Cerebrovascular Disease in Rheumatic Diseases
A Systematic Review and Meta-Analysis

Stewart J. Wiseman, BSc; Stuart H. Ralston, FRCP; Joanna M. Wardlaw, FRCR

Background and Purpose—Some rheumatic diseases are associated with stroke. Less is known about associations with stroke subtypes or stroke risk by age. We quantified the association between stroke, its subtypes, and rheumatic diseases and identified when stroke risk is greatest.

Methods—Searches of EMBASE (from 1980) and MEDLINE (from inception) to end 2014 and manual search of reference lists for studies of stroke and stroke subtypes in rheumatic diseases as well as studies measuring cerebrovascular disease from magnetic resonance imaging.

Results—Prior published meta-analyses and new pooled analyses of any stroke in rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, gout, and psoriasis show an excess risk of stroke over the general population with odds ratio (OR) ranging from 1.51 (95% confidence interval: 1.39–1.62) to 2.13 (1.53–2.98). New meta-analyses of stroke subtypes in rheumatoid arthritis [ischemic: OR, 1.64 (1.32–2.05); hemorrhagic: OR, 1.68 (1.11–2.53)] and systemic lupus erythematosus [ischemic: OR, 2.11 (1.66–2.67); hemorrhagic: OR, 1.82 (1.07–3.09)] show an excess risk of stroke over the general population. Stroke risk across rheumatic diseases is highest in those aged <50 years [OR, 1.79 (1.46–2.20)] and reduces relatively with ageing [≥65 years: OR, 1.14 (0.94–1.38); difference P<0.007]. Inflammatory arthropathies conveyed higher stroke risk than noninflammatory diseases (OR, 1.3, 1.2–1.3). It was not possible to adjust ORs for risk factors or treatments.

Conclusions—Risk of any stroke is higher in most rheumatic diseases than in the general population, particularly <50 years. Rheumatoid arthritis and systemic lupus erythematosus increase ischemic and hemorrhagic stroke risk by 60% to 100% relative to the general population. (Stroke. 2016;47:943-950. DOI: 10.1161/STROKEAHA.115.012052.)

Key Words: arthritis ■ atrophy ■ inflammation ■ rheumatology ■ stroke

Stroke is a major health problem. Overall incidence rates are falling, but better access to medical care and improvements in secondary prevention increase survival, so stroke prevalence, and thus health-care costs, remain high. An ageing population will increase this trend.

Rheumatic diseases such as rheumatoid arthritis (RA) are an independent risk factor for stroke. People with these diseases die prematurely from cardiovascular disease including stroke, so an understanding of stroke risk among these patients is needed to reduce mortality. However, data linking rheumatic diseases with higher stroke risk are based mostly on stroke reported from large population studies, ie, a composite outcome of any stroke. Less is known about associations between rheumatic diseases (inflammatory or noninflammatory) and major stroke subtypes whose mechanisms differ, eg, ischemic versus hemorrhagic stroke, or large artery atheromatous versus intrinsic small vessel ischemic stroke, or with conditions associated with cerebral small vessel disease (SVD), such as cognitive decline and gait disturbances.

Population stroke incidence rises with age. Stroke early in life is rare, yet most of the stroke associated with rheumatic diseases seems to be at younger ages and may level off, as some studies report no risk difference in those ≥65 years. However, there is currently no meta-analysis on the overall association of rheumatic diseases with stroke by age. Clarifying timing of greatest stroke risk has important clinical implications.

Studies to date do not fully explain the increased stroke risk among rheumatic populations by vascular risk factors. A proportion of stroke risk in rheumatic diseases could relate to the higher inflammatory activity seen in many arthropathies, which is systemic, nonresolving, and often only controlled with aggressive antirheumatic drugs. Inflammation, therefore, plausibly explains some of the excess risk because of atheromatous stroke as inflammation is involved in all stages of atherosclerosis from fatty streak formation to plaque disruption. The role of inflammation in SVD is less certain, but inflammation is seen pathologically in the perforating...
arteriolar walls and perivascular tissue. Endothelial damage is a primary step in atherosclerosis and SVD and factors that contribute to endothelial damage (eg, immune complex formation and complement activation) are also seen in rheumatic diseases.

Our aims are to review associations between stroke and rheumatic disease, to summarize incidence rates for stroke subtypes, to calculate pooled rate ratios for stroke subtypes versus the general population, to see if risk is greatest at specific ages; and to determine if rheumatic diseases increase the risk of silent vascular disease on neuroimaging.

Methods

Study Design
We used a systematic approach to assess stroke and stroke subtypes as the outcome measure and various rheumatic diseases as the exposure. Research ethics committee approval was not required. The study was not registered in any database.

Data Sources
We prepared this review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. We used structured MeSH search terms (Table I in the online-only Data Supplement) in Ovid to search EMBASE (from 1980) and MEDLINE (from inception) to 2014 on 14 December 2014. Data were extracted in accordance with MOOSE (Meta-Analyses and Systematic Reviews of Observational Studies) guidelines. We categorized magnetic resonance imaging (MRI) findings according to STRIVE (Standards for Reporting Vascular Changes on Neuroimaging) guidelines. We identified additional papers from reference lists and contacted authors for additional data when required.

Study Selection
We included English language studies reporting on stroke in rheumatic disease and studies that assessed brain imaging features of SVD on MRI. We excluded studies using functional MRI, positron emission tomography, single photon emission computed tomography, and Doppler ultrasound.

Data Extraction
We extracted data on study population demographics, control groups, stroke type (ischemic/hemorrhagic), ischemic stroke subtypes (large artery/lacunar), findings on stroke risk relative to a comparator group, and MRI findings. We noted if studies controlled for age and vascular risk factors.

Quality Assessment
We developed a checklist adapted from STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) to assess the quality of included studies (Table II in the online-only Data Supplement).

Data Synthesis and Analysis
We defined SVD from MRI features as per recent STRIVE neuroimaging standards, being any of recent small subcortical infarcts, white matter hyperintensities (WMH), lacunes, microbleeds, prominent peri-vascular spaces, or atrophy. Clinically, patients might show no symptoms, or they might suffer cognitive impairment or other neurological involvement in addition to stroke (lacunar stroke accounts for ~25% of all ischemic strokes).

We defined stroke incidence rates as number of strokes as a function of a follow-up period and stroke rate ratios as the ratio of stroke incidence rate in the observed group (eg, RA) over incidence rates in the general population. We used unadjusted (crude) rates throughout as different studies controlled for different variables making comparison of uniform adjustments impossible.

We recorded stroke incidence rates when reported and calculated them when not reported but where data (ie, number of stroke events and a follow-up period) were available. We converted all incidence rates to per 100 000 person-years. If follow-up duration (in patient-years) was not specifically reported, we estimated this by multiplying number of patients by the average years of follow-up.

Where a rheumatic disease had contributing data from >1 study, we pooled incidence rates by taking the range of available values, which did not allow us to assess heterogeneity. Next, we calculated a point estimate for incidence rate per 100 000 person-years for individual rheumatic diseases based on the weighted mean, using study size as the weighting factor and then estimated a 95% confidence interval (CI) based on the Poisson distribution as implemented in the epitools package for the statistical programming language R version 3.0.1 (http://www.r-project.org/).

We calculated rate ratios using the Cochrane Collaboration’s Review Manager 5 software when not reported but where required data were available.

Some studies did not provide number of strokes and number of patient-years observed for the control group but instead only provided the rate ratio together with a CI. As per Cochrane Handbo, CI can be converted to standard errors and the natural logarithms of rate ratios may be combined across studies using the generic inverse-variance method. We used this approach to pool stroke risk for ischemic stroke and hemorrhagic stroke and for the age category pooled analysis.

We assessed between-study heterogeneity using the I² statistic.

Results

The search returned 434 titles and abstracts; 69 papers were reviewed in full and 23 studies contributed data to new meta-analyses. We excluded studies that did not measure stroke with appropriate imaging (n=12), pathology studies (n=5), guidelines and review papers (n=4), and small studies (<50 patients) that only described imaging features of SVD (n=25) (Figure I in the online-only Data Supplement).

Any Stroke
Prior meta-analyses and large registry studies of any stroke are reported for completeness (Table III in the online-only Data Supplement). RA [incidence rate ratio (RR), 1.91; 95% CI, 1.73–2.12], ankylosing spondylitis [odds ratio (OR), 1.51; 1.39–1.62] and gout (RR, 1.71; 1.68–1.75), but not osteoarthritis (OA; OR, 1.11; 0.95–1.29), showed higher risk of stroke than the general population.

We add new meta-analyses on any stroke in systemic lupus erythematosus (SLE), psoriasis, and psoriatic arthritis. The pooled odds of any stroke in SLE from 5 studies[13,17,32–34] (772 strokes, 40 652 SLE patients) was 2.13 (1.53–2.98) (Figure II in the online-only Data Supplement). We updated 2 psoriasis meta-analyses[35,36] and added a new meta-analysis for psoriatic arthritis. The pooled odds of any stroke in psoriasis (9 studies[35–45]; 6925 strokes; 400 767 patients) was 1.08 (1.00–1.16) (Figure III in the online-only Data Supplement), and of any stroke in psoriatic arthritis (3 studies[36,41,46] 217 strokes; 12 051 patients) was 1.27 (0.98–1.64) (Figure III in the online-only Data Supplement).

RA (prototypical inflammatory rheumatic disease) showed significant risk of stroke over the general population (n=26 143
patients; OR, 1.91; 1.73–2.12) whereas OA (degenerative) did not (n=40,817 patients; OR, 1.11; 0.95–1.29). In direct comparison, patients with OA alone had lower stroke risk (11,633 RA versus 16,327 OA patients; OR, 1.3; 1.2–1.3, ie, higher stroke risk in RA).

**Stroke Subtypes: Ischemic and Hemorrhagic**

**Incidence**
Table summarizes our meta-analysis of incidence of ischemic and hemorrhagic stroke by different rheumatic diseases with a general population comparator.

**Stroke Risk: Pooled Rate Ratios**
Sufficient data to perform meta-analysis of rate ratios for stroke incidence among stroke subtypes versus the general population were only available for RA and SLE. In RA versus the general population, the pooled odds of ischemic stroke (3,481 strokes; 86,280 patients) and hemorrhagic stroke (562 strokes; 84,419 patients) were 1.64 (95% CI, 1.32–2.05) and 1.68 (1.11–2.53), respectively (Figures 1 and 2). In SLE versus the general population, the pooled odds of ischemic stroke (945 strokes; 55,699 patients) and hemorrhagic stroke (164 strokes; 44,062 patients) were 2.11 (1.66–2.67) and 1.82 (1.07–3.09), respectively (Figures 1 and 2).

**Subtypes of Ischemic Stroke**
For SLE, 2 studies provide incidence rate data for ischemic stroke subtypes: among 490 SLE patients, 13 had cortical strokes (equivalent to 271 cortical strokes per 100,000 person-years) and 4 had lacunar strokes (83 per 100,000) from 4,802 person-years follow-up; among 232 SLE patients, 20 had large artery strokes (1,150 per 100,000), 17 had small vessel

<p>| Table. Stroke Incidence Rates by Stroke Subtype Among Different Rheumatic Diseases |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Rheumatic Disease</th>
<th>Included Studies</th>
<th>Strokes</th>
<th>Person-Years Follow-Up</th>
<th>Range of Incidence Rates, per 100,000 Person-Years</th>
<th>Mean IR, per 100,000 Person-Years (95% CI)</th>
<th>References</th>
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<tr>
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<td></td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>6</td>
<td>3611</td>
<td>1,932,49</td>
<td>178–1077</td>
<td>303 (269–337)</td>
<td>14,51–55</td>
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<tr>
<td>Gout</td>
<td>1</td>
<td>5391</td>
<td>767,725</td>
<td>702</td>
<td>702 (650–754)</td>
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<td>Ankylosing spondylitis</td>
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<td>111</td>
<td>76,494</td>
<td>145</td>
<td>145 (121–169)</td>
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<td>Reiter’s</td>
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<td>13</td>
<td>7436</td>
<td>175</td>
<td>175 (149–201)</td>
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<tr>
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<tr>
<td>Polyanteritis nodosa</td>
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<td>46</td>
<td>18,106</td>
<td>254</td>
<td>254 (223–285)</td>
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<td>Polyarthritis nodosa</td>
<td>1</td>
<td>1777</td>
<td>362,912</td>
<td>489</td>
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<td>7</td>
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<td>367 (329–404)</td>
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<td>44</td>
<td>11,264</td>
<td>391</td>
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<td>68</td>
<td>28,600</td>
<td>238</td>
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<td>52</td>
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<tr>
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<td><strong>Hemorrhagic</strong></td>
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<td>Rheumatoid arthritis</td>
<td>3</td>
<td>562</td>
<td>1,096,594</td>
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<td>35–118</td>
<td>74 (57–91)</td>
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<td>28,600</td>
<td>17</td>
<td>17 (9–25)</td>
<td>52</td>
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<tr>
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<td></td>
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</tr>
<tr>
<td>General population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 (9–17)</td>
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</tbody>
</table>

CI indicates confidence interval; Mean IR, mean incident rate (weight based on study size, ie, person-years observed); PsA, psoriatic arthritis; and SLE, systemic lupus erythematosus.
strokes (997 per 100,000) and 4 had cardioembolic strokes (230 per 100,000) from 1739 person-years follow-up. There are limited comparative data from the general population but Sacco et al. report annual incidence rates for lacunar stroke as 33 per 100,000 population. There were insufficient data to pool rate ratios among ischemic stroke subtypes.

Age, Rheumatic Disease and Stroke

The pooled odds of any stroke (11,879 strokes; 340,548 patients) across 5 rheumatic diseases (data were available for RA, SLE, psoriasis, ankylosing spondylitis, and gout) versus the general population was 1.38 (95% CI, 1.21–1.57) (Figure 3). When split by age, the pooled odds were 1.79 (1.46–2.20) for age <50 years, 1.49 (1.07–2.06) for age 50 to 65 and 1.14 (0.94–1.38) for age 65 and above (Figure 3). The age categories were significantly different ($\chi^2$ test for subgroups, $P=0.007$). We include a study by study review of stroke by age categories across stroke in general and by ischemic and hemorrhagic stroke subtypes in Table IV in the online-only Data Supplement.

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**Figure 1.** Forest plot—ischemic stroke in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) versus general population. CI indicates confidence interval.

**Figure 2.** Forest plot—hemorrhagic stroke in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) versus general population. CI indicates confidence interval.
We reviewed numerous MRI studies of the brain in rheumatic diseases. The details are provided in Table V in the online-only Data Supplement. Most were small, many investigated neurologically symptomatic patients only (for example comparing neurolupus with SLE), and few controlled for age and known vascular risk factors.

**Discussion**

Brain damage from any type of stroke, from ischemic and hemorrhagic stroke, and silent vascular damage such as WMHs is increased in most rheumatic diseases. Most data are for stroke in general, but ischemic and hemorrhagic strokes were also increased in our new pooled analyses of RA and SLE, as were silent vascular disease markers.

RA, SLE, AS, gout, and to a lesser degree psoriasis carry a higher risk of stroke over the general population. Stroke incidence varies across rheumatic diseases (Table) and seem higher than the general population (eg, Rothwell et al report annual incidence rates for ischemic and hemorrhagic stroke as 141 (95% CI, 127–156) and 12 (9–17) per 100 000 population, respectively).

Rheumatic disease patients aged <50 have a particularly high stroke risk compared with the general population. There was no additional stroke risk in OA. Other rheumatic diseases are understudied. Although increased stroke risk may reflect impact on lifestyle through the physical effects of rheumatic diseases, the possibility that increased systemic inflammation affects the brain directly is suggested by the higher stroke risk in inflammatory versus noninflammatory arthropathies. A better understanding of stroke in rheumatic disease would help focus clinical practice on prevention of vascular brain damage, including early lifestyle interventions and any vascular prevention role for anti-inflammatory agents, in these patients.

This is the first analysis to quantify stroke subtype rates and risk in rheumatic disease including by age. Our results are
cating a need to a) unravel the extent to which inflammation, including SVD in rheumatic patients. A clear picture of phenotyping is needed to fully characterize stroke subtypes and overt brain lesions, and increased risk at younger ages.

The review’s strengths include data mostly from large population-based studies although we only included English language publications. We could not adjust for vascular risk factors or treatments, limiting generalizability, and cannot exclude the possibility of study bias. Patients with rheumatic disease are often assiduously monitored (because of the disease and treatments), and so might have minor neurological problems investigated more compared with the general population.

Data on ischemic stroke subtypes were limited to 2 studies in SLE. More studies reported on SVD features among patients with several rheumatic diseases. Although small size and disparate reporting precluded meta-analysis, the general impression was of more vascular lesions in rheumatic diseases.

The increased stroke risk at earlier ages uses data from 340,548 patients (11,879 strokes). The excess risk was almost double that of the general population, highest in those <50 years, and declined steadily to approach that of the general population >65. However, there was heterogeneity in study reporting and inconsistencies in age categories (despite guidance to use mid-decade age bands). The clear trend for higher stroke risk <50 years suggests that atherosclerosis is unlikely to be the sole pathogenic driver. Systemic inflammation may play a role. The increased risk at younger ages might reflect more rheumatic disease activity before the inflammation is well controlled.

The risk of any stroke, ischemic or hemorrhagic stroke, and MRI findings seem worse in inflammatory arthropathies (RA, SLE, AS, gout, psoriatic arthritis) than noninflammatory arthropathies (OA). Inflammation is a risk factor for stroke and plasma markers of inflammation (C-reactive protein, tumor necrosis factor-a, interleukin-6) are associated with stroke and increased WMH burden. Antiphospholipid antibodies increase the risk of thrombus: in RA, strokes (and preclinical brain abnormalities such as WMH) are more common in those with antiphospholipid than those without. Therefore, inflammation generated in the rheumatic diseases may be at least in part responsible for the marked stroke risk and overt brain lesions, and increased risk at younger ages.

A large brain imaging population study with detailed stroke phenotyping is needed to fully characterize stroke subtypes including SVD in rheumatic patients. A clear picture of increased stroke risk in younger patients is established indicating a need to a) unravel the extent to which inflammation, lifestyle, antirheumatic treatments, and risk factors (traditional as well as new) contribute to stroke risk and b) whether aggressive management of these risk factors including inflammation can ameliorate the stroke risk. Imaging features such as WMH might assist in identifying rheumatic disease patients who are at particularly high risk of stroke, as do WMH in the general ageing population.

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Disclosures
None.

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Cerebrovascular Disease in Rheumatic Diseases


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SUPPLEMENTAL MATERIAL

Title:
Cerebrovascular disease in rheumatic diseases: A systematic review and meta-analysis

Authors:
Stewart J. Wiseman, ¹ Stuart H. Ralston, ² Joanna M. Wardlaw. ¹

Affiliation:
¹ Centre for Clinical Brain Sciences, University of Edinburgh, UK
² Centre for Genomic and Experimental Medicine, University of Edinburgh, UK
Structural MRI brain imaging findings

White matter hyperintensities, a key marker of SVD

We reviewed numerous MRI studies of the brain in rheumatic diseases. Most were small, many investigated neurologically symptomatic patients only (for example comparing neurolupus with SLE), and few controlled for age and known vascular risk factors.

Of the larger studies (>50 patients) that provided information on features of SVD, there were consistent reports of WMH and brain atrophy in rheumatic disease patients (n=13 studies (11 in SLE) involving 1,411 patients) (Supplementary Table V, please see http://stroke.ahajournals.org)\textsuperscript{1–13}. However, only five studies\textsuperscript{2,3,6,10,13} compared rheumatic disease patients (n=414 patients) to non-rheumatic healthy controls, and three of these were from the same research group and so only ~224 patients contribute data versus healthy controls. Two studies report on WMH: Hamed et al.\textsuperscript{13} found no difference in WMH between 55 patients with RA and 40 healthy controls, although they excluded seven patients with white matter disease before comparing the remaining 48 patients, and they did not report on whether a grading system or a volumetric calculation was used to assess the WMHs. Harboe et al.\textsuperscript{10} report more WMH in 62 patients with SLE versus 62 age- and sex-matched healthy controls (6.0 vs 4.1, p=0.05, Scheltens’ score).

Longitudinal data were also limited. Appenzeller et al.\textsuperscript{3} followed 75 SLE patients over almost two years and found significant brain atrophy particularly in the corpus callosum (baseline versus follow-up scan, p=0.001). Additionally, predictors of new or increased WMH included antiphospholipid antibodies, SLE damage scores and higher dose of corticosteroids\textsuperscript{4}.

Supplementary Table I. Search Strategy

| 1. brain ischemia/ or brain infarction/ or brain stem infarctions/ or cerebral infarction/ or hypoxia-ischemia, brain/ or stroke/ |
| 2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw. |
| 3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw. |
| 4. 1 or 2 or 3 |
| 5. Arthritis/ or Arthritis, Rheumatoid/ or Autoimmune Diseases/ or Musculoskeletal Diseases/ or Rheumatic Diseases/ |
| 6. 4 and 5 |
| 7. limit 6 to humans |
**Supplementary Table II. Quality Checklist for Included Studies**

<table>
<thead>
<tr>
<th>Question</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Prospective or retrospective?</td>
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</tr>
<tr>
<td>Was stroke subtyped: ischaemic / haemorrhagic / large artery / lacunar?</td>
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</tr>
<tr>
<td>Was criteria/system used to subtype stroke well explained?</td>
<td></td>
</tr>
<tr>
<td>Was neuroimaging used to confirm stroke diagnosis?</td>
<td></td>
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<tr>
<td>Was diffusion-weighted imaging used?</td>
<td></td>
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<tr>
<td>Was the grade of clinician making the stroke diagnosis reported?</td>
<td></td>
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<tr>
<td>Did authors adequately describe and/or rule out stroke mimics?</td>
<td></td>
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<tr>
<td>Did authors provide number of stroke events and number of person-years observation?</td>
<td></td>
</tr>
<tr>
<td>Was the comparison group well described (including number of stroke events and number of person-years observation)?</td>
<td></td>
</tr>
<tr>
<td>Did the study match comparators on age, sex and traditional vascular risk factors (hypertension, diabetes, hyperlipidaemia) or control for these at the analysis stage?</td>
<td></td>
</tr>
</tbody>
</table>
Supplementary Table III. Summary of prior (and new) stroke risk findings – any stroke

<table>
<thead>
<tr>
<th>Rheumatic disease</th>
<th>Stroke in general</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>Meune et al.(^{14}) meta-analysed stroke death among nine studies involving 88,500 rheumatoid arthritis (RA) patients and stroke incidence among three studies involving 26,143 RA patients: risk of death (standardised mortality ratio 1.46, 95% CI 1.31–1.63) and stroke incidence (incidence rate ratio 1.91, 95% CI 1.73–2.12) were higher than the general population, respectively. Lindhardsen et al.(^{15}) linked Danish national registers to follow 18,247 RA patients over 13 years. Stroke incidence in RA was significantly higher than in the general population (rate ratio 1.33, 95% CI 1.23–1.43).</td>
</tr>
<tr>
<td>SLE</td>
<td>New meta-analysis (See main text and Supplementary Figure 2). Included studies(^{16–20}).</td>
</tr>
<tr>
<td>AS</td>
<td>Meta-analysis(^{21}) of three studies of 9,791 ankylosing spondylitis (AS) patients found an increased risk of stroke versus the general population (odds ratio (OR) 1.51, 95% CI 1.39–1.62). Two subsequent studies (n=5,000 AS patients)(^{22,23}) not included in the meta-analysis show similar risk of stroke (hazards ratio 1.2 (1.0–1.5) and 2.3 (1.9–2.8)) over the general population, while a third study(^{24}) reported an increased risk of vascular death (a composite end point of heart attack and stroke) among n=21,473 patients of 1.36 (1.13–1.65) versus healthy controls.</td>
</tr>
<tr>
<td>Gout</td>
<td>Gout patients have 1.71 (95% CI 1.68–1.75) times the risk (rate ratio) of stroke over the general population from a study of 767,725 person-years follow-up(^{25}).</td>
</tr>
<tr>
<td>Psoriasis and PsA</td>
<td>New meta-analysis (See main text and Supplementary Figure 3). Included studies(^{26–37}). Additionally, Chin et al.(^{38}) compared psoriasis patients (n=383 strokes; n=7,397 patients) to PsA patients (n=23 strokes; n=225 patients) in a population-based retrospective cohort study and found a non-significant increase in stroke risk in PsA patients (hazard ratio 1.5, 95% CI 0.98–2.29) which became significant on multivariate modelling controlling for age, hypertension diabetes, dyslipidemia and phototherapy (HR 1.82, 95% CI 1.17–2.82).</td>
</tr>
<tr>
<td>OA</td>
<td>Compared to RA, patients with osteoarthritis (OA) alone (eg, no comorbid RA) are at lower risk of stroke (11,633 RA patients versus 163,274 OA patients; rate ratio 1.3, 95% CI 1.2–1.3), ie, RA has higher risk(^{39}). A more recent study(^{40}) of 40,817 patients with OA concluded there was no additional stroke risk in OA versus the general population, although the strokes were self-reported.</td>
</tr>
</tbody>
</table>

AS = ankylosing spondylitis, OA = osteoarthritis, PsA = psoriatic arthritis, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus
**Supplementary Table IV.** Summary of stroke risk findings by age – stroke in general and by stroke subtype

<table>
<thead>
<tr>
<th>Stroke type</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any stroke</strong></td>
<td>Lindhardsen et al.(^1)(^5) report a rate ratio for stroke among male RA patients versus the general population as 3.61 (95% CI 2.05–6.36) for those aged &lt; 50 years, 1.70 (1.34–2.15) for those aged 50–65 years and 1.21 (1.05–1.40) for those aged 65 years and older. A similar trend was seen among women. Solomon et al.(^4)(^1) report a rate ratio for any cardiovascular event including stroke among 18–49 year-old RA patients versus the general population as 3.3 (95% CI 2.4–4.5), 2.2 (1.9–2.5) for those aged 50–64 years, 1.9 (1.7 to 2.1) for those aged 65–74 years and 1.6 (1.5–1.7) for those aged 75 years and older. Ward(^4)(^2) reports twice as many strokes among 18–44 year old women with SLE compared with the general population (rate ratio 2.05; 95% CI 1.17–2.93) whereas in those aged 45–64 years and ≥ 65 years there was no such significant increase in stroke rates. Among 13,689 SLE patients followed for over 5 years, Wang et al.(^2)(^0) found stroke risk relative to the general population to diminish over the lifecourse. Hazards ratios were: 31.1 (95% CI 14.2–68.3) in 18–24 year olds, 15.1 (9.3–24.5) in 25–34 year olds, 5.3 (3.8–7.5) in 35–44 year olds, 2.3 (1.7–3.1) in 45–54 year olds, 2.2 (1.6–3.0) in 55–64 year olds with no risk difference in those 65 years and older (0.97, 0.7–1.3). Bessant et al.(^4)(^3) assessed stroke risk in 202 SLE patients (92% female; mean age 42 years) using software (with Framingham data) against hypothetical age- and sex-matched controls. Patients had a higher 10-year risk of stroke versus control data (p&lt;0.0001). When stratified by age, patients under 40 years continued to be at significantly higher risk but patients over 40 years showed no difference to controls. Szabo et al.(^4)(^4) found the excess risk for stroke in ankylosing spondylitis (AS) over the general population was highest among younger AS patients (example: females aged 20–39 years had a risk ratio of 1.69 (95% CI 1.23–2.33) while females aged 40–59 years and ≥60 years had non-significant risk ratios of 1.15 and 1.14 respectively). Ahlehoff et al.(^3)(^5) report reducing stroke risk with increasing age in mild psoriasis over the general population: 18-50 years (1.61 (95% CI 1.32–1.97)), 51-70 years (1.22 (95% CI 1.10–1.35)) and &gt;70 years (1.15 (95% CI 1.05–1.20)).</td>
</tr>
</tbody>
</table>

| **Ischaemic and haemorrhagic subtype** | Among prevalent RA, Holmqvist et al.\(^4\)\(^5\) report a hazard ratio for ischaemic stroke versus the general population to be 0.81 (95% CI 0.43–1.54) for those aged 16–52 years, 1.47 (1.13–1.90) for those aged 53–62 years, 1.36 (1.14–1.62) for those aged 63–71 years and 1.25 (1.12–1.41) for those aged 72–94 years. The hazard ratios for haemorrhagic stroke among the same age bands were: 1.76 (0.85–3.63), 1.00 (0.61–1.65), 0.82 (0.53–1.25) and 1.75 (1.34–2.29) respectively. |
Mok et al. report significantly higher levels of ischaemic stroke in young SLE patients (in each 10-year age band up to 50 years) versus the general population, but the difference becomes non-significant in each 10-year age band in those over 50 years. Young SLE patients (below 40 years) had significantly higher rates of haemorrhagic stroke versus the general population, but data were limited with no cases of haemorrhagic stroke in those over 40 years.

From 25,704 SLE patients hospitalised in the US between 2001–2002, Krishnan found 313 strokes (206 as the primary diagnosis) giving an age- and sex-adjusted risk estimate for stroke in young (< 50 years) SLE patients of 1.5 (95% CI 1.3–1.8). SLE patients had higher stroke risk for all stroke subtypes except in subarachnoid haemorrhage where a trend to lower risk was observed (OR 0.57, 95% CI 0.34–0.96). The study was limited to those aged < 50 years.

Seminog and Goldacre report the relative risk for ischaemic stroke among gout patients versus the general population as 4.68 (95% CI 2.89–7.18) in those aged 20–44 years, 2.68 (95% CI 2.51–2.86) in those aged 45–69 years and 1.56 (95% CI 1.51–1.61) in those over 70 years. The relative risk for haemorrhagic stroke was 7.49 (95% CI 4.67–11.40) in those aged 20–44 years, 3.02 (95% CI 2.72–3.34) in those aged 45–69 years and 1.49 (95% CI 1.41–1.58) in those over 70 years.
Supplementary Table V. Summary of structural MR brain imaging findings in rheumatic diseases

<table>
<thead>
<tr>
<th>Study</th>
<th>Rheumatic disease</th>
<th>N</th>
<th>Mean age (years)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaichi, 2013$^1$</td>
<td>SLE</td>
<td>256</td>
<td>39.0</td>
<td>Irrespective of age, significantly more patients with APS had lacunar infarcts in the deep white matter (p&lt;0.01) (but not the basal ganglia), cortical infarcts in the MCA territory (p&lt;0.01), bilateral borderzone infarcts (p&lt;0.01) and basal ganglia lesions (p=0.01) versus SLE patients without APS. WMH (rated with Fazekas) did not differ between SLE patients with and SLE patients without APS.</td>
</tr>
<tr>
<td>Steup-Beekman, 2013$^8$</td>
<td>SLE</td>
<td>155</td>
<td>27.5</td>
<td>Among n=102 with NPSLE, 47% had a normal MRI. WMH were found in 31/102 (30%) and atrophy in 20/102 (20%).</td>
</tr>
<tr>
<td>Akasbi, 2012$^7$</td>
<td>SS</td>
<td>51</td>
<td></td>
<td>Dichotomised 51 Sjögren’s Syndrome patients into those with WMH (n=25) and those without (n=26) using Wahlund scale. Those with WMH were older (70.3 v 58.3; p=0.004) and had higher frequency of cardiovascular risk factors.</td>
</tr>
<tr>
<td>Hamed, 2012$^{13}$</td>
<td>RA</td>
<td>55</td>
<td>45.6</td>
<td>Removed 7 patients with probable white matter disease, then compared n=48 patients with 40 healthy controls and found no difference in T2 or FLAIR ‘hyperintense signals’ (p=0.245). Unclear how the hyperintensities were measured.</td>
</tr>
<tr>
<td>Katsumata, 2010$^9$</td>
<td>SLE</td>
<td>191</td>
<td>32.0</td>
<td>Compared those with (n=57) and without (n=134) neurolupus. Abnormal MRI signals were more often found in those with neurolupus (RR 1.7, 95% CI 1.1–2.7). Large abnormal signals (&gt;10mm) were only seen in the neurolupus group (n=7) whereas small abnormal signals were seen in both groups with no statistical difference.</td>
</tr>
<tr>
<td>Harboe, 2008$^{10}$</td>
<td>SLE</td>
<td>62</td>
<td>44.3</td>
<td>SLE patients have more fatigue (p&lt;0.0001) and WMH compared with healthy controls (p=0.05). Total WMH increased more with age in patients than in controls.</td>
</tr>
<tr>
<td>Valdes-Ferrer, 2008$^5$</td>
<td>SLE</td>
<td>71</td>
<td>32</td>
<td>Compared SLE patients with and without APS. WMH were found in more than 40% of patients from both groups; no significant difference between groups. There was no difference in atrophy between groups.</td>
</tr>
<tr>
<td>Appenzeller, 2008$^4$</td>
<td>SLE</td>
<td>120 (80 with repeat MRI)</td>
<td>33.3</td>
<td>At baseline, 50% of patients had WMH: mean volume 197 mm3 (FLAIR images). WMH were associated with age (p=0.01), total corticosteroid dose (p=0.001) and damage from SLE (p=0.002). Predictors for new or increased WMH at follow-up (median 24 months) were past CNS involvement, antiphospholipid antibodies, SLE damage score and higher dose of corticosteroid dose.</td>
</tr>
<tr>
<td>Author</td>
<td>Diagnosis</td>
<td>n</td>
<td>Age</td>
<td>Additional Findings</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------</td>
<td>----</td>
<td>------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Appenzeller, 2007&lt;sup&gt;3&lt;/sup&gt;</td>
<td>SLE</td>
<td>75</td>
<td>32.3</td>
<td>SLE patients have reduced white and grey matter volumes versus healthy controls (p=0.001). On follow-up, there is progressive white and grey matter atrophy in patients (p=0.001)</td>
</tr>
<tr>
<td>Appenzeller, 2006&lt;sup&gt;6&lt;/sup&gt;</td>
<td>SLE</td>
<td>107</td>
<td>32.2</td>
<td>SLE patients have smaller hippocampal volumes versus controls (p&lt;0.001). At follow-up (n=60 patients, mean 19 months) there was significant reduction in hippocampal volume over baseline volumes. Severity of cognitive impairment was associated with hippocampal volume loss (r=0.89; p=0.001).</td>
</tr>
<tr>
<td>Appenzeller, 2005&lt;sup&gt;2&lt;/sup&gt;</td>
<td>SLE</td>
<td>115</td>
<td>33.5</td>
<td>Cerebral and corpus callosum volumes were significantly smaller in SLE patients versus controls (p&lt;0.001). Patients with cognitive impairment had significantly reduced cerebral and corpus callosum volumes compared with SLE patients without cognitive impairment (p=0.001).</td>
</tr>
<tr>
<td>Jennings, 2004&lt;sup&gt;11&lt;/sup&gt;</td>
<td>SLE</td>
<td>85</td>
<td>40.4</td>
<td>115 scans in 85 SLE patients in which 39 (34%) were normal, 70 (60%) had WMH, 50 (43%) had brain tissue loss, 24 (21%) had infarcts and 6 (5%) had haemorrhage.</td>
</tr>
<tr>
<td>Sanna, 2000&lt;sup&gt;12&lt;/sup&gt;</td>
<td>SLE</td>
<td>68</td>
<td>38.0</td>
<td>Among 68 patients, 24 showed overt neuropsychiatric manifestations; none had acute presentation at time of scanning. Abnormal MRI was found in 30/68 (44%). Neuropsychiatric manifestations are significantly associated with serum antibody against anti-glia fibrillary acidic protein.</td>
</tr>
</tbody>
</table>

APS = antiphospholipid syndrome. FLAIR = fluid attenuated inversion recovery. MCA = middle cerebral artery. NPSLE = neuropsychiatric systemic lupus erythematosus. RA = rheumatoid arthritis. SLE = systemic lupus erythematosus. SS = Sjogren’s syndrome. WMH = white matter hyperintensities
**Supplementary Figure I.** Summary of Search and Selection

fMRI = functional magnetic resonance imaging; PET = positron emission computed tomography
Supplementary Figure II. Any stroke in systemic lupus erythematosus\textsuperscript{16–20}

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SLE Events</th>
<th>Total</th>
<th>Controls Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M.H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hak 2008</td>
<td>4</td>
<td>140</td>
<td>185</td>
<td>17000</td>
<td>0.1%</td>
<td>2.50 [1.83, 3.67]</td>
</tr>
<tr>
<td>Krishan 2005</td>
<td>313</td>
<td>25704</td>
<td>20925</td>
<td>3130405</td>
<td>28.1%</td>
<td>1.80 [1.56, 2.08]</td>
</tr>
<tr>
<td>Liu 2014</td>
<td>21</td>
<td>621</td>
<td>47</td>
<td>2434</td>
<td>17.0%</td>
<td>1.81 [1.38, 3.06]</td>
</tr>
<tr>
<td>Mok 2009</td>
<td>20</td>
<td>490</td>
<td>26402</td>
<td>1060000</td>
<td>19.1%</td>
<td>1.67 [1.06, 2.64]</td>
</tr>
<tr>
<td>Wang 2012</td>
<td>414</td>
<td>15889</td>
<td>551</td>
<td>54758</td>
<td>27.8%</td>
<td>3.07 [2.70, 3.49]</td>
</tr>
</tbody>
</table>

Total (95% CI) 40652 4417645 100.0% 2.13 [1.53, 2.98]

Total events 772 49460

Heterogeneity: Tau\textsuperscript{2} = 0.10, Chi\textsuperscript{2} = 35.79, df = 4 (P < 0.00001); I\textsuperscript{2} = 89%

Test for overall effect Z = 4.45 (P = 0.00001)

Supplementary Figure III. Any stroke in psoriasis and psoriatic arthritis\textsuperscript{26–33,36,37}

PsA = psoriatic arthritis
References


リウマチ性疾患を背景とする脳血管障害
一系統的レビューとメタ解析
Cerebrovascular Disease in Rheumatic Diseases
A Systematic Review and Meta-Analysis

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脳卒中は重大な健康問題である。全体の発生率は下がっているが12, 医療の利用・向上を含む予防の改悪にによって生存率が上がることによる脳卒中の発症率が上昇したため、医療の負担はまだ大きい。人口の高齢化によりこの傾向はさらに加速すると予測される。

関節リウマチ（rheumatoid arthritis; RA）などのリウマチ性疾患は、脳卒中の独立した危険因子である34。リウマチ性疾患の患者は脳卒中などの心血管疾患を早く発症するため、その死亡率を抑制するにはこのような患者の脳卒中リスクを解明する必要がある。しかし、リウマチ性疾患と脳卒中リスクの増加に関連付けられたデータのほとんどは、大規模な患者集団の試験で報告された脳卒中、すなわち全体の脳卒中を含む複合的転帰に基づいている。リウマチ性疾患（炎症性/非炎症性）と発症機序の異なる主な脳卒中サブタイプ（虚血性脳卒中と出血性脳卒中、脳卒中と心臓のアテロームに起因する脳卒中と細い血管の虚血性脳卒中など）の関連性、あるいは脳小血管病（small vessel disease; SVD）に伴う症状（認知機能低下や歩行障害など）との関連性は、ほとんどわからていない35。

脳卒中の集団発生率は加齢により上昇する。幼児期の脳卒中は稀であるが、リウマチ性疾患に伴う脳卒中は低年齢で発症することが少なく、65歳を超えるリスクに差はないと報告されているように12,13,16,17. それ以降を安定するようである。しかし、リウマチ性疾患と脳卒中の全般的関連性を年齢別に解析したメタ解析は存在しない。脳卒中リスクが最大になるタイミングを明らかにすることは、臨床的に重要な意義をもつ。

これまでの研究は、リウマチ集団の脳卒中リスクを心血管危険因子により完全に説明されていない13,19. リウマチ性疾患に伴う脳卒中リスクについては、強力な抵抗リウマチ薬でしかコントロールできない全生性、難治性の関節症でよくみられる高度な炎症活動が関係している部分があると考えられる。炎症は脂肪線の形成からプラック破壊までアテローム性動脈硬化のすべての段階に関わっているため、アテロームに起因する脳卒中に

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よるリスク増加の一端は炎症により説明がつく20-22。脳卒中では炎症反応が一因であり、破れた細動脈が脳卒中リスク増加の一因である。そして、脳卒中リスクの増加の一部は、炎症が脳卒中リスク増加の一因であると考えられる。\( \text{SVD} \)での炎症反応の増加は、血栓の発生を抑制することが示唆される。23,24。内皮の損傷は、アテローム性動脈硬化および\( \text{SVD} \)の第一段階であり、リウマチ性疾患は内皮の損傷を誘発する因子（免疫複合体の形成、補体活性化）もみられる。

本研究の目的は、脳卒中とリウマチ性疾患の関連性を検証することである。脳卒中サブタイプで発生率をまとめること。プラクスリヴァーに対する脳卒中サブタイプの組合せ発生率比（pooled rate ratio）を算出すること。特定の年齢でリスクが最大になるか否かを調べること。そしてリウマチ性疾患が不調性血管疾患のリスクを高めるか否かを脳神経画像で判断することである。

方 法

研究デザイン
脳卒中および脳卒中サブタイプを基準評価項目として、さまざまなリウマチ性疾患を原因と介素として評価するため、統合的考えを取った。研究委員会の承認が必要であった。本研究は第2のデータベースにも登録しなかった。

データソース
PRISMA（Preferred Reporting Items for Systematic Reviews and Meta-Analyses）の報告23に従って調査の準備をした。2014年12月14日には、Ovidの構造化されたMeSH検索オプション（オンラインデータ補遺表）を使用して2014年までのEMBASE（1980年から）およびMEDLINE（開始時）を検索した。MOOSE（Meta-Analyses and Systematic Reviews of Observational Studies）のガイドライン24に従ってデータを抽出した。統合的公表影像（MRI）の所見はSTRIVE（Standards for Reporting Vascular Changes on Neuroimaging）のガイドライン25でカテゴリー化した。さらに参考文献リストから論文を探し出し、必要な場合は著者に連絡して追加データを入手した。

研究の選択
対象は、リウマチ性疾患を背景とする脳卒中の研究と、\( \text{SVD} \)の脳MRI画像上の特徴を評価した研究の英語論文である。機能的MRI、PET、SPECT、ドップラー超音波を使用した研究は除外した。

データの抽出
研究対象群の人口統計学的特徴、対照群、脳卒中タイプ（脳出血、脳梗塞）にサブタイプ（大血管、小血管）を区別し、比較群に対する脳卒中リスク増加の可能性を検討した。年齢および心血管危険因子について調整してあるか否かに留意した。

質的評価
対象とした研究の質を評価するため、STROBE（Strengthening the Reporting of Observational Studies in Epidemiology）28から改変したチェックリストを用いた（オンラインデータ補遺表II）。

データの合成および解析
\( \text{SVD} \)の定義には最新のSTRIVE脳神経画像基準27のMRIにおける特徴を使用し、最近発症した皮膚小血管炎、白質高信号病変（white matter hyperintensities；WMH）、脳神経病変、微小出血、脳血管周囲性脳病変があれSVDとした。臨床的にはまったく症状がなかったり、脳卒中の他に認知機能障害などの精神症状が原因となる場合がある（全脳神経性脳卒中の約25%をラクナ脳梗塞が占める29）。

脳卒中の発生率は推定期間の関数として表される脳卒中の症例数とし、脳卒中の発生率は一般集団の発生率に対する観察群（例：RA）の脳卒中発生率の比とした。研究ごとに調整された変数が異なり、変数調整を含めて比較するのが困難であるため、すべて未調整（粗）の比率を使用した。

報告されている脳卒中発生率を記録し、報告がないデータが含まれる脳卒中の症例数を報告した推定期間の発生率は、100,000人年当たりの発生率を基準とした。脳卒中発生率は、脳卒中発生率を基準とした。脳卒中発生率は、脳卒中発生率を基準とした。

あるリウマチ性疾患について、2つ以上の研究から使われるデータが検出された場合、使用可能な範囲の値を取り出して発生率を統合したため、不均一性の評価はできなかった。次に、研究の規模を加算因子とする加算平均に基づき、100,000人年当たりの各リウマチ性疾患の発生率推定値を算出し、統計統合を基にした、統計的統合を基にした。

報告されていないが重要なデータが挙げられている場合、コラボ連携を基にしたソフトウェアReview Manager 5で率比を計算した。

なかには、対照群で観察された脳卒中症例数および患者年数を報告せず、率比とCIのみを報告した研究もあり、
た。コクランハンドブック 31 によれば、CI は標準誤差
に変換することができ、比率の自然対数は一般的逆分
散 (inverse variance) 法により研究間で結合してもよい。
虚血性脳卒中と出血性脳卒中のリスクの統合および年齢
別の統合解析には、この方法を使用した。

研究間の不均一性は F 統計数により評価した。すべて
のメタ解析でランダム効果モデルを使用した。

## 結果

検討の結果、434 件の標題と抄録が該当した。69 報の
論文を全面的に検討し、23 研究のデータを新しいメタ
解析に用いた。適切な画像で脳卒中に評価しなかった研
究 (n = 12)、病理研究 (n = 5)、ガイドラインおよび
レビューレビュー (n = 2)、SVD の画像上の特徴しか記載
されていない小規模 (50 例未満) の研究 (n = 25) は除
外した（オンラインデータ補遺図 I）。

全タイプの脳卒中

完全性を調べ、全タイプの脳卒中に関する過去の
メタ解析および大規模な患者登録研究を報告しておく
（オンラインデータ補遺図 III）。RA [発生率 (RR) 1.91、
95% CI 1.73 ～ 2.12]、強直性脊椎炎 [オッズ比 (OR)
1.51, 1.39 ～ 1.62], 痛風 (RR 1.71, 1.68 ～ 1.75) の脳卒中リスクは統合オッズが一般統合より高かったが、変形性関節症
(osteoarthritis; OA: OR 1.11, 0.95 ～ 1.29) のリスク
は高くなかった。

全身性エリテマトーデス (systemic lupus erythematosus; SLE)、乾癬、乾癬性関節炎を背景とする
全タイプの脳卒中の新規メタ解析を追加した。5 研
究 31,17,32,34 から集めた SLE 患者 (脳卒中 772 例、SLE
患者 40,652 人) に全タイプの脳卒中が発症した統合オッズ (pooled odds) は、2.13 (1.53 ～ 2.98) であった（オ
ラインデータ補遺図 II）。2 つの乾癬のメタ解析 35,36 を
更新し、乾癬性関節炎の新規メタ解析を追加した。乾癬
患者 (9 研究 31,44,45、脳卒中 6,925 例、患者 400,767 人) に
全タイプの脳卒中が発症する統合オッズは、1.08 (1.00 ～
1.16) であり（オンラインデータ補遺図 III）、乾癬性関
節炎患者 (3 研究 42,43,45、脳卒中 217 例、患者 12,051 人)
は 1.27 (0.98 ～ 1.64) であった（オンラインデータ補遺
図 III）。

RA（典型的な炎症性リウマチ性疾患）の脳卒中リスク
は統合オッズより高く（患者 n = 26,143, OR 1.91、
1.73 ～ 2.12)32、OA（変性）は高くなかった（患者 n =
40,817, OR 1.11, 0.95 ～ 1.29)14。直接比較では OA
患者の脳卒中リスクのみが高かった (RA 患者 11,633
人 vs. OA 患者 163,274 人。OR 1.3、1.2 ～ 1.3 で RA の
脳卒中リスクが高い)30。

脳卒中サブタイプ：虚血性と出血性
発生率

リウマチ性疾患ごとに一般集団 38 と比較した虚血性脳
卒中 13,15,17,31,50 および出血性脳卒中 13,15,17,31,52,53 の発生
率のメタ解析を表に要約した。

脳卒中リスク：統合発生率

一般集団に対する各脳卒中サブタイプの脳卒中発生率
について、メタ解析を実施する十分なデータが得られ
たのは RA と SLE のみであった。一般集団との比較で,
RA 患者に虚血性脳卒中 (脳卒中 3,481 例、患者 86,280
人) および出血性脳卒中 (脳卒中 562 例、患者 84,419 人)
が発症する統合オッズはそれぞれ 1.64 (95% CI 1.32 ～
2.05) および 1.68 (1.11 ～ 2.53) であった (図 1 およ
び 2)。一般集団と SLE の比較では、虚血性脳卒中
(脳卒中 945 例、患者 55,699 人) および出血性脳卒中
(脳卒中 164 例、患者 44,062 人) の統合オッズはそれぞれ
2.11 (1.66 ～ 2.67) および 1.82 (1.07 ～ 3.09) であった
(図 1 および 2)。

虚血性脳卒中のサブタイプ

SLE に関しては、2 研究 33,35 が虚血性脳卒中のサ
ブタイプの発生率データを提示している。SLE 患者
490 人52、4,802 年の追跡調査で、13 人に皮膚脳卒
中 (皮膚脳卒中 271 例/100,000 人年にて、および 4
人にラクナ梗塞 (83/100,000) が認められた。SLE 患
者 232 人50、1,739 年の追跡調査では、20 人に大血
管の脳卒中 (1,150/100,000)、17 人に小血管の脳卒中
(997/100,000)、4 人に心原性脳塞栓症 (230/100,000)
が認められた。一般集団の比較データは少ないが、
Sacco ら 39 はラクナ梗塞の年発生率を 33/100,000 人と
報告している。虚血性脳卒中にサブタイプで発生率を統合す
るにはデータ不足であった。

年齢、リウマチ性発、脳卒中

一般集団と比較して 5 つのリウマチ性疾患 (RA、
SLE、乾癬、強直性脊椎炎、痛風のデータを入手) 患
者に全タイプの脳卒中が発症する統合オッズ (脳卒中
11,879 例、患者 340,548 人)12,17,33,67 は、1.38 (95% CI
1.21 ～ 1.57) であった (図 3)。年齢別の統合オッズは
50 歳未満 1.79 (1.46 ～ 2.20), 50 ～ 65 歳 1.49 (1.07 ～
2.06), 65 歳以上 1.14 (0.94 ～ 1.38) であった (図 3)。
年齢カテゴリでは有意差があった (サブグループの χ²
検定、$P = 0.007$）、オンラインデータ補遺表 IV の研究は、
脳卒中全体および虚血性／出血性脳卒中サブタイプごと
に年齢カテゴリーで調査した脳卒中研究である。

脳 MRI 画像の構造所見

リウマチ性疾患患者のクラスター結果は、
虚血性脳卒中および出血性脳卒中における脳梗塞の
他、WMA のような不整脈性管塞障害が増加する。一般的
に脳卒中のデータがほとんどであるが、RA および SLE
の新しい統合解析では虚血性および出血性脳卒中とも増加
し、不整脈性血管障害のマーカーも同様であった。

RA、SLE、AS、痛風、そして比較的軽度ではあるが
乾燥も、一般集団よりも高い脳卒中リスクとなる。脳卒中
発生率はリウマチ性疾患によって異なるため（表）、一般集
団よりも高いものである [Rothwellら 28] は虚血性／出血性
脳卒中の発生率をそれぞれ 141（95% CI 127 ～
156）および 12（9 ～17）/100,000 人と報告している。

特に、50 歳未満のリウマチ性疾患者は一般集団と
比較して脳卒中のリスクが高い。OA による脳卒中リスク
の増加は認められなかった。その他のリウマチ性疾患
については研究されていない。脳卒中リスクの増加はリ
ウマチ性疾患の身体的影響による生活習慣への影響を反
映したものと思われるが、非炎症性関節症に比べ炎症性
関節症で脳卒中リスクが増加することから、全身炎症的
の病状が脳に直接影響する可能性が示唆されている。リ,
ウマチ性疾患を背景とする脳卒中が解明されれば、早期の
生活習慣改善や何らかの血管保護作用がある抗炎症薬の

| 考 察 |

リウマチ性疾患では大抵の場合、虚血性脳卒中から出,
血性脳卒中まであらゆるタイプの脳卒中による脳障害の,
他、WMA のような不整脈性管塞障害が増加する。一般的
に脳卒中のデータがほとんどであるが、RA および SLE
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生活習慣改善や何らかの血管保護作用がある抗炎症薬の

| 表 さまざまなリウマチ性疾患のサブタイプ別脳卒中発生率 |

<table>
<thead>
<tr>
<th>疾患</th>
<th>対象研究</th>
<th>脳卒中</th>
<th>研究者</th>
<th>発生率の範囲／100,000人／年</th>
<th>平均IR／100,000人／年（95% CI）</th>
<th>参考文献</th>
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CI：信頼区間，平均IR：平均発生率（研究規模一覧表に基づいて加重），PsA：乾燥性関節炎，SLE：全身性エリテマトーデス。
使用によりこのような患者の脳血管損傷を予防する診療が中心になっていくであろう。

本研究はリウマチ性疾患で脳卒中サブタイプの発症率およびリスクを年齢別に定量化した初めての解析である。50歳未満の患者で脳卒中リスクが増加するなどHolmqvistら61がSLEで実施した脳卒中のメタ解析と類似点があるが、本研究にはその他のリウマチ性疾患も含まれており、主な研究で使用された方法が一様ではないという制限はあったが、ランダム効果のメタ解析でその補正を試みた。脳卒中発生率の報告の仕方について一貫性の問題は認識されており、今後はその方法の標準化に取り組むべきである62。

RAおよびSLEにおける血管内膜症の増加は大体予想がつくが、痛風(1.71, 1.68～1.75)、脳卒中症例
図3 フォレストプロット - 3つの年齢カテゴリー別に示したリウマチ性疾患の脳卒中オッズ比8.12-17,33,60。
AS: 強直性脊椎炎, CI: 置信間隔, RA: 関節リウマチ, SLE: 全身性エリテマトーデス。

n = 9,951, 患者 n = 202,033) でも脳卒中が一般集団のほぼ2倍に増加していることが注目される。これは風とメタボリックシンドロームの関連性か、虚血性/出血性脳卒中サブタイプと尿酸の独立した関連性によるものと思われる63。

本研究は英語文献のみを対象としたが、ほとんどが大規模な地域住民を対象とした研究のデータであることは強みである。しかし、心血管危険因子や治療法を調整できなかったため一般化可能性は低下し、研究バイアスの可能性を否定できない。大抵、リウマチ性疾患は地道に經過観察を続けるので（病態および治療のため）、少しでも神経に異常があれば一般集団より検査される機会が多い。

SLE で虚血性脳卒中のサブタイプに関するデータは2研究しかなかった17,50。複数のリウマチ性疾患を合併した患者の SVD の特徴を報告した研究が多かった。研究规模の小ささと報告方法の違いによりメタ解析はできなかったが、全般にリウマチ性疾患では血管病変が増える印象であった。

若年期の脳卒中リスク増加については、340,548人（脳卒中11,879例）のデータを使用している。リスクの増加量は一般集団のほぼ2倍で、50歳未満が最も高く、以後段階的に低下して65歳越の一般集団に近づいた。しかし研究の仕方と（中年の年齢層の使用が推奨されているにも関わらず63）年齢カテゴリーが一致しなかった。50歳未満で脳卒中リスクが増加する明らかない傾向は、アテローム動脈硬化だけが単一の発症要因でないことを示唆する。全身の炎症が関与している可能性もあ
リウマチ性疾患を背景とする脳血管障害

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情報開示
なし。

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