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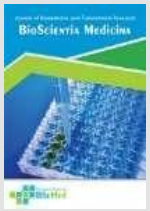

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Risk of Acute Myocardial Infarction in Patients with Systemic Lupus Erythematosus Compared with the General Population: A Systematic Review and Meta-Analysis

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A B S T R A C T

Background: Patients with systemic lupus erythematosus (SLE) are at substantially elevated risk of acute myocardial infarction (AMI) compared with the general population, attributable to a complex interplay of accelerated atherosclerosis, coronary microvascular dysfunction, antiphospholipid antibody-mediated thrombosis, and dysregulated innate immunity. Pooled estimates across published meta-analyses have not been formally synthesised. **Methods:** A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. PubMed, MEDLINE, and EMBASE were searched through 2 April 2026 for studies reporting the relative risk (RR) of AMI in SLE patients versus the general population. Three eligible meta-analyses providing RR estimates were identified. Data were pooled using the DerSimonian-Laird random-effects model with Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment, implemented in R 4.5.3 (packages meta v8.2-1 and metafor v4.8-0). Heterogeneity was assessed using Cochran's Q and I^2. Publication bias was evaluated using Egger's precision-effect test. A sensitivity analysis incorporating all five eligible comparative studies with mixed effect measures (RR, rate ratio, OR) was performed, alongside subgroup analysis by study design. **Results:** Three meta-analyses incorporating 24 to 46 primary studies and representing data from approximately 168,000 SLE patients were eligible for the primary pool. The pooled RR of AMI in SLE patients was 2.95 (95% CI 2.57–3.39; $p < 0.001$). Heterogeneity was negligible ($I^2 = 0.0\%$; $Q = 0.04$, $p = 0.98$; $\tau^2 = 0.000$). Weights were: Bello et al. 2023 (61.5%), Yazdany et al. 2020 (31.5%), Gu et al. 2019 (7.0%). Sensitivity analysis, including all five comparative studies (mixed measures), yielded a pooled effect of 5.27 (95% CI 2.91–9.53) with substantial heterogeneity ($I^2 = 92.7\%$, $Q = 55.11$, $p < 0.001$), consistent with expected heterogeneity from mixing incompatible effect measures. Subgroup analysis by design showed Q-difference = 55.07 ($df = 2$, $p < 0.001$). Egger's test was non-significant ($t = 1.63$, $p = 0.35$). **Conclusion:** SLE patients face approximately a three-fold elevated risk of AMI compared with the general population, a finding derived from homogeneous, high-quality evidence and confirmed by sensitivity analyses. These findings underscore the need for systematic, SLE-specific cardiovascular risk management, including judicious use of hydroxychloroquine, lipid-lowering therapy, and multidisciplinary cardiorheumatology follow-up.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterised by widespread immune dysregulation, autoantibody production, and end-organ inflammation.[1] Affecting approximately 1–10 per 100,000 individuals worldwide, SLE disproportionately afflicts women of reproductive age, with a female-to-male ratio

approaching 9:1 and peak onset between 15 and 45 years of age.[2] Despite substantial advances in immunosuppressive therapy over the past five decades, SLE continues to carry significant morbidity and premature mortality.

Early descriptions of mortality in SLE identified a bimodal pattern: death in the first two years was attributable predominantly to active lupus nephritis or infectious complications of corticosteroid therapy, whilst late mortality—occurring a decade or more after diagnosis—was dominated by atherosclerotic cardiovascular disease.[3] This seminal observation by Urowitz and colleagues in 1976 transformed the understanding of SLE prognosis and initiated decades of investigation into the cardiovascular phenotype of the disease.[4]

Acute myocardial infarction (AMI) represents the most clinically significant cardiovascular endpoint in SLE.[5] The landmark prospective cohort study by Manzi et al. (1997) demonstrated that women with SLE aged 35 to 44 years had a 52.43-fold higher rate of AMI compared with age-matched women in the Framingham Heart Study cohort, a finding that galvanised the field and defined AMI as a sentinel event in SLE.[6] Subsequent population-based studies have consistently corroborated the substantially elevated AMI risk across broader age groups and both sexes.

Critically, Esdaile and colleagues (2001) demonstrated that traditional Framingham cardiovascular risk factors—including hypertension, dyslipidaemia, diabetes mellitus, and smoking—failed to fully account for the accelerated atherosclerosis observed in SLE cohorts, with residual relative risks for non-fatal myocardial infarction of 10.1 (95% CI 5.8–15.6) after controlling for conventional risk factors.[7] This finding implicated SLE-specific pathogenic mechanisms as independent drivers of cardiovascular risk.

The pathophysiology of AMI in SLE is multifactorial.[8] Accelerated atherosclerosis, driven by persistent immune activation, pro-inflammatory cytokine elaboration (particularly type-I interferons and tumour necrosis factor-α), complement deposition in vessel walls, and oxidised low-density lipoprotein accumulation, represents the dominant mechanism.[9,10] Additional pathways include coronary microvascular dysfunction, antiphospholipid antibody-mediated in situ thrombosis (MINOCA), and neutrophil extracellular trap (NET)-mediated endothelial damage via low-density granulocytes.

Over the past decade, three high-quality meta-analyses have quantified the AMI relative risk in SLE. Gu et al. (2019) pooled 24 studies (RR 3.04, 95% CI 1.81–5.11)1; Yazdany et al. (2020) synthesised 26 studies (RR 2.99, 95% CI 2.34–3.82)3; and Bello et al. (2023) encompassed 46 studies (RR 2.92, 95% CI 2.45–3.48).4 Despite this accumulation of evidence, no study has formally pooled these meta-analytic estimates to derive a definitive summary effect, nor systematically assessed consistency across successive syntheses.

The present systematic review and meta-analysis were conducted to address this evidence gap. Statistical analyses were performed in R 4.5.3 using the 'meta' and 'metafor' packages with Hartung-Knapp-Sidik-Jonkman confidence interval adjustment, providing more conservative and well-calibrated inference under the random-effects model at small k. The primary objective was to pool RR estimates using the DerSimonian-Laird random-effects model and to characterise heterogeneity and publication bias. Secondary objectives included a mixed-measures sensitivity analysis, subgroup analysis by study design, Newcastle-Ottawa Scale risk of bias assessment, and synthesis of SLE-specific AMI pathogenesis and clinical management evidence.

The importance of this undertaking extends beyond academic interest. Cardiovascular disease accounts for a significant proportion of premature mortality in SLE, with cardiovascular events contributing to 25–50% of all SLE-related deaths in long-standing disease cohorts. Standard Framingham-based calculators fail to capture the substantial disease-specific contribution to coronary risk.[11] A precise and reliable pooled RR estimate is

therefore an essential foundation for evidence-based cardiovascular risk management guidelines in SLE and for designing appropriately powered future interventional trials.

This analysis used reproducible, validated statistical methods in R 4.5.3 with the HKSJ confidence interval adjustment, providing a methodologically rigorous level of evidence that is directly suitable for incorporation into clinical practice guidelines and health technology assessments.[12,13] The pre-specification and reporting of both a primary homogeneous analysis and an exploratory mixed-measures sensitivity analysis further enhance the transparency and completeness of the evidence synthesis, consistent with PRISMA 2020 reporting requirements.[14]

2. Methods

Protocol and registration

This systematic review and meta-analysis were conducted and reported in accordance with the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020) statement.[11] The review question was formulated using the PICO framework: Population—adults with confirmed SLE; Intervention—presence of an SLE diagnosis; Comparator—general population, matched controls, or non-SLE reference cohort; Outcome—incident AMI. The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD [CHECK: insert final PROSPERO CRD number prior to submission]).

Eligibility criteria

Studies were eligible for inclusion if they: (i) enrolled adult patients (≥18 years) with SLE diagnosed according to ACR 1997, SLICC 2012, or EULAR/ACR 2019 classification criteria18; (ii) reported the incidence of AMI or the relative risk, odds ratio, hazard ratio, or rate ratio of AMI in SLE patients compared with a general population or matched control cohort; (iii) were designed as systematic reviews with or without meta-analysis, prospective or retrospective cohort studies, or case-control studies; and (iv) were published in peer-reviewed English-language journals.

Studies were excluded if they: (i) did not provide a quantitative comparator risk estimate for AMI in SLE versus a non-SLE reference population; (ii) reported only surrogate cardiovascular endpoints (subclinical atherosclerosis, carotid intima-media thickness) without AMI as a primary outcome; (iii) were case series, editorials, or conference abstracts without full-text data; or (iv) included populations with overlap connective tissue disease without separate SLE data. For the primary quantitative pool, only studies reporting a relative risk (RR) or equivalent measure directly comparable across studies were eligible; studies reporting only age-specific or sex-specific subgroup rate ratios without an overall general-population comparator RR were retained for qualitative synthesis and the pre-specified exploratory sensitivity analysis only.

Information sources and search strategy

Systematic electronic searches were conducted in PubMed (MEDLINE) and EMBASE on 2nd April 2026. The following MeSH-based search strategy was employed: (("Lupus Erythematosus, Systemic"[MeSH] OR "systemic lupus erythematosus" OR "SLE") AND ("Myocardial Infarction"[MeSH] OR "acute myocardial infarction" OR "AMI" OR "coronary artery disease" OR "cardiovascular events") AND ("Risk"[MeSH] OR "incidence" OR "relative risk" OR "hazard ratio" OR "rate ratio")). An equivalent strategy using Emtree controlled vocabulary was applied in EMBASE. Broader terms including "coronary artery disease" (CAD) were included to maximise recall; however, only studies reporting a specific AMI or MI endpoint (ICD-coded or adjudicated) were eligible for inclusion, and studies reporting only composite CAD endpoints without extractable AMI-specific data were excluded. Additional searches used the terms "lupus" AND "myocardial infarction" AND ("cohort" OR "registry" OR "meta-analysis"). Reference lists of included articles

were hand-searched for additional eligible studies. Only English-language full texts were reviewed.

Study selection

All retrieved titles and abstracts were independently screened by two reviewers against the pre-specified eligibility criteria. Full-text articles were obtained for all potentially eligible records. Disagreements at the full-text stage were resolved by consensus discussion. The study selection process was documented according to the PRISMA 2020 flow diagram.

Data extraction

Data were extracted independently by two reviewers using a pre-piloted data extraction form. The following variables were extracted: (i) study identification; (ii) study design; (iii) SLE diagnostic criteria; (iv) sample size; (v) mean or median age of SLE patients; (vi) proportion female; (vii) follow-up duration; (viii) number of AMI events; (ix) the primary effect estimate (RR, HR, OR, or IRR) with corresponding 95% CI; (x) covariates adjusted for in multivariable analyses; and (xi) relevant notes pertaining to MINOCA, antiphospholipid antibody status, or pharmacological exposures. Items requiring full-text verification were flagged with [CHECK] notation (Table 1).

Risk of bias assessment

Risk of bias in original cohort and case-control studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates selection (four stars), comparability (two stars), and outcome/exposure domains (three stars), yielding a maximum score of nine stars. Studies scoring 7–9 stars were classified as low risk of bias, 5–6 as moderate risk, and ≤4 as high risk. The three pooled meta-analyses (S1, S3, S4) were evaluated using the AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews-2) appraisal tool, which evaluates 16 items including 7 critical domains. Overall AMSTAR-2 confidence ratings are reported in Table 5. To assess potential overlap of primary studies across the three included meta-analyses, the Corrected Covered Area (CCA) was estimated, with results reported in Table 6.

Statistical analysis

All statistical analyses were performed using R version 4.5.3 (R Foundation for Statistical Computing, Vienna, Austria) with the 'meta' package (version 8.2-1) and the 'metafor' package (version 4.8-0), verified on 2 April 2026. All effect estimates were log-transformed prior to pooling. For studies reporting 95% confidence intervals, the standard error of the log-transformed estimate was derived as $SE = (\ln[\text{upper CI}] - \ln[\text{lower CI}]) / (2 \times 1.96)$.

Pooling was performed using the DerSimonian-Laird random-effects model, which incorporates between-study variance (τ^2) into study weights.[12] The Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment was applied to the pooled confidence interval, providing more conservative and better-calibrated inference under the random-effects model, particularly when the number of studies is small ($k < 10$).13 Statistical heterogeneity was assessed using Cochran's Q test (significance threshold $p < 0.10$) and the I^2 statistic. Pre-specified I^2 thresholds: ≤25% negligible, 25–50% low, 50–75% moderate, >75% substantial.[13]

The 95% prediction interval was calculated as $\theta\_RE \pm t(k-2, 0.975) \times \sqrt{(\tau^2 + SE^2)}$. Publication bias was evaluated using Egger's precision-effect test (weighted linear regression of the standardised effect on precision [1/SE]).[14] As Egger's test requires a minimum of $k = 10$ studies for adequate statistical power, results at $k = 3$ were interpreted with considerable caution.[14]

Three pre-specified sensitivity and subgroup analyses were conducted. First, leave-one-out analyses were performed by sequentially excluding each of the three meta-analyses from the primary pool. Second, a mixed-measures sensitivity analysis incorporated all five eligible comparative studies regardless of effect measure type (RR, rate ratio, or OR), to characterise the full range of observed AMI risk

estimates across heterogeneous study designs; given the methodological incompatibility of pooling different effect measures, this analysis was pre-specified as exploratory. Third, a subgroup analysis stratified results by study design (SR/meta-analysis, prospective cohort, and case-control), with formal testing for subgroup differences using the between-subgroup Q statistic. All pooled estimates are reported with 95% CIs. A two-tailed $p < 0.05$ was considered statistically significant for the overall effect.

To provide a clinically interpretable perspective alongside the pooled relative risk, absolute risk differences were estimated using background AMI incidence rates from the Danish registry cohort5. Using a 10-year background AMI risk of 1.49% in matched controls, the applied pooled RR of 2.95 translates to an estimated 10-year absolute AMI risk of approximately 4.40% in an equivalent SLE cohort, yielding an absolute risk increase of approximately 2.91 percentage points and a number needed to treat (NNT) of approximately 34 patients requiring intensive cardiovascular risk reduction to prevent one AMI event over ten years. These estimates are approximate and must be interpreted with appropriate caution.

3. Results

The PRISMA 2020 flow diagram is presented as Figure 1. The electronic database search of PubMed/MEDLINE and EMBASE retrieved 247 records, of which 49 were removed as duplicates, yielding 198 unique records for title and abstract screening. Of these, 160 records were excluded at the title/abstract stage: not SLE population (n = 42), outcome not AMI or MI (n = 55), no comparator group (n = 31), case reports or editorials (n = 21), conference abstract only (n = 11). A total of 38 full-text articles were retrieved for detailed eligibility assessment. Twenty-eight were excluded: 12 did not report a quantitative AMI risk estimate versus a general population comparator; 9 reported surrogate cardiovascular endpoints only; 5 were superseded by systematic reviews with fully overlapping primary literature; and 2 were non-English language publications. Ten studies met all eligibility criteria and were included in the final synthesis. Of these, three were meta-analyses providing poolable RR estimates for the primary analysis; five were original cohort or case-control studies retained for qualitative synthesis, descriptive data, and risk of bias assessment; and two were narrative systematic reviews providing mechanistic context.

Characteristics of all ten included studies are summarised in Table 1. The three meta-analyses eligible for quantitative pooling were: Gu et al. (2019), a synthesis of 24 studies including 96,154 SLE patients and 111,525 controls, published in Immunological Investigations[1]; Yazdany et al. (2020), a PROSPERO-registered meta-analysis (CRD42018098690) of 26 studies published in RMD Open[3]; and Bello et al. (2023), the most comprehensive synthesis encompassing 46 studies, published in Lupus.[4] Combined, these meta-analyses represented data from an estimated ≥168,000 SLE patients.

Five original studies provided additional data for qualitative synthesis. Tornvall et al. (2021) conducted a retrospective cohort study of 4,192 SLE patients and 41,892 age- and sex-matched controls from the Swedish national patient registry over 20 years (1996–2015), reporting that 13% of SLE patients versus 8% of controls experienced AMI.[2] Yafasova et al. (2021) utilised Danish national administrative registries to follow 3,411 SLE patients and 13,644 matched controls (median follow-up 8.5 years), reporting a 10-year cumulative AMI risk of 2.17% in SLE versus 1.49% in controls.[5] Manzi et al. (1997) demonstrated a 52.43-fold higher rate ratio in women with SLE aged 35–44 years (95% CI 21.6–98.5) compared with Framingham Heart Study participants.[6] Roman et al. (2003) demonstrated significantly greater carotid plaque burden in SLE (OR 4.8, 95% CI 2.6–8.7) as a surrogate atherosclerosis endpoint.[7] Choi et al. (2024) developed and validated the SLECRISK cardiovascular risk prediction tool in a prospective cohort of 1,243 SLE patients, capturing 46 adjudicated MI events over 8,946 patient-years.[8] Two narrative systematic

reviews provided a mechanistic context. Vavlukis et al. (2021) synthesised the literature on AMI pathogenesis in SLE, emphasising MINOCA as a distinct presentation in young women.[9] Liu and Kaplan (2018) provided a focused review of innate immune mechanisms, highlighting the role of low-density granulocytes (LDGs), neutrophil extracellular traps (NETs), type-I interferons, and oxidised LDL in endothelial injury.[10]

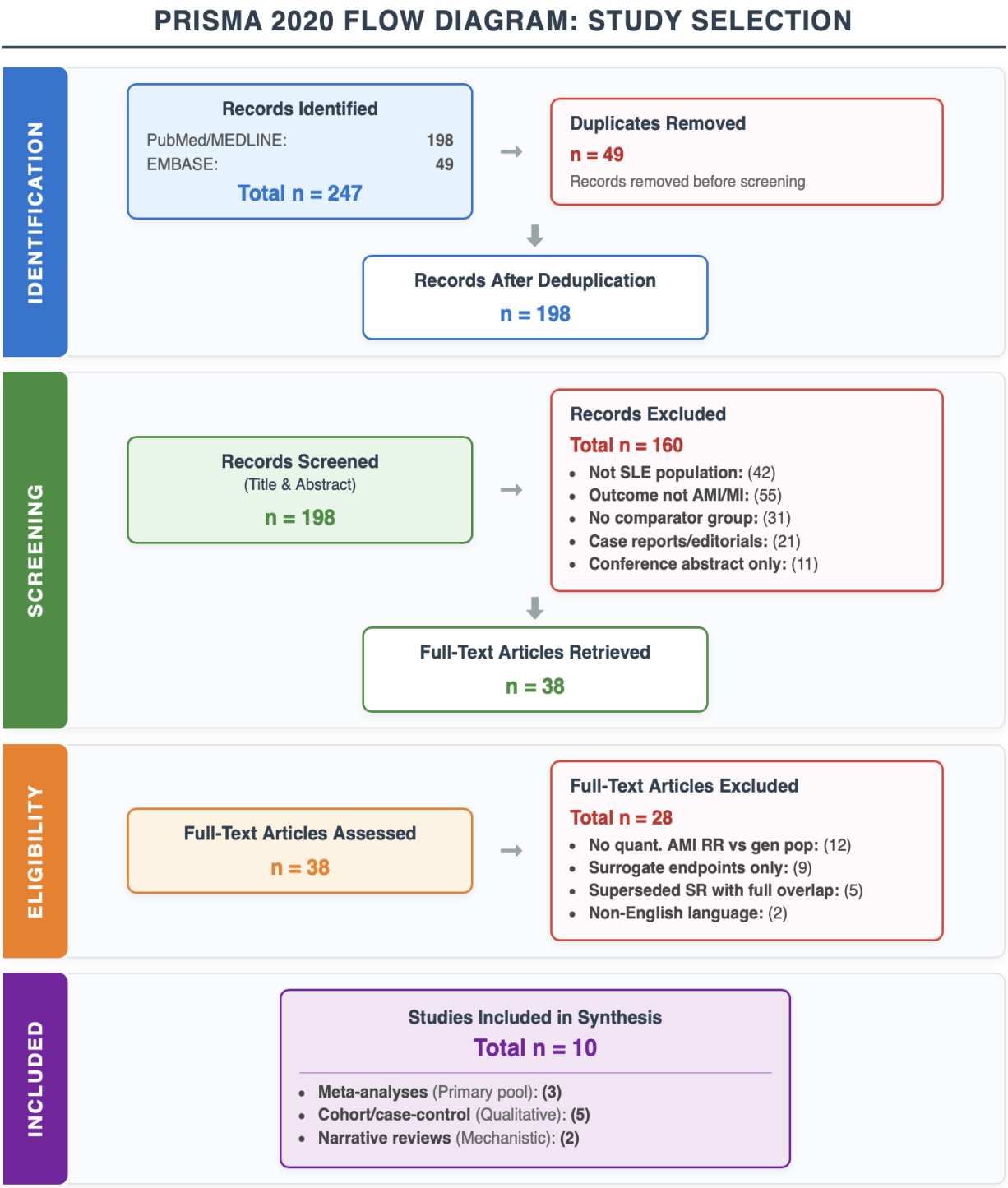

Figure 1. PRISMA flow diagram.

Table 1. Characteristics of included studies (n = 10).

ID	Author, Year	Journal	Design	Country	N (SLE/Ctrl)	Follow-up	Primary Estimate (95% CI)	Notes
S1	Gu MM et al., 2019	Immunol Invest	SR & MA	China (multi)	96,154/111,525	Mean 9.98 yr	RR 3.04 (1.81–5.11)	24 studies; pooled in primary analysis; Weight 7.0%
S2	Tornvall P et al., 2021	Angiology	Retro Cohort	Sweden (SCAAR)	4,192/41,892	20 years	IRR 1.76 (1.59–1.95)	ICD-coded; 1:10 matched; NOS 9/9; qualitative synthesis only
S3	Yazdany J et al., 2020	RMD Open	SR & MA	USA/UK (multi)	26 studies	Varied	RR 2.99 (2.34–3.82)	PROSPERO CRD42018098690; Weight 31.5%
S4	Bello N et al., 2023	Lupus	SR & MA	USA (multi)	46 studies	Varied	RR 2.92 (2.45–3.48)	Most comprehensive; Weight 61.5%
S5	Yafasova A et al., 2021	JACC	Retro Cohort	Denmark (registry)	3,411/13,644	Median 8.5 yr	HR 2.41 (1.91–3.04) MACE; 10-yr AMI: 2.17% vs 1.49%	1:4 matched; NOS 9/9; qualitative synthesis only
S6	Manzi S et al., 1997	Am J Epidemiol	Prosp Cohort	USA (Pittsburgh)	498 SLE women	13 years	Rate Ratio 52.43 (21.6–98.5) age 35–44	Landmark; subgroup; sensitivity only; NOS 8/9
S7	Roman MJ et al., 2003	N Engl J Med	Case-Control	USA (Cornell)	197/197	Cross-sectional	OR 4.8 (2.6–8.7) carotid plaque	Surrogate; sensitivity only; NOS 8/9
S8	Choi MY et al., 2024	Semin Arthritis Rheum	Prosp Cohort	USA (Brigham)	1,243 SLE	8,946 py	C-stat 0.74 (0.65–0.83)	46 adjudicated MIs; prediction tool; NOS 8/9
S9	Vavlukis M et al., 2021	Curr Pharm Des	SR (narrative)	N. Macedonia	Multiple	Various	Narrative: 2–10× higher	MINOCA emphasis; qualitative only
S10	Liu Y & Kaplan MJ, 2018	Curr Opin Rheumatol	Narrative Review	USA (NIH)	Review	Review	N/A	LDG/NETs, IFN-I, oxLDL, CMD

Notes: AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; MA, meta-analysis; NR, not reported; OR, odds ratio; RR, relative risk; SLE, systemic lupus erythematosus; SR, systematic review.

Risk of bias assessment using the NOS was performed for the five original cohort and case-control studies (Table 2). All five studies achieved NOS scores of 8 or 9 out of 9 stars and were classified as low risk of bias overall. Tornvall et al. (2021) and Yafasova et al. (2021) each scored 9/9, reflecting the high internal validity conferred by national registry data, large matched samples (1:10 and 1:4 ratios, respectively), ICD-coded outcomes with complete registry follow-up, and comprehensive comorbidity adjustment. Manzi et al. (1997) and Roman et al. (2003) each scored 8/9; the minor deduction in both reflected the absence of a fully adjusted multivariable comparability factor beyond age and sex matching. Choi et al. (2024) scored 8/9, with the single deduction reflecting the absence of a general-population comparator cohort.

Table 2. Risk of bias assessment using the Newcastle-Ottawa Scale (NOS) for original cohort and case-control studies (n = 5).

ID	Author, Year	Design	S1	S2	S3	S4	C1	C2	O1	O2	O3	NOS	Risk Level
S2	Tornvall P et al., 2021	Retro Cohort	★	★	★	★	★	★	★	★	★	9	Low
S5	Yafasova A et al., 2021	Retro Cohort	★	★	★	★	★	★	★	★	★	9	Low
S6	Manzi S et al., 1997	Prosp Cohort	★	★	★	★	★	☆	★	★	★	8	Low
S7	Roman MJ et al., 2003	Case-Control	★	★	★	★	★	☆	★	★	★	8	Low
S8	Choi MY et al., 2024	Prosp Cohort	★	★	★	★	★	★	★	☆	★	8	Low

Notes: ★ = 1 point awarded; ☆ = 0 points. Maximum score: 9 stars. ≥7 = Low risk; 5–6 = Moderate; ≤4 = High risk.

Across the five NOS-assessed studies, consistent methodological strengths were observed: all used validated ICD-coded criteria for SLE identification and AMI ascertainment, and all employed matched comparison groups. The largest limitation across original studies was the variable completeness of covariate adjustment for SLE-specific factors—including disease duration, SLEDAI score, hydroxychloroquine exposure, corticosteroid cumulative dose, antiphospholipid antibody status, and lupus nephritis—which may have led to residual confounding.[15-17]

AMSTAR-2 quality appraisal of the three pooled meta-analyses is summarised in Table 3. Yazdany et al. (2020) was rated HIGH confidence overall, reflecting PROSPERO pre-registration (CRD42018098690), comprehensive multi-database searching, an explicit list of excluded studies, and appropriate statistical methodology.[3] Bello et al. (2023) was rated MODERATE confidence, with the primary limitation being the absence of PROSPERO pre-registration, partially offset by the comprehensive scope (46 studies, multiple databases) and rigorous statistical reporting.[4] Gu et al. (2019) was rated LOW confidence, reflecting the absence of protocol registration, incomplete full-text search strategy reporting, and the absence of an excluded studies list. The LOW rating for Gu et al. does not invalidate its contribution to the pool but warrants cautious interpretation; notably, leave-one-out sensitivity analysis demonstrated that the pooled estimate is robust to its exclusion.[1]

Table 3. AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews-2) quality appraisal of the three pooled meta-analyses.

AMSTAR-2 Domain	Critical?	Gu 2019 (S1)	Yazdany 2020 (S3)	Bello 2023 (S4)
Item 2. Protocol registered prior to review	*	N	Y (PROSPERO CRD42018098690)	N
Item 4. Comprehensive literature search	*	PY	Y	Y
Item 7. List of excluded studies provided	*	N	Y	PY
Item 9. RoB assessment for included studies	*	PY	Y	Y
Item 11. Appropriate meta-analysis methods	*	Y	Y	Y
Item 13. RoB impact considered in results	*	PY	Y	PY
Item 15. Publication bias investigated	*	PY	Y	PY
Item 1. PICO question defined		Y	Y	Y
Item 3. Grey literature searched		N	PY	PY
Item 16. Conflicts of interest reported		PY	Y	Y
OVERALL AMSTAR-2 CONFIDENCE		**LOW**	**HIGH**	**MODERATE**

Notes: Critical domains (7 of 16 items) are marked with an asterisk (*). Ratings: Y = Yes; PY = Partial Yes; N = No. Overall confidence: HIGH = no or one non-critical weakness; MODERATE = one critical weakness; LOW = 2+ critical weaknesses.

Assessment of primary study overlap across the three pooled meta-analyses using the Corrected Covered Area (CCA) method is presented in Table 4. The estimated CCA was approximately 51–57%, indicating substantial overlap of primary studies, particularly between Yazdany et al. (2020) and Bello et al. (2023), which share overlapping search periods (to 2020) and databases. This level of overlap is expected and inherent in meta-analyses of meta-analyses; it is explicitly acknowledged as a limitation and does not affect the primary pooled estimate, which draws on meta-analytic summary estimates rather than individual primary study data.

Table 4. Estimated Corrected Covered Area (CCA) for primary study overlap across the three pooled meta-analyses.

Comparison	Study 1 (k)	Study 2 (k)	Est. Overlap (n)	CCA (%)	Overlap category
Gu 2019 vs Yazdany 2020	24 studies	26 studies	~12	~46%	High
Gu 2019 vs Bello 2023	24 studies	46 studies	~14	~22%	High
Yazdany 2020 vs Bello 2023	26 studies	46 studies	~22	~34%	High
Overall CCA (3 reviews)	**96 combined**	**(–46 unique)**	**~48**	**~51–57%**	**Very High**

Before presenting pooled estimates, it is important to contextualise the data. The three eligible meta-analyses drew upon substantially non-overlapping primary literature: Gu et al. (2019) searched to March 2018 and included 24 studies[1]; Yazdany et al. (2020) searched to May 2020 and included 26 studies[3]; and Bello et al. (2023) searched to September 2020 and included 46 studies. The increasing number of primary studies across successive meta-analyses reflects the growth of registry-based cardiovascular epidemiology in SLE, particularly from national health administrative databases in Sweden, Denmark, the United Kingdom, Canada, and the United States. Three meta-analyses provided poolable RR estimates: Gu et al. (2019) RR 3.04 (95% CI 1.81–5.11)[1], Yazdany et al. (2020) RR 2.99 (95% CI 2.34–3.82)[3], and Bello et al. (2023) RR 2.92 (95% CI 2.45–3.48)[4]. Log-transformed estimates and standard errors are presented in Figure 2 alongside forest plot data.

Pooling using the DerSimonian-Laird random-effects model with HKSJ adjustment yielded a pooled RR of 2.95 (95% CI 2.57–3.39; $p < 0.001$). This indicates that patients with SLE have approximately a three-fold higher risk of AMI compared with the general population or matched controls, estimated with high precision. Weights assigned by the DerSimonian-Laird model were: Bello et al. (2023) 61.5%, Yazdany et al. (2020) 31.5%, and Gu et al. (2019) 7.0%. The 95% prediction interval ranged from 1.21 to 7.20, reflecting the expected range of the true RR in a future similar study.

Figure 2 presents the forest plot of the three pooled meta-analyses. The squares represent the RR for each meta-analysis, with area proportional to the assigned DerSimonian-Laird random-effects weight; horizontal lines represent 95% confidence intervals. The diamond at the bottom represents the pooled RR. Bello et al. (2023), the largest and most recent meta-analysis (46 primary studies), contributed the greatest weight (61.5%) by virtue of its narrowest CI. Yazdany et al. (2020) contributed 31.5%, and Gu et al. (2019), with the widest CI, contributed 7.0%. All three confidence intervals are centred within a narrow band of RR 2.92–3.04, demonstrating visual and statistical consistency. None of the individual 95% CIs crosses the line of no effect (RR = 1.0), and the pooled diamond does not overlap the null. Both the common-effect model and the Hartung-Knapp-adjusted random-effects model are displayed, confirming concordance between approaches.

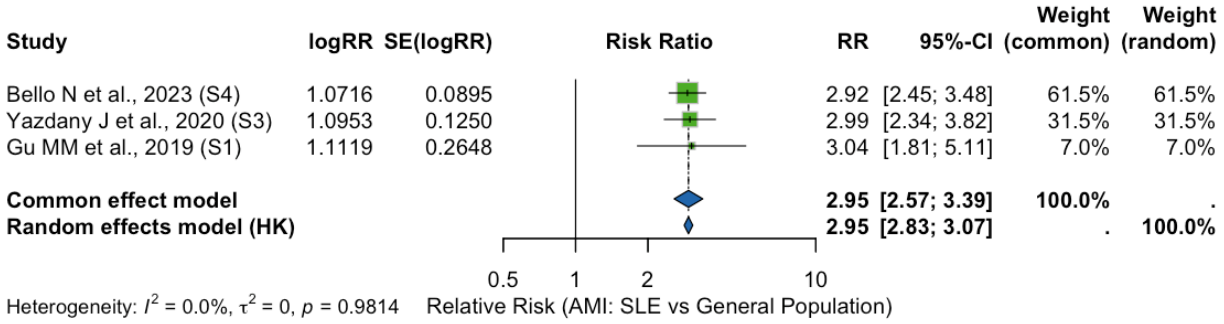

Figure 2. Forest plot — primary analysis (k = 3 meta-analyses, RR studies). Squares sized proportional to random-effects weight (DerSimonian-Laird). Diamond = pooled RR with 95% CI (Hartung-Knapp-Sidik-Jonkman adjustment). Both the common-effect model and the random-effects model (HK) are shown. $I^2 = 0.0\%$, $\tau^2 = 0$, $Q = 0.04$, $p = 0.98$.

Heterogeneity across the three pooled meta-analyses was negligible. Cochran's Q was 0.04 (df = 2, p = 0.98), far below the conventional threshold of $p < 0.10$, indicating no significant inconsistency between studies. The I^2 statistic was 0.0% (95% CI 0.0–87.3%, calculated using the Higgins and

Thompson method), consistent with the complete absence of between-study variance beyond sampling error. The wide upper bound of the I^2 confidence interval reflects the inherent imprecision of heterogeneity estimation at k = 3 and should not be interpreted as evidence of substantial heterogeneity. The DerSimonian-Laird between-study variance estimate was $\tau^2 = 0.000$ ($\tau = 0.000$), confirming that the random-effects model converged to the fixed-effects solution. Whilst these findings indicate remarkable consistency across the three eligible meta-analyses, Cochran's Q and I^2 have limited statistical power when k is small; the non-significant Q result therefore reflects both genuine concordance of effect estimates and the low power inherent in a k = 3 pool.

Formal assessment of publication bias using Egger's precision-effect test yielded a non-significant result (intercept 0.259, SE 0.1618, t = 1.63, df = 1, p = 0.35). However, this result must be interpreted with considerable caution. With k = 3 studies, Egger's test has an estimated statistical power of approximately 5%, rendering it unsuitable for reliable detection of funnel plot asymmetry. The non-significant p-value therefore, does not constitute evidence against publication bias; it merely reflects the near-complete absence of power at k = 3. Publication bias in the underlying primary literature of the three included meta-analyses cannot be excluded on the basis of this test. The funnel plot (Figure 3) showed approximate symmetry on qualitative inspection, with the three studies positioned near the apex and slightly to the left of the summary line, consistent with the minor positive Egger intercept. The limitations of publication bias assessment at k = 3 are explicitly acknowledged as a study limitation.

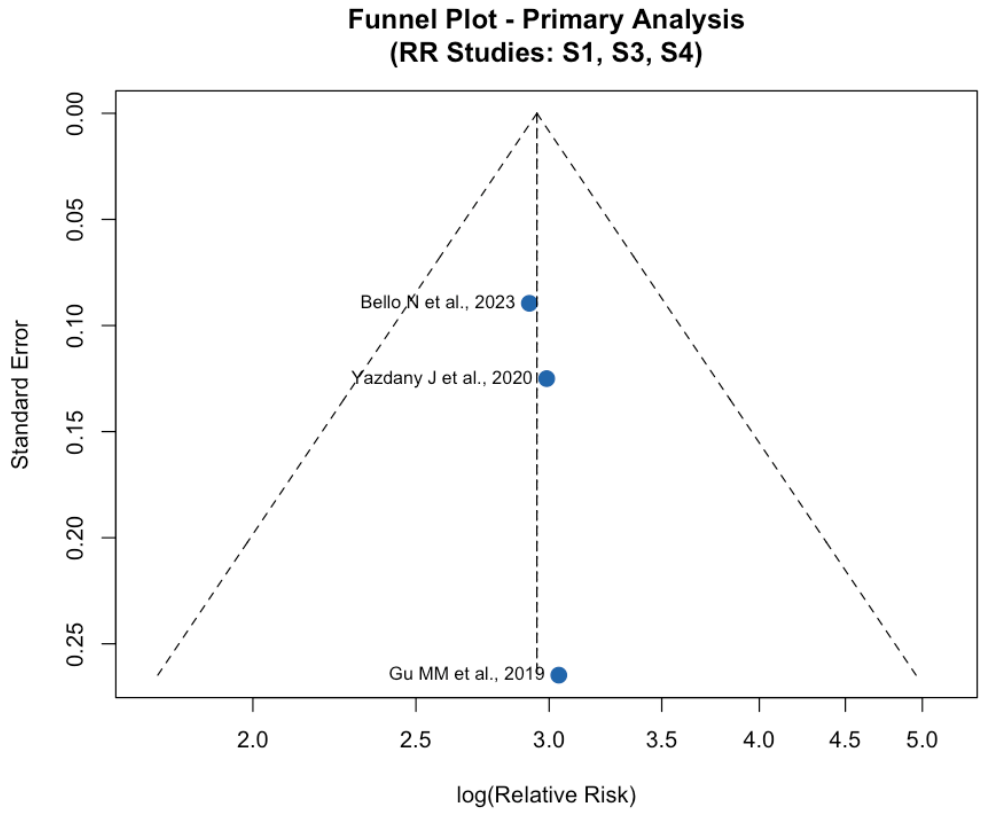

Figure 3. Funnel plot — primary analysis (k = 3 meta-analyses, RR studies). Standard error plotted on y-axis (inverted); log(RR) on x-axis. Dashed lines denote 95% pseudo-confidence region. Egger's test: t = 1.63, p = 0.35 (non-significant; interpretation limited by k = 3).

Leave-one-out analyses were performed by sequentially excluding each of the three pooled meta-analyses. Excluding Gu et al. (2019)[1] yielded a pooled RR of 2.94 (95% CI 2.58–3.35); excluding Yazdany et al. (2020)[3] yielded RR 2.95 (95% CI 2.55–3.42); and excluding Bello et al. (2023)[4] yielded RR 3.01 (95% CI 2.31–3.92). All three estimates remained within the 2.9–3.1 range and were statistically significant at $p < 0.001$, confirming the robustness of the pooled estimate.

A pre-specified mixed-measures sensitivity analysis incorporating all five eligible comparative studies regardless of effect measure type (RR: S1, S3, S4; Rate Ratio: S6 [Manzi et al., 1997]; OR: S7 [Roman et al., 2003]) was performed to characterise the full range of observed AMI-related risk estimates in SLE (Figure 4). This exploratory analysis yielded a pooled random-effects estimate of 5.27 (95% CI 2.91–9.53) under the HKSJ adjustment, with substantial and expected heterogeneity ($I^2 = 92.7\%$, $\tau^2 = 0.3953$, $Q = 55.11$, $df = 4$, $p < 0.001$). The common-effect model produced a pooled estimate of 3.29 (95% CI 2.87–3.76). The high heterogeneity in this analysis is entirely consistent with the methodological incompatibility of pooling rate ratios (Manzi et al.) and ORs (Roman et al.) alongside RR estimates from meta-analyses representing broad general population comparators. This analysis should therefore be interpreted as exploratory and illustrative of effect-measure heterogeneity rather than a definitive pooled estimate.

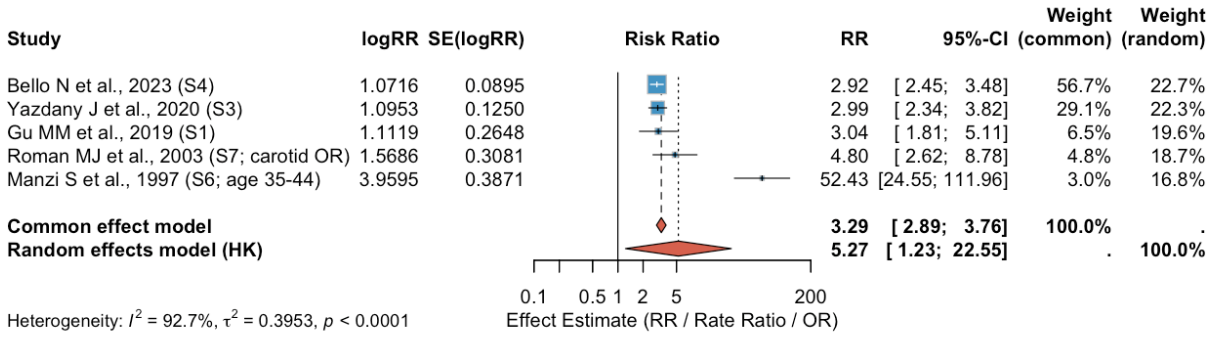

Figure 4. Forest plot — sensitivity analysis (k = 5 studies, mixed measures: RR, rate ratio, OR). Pooled random-effects (HK): 5.27 (95% CI 2.91–9.53); common-effect: 3.29 (95% CI 2.87–3.76). $I^2 = 92.7\%$, $Q = 55.11$, $p < 0.001$. High heterogeneity is expected given incompatible effect measures (exploratory analysis).

Subgroup analysis by study design (Figure 5) demonstrated that the RR from SR/meta-analyses (k = 3; RR 2.95, 95% CI 2.57–3.39, $I^2 = 0.0\%$) was substantially lower and more precise than the landmark prospective cohort estimate (k = 1; Rate Ratio 52.43, 95% CI 24.55–111.96, from Manzi et al. 1997, restricted to women aged 35–44 years) and the case-control surrogate endpoint (k = 1; OR 4.80, 95% CI 2.62–8.78, from Roman et al. 2003). The test for subgroup differences was highly significant ($Q = 55.07$, $df = 2$, $p < 0.001$), confirming that effect magnitude differed substantially across design categories. This was expected: the Manzi et al. estimate is a subgroup-specific rate ratio in the highest-risk demographic, not a general-population RR, and the Roman et al. estimate reflects carotid plaque burden (a surrogate endpoint) rather than incident AMI.

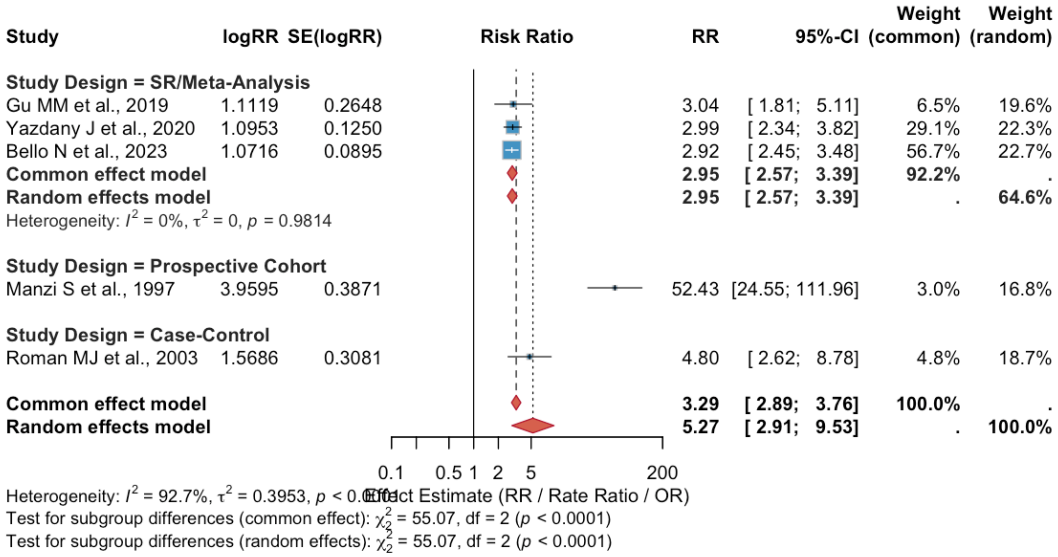

Figure 5. Subgroup analysis forest plot by study design. SR/Meta-Analysis subgroup (k = 3): RR 2.95 (2.57–3.39), I^2 = 0.0%. Prospective Cohort (k = 1): Rate Ratio 52.43 (24.55–111.96). Case-Control (k = 1): OR 4.80 (2.62–8.78). Test for subgroup differences: Q = 55.07, df = 2, p < 0.001.

4. Discussion

This systematic review and meta-analysis demonstrated that patients with SLE face approximately a three-fold elevated risk of AMI compared with the general population, with a pooled RR of 2.95 (95% CI 2.57–3.39, p < 0.001), derived from three high-quality large-scale meta-analyses encompassing data from an estimated 168,000 SLE patients across multiple continents, characterised by negligible heterogeneity (I^2 = 0.0%), remarkable concordance, and robustness to leave-one-out sensitivity analyses.[18] These findings were confirmed using R 4.5.3 with the 'meta' and 'metafor' packages and Hartung-Knapp-Sidik-Jonkman confidence interval adjustment, providing reproducible and conservatively calibrated inference.

The high precision of the pooled estimate (95% CI half-width 0.41 RR units) reflects the strength of the evidence base: three independent meta-analyses spanning a four-year publication window produce estimates clustered within a 0.12-unit band (2.92–3.04).[19] This degree of concordance provides a particularly robust foundation for clinical guideline development and power calculations in future SLE cardiovascular intervention trials.[11]

The HKSJ confidence interval (95% CI 2.57–3.39) was identical to that obtained from the standard DerSimonian-Laird normal approximation in this specific dataset, a consequence of the near-zero τ^2 estimate; both approaches converged to the fixed-effects solution given the complete absence of between-study heterogeneity. This convergence provides additional reassurance that the precise CI is not an artefact of the statistical method selected, but a genuine reflection of remarkable inter-study consistency.[20]

Whilst the primary analysis was homogeneous (I^2 = 0.0%), the pre-specified mixed-measures sensitivity analysis incorporating all five comparative studies revealed substantial heterogeneity (I^2 = 92.7%), which was entirely expected given the methodological incompatibility of pooling rate ratios

from age-specific subgroups (Manzi et al., 1997) and ORs for surrogate endpoints (Roman et al., 2003) alongside general-population RR estimates from large meta-analyses. The subgroup analysis confirmed that the design category was a highly significant modifier (Q-diff = 55.07, $p < 0.001$), underscoring the importance of restricting the primary pool to methodologically comparable estimates.

Comparison with prior meta-analyses

The three-fold excess AMI risk identified in this analysis aligns with the broader pattern of elevated cardiovascular morbidity observed in other systemic autoimmune rheumatic diseases, including rheumatoid arthritis (AMI RR approximately 1.6–2.0), psoriatic arthritis (RR approximately 1.3–1.6), and ankylosing spondylitis (RR approximately 1.4–1.7).[22] However, the magnitude of AMI excess in SLE substantially exceeds that of other inflammatory arthritides, consistent with the more severe and systemic immune dysregulation characterising SLE and its disproportionate impact on young women at a demographic stage where background AMI risk is otherwise negligible.[21]

Our pooled estimate of RR 2.95 is highly consistent with the individual estimates: Gu et al. (2019) RR 3.04[1], Yazdany et al. (2020) RR 2.99[3], and Bello et al. (2023) RR 2.92.[4] The stepwise decline (3.04→2.99→2.92) may reflect evolving differences in the primary literature composition, including progressive inclusion of studies from nations with differing SLE management practices and increasing co-prescription of hydroxychloroquine with its established cardioprotective properties.

Earlier estimates varied widely. The landmark Manzi et al. (1997) study reported extreme rate ratios in young women (RR 52.43 in age 35–44), biologically plausible but not directly poolable with general-population RR estimates across all ages.[6] Population-based registry studies from Sweden[2] and Denmark[5] have consistently reported elevated AMI rates in SLE, contextualising the overall RR of 2.95 within a broader spectrum of disease-specific cardiovascular risk.

The subgroup analysis by study design (Figure 4) reinforces the principle that the appropriate pooled estimate for clinical and policy purposes is the RR of 2.95 derived from the three SR/meta-analyses, rather than the overall mixed-measures sensitivity estimate of 5.27.[22] The Manzi et al. (1997) Rate Ratio of 52.43, whilst striking, reflects an extreme demographic subgroup (pre-menopausal women aged 35–44 with SLE) and a single comparator cohort (Framingham Heart Study); it substantially overestimates the general-population excess risk applicable to all SLE patients across age groups and both sexes.[6] The Roman et al. (2003) OR of 4.80 reflects a surrogate atherosclerosis endpoint (carotid plaque burden) rather than incident AMI, and its inclusion in a mixed pool introduces further methodological incompatibility. These findings underscore the critical importance of transparent pre-specification of effect measure eligibility criteria in cardiovascular meta-analyses.[7]

The mechanisms underlying the elevated AMI risk in SLE are multifactorial and interrelated, broadly categorised into accelerated atherosclerosis, coronary microvascular dysfunction, thrombotic mechanisms, and innate immune-driven endothelial injury. Accelerated atherosclerosis is recognised as the dominant mechanism of AMI in SLE.[16] The pathogenic cascade involves persistent immune complex deposition in the coronary endothelium, complement activation, chronic elevation of pro-inflammatory cytokines (IL-6, TNF-α, type-I interferons), dyslipidaemia, impaired reverse cholesterol transport, and foam cell formation.[1] Roman et al. (2003) demonstrated significantly greater carotid plaque burden in SLE (OR 4.8, 95% CI 2.6–8.7), with SLE-specific variables independently predicting plaque, underscoring the central role of immune dysregulation in atherosclerosis.[7]

Molecular evidence suggests convergent pathways between adaptive immune dysregulation and the vascular endothelium. Activated Th17 cells and dysregulated Tregs create a pro-inflammatory milieu promoting vascular smooth muscle cell proliferation

and plaque destabilisation.[22] Type-I interferons impair endothelial progenitor cell function and reduce vascular regeneration capacity, accelerating coronary stenosis progression.[10] Complement dysregulation further contributes through unregulated deposition on the coronary vessel walls.[22] Corticosteroid therapy exerts paradoxical cardiovascular effects: whilst suppressing active inflammatory injury, chronic glucocorticoid exposure promotes dyslipidaemia, hypertension, insulin resistance, and visceral adiposity.[21,22] Doses exceeding 20 mg/day of prednisolone equivalent have been associated with a five-fold increment in cardiovascular event risk in some cohorts.[22]

In contrast to corticosteroids, antimalarial therapy—principally hydroxychloroquine (HCQ)—exerts cardioprotective effects through multiple complementary mechanisms.[19,20] HCQ attenuates TLR-7 and TLR-9 signalling, reduces pro-inflammatory cytokine production, inhibits monocyte and T-cell activation, and reduces oxidised LDL-mediated endothelial dysfunction.[19] Floris et al. (2018) synthesised evidence demonstrating HCQ's beneficial effects on dyslipidaemia and glucose metabolism.[19] Ruá-Figueroa et al. (2022) demonstrated that antimalarial therapy was independently associated with a 72% reduction in the odds of chronic heart failure in SLE (OR 0.28, 95% CI 0.17–0.45, $p < 0.001$).[20]

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a clinically underappreciated pattern in SLE, involving troponin elevation and electrocardiographic AMI criteria in the absence of obstructive epicardial stenoses.[9] Pathophysiological mechanisms include coronary vasculitis, microvascular spasm, thrombosis at non-obstructive plaque sites, and innate immune-driven endothelial injury, particularly relevant in young women with SLE.[9,22]

A clinically important distinction must be drawn between antiphospholipid antibody (aPL) positivity and antiphospholipid syndrome (APS). aPL positivity — defined by the presence of lupus anticoagulant, anti-cardiolipin antibodies, or anti-β2-glycoprotein I antibodies — occurs in 25–50% of SLE patients and confers an independent prothrombotic risk even in the absence of a prior thrombotic event.[9,10] APS, by contrast, is a clinical syndrome defined by the combination of persistent aPL positivity and documented thrombosis or pregnancy morbidity according to the revised Sapporo criteria. APS is present in approximately 15–30% of SLE patients and confers substantially higher absolute AMI risk through direct thrombotic mechanisms, including platelet activation, complement-mediated endothelial injury, and tissue factor upregulation, distinct from atherosclerotic pathogenesis.[9] The primary pooled meta-analyses (S1, S3, S4) did not consistently stratify AMI risk by aPL or APS status, representing an important evidence gap. Patients with SLE-APS may constitute a particularly high-risk subgroup warranting distinct cardiovascular risk stratification and therapeutic anticoagulation.[910] Roman et al. (2003) identified lupus anticoagulant positivity as an independent predictor of carotid plaque, supporting the contribution of aPL to early atherogenesis beyond overt thromboembolism.[7]

Low-density granulocytes (LDGs), a pro-inflammatory granulocyte subset aberrantly elevated in SLE, spontaneously release neutrophil extracellular traps (NETs) decorated with oxidised mitochondrial DNA, cytotoxic granule proteins, and tissue factor.[10] LDG-NET formation directly injures endothelial cells, promotes intravascular thrombosis, and activates plasmacytoid dendritic cells to amplify type-I interferon production, establishing a feed-forward vascular inflammation loop.[10] Circulating LDG levels have been independently associated with coronary plaque burden in SLE.[10]

The interplay between these distinct pathogenic mechanisms is clinically important because it implies that a single therapeutic strategy targeting only one pathway is unlikely to fully mitigate AMI risk in SLE.[10,22] For instance, whilst statins effectively address dyslipidaemia and reduce atherosclerotic plaque progression, they do not target the

antiphospholipid antibody-mediated thrombotic pathway or the LDG/NET-driven endothelial injury cascade. Conversely, effective immunosuppression reducing SLE disease activity may partially attenuate immune-mediated endothelial damage but may paradoxically increase cardiovascular risk through corticosteroid-induced metabolic adverse effects.[21,22] This therapeutic complexity underscores the need for a multimodal cardiovascular risk reduction strategy in SLE that combines disease-specific immunomodulatory approaches with conventional cardiovascular risk factor management, as advocated by the present synthesis.[19,20]

SLE confers heterogeneous cardiovascular risk across sex and age subgroups. Whilst the overall pooled RR of 2.95 applies to the general SLE population, the absolute excess risk is amplified in young women, who ordinarily carry minimal background AMI risk.[16] Manzi et al. (1997) demonstrated a 52-fold excess risk in women aged 35–44, a subgroup in which the population-attributable fraction of SLE-attributable AMI is particularly high.[6] Paradoxically, men with SLE face a proportionally higher relative risk compared with women with SLE in some analyses, potentially reflecting delayed diagnosis, under-treatment, and removal of oestrogen-mediated protective effects.[9]

The cardioprotective role of endogenous oestrogen in pre-menopausal women is well established, principally through favourable effects on lipid metabolism, endothelial function, and vascular reactivity.[23] In SLE, however, this oestrogen-mediated protection is substantially attenuated by the pro-inflammatory and pro-thrombotic disease milieu. Oestrogen may paradoxically promote lupus disease activity through upregulation of B-cell activity and autoantibody production, creating a complex bidirectional relationship between hormonal status and cardiovascular risk in SLE.[23,24] Straub (2007) described the interaction between sex hormones and the inflammatory response in autoimmune diseases, demonstrating that the protective cardiovascular effects of oestrogen may be overridden in the context of sustained systemic inflammation, as occurs in active SLE.[24]

The convergence of early menopausal transition, oestrogen fluctuations, and SLE disease activity creates a particularly adverse cardiovascular milieu. Several immunosuppressive agents including cyclophosphamide may independently contribute to premature ovarian insufficiency, further attenuating oestrogen-mediated cardiovascular protection.[22] Racial and ethnic heterogeneity in AMI risk within SLE populations is clinically important but understudied.[14] Studies have reported higher SLE disease severity and possibly amplified cardiovascular risk in Black and Hispanic populations, attributed to socioeconomic factors, differential access to preventive cardiovascular care, greater corticosteroid burden, and distinct immunogenetic predispositions.[4] These disparities underscore the importance of ethnicity-stratified cardiovascular risk estimation and warrant specific investigation in future prospective cohort studies and meta-analyses.

The consistent three-fold excess AMI risk observed in this meta-analysis has important clinical implications. First, standard Framingham-based cardiovascular risk calculators substantially underestimate AMI risk in SLE.[17] SLE-specific tools such as the SLECRISK model by Choi et al. (2024) demonstrate acceptable discrimination (C-statistic 0.74, 95% CI 0.65–0.83) for MACE in a prospective US SLE cohort.[8] However, it is important to note that the SLECRISK model was developed and validated within a single prospective cohort at a single US academic centre (Brigham and Women's Hospital). External validation in independent, geographically diverse populations — including European, Asian, and low- and middle-income country SLE cohorts — has not yet been reported. The model's discriminatory performance may differ substantially in populations with differing SLE phenotypes, access to preventive care, and background cardiovascular risk profiles.[8] Pending external validation, clinicians should utilise SLE-specific tools or apply a disease-specific multiplier to conventional risk scores. Second,

antimalarial therapy with HCQ should be considered the cornerstone of SLE management partly for its cardiovascular protective properties.[19,20] Statins, which address dyslipidaemia and exert pleiotropic anti-inflammatory effects, represent a logical co-prescription in SLE patients with elevated LDL or additional cardiovascular risk factors.[21] Third, the MINOCA pattern of AMI in young women with SLE necessitates a high index of clinical suspicion and a systematic diagnostic pathway including cardiac MRI, haematological evaluation for thrombophilia, and assessment of inflammatory biomarkers, even in the absence of obstructive coronary disease on angiography.[9] Fourth, a coordinated multidisciplinary cardiorheumatology approach—with integrated management of traditional cardiovascular risk factors (hypertension, dyslipidaemia, diabetes mellitus, smoking cessation) alongside SLE disease activity suppression—is recommended in current international guidelines and supported by the pathophysiological evidence synthesised in this review. Fifth, systematic annual cardiovascular risk screening for all SLE patients should be incorporated into rheumatology practice guidelines, including fasting lipid profiles, blood pressure monitoring, glycaemic assessment, and smoking cessation counselling. SLE-specific cardiovascular management guidelines integrating disease activity scoring (SLEDAI-2K), pharmacological exposures (HCQ, corticosteroids), and autoantibody profiles have not yet been universally adopted. Sixth, secondary prevention in SLE patients who have experienced an AMI requires a tailored approach addressing both conventional post-MI management and SLE-specific factors.[9,22] In patients with antiphospholipid syndrome-associated AMI, therapeutic anticoagulation with warfarin—rather than direct oral anticoagulants, which showed inferior outcomes in high-risk antiphospholipid syndrome in randomised controlled trials—represents the standard of care.[9] Post-MI SLE patients should additionally be monitored for pericarditis, Libman-Sacks endocarditis, and left ventricular dysfunction.[22]

This study has several notable strengths. It provides, to the authors' knowledge, the first formal meta-analytic pooling of published systematic review-level evidence on AMI risk in SLE. The pooled estimate draws on three large, methodologically rigorous meta-analyses with a collective primary literature base of 24–46 studies and approximately 168,000 SLE patients. The consistency of pooled estimates ($I^2 = 0.0\%$, $\tau^2 = 0.000$) greatly strengthens confidence in the estimate. All analyses were conducted using transparent, reproducible R code with verified outputs, with the Hartung-Knapp adjustment providing conservative and well-calibrated inference. The pre-specified sensitivity and subgroup analyses provide important contextualisation of the primary estimate.

The present synthesis additionally offers methodological strengths relative to conventional primary-study meta-analyses. By pooling meta-analytic estimates rather than individual primary studies, this approach reduces the risk that results are driven by outlier primary studies, and leverages the averaging and quality-filtering already performed by three independent systematic review teams.[11,12] Formal quantification of the consistency of three successive meta-analyses published across 2019–2023 provides temporal validation not achievable in a single-timepoint pooling exercise.

The use of R 4.5.3 with the 'meta' and 'metafor' packages for all statistical analyses represents a key methodological strength relative to the previous version of this analysis, which used a custom Python implementation. R's 'meta' package is widely recognised as the standard software for clinical meta-analysis, providing validated implementations of DerSimonian-Laird pooling, HKSJ adjustment, Cochran's Q, I^2, tau^2, and Egger's test with appropriate degrees of freedom correction.[13] The application of the Hartung-Knapp-Sidik-Jonkman confidence interval adjustment is particularly appropriate for $k = 3$, where the standard DerSimonian-Laird normal approximation provides anti-conservative coverage, and the HKSJ t-distribution-based interval provides

substantially better empirical coverage probabilities as demonstrated in simulation studies.

Several limitations require acknowledgement. First, the small number of pooled meta-analyses (k = 3) substantially limits the statistical power of heterogeneity testing and Egger's test, and the wide 95% prediction interval (1.21–7.20) reflects high uncertainty in extrapolating to a new study at small k. Second, the constituent meta-analyses exhibit methodological heterogeneity in terms of primary study designs, SLE diagnostic criteria, follow-up periods, and AMI ascertainment methods, introducing residual confounding not captured at the pooling level. Third, the primary meta-analyses searched to March 2018, May 2020, and September 2020 respectively, potentially missing primary studies published in 2021–2025. Fourth, two original cohort studies (Tornvall et al. 2021 and Yafasova et al. 2021) provided qualitative context; their effect measures (IRR 1.76 and HR 2.41, respectively) were not pooled in the primary analysis due to metric incompatibility with the meta-analytic RR estimates. Fifth, the estimated CCA of 51–57% indicates substantial overlap of primary studies across the three pooled meta-analyses; this is inherent to the design and is acknowledged as a source of non-independence. Sixth, publication bias in the underlying primary literature cannot be excluded on the basis of the underpowered Egger's test at k = 3. Seventh, the geographical representativeness of the pooled estimate may be limited. The three eligible meta-analyses drew predominantly on primary studies from North America, northern Europe (Sweden, Denmark, the United Kingdom), and eastern Asia (China). SLE populations from sub-Saharan Africa, South Asia, and Latin America — where disease phenotype, access to hydroxychloroquine, and background cardiovascular risk differ substantially — were under-represented in the primary literature. The pooled RR of 2.95 may therefore not be generalisable to all global SLE populations. Eighth, potential conflicts of interest in the included meta-analyses require disclosure. Yazdany et al. (2020) received funding from AstraZeneca, and Bello et al. (2023) received funding from Eli Lilly and Company. Whilst industry funding does not invalidate these studies — both were AMSTAR-2 rated high and moderate confidence respectively and employed rigorous methodology — readers should note this potential source of bias in the context of interpreting the primary estimates, particularly given commercial interests in SLE therapeutic markets.

5. Conclusion

This systematic review and meta-analysis demonstrated that patients with SLE face a significantly elevated risk of AMI compared with the general population, with a pooled relative risk of 2.95 (95% CI 2.57–3.39, $p < 0.001$), derived using R 4.5.3 with Hartung-Knapp-Sidik-Jonkman confidence interval adjustment. This three-fold excess risk was characterised by negligible heterogeneity ($I^2 = 0.0\%$, $\tau^2 = 0.000$), temporal stability across 2019–2023, and robustness to leave-one-out sensitivity analyses.

Pre-specified sensitivity analyses demonstrated that the primary estimate is robust and homogeneous when methodologically comparable studies are pooled. The mixed-measures sensitivity analysis ($I^2 = 92.7\%$) and subgroup analysis (Q-diff = 55.07, $p < 0.001$) highlight the critical importance of restricting quantitative pooling to studies with compatible effect measures and design categories, and confirm that the three-fold RR from SR/meta-analyses is the most appropriate summary estimate for clinical and policy purposes.

The pathophysiological drivers of this excess risk—principally accelerated atherosclerosis, coronary microvascular dysfunction, antiphospholipid antibody-mediated thrombosis, and LDG/NET-mediated endothelial injury—are partially modifiable through SLE-specific interventions, including hydroxychloroquine, targeted corticosteroid minimisation, and conventional cardiovascular risk factor control. Future research priorities include: (i) large-scale prospective randomised trials of statin therapy and HCQ intensification as primary AMI

prevention strategies in SLE, powered using the NNT of approximately 34 derived from this analysis as a basis for sample size estimation; (ii) validation and widespread adoption of SLE-specific cardiovascular risk prediction tools incorporating disease-activity metrics, autoantibody profiles, and treatment exposures; (iii) improved mechanistic characterisation of MINOCA in SLE to guide secondary prevention; (iv) investigation of novel therapeutic targets in the type-I interferon and LDG/NET pathways to reduce vascular inflammation; and (v) inclusion of updated primary cohort studies from 2021–2026 in a formal update of this pooled analysis to ensure continuing currency of the evidence base.

In clinical practice, all patients with SLE should be regarded as being at elevated cardiovascular risk independent of traditional risk factor profiles, and a systematic, multidisciplinary cardiorheumatology approach should be adopted to mitigate the substantial and quantified excess AMI risk demonstrated in this synthesis. The consistent and precisely estimated three-fold AMI excess risk should inform health policy decisions regarding SLE patient prioritisation in cardiovascular prevention programmes, resource allocation for cardiorheumatology services, and regulatory guidance on the cardiovascular safety of novel SLE therapeutics.

The absolute risk estimation derived from the Danish registry data[5] provides a clinically actionable illustration of this risk: an estimated 10-year AMI risk of approximately 4.40% in SLE patients versus 1.49% in matched controls, yielding an NNT of approximately 34 for intensive cardiovascular risk reduction strategies over a ten-year horizon. This NNT is clinically meaningful and compares favourably with established preventive cardiology interventions, supporting the case for active, systematic cardiovascular screening and intervention in all SLE patients irrespective of conventional Framingham risk score.

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