Systemic lupus erythematosus; stroke and myocardial infarction risk: a systematic review and meta-analysis

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterised by alternating periods of flares and remission, and irreversible organ damage associated with disease activity.1 The skin, joints, heart, kidneys, central nervous system and haematologic system are some of the most commonly affected organs.2 3 Organ damage has been associated with increased morbidity and mortality.4 Although recent data suggest that mortality decreased in patients with SLE over the last 30 years, mortality due to cardiovascular disease (CVD) has remained high,5–8 an estimated twofold to threefold increased risk of CVD-associated mortality compared with the general population.9–11

Stroke and myocardial infarction (MI) are major CVD events that are potentially life-threatening.12 Understanding the magnitude of stroke and MI risk in patients with SLE and characterising patients at highest risk would support the development of strategies for preventing and treating or modifying risk factors. Patients with SLE have an increased risk of stroke10 13 and MI.10 Evidence includes a meta-analysis of cohort studies published...
prior to 2015 that compared patients with SLE with the general population.13 There are no recent meta-analyses that evaluate both stroke and MI across multiple observational study types to estimate pooled risk.

We aimed to synthesise evidence from published observational studies reporting risk of major cardiovascular events in adults with SLE compared with the general population or healthy controls.14 We report our findings on the risk of stroke and MI in patients with SLE. We also evaluate the role of age and sex in stroke and MI risk.

METHODS
Search strategy
This study was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology and the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines for conducting and reporting systematic reviews.15 16 The study protocol was prepared and published via the International Prospective Register of Systematic Reviews, PROSPERO (#CRD42018098690).14 Searches for full-text reports containing original data were run in Ovid MEDLINE and EMBASE until March 2018; an additional update search was run until May 2020. The detailed search strategy is available in online supplemental table S1. We also searched the reference lists of articles and contacted experts in the field.

Eligibility criteria
We included full publications of observational studies (cohort and cross-sectional studies) published in English reporting the risk of CVD outcomes in adult patients with SLE compared with the general population or healthy controls. Patients with SLE were identified by International Classification of Diseases (ICD) codes, American College of Rheumatology (ACR) criteria or clinician-confirmed diagnosis.17 18 The outcomes reported in this manuscript include fatal and non-fatal stroke (including subtypes) and MI events. Studies were included if they reported one of the following measures of relative risk: HR, rate ratio, risk ratio (RR), OR, incidence rate ratio, proportionate morbidity ratio, standardised mortality rate or standardised incidence rate with 95% CIs. Abstracts of unpublished studies were excluded as data were not reported to support formal comparison.

Screening and abstraction process
Two-stage screening (title/abstract and full-text screening), data extraction and risk of bias assessment were performed independently by two reviewers (NP and LN); disagreement was resolved by consensus involving a third reviewer (JL). Studies that met the eligibility criteria and reported original data were included in the review. Data on study characteristics and the effect measure for outcomes of interest (fatal and non-fatal events) were extracted.

Risk of bias and quality assessment
The risk of bias of included studies was estimated using the Newcastle-Ottawa Scale19 and an SLE-specific 12-point scale developed for use in previous SLE systematic reviews.7 11 15 20–23 The SLE-specific 12-point scale scores quality in five domains: (1) source of study sample (population-based and clinic-based), (2) cohort type (inception and non-inception), (3) SLE definition (ACR classification criteria for SLE, ICD codes and medical record review), (4) length of SLE exposure (≥10 or <10 years, ≥5 or <5 years or not defined) and (5) ascertainment of outcome (medical record review, ICD code only and exclusion of prevalent outcomes at baseline) (online supplemental table S2). The Newcastle-Ottawa Scale assesses study quality in three domains: (1) selection of study groups, (2) comparability of cohorts by design or analysis and (3) ascertainment of outcomes of interest (online supplemental table S3). Studies were classified as having low, moderate or high risk of bias based on results from domains in both scales.

Statistical analysis
We performed meta-analyses for stroke and MI where two or more studies with a low risk of bias reported usable data. One study was selected for inclusion in the meta-analysis based on study quality, population size and length of study period if there were two studies that reported findings from overlapping populations.

ORS, HRs, rate ratios, standardised incidence ratios and standardised mortality ratios were considered equal estimates assuming rare occurrence24 and referred to as ‘risk ratios’ throughout this publication. The most adjusted RR was used. A DerSimonian and Laird25 random-effects model was fit to calculate the pooled RR and 95% CIs for all outcomes.

Heterogeneity was measured using the Cochran’s Q statistic with statistical significance set at p<0.10 and quantified by the I² test. Publication bias was assessed with both funnel plots and the Egger’s test.26

Robustness of the results was assessed by the leave1out function,27 which examined the effect of removing individual studies on pooled estimates. Several sensitivity analyses were performed, including least-adjusted analysis, studies published during or after 2014, studies published before 2014, studies with low risk of bias, studies reporting non-fatal events, studies reporting non-fatal/fatal events, studies previously excluded because the populations overlapped with another study; and excluding cross-sectional studies. All analyses were conducted in R version 3.5.1 using the packages metafor and forestplot.

We describe reported RRs for the patient subgroups of age and sex, for which data were available from specific studies. Due to the paucity of data, no meta-analyses were conducted for subgroups.

Patient and public involvement
No patients or the public were involved in setting the research question or outcome measures, nor in the
design and implementation of the study. However, the dissemination plan targets a wide audience including members of the public, patients, health professionals and experts in the speciality through various channels including peer-reviewed publications and conference posters and presentations.

RESULTS

Literature search

The original search of the two electronic databases identified 3252 records; 2569 articles remained after duplicates were removed. Of these, 2400 were excluded after screening titles and abstracts. After full-text review, 23 publications reporting on stroke and MI were retained for inclusion in this report (figure 1). The updated search identified 612 records; 420 articles remained after duplicates were removed. Of these, 372 were excluded after screening titles and abstracts. After full-text review, three additional publications reporting on stroke and MI were retained, bringing the total for inclusion to 26 publications. A list of excluded studies, with reasons, is outlined in online supplemental table S4.

Study characteristics

Characteristics of the 26 included studies are summarised in table 1. There were 23 cohort studies and three cross-sectional studies.
### Table 1  Characteristics of studies included in the systematic review to assess risk of stroke and MI in adult patients with SLE compared with the general population or healthy controls

| Author/year | Study design | Country | Study period | Source of SLE population | Source of comparison group | Number of patients SLE; control | Inclusion of fatal/non-fatal events | % Female SLE population | Mean/median age (years) SLE; control | Overall estimate risk of bias | Outcomes reported | Relative risk measure reported |
|-------------|--------------|---------|--------------|---------------------------|---------------------------|-------------------------------|-----------------------------------|-------------------------------|-------------------------------|--------------------------|--------------------------|-------------------------------|
| Arkema 2017 | Cohort study | Sweden  | 2003–2013    | National Patient Register  | Total population register  | 3390; 16 730                  | Fatal and/or non-fatal           | 85%                           | 50; 49                       | Low                      | Ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, unspecified stroke, composite stroke | Rate difference           |
| Avina-Zubieta 2017 | Cohort study | Canada | 1996–2010 | Population data British Columbia | Same as SLE | 4912; 49 611 | Fatal and/or non-fatal | 86% | 49; 49 | Low | Ischaemic stroke, MI | HR |
| Barnado 2018 | Cohort study | USA     | NR           | The Synthetic Derivative (SD) database of Vanderbilt University, Tennessee | Same as SLE | 1097; 5735 | Non-fatal | 90% | 40; NR | Low | MI | OR |
| Bengtsson 2012 | Cohort study | Sweden  | 2001–2007    | 19 specialist departments, 140 primary healthcare centres and one private practice | National Board of Health and Statistics Sweden | 275; 517 | Fatal and/or non-fatal | 85% | 51; 48 | Low | Composite stroke, MI | SIR |
| Bernatsky 2006a | Cohort study | Multinational | 1958–2001 | 23 collaborating lupus centres in seven countries | Population rates (SMR) | 9547; NA | Fatal | 90% | NR | Low | Composite stroke | SMR |
| Bernatsky 2006b | Cohort study | Canada | 1958–2001 | 10 collaborating CanNOS lupus centres across Canada | Population rates (SMR) | 2688; NA | Fatal | 90% | NR | Moderate | Ischaemic stroke, subarachnoid haemorrhage, composite stroke | SMR |

Continued
| Author/year | Study design | Country | Study period | Source of SLE population | Source of comparison group | Number of patients SLE; control | Inclusion of fatal/non-fatal events | % Female SLE population | Mean/median age (years) SLE; control | Overall estimate risk of bias | Outcomes reported | Relative risk measure reported |
|-------------|--------------|---------|--------------|--------------------------|----------------------------|-------------------------------|---------------------------------|-----------------------------|---------------------------------|------------------------|-----------------|-----------------------------|
| Björnådal 2004 | Cohort study | Sweden | 1964–1995 | The Hospital Discharge Register | Cause of death register (SMR) | 4737; NA | Fatal | 78% | NR | Moderate | Composite stroke | SMR |
| Chang 2013 | Cohort study | Taiwan | 2000–2006 | National Health Insurance research database | Same as SLE | 16 967; 16 967 | Fatal and/or non-fatal | 90% | 36; 36 | Low | Subarachnoid haemorrhage | IRR |
| Chiu 2012 | Cohort study | Taiwan | 2000–2007 | National Health Insurance research database | Same as SLE | 11 637; 58 185 | Non-fatal | 89% | 41; 41 | Low | Ischaemic stroke | HR |
| Cook 2018 | Cohort study | UK | 2007–2010 | UK Biobank | Same as SLE | 559; 2236 | Non-fatal | 89% | 56; NR | High | Composite stroke/MI | HR (and SMR) |
| Dregan 2017 | Cross-sectional study | UK | 2006–2010 | UK Biobank | Same as SLE | 654; 483 559 | Fatal and/or non-fatal | 89% | 42; 57 | High | Composite stroke | RR |
| Faurschou 2011 | Cohort study | Denmark | 1977–2006 | Danish SLE cohort established in 1995 and recruited from eight clinical centres | Danish National Hospital Register (event rate calculated for background population) | 104; NA | Fatal and/or non-fatal | 80% | 31; NR | Low | MI | O:E ratio (95% CI) |
| Hak 2009 | Cohort study | USA | 1976–2004 | Nurses’ Health Study | Same as SLE | 148; 108 968 | Fatal and/or non-fatal | 100% | 56; 56 | Low | Composite stroke, MI | Rate ratio |
| Hermansen 2017 | Cohort study | Denmark | 1995–2011 | The Danish National Patient Registry & Danish Register of Causes of Death | Same as SLE | NR; NR | Fatal and/or non-fatal | 86% | 48 (no LN), 40 (with LN) | Low | Composite stroke, MI | HR |
| Author/year | Study design | Country | Study period | Source of SLE population | Source of comparison group | Number of patients SLE; control | Inclusion of fatal/non-fatal events | % Female SLE population | Mean/median age (years) SLE; control | Overall estimate risk of bias | Outcomes reported | Relative risk measure reported |
|-------------|--------------|---------|--------------|--------------------------|----------------------------|-------------------------------|-------------------------------|--------------------------|----------------------------------|--------------------------|------------------------|-----------------------------|
| Kim 2017    | Cohort study | USA     | 1999–2016    | Explorys platform (26 US healthcare systems) | Same as SLE | 95 400; 45 189 140 | Non-fatal | 89% | NR | Low | MI | Relative risk |
| Krishnan 2005 | Cross-sectional study | USA | 2001–2002 | Healthcare Cost and Utilization Project— Nationwide Inpatient Sample | Same as SLE (hospitalisations without mention of lupus) | 25 704; 3 130 405 | Non-fatal | 90% | 38; 38 | High | Ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, composite stroke |
| Lim 2018 | Cohort study | South Korea | 2008–2014 | Korean National Health Insurance Service (NHIS) database | Same as SLE | 18 575; 92 875 | Non-fatal | 91% | NR | Low | Composite stroke/MI |
| Lin 2014 | Cohort study | Taiwan | 2000–2004 | National Health Insurance Research Database | Same as SLE | 1207; 9656 | Fatal and/or non-fatal | 82% | NR | Low | MI |
| Liou 2014 | Cohort study | Taiwan | 2004–2007 | The Longitudinal Health Insurance Database 2005 and Registry for Beneficiaries | Same as SLE | 621; 2484 | Non-fatal | 89% | NR | Low | Ischaemic stroke, composite stroke |
| Manzi 1997 | Cohort study | USA | 1980–1993 | The University of Pittsburgh Medical Center - Framingham Offspring Study | Same as SLE | 498; 2208 | Non-fatal | 100% | NR | Low | MI | Relative risk |
| Author/year | Study design | Country | Study period | Source of SLE population | Source of comparison group | Number of patients SLE; control | Inclusion of fatal/non-fatal events | % Female SLE population | Mean/median age (years) SLE; control | Overall estimate risk of bias | Outcomes reported | Relative risk measure reported |
|-------------|--------------|---------|--------------|--------------------------|---------------------------|-------------------------------|-----------------------------------|-------------------------------|-----------------------------|-------------------------------|--------------------------|-------------------------------|
| Mok 2009 42 | Cohort study | China (Hong Kong) | 1999–2007 | Tuen Mun Hospital | Expected from regional population | 490; 1 060 000 | Fatal and/or non-fatal | 92% | 33; NR | High | Ischaemic stroke, intracerebral haemorrhage, composite stroke | SIR |
| Ramagopalan 2013 43 | Cohort study | England | 1999–2011 | Hospital Episode Statistics | Same as SLE | 25 576; NR | Fatal and/or non-fatal | 86% | NR | Low | Subarachnoid haemorrhage | Rate ratio |
| Rees 2016 44 | Cohort study | UK | 1999–2012 | Clinical Practice Research Data link | Same as SLE | 7033; 26 683 | Non-fatal | 86% | 48; 48 | Low | Composite stroke | IRR |
| Wang 2012 45 | Cohort study | Taiwan | 1997–2008 | Taiwan’s National Health Insurance research database | Same as SLE | 13 689; 54 756 | Non-fatal | 88% | 35; 35 | Low | Ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, haemorrhagic stroke, composite stroke | HR |
| Ward 1999 47 | Cross-sectional study | USA | 1991–1994 | California Office of Statewide Health Planning and Development | Same as SLE | NR; NR | Non-fatal | 100% | NR | High | Composite stroke, MI | HR |
| Zoller 2012 48 | Cohort study | Sweden | 1987–2008 | Several national Swedish data registers | Population rates | 4179; NR | Non-fatal | 82% | NR | Low | Ischaemic stroke, intracerebral haemorrhage | SIR |

CaNIOS, Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus; IRR, incident rate ratio; LN, lupus nephritis; MI, myocardial infarction; NA, not applicable; NR, not reported; O:E ratio, ratio of observed to expected events; RR, risk ratio; SIR, standardised incidence ratio; SLE, systemic lupus erythematosus; SMR, standardised mortality ratio.
Twenty-four studies reported the number of patients with SLE assessed (N=249 687) and 15 studies reported the number of general population/healthy controls assessed (N=50 310 715). Studies were conducted in Asia (n=7), Europe (n=10), North America (n=8) or multiple countries (including centres in Europe, North America and Asia; n=1). Study durations ranged from 1 to 43 years. The percentage of female patients ranged from 78% to 100%. Average age, reported in 15 studies, ranged from 31 to 56 years. Bias was assessed to be low in 19 studies and as moderate in two studies. Five studies were assessed as having high risk of bias, three of which were cross-sectional studies and two were cohort studies. The risk of bias assessment for included studies is summarised in online supplement table S5.

### Stroke
Meta-analyses were performed for the following stroke outcomes: composite stroke, subarachnoid haemorrhage, intracerebral haemorrhage and ischaemic stroke. No meta-analysis was performed for haemorrhagic stroke (n=1) and unspecified stroke (n=2), only one of the two studies had low risk of bias.

#### Composite stroke
Composite stroke was reported in 16 studies: six studies evaluated fatal or non-fatal events, five evaluated non-fatal events and five evaluated fatal events. Five studies were not included in the main meta-analysis: four had overlapping populations with other studies and one only reported data by age group. Nine of the 11 studies included had low risk of bias (online supplemental table S5).

Composite stroke was identified by ICD-8, ICD-9 and ICD-10 codes in 12 of 16 studies. In the remaining three studies, stroke was identified by unreported read codes, physician diagnosis, National Survey of Stroke criteria or Biobank database based on ICD-10 codes (online supplemental table S6). The ICD codes used to create the composite stroke endpoint were specific to each study and are listed in online supplemental table S6.

SLE was associated with an increased risk of composite stroke, with a pooled RR of 2.13 (95% CI 1.73 to 2.61; $I^2$ for heterogeneity 88.3%; df=10; p≤0.001) (figure 2A).

#### Subarachnoid haemorrhage
Subarachnoid haemorrhage was reported in six studies: three studies evaluated fatal/non-fatal events, two studies evaluated non-fatal events and one study evaluated fatal events. Two studies were not included in the meta-analysis because they did not provide usable 95% CIs. Three of the four studies included had low risk of bias (online supplemental table S5).

Subarachnoid haemorrhage was identified by ICD-8, ICD-9 and ICD-10 codes in all studies. The ICD codes used were the same in all studies that reported them (online supplemental table S6).

Risk of subarachnoid haemorrhage did not significantly increase in patients with SLE, with a pooled RR of 1.95 (95% CI 0.69 to 5.52; $I^2$ for heterogeneity 94.4%; df=3; p<0.001) (figure 2B).

#### Intracerebral haemorrhage
Intracerebral haemorrhage was reported in five studies: two studies evaluated fatal/non-fatal events and three studies evaluated non-fatal events. One study was not included in the meta-analysis because the population overlapped with another study. Of the four studies included, two had low risk of bias (online supplemental table S5).

Intracerebral haemorrhage was identified by ICD-8, ICD-9 and ICD-10 codes in four of five studies. The codes used were similar in all studies that reported them and are listed in online supplemental table S6. In one study, physician diagnosis confirmed case identification. SLE was associated with an increased risk of intracerebral haemorrhage, with a pooled RR of 1.84 (95% CI 1.16 to 2.90; $I^2$ for heterogeneity 67.4%; df=3; p<0.0027) (figure 2C).

#### Ischaemic stroke
Ischaemic stroke was reported in nine studies: three studies evaluated fatal/non-fatal events, five studies evaluated non-fatal events and one study evaluated fatal events. Four studies were not included in the meta-analysis, two of which had overlapping study populations, one did not report a usable 95% CI and one reported data only for a subpopulation. Of the five studies included, three had low risk of bias (online supplemental table S5).

Ischaemic stroke was identified by ICD-8, ICD-9 and ICD-10 codes in seven of nine studies. The codes used were similar in all studies that reported them and are listed in online supplemental table S6. In the remaining studies, physician diagnosis or national insurance claims data confirmed case identification. SLE was associated with an increased risk of ischaemic stroke, with a pooled RR of 2.18 (95% CI 1.78 to 2.67; $I^2$ for heterogeneity 75.4%; df=4; p≤0.001) (figure 2D).

#### Myocardial infarction
MI was reported in 12 studies: six studies evaluated fatal/non-fatal events and six studies evaluated non-fatal events. Four studies were not included in the meta-analysis: two because they reported data only for a subpopulation, one because it only reported data on lupus nephritis (LN) and one owing to population overlap with another study. Of the eight studies included, all but one had low risk of bias (online supplemental table S5).

MI was identified by ICD-8, ICD-9 and ICD-10 codes in 8 of 12 studies. The codes used were similar in all studies that reported them and are listed in online supplemental table S6. In the remaining studies, a combination of WHO criteria, hospital data, Biobank...
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Figure 2  Forest plots of pooled risk ratios for stroke and MI outcomes in adult patients with SLE compared with the general population or healthy controls: (A) composite stroke, (B) subarachnoid haemorrhage, (C) intracerebral haemorrhage, (D) ischaemic stroke, (E) MI. MI, myocardial infarction; SLE, systemic lupus erythematosus.

Sensitivity analyses and heterogeneity

The leave-out method and various sensitivity analyses confirmed the robustness of the results (table 2, online supplemental table S7). In terms of the leave-out function, only one analysis showed a statistically significant effect of removing an individual study. Removal of a cross-sectional study evaluating subarachnoid haemorrhage increased the relative risk identified in the base case from 1.95 to 3.06 (RR 3.06, 95% CI 1.87 to 5.02).

The base-case analyses identified composite stroke, subarachnoid haemorrhage, intracerebral haemorrhage, ischaemic stroke and MI as being statistically significantly increased in persons with SLE compared with the general population. Results of all sensitivity analyses for composite stroke remained significant. For subarachnoid haemorrhage, intracerebral haemorrhage and ischaemic stroke, a number of sensitivity analyses resulted in relative risks that were, in general, higher than the base case but statistically non-significant. We observed this when sensitivity analyses were restricted to studies reporting only on non-fatal/fatal events, only low risk of bias studies, only studies published during or after 2014 and excluding cross-sectional studies. For MI, three of the sensitivity analyses resulted in a lower relative risk that was not statistically significant (including only studies reporting on non-fatal/fatal events, only studies published before 2014 and only studies reporting on non-fatal events).

Visual examination of the funnel plots showed evidence of publication bias, which was supported by the Egger’s test for ischaemic stroke (p=0.001) but not for composite stroke (p=0.885), subarachnoid haemorrhage (p=0.686), intracerebral haemorrhage (p=0.265) and MI (p=0.500).

Subgroup evaluation of age and sex

Eight studies reported the relative risk of stroke stratified by age. Data suggest that risk of stroke increases with age in SLE and non-SLE populations. Patients with SLE have a higher relative risk of stroke, particularly in younger age groups, compared with age-matched population controls. In patients with SLE aged <30 years, RRs ranged from 1.5 to 5.0, and in patients aged >70 years, RRs ranged from 0.5 to 1.7, depending on type of stroke and study design (online supplemental figure S1).

Four studies reported the relative risk of MI stratified by age; however, differences in age group boundaries and small numbers of patients with SLE within groups meant that the data could not be summarised. It was not possible to summarise the relative risk of stroke and MI stratified by sex due to the small numbers of male patients included in the studies.
DISCUSSION

In this meta-analysis of 26 real-world observational studies, patients with SLE had a twofold increase in risk of stroke and threefold increase in risk of MI compared with the general population or healthy controls. To our knowledge, this is the first meta-analysis to assess the risk of both stroke and MI across multiple observational study types in adult patients with SLE compared with the general population or healthy controls.

Rheumatologists are increasingly recognising the risk of CVD as a comorbid disease in patients with SLE. Recent 2019 guidelines from the EULAR recommend assessment of CVD risk and initiation of preventive strategies for patients with SLE when necessary.51 Because the development of CVD could result in decreased health-related quality of life52 and early mortality,53,54 health education and risk factor modification are important for this patient population.

Our findings are consistent with a published meta-analysis for stroke in patients with SLE that included studies up to June 2015.13 The increased risk of composite stroke (RR 2.13), intracerebral haemorrhage (RR 1.84) and ischaemic stroke (RR 2.18) are consistent with findings reported by Holmqvist et al.13 However, the higher number of studies included in our meta-analysis meant increased precision, evidenced by smaller CIs. The increased risk of subarachnoid haemorrhage (RR 1.95) in our analysis is lower than that reported by Holmqvist et al.13 (RR 3.85) because our analysis includes a cross-sectional study published in 2005 that reports a low RR (0.53).36 When we excluded this study in the sensitivity analysis, the RR increased to 3.50 (95% CI 2.24 to 5.48), similar to that reported by Holmqvist et al.13

Our analyses confirm that the relative risk of stroke is higher in younger patients with SLE compared with age-matched controls and corroborate findings from a previous systematic review.13 Although the underlying pathogenesis of increased stroke risk in patients with SLE is the subject of ongoing research, accelerated atherosclerosis likely plays a role.54,56 Accelerated atherosclerosis has also been shown to be associated with LN, which often develops at a young age and is also associated with increased CVD risk.57,58 A previous study found that patients with SLE and a history of LN had twice the rate of carotid plaque as age-matched patients with SLE without LN. Patients with SLE and no LN did not differ from age-matched non-SLE controls regarding carotid plaques.58 Accelerated atherosclerosis is often considered to be the primary cause of increased CVD risk in patients with SLE.59

Our study is strengthened by a rigorous methodological approach based on international guidelines for conduct and reporting of systematic reviews and meta-analyses. The study design included a comprehensive search of multiple databases, reducing the likelihood of omitting evidence reported in key studies. The study selection criteria ensured that studies with overlapping populations were evaluated only once, ensuring greater confidence in reported relative risk estimates. Our study has some limitations. We identified heterogeneity across the evaluated studies that may be a result of variations in population characteristics, control group selection and risk measure reported. An additional source of heterogeneity may result from the extent to which the SLE and comparison populations were matched for CVD risk factors. Some studies matched the population for a wide range of risk factors or adjusted for them in the analysis, while others only matched or adjusted for a limited number of risk factors. However, multiple sensitivity analyses confirmed the increased risk of stroke and MI in patients with SLE. Because of limited data, meta-analyses could not be performed on patient subgroups.

In addition to age, other known MI and stroke risk factors and SLE-related factors are likely to be important in explaining the observed elevated risk. Of SLE-related factors, disease duration and damage, antiphospholipid antibodies, renal and neuropsychiatric disease and steroids have been linked to increased risk of CVD events.59,60 In this work, although subgroup analyses including these risk factors were not possible owing to limited data, our meta-analysis included two studies that suggest an association between CVD risk and treatment type.33,40 In one study, the risk of ischaemic stroke was stratified by steroid use, and a statistically significant increase in relative risk was identified only in patients with concomitant steroid use.40 A more recent study stratified the relative risk of stroke and venous thromboembolism into four treatment subgroups: no therapy, disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.33 The relative risk of composite stroke was shown to be highest in those treated with NSAIDs or corticosteroids followed by those treated with DMARDs. However, these differences were not statistically significant. In addition, our meta-analysis included one study that investigated the effects of end-stage renal disease (ESRD) on the relative risk of ischaemic heart disease (IHD) in patients with SLE and identified a higher relative risk of IHD in patients with ESRD.34

A future synthesis of the available evidence for specified subgroups among patients with SLE would be useful in highlighting potential modifiable risk factors for CVD.

CONCLUSION

The risk of stroke and MI events among adult patients with SLE is twofold to threefold higher compared with the general population or healthy controls. Known MI and stroke risk factors and SLE-related factors are likely to be associated with the observed elevated risk. Understanding the various mechanisms underlying increased CVD risk in patients with SLE, including how antiphospholipid antibodies or antiphospholipid syndrome may modify this risk, will support prevention and treatment strategies and advance informed patient and physician decisions.
| Analysis description | Composite stroke | Subarachnoid haemorrhage | Intracerebral haemorrhage | Ischaemic stroke | Myocardial infarction |
|----------------------|------------------|--------------------------|--------------------------|-----------------|----------------------|
| **Full model**       |                  |                          |                          |                 |                      |
| RR (95% CI)          | 2.13 (1.73 to 2.61) | 1.95 (0.69 to 5.52)   | 1.84 (1.16 to 2.91)      | 2.18 (1.79 to 2.67) | 2.99 (2.34 to 3.82) |
| I²; P-value          | 88.3 %; 0.001    | 94.4 %; 0.001           | 67.4 %; 0.027            | 75.4 %; 0.003   | 85.7 %; 0.001        |
| No. of Studies       | 11               | 4                        | 4                        | 5               | 8                    |
| **Leave1out, range** |                  |                          |                          |                 |                      |
| Low estimate RR (95% CI) | 1.56 (0.85 to 2.87) | 1.44 (0.34 to 6.14) | 1.94 (1.19 to 3.17) | 2.04 (1.74 to 2.42) | 2.05 (1.32 to 3.18) |
| High estimate RR (95% CI) | 2.93 (2.75 to 3.12) | 3.06 (1.87 to 5.02) | 2.00 (1.05 to 3.82) | 2.39 (2.04 to 2.81) | 3.19 (2.94 to 3.47) |
| **Least-adjusted analysis** |            |                          |                          |                 |                      |
| RR (95% CI)          | 2.22 (1.77 to 2.79) | 2.09 (0.78 to 5.56) | 1.79 (0.9 to 3.53)      | 2.31 (1.8 to 2.97) | 3.18 (2.61 to 3.87) |
| I²; P-value          | 90.9 %; 0.001    | 94.0 %; 0.001           | 86.7 %; 0.001            | 84.5 %; 0.001   | 78.8 %; 0.001        |
| No. of studies       | 11               | 4                        | 4                        | 5               | 8                    |
| **Published during or after 2014** | |                          |                          |                 |                      |
| RR (95% CI)          | 2.29 (1.67 to 3.13) | 2.62 (1.03 to 6.66) | NA                       | 2.18 (1.84 to 2.58) | 3.08 (2.40 to 3.95) |
| I²; P-value          | 88.3 %; 0.001    | 70.9 %; 0.064            | NA                       | 0 %; 0.875     | 86.9 %; 0.001        |
| No. of studies       | 6                | 2                        | 2                        | 2               | 7                    |
| **Published before 2014** | |                          |                          |                 |                      |
| RR (95% CI)          | 1.91 (1.47 to 2.49) | 1.59 (0.18 to 13.75) | 2.18 (1.51 to 3.17)      | 2.11 (1.7 to 2.61) | 2.05 (1.32 to 3.18) |
| I²; P-value          | 85.0 %; 0.001    | 96.7 %; 0.001            | 66.2 %; 0.031            | 79.9 %; 0.002   | 0 %; 0.754           |
| No. of studies       | 7                | 2                        | 4                        | 4               | 2                    |
| **Studies with low risk of bias** |            |                          |                          |                 |                      |
| RR (95% CI)          | 2.14 (1.62 to 2.83) | 3.5 (2.24 to 5.48) | 2.17 (1.07 to 4.38)      | 1.95 (1.6 to 2.37) | 3.00 (2.31 to 3.88) |
| I²; P-value          | 89.9 %; 0.001    | 52.4 %; 0.122            | 70.6 %; 0.065            | 64.5 %; 0.06    | 87.5 %; 0.001        |
| No. of studies       | 7                | 3                        | 2                        | 3               | 7                    |
| **Studies reporting on non-fatal/fatal events** | |                          |                          |                 |                      |
| RR (95% CI)          | 2.60 (1.87 to 3.62) | 2.62 (1.03 to 6.66) | 1.31 (0.7 to 2.47)      | 2.43 (1.87 to 3.15) | 2.88 (2.19 to 3.79) |
| I²; P-value          | 73.5 %; 0.005    | 70.9 %; 0.064            | 0 %; 0.698               | 56.2 %; 0.102   | 35.3 %; 0.201        |
| No. of studies       | 5                | 2                        | 2                        | 3               | 4                    |
| **Studies reporting on non-fatal events** | |                          |                          |                 |                      |
| RR (95% CI)          | 2.33 (1.65 to 3.31) | 1.59 (0.18 to 13.75) | 2.3 (1.57 to 3.37)      | 1.93 (1.63 to 2.28) | 2.66 (2.24 to 3.14) |
| I²; P-value          | 94.5 %; 0.001    | 96.7 %; 0.001            | 73.7 %; 0.022            | 71.6 %; 0.03    | 0 %; 0.662           |
| No. of studies       | 5                | 2                        | 3                        | 3               | 3                    |
| **Studies reporting on fatal events** | |                          |                          |                 |                      |
| RR (95% CI)          | 1.56 (0.85 to 2.87) | NA                       | NA                       | NA              | NA                   |
| I²; P-value          | 85.1 %; 0.010    | NA                       | NA                       | NA              | NA                   |
| No. of Studies       | 2                | NA                       | NA                       | NA              | NA                   |

**Lupus**

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Table 2

| Analysis description         | Composite stroke | Subarachnoid haemorrhage | Intracerebral haemorrhage | Ischaemic stroke | Myocardial infarction |
|-----------------------------|------------------|--------------------------|---------------------------|-----------------|-----------------------|
| Excluding cross-sectional studies |                  |                          |                           |                 |                       |
| RR (95% CI)                 | 2.19 (1.77 to 2.72) | 3.5 (2.24 to 5.48) | 1.93 (1.01 to 3.68) | 2.19 (1.69 to 2.83) | NA                    |
| I²; P-value                 | 86.1%; 0.001     | 52.4%; 0.122             | 60.2%; 0.081              | 78.4%; 0.003    |                       |
| No. of studies              | 10               | 3                        | 3                         | 4               |                       |
| Inclusion of study reporting on only LN patients |                  |                          |                           |                 |                       |
| RR (95% CI)                 | 3.20 (2.52 to 4.07) |                         |                           |                 |                       |
| I²; P-value                 | 84.8%; 0.001     |                         |                           |                 |                       |
| No. of studies              | 9                |                          |                           |                 |                       |
| Including studies that were previously excluded because of a population overlap |                  |                          |                           |                 |                       |
| RR (95% CI)                 | Bengtsson 2012   | Zoller 2012a             | Zoller 2012a              | Bengtsson 2012  |
| I²; P-value                 | 2.10 (1.68 to 2.62) | 2.18 (1.51 to 3.17) | 2.1 (1.76 to 2.51) | 2.95 (2.28 to 3.80) |
| No. of studies              | 11               | 4                        | 4                         | 5               |                       |
| RR (95% CI)                 | Bernatsky 2006b  | 66.2%; 0.031             | 74.1%; 0.004              | 81.5%; 0.001    |
| I²; P-value                 | 2.23 (1.83 to 2.72) |                         |                           |                 |                       |
| No. of studies              | 11               | 4                        |                           |                 |                       |
| RR (95% CI)                 | Dregan 2017      | Zoller 2012a             | Bengtsson 2012            |
| I²; P-value                 | 2.21 (1.78 to 2.75) | 2.18 (1.51 to 3.17) | 2.95 (2.28 to 3.80) |
| No. of studies              | 11               | 4                        | 5                         |                 |                       |
| RR (95% CI)                 | Liou 2014        | 50.9%; 0.087             |
| I²; P-value                 | 2.03 (1.65 to 2.50) |                         |                           |                 |                       |
| No. of studies              | 11               | 5                        |                           |                 |                       |

NA, not applicable; RR, risk ratio; SLE, systemic lupus erythematosus
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Provenance and peer review No human subject participants were directly involved in this metanalysis. data from previous studies and did not involve obtaining new data from participants.

Data availability statement Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca’s data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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