

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014233
Article Type:	Research
Date Submitted by the Author:	10-Sep-2016
Complete List of Authors:	Tsai, Tzung-Yi; Buddhist Dalin Tzu Chi General Hospital, Department of Medical Research Lu, Ming-Chi ; Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, Division of Allergy, Immunology and Rheumatology Livneh, Hanoch ; Portland State University, Portland, OR 97207-0751, USA Chiu, Shan-Yan ; Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, Department of Nursing Lai, Ning-Sheng; Buddhist Dalin Tzu Chi General Hospital, Division of Allergy, Immunology and Rheumatology Guo, How-Ran; National Cheng Kung University, Department of Environmental and Occupational Health, College of Medicine
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rheumatology, Mental health, Neurology
Keywords:	rheumatoid arthritis, Depression & mood disorders < PSYCHIATRY, Stroke < NEUROLOGY, cohort study

SCHOLARONE™
Manuscripts

only

1
2
3 **Does depression increase the risk of stroke in patients with rheumatoid arthritis? A**
4
5 **population-based cohort study**
6
7

8
9 Tzung-Yi Tsai^{1,2,3}, Ming-Chi Lu^{4,5}, Hanoch Livneh⁶, Shan-Yan Chiu⁷, Ning-Sheng Lai^{4,5},
10
11 How-Ran Guo^{2,8,9*}
12
13

14
15
16
17 ¹ Department of Medical Research, Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical
18 Foundation, 2 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan
19

20
21 ² Department of Environmental and Occupational Health, College of Medicine, National
22 Cheng Kung University, 138 Sheng-Li Road, Tainan 70428, Taiwan
23

24
25
26 ³ Department of Nursing, Tzu Chi University of Science and Technology, 880 Chien-Kuo
27 Road Section 2, Hualien 62247, Taiwan
28

29
30 ⁴ Division of Allergy, Immunology and Rheumatology, Dalin Tzuchi Hospital, The Buddhist
31 Tzuchi Medical Foundation, 2 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan
32

33
34
35 ⁵ School of Medicine, Tzu Chi University, 701 Jhongyang Road Section 3, Hualien 97004,
36 Taiwan
37

38
39 ⁶ Rehabilitation Counseling Program, Portland State University, Portland, OR 97207-0751,
40 USA
41

42
43
44 ⁷ Department of Nursing, Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, 2
45 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan
46

47
48 ⁸ Department of Occupational and Environmental Medicine, National Cheng Kung University
49 Hospital, 138 Sheng-Li Road, Tainan 70428, Taiwan
50

51
52
53 ⁹ Occupational Safety, Health, and Medicine Research Center, National Cheng Kung
54 University, 138 Sheng-Li Road, Tainan 70428, Taiwan
55

1
2
3
4 Correspondence and requests for materials should be addressed to Guo HR.
5
6

7 Email: dm732024@tzuchi.com.tw
8

9 TEL: 886-5-2648000 ext. 3209
10

11 FAX: 886-5-2648000 ext. 3241
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

1
2
3 facilitate the provision of appropriate rehabilitation.
4

5 **Keywords** : rheumatoid arthritis, depression, stroke, cohort study
6
7
8
9
10

11 **Strengths and limitations of this study**

- 14 ● The main outcome measures employed in this work are validated due to the application
15 of population-based cohort study, based on a nationwide claim database, thus decreasing
16 recall and selection bias.
17
18
- 20 ● This is the first report to clarify the effect of comorbid depression on the stroke risk
21 among RA subjects, which was beneficial for healthcare providers in guiding more
22 effective treatment strategies to improve the clinical outcomes for them.
23
24
- 26 ● Misclassification of diseases may occur when using an administrative database.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 recent meta-analysis estimated that the prevalence of depression among patients with RA
4 ranges from 14.8 to 38.8%,¹² and findings from our previous study indicated that RA patients
5 were nearly twice as likely to experience depression as the general population.¹³ Indeed, once
6 patients with RA suffered from concomitant depression, they had a 7.2% increase in medical
7 costs (\$12,225 vs. \$11,404),¹⁴ and their likelihood of mortality more than doubled.¹¹
8
9 Therefore, information as to whether symptoms of depression increase the risk of stroke in
10 patients with RA would be of utmost importance in laying the groundwork for the
11 implementation of more effective therapeutic interventions to achieve more favorable
12 prognoses, thus serving to extend the life expectancy of patients with RA.
13
14

15
16
17
18
19
20
21
22
23 Given the alarming rate of depression in patients with RA, and the link between depression
24 and increased cardiovascular events, it becomes imperative to investigate if comorbid
25 depression is related to poor clinical outcomes, stroke in particular, among RA patients.
26
27 However, to date, no clinical observations or empirical data have documented this concern,
28 and evidence from prospective studies is still lacking. The aim of this cohort study, therefore,
29 was to determine if RA patients with the comorbid depression were at an increased risk for
30 stroke as compared to those with (a) neither RA nor depression, (b) RA only, and (c)
31 depression only, using claims data from the National Health Insurance (NHI) of Taiwan.
32
33
34
35
36
37
38
39
40
41

42 **METHODS**

43 **Data sources**

44
45
46
47 The data analyzed in this cohort study were retrieved from the Longitudinal Health Insurance
48 Database (LHID), maintained by the Bureau of NHI (BNHI) and provided to scientists in
49 Taiwan for research purposes. Taiwan launched a single-payer NHI Program in 1995 in order
50 to remove financial barriers to medical care for all legal residents. At the end of 2010, more
51 than 99% of Taiwan's population had enrolled in this program.¹⁵ The LHID is a subset of the
52
53
54
55
56
57
58
59
60

1
2
3 NHI database, and contains comprehensive utilization and enrollment information for one
4
5 million randomly selected NHI beneficiaries, representing 5% of all enrollees in Taiwan in
6
7 2000. Because a multistage stratified systematic sampling method was used for this study,
8
9 there were no statistically significant differences regarding gender or age between the
10
11 sampled group and the total number of enrollees.¹⁵ This study complied with the guidelines
12
13 of the Declaration of Helsinki and was approved by the local institutional review board and
14
15 ethics committee of Buddhist Dalin Tzu Chi Hospital, Taiwan (No. B10004021-1). As the
16
17 LHID data files contained only de-identified secondary data, the need for informed consent
18
19 from individual patient consent was waived by the institutional review board.
20
21
22
23
24

25 **Study subjects**

26
27 Diagnoses in the insurance claims data were coded according to the International
28
29 Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM). The LHID
30
31 records were used to identify patients with RA in the age bracket 20-to-90 years of age, and
32
33 newly diagnosed patients between 1997 and 2010. Those who were diagnosed with an
34
35 ICD-9-CM code of 714.0 comprised the RA cohort. To improve the diagnostic accuracy, we
36
37 selected only those who had at least three outpatient visits for RA treatment or those patients
38
39 who were admitted to the hospital with a primary diagnosis of RA during the study period.¹³
40
41
42

43 The year when a patient was newly diagnosed with RA was defined as the index year.
44

45 For each case of RA, we randomly selected, from the remaining insured population
46
47 without RA, four control subjects who were frequency matched to the RA case in terms of
48
49 gender, age and index year. After the exclusion of subjects with a diagnosis of depression
50
51 (ICD-9-CM 296.2, 296.3, 300.4 or 311) or stroke (ICD-9-CM 430-438) before the index date,
52
53 a total of 8045 RA patients and 32600 non-RA subjects were included in the data analysis.
54
55
56 Occurrence of stroke or depression was defined based on the subject who had at least 3
57
58
59
60

1
2
3 outpatient service claims, or at least 1 inpatient hospitalization claim since 1996, when the
4 computerized claims from the LHID were available, until the date of cohort entry. Thereafter,
5 all subjects were followed up until the end of 2012 to measure the incidence of stroke. Only
6 verified strokes that occurred one year following the first diagnosis of RA were included in
7 order to render the temporal link between RA and stroke more plausible. We further stratified
8 the RA cohort into two groups based on whether they were diagnosed with comorbid
9 depression between the index date and the follow-up period. In accordance with the same
10 rationale, the non-RA cohort was divided into two groups based on the existence (or no
11 existence) of depression. Follow-up person-years (PYs) were calculated as the time interval
12 from the entry date to the earliest occurrence of one of the following: a diagnosis of stroke,
13 the date of withdrawal from insurance, or December 31, 2012, whichever came first.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29

30 **Demographic characteristics and comorbid conditions**

31 Demographic characteristics analyzed in this study included age, gender, monthly income,
32 and level of urbanization of the subject's employment or residential area. Monthly income
33 was grouped into 3 levels: $\leq 17,880$ New Taiwan Dollars (NTD)\$, 17,881-43,900 NTD\$, and
34 $\geq 43,901$ NTD\$. All 316 cities and townships in Taiwan were classified into 7 ordered levels
35 of urbanization based on various indicators including population density, proportion of
36 residents with college or higher education, percentage of elderly (> 65 years of age) people,
37 proportion of the workforce in agriculture, and number of physicians per 10^5 people.¹⁶ Level
38 1 refers to the “most urbanized” and level 7 refers to the “least urbanized” areas. The level of
39 urbanization was further divided into 3 strata: urban (levels 1-2), suburban (levels 3-4), and
40 rural (levels 5-7) areas. Baseline comorbid conditions for each subject included hypertension
41 (ICD-9-CM 401-405), diabetes (ICD-9-CM 250), heart disease (ICD-9-CM 410-429),
42 chronic kidney disease (ICD-9-CM 585), tobacco use (ICD-9-CM 305.1), alcohol
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 dependence syndrome (ICD-9-CM 303), and cancer (ICD-9-CM 140-208). The frequency of
4
5 ambulatory care visits within the study period for each subject was considered to correct for
6
7 surveillance bias.
8
9

10 11 **Statistical analysis**

12
13 Intergroup differences were evaluated using the independent-sample t-test or nonparametric
14
15 Kolmogorov-Smirnov test for continuous variables, and the χ^2 test or Fisher exact test for
16
17 categorical variables. The incidence rate of stroke in the four groups is presented as the
18
19 number of cases per 1,000 PYs. To assess the risk of developing stroke across the four groups,
20
21 Cox proportional hazards regression model was applied to compute the crude and adjusted
22
23 hazard ratios (HRs) and the 95% confidence intervals (CI) for stroke among them. A
24
25 multivariate Cox proportional hazards regression model was then used to identify risk factors
26
27 that might be related to the incident of stroke and their adjusted HRs within RA cohorts. All
28
29 analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA), and $p <$
30
31 0.05 was considered statistically significant.
32
33
34
35
36
37
38

39 **RESULTS**

40
41 Table 1 shows the distribution of demographic data and comorbid medical disorders for the
42
43 RA and non-RA cohorts. The RA cohorts were more likely to have a lower monthly income
44
45 ($p = 0.001$), reside in a rural area ($p < 0.001$), have more visits seeking medical care ($p <$
46
47 0.001), and suffer comorbid conditions including hypertension, diabetes, heart disease,
48
49 chronic kidney disease or alcohol dependence syndrome (all $p < 0.01$).
50

51
52 Of the total sample of 40,645 patients, 4550 had an incident stroke during the follow-up
53
54 period. The crude and adjusted HRs for stroke in patients with depression only, RA only, and
55
56 both, as a group, are shown in Table 2. Overall, after adjustment for potential confounders,
57
58
59
60

1
2
3 relative to those with neither RA nor depression, subjects with RA and depression exhibited
4 the highest risk of developing a stroke, with an adjusted HRs of 2.18 (95% CI = 1.87-2.54),
5 followed by those with depression (adjusted HRs = 1.57, 95% CI = 1.41-1.75), and those
6 with RA only (adjusted HRs = 1.43, 95% CI = 1.12-1.55).
7
8
9
10

11 Table 3 presents Cox regression model of factors related to the onset of stroke among
12 individuals with RA. Compared to those without depression, those with depression were
13 significantly more likely to develop a stroke (adjusted HRs = 1.63, 95% CI = 1.37-1.92) after
14 adjustment for confounding factors. Results also showed that age was related to the risk of
15 stroke. There was a 5% increase in the risk of stroke for each 1-year increment (95% CI =
16 1.03-1.08). Compared with females, males had an adjusted HRs of 1.17 for stroke (95% CI =
17 1.03-1.28). Additionally, some comorbid conditions including hypertension, heart disease and
18 diabetes increased the risk of stroke with adjusted HRs of 1.51 (95% CI = 1.40-1.84), 1.48
19 (95% CI = 1.31-1.73) and 1.34 (95% CI = 1.16-1.56), respectively.
20
21
22
23
24
25
26
27
28
29
30
31
32

33 DISCUSSION

34 Previous studies of the association between RA and the risk of stroke using
35 hospital/community-based populations yielded mixed findings.^{4 8 9 17} It is noteworthy that
36 these studies essentially ignored the effect of accompanying depressive symptoms, a common
37 psychological problem among RA patients, on the relationship between the two diseases. To
38 the best of our knowledge, this was the first population-based, nationwide study which
39 attempted to determine if depression modified the association between RA and stroke, and
40 could therefore help to facilitate the provision of more appropriate interventions to
41 successfully manage rheumatological disorders and prevent the subsequent risk of
42 cardiovascular diseases.
43
44
45
46
47
48
49
50
51
52
53
54

55 This 15-year follow-up study found that individuals with RA had a 43% greater-adjusted
56 risk of stroke when compared with the general population. These findings are in agreement
57
58
59
60

1
2
3 with the results of prior studies conducted in Western populations.^{8,9} It has been argued that
4
5 rheumatological disorders are an overlapping group of conditions that are characterized by
6
7 chronic inflammation involving connective tissues and organs.^{1,6,18} Once inflammation occurs
8
9 in the body, the vascular endothelial cells secrete proinflammatory cytokines, such as tumor
10
11 necrosis factor-alpha (TNF- α) or interleukin (IL)-6, which activate and attract massive
12
13 numbers of white blood cells to the damaged region within the lumen of the vessel.
14
15 Following infiltration into the tunica media, white blood cells absorb oxidized LDL-C and
16
17 become foam cells, consequently accelerating the risk of thromboembolism.¹⁹ In addition, a
18
19 growing body of evidence has shown that inflammatory cytokines stimulate the production of
20
21 matrix metalloproteinases (MMPs) as well, and this may cause further injury to
22
23 the blood-brain barrier, thereby provoking a greater susceptibility to stroke.^{20,21}
24
25
26

27
28 A noteworthy feature of the current study herein was that once patients with RA were
29
30 diagnosed with comorbid depression during the treatment process, they exhibited more than
31
32 double the likelihood of stroke than the general population. We speculate that there are
33
34 several potential reasons as to why depression exacerbate the risk of stroke in these patients.
35
36 First, the presence of symptoms of depression is likely linked to treatment nonadherence and
37
38 an increase in unhealthy lifestyles, such as poor nutrition and physical inactivity, and these
39
40 may contribute to the development of a stroke.²² Second, symptoms of depression can cause
41
42 systematic inflammation that worsens the manifestations of RA. Recent studies have
43
44 demonstrated that depressed individuals with RA had higher circulating levels of
45
46 inflammatory markers such as IL-6, TNF- α and C-reactive protein (CRP)¹⁰; all of which play
47
48 important roles in the pathogenesis of cardiovascular events.¹⁹ It is also noteworthy that only
49
50 one in five patients with depression is estimated to have been treated and referred to
51
52 appropriate psychiatric services after the onset of RA.²³ The implementation of a
53
54 standardized psychosocial assessment, and of patient care procedures, as part of routine care
55
56
57
58
59
60

1
2
3 may therefore help in the early referral of high-risk patients for further therapeutic
4
5 interventions.
6

7
8 This study also indicated that males were at a 1.17-fold greater risk of stroke than females
9
10 in the RA cohorts. No previous study has examined gender differences in the risk of stroke
11
12 among patients with RA, which renders a comparison of results impossible. Nevertheless,
13
14 this is consistent with the observation that males have a higher risk of stroke than females
15
16 among the general population.²⁴ There are several possible explanations for this result. First,
17
18 women appear to have greater health consciousness with regard to stroke prevention than
19
20 men, and immediately seek medical therapy at the slightest irregularity in well-being, so the
21
22 onset of chronic diseases may be expected to be lower in women than in men.²⁵ Second,
23
24 lifetime exposure to ovarian estrogens may protect against the risk of stroke for females.
25
26 Extensive animal experiments and human studies have supported the function of estrogens as
27
28 neuroprotectants against neurodegenerative diseases, particularly stroke, through enhancing
29
30 basal release of Nitric Oxide (NO) to curb coronary thrombosis and atherosclerosis.^{24 26}
31
32 Recently, estrogenic agents have been suggested as a novel therapeutic approach to treat the
33
34 neuronal damages associated with global ischemia.^{24 27}
35
36
37

38
39 Consistent with the findings of prior studies conducted in the general population,^{18 24} age
40
41 was positively correlated with the risk of stroke among patients with RA. We speculate that
42
43 with aging, blood vessels gradually lose elasticity and gain resistance, slowing the flow of
44
45 blood. Moreover, with poor circulation, fat is prone to accumulate in the abdomen and release
46
47 free fatty acids into the serum, leading to higher insulin resistance, elevated serum
48
49 triglycerides, and increased levels of LDL-C,²⁸ thereby resulting in the greater risk of stroke.
50
51

52
53 Findings of this study indicate that patients with RA and several comorbid conditions such
54
55 as hypertension, diabetes or heart disease had a significantly greater risk for stroke. Those
56
57 with chronic kidney disease and cancer showed a tendency for stroke, but the association
58
59
60

1
2
3 failed to reach statistical significance. Despite the lack of comparative studies on the effects
4
5 of comorbid conditions on stroke among patients with RA, our findings are consistent with
6
7 past arguments made in the literature.⁶ The elevated risk of stroke may be attributed to
8
9 several causes. For example, insulin resistance and hypertension are common cardiovascular
10
11 risk factors among individuals with RA.²⁹ Moreover, the functional impairment induced by
12
13 comorbid conditions may lead to limited physical activity which could, very likely, trigger
14
15 additional risk of stroke. Finally, the immunosuppressive therapies used for patients with RA
16
17 have been found to have deleterious effects. Some review articles indicated that the use of
18
19 corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) may be related to the risk
20
21 of cardiovascular events.^{6 19} Before prescribing these drugs, rheumatologists should carefully
22
23 appraise the inherent cerebrovascular or cardiovascular risk among patients with RA.
24
25
26

27
28 Several limitations of this study should be considered when interpreting these results. First,
29
30 we could not account for some potential confounding factors such as social networks, coping
31
32 modes, or educational level because these data were unavailable in the LHID. Future research
33
34 controlling for those untested variables is needed to better determine if the present findings
35
36 are replica across diverse groups of individuals. Second, the identification of exposure and
37
38 outcome were based on the ICD-9-CM, and misclassification is inevitable. However, as the
39
40 approach to coding and the availability of data were similar regardless of case/control status,
41
42 we believe this bias is rather inconsequential. Additionally, we selected only those cases with
43
44 RA, depression or stroke after they were recorded as having either at least three outpatient
45
46 visits reporting consistent diagnoses, or one inpatient admission. Therefore, the approach
47
48 adopted is likely to minimize this error. It should also be noted that the NHI of Taiwan
49
50 randomly samples claims from hospitals, interviews patients, and reviews medical charts to
51
52 verify the accuracy of medical records. Third, since data regarding the severity of RA were
53
54 unavailable in this database, failure to adjust for the level of disability might lead to bias in
55
56
57
58
59
60

1
2
3 subject selection. Nonetheless, the multivariate analysis applied in this study considered the
4 impact of several comorbid conditions including hypertension, diabetes, heart disease,
5 chronic kidney disease, tobacco use, alcohol dependence syndrome and cancer. Furthermore,
6 we performed a sensitivity analysis focusing on those RA subjects without comorbid
7 conditions to test the robustness of our findings. This showed that depressed RA subjects with
8 no known comorbid condition still had a higher risk of stroke when compared to those
9 without RA and depression, with adjusted HRs of 1.65 (95% CI = 1.23-2.03). Fourth,
10 evidence derived from any observational cohort study is generally less robust than that
11 obtained from randomized control trials since cohort studies are subject to various biases
12 related to confounding effects. Despite our careful efforts to maintain adequate control of
13 confounding factors, unpredictable biases could still remain if they stem from unmeasured or
14 unknown confounders. Notwithstanding these limitations, the strengths of this study must
15 also be acknowledged and these include the immediate availability of data, the
16 comprehensiveness of the database, and the statistical power derived from the samples' large
17 sizes. In addition, this retrospective 15-year cohort study allowed us to clearly determine if
18 the symptoms of depression exacerbated the risk of stroke for those with RA, and the
19 corresponding findings could serve as a reference for future treatment strategies.

20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41 In conclusion, this study demonstrated that patients with RA and comorbid depression
42 were more than twice as likely to have a stroke than were those of the healthy controls. We
43 further found that the factors contributing to the high risk of stroke included being male, older,
44 as well as having depression and a comorbid condition such as hypertension, diabetes or heart
45 disease. Healthcare providers may, therefore, be able to better recognize those demographic
46 and diseases characteristics that contribute to the risk of stroke among patients with RA from
47 this population-based study. The need to routinely screen RA patients for depression and
48 institute culturally appropriate interventions should be emphasized. Healthcare providers
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 would benefit from being cognizant of the possible occurrence of depression among patients
4
5 with RA, discuss this often underreported issue with them, and strive to achieve better
6
7 clinical outcomes.
8
9

10 11 12 **Author affiliations**

13
14 ¹ Department of Medical Research, Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical
15
16 Foundation, 2 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan

17
18 ² Department of Environmental and Occupational Health, College of Medicine, National
19
20 Cheng Kung University, 138 Sheng-Li Road, Tainan 70428, Taiwan

21
22 ³ Department of Nursing, Tzu Chi University of Science and Technology, 880 Chien-Kuo
23
24 Road Section 2, Hualien 62247, Taiwan

25
26 ⁴ Division of Allergy, Immunology and Rheumatology, Dalin Tzuchi Hospital, The Buddhist
27
28 Tzuchi Medical Foundation, 2 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan

29
30 ⁵ School of Medicine, Tzu Chi University, 701 Jhongyang Road Section 3, Hualien 97004,
31
32 Taiwan

33
34 ⁶ Rehabilitation Counseling Program, Portland State University, Portland, OR 97207-0751,
35
36 USA

37
38 ⁷ Department of Nursing, Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, 2
39
40 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan

41
42 ⁸ Department of Occupational and Environmental Medicine, National Cheng Kung University
43
44 Hospital, 138 Sheng-Li Road, Tainan 70428, Taiwan

45
46 ⁹ Occupational Safety, Health, and Medicine Research Center, National Cheng Kung
47
48 University, 138 Sheng-Li Road, Tainan 70428, Taiwan

49
50
51
52
53
54
55
56
57
58 **Acknowledgements** The study is based in part on data from the National Health Insurance
59
60

1
2
3 Research Database provided by the Bureau of National Health Insurance, Department of
4 Health and managed by National Health Research Institutes. The interpretation and
5 conclusions contained herein do not represent those of the Bureau of National Health
6 Insurance, Department of Health or National Health Research Institutes. This research was
7 supported by Dalin Tzuchi Hospital (Grant Number DTCRD103(2)-E-05). Chiu SY and Guo
8 HR contributed equally to this work.
9
10
11
12
13
14
15
16
17
18

19 **Contributors** All the authors approved the contents of the submitted article. Conceived and
20 designed the experiments: TTY CSY. Analyzed the data: TTY GHR. Contributed
21 reagents/materials/analysis tools: TTY LNS LMC GHR. Wrote the paper: TTY LH GHR.
22 Final approval of manuscript: TTY LNS LH CSY LMC GHR.
23
24
25
26
27
28

29 **Competing interests** The authors declare no competing financial interests.
30
31
32
33

34 **Ethics approval** This study was approved by the Research Ethics Committee of Dalin Tzuchi
35 Hospital (No. No. B10004021-1).
36
37
38
39

40 **Data sharing statement** No additional data are available.
41
42
43
44

45 **Funding** The researcher received no specific grant from any funding agency in the public,
46 commercial or not-for-profit sectors.
47
48
49
50

51 52 53 54 55 56 **References** 57 58 59 60

- 1 Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. *Am Fam Physician* 2005;72:1037-47.
- 2 Birnbaum H, Pike C, Kaufman R, *et al.* Societal cost of rheumatoid arthritis patients in the US. *Curr Med Res Opin* 2010;26:77-90.
- 3 Lassere MN, Rappo J, Portek IJ, *et al.* How many life years are lost in patients with rheumatoid arthritis? Secular cause-specific and all-cause mortality in rheumatoid arthritis, and their predictors in a long-term Australian cohort study. *Intern Med J* 2013;43:66-72.
- 4 Lévy L, Fautrel B, Barnetche T, *et al.* Incidence and risk of fatal myocardial infarction and stroke events in rheumatoid arthritis patients. A systematic review of the literature. *Clin Exp Rheumatol* 2008;26:673-79.
- 5 Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008;26:S35-61.
- 6 Zha AM, Napoli M, Behrouz R. Prevention of stroke in rheumatoid arthritis. *Curr Neurol Neurosci Rep* 2015;15:1-10.
- 7 Farmer A, Korszun A, Owen MJ, *et al.* Medical disorders in people with recurrent depression. *Br J Psychiatry* 2008;192:351-5.
- 8 Meune C, Touzé E, Trinquart L, *et al.* High risk of clinical cardiovascular events in rheumatoid arthritis: levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. *Arch Cardiovasc Dis* 2010;103:253-61.
- 9 Lindhardsen J, Ahlehoff O, Gislason GH, *et al.* Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ* 2012;344:e1257.
- 10 Margaretten M, Julian L, Katz P, *et al.* Depression in patients with rheumatoid arthritis: description, causes and mechanisms. *Int J Clin Rheumatol* 2011;6:617-23.
- 11 Ang DC, Choi H, Kroenke K, *et al.* Comorbid depression is an independent risk factor for mortality in patients with rheumatoid arthritis. *J Rheumatol* 2005;32:1013-19.
- 12 Matcham F, Rayner L, Steer S, *et al.* The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)* 2013;52:2136-48.
- 13 Lu M, Guo HR, Lin MC, *et al.* Bidirectional associations between rheumatoid arthritis and depression: a nationwide longitudinal study. *Sci Rep* 2016;6:20647.
- 14 Joyce AT, Smith P, Khandker R, *et al.* Hidden cost of rheumatoid arthritis (RA): estimating cost of comorbid cardiovascular disease and depression among patients with RA. *J Rheumatol* 2009;36:743-52.
- 15 National Health Insurance Research Database, Taiwan. http://nhird.nhri.org.tw/date_cohort.html (accessed 8 May 2015).
- 16 Liu CY, Hung YT, Chuang YL, *et al.* Incorporating development stratification of

- 1
2
3 Taiwan townships into sampling design of large scale health interview survey. *J*
4 *Health Manag* 2006;4:1-22.
5
6 17 Liou TH, Huang SW, Lin JW, *et al.* Risk of stroke in patients with rheumatism: a
7 nationwide longitudinal population-based study. *Sci Rep* 2014;4: 5110.
8
9 18 Behrouz R. The risk of ischemic stroke in major rheumatic disorders. *J Neuroimmunol*
10 2014;277:1-5.
11
12 19 van den Oever, IA, van Sijl AM, Nurmohamed MT. Management of cardiovascular
13 risk in patients with rheumatoid arthritis: evidence and expert opinion. *Ther Adv*
14 *Musculoskelet Dis* 2013;5:166-81.
15
16 20 Lakhan SE, Kirchgessner A, Tepper D, *et al.* Matrix metalloproteinases and
17 blood-brain barrier disruption in acute ischemic stroke. *Front Neurol* 2013;4:32.
18
19 21 Yang Y, Rosenberg GA. Matrix metalloproteinases as therapeutic targets for stroke.
20 *Brain Res* 2015;1623:30-8.
21
22 22 Lee HC, Lin HC, Tsai SY. Severely depressed young patients have over five times
23 increased risk for stroke: a 5-year follow-up study. *Biol Psychiatry* 2008;64:912-5.
24
25 23 Sleath B, Chewing B, de Vellis BM, *et al.* Communication about depression during
26 rheumatoid arthritis patient visits. *Arthritis Rheum* 2008;59:186-91.
27
28 24 Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology: a
29 systematic review. *Stroke* 2009;40:1082-90.
30
31 25 Stroebele N, Müller-Riemenschneider F, Nolte CH, *et al.* Knowledge of risk factors,
32 and warning signs of stroke: a systematic review from a gender perspective. *Int J*
33 *Stroke* 2011;6:60-6.
34
35 26 Liu R, Yang SH. Window of opportunity: estrogen as a treatment for ischemic stroke.
36 *Brain Res* 2013;1514:83-90.
37
38 27 Etgen AM, Jover-Mengual T, Zukin RS. Neuroprotective actions of estradiol and
39 novel estrogen analogs in ischemia: translational implications. *Front Neuroendocrinol*
40 2011;32:336-52.
41
42 28 Ai M, Otokozawa S, Asztalos BF, *et al.* Small dense LDL cholesterol and coronary
43 heart disease: results from the Framingham offspring study. *Clin Chem*
44 2010;56:967-76.
45
46 29 Liao KP, Solomon DH. Traditional cardiovascular risk factors, inflammation and
47 cardiovascular risk in rheumatoid arthritis. *Rheumatology* 2013;52:45-52.
48
49
50
51
52
53
54
55
56
57
58
59
60

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

Variables	Non-RA cohort	RA cohort	P
	N = 32600 (%)	N = 8045(%)	
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)

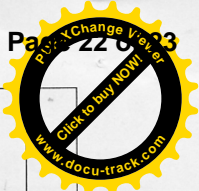
per 1,000 person-years for incidence rate.

*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

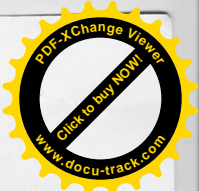
Adjusted for all variables in the model.



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	P6
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			

2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	p9-p10 NA 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 p9, p20
Outcome data	15*	Report numbers of outcome events or summary measures over time	p10, 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	p20
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	p20
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014233.R1
Article Type:	Research
Date Submitted by the Author:	03-Nov-2016
Complete List of Authors:	Tsai, Tzung-Yi; Buddhist Dalin Tzu Chi General Hospital, Department of Medical Research Lu, Ming-Chi ; Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, Division of Allergy, Immunology and Rheumatology Livneh, Hanoch ; Portland State University, Portland, OR 97207-0751, USA Chiu, Shan-Yan ; Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, Department of Nursing Lai, Ning-Sheng; Buddhist Dalin Tzu Chi General Hospital, Division of Allergy, Immunology and Rheumatology Guo, How-Ran; National Cheng Kung University, Department of Environmental and Occupational Health, College of Medicine
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rheumatology, Mental health, Neurology
Keywords:	rheumatoid arthritis, Depression & mood disorders < PSYCHIATRY, Stroke < NEUROLOGY, cohort study

SCHOLARONE™
Manuscripts

only

1
2
3 1 **Does depression increase the risk of stroke in patients with rheumatoid arthritis? A**
4
5 2 **population-based cohort study**
6
7
8
9
10
11
12
13

14
15
16
17 4 Tzung-Yi Tsai^{1,2,3}, Ming-Chi Lu^{4,5}, Hanoch Livneh⁶, Shan-Yun Chiu⁷, Ning-Sheng Lai^{4,5},
18
19 5 How-Ran Guo^{2,8,9*}
20
21
22
23
24
25
26
27
28
29

30
31
32 7 ¹ Department of Medical Research, Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical
33
34 8 Foundation, 2 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan
35
36
37
38
39
40
41
42

43
44 9 ² Department of Environmental and Occupational Health, College of Medicine, National
45
46 10 Cheng Kung University, 138 Sheng-Li Road, Tainan 70428, Taiwan
47
48
49
50
51
52
53
54

55
56 11 ³ Department of Nursing, Tzu Chi University of Science and Technology, 880 Chien-Kuo
57
58 12 Road Section 2, Hualien 62247, Taiwan
59
60
61
62
63
64
65
66

67
68 13 ⁴ Division of Allergy, Immunology and Rheumatology, Dalin Tzuchi Hospital, The Buddhist
69
70 14 Tzuchi Medical Foundation, 2 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan
71
72
73
74
75
76
77
78

79
80 15 ⁵ School of Medicine, Tzu Chi University, 701 Jhongyang Road Section 3, Hualien 97004,
81
82 16 Taiwan
83
84
85
86
87
88
89
90

91
92 17 ⁶ Rehabilitation Counseling Program, Portland State University, Portland, OR 97207-0751,
93
94 18 USA
95
96
97
98
99
100
101
102

103
104 19 ⁷ Department of Nursing, Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, 2
105
106 20 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan
107
108
109
110
111
112
113
114

115
116 21 ⁸ Department of Occupational and Environmental Medicine, National Cheng Kung University
117
118 22 Hospital, 138 Sheng-Li Road, Tainan 70428, Taiwan
119
120
121
122
123
124
125
126

127
128 23 ⁹ Occupational Safety, Health, and Medicine Research Center, National Cheng Kung
129
130 24 University, 138 Sheng-Li Road, Tainan 70428, Taiwan
131
132
133
134
135
136
137
138

139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160

1 Correspondence and requests for materials should be addressed to Guo HR.

2 Email: dm732024@tzuchi.com.tw or hrguo@mail.ncku.edu.tw

3 TEL: 886-5-2648000 ext. 3209

4 FAX: 886-5-2648000 ext. 3241

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

1
2
3 1 **ABSTRACT**

4
5 2 **Objectives:** Comorbid depression is common and undertreated in patients with rheumatoid
6
7 3 arthritis (RA). It remains uncertain whether comorbid depression provoked the risk of poor
8
9 4 clinical outcome, stroke in particular, among RA patients. This work aimed to determine if
10
11 5 depression onset during the treatment process increases stroke risk for patients with RA as
12
13 6 compared to those with (a) neither RA nor depression, (b) RA only, and (c) depression only.

14
15
16 7 **Design:** A nationwide, population-based cohort study.

17
18 8 **Setting:** Taiwan's Longitudinal Health Insurance Database.

19
20
21 9 **Participants:** We identified 8,045 subjects with a newly diagnosed RA between 1997 and
22
23 10 2010, together with 32,600 subjects without RA matched by age, gender and index date. All
24
25 11 subjects were further divided into four groups based on whether they were diagnosed with
26
27 12 comorbid depression during the follow-up period.

28
29
30 13 **Main outcome measure:** The incidence rate and hazard ratio for incident stroke were
31
32 14 estimated by the end of 2012 using Cox proportional-hazard regression.

33
34 15 **Results:** We discovered that RA patients with the comorbid depression exhibited the highest
35
36 16 risk of stroke, with an adjusted hazard ratios (HRs) of 2.18 (95% confidence interval =
37
38 17 1.87-2.54). Those with RA only or those with depression only still had the higher risk of
39
40 18 stroke by 43% and 57% as compared with subjects without either condition. Multivariate
41
42 19 analysis showed RA subjects who were male or older, incurred the onset of depression, or had
43
44 20 comorbidities such as hypertension, diabetes as well as heart disease had a greater risk of
45
46 21 stroke.

47
48
49 22 **Conclusions:** This study cleared up the significant association between RA and the
50
51 23 subsequent risk of stroke, and further highlighted that the onset of depression within the
52
53 24 treatment process may increase stroke risk for RA subjects. Findings could assist healthcare
54
55 25 providers to pinpoint RA individuals with a higher predisposition of stroke, which could

1 facilitate the provision of appropriate rehabilitation.

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

3
4
5 **Strengths and limitations of this study**

6 ● The main outcome measures employed in this work are validated due to the application
7 of population-based cohort study, based on a nationwide claim database, thus decreasing
8 recall and selection bias.

9 ● This is the first report to clarify the effect of comorbid depression on the stroke risk
10 among RA subjects, which was beneficial for healthcare providers in guiding more
11 effective treatment strategies to improve the clinical outcomes for them.

12 ● Misclassification of diseases and failure to adjust for disease severity might lead to
13 somewhat skewed findings

1 INTRODUCTION

2 Rheumatoid arthritis (RA) is a systemic autoimmune disease manifested as long-term joint
3 damage, chronic debilitating pain, and premature mortality. This disease often affects people
4 30 to 50 years of age and results in disability and inability to work, thus posing a heavy
5 burden on patients with RA, their families and the healthcare system.¹ A review of the
6 financial burdens of RA in the United States showed that the annual direct medical costs of
7 RA reached about \$9 billion, and the total societal costs (the sum of direct and indirect costs)
8 was estimated to exceed \$39 billion.²

9 Despite improvements in the diagnosis and treatment of RA, patients with RA still have a
10 lower life expectancy (6-7 years) when compared with the general population.³ This
11 increased mortality is due primarily to cardiovascular diseases such as myocardial infarction
12 (MI) or stroke.⁴⁻⁶ Nevertheless, unlike the studies of RA predicting the onset of MI,^{4 7 8}
13 evidence for an association between RA and the development of stroke remains conflicting. A
14 meta-analysis of 15 articles indicated that individuals with RA had a 63% higher risk for MI,
15 but not for stroke [odds ratio (OR)= 1.14, 95% confidence interval (CI) = 0.86-1.51] when
16 compared to the general population.⁴ On the other hand, a recent Danish study involving
17 18,247 patients with RA, who were followed for a median of 4.8 years, indicated that those
18 with RA had a 30% higher risk of stroke than a non-RA group.⁹ Another meta-analysis of 17
19 studies reported that patients with RA had a higher predisposition to develop stroke than did
20 non-RA subjects, with a pool risk of 1.91.⁸

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

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

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

22 **METHODS**

23 **Data sources**

24 The data analyzed in this cohort study were retrieved from the Longitudinal Health Insurance
25

1 Database (LHID), maintained by the Bureau of NHI (BNHI) and provided to scientists in
2 Taiwan for research purposes. Taiwan launched a single-payer NHI Program in 1995 in order
3 to remove financial barriers to medical care for all legal residents. At the end of 2010, more
4 than 99% of Taiwan's population had enrolled in this program.¹⁹ The LHID is a subset of the
5 NHI database, and contains comprehensive utilization and enrollment information for one
6 million randomly selected NHI beneficiaries, representing 5% of all enrollees in Taiwan in
7 2000. Because a multistage stratified systematic sampling method was used for this study,
8 there were no statistically significant differences regarding gender or age between the
9 sampled group and the total number of enrollees.¹⁹ This study complied with the guidelines
10 of the Declaration of Helsinki and was approved by the local institutional review board and
11 ethics committee of Buddhist Dalin Tzu Chi Hospital, Taiwan (No. B10004021-1). As the
12 LHID data files contained only de-identified secondary data, the need for informed consent
13 from individual patient consent was waived by the institutional review board.

14 **Study subjects**

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

23 For each case of RA, we randomly selected, from the remaining insured population
24 without RA, four control subjects who were frequency matched to the RA case in terms of
25

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

17 **Demographic characteristics and comorbid conditions**

18 Demographic characteristics analyzed in this study included age, gender, monthly income,
19 and level of urbanization of the subject's employment or residential area. Monthly income
20 was grouped into 3 levels: $\leq 17,880$ New Taiwan Dollars (NTD)\$, 17,881-43,900 NTD\$, and
21 $\geq 43,901$ NTD\$. All 316 cities and townships in Taiwan were classified into 7 ordered levels
22 of urbanization based on various indicators including population density, proportion of
23 residents with college or higher education, percentage of elderly (> 65 years of age) people,
24 proportion of the workforce in agriculture, and number of physicians per 10^5 people.²⁰ Level
25 1 refers to the "most urbanized" and level 7 refers to the "least urbanized" areas. The level of

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

9 **Statistical analysis**

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

23 **RESULTS**

24 Table 1 shows the distribution of demographic data and comorbid medical disorders for the
25 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 stroke 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

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

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

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

1
2
3 1 First, the presence of symptoms of depression is likely linked to treatment nonadherence and
4
5 2 an increase in unhealthy lifestyles, such as poor nutrition and physical inactivity, and these
6
7 3 may contribute to the development of a stroke.¹⁵ Second, symptoms of depression can cause
8
9 4 systematic inflammation that worsens the manifestations of RA. Recent studies demonstrated
10
11 5 that depressed individuals with RA had higher circulating levels of inflammatory markers
12
13 6 such as IL-6, TNF- α and C-reactive protein (CRP)¹⁰; all of which play key roles in the
14
15 7 pathogenesis of stroke.¹⁸ Additionally, recent research have focused on another signaling
16
17 8 pathway, namely, gut-to-brain communication, which suggested that intestinal dysfunction
18
19 9 induced by negative moods may cause the activation of immune cells and the production of
20
21 10 cytokines in the gut as well, thereby inducing the expression of inflammatory markers, which
22
23 11 in turn induce initiation and progression of neurological disorders.^{24 25} It is also noteworthy
24
25 12 that only one in five patients with depression is estimated to have been treated and referred to
26
27 13 appropriate psychiatric services after the onset of RA.²⁶ The implementation of a
28
29 14 standardized psychosocial assessment, and of patient care procedures, as part of routine care
30
31 15 may therefore help in the early referral of high-risk patients for further therapeutic
32
33 16 interventions.

34
35
36
37
38 17 This study also indicated that males were at a 1.17-fold greater risk of stroke than females
39
40 18 in the RA cohorts. No previous study has examined gender differences in the risk of stroke
41
42 19 among patients with RA, which renders a comparison of results impossible. Nevertheless,
43
44 20 this is consistent with the observation that males have a higher risk of stroke than females
45
46 21 among the general population.²⁷ There are several possible explanations for this result. First,
47
48 22 women appear to have greater health consciousness with regard to stroke prevention than
49
50 23 men, and immediately seek medical therapy at the slightest irregularity in well-being, so the
51
52 24 onset of chronic diseases may be expected to be lower in women than in men.²⁸ Second,
53
54 25 lifetime exposure to ovarian estrogens may protect against the risk of stroke for females.
55
56
57
58
59
60

1
2
3 1 Extensive animal experiments and human studies have supported the function of estrogens as
4
5 2 neuroprotectants against neurodegenerative diseases, particularly stroke, through enhancing
6
7 3 basal release of Nitric Oxide (NO) to curb coronary thrombosis and atherosclerosis.^{27 29}
8
9
10 4 Recently, estrogenic agents have been suggested as a novel therapeutic approach to treat the
11
12 5 neuronal damages associated with global ischemia.^{27 30}

13
14 6 Consistent with the findings of prior studies conducted in the general population,^{16 27} age
15
16 7 was positively correlated with the risk of stroke among patients with RA. We speculate that
17
18 8 with aging, blood vessels gradually lose elasticity and gain resistance, slowing the flow of
19
20 9 blood. Moreover, with poor circulation, fat is prone to accumulate in the abdomen and release
21
22 10 free fatty acids into the serum, leading to higher insulin resistance, elevated serum
23
24 11 triglycerides, and increased levels of LDL-C,³¹ thereby resulting in the greater risk of stroke.

25
26
27 12 Findings of this study indicate that patients with RA and several comorbid conditions such
28
29 13 as hypertension, diabetes or heart disease had a significantly greater risk for stroke. Those
30
31 14 with chronic kidney disease and cancer showed a tendency for stroke, but the association
32
33 15 failed to reach statistical significance. Despite the lack of comparative studies on the effects
34
35 16 of comorbid conditions on stroke among patients with RA, our findings are consistent with
36
37 17 past arguments made in the literature.⁶ The elevated risk of stroke may be attributed to
38
39 18 several causes. For example, insulin resistance and hypertension are common cardiovascular
40
41 19 risk factors among individuals with RA.³² Moreover, the functional impairment induced by
42
43 20 comorbid conditions may lead to limited physical activity which could, very likely, trigger
44
45 21 additional risk of stroke. Finally, the immunosuppressive therapies used for patients with RA
46
47 22 have been found to have deleterious effects. Some review articles indicated that the use of
48
49 23 corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) may be related to the risk
50
51 24 of cardiovascular events.^{6 18} Before prescribing these drugs, rheumatologists should carefully
52
53 25 appraise the inherent cerebrovascular or cardiovascular risk among patients with RA.
54
55
56
57
58
59
60

1
2
3 1 Several limitations of this study should be considered when interpreting these results. First,
4
5 2 we could not account for some potential confounding factors such as social networks, coping
6
7 3 modes, or educational level because these data were unavailable in the LHID. Future research
8
9 4 controlling for those untested variables is needed to better determine if the present findings
10
11 5 are replicated across diverse groups of individuals. Second, the identification of exposure and
12
13 6 outcome were based on the ICD-9-CM, and misclassification is inevitable. However, we
14
15 7 selected only those cases with RA, depression, or stroke after they were recorded as having
16
17 8 either at least three outpatient visits reporting consistent diagnoses, or one inpatient
18
19 9 admission. This approach is likely to minimize such errors. Furthermore, as the approach to
20
21 10 coding and the availability of data were similar regardless of the RA and depression status,
22
23 11 we believe the misclassification was likely to be random and thus, if indeed occurring, would
24
25 12 tend to draw the estimated HRs to the direction of the null values. Second, it should also be
26
27 13 noted that the NHI of Taiwan randomly samples claims from hospitals, interviews patients,
28
29 14 and reviews medical charts to verify the accuracy of medical records. Third, because data
30
31 15 regarding the severity of RA were unavailable in this databases. Nonetheless, the multivariate
32
33 16 analysis applied in this study considered the impact of several comorbid conditions including
34
35 17 hypertension, diabetes, heart disease, chronic kidney disease, tobacco use, alcohol
36
37 18 dependence syndrome and cancer. Furthermore, we performed a sensitivity analysis using on
38
39 19 those RA subjects without comorbid conditions to test the robustness of our findings and
40
41 20 found that depressed RA subjects with no known comorbid condition still had a higher risk of
42
43 21 stroke when compared to those without RA and depression, with an adjusted HR of 1.65
44
45 22 (95% CI = 1.23-2.03). Thus, the impact of disease severity is unlikely to compromise
46
47 23 findings of this study. Fourth, evidence derived from any observational cohort study is
48
49 24 generally less robust than that obtained from randomized control trials since cohort studies
50
51 25 are subject to various biases related to confounding effects. Despite our careful efforts to
52
53
54
55
56
57
58
59
60

1
2
3 1 maintain adequate control of confounding factors, unpredictable biases could still remain if
4
5 2 they stem from unmeasured or unknown confounders. Notwithstanding these limitations, the
6
7 3 strengths of this study must also be acknowledged and these include the immediate
8
9 4 availability of data, the comprehensiveness of the database, and the statistical power derived
10
11 5 from the samples' large sizes. In addition, this retrospective 15-year cohort study allowed us
12
13 6 to clearly determine if the symptoms of depression exacerbated the risk of stroke for those
14
15 7 with RA, and the corresponding findings could serve as a reference for future treatment
16
17 8 strategies.

19
20
21 9 In conclusion, this study demonstrated that patients with RA and comorbid depression
22
23 10 were more than twice as likely to have a stroke than were those of the healthy controls. We
24
25 11 further found that the factors contributing to the high risk of stroke included being male, older,
26
27 12 as well as having depression and a comorbid condition such as hypertension, diabetes or heart
28
29 13 disease. Healthcare providers may, therefore, be able to better recognize those demographic
30
31 14 and diseases characteristics that contribute to the risk of stroke among patients with RA from
32
33 15 this population-based study. Findings also supported that the routine screening of depression
34
35 16 and the institution of patient-centered interventions may represent an important strategy for
36
37 17 improving clinical outcomes for RA patients.

38
39
40
41
42 18

43 44 19 **Author affiliations**

45
46 20 ¹ Department of Medical Research, Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical
47
48 21 Foundation, 2 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan

49
50 22 ² Department of Environmental and Occupational Health, College of Medicine, National
51
52 23 Cheng Kung University, 138 Sheng-Li Road, Tainan 70428, Taiwan

53
54 24 ³ Department of Nursing, Tzu Chi University of Science and Technology, 880 Chien-Kuo
55
56 25 Road Section 2, Hualien 62247, Taiwan

1
2
3 1 ⁴Division of Allergy, Immunology and Rheumatology, Dalin Tzuchi Hospital, The Buddhist
4
5 2 Tzuchi Medical Foundation, 2 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan

6
7 3 ⁵School of Medicine, Tzu Chi University, 701 Jhongyang Road Section 3, Hualien 97004,
8
9 4 Taiwan

10
11 5 ⁶Rehabilitation Counseling Program, Portland State University, Portland, OR 97207-0751,
12
13 6 USA

14
15 7 ⁷Department of Nursing, Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, 2
16
17 8 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan

18
19 9 ⁸Department of Occupational and Environmental Medicine, National Cheng Kung University
20
21 10 Hospital, 138 Sheng-Li Road, Tainan 70428, Taiwan

22
23 11 ⁹Occupational Safety, Health, and Medicine Research Center, National Cheng Kung
24
25 12 University, 138 Sheng-Li Road, Tainan 70428, Taiwan

26
27
28
29
30
31 13

32 14 **Acknowledgements** The study is based in part on data from the National Health Insurance
33
34 15 Research Database provided by the Bureau of National Health Insurance, Department of
35
36 16 Health and managed by National Health Research Institutes. The interpretation and
37
38 17 conclusions contained herein do not represent those of the Bureau of National Health
39
40 18 Insurance, Department of Health or National Health Research Institutes. This research was
41
42 19 supported by Dalin Tzuchi Hospital (Grant Number DTCRD103(2)-E-05). Lu MC, Chiu SY
43
44 20 and Guo HR contributed equally to this work.

45
46
47
48 21

49
50 22 **Contributors** All the authors approved the contents of the submitted article. Conceived and
51
52 23 designed the experiments: TTY CSY. Analyzed the data: TTY GHR. Contributed
53
54 24 reagents/materials/analysis tools: TTY LNS LMC GHR. Wrote the paper: TTY LH GHR.
55
56 25 Final approval of manuscript: TTY LNS LH CSY LMC GHR.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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. B10004021-1).

Data sharing statement No additional data are available.

Funding The researcher received no specific grant form any funding agency in the public, commercial or not-for-profit sectors.

For peer review only

References

- 1 Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. *Am Fam Physician* 2005;72:1037-47.
- 2 Birnbaum H, Pike C, Kaufman R, *et al.* Societal cost of rheumatoid arthritis patients in the US. *Cur Med Res Opin* 2010;26:77-90.
- 3 Lassere MN, Rappo J, Portek IJ, *et al.* How many life years are lost in patients with rheumatoid arthritis? Secular cause-specific and all-cause mortality in rheumatoid arthritis, and their predictors in a long-term Australian cohort study. *Intern Med J* 2013;43:66-72.
- 4 Lévy L, Fautrel B, Barnetche T, *et al.* Incidence and risk of fatal myocardial infarction and stroke events in rheumatoid arthritis patients. A systematic review of the literature. *Clin Exp Rheumatol* 2008;26:673-79.
- 5 Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008;26:S35-61.
- 6 Zha AM, Napoli M, Behrouz R. Prevention of stroke in rheumatoid arthritis. *Curr Neurol Neurosci Rep* 2015;15:1-10.
- 7 Farmer A, Korszun A, Owen MJ, *et al.* Medical disorders in people with recurrent depression. *Br J Psychiatry* 2008;192:351-5.
- 8 Meune C, Touzé E, Trinquart L, *et al.* High risk of clinical cardiovascular events in rheumatoid arthritis: levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. *Arch Cardiovasc Dis* 2010;103:253-61.
- 9 Lindhardsen J, Ahlehoff O, Gislason GH, *et al.* Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ* 2012;344:e1257.
- 10 Margaretten M, Julian L, Katz P, *et al.* Depression in patients with rheumatoid arthritis: description, causes and mechanisms. *Int J Clin Rheumatol* 2011;6:617-23.
- 11 Ang DC, Choi H, Kroenke K, *et al.* Comorbid depression is an independent risk factor for mortality in patients with rheumatoid arthritis. *J Rheumatol* 2005;32:1013-19.
- 12 Matcham F, Rayner L, Steer S, *et al.* The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)* 2013;52:2136-48.
- 13 Lu M, Guo HR, Lin MC, *et al.* Bidirectional associations between rheumatoid arthritis and depression: a nationwide longitudinal study. *Sci Rep* 2016;6:20647.
- 14 Joyce AT, Smith P, Khandker R, *et al.* Hidden cost of rheumatoid arthritis (RA): estimating cost of comorbid cardiovascular disease and depression among patients with RA. *J Rheumatol* 2009;36:743-52.

- 1
2
3 1 15 Lee HC, Lin HC, Tsai SY. Severely depressed young patients have over five times
4 2 increased risk for stroke: a 5-year follow-up study. *Biol Psychiatry* 2008;64:912-5.
5 3 16 Behrouz R. The risk of ischemic stroke in major rheumatic disorders. *J Neuroimmunol*
6 4 2014;277:1-5.
7 5 17 Irwin MR, Davis M, Zautra A. Behavioral comorbidities in rheumatoid arthritis: a
8 6 psychoneuroimmunological perspective. *Psychiatr Times* 2008;25:1.
9 7 18 van den Oever IA, van Sijl AM, Nurmohamed MT. Management of cardiovascular
10 8 risk in patients with rheumatoid arthritis: evidence and expert opinion. *Ther Adv*
11 9 *Musculoskelet Dis* 2013;5:166-81.
12 10 19 National Health Insurance Research Database, Taiwan.
13 11 http://nhird.nhri.org.tw/date_cohort.html (accessed 8 May 2015).
14 12 20 Liu CY, Hung YT, Chuang YL, *et al.* Incorporating development stratification of
15 13 Taiwan townships into sampling design of large scale health interview survey. *J*
16 14 *Health Manag* 2006;4:1-22.
17 15 21 Liou TH, Huang SW, Lin JW, *et al.* Risk of stroke in patients with rheumatism: a
18 16 nationwide longitudinal population-based study. *Sci Rep* 2014;4: 5110.
19 17 22 Lakhan SE, Kirchgessner A, Tepper D, *et al.* Matrix metalloproteinases and
20 18 blood-brain barrier disruption in acute ischemic stroke. *Front Neurol* 2013;4:32.
21 19 23 Yang Y, Rosenberg GA. Matrix metalloproteinases as therapeutic targets for stroke.
22 20 *Brain Res* 2015;1623:30-8.
23 21 24 Muscatello MR, Bruno A, Scimeca G, Pandolfo G, Zoccali RA. Role of negative
24 22 affects in pathophysiology and clinical expression of irritable bowel syndrome. *World*
25 23 *J Gastroenterol* 2014;20:7570-86.
26 24 25 D'Mello C, Swain MG. Immune-to-brain communication pathways in
27 25 inflammation-associated sickness and depression. *Curr Top Behav Neurosci* 2016
28 26 [Epub ahead of print]
29 27 26 Sleath B, Chewning B, de Vellis BM, *et al.* Communication about depression during
30 28 rheumatoid arthritis patient visits. *Arthritis Rheum* 2008;59:186-91.
31 29 27 Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology: a
32 30 systematic review. *Stroke* 2009;40:1082-90.
33 31 28 Stroebele N, Müller-Riemenschneider F, Nolte CH, *et al.* Knowledge of risk factors,
34 32 and warning signs of stroke: a systematic review from a gender perspective. *Int J*
35 33 *Stroke* 2011;6:60-6.
36 34 29 Liu R, Yang SH. Window of opportunity: estrogen as a treatment for ischemic stroke.
37 35 *Brain Res* 2013;1514:83-90.
38 36 30 Etgen AM, Jover-Mengual T, Zukin RS. Neuroprotective actions of estradiol and
39 37 novel estrogen analogs in ischemia: translational implications. *Front Neuroendocrinol*
40 38 2011;32:336-52.

- 1
2
3 1 31 Ai M, Otokozawa S, Asztalos BF, *et al.* Small dense LDL cholesterol and coronary
4 2 heart disease: results from the Framingham offspring study. *Clin Chem*
5 3 2010;56:967-76.
6 4 32 Liao KP, Solomon DH. Traditional cardiovascular risk factors, inflammation and
7 5 cardiovascular risk in rheumatoid arthritis. *Rheumatology* 2013;52:45-52.
8 6
9 7
10 8
11 9
12 10
13 11
14 12
15 13
16 14
17 15
18 16
19 17
20 18
21 19
22 20
23 21
24 22
25 23
26 24
27 25
28 26
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **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

2

3

4

5

6

7

8

9

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

1
2
3
4 1
5
6 2 **Table 3 Multivariate analysis of factors for the incidence of stroke among patients with**
7
8 3 **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

4 Adjusted for all variables in the model.

5

6

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014233.R2
Article Type:	Research
Date Submitted by the Author:	07-Dec-2016
Complete List of Authors:	Tsai, Tzung-Yi; Buddhist Dalin Tzu Chi General Hospital, Department of Medical Research Lu, Ming-Chi ; Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, Division of Allergy, Immunology and Rheumatology Livneh, Hanoch ; Portland State University, Portland, OR 97207-0751, USA Chiu, Shan-Yan ; Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, Department of Nursing Lai, Ning-Sheng; Buddhist Dalin Tzu Chi General Hospital, Division of Allergy, Immunology and Rheumatology Guo, How-Ran; National Cheng Kung University, Department of Environmental and Occupational Health, College of Medicine
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rheumatology, Mental health, Neurology
Keywords:	rheumatoid arthritis, Depression & mood disorders < PSYCHIATRY, Stroke < NEUROLOGY, cohort study

SCHOLARONE™
Manuscripts

only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

3
4 Tzung-Yi Tsai^{1,2,3}, Ming-Chi Lu^{4,5}, Hanoch Livneh⁶, Shan-Yun Chiu⁷, Ning-Sheng Lai^{4,5},
5 How-Ran Guo^{2,8,9*}

6
7 ¹ Department of Medical Research, Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical
8 Foundation, 2 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan

9 ² Department of Environmental and Occupational Health, College of Medicine, National
10 Cheng Kung University, 138 Sheng-Li Road, Tainan 70428, Taiwan

11 ³ Department of Nursing, Tzu Chi University of Science and Technology, 880 Chien-Kuo
12 Road Section 2, Hualien 62247, Taiwan

13 ⁴ Division of Allergy, Immunology and Rheumatology, Dalin Tzuchi Hospital, The Buddhist
14 Tzuchi Medical Foundation, 2 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan

15 ⁵ School of Medicine, Tzu Chi University, 701 Jhongyang Road Section 3, Hualien 97004,
16 Taiwan

17 ⁶ Rehabilitation Counseling Program, Portland State University, Portland, OR 97207-0751,
18 USA

19 ⁷ Department of Nursing, Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, 2
20 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan

21 ⁸ Department of Occupational and Environmental Medicine, National Cheng Kung University
22 Hospital, 138 Sheng-Li Road, Tainan 70428, Taiwan

23 ⁹ Occupational Safety, Health, and Medicine Research Center, National Cheng Kung
24 University, 138 Sheng-Li Road, Tainan 70428, Taiwan

25

1 Correspondence and requests for materials should be addressed to Guo HR.

2 Email: dm732024@tzuchi.com.tw or hrguo@mail.ncku.edu.tw

3 TEL: 886-6-2353535 ext. 5802

4 FAX: 886-6-2752484

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

1
2
3 1 **ABSTRACT**

4
5 2 **Objectives:** Comorbid depression is common and undertreated in patients with rheumatoid
6
7 3 arthritis (RA). It remains uncertain whether comorbid depression provoked the risk of poor
8
9 4 clinical outcome, stroke in particular, among RA patients. This work aimed to determine if
10
11 5 depression onset during the treatment process increases stroke risk for patients with RA as
12
13 6 compared to those with (a) neither RA nor depression, (b) RA only, and (c) depression only.

14
15
16 7 **Design:** A nationwide, population-based cohort study.

17
18 8 **Setting:** Taiwan's Longitudinal Health Insurance Database.

19
20
21 9 **Participants:** We identified 8,045 subjects with a newly diagnosed RA between 1997 and
22
23 10 2010, together with 32,600 subjects without RA matched by age, gender and index date. All
24
25 11 subjects were further divided into four groups based on whether they were diagnosed with
26
27 12 comorbid depression during the follow-up period.

28
29
30 13 **Main outcome measure:** The incidence rate and hazard ratio for incident stroke were
31
32 14 estimated by the end of 2012 using Cox proportional-hazard regression.

33
34 15 **Results:** We discovered that RA patients with the comorbid depression exhibited the highest
35
36 16 risk of stroke, with an adjusted hazard ratios (HRs) of 2.18 (95% confidence interval =
37
38 17 1.87-2.54). Those with RA only or those with depression only still had the higher risk of
39
40 18 stroke by 43% and 57% as compared with subjects without either condition. Multivariate
41
42 19 analysis showed RA subjects who were male or older, incurred the onset of depression, or had
43
44 20 comorbidities such as hypertension, diabetes as well as heart disease had a greater risk of
45
46 21 stroke.

47
48
49 22 **Conclusions:** This study cleared up the significant association between RA and the
50
51 23 subsequent risk of stroke, and further highlighted that the onset of depression within the
52
53 24 treatment process may increase stroke risk for RA subjects. Findings could assist healthcare
54
55 25 providers to pinpoint RA individuals with a higher predisposition of stroke, which could

1 facilitate the provision of appropriate rehabilitation.

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

3
4
5 **Strengths and limitations of this study**

6 ● The main outcome measures employed in this work are validated due to the application
7 of population-based cohort study, based on a nationwide claim database, thus decreasing
8 recall and selection bias.

9 ● This is the first report to clarify the effect of comorbid depression on the stroke risk
10 among RA subjects, which was beneficial for healthcare providers in guiding more
11 effective treatment strategies to improve the clinical outcomes for them.

12 ● Misclassification of diseases and failure to adjust for disease severity might lead to
13 somewhat skewed findings

1 INTRODUCTION

2 Rheumatoid arthritis (RA) is a systemic autoimmune disease manifested as long-term joint
3 damage, chronic debilitating pain, and premature mortality. This disease often affects people
4 30 to 50 years of age and results in disability and inability to work, thus posing a heavy
5 burden on patients with RA, their families and the healthcare system.¹ A review of the
6 financial burdens of RA in the United States showed that the annual direct medical costs of
7 RA reached about \$9 billion, and the total societal costs (the sum of direct and indirect costs)
8 was estimated to exceed \$39 billion.²

9 Despite improvements in the diagnosis and treatment of RA, patients with RA still have a
10 lower life expectancy (6-7 years) when compared with the general population.³ This
11 increased mortality is due primarily to cardiovascular diseases such as myocardial infarction
12 (MI) or stroke.⁴⁻⁶ Nevertheless, unlike the studies of RA predicting the onset of MI,^{4 7 8}
13 evidence for an association between RA and the development of stroke remains conflicting. A
14 meta-analysis of 15 articles indicated that individuals with RA had a 63% higher risk for MI,
15 but not for stroke [odds ratio (OR)= 1.14, 95% confidence interval (CI) = 0.86-1.51] when
16 compared to the general population.⁴ On the other hand, a recent Danish study involving
17 18,247 patients with RA, who were followed for a median of 4.8 years, indicated that those
18 with RA had a 30% higher risk of stroke than a non-RA group.⁹ Another meta-analysis of 17
19 studies reported that patients with RA had a higher predisposition to develop stroke than did
20 non-RA subjects, with a pool risk of 1.91.⁸

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

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

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

22

23 **METHODS**

24 **Data sources**

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

1 Database (LHID), maintained by the Bureau of NHI (BNHI) and provided to scientists in
2 Taiwan for research purposes. Taiwan launched a single-payer NHI Program in 1995 in order
3 to remove financial barriers to medical care for all legal residents. At the end of 2010, more
4 than 99% of Taiwan's population had enrolled in this program.¹⁹ The LHID is a subset of the
5 NHI database, and contains comprehensive utilization and enrollment information for one
6 million randomly selected NHI beneficiaries, representing 5% of all enrollees in Taiwan in
7 2000. Because a multistage stratified systematic sampling method was used for this study,
8 there were no statistically significant differences regarding gender or age between the
9 sampled group and the total number of enrollees.¹⁹ This study complied with the guidelines
10 of the Declaration of Helsinki and was approved by the local institutional review board and
11 ethics committee of Buddhist Dalin Tzu Chi Hospital, Taiwan (No. B10004021-1). As the
12 LHID data files contained only de-identified secondary data, the need for informed consent
13 from individual patient consent was waived by the institutional review board.

14 **Study subjects**

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

23 For each case of RA, we randomly selected, from the remaining insured population
24 without RA, four control subjects who were frequency matched to the RA case in terms of
25

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

17 **Demographic characteristics and comorbid conditions**

18 Demographic characteristics analyzed in this study included age, gender, monthly income,
19 and level of urbanization of the subject's employment or residential area. Monthly income
20 was grouped into 3 levels: $\leq 17,880$ New Taiwan Dollars (NTD)\$, 17,881-43,900 NTD\$, and
21 $\geq 43,901$ NTD\$. All 316 cities and townships in Taiwan were classified into 7 ordered levels
22 of urbanization based on various indicators including population density, proportion of
23 residents with college or higher education, percentage of elderly (> 65 years of age) people,
24 proportion of the workforce in agriculture, and number of physicians per 10^5 people.²⁰ Level
25 1 refers to the "most urbanized" and level 7 refers to the "least urbanized" areas. The level of

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

9 **Statistical analysis**

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

23 **RESULTS**

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

1 (p = 0.001), reside in a rural area (p < 0.001), have more visits seeking medical care (p <
2 0.001), and suffer comorbid conditions including hypertension, diabetes, heart disease,
3 chronic kidney disease or alcohol dependence syndrome (all p < 0.01).

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

11 Table 3 presents Cox regression model of factors related to the onset of stroke among
12 individuals with RA. Compared to those without depression, those with depression were
13 significantly more likely to develop a stroke (adjusted HRs = 1.63, 95% CI = 1.37-1.92) after
14 adjustment for confounding factors. Results also showed that age was related to the risk of
15 stroke. There was a 5% increase in the risk of stroke for each 1-year increment (95% CI =
16 1.03-1.08). Compared with females, males had an adjusted HRs of 1.17 for stroke (95% CI =
17 1.03-1.28). Additionally, some comorbid conditions including hypertension, heart disease and
18 diabetes increased the risk of stroke with adjusted HRs of 1.51 (95% CI = 1.40-1.84), 1.48
19 (95% CI = 1.31-1.73) and 1.34 (95% CI = 1.16-1.56), respectively.

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

24 25 **DISCUSSION**

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

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

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

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

1
2
3 1 First, the presence of symptoms of depression is likely linked to treatment nonadherence and
4
5 2 an increase in unhealthy lifestyles, such as poor nutrition and physical inactivity, and these
6
7 3 may contribute to the development of a stroke.¹⁵ Second, symptoms of depression can cause
8
9 4 systematic inflammation that worsens the manifestations of RA. Recent studies demonstrated
10
11 5 that depressed individuals with RA had higher circulating levels of inflammatory markers
12
13 6 such as IL-6, TNF- α and C-reactive protein (CRP)¹⁰; all of which play key roles in the
14
15 7 pathogenesis of stroke.¹⁸ Additionally, recent research have focused on another signaling
16
17 8 pathway, namely, gut-to-brain communication, which suggested that intestinal dysfunction
18
19 9 induced by negative moods may cause the activation of immune cells and the production of
20
21 10 cytokines in the gut as well, thereby inducing the expression of inflammatory markers, which
22
23 11 in turn induce initiation and progression of neurological disorders.^{24 25} It is also noteworthy
24
25 12 that only one in five patients with depression is estimated to have been treated and referred to
26
27 13 appropriate psychiatric services after the onset of RA.²⁶ The implementation of a
28
29 14 standardized psychosocial assessment, and of patient care procedures, as part of routine care
30
31 15 may therefore help in the early referral of high-risk patients for further therapeutic
32
33 16 interventions.

34
35
36
37
38 17 This study also indicated that males were at a 1.17-fold greater risk of stroke than females
39
40 18 in the RA cohorts. No previous study has examined gender differences in the risk of stroke
41
42 19 among patients with RA, which renders a comparison of results impossible. Nevertheless,
43
44 20 this is consistent with the observation that males have a higher risk of stroke than females
45
46 21 among the general population.²⁷ There are several possible explanations for this result. First,
47
48 22 women appear to have greater health consciousness with regard to stroke prevention than
49
50 23 men, and immediately seek medical therapy at the slightest irregularity in well-being, so the
51
52 24 onset of chronic diseases may be expected to be lower in women than in men.²⁸ Second,
53
54 25 lifetime exposure to ovarian estrogens may protect against the risk of stroke for females.
55
56
57
58
59
60

1
2
3 1 Extensive animal experiments and human studies have supported the function of estrogens as
4
5 2 neuroprotectants against neurodegenerative diseases, particularly stroke, through enhancing
6
7 3 basal release of Nitric Oxide (NO) to curb coronary thrombosis and atherosclerosis.^{27 29}
8
9
10 4 Recently, estrogenic agents have been suggested as a novel therapeutic approach to treat the
11
12 5 neuronal damages associated with global ischemia.^{27 30}

13
14 6 Consistent with the findings of prior studies conducted in the general population,^{16 27} age
15
16 7 was positively correlated with the risk of stroke among patients with RA. We speculate that
17
18 8 with aging, blood vessels gradually lose elasticity and gain resistance, slowing the flow of
19
20 9 blood. Moreover, with poor circulation, fat is prone to accumulate in the abdomen and release
21
22 10 free fatty acids into the serum, leading to higher insulin resistance, elevated serum
23
24 11 triglycerides, and increased levels of LDL-C,³¹ thereby resulting in the greater risk of stroke.

25
26
27 12 Findings of this study indicate that patients with RA and several comorbid conditions such
28
29 13 as hypertension, diabetes or heart disease had a significantly greater risk for stroke. Those
30
31 14 with chronic kidney disease and cancer showed a tendency for stroke, but the association
32
33 15 failed to reach statistical significance. Despite the lack of comparative studies on the effects
34
35 16 of comorbid conditions on stroke among patients with RA, our findings are consistent with
36
37 17 past arguments made in the literature.⁶ The elevated risk of stroke may be attributed to
38
39 18 several causes. For example, insulin resistance and hypertension are common cardiovascular
40
41 19 risk factors among individuals with RA.³² Moreover, the functional impairment induced by
42
43 20 comorbid conditions may lead to limited physical activity which could, very likely, trigger
44
45 21 additional risk of stroke. Finally, the immunosuppressive therapies used for patients with RA
46
47 22 have been found to have deleterious effects. Some review articles indicated that the use of
48
49 23 corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) may be related to the risk
50
51 24 of cardiovascular events.^{6 18} Before prescribing these drugs, rheumatologists should carefully
52
53 25 appraise the inherent cerebrovascular or cardiovascular risk among patients with RA.
54
55
56
57
58
59
60

1
2
3 1 Several limitations of this study should be considered when interpreting these results. First,
4
5 2 we could not account for some potential confounding factors such as social networks, coping
6
7 3 modes, or educational level because these data were unavailable in the LHID. Future research
8
9 4 controlling for those untested variables is needed to better determine if the present findings
10
11 5 are replicated across diverse groups of individuals. Second, the identification of exposure and
12
13 6 outcome were based on the ICD-9-CM, and misclassification is inevitable. However, we
14
15 7 selected only those cases with RA, depression, or stroke after they were recorded as having
16
17 8 either at least three outpatient visits reporting consistent diagnoses, or one inpatient
18
19 9 admission. This approach is likely to minimize such errors. Furthermore, as the approach to
20
21 10 coding and the availability of data were similar regardless of the RA and depression status,
22
23 11 we believe the misclassification was likely to be random and thus, if indeed occurring, would
24
25 12 tend to draw the estimated HRs to the direction of the null values. Second, it should also be
26
27 13 noted that the NHI of Taiwan randomly samples claims from hospitals, interviews patients,
28
29 14 and reviews medical charts to verify the accuracy of medical records. Third, because data
30
31 15 regarding the severity of RA were unavailable in this databases. Nonetheless, the multivariate
32
33 16 analysis applied in this study considered the impact of several comorbid conditions including
34
35 17 hypertension, diabetes, heart disease, chronic kidney disease, tobacco use, alcohol
36
37 18 dependence syndrome and cancer. Furthermore, we performed a sensitivity analysis using on
38
39 19 those RA subjects without comorbid conditions to test the robustness of our findings and
40
41 20 found that depressed RA subjects with no known comorbid condition still had a higher risk of
42
43 21 stroke when compared to those without RA and depression, with an adjusted HR of 1.65
44
45 22 (95% CI = 1.23-2.03). Thus, the impact of disease severity is unlikely to compromise
46
47 23 findings of this study. Fourth, evidence derived from any observational cohort study is
48
49 24 generally less robust than that obtained from randomized control trials since cohort studies
50
51 25 are subject to various biases related to confounding effects. Despite our careful efforts to
52
53
54
55
56
57
58
59
60

1
2
3 1 maintain adequate control of confounding factors, unpredictable biases could still remain if
4
5 2 they stem from unmeasured or unknown confounders. Notwithstanding these limitations, the
6
7 3 strengths of this study must also be acknowledged and these include the immediate
8
9 4 availability of data, the comprehensiveness of the database, and the statistical power derived
10
11 5 from the samples' large sizes. In addition, this retrospective 15-year cohort study allowed us
12
13 6 to clearly determine if the symptoms of depression exacerbated the risk of stroke for those
14
15 7 with RA, and the corresponding findings could serve as a reference for future treatment
16
17 8 strategies.

19
20
21 9 In conclusion, this study demonstrated that patients with RA and comorbid depression
22
23 10 were more than twice as likely to have a stroke than were those of the healthy controls. We
24
25 11 further found that the factors contributing to the high risk of stroke included being male, older,
26
27 12 as well as having depression and a comorbid condition such as hypertension, diabetes or heart
28
29 13 disease. Healthcare providers may, therefore, be able to better recognize those demographic
30
31 14 and diseases characteristics that contribute to the risk of stroke among patients with RA from
32
33 15 this population-based study. Findings also supported that the routine screening of depression
34
35 16 and the institution of patient-centered interventions may represent an important strategy for
36
37 17 improving clinical outcomes for RA patients.

38
39
40
41 18

42 43 44 19 **Author affiliations**

45
46 20 ¹ Department of Medical Research, Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical
47
48 21 Foundation, 2 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan

49
50 22 ² Department of Environmental and Occupational Health, College of Medicine, National
51
52 23 Cheng Kung University, 138 Sheng-Li Road, Tainan 70428, Taiwan

53
54 24 ³ Department of Nursing, Tzu Chi University of Science and Technology, 880 Chien-Kuo
55
56 25 Road Section 2, Hualien 62247, Taiwan

1
2
3 1 ⁴Division of Allergy, Immunology and Rheumatology, Dalin Tzuchi Hospital, The Buddhist
4
5 2 Tzuchi Medical Foundation, 2 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan

6
7 3 ⁵School of Medicine, Tzu Chi University, 701 Jhongyang Road Section 3, Hualien 97004,
8
9 4 Taiwan

10
11 5 ⁶Rehabilitation Counseling Program, Portland State University, Portland, OR 97207-0751,
12
13 6 USA

14
15
16 7 ⁷Department of Nursing, Dalin Tzuchi Hospital, The Buddhist Tzuchi Medical Foundation, 2
17
18 8 Minsheng Road, Dalin Township, Chiayi 62247, Taiwan

19
20
21 9 ⁸Department of Occupational and Environmental Medicine, National Cheng Kung University
22
23 10 Hospital, 138 Sheng-Li Road, Tainan 70428, Taiwan

24
25 11 ⁹Occupational Safety, Health, and Medicine Research Center, National Cheng Kung
26
27 12 University, 138 Sheng-Li Road, Tainan 70428, Taiwan

28
29
30
31 13

32
33 14 **Acknowledgements** The study is based in part on data from the National Health Insurance
34
35 15 Research Database provided by the Bureau of National Health Insurance, Department of
36
37 16 Health and managed by National Health Research Institutes. The interpretation and
38
39 17 conclusions contained herein do not represent those of the Bureau of National Health
40
41 18 Insurance, Department of Health or National Health Research Institutes. This research was
42
43 19 supported by Dalin Tzuchi Hospital (Grant Number DTCRD103(2)-E-05). Lu MC, Chiu SY
44
45 20 and Guo HR contributed equally to this work.

46
47
48 21

49
50 22 **Contributors** All the authors approved the contents of the submitted article. Conceived and
51
52 23 designed the experiments: TTY CSY. Analyzed the data: TTY GHR. Contributed
53
54 24 reagents/materials/analysis tools: TTY LNS LMC GHR. Wrote the paper: TTY LH GHR.
55
56 25 Final approval of manuscript: TTY LNS LH CSY LMC GHR.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

Funding The researcher received no specific grant form any funding agency in the public, commercial or not-for-profit sectors.

For peer review only

References

- 1 Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. *Am Fam Physician* 2005;72:1037-47.
- 2 Birnbaum H, Pike C, Kaufman R, *et al.* Societal cost of rheumatoid arthritis patients in the US. *Curr Med Res Opin* 2010;26:77-90.
- 3 Lassere MN, Rappo J, Portek IJ, *et al.* How many life years are lost in patients with rheumatoid arthritis? Secular cause-specific and all-cause mortality in rheumatoid arthritis, and their predictors in a long-term Australian cohort study. *Intern Med J* 2013;43:66-72.
- 4 Lévy L, Fautrel B, Barnetche T, *et al.* Incidence and risk of fatal myocardial infarction and stroke events in rheumatoid arthritis patients. A systematic review of the literature. *Clin Exp Rheumatol* 2008;26:673-79.
- 5 Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008;26:S35-61.
- 6 Zha AM, Napoli M, Behrouz R. Prevention of stroke in rheumatoid arthritis. *Curr Neurol Neurosci Rep* 2015;15:1-10.
- 7 Farmer A, Korszun A, Owen MJ, *et al.* Medical disorders in people with recurrent depression. *Br J Psychiatry* 2008;192:351-5.
- 8 Meune C, Touzé E, Trinquart L, *et al.* High risk of clinical cardiovascular events in rheumatoid arthritis: levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. *Arch Cardiovasc Dis* 2010;103:253-61.
- 9 Lindhardsen J, Ahlehoff O, Gislason GH, *et al.* Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ* 2012;344:e1257.
- 10 Margaretten M, Julian L, Katz P, *et al.* Depression in patients with rheumatoid arthritis: description, causes and mechanisms. *Int J Clin Rheumatol* 2011;6:617-23.
- 11 Ang DC, Choi H, Kroenke K, *et al.* Comorbid depression is an independent risk factor for mortality in patients with rheumatoid arthritis. *J Rheumatol* 2005;32:1013-19.
- 12 Matcham F, Rayner L, Steer S, *et al.* The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)* 2013;52:2136-48.
- 13 Lu M, Guo HR, Lin MC, *et al.* Bidirectional associations between rheumatoid arthritis and depression: a nationwide longitudinal study. *Sci Rep* 2016;6:20647.
- 14 Joyce AT, Smith P, Khandker R, *et al.* Hidden cost of rheumatoid arthritis (RA): estimating cost of comorbid cardiovascular disease and depression among patients with RA. *J Rheumatol* 2009;36:743-52.

- 1
2
3 1 15 Lee HC, Lin HC, Tsai SY. Severely depressed young patients have over five times
4 2 increased risk for stroke: a 5-year follow-up study. *Biol Psychiatry* 2008;64:912-5.
5 3 16 Behrouz R. The risk of ischemic stroke in major rheumatic disorders. *J Neuroimmunol*
6 4 2014;277:1-5.
7 5 17 Irwin MR, Davis M, Zautra A. Behavioral comorbidities in rheumatoid arthritis: a
8 6 psychoneuroimmunological perspective. *Psychiatr Times* 2008;25:1.
9 7 18 van den Oever IA, van Sijl AM, Nurmohamed MT. Management of cardiovascular
10 8 risk in patients with rheumatoid arthritis: evidence and expert opinion. *Ther Adv*
11 9 *Musculoskelet Dis* 2013;5:166-81.
12 10 19 National Health Insurance Research Database, Taiwan.
13 11 http://nhird.nhri.org.tw/date_cohort.html (accessed 8 May 2015).
14 12 20 Liu CY, Hung YT, Chuang YL, *et al*. Incorporating development stratification of
15 13 Taiwan townships into sampling design of large scale health interview survey. *J*
16 14 *Health Manag* 2006;4:1-22.
17 15 21 Liou TH, Huang SW, Lin JW, *et al*. Risk of stroke in patients with rheumatism: a
18 16 nationwide longitudinal population-based study. *Sci Rep* 2014;4: 5110.
19 17 22 Lakhan SE, Kirchgessner A, Tepper D, *et al*. Matrix metalloproteinases and
20 18 blood-brain barrier disruption in acute ischemic stroke. *Front Neurol* 2013;4:32.
21 19 23 Yang Y, Rosenberg GA. Matrix metalloproteinases as therapeutic targets for stroke.
22 20 *Brain Res* 2015;1623:30-8.
23 21 24 Muscatello MR, Bruno A, Scimeca G, Pandolfo G, Zoccali RA. Role of negative
24 22 affects in pathophysiology and clinical expression of irritable bowel syndrome. *World*
25 23 *J Gastroenterol* 2014;20:7570-86.
26 24 25 D'Mello C, Swain MG. Immune-to-brain communication pathways in
27 25 inflammation-associated sickness and depression. *Curr Top Behav Neurosci* 2016
28 26 [Epub ahead of print]
29 27 26 Sleath B, Chewing B, de Vellis BM, *et al*. Communication about depression during
30 28 rheumatoid arthritis patient visits. *Arthritis Rheum* 2008;59:186-91.
31 29 27 Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology: a
32 30 systematic review. *Stroke* 2009;40:1082-90.
33 31 28 Stroebele N, Müller-Riemenschneider F, Nolte CH, *et al*. Knowledge of risk factors,
34 32 and warning signs of stroke: a systematic review from a gender perspective. *Int J*
35 33 *Stroke* 2011;6:60-6.
36 34 29 Liu R, Yang SH. Window of opportunity: estrogen as a treatment for ischemic stroke.
37 35 *Brain Res* 2013;1514:83-90.
38 36 30 Etgen AM, Jover-Mengual T, Zukin RS. Neuroprotective actions of estradiol and
39 37 novel estrogen analogs in ischemia: translational implications. *Front Neuroendocrinol*
40 38 2011;32:336-52.

1
2
3 1 31 Ai M, Otokozawa S, Asztalos BF, *et al.* Small dense LDL cholesterol and coronary
4 2 heart disease: results from the Framingham offspring study. *Clin Chem*
5 3 2010;56:967-76.

6 4 32 Liao KP, Solomon DH. Traditional cardiovascular risk factors, inflammation and
7 5 cardiovascular risk in rheumatoid arthritis. *Rheumatology* 2013;52:45-52.
8 6
9 7
10 8
11 9
12 10
13 11
14 12
15 13
16 14
17 15
18 16
19 17
20 18
21 19
22 20
23 21
24 22
25 23
26 24
27 25
28 26
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **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

2

3

4

5

6

7

8

9

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

1
2
3
4 1
5
6 2 **Table 3 Multivariate analysis of factors for the incidence of stroke among patients with**
7
8 3 **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

4 Adjusted for all variables in the model.

5

6

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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	P3 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 (b) For matched studies, give matching criteria and number of exposed and unexposed	P7-P8 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	P8-P9 P9 NA P9 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	P9-P10 NA NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	P9-P10 NA 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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	P10, P22 P21 NA

1				
2	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and	
3			sensitivity analyses	P10
4				
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	P11
7	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or	P14-P15
8			imprecision. Discuss both direction and magnitude of any potential bias	
9				
10	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	P14-P15
11			multiplicity of analyses, results from similar studies, and other relevant evidence	
12	Generalisability	21	Discuss the generalisability (external validity) of the study results	P15
13				
14	Other information			
15	Funding	22	Give the source of funding and the role of the funders for the present study and, if	P17
16			applicable, for the original study on which the present article is based	
17				

18
19 *Give information separately for exposed and unexposed groups.

20
21 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
22 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
23 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
24 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
25 available at <http://www.strobe-statement.org>.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60