Risk of major cardiovascular events in patients with systemic sclerosis: insights into an underestimated concern from a systematic literature review and meta-analysis

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Abstract

Objective

Systemic sclerosis (SSc) is a chronic autoimmune disease characterised by skin and internal organ involvement. Despite the acknowledgment that cardiovascular (CV) complications are a leading cause of death in SSc, the extent of CV risk and major adverse cardiac events (MACEs) remains unclear. The aim of this study is to evaluate the association between SSc and the risk of MACEs through a systematic literature review and meta-analysis, focusing on non-fatal stroke (nfS) and non-fatal myocardial infarction (nfMI) as secondary outcomes.

Methods

We systematically searched for cohort and prospective studies published up to November 2024. We included studies reporting hazard ratios (HRs) with 95% confidence intervals (CIs) for SSc and cardiovascular outcomes. Random-effects meta-analyses were conducted to estimate pooled HRs. Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated via Egger's test.

Results

Eleven studies (n=12,235 SSc patients included) were included initially; SSc was associated with an increased risk of MACE (pooled HR 1.8, 95% CI 1.4–2.3), albeit with high heterogeneity (I^2=89.2%). Removal of overlapping datasets confirmed a significantly elevated risk (pooled HR 1.9, 95% CI 1.3–2.7), with persistent heterogeneity (I^2=88.72%). Subgroup analyses showed significant geographic variation. For secondary outcomes, SSc was associated with higher risks of nfS (pooled HR 1.5, 95% CI 1.2–1.9) and nfMI (pooled HR 2.5, 95% CI 1.9–3.5), with a decrease in heterogeneity.

Conclusion

Patients with SSc face a significantly increased risk of major CV events, including stroke and myocardial infarction. These findings underscore the need for tailored CV risk assessment and management strategies in SSc.

Key words

systemic sclerosis, major adverse cardiac events, non-fatal stroke, non-fatal myocardial infarction, meta-analysis

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Received on May 27, 2025; accepted in revised form on October 7, 2025.

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Funding: this work was supported and funded by the Italian Ministry of Health, "Ricerca Corrente". The APC was funded by the Italian Ministry of Health, "Ricerca Corrente".

Competing interests: none declared.

Introduction

Systemic sclerosis (SSc) is an autoimmune chronic disease, targeting skin and several internal organs, with a profound impact on life expectancy (1, 2). According to data from the European Scleroderma Trial and Research (EUSTAR) database, patients with SSc have a 10-year survival rate of 62.5%, and cardiovascular (CV) diseases represent the leading cause of death in this population (3). While the association between chronic inflammation, a hallmark of numerous rheumatological disorders, and elevated CV risk is well established, the etiopathogenesis of CV risk in SSc patients remains controversial and incompletely understood (4).

The impact of traditional risk factor in SSc appears less pronounced compared to other rheumatological conditions. The contribution of lipid abnormalities and arterial hypertension in this context remains unclear and warrants further investigation, while the prevalence of diabetes mellitus and obesity is less pronounced than general population (5, 6).

However, in addition to chronic inflammation both macro and microvascular systems are affected in SSc (1). Endothelial dysfunction plays a pivotal role, contributing to immune dysregulation, fibrosis and vascular damage (4, 7). These processes may underlie the increased CV risk observed in SSc patients. Additionally, structural vascular changes, such as intimal thickening and capillary loss, further highlight the complexity of the vascular pathology in SSc (7).

The increased CV risk and its implications are well-recognised within the context of rheumatologic diseases burden (8). Recent years have seen growing awareness of the need to assess and manage this risk in various rheumatologic conditions, particularly inflammatory arthritis (9-12) and connective tissue disorders such as systemic lupus erythematosus (SLE) and antiphospholipid syndrome (11, 12). However, SSc has not received similar emphasis, and the European Alliance of Associations for Rheumatology (EULAR) recommends applying the same CV risk management strategies used for the general population (13). This is partly due to inconsistent data regarding the magnitude of CV risk in SSc, with contradictory findings across studies.

Therefore, the primary objective of this meta-analysis was to synthesise current evidence on the association between SSc and major CV events. Secondary objectives included evaluating the separate risks of non-fatal stroke (nfS) and non-fatal myocardial infarction (nfMI).

Methods

Study design

This meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (14) and performed following the checklist of Meta-analysis of Observational Studies in Epidemiology (15). Three different investigators independently conducted the literature searched on electronic database such as PubMed, Google Scholar, Cochrane Library for potential study from January 2013 to November 2024. Following search terms were used: "systemic sclerosis", "scleroderma", "systemic scleroderma", "connective tissue diseases", "major adverse cardiac event", "MACE", "cardiovascular diseases", "stroke", "ischemic stroke", "myocardial infarction", "cardiovascular death". The title and abstract of articles were screened for relevancy and the full text of relevant studies was reviewed for eligibility. Only full-text articles from published sources were included, with no attempts made to identify unpublished studies.

Eligibility criteria

Studies were eligible if they were cohort or prospective studies and if they evaluated the association between MACE and SSc, that represents the primary endpoint of this meta-analysis. Secondary endpoints were the association between the risk of non-fatal stroke (nfS) and non-fatal myocardial infarction (nfMI) and SSc. As for the definition of MACE, we initially intended to adopt the one provided in each article itself. However, given the limited number of studies using that definition, we decided to include in the primary analysis all articles that assessed the risk of

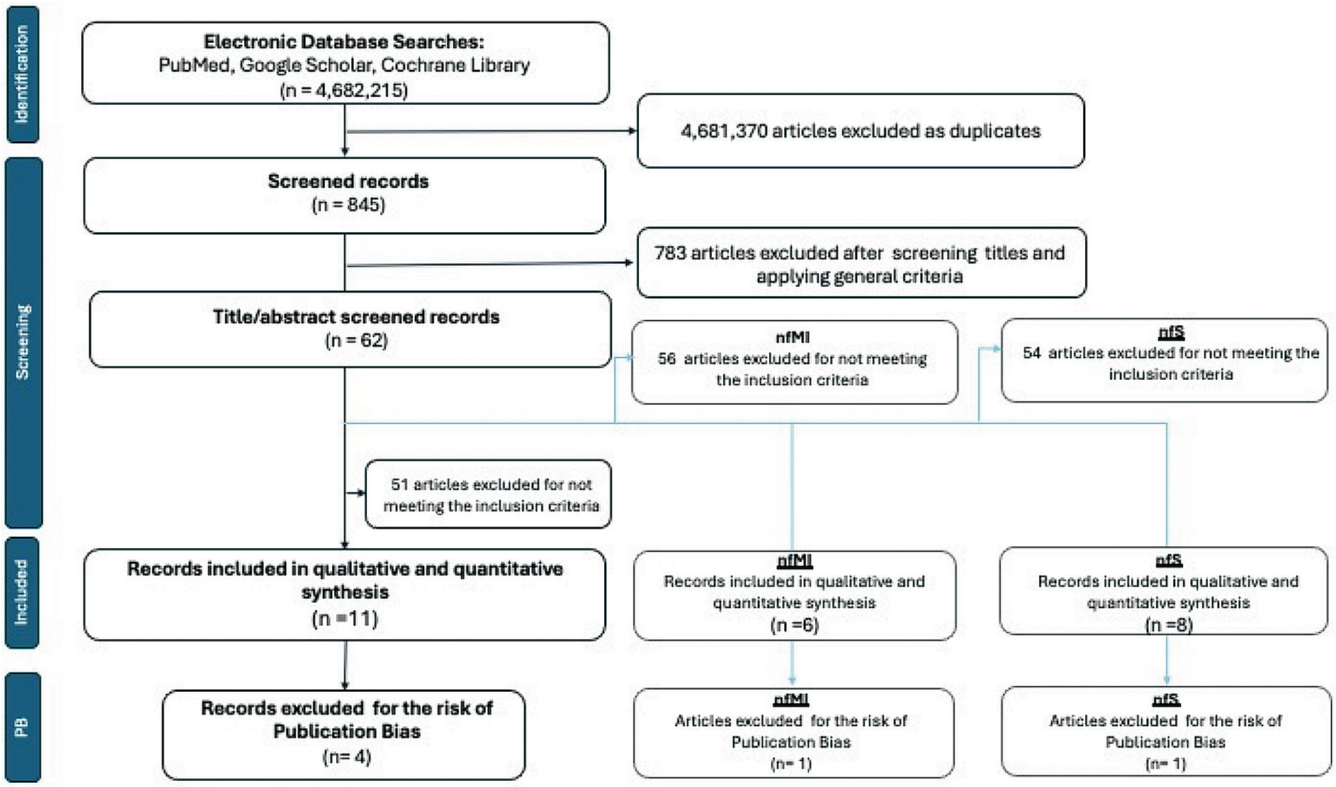


Fig. 1. PRISMA flowchart of inclusion and exclusion of studies.
n: numbers; PB: publication bias; nfMI: non-fatal myocardial infarction; nfS: non-fatal stroke.

CV death and/or nfS and/or nfMI (the classical 3-point definition), whether evaluated as a composite outcome or as individual events. This approach aligns with the 2008 FDA Guidance for Industry on Evaluating Cardiovascular Risk in New Antidiabetic Therapies for Type 2 Diabetes, which has been recommended and widely adopted in subsequent clinical trials (16).

Studies included must showed association estimates with 95% confidence intervals (CI) or necessary data for such calculations. Studies were included regardless of sample size. If multiple publications regarding the same study were identified, then we only included the study with the largest number of cases. Only studies in English were eligible.

Data extraction and quality assessment

We reviewed the full manuscript of all articles extracted by primary search. A manual search of the reference list of the retrieved studies was also conducted to identify additional relevant studies. Then, we applied the previously mentioned eligibility criteria to these articles to create the final list of studies for the meta-analysis. Any disagreements were resolved through joint evaluation. Data extracted from each study included the following: first author's name, publication year, country, study design, assessment of exposure and outcome, confounding variables, and crude and adjusted risk estimates with corresponding 95% CIs. If only unadjusted estimates were provided, we included the crude estimate. For studies reporting multiple estimates of the association, we use those adjusted for the most appropriate covariates. For studies that did not report an estimate for MACE but only for nfS and nfMI, we used the highest available estimate (MACE_H). Where available, the lowest estimate was included separately in a sensitivity analysis (MACE_L).

The complete process of the extraction of the included studies is illustrated in Figure 1.

The quality of individual studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS). This scale evaluates the aspects of the population and sample methods, exposure and outcome description, and statistical matching/adjustments of the data. The quality scores were determined for each study, with a maximum score of nine. Studies with score ≥7 were classified as high-quality studies; the others were classified as low-quality studies.

Statistical analysis

The hazard ratio (HR) and their CIs were used as measures of the association. We calculate I^2 to examine statistical heterogeneity across studies. Since a high heterogeneity was expected, based on the experience of previous studies, we used a random-effects model throughout the analysis estimate the summary HRs (17). We also performed a sub-grouped analysis by comparing studies of high and low quality, by the country where the studies were conducted (dividing them into Europe, Asia, and America), and basing on the use of adjusted or unadjusted estimates, where feasible. This was done to explore the possible source of heterogeneity and effect of modification. Meta-regression was used for the interaction test. A sensitivity analysis

Table I. Characteristics of the study included in the analyses.

First Author	Year of publication	Nation	Study design	SSc n=17905	HC n=1,082,454	mean age-years (SSc *vs.* HC)	Female- % (SSc *vs.* HC)	MACE HR	nfMIA HR	nfS HR	Adjusted estimates	Outcome assessment
Man (6)	2012	USA	cohort	865	8643	58.7 *vs.* 58.7	86 *vs.* 86	-	1.93	2.56	Yes	Read Classification
Chu (19)	2013	Taiwan	cohort	1344	13,440	50.6 *vs.* 50.6	75.7 *vs.* 75.7	-	2.45	-	Yes	ICD-9
Chiang (20)	2013	Taiwan	cohort	1238	13,380	49.4 *vs.* 49.4	76 *vs.* 76	-	-	1.52	Yes	ICD-9
Aviña-Zubieta (22)	2016	Canada	cohort	1223	12,433	56 *vs.* 56	83 *vs.* 83	-	3.59	2.35	Yes	ICD-9 and ICD-10
Hesselvig (23)	2018	Denmark	cohort	1962	5,428,380	49.2 *vs.* 40.2	80 *vs.* 50.9	2.22	-	-	Yes	ICD-10
Butt (24)	2019	Denmark	cohort	2778	13,520	55 *vs.* 55	76 *vs.* 76	-	2.08	1.28	Yes	ICD-8 or ICD-10
Ying (21)	2020	USA	cohort	4545	9,090	60.9 *vs.* 61	17 *vs.* 17	-	-	1.21	Yes	ICD-9
Kurmann (25)	2020	USA	cohort	78	156	56.1 *vs.* 56	91 *vs.* 91	-	4.88	1.92	Yes	Physician diagnosis
Sun (26)	2022	Denmark	cohort	1569	6,276	55 *vs.* 55	80.4	-	1.66	1.57	Yes	ICD-8 or ICD-10
Yen (27)	2024	Taiwan	cohort	1379	2,758	53.1 *vs.* 53.2	71 *vs.* 71	1.04	-	-	Yes	ICD-9
Huang (28)	2024	Taiwan	cohort	1507	1,000,000	52.8 *vs.* 43.9	72 *vs.* 50	-	-	1.11	Yes	ICD-9

SSc: systemic sclerosis; n: number; HC: health control; MACE: major adverse cardiac event; nfMI: non-fatal myocardial infarction; HR: hazard ratio; nfS: non-fatal stroke; ICD: The International Classification of Diseases.

Table II. Representation of the scores assigned to the various questions for the risk of bias assessment of included articles according to the Newcastle-Ottawa Scale for observational cohort studies.

	Item	Man *et al.* 2012	Chu *et al.* 2013	Chiang *et al.* 2013	Aviña-Zubieta *et al.* 2016	Hesselvig *et al.* 2018	Butt *et al.* 2019	Kurmann *et al.* 2020	Ying *et al.* 2020	Sun *et al.* 2022	Yen *et al.* 2023	Huang *et al.* 2024
A	*Selection*											
	Is the case definition adequate?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗
	Representativeness of the cases	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Selection of controls	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Definition of controls	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✓
B	*Comparability*											
	Study controls for certain variables (or any variables)	✓ ✓	✓ ✗	✓ ✓	✓ ✓	✓ ✗	✓ ✗	✓ ✓	✓ ✓	✓ ✓	✗ ✗	✓ ✓
C	*Exposure*											
	Ascertainment of outcome	✓ ✗	✓ ✗	✓ ✗	✓ ✗	✓ ✗	✓ ✗	✓ ✗	✓ ✗	✓ ✗	✓ ✗	✓ ✗
	Was follow-up long enough for outcomes to occur	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓
	Adequacy of follow-up of cohorts	✗ ✗	✗ ✗	✓ ✗	✗ ✗	✗ ✗	✓ ✗	✗ ✗	✓ ✗	✗ ✗	✓ ✗	✗ ✗
	SCORE	8	7	9	8	6	8	8	9	7	6	7

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was conducted to examine the influence of a single study on the overall risk estimate by omitting one study and combining the remaining in each turn. Potential publication bias was assessed by Egger's test (18). In case of evidence suggesting potential publication bias, the primary causes of this bias were investigated and mitigated by excluding studies considered to be biased. Statistical analysis was performed using the RStudio graphical interface v 0.98 for R software environment v 3.0.2 with the "metafor" package. For all primary analyses, we used a conventional two-tailed significance threshold of $p<0.05$. However, for publication bias assessment, we employed a less stringent threshold of $p<0.10$ to enhance the sensitivity of detection, given the typically limited power of these tests. This approach follows standard meta-analytic practice, allowing for more conservative identification of potential reporting biases that could influence interpretation of results.

Results

Figure 1 summarises the search results. From an initial pool of 4,682,215 articles identified, 4,681,370 duplicates were removed. After the first preliminary screening in which titles and abstracts were evaluated, the majority of the citations were excluded mainly because they were not cohort studies, or they didn't examine relevant exposure or outcomes. After a rigorous assessment of inclusion or exclusion criteria 834 articles were excluded and a final set of 11 articles (6, 19-28) were included for the main analysis (MACE_H and its sensitivity analysis MACE_L).

Table II summarises the risk of bias among cohort studies included in the main and secondary analyses, assessed using NOS.

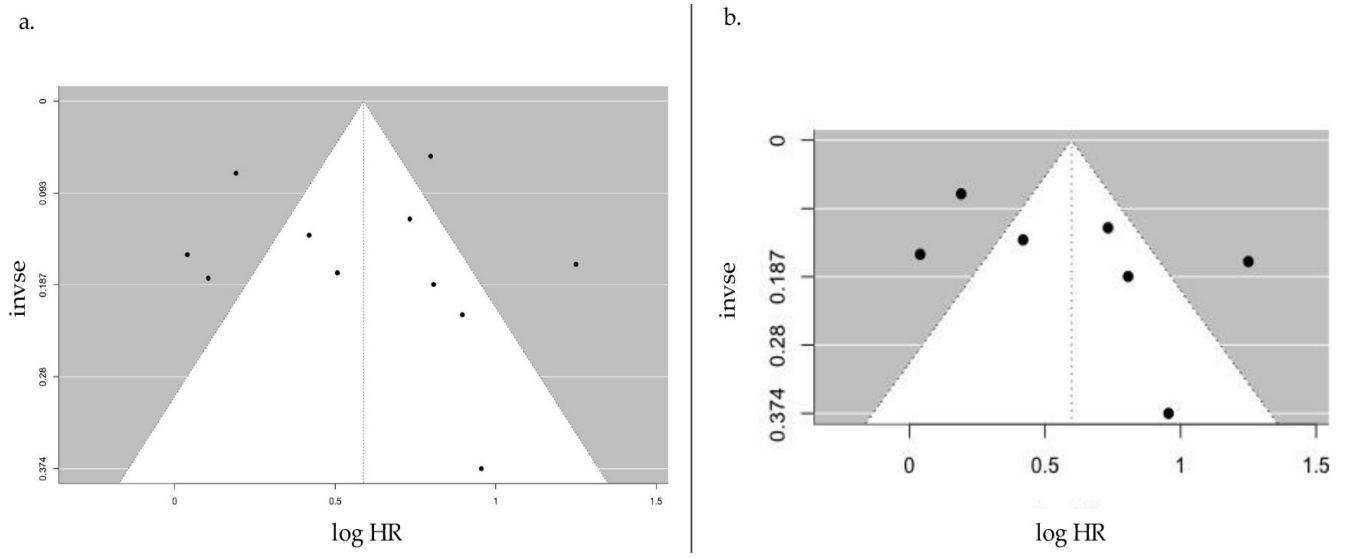


Fig. 2. Funnel plots indicating a potential publication bias on the association between systemic sclerosis and major adverse cardiac event in the first meta-nalyses of 11 studies (**a**) and after removing 4 studies possible sources of bias (**b**).
inv se: inverse standard error; logHR: logarithm of hazard ratio.

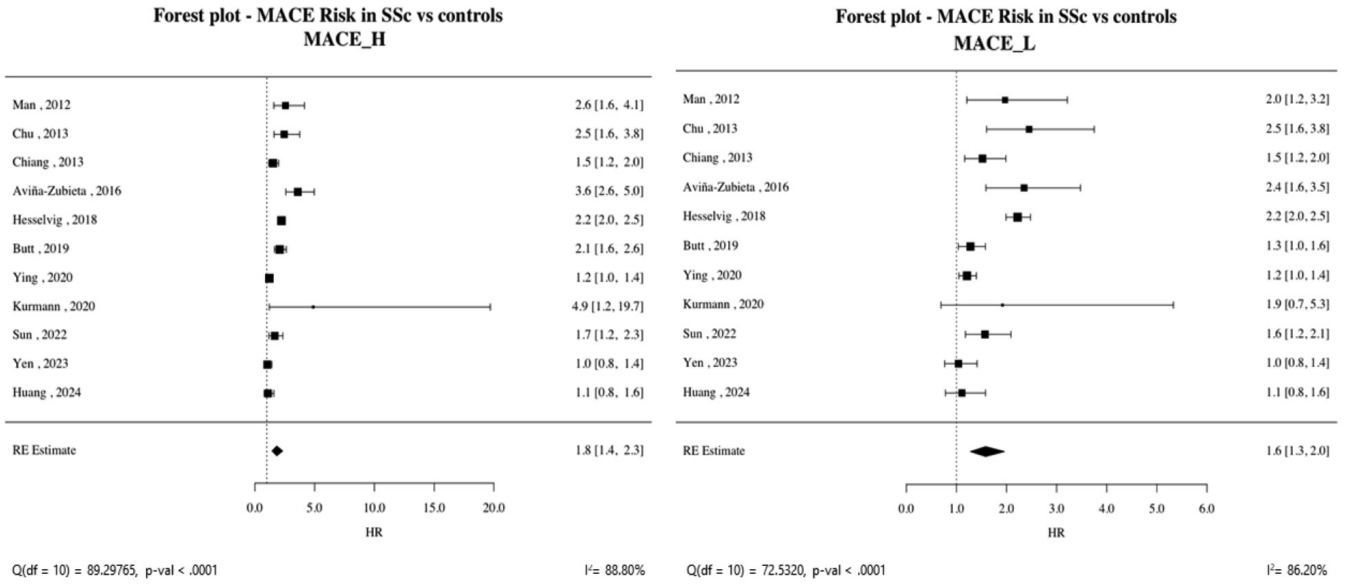


Fig. 3. Forest plot of the association between systemic sclerosis and major adverse cardiac event. MACE_H includes higher risk estimates from included studies (main analysis), while MACE_L reflects lower estimates (sensitivity analysis).
MACE: major adverse cardiovascular event; SSc: systemic sclerosis; vs: versus; RE: random effects; HR: hazard ratio.

SSc and risk of MACE

For the purpose of our study, we firstly conducted a random-effect meta-analysis to assess the association between SSc and MACE. Eleven studied were included with a total population of 1,100,358, of which 17905 were patients affected by SSc and 1,081,454 were controls. Characteristics of the included studies are showed in Table I. The individual studies were published between 2012 and 2024, and the studies areas included United States, Canada, Europe (Denmark) and Taiwan. Assessments for SSc was mostly based on International Classification of Diseases (ICD) as well as the outcomes.

Results from individual studies showed a significant increased risk of overall MACE in SSc (pooled HR 1.8, 95% CI 1.4–2.3) when the highest estimates were included (MACE_H), confirmed by the sensitivity analysis (MACE-L: pooled HR 1.6, 95% CI 1.3–2.0) (Fig. 3). In both main and sensitivity analysis a high degree of heterogeneity across studies emerged (MACE_H: I^2 = 88.4%, *p*-value for heterogeneity <0.001. MACE-L: I^2 =86.2%, p-value for heterogeneity <0.001). We conducted subgroup analyses based on geographic regions to explore potential causes of heterogeneity. In the United Stated (2 studies only), the estimated effect was not statistically significant (pooled HR=1.62, 95% CI: 0.78–3.37, *p*=0.1923). However, the analysis revealed considerable heterogeneity between studies (I^2= 75.20%), similar

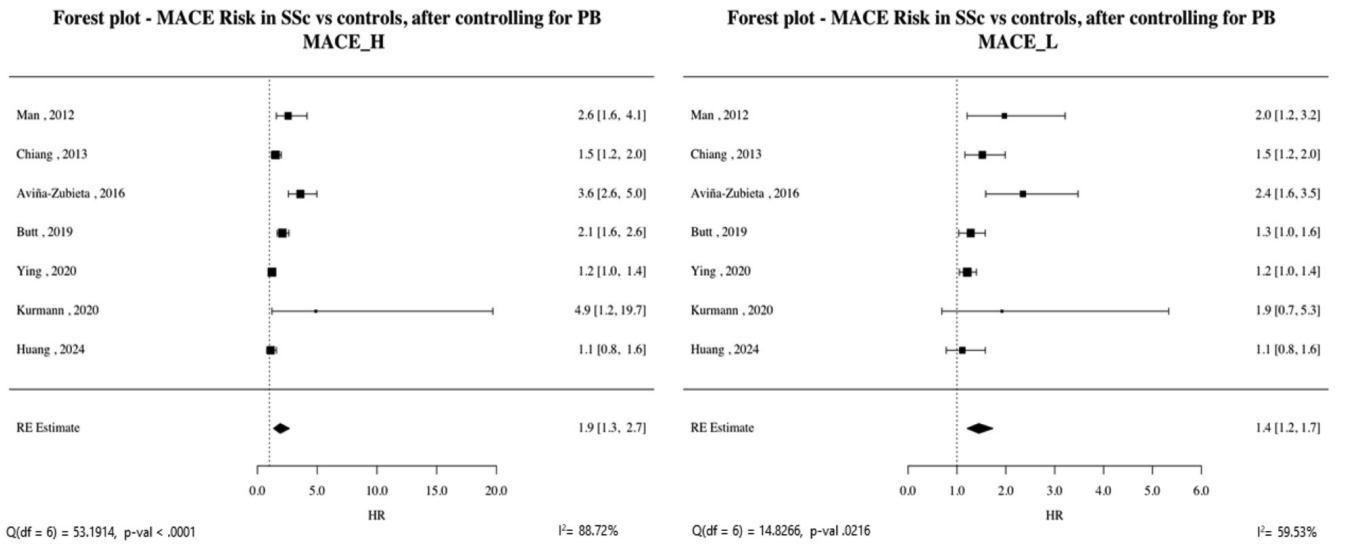


Fig. 4. Forest plot of the association between systemic sclerosis and major adverse cardiac event, after excluding studies impacting on the risk of publication bias. MACE_H includes higher risk estimates from included studies (main analysis), while MACE_L reflects lower estimates (sensitivity analysis). MACE: major adverse cardiovascular event; SSc: systemic sclerosis; vs: versus; RE: random effects; HR: hazard ratio.

to what was observed in the analysis among Asian studies (4 studies), even if a higher risk of MACE in SSc population was statistically significant in this case (pooled HR=2.20, 95% CI: 2.00–2.42, $p<0.0001$, $I^2=75.45\%$). Analysis of studies from Europe revealed the strongest and most consistent association. In this region, patients with SSc exhibited more than doubled MACE risk compared to controls (pooled HR=2.20, 95% CI: 2.00–2.42, $p<0.0001$). Notably, no significant heterogeneity was detected among these studies ($I^2 = 0.00\%$).

A subgroup analysis comparing studies based on their quality, as assessed by the NOS (Table II), was not feasible since there were not studies classified as "low-quality", such as all studies showed adjusted association estimates.

However, we then conducted a mixed-effect meta-regression analysis, using the quality of the study and the country of origin as moderators. This analysis confirmed the low impact of the quality of the studies in the influence of effect size ($p=0.2290$), while the country of origin was confirmed as significant moderator (HR=0.85, $p=0.0183$). However, the residual heterogeneity (tau^2) was 0.0721, indicating substantial unexplained variance, with a significant unexplained heterogeneity remained ($I^2 = 78.58\%$, QE (df=8) =26.17, $p=0.06$)

Sensitivity analysis did not identify studies that had substantial influences on the overall risk estimate, with pooled HRs ranging from 1.68 to 1.90.

Finally, it was explored the possibility of publication bias through the visual analysis of Funnel Plot (Fig. 2) and Egger test, with the evidence of possible presence of it ($p=0.0015$). For this reason, from a closer evaluation of the databases used in the included studies, it was found that some (Chu *et al*. (19), Yen *et al*. (27), Huang *et al*. (28) among Taiwanese paper and Hesselvig *et al*. (23), Butt *et al*. (24), Sun *et al*. (26) for Denmark) had used data from the same databases. For this reason, a second meta-analysis was conducted, excluding the studies that had used the same databases and included the study among them with a higher sample size (Fig. 4).

After excluding overlapping datasets, 7 studies remained (n=71,930 total; 12,106 SSc patients *vs*. 59,824 controls). Also in the previous analysis, two separate analyses were performed: for studies reporting both HRs for nfS and nfMI, we used the higher estimate for main analysis (MACE_H) and the lower one for the sensitivity analysis (MACE_L) (Fig. 4).

The pooled HR for MACE in the main analysis (MACE_H) was 1.9 (95% CI 1.3–2.7, $p=0.002$), with persistent high heterogeneity ($I^2=88.72\%$, $p<0.0001$) (Fig. 4). Besides, in the MACE_L analysis, although the pooled HR remained consistent with the main one, the heterogeneity decreased ($I^2=59.53\%$, $p=0.0216$). Funnel plot analysis and Egger's test no longer indicated significant publication bias in this reduced dataset (Fig. 2).

The subgroup analysis by country of origin confirmed a high variability between studies conducted in Asia and the USA ($I^2=70.16\%$ and $I^2=75.20\%$, respectively), which in this case showed estimates that were not statistically significant, probably due to the reduced sample size. In contrast, significant data associated with low heterogeneity persisted among European studies ($I^2 = 0.00\%$), which were confirmed as the studies with the most consistent data (pooled HR 1.64, $p<0.0001$). However, in this case the mixed-effects meta-regression model of the seven included studies does not confirm the country of origin of the study as a moderator of variability: the results of this analysis in fact showed that the residual heterogeneity after considering the potential moderators remains high (QE (df=4) =20.9411, $p=0.0003$, $tau^2=0.1482$).

SSc and risk of ischaemic ictus and IMA

From the initial set of 11 studies included for assessing the overall risk of MACE, we specifically selected those that reported data on the risk of non-fatal stroke (nfS) and non-fatal myo-

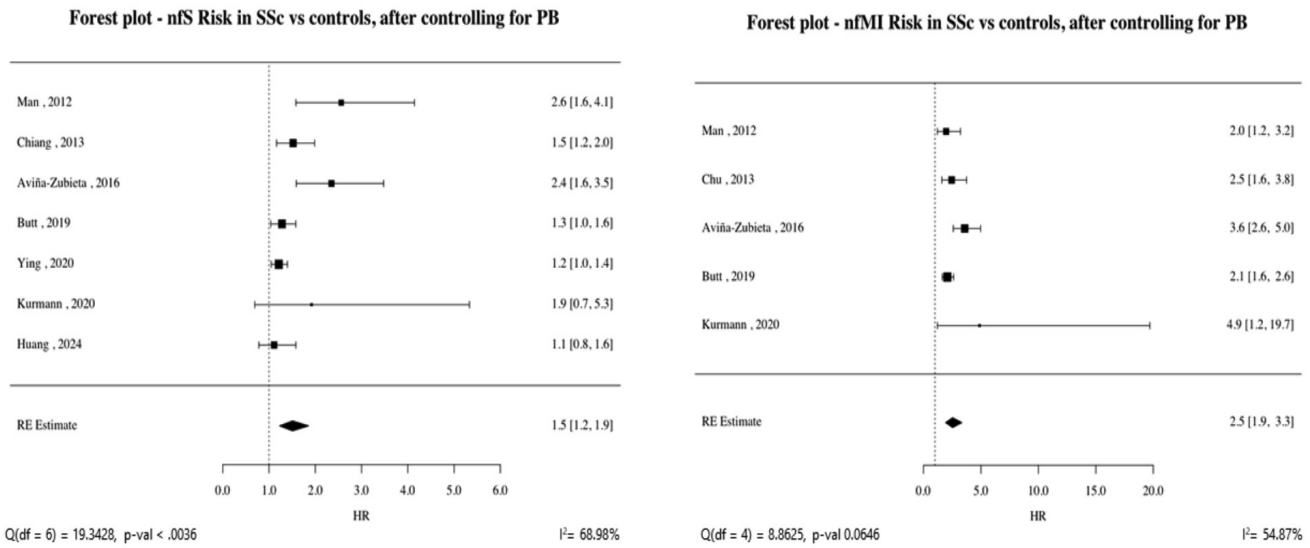


Fig. 5. Forest plots of the association of systemic sclerosis with non-fatal stroke (nfS) and non-fatal myocardial infarction (nfMI), after removing studies possible sources of publication bias.
nfS: non-fatal stoke; nfMI: non-fatal myocardial infarction; SSc: systemic sclerosis; vs: versus; RE: random effects; HR: hazard ratio.

cardial infarction (nfMI) separately (Fig. 1). This selection followed a careful evaluation and exclusion of studies using data from the same database to avoid publication bias.

To analyse the risk of nfS in patients with SSc, 7 studies (6, 20-22, 24, 25, 28) with a total population of 1,069,456 individuals was included, comprising 12,235 patients with SSc and 1,057,222 controls. All selected studies were assessed as high-quality according to the NOS. The publication year ranged from 2012 and 2024, with 2 studies from Taiwan, 4 from the United States, and the remaining 1 from Europe.

The random-effect meta-analysis revealed a significant increased risk of nfS in the SSc population compared to controls, with a pooled HR of 1.5 (95% CI 1.2–1.9, I^2= 68.98%) (Fig. 5).

For the risk of nfMI, 5 studies (6, 19, 22, 24, 25) were included in the random-effect meta-analysis. The studies reported an even higher risk for SSc patients compared to controls, with a pooled HR of 2.5 (95% CI 1.9–3.3). The studies were published between 2012 to 2020, three of which from USA, one from Taiwan and one from Europe. These studies were also rated as "high-quality" on the NOS. However, this analysis also showed substantial variability between studies, with an I^2 value lower than previous analyses (I^2= 54.87%) (Fig. 5).

Discussion

This meta-analysis demonstrates a significant association between SSc and an increased risk of MACE, including nfS and nfMI. Our findings update and extend previous work by focusing on MACE as the primary endpoint, highlighting the CV burden in SSc beyond traditional risk factors.

A prior meta-analysis by Chen *et al*. (29) examined the risk of stroke in SSc, although its inclusion criteria and primary endpoint differed from those of this analysis. Moreover, some studies in that meta-analysis featured overlapping or non-SSc cohorts (*e.g*. multiple sclerosis), raising concerns about potential bias in the estimates (30, 31). The stringent selection criteria chosen in the current analysis excluded such studies and prioritised MACE, a composite endpoint not previously analysed in this context.

Furthermore, Chen and colleagues (29) incorporated the results from Conrad *et al*. in their assessment of CV disease risk as a secondary outcome. The exclusion of the latter study was a significant limitation, given the relevance and its significant impact on the rheumatology scientific community (33). Notably, it was the first large-scale national study that identified, among the 19 rheumatological conditions analysed, patients with SSc and SLE as those at the highest risk CV risk (33).

As previous stated, significant efforts have been made in recent years to enhance the management of CV risk in patients with rheumatological diseases (16, 34, 35). However, the focus has predominantly been on specific diseases such as inflammatory joint diseases, and SLE (whether or not associated with antiphospholipid antibody syndrome) (32, 36, 37), for which we have well-defined CV risk management recommendation or guidelines (9, 11-13). In contrast, the EULAR recommendations for CV risk management, which cover many diseases including SSc, acknowledge the increased CV risk in these patients. However, they do not suggest significant changes in management to the general population, mainly due to a lack of supporting evidence.

Traditional CV risk factors appear less influential in SSc compared to other rheumatological conditions (38), although hypertension has been identified as an independent predictor of subclinical atherosclerosis (39). Its interpretation, however, is complicated by the widespread use of calcium channel blockers for Raynaud's phenomenon and, unlike in RA, data on the impact of hypertension on the risk of MACE in SSc are lacking (5, 40). Prevalence of diabetes and obesity generally reflects that of the general population, while data on hyperlipidaemia remain conflicting (5).

Finally, both macro and microvascular

systems are affected in SSc, as they represent the hallmark of the diseases and probably the most impactful alteration on the CV risk (41, 42). Endothelial dysfunction is a key feature in both SSc and atherosclerosis, suggesting a potential interplay that may explain the association between the disease and CV risk (4). Clinical evidence from a large cohort of SSc patients demonstrates that several vascular manifestations serve as independent predictors of atherosclerosis (39).

A point to address is the definition of MACE: as detailed in a review by Bosco *et al*. the definition of "MACE" varies significantly across clinical studies where authors may choose to use three-, four-, or five-point outcomes, including or excluding hospitalisation for unstable angina or revascularisation, or heart failure. This heterogeneity introduces potential biases and complicates the comparability of studies (43).

In the present study, a MACE definition proposed by the FDA in 2008 was used (16). It, although would not be the most widely used or recent, remains a standard endorsed by regulatory authorities. Notably, it was chosen an outcome that exclude heart failure, as this condition is a frequent manifestation in SSc due to various disease-related mechanisms (41). However, the focus of our study was to evaluate CV features as comorbidities rather than as disease-specific manifestations. This rationale also informed the decision to exclude the data from Conrad *et al*. study (33).

It emerged another important issue in this research field: the lack of study that have been analysed the risk of MACE with a composite endpoint in SSc patients (44). The initial intent of this study was to conduct a meta-analysis estimating the risk of MACE, using the definition provided in the articles. However, the literature search yielded only two studies evaluating this risk in patients with SSc (23, 27), an insufficient number for meaningful statistical analysis. Consequently, it was decided to expand criteria to include estimates of nfS and nfMI as defined in the literature. While this approach introduced greater heterogeneity between studies, a significant limitation of this paper, it enabled to provide the first assessment of MACE risk in a large population.

Taken together these considerations highlight the need future research should prioritise investigating the interplay between inflammatory and prothrombotic mechanisms, hallmark features of SSc (42). Such studies could help define distinct phenotypes of SSc-related CV disease and establish disease-specific MACE definition, which may, in turn, guide more effective management strategies for these patients.

This meta-analysis faced several limitations, including, as stated above, high heterogeneity across studies and potential publication bias. The exclusion of studies using the same databases did not fully eliminate heterogeneity. As expected, a decrease emerged when the analyses were conducted only on estimates referring to nfS and/or nfMI, confirming what discussed above about the MACE definition. Surprising after controlling for publication bias, a difference in term of heterogeneity was found in the sensitivity analysis (MACE_L,) (Fig. 4). The observed difference is primarily attributable to the non-significant findings of Kurmann *et al*. (25), which consistently showed the widest 95% CIs across analyses.

Conclusion

In conclusion this meta-analysis, with more than 70000 patients evaluated, provides compelling evidence that patients with SSc have an increased risk of MACE, including nfS and nfMI. It highlights an important comorbidity that should be carefully considered in the management of these patients, managing them as potential "high CV risk patients" also without alteration on traditional risk factors.

Despite current guidelines that treat them similarly to the general population, individuals with SSc may indeed benefit from more aggressive and targeted CV risk assessment and management strategies. Further large-scale, prospective studies are needed to clarify the pathophysiological mechanisms, refine risk stratification, and establish dedicated guidelines that address both traditional and disease-specific factors contributing to CV disease in SSc.

Acknowledgments

The 4.0 version of ChatGPT, developed by OpenAI, was used as a language tool to refine our writing and enhancing the clarity of our work.

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