hypertension, heart disease and diabetes increased the risk of stoke with adjusted HRs of 1.51 (95% CI = 1.40-1.84), 1.48 (95% CI = 1.31-1.73) and 1.34 (95% CI = 1.16-1.56), respectively.

In the sensitivity analysis, we compared the risks of stroke across three groups: reference, RA only, and RA with asthma. We found that the RA with asthma group had an adjusted HR of 1.18 with a 95% CI of 0.89-1.34, which is not statistically significant. This indicates the validity of our methodology.

## DISCUSSION

Previous studies of the association between RA and the risk of stroke using

hospital/community-based populations yielded mixed findings.[4 8 9 21] It is noteworthy that these studies essentially ignored the effect of accompanying depressive symptoms, a common psychological problem among RA patients, on the relationship between the two diseases. To the best of our knowledge, this was the first population-based, nationwide study which attempted to determine if depression modified the association between RA and stroke, and could therefore help to facilitate the provision of more appropriate interventions to successfully manage rheumatological disorders and prevent the subsequent risk of cardiovascular diseases.

This 15-year follow-up study found that individuals with RA had a 43% greater-adjusted risk of stroke when compared with the general population. These findings are in agreement with the results of prior studies conducted in Western populations.[8 9] It has been argued that rheumatologic disorders are an overlapping group of conditions that are characterized by chronic inflammation involving connective tissues and organs.[1 6 16] Once inflammation occurs in the body, the vascular endothelial cells secrete proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) or interleukin (IL)-6, which activate and attract massive numbers of white blood cells to the damaged region within the lumen of the vessel. Following infiltration into the tunica media, white blood cells absorb oxidized LDL-C and become foam cells, consequently accelerating the risk of thromboembolism.[18] In addition, a growing body of evidence has shown that inflammatory cytokines stimulate the production of matrix metalloproteinases (MMPs) as well, and this may cause further injury to the blood-brain barrier, thereby provoking a greater susceptibility to stroke.[22 23]

A noteworthy feature of the current study herein was that once patients with RA were diagnosed with comorbid depression during the treatment process, they exhibited more than double the likelihood of stroke than the general population. We speculate that there are several potential reasons as to why depression exacerbate the risk of stroke in these patients.

First, the presence of symptoms of depression is likely linked to treatment nonadherence and an increase in unhealthy lifestyles, such as poor nutrition and physical inactivity, and these may contribute to the development of a stroke.[15] Second, symptoms of depression can cause systematic inflammation that worsens the manifestations of RA. Recent studies demonstrated that depressed individuals with RA had higher circulating levels of inflammatory markers such as IL-6, TNF-α and C-reactive protein (CRP)[10]; all of which play key roles in the pathogenesis of stroke.[18] Additionally, recent research have focused on another signaling pathway, namely, gut-to-brain communication, which suggested that intestinal dysfunction induced by negative moods may cause the activation of immune cells and the production of cytokines in the gut as well, thereby inducing the expression of inflammatory markers, which in turn induce initiation and progression of neurological disorders.[24 25] It is also noteworthy that only one in five patients with depression is estimated to have been treated and referred to appropriate psychiatric services after the onset of RA.[26] The implementation of a standardized psychosocial assessment, and of patient care procedures, as part of routine care may therefore help in the early referral of high-risk patients for further therapeutic interventions.

This study also indicated that males were at a 1.17-fold greater risk of stroke than females in the RA cohorts. No previous study has examined gender differences in the risk of stroke among patients with RA, which renders a comparison of results impossible. Nevertheless, this is consistent with the observation that males have a higher risk of stroke than females among the general population.[27] There are several possible explanations for this result. First, women appear to have greater health consciousness with regard to stroke prevention than men, and immediately seek medical therapy at the slightest irregularity in well-being, so the onset of chronic diseases may be expected to be lower in women than in men.[28] Second, lifetime exposure to ovarian estrogens may protect against the risk of stroke for females.

Extensive animal experiments and human studies have supported the function of estrogens as neuroprotectants against neurodegenerative diseases, particularly stroke, through enhancing basal release of Nitric Oxide (NO) to curb coronary thrombosis and atherosclerosis.[27 29] Recently, estrogenic agents have been suggested as a novel therapeutic approach to treat the neuronal damages associated with global ischemia.[27 30]

Consistent with the findings of prior studies conducted in the general population,[16 27] age was positively correlated with the risk of stroke among patients with RA. We speculate that with aging, blood vessels gradually lose elasticity and gain resistance, slowing the flow of blood. Moreover, with poor circulation, fat is prone to accumulate in the abdomen and release free fatty acids into the serum, leading to higher insulin resistance, elevated serum triglycerides, and increased levels of LDL-C,[31] thereby resulting in the greater risk of stroke.

Findings of this study indicate that patients with RA and several comorbid conditions such as hypertension, diabetes or heart disease had a significantly greater risk for stroke. Those with chronic kidney disease and cancer showed a tendency for stroke, but the association failed to reach statistical significance. Despite the lack of comparative studies on the effects of comorbid conditions on stroke among patients with RA, our findings are consistent with past arguments made in the literature.[6] The elevated risk of stroke may be attributed to several causes. For example, insulin resistance and hypertension are common cardiovascular risk factors among individuals with RA.[32] Moreover, the functional impairment induced by comorbid conditions may lead to limited physical activity which could, very likely, trigger additional risk of stroke. Finally, the immunosuppressive therapies used for patients with RA have been found to have deleterious effects. Some review articles indicated that the use of corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) may be related to the risk of cardiovascular events.[6 18] Before prescribing these drugs, rheumatologists should carefully appraise the inherent cerebrovascular or cardiovascular risk among patients with RA.

Several limitations of this study should be considered when interpreting these results. First, we could not account for some potential confounding factors such as social networks, coping modes, or educational level because these data were unavailable in the LHID. Future research controlling for those untested variables is needed to better determine if the present findings are replicated across diverse groups of individuals. Second, the identification of exposure and outcome were based on the ICD-9-CM, and misclassification is inevitable. However, we selected only those cases with RA, depression, or stroke after they were recorded as having either at least three outpatient visits reporting consistent diagnoses, or one inpatient admission. This approach is likely to minimize such errors. Furthermore, as the approach to coding and the availability of data were similar regardless of the RA and depression status, we believe the misclassification was likely to be random and thus, if indeed occurring, would tend to draw the estimated HRs to the direction of the null values. Second, it should also be noted that the NHI of Taiwan randomly samples claims from hospitals, interviews patients, and reviews medical charts to verify the accuracy of medical records. Third, because data regarding the severity of RA were unavailable in this databases. Nonetheless, the multivariate analysis applied in this study considered the impact of several comorbid conditions including hypertension, diabetes, heart disease, chronic kidney disease, tobacco use, alcohol dependence syndrome and cancer. Furthermore, we performed a sensitivity analysis using on those RA subjects without comorbid conditions to test the robustness of our findings and found that depressed RA subjects with no known comorbid condition still had a higher risk of stroke when compared to those without RA and depression, with an adjusted HR of 1.65 (95% CI = 1.23-2.03). Thus, the impact of disease severity is unlikely to compromise findings of this study. Fourth, evidence derived from any observational cohort study is generally less robust than that obtained from randomized control trials since cohort studies are subject to various biases related to confounding effects. Despite our careful efforts to

maintain adequate control of confounding factors, unpredictable biases could still remain if they stem from unmeasured or unknown confounders. Notwithstanding these limitations, the strengths of this study must also be acknowledged and these include the immediate availability of data, the comprehensiveness of the database, and the statistical power derived from the samples' large sizes. In addition, this retrospective 15-year cohort study allowed us to clearly determine if the symptoms of depression exacerbated the risk of stroke for those with RA, and the corresponding findings could serve as a reference for future treatment strategies.

In conclusion, this study demonstrated that patients with RA and comorbid depression were more than twice as likely to have a stroke than were those of the healthy controls. We further found that the factors contributing to the high risk of stroke included being male, older, as well as having depression and a comorbid condition such as hypertension, diabetes or heart disease. Healthcare providers may, therefore, be able to better recognize those demographic and diseases characteristics that contribute to the risk of stroke among patients with RA from this population-based study. Findings also supported that the routine screening of depression and the institution of patient-centered interventions may represent an important strategy for improving clinical outcomes for RA patients.

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**Table 1 Demographic data and comorbidity comparison of the study subjects.**

| Variables | Non-RA cohort N = 32600 (%) | RA cohort N = 8045(%) | p |
|---|---|---|---|
| Age (years) | | | 0.85 |
| <=40 | 5378(16.5) | 1331(16.5) | |
| 41-60 | 15569(47.8) | 3814(47.4) | |
| $60^{+}$ | 11653(35.7) | 2900(36.0) | |
| Mean ± Standard Deviation (SD) | 55.00±14.63 | 55.01±14.65 | 0.94 |
| Gender | | | 0.95 |
| Female | 22461(68.9) | 5540(68.9) | |
| Male | 10139(31.1) | 2505(31.1) | |
| Monthly income | | | <0.001 |
| Low | 15218(46.7) | 3513(43.7) | |
| Median | 15985(49.0) | 4213(52.4) | |
| High | 1397(4.3) | 319(4.0) | |
| Level of urbanization | | | <0.001 |
| Urban | 18839(57.8) | 4485(55.7) | |
| Suburban | 5311(16.3) | 1258(15.6) | |
| Rural | 8450(25.9) | 2302(28.6) | |
| Comorbidity | | | |
| Hypertension | 5965(21.2) | 2216(27.6) | <0.001 |
| Diabetes | 2717(9.6) | 1046(13.0) | <0.001 |
| Heart disease | 3054(10.8) | 1273(15.8) | <0.001 |
| Chronic kidney disease | 264(0.9) | 123(1.5) | <0.001 |
| Cancer | 959(3.4) | 268(3.3) | 0.75 |
| Alcohol dependence syndrome | 30(0.1) | 18(0.2) | 0.002 |
| Tobacco use | 36(0.1) | 10(0.1) | 0.74 |
| Visits seeking medical care | | | |
| Mean ± SD (median, $25^{th}$-$75^{th}$ percentile) | 234.55 ± 194.08 (185, 97-319) | 159.90 ±155.87 (114, 52-219) | <0.001 |

**Table 2 Crude and adjusted HRs of stroke for those with RA and comorbid depression, those with RA only, those with depression only as compared to those with neither RA nor depression.**

| Patient group | Event | PY | Incidence | Crude HRs (95% CI) | Adjusted HRs * (95% CI) |
|---|---|---|---|---|---|
| **Non-RA cohort** | | | | | |
| Neither RA nor depression (n=29,925) | 3063 | 245086.81 | 12.50 | 1.00 | 1.00 |
| Depression only (n=2,675) | 377 | 24540.32 | 15.36 | 1.23 (1.11-1.37) | 1.57 (1.41-1.75) |
| **RA cohort** | | | | | |
| RA only (n=6,909) | 929 | 55223.83 | 16.82 | 1.35 (1.25-1.45) | 1.43 (1.12-1.55) |
| RA and depression (n=1,136) | 181 | 9901.31 | 18.28 | 1.48 (1.26-1.71) | 2.18 (1.87-2.54) |

per 1,000 person-years for incidence rate.

*Adjusted for age, gender, level of urbanization, income, visits seeking medical care, and comorbidity

**Table 3 Multivariate analysis of factors for the incidence of stroke among patients with RA.**

| Variables | Cox regression model (n=8045) | |
|---|---|---|
| | Adjusted HRs* | 95% CI |
| Depression | | |
| No | 1 | |
| Yes | 1.63 | 1.37-1.92 |
| Age | 1.05 | 1.03-1.08 |
| Gender | | |
| Female | 1 | |
| Male | 1.17 | 1.03-1.28 |
| Monthly income | | |
| Low | 1 | |
| Median | 0.97 | 0.85-1.10 |
| High | 0.85 | 0.58-1.26 |
| Level of urbanization | | |
| Urban | 1 | |
| Suburban | 1.10 | 0.92-1.30 |
| Rural | 1.06 | 0.92-1.22 |
| Comorbidity | | |
| Hypertension | | |
| No | 1 | |
| Yes | 1.51 | 1.40-1.84 |
| Diabetes | | |
| No | 1 | |
| Yes | 1.34 | 1.16-1.56 |
| Heart disease | | |
| No | 1 | |
| Yes | 1.48 | 1.31-1.73 |
| Chronic kidney disease | | |
| No | 1 | |
| Yes | 1.02 | 0.76-1.30 |
| Cancer | | |
| No | 1 | |
| Yes | 1.12 | 0.84-1.47 |
| Visits seeking medical care | 0.99 | 0.98-1.01 |

Adjusted for all variables in the model.

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# Does depression increase the risk of stroke in patients with rheumatoid arthritis? A population-based cohort study

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| | |

# Does depression increase the risk of stroke in patients with rheumatoid arthritis? A population-based cohort study

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## ABSTRACT

**Objectives:** Comorbid depression is common and undertreated in patients with rheumatoid arthritis (RA). It remains uncertain whether comorbid depression provoked the risk of poor clinical outcome, stroke in particular, among RA patients. This work aimed to determine if depression onset during the treatment process increases stroke risk for patients with RA as compared to those with (a) neither RA nor depression, (b) RA only, and (c) depression only.

**Design:** A nationwide, population-based cohort study.

**Setting:** Taiwan's Longitudinal Health Insurance Database.

**Participants:** We identified 8,045 subjects with a newly diagnosed RA between 1997 and 2010, together with 32,600 subjects without RA matched by age, gender and index date. All subjects were further divided into four groups based on whether they were diagnosed with comorbid depression during the follow-up period.

**Main outcome measure:** The incidence rate and hazard ratio for incident stroke were estimated by the end of 2012 using Cox proportional-hazard regression.

**Results:** We discovered that RA patients with the comorbid depression exhibited the highest risk of stroke, with an adjusted hazard ratios (HRs) of 2.18 (95% confidence interval = 1.87-2.54). Those with RA only or those with depression only still had the higher risk of stroke by 43% and 57% as compared with subjects without either condition. Multivariate analysis showed RA subjects who were male or older, incurred the onset of depression, or had comorbidities such as hypertension, diabetes as well as heart disease had a greater risk of stroke.

**Conclusions:** This study cleared up the significant association between RA and the subsequent risk of stroke, and further highlighted that the onset of depression within the treatment process may increase stroke risk for RA subjects. Findings could assist healthcare providers to pinpoint RA individuals with a higher predisposition of stroke, which could

facilitate the provision of appropriate rehabilitation.

**Keywords**：rheumatoid arthritis, depression, stroke, cohort study

**Strengths and limitations of this study**

- The main outcome measures employed in this work are validated due to the application of population-based cohort study, based on a nationwide claim database, thus decreasing recall and selection bias.
- This is the first report to clarify the effect of comorbid depression on the stroke risk among RA subjects, which was beneficial for healthcare providers in guiding more effective treatment strategies to improve the clinical outcomes for them.
- Misclassification of diseases and failure to adjust for disease severity might lead to somewhat skewed findings

## INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease manifested as long-term joint damage, chronic debilitating pain, and premature mortality. This disease often affects people 30 to 50 years of age and results in disability and inability to work, thus posing a heavy burden on patients with RA, their families and the healthcare system.[1] A review of the financial burdens of RA in the United States showed that the annual direct medical costs of RA reached about $9 billion, and the total societal costs (the sum of direct and indirect costs) was estimated to exceed $39 billion.[2]

Despite improvements in the diagnosis and treatment of RA, patients with RA still have a lower life expectancy (6-7 years) when compared with the general population.[3] This increased mortality is due primarily to cardiovascular diseases such as myocardial infarction (MI) or stroke.[4-6] Nevertheless, unlike the studies of RA predicting the onset of MI,[4 7 8] evidence for an association between RA and the development of stroke remains conflicting. A meta-analysis of 15 articles indicated that individuals with RA had a 63% higher risk for MI, but not for stroke [odds ratio (OR)= 1.14, 95% confidence interval (CI) = 0.86-1.51] when compared to the general population.[4] On the other hand, a recent Danish study involving 18,247 patients with RA, who were followed for a median of 4.8 years, indicated that those with RA had a 30% higher risk of stroke than a non-RA group.[9] Another meta-analysis of 17 studies reported that patients with RA had a higher predisposition to develop stroke than did non-RA subjects, with a pool risk of 1.91.[8]

One cause for concern is that the former studies did not consider the effect of accompanying psychological factors on the risk of stroke; depression, in particular, which is often underdiagnosed and undertreated.[10] Depression, a well-documented comorbidity among people with chronic diseases, specifically arthritis, may exacerbate functional disabilities, affect adherence to treatment, and be a barrier to self-care and self-management behaviors.[11]

A recent meta-analysis estimated that the prevalence of depression among patients with RA ranges from 14.8 to 38.8%,[12] and findings from our previous study indicated that RA patients were nearly twice as likely to experience depression as the general population.[13] Indeed, once patients with RA suffered from concomitant depression, they had a 7.2% increase in medical costs ($12,225 vs. $11,404),[14] and their likelihood of mortality more than doubled.[11] Given the alarming rate of depression and the corresponding physical burden on patients with RA, it is imperative to implement effective therapeutic interventions to achieve more favorable therapeutic outcomes, thus serving to extend the life expectancy of patients with RA. Notably, based on former research, the activation of innate inflammatory mechanisms that accompany depressive mood was assumed to affect the susceptibility to development of cardiovascular diseases in addition to the influence of behavioral factors, [15-18] implying that the causative role of depression should not be neglected as determining the association of RA with stroke.

With this growing evidence on the association between RA and subsequent risk of stroke, and the limited information on whether depression serves as a potential factor that affects the relationship between these two conditions, findings from a long-term population-based nationwide study could be useful in allocating medical resources and in instituting fact-based policymaking. Nevertheless, to date, no clinical observations or empirical data have documented this concern. The aim of this cohort study, therefore, was to determine if RA patients with the comorbid depression were at an increased risk for stroke as compared to those with (a) neither RA nor depression, (b) RA only, and (c) depression only, using claims data from the National Health Insurance (NHI) of Taiwan.

## METHODS

### Data sources

The data analyzed in this cohort study were retrieved from the Longitudinal Health Insurance

Database (LHID), maintained by the Bureau of NHI (BNHI) and provided to scientists in Taiwan for research purposes. Taiwan launched a single-payer NHI Program in 1995 in order to remove financial barriers to medical care for all legal residents. At the end of 2010, more than 99% of Taiwan's population had enrolled in this program.[19] The LHID is a subset of the NHI database, and contains comprehensive utilization and enrollment information for one million randomly selected NHI beneficiaries, representing 5% of all enrollees in Taiwan in 2000. Because a multistage stratified systematic sampling method was used for this study, there were no statistically significant differences regarding gender or age between the sampled group and the total number of enrollees.[19] This study complied with the guidelines of the Declaration of Helsinki and was approved by the local institutional review board and ethics committee of Buddhist Dalin Tzu Chi Hospital, Taiwan (No. B10004021-1). As the LHID data files contained only de-identified secondary data, the need for informed consent from individual patient consent was waived by the institutional review board.

**Study subjects**

Diagnoses in the insurance claims data were coded according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM). The LHID records were used to identify patients with RA in the age bracket 20-to-90 years of age, and newly diagnosed patients between 1997 and 2010. Those who were diagnosed with an ICD-9-CM code of 714.0 comprised the RA cohort. To improve the diagnostic accuracy, we selected only those who had at least three outpatient visits for RA treatment or those patients who were admitted to the hospital with a primary diagnosis of RA during the study period.[13] The year when a patient was newly diagnosed with RA was defined as the index year.

For each case of RA, we randomly selected, from the remaining insured population without RA, four control subjects who were frequency matched to the RA case in terms of

gender, age and index year. After the exclusion of subjects with a diagnosis of depression (ICD-9-CM 296.2, 296.3, 300.4 or 311) or stroke (ICD-9-CM 430-438) before the index date, a total of 8045 RA patients and 32600 non-RA subjects were included in the data analysis. Occurrence of stroke or depression was defined based on a criterion that indicated at least 3 outpatient service claims, or at least 1 inpatient hospitalization claim, since 1996, when the computerized claims from the LHID became available, until the date of cohort entry. Thereafter, all subjects were followed up until the end of 2012 to measure the incidence of stroke. Only verified strokes that occurred one year following the first diagnosis of RA were included in order to render the temporal link between RA and stroke more plausible. We further stratified the RA cohort into two groups based on whether they were diagnosed with comorbid depression between the index date and the follow-up period. In accordance with the same rationale, the non-RA cohort was divided into two groups based on the existence (or no existence) of depression. Follow-up person-years (PYs) were calculated as the time interval from the entry date to the earliest occurrence of one of the following: a diagnosis of stroke, the date of withdrawal from insurance, or December 31, 2012, whichever came first.

**Demographic characteristics and comorbid conditions**

Demographic characteristics analyzed in this study included age, gender, monthly income, and level of urbanization of the subject's employment or residential area. Monthly income was grouped into 3 levels: ≤ 17,880 New Taiwan Dollars (NTD)$, 17,881-43,900 NTD$, and ≥ 43,901NTD$. All 316 cities and townships in Taiwan were classified into 7 ordered levels of urbanization based on various indicators including population density, proportion of residents with college or higher education, percentage of elderly (> 65 years of age) people, proportion of the workforce in agriculture, and number of physicians per $10^5$ people.[20] Level 1 refers to the “most urbanized” and level 7 refers to the “least urbanized” areas. The level of

urbanization was further divided into 3 strata: urban (levels 1-2), suburban (levels 3-4), and rural (levels 5-7) areas. Baseline comorbid conditions for each subject included hypertension (ICD-9-CM 401-405), diabetes (ICD-9-CM 250), heart disease (ICD-9-CM 410-429), chronic kidney disease (ICD-9-CM 585), tobacco use (ICD-9-CM 305.1), alcohol dependence syndrome (ICD-9-CM 303), and cancer (ICD-9-CM 140-208). The frequency of ambulatory care visits within the study period for each subject was considered to correct for surveillance bias.

**Statistical analysis**

Intergroup differences were evaluated using the independent-sample t-test or nonparametric Kolmogorov-Smirnov test for continuous variables, and the $\chi^2$ test or Fisher exact test for categorical variables. The incidence rate of stroke in the four groups is presented as the number of cases per 1,000 PYs. To assess the risk of developing stroke across the four groups, Cox proportional hazards regression model was applied to compute the crude and adjusted hazard ratios (HRs) and the 95% confidence intervals (CI) for stroke among them. We also performed a sensitivity analysis to test the robustness of the findings using asthma, a disease not related to stroke, to replace depression. Finally, a multivariate Cox proportional hazards regression model was then used to identify risk factors that might be related to the incident of stroke and their adjusted HRs within RA cohorts. All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA), and $p < 0.05$ was considered statistically significant.

**RESULTS**

Table 1 shows the distribution of demographic data and comorbid medical disorders for the RA and non-RA cohorts. The RA cohorts were more likely to have a lower monthly income

(p = 0.001), reside in a rural area (p < 0.001), have more visits seeking medical care (p < 0.001), and suffer comorbid conditions including hypertension, diabetes, heart disease, chronic kidney disease or alcohol dependence syndrome (all p < 0.01).

Of the total sample of 40,645 patients, 4550 had an incident stroke during the follow-up period. The crude and adjusted HRs for stroke in patients with depression only, RA only, and both, as a group, are shown in Table 2. Overall, after adjustment for potential confounders, relative to those with neither RA nor depression, subjects with RA and depression exhibited the highest risk of developing a stroke, with an adjusted HRs of 2.18 (95% CI = 1.87-2.54), followed by those with depression (adjusted HRs = 1.57, 95% CI = 1.41-1.75), and those with RA only (adjusted HRs = 1.43, 95% CI = 1.12-1.55).

Table 3 presents Cox regression model of factors related to the onset of stroke among individuals with RA. Compared to those without depression, those with depression were significantly more likely to develop a stroke (adjusted HRs = 1.63, 95% CI = 1.37-1.92) after adjustment for confounding factors. Results also showed that age was related to the risk of stroke. There was a 5% increase in the risk of stroke for each 1-year increment (95% CI = 1.03-1.08). Compared with females, males had an adjusted HRs of 1.17 for stroke (95% CI = 1.03-1.28). Additionally, some comorbid conditions including hypertension, heart disease and diabetes increased the risk of stoke with adjusted HRs of 1.51 (95% CI = 1.40-1.84), 1.48 (95% CI = 1.31-1.73) and 1.34 (95% CI = 1.16-1.56), respectively.

In the sensitivity analysis, we compared the risks of stroke across three groups: reference, RA only, and RA with asthma. We found that the RA with asthma group had an adjusted HR of 1.18 with a 95% CI of 0.89-1.34, which is not statistically significant. This indicates the validity of our methodology.

## DISCUSSION

Previous studies of the association between RA and the risk of stroke using

hospital/community-based populations yielded mixed findings.[4 8 9 21] It is noteworthy that these studies essentially ignored the effect of accompanying depressive symptoms, a common psychological problem among RA patients, on the relationship between the two diseases. To the best of our knowledge, this was the first population-based, nationwide study which attempted to determine if depression modified the association between RA and stroke, and could therefore help to facilitate the provision of more appropriate interventions to successfully manage rheumatological disorders and prevent the subsequent risk of cardiovascular diseases.

This 15-year follow-up study found that individuals with RA had a 43% greater-adjusted risk of stroke when compared with the general population. These findings are in agreement with the results of prior studies conducted in Western populations.[8 9] It has been argued that rheumatologic disorders are an overlapping group of conditions that are characterized by chronic inflammation involving connective tissues and organs.[1 6 16] Once inflammation occurs in the body, the vascular endothelial cells secrete proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) or interleukin (IL)-6, which activate and attract massive numbers of white blood cells to the damaged region within the lumen of the vessel. Following infiltration into the tunica media, white blood cells absorb oxidized LDL-C and become foam cells, consequently accelerating the risk of thromboembolism.[18] In addition, a growing body of evidence has shown that inflammatory cytokines stimulate the production of matrix metalloproteinases (MMPs) as well, and this may cause further injury to the blood-brain barrier, thereby provoking a greater susceptibility to stroke.[22 23]

A noteworthy feature of the current study herein was that once patients with RA were diagnosed with comorbid depression during the treatment process, they exhibited more than double the likelihood of stroke than the general population. We speculate that there are several potential reasons as to why depression exacerbate the risk of stroke in these patients.

First, the presence of symptoms of depression is likely linked to treatment nonadherence and an increase in unhealthy lifestyles, such as poor nutrition and physical inactivity, and these may contribute to the development of a stroke.[15] Second, symptoms of depression can cause systematic inflammation that worsens the manifestations of RA. Recent studies demonstrated that depressed individuals with RA had higher circulating levels of inflammatory markers such as IL-6, TNF-α and C-reactive protein (CRP)[10]; all of which play key roles in the pathogenesis of stroke.[18] Additionally, recent research have focused on another signaling pathway, namely, gut-to-brain communication, which suggested that intestinal dysfunction induced by negative moods may cause the activation of immune cells and the production of cytokines in the gut as well, thereby inducing the expression of inflammatory markers, which in turn induce initiation and progression of neurological disorders.[24 25] It is also noteworthy that only one in five patients with depression is estimated to have been treated and referred to appropriate psychiatric services after the onset of RA.[26] The implementation of a standardized psychosocial assessment, and of patient care procedures, as part of routine care may therefore help in the early referral of high-risk patients for further therapeutic interventions.

This study also indicated that males were at a 1.17-fold greater risk of stroke than females in the RA cohorts. No previous study has examined gender differences in the risk of stroke among patients with RA, which renders a comparison of results impossible. Nevertheless, this is consistent with the observation that males have a higher risk of stroke than females among the general population.[27] There are several possible explanations for this result. First, women appear to have greater health consciousness with regard to stroke prevention than men, and immediately seek medical therapy at the slightest irregularity in well-being, so the onset of chronic diseases may be expected to be lower in women than in men.[28] Second, lifetime exposure to ovarian estrogens may protect against the risk of stroke for females.

Extensive animal experiments and human studies have supported the function of estrogens as neuroprotectants against neurodegenerative diseases, particularly stroke, through enhancing basal release of Nitric Oxide (NO) to curb coronary thrombosis and atherosclerosis.[27 29] Recently, estrogenic agents have been suggested as a novel therapeutic approach to treat the neuronal damages associated with global ischemia.[27 30]

Consistent with the findings of prior studies conducted in the general population,[16 27] age was positively correlated with the risk of stroke among patients with RA. We speculate that with aging, blood vessels gradually lose elasticity and gain resistance, slowing the flow of blood. Moreover, with poor circulation, fat is prone to accumulate in the abdomen and release free fatty acids into the serum, leading to higher insulin resistance, elevated serum triglycerides, and increased levels of LDL-C,[31] thereby resulting in the greater risk of stroke.

Findings of this study indicate that patients with RA and several comorbid conditions such as hypertension, diabetes or heart disease had a significantly greater risk for stroke. Those with chronic kidney disease and cancer showed a tendency for stroke, but the association failed to reach statistical significance. Despite the lack of comparative studies on the effects of comorbid conditions on stroke among patients with RA, our findings are consistent with past arguments made in the literature.[6] The elevated risk of stroke may be attributed to several causes. For example, insulin resistance and hypertension are common cardiovascular risk factors among individuals with RA.[32] Moreover, the functional impairment induced by comorbid conditions may lead to limited physical activity which could, very likely, trigger additional risk of stroke. Finally, the immunosuppressive therapies used for patients with RA have been found to have deleterious effects. Some review articles indicated that the use of corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) may be related to the risk of cardiovascular events.[6 18] Before prescribing these drugs, rheumatologists should carefully appraise the inherent cerebrovascular or cardiovascular risk among patients with RA.

Several limitations of this study should be considered when interpreting these results. First, we could not account for some potential confounding factors such as social networks, coping modes, or educational level because these data were unavailable in the LHID. Future research controlling for those untested variables is needed to better determine if the present findings are replicated across diverse groups of individuals. Second, the identification of exposure and outcome were based on the ICD-9-CM, and misclassification is inevitable. However, we selected only those cases with RA, depression, or stroke after they were recorded as having either at least three outpatient visits reporting consistent diagnoses, or one inpatient admission. This approach is likely to minimize such errors. Furthermore, as the approach to coding and the availability of data were similar regardless of the RA and depression status, we believe the misclassification was likely to be random and thus, if indeed occurring, would tend to draw the estimated HRs to the direction of the null values. Second, it should also be noted that the NHI of Taiwan randomly samples claims from hospitals, interviews patients, and reviews medical charts to verify the accuracy of medical records. Third, because data regarding the severity of RA were unavailable in this databases. Nonetheless, the multivariate analysis applied in this study considered the impact of several comorbid conditions including hypertension, diabetes, heart disease, chronic kidney disease, tobacco use, alcohol dependence syndrome and cancer. Furthermore, we performed a sensitivity analysis using on those RA subjects without comorbid conditions to test the robustness of our findings and found that depressed RA subjects with no known comorbid condition still had a higher risk of stroke when compared to those without RA and depression, with an adjusted HR of 1.65 (95% CI = 1.23-2.03). Thus, the impact of disease severity is unlikely to compromise findings of this study. Fourth, evidence derived from any observational cohort study is generally less robust than that obtained from randomized control trials since cohort studies are subject to various biases related to confounding effects. Despite our careful efforts to

maintain adequate control of confounding factors, unpredictable biases could still remain if they stem from unmeasured or unknown confounders. Notwithstanding these limitations, the strengths of this study must also be acknowledged and these include the immediate availability of data, the comprehensiveness of the database, and the statistical power derived from the samples' large sizes. In addition, this retrospective 15-year cohort study allowed us to clearly determine if the symptoms of depression exacerbated the risk of stroke for those with RA, and the corresponding findings could serve as a reference for future treatment strategies.

In conclusion, this study demonstrated that patients with RA and comorbid depression were more than twice as likely to have a stroke than were those of the healthy controls. We further found that the factors contributing to the high risk of stroke included being male, older, as well as having depression and a comorbid condition such as hypertension, diabetes or heart disease. Healthcare providers may, therefore, be able to better recognize those demographic and diseases characteristics that contribute to the risk of stroke among patients with RA from this population-based study. Findings also supported that the routine screening of depression and the institution of patient-centered interventions may represent an important strategy for improving clinical outcomes for RA patients.

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**Contributors** All the authors approved the contents of the submitted article. Conceived and designed the experiments: TTY CSY. Analyzed the data: TTY GHR. Contributed reagents/materials/analysis tools: TTY LNS LMC GHR. Wrote the paper: TTY LH GHR. Final approval of manuscript: TTY LNS LH CSY LMC GHR.

**Competing interests** None declared.

**Ethics approval** This study was approved by the Research Ethics Committee of Dalin Tzuchi Hospital (No. B10004021-1).

**Data sharing statement** No additional data are available.

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**Table 1 Demographic data and comorbidity comparison of the study subjects.**

| Variables | Non-RA cohort N = 32600 (%) | RA cohort N = 8045(%) | p |
|---|---|---|---|
| Age (years) | | | 0.85 |
| <=40 | 5378(16.5) | 1331(16.5) | |
| 41-60 | 15569(47.8) | 3814(47.4) | |
| $60^{+}$ | 11653(35.7) | 2900(36.0) | |
| Mean ± Standard Deviation (SD) | 55.00±14.63 | 55.01±14.65 | 0.94 |
| Gender | | | 0.95 |
| Female | 22461(68.9) | 5540(68.9) | |
| Male | 10139(31.1) | 2505(31.1) | |
| Monthly income | | | <0.001 |
| Low | 15218(46.7) | 3513(43.7) | |
| Median | 15985(49.0) | 4213(52.4) | |
| High | 1397(4.3) | 319(4.0) | |
| Level of urbanization | | | <0.001 |
| Urban | 18839(57.8) | 4485(55.7) | |
| Suburban | 5311(16.3) | 1258(15.6) | |
| Rural | 8450(25.9) | 2302(28.6) | |
| Comorbidity | | | |
| Hypertension | 5965(21.2) | 2216(27.6) | <0.001 |
| Diabetes | 2717(9.6) | 1046(13.0) | <0.001 |
| Heart disease | 3054(10.8) | 1273(15.8) | <0.001 |
| Chronic kidney disease | 264(0.9) | 123(1.5) | <0.001 |
| Cancer | 959(3.4) | 268(3.3) | 0.75 |
| Alcohol dependence syndrome | 30(0.1) | 18(0.2) | 0.002 |
| Tobacco use | 36(0.1) | 10(0.1) | 0.74 |
| Visits seeking medical care | | | |
| Mean ± SD (median, $25^{th}$-$75^{th}$ percentile) | 234.55 ± 194.08 (185, 97-319) | 159.90 ±155.87 (114, 52-219) | <0.001 |

**Table 2 Crude and adjusted HRs of stroke for those with RA and comorbid depression, those with RA only, those with depression only as compared to those with neither RA nor depression.**

| Patient group | Event | PY | Incidence | Crude HRs (95% CI) | Adjusted HRs * (95% CI) |
|---|---|---|---|---|---|
| **Non-RA cohort** | | | | | |
| Neither RA nor depression (n=29,925) | 3063 | 245086.81 | 12.50 | 1.00 | 1.00 |
| Depression only (n=2,675) | 377 | 24540.32 | 15.36 | 1.23 (1.11-1.37) | 1.57 (1.41-1.75) |
| **RA cohort** | | | | | |
| RA only (n=6,909) | 929 | 55223.83 | 16.82 | 1.35 (1.25-1.45) | 1.43 (1.12-1.55) |
| RA and depression (n=1,136) | 181 | 9901.31 | 18.28 | 1.48 (1.26-1.71) | 2.18 (1.87-2.54) |

per 1,000 person-years for incidence rate.

*Adjusted for age, gender, level of urbanization, income, visits seeking medical care, and comorbidity

**Table 3 Multivariate analysis of factors for the incidence of stroke among patients with RA.**

| Variables | Cox regression model (n=8045) | |
|---|---|---|
| | Adjusted HRs* | 95% CI |
| Depression | | |
| No | 1 | |
| Yes | 1.63 | 1.37-1.92 |
| Age | 1.05 | 1.03-1.08 |
| Gender | | |
| Female | 1 | |
| Male | 1.17 | 1.03-1.28 |
| Monthly income | | |
| Low | 1 | |
| Median | 0.97 | 0.85-1.10 |
| High | 0.85 | 0.58-1.26 |
| Level of urbanization | | |
| Urban | 1 | |
| Suburban | 1.10 | 0.92-1.30 |
| Rural | 1.06 | 0.92-1.22 |
| Comorbidity | | |
| Hypertension | | |
| No | 1 | |
| Yes | 1.51 | 1.40-1.84 |
| Diabetes | | |
| No | 1 | |
| Yes | 1.34 | 1.16-1.56 |
| Heart disease | | |
| No | 1 | |
| Yes | 1.48 | 1.31-1.73 |
| Chronic kidney disease | | |
| No | 1 | |
| Yes | 1.02 | 0.76-1.30 |
| Cancer | | |
| No | 1 | |
| Yes | 1.12 | 0.84-1.47 |
| Visits seeking medical care | 0.99 | 0.98-1.01 |

Adjusted for all variables in the model.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | P3 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | P3-P4 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | P5-P6 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | P6 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | P6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | P7-P8 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | P7-P8 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | P7-P8 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | P8-P9 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | P6-P9 |
| Bias | 9 | Describe any efforts to address potential sources of bias | P9 |
| Study size | 10 | Explain how the study size was arrived at | P7 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | P9 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | P8-P9 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | P9 |
| | | (*c*) Explain how missing data were addressed | NA |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | P9 |
| | | (*e*) Describe any sensitivity analyses | P9 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | P9-P10 |
| | | (b) Give reasons for non-participation at each stage | NA |
| | | (c) Consider use of a flow diagram | NA |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | P9-P10 |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA |
| | | (c) Summarise follow-up time (eg, average and total amount) | P10 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | P10 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | P10, P22 |
| | | (*b*) Report category boundaries when continuous variables were categorized | P21 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |

| | | | |
|---|---|---|---|
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | P10 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | P11 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | P14-P15 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | P14-P15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | P15 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | P17 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.