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

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To cite: Yazdany J, Pooley N, Langham J, *et al*. Systemic lupus erythematosus; stroke and myocardial infarction risk: a systematic review and meta-analysis. *RMD Open* 2020;**6**:e001247. doi:10.1136/rmdopen-2020-001247

► Supplemental material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2020-001247).

Received 20 March 2020
Revised 25 June 2020
Accepted 11 July 2020

Check for updates

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ABSTRACT

Objective To evaluate the risk of stroke and myocardial infarction (MI) in adult patients with systemic lupus erythematosus (SLE) through a systematic review and meta-analysis.

Methods We searched MEDLINE and EMBASE from inception to May 2020 to identify observational studies (cohort and cross-sectional) that evaluated risk of stroke and MI in adult patients with SLE compared with the general population or healthy controls. Studies were included if they reported effect-size estimates that could be used for calculating pooled-effect estimates. Random-effects models were used to calculate pooled risk ratios (RRs) and 95% CIs for stroke and MI. Heterogeneity quantified by the I^2 test and sensitivity analyses assessed bias.

Results In total, 26 studies were included in this meta-analysis: 14, 5 and 7 studies on stroke, MI and both stroke and MI, respectively. The pooled RR for ischaemic stroke was 2.18 (95% CI 1.78 to 2.67; I^2 75%), intracerebral haemorrhage 1.84 (95% CI 1.16 to 2.90; I^2 67%), subarachnoid haemorrhage 1.95 (95% CI 0.69 to 5.52; I^2 94%), composite stroke 2.13 (95% CI 1.73 to 2.61; I^2 88%) and MI 2.99 (95% CI 2.34 to 3.82; I^2 85%). There was no evidence for publication bias, and sensitivity analyses confirmed the robustness of the results.

Conclusions Overall, patients with SLE were identified to have a twofold to threefold higher risk of stroke and MI. Future research on the interaction between known SLE-specific modifiable risk factors and risk of stroke and MI to support development of prevention and treatment strategies are needed.

PROSPERO registration number CRD42018098690.

Key messages

What is already known about this subject?

- Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder associated with increased comorbidities.
- Epidemiological studies have suggested an increased risk of cardiovascular events, including stroke and myocardial infarction (MI), in patients with SLE.

What does this study add?

- The pooled relative risk of stroke (intracerebral haemorrhage, ischaemic stroke and subarachnoid haemorrhage) and MI from epidemiological studies was found to be twofold to threefold higher among patients with SLE compared with the general population or healthy controls.
- This magnitude of risk was 1.84-fold higher for intracerebral haemorrhage, 1.95-fold for subarachnoid haemorrhage, 2.13-fold for composite stroke, 2.18-fold for ischaemic stroke and 2.99-fold for MI.

How might this impact clinical practice?

- This study confirms the need for treatment strategies that consider prevention and treatment of modifiable cardiovascular risk factors in addition to SLE management.

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 stroke[10 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 Scale[19] and an SLE-specific 12-point scale developed for use in previous SLE systematic reviews.[8 11 13 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 occurrence[24] and referred to as 'risk ratios' throughout this publication. The most adjusted RR was used. A DerSimonian and Laird[25] 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 I^2 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[5–7 28–50] are summarised in table 1. There were 23 cohort studies and three cross-sectional studies.

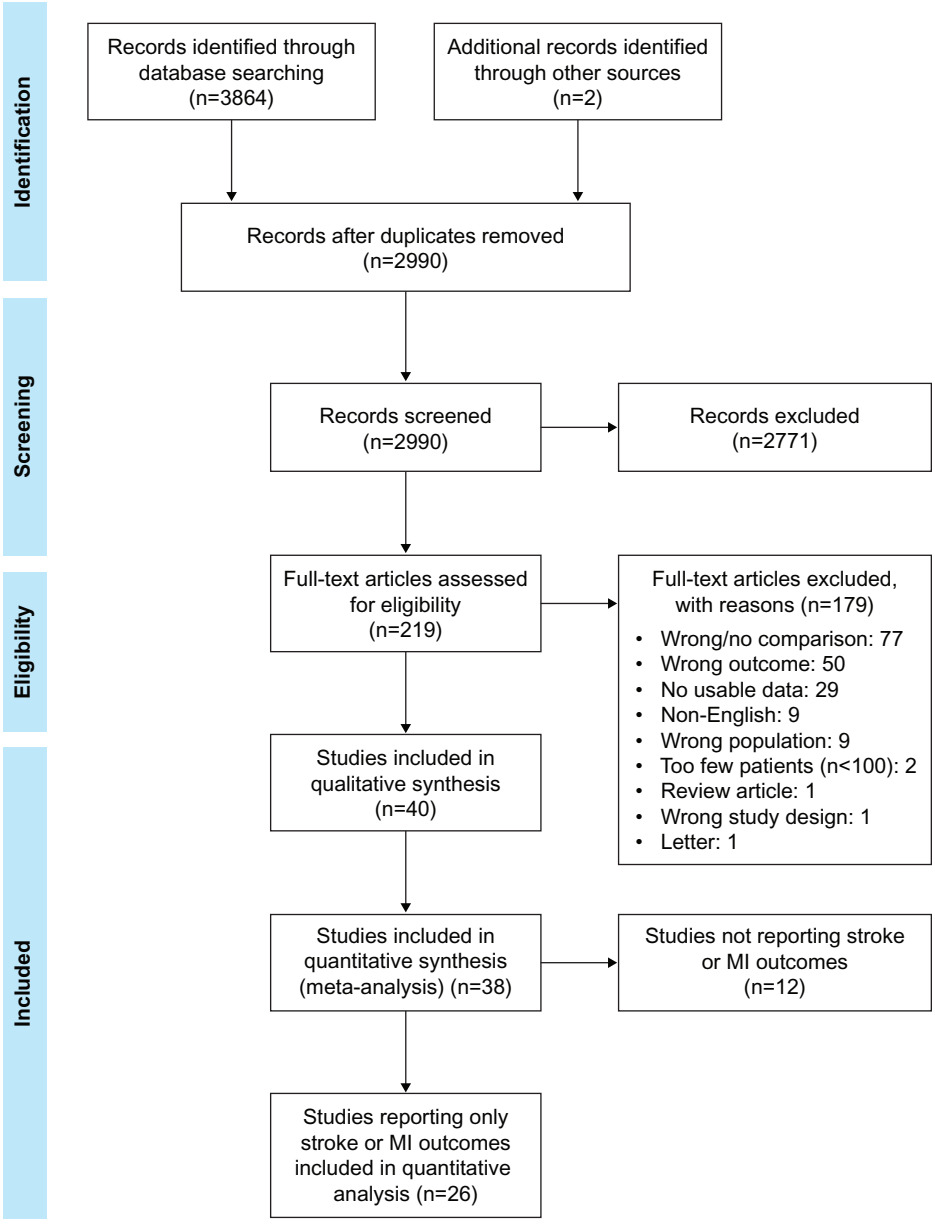

Figure 1 Flow diagram of the systematic literature review process to evaluate the risk of stroke and MI in patients with SLE compared with the general population or healthy controls. MI, myocardial infarction; SLE, systemic lupus erythematosus.

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[28]	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[29]	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[48]	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[30]	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[6]	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[5]	Cohort study	Canada	1958–2001	10 collaborating CaNIOS lupus centres across Canada	Population rates (SMR)	2688; NA	Fatal	90%	NR	Moderate	Ischaemic stroke, subarachnoid haemorrhage, composite stroke	SMR

Continued

Table 1 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[7]	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[31]	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[32]	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[49]	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[33]	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[34]	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[35]	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[36]	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); 48 (no LN), 40 (with LN)	Low	Composite stroke, MI	HR

Continued

Table 1 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
Kim 2017[37]	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[38]	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	OR
Lim 2018[50]	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	HR
Lin 2014[39]	Cohort study	Taiwan	2000–2004	National Health Insurance Research Database	Same as SLE	1207; 9656	Fatal and/or non-fatal	82%	NR	Low	MI	IRR
Liou 2014[40]	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	HR
Manzi 1997[41]	Cohort study	USA	1980–1993	The University of Pittsburgh Medical Center	Framingham Offspring Study	498; 2208	Non-fatal	100%	NR	Low	MI	Relative risk

Continued

Table 1 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
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 Datalink	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[46]	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[6 28–32 34–37 39–41 43–46] and as moderate in two studies.[5 7] Five studies were assessed as having high risk of bias, three of which were cross-sectional studies[33 38 47] and two were cohort studies.[42 49] The risk of bias assessment for included studies is summarised in online supplemental 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,[28 30 33 35 36 42] five evaluated non-fatal events[38 40 44 45 47] and five evaluated fatal events.[5–7] Five studies were not included in the main meta-analysis: four had overlapping populations with other studies[5 30 33 40] and one only reported data by age group.[47] 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,[28 31 43] two studies evaluated non-fatal events[38 45] and one study evaluated fatal events.[5] Two studies were not included in the meta-analysis because they did not provide usable 95% CIs.[5 31] 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[28 42] and three studies evaluated non-fatal events.[38 45 46] One study was not included in the meta-analysis because the population overlapped with another study.[46] 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,[28 29 42] five studies evaluated non-fatal events[32 38 40 45 46] and one study evaluated fatal events.[5] Four studies were not included in the meta-analysis, two of which had overlapping study populations,[45 46] one did not report a usable 95% CI[5] and one reported data only for a subpopulation.[40] 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[29 30 34–36 39] and six studies evaluated non-fatal events.[37 41 47–50] Four studies were not included in the meta-analysis: two because they reported data only for a subpopulation,[41 47] one because it only reported data on lupus nephritis (LN)[34] and one owing to population overlap with another study.[30] Of the eight studies included, all but one had low risk of bias[49] (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

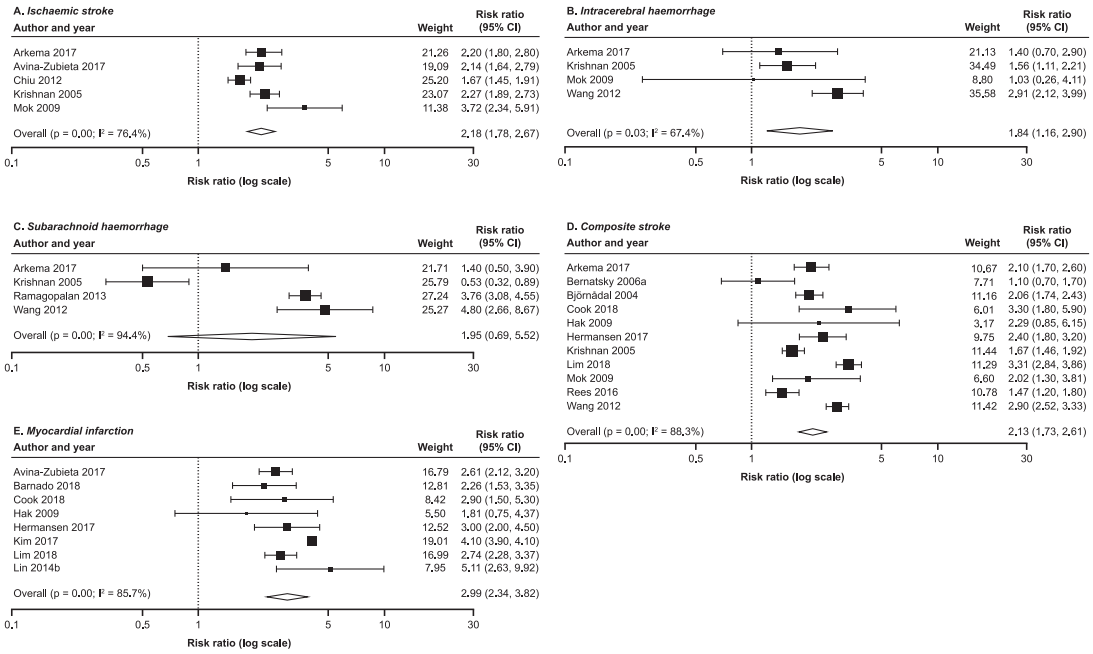

Figure 2 Forest plots of pooled risk ratios for stroke and MI outcomes in adult patients with SLE compared with the general population or healthy controls: (A) composite stroke, (B) subarachnoid haemorrhage, (C) intracerebral haemorrhage, (D) ischaemic stroke, (E) MI. MI, myocardial infarction; SLE, systemic lupus erythematosus.

database based on ICD-10 codes or autopsy evidence confirmed identification. One study did not report how MI was identified.

SLE was associated with an increased risk of MI, with a pooled RR of 2.99 (95% CI 2.34 to 3.82; I^2 for heterogeneity 85.7%; df=7; p≤0.001) (figure 2E).

Sensitivity analyses and heterogeneity

The leave1out method and various sensitivity analyses confirmed the robustness of the results (table 2, online supplemental table S7).

In terms of the leave1out function, only one analysis showed a statistically significant effect of removing an individual study. Removal of a cross-sectional study[38] 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.[28 29 36 42 44–47] 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 14.5 to 53.9, and in patients aged >70 years, RRs ranged from 0.53 to 1.76, 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.[29 30 41 47] 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 life[52] and early mortality,[9 53] 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).[38] 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 antirheumatic 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.

Table 2 Sensitivity analyses for risk of stroke and MI in adult patients with SLE compared with the general population or healthy controls: risk ratios (95% confidence intervals)

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)
I^2; 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)
I^2; 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)
I^2; P-value	88.3 %; 0.001	70.9 %; 0.064		0 %; 0.875	86.9 %; 0.001
No. of studies	6	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)
I^2; 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)
I^2; 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)
I^2; 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)
I^2; 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
I^2; P-value	85.1 %; 0.010				
No. of Studies	2				

Continued

Table 2 Continued

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
I^2; 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)	NA	NA	NA	NA	3.20 (2.52 to 4.07)
I^2; 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	NA	Zoller 2012a	Zoller 2012a	Bengtsson 2012
I^2; 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	88.4 %; 0.001		66.2 %; 0.031	74.1 %; 0.004	81.5 %; 0.001
	11		4	5	8
RR (95 % CI)	Bernatsky 2006b			Wang 2012	
I^2; P-value	2.23 (1.83 to 2.72)			2.46 (2.12 to 2.85)	
No. of studies	86.8 %; 0.001			50.9 %; 0.087	
	11			5	
RR (95 % CI)	Dregan 2017				
I^2; P-value	2.21 (1.78 to 2.75)				
No. of studies	90.0 %; 0.001				
	11				
RR (95 % CI)	Liou 2014				
I^2; P-value	2.03 (1.65 to 2.50)				
No. of studies	85.2 %; 0.001				
	11				

NA, not applicable; RR, risk ratio; SLE, systemic lupus erythematosus

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Acknowledgements Writing and editing assistance was provided by Sarah Thornburg of JK Associates Inc, a Fishawack Health Company. This support was funded by AstraZeneca.

Contributors NP, JL, LN, SL and EH designed the research. NP, JL, LN, SL and NE conducted the research. NP and NE performed the statistical analysis. NP drafted the manuscript. JL and SL supervised the writing. JY, NP, JL, LN, SL, NE, XW, BD, VB and EH contributed to the data interpretation and revised each draft for important intellectual content. All authors read and approved the final manuscript. EH had primary responsibility for the final content and is the guarantor. The corresponding author (BD) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding The current analysis was supported by funding from AstraZeneca. The funder of the study had a role in its design, interpretation of the data and in the writing of the manuscript. The funder had no role in the conduct, collection or analysis of the data. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that NP, JL, LN, SL and NE have received personal fees from AstraZeneca during the conduct of the study and outside the submitted work. VB, XW, BD and EH are employees of AstraZeneca.

Patient consent for publication Not required.

Ethics approval Ethics approval was not required because the study involved only data from previous studies and did not involve obtaining new data from participants. No human subject participants were directly involved in this metanalysis.

Provenance and peer review Not commissioned; externally peer reviewed.

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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