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ORIGINAL PAPER

Cardiovascular events risk in patients with systemic autoimmune diseases: a prognostic systematic review and meta-analysis

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Abstract

Background Chronic inflammation is considered a risk factor for the development of atherosclerosis and cardiovascular (CV) events. We seek to assess the risk of CV events in patients with Systemic autoimmune diseases (SAD), such as Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Psoriasis (Ps) and Ankylosing Spondylitis (AS), compared with the general population.

Methods and results A systematic search of MEDLINE from inception up to May 2021 was performed. Observational studies including individuals with and without autoimmune diseases (SLE, RA, Ps, AS), which reported a measure of association and variability for the effect of SAD on CV events, were included. The random effects meta-analysis was performed using the Hartung–Knapp–Sidik–Jonkman approach to obtain the pooled estimates. Cardiovascular Events including CV mortality, non-fatal myocardial infarction (MI), non-fatal stroke and coronary revascularization were the main outcomes evaluated. Fifty-four studies were selected, with a total of 24,107,072 participants. The presence of SAD was associated with an increased risk of CV mortality (HR 1.49 [95% CI 1.10–2.03]), non-fatal MI (HR 1.42 [95% CI 1.23–1.62]), and non-fatal stroke (HR 1.47 [95% CI 1.28–1.70]). RA, SLE, and Ps (particularly with arthritis) were significantly associated with a higher risk of MI and stroke. SAD was also associated with an increased risk of Major Adverse Cardiovascular Events (MACE) (HR 1.45 [95% CI 1.16–1.83]).

Conclusion Patients with SAD present an increased risk of CV morbidity and mortality, which should be considered when establishing therapeutic strategies. These findings support the role of systemic inflammation in the development of atherosclerosis-driven disease.

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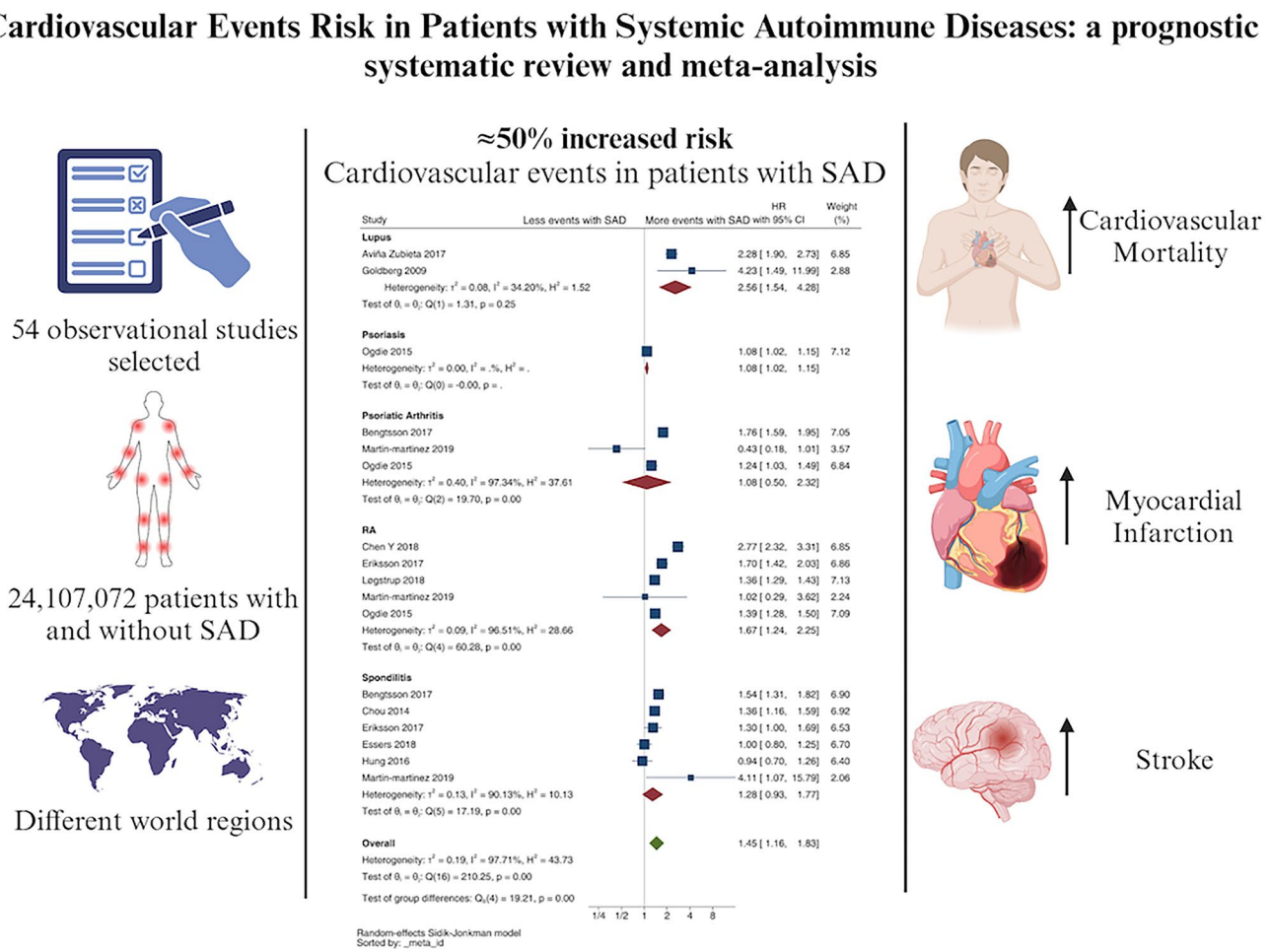
Graphical abstract



Keywords Cardiovascular disease · Systemic inflammatory disease · Meta-analysis · Prognosis

Introduction

Cardiovascular diseases (CVD) are the leading cause of death and disability worldwide [1]. Ischemic heart disease and stroke are the main contributors to cardiovascular-associated mortality, both having as common denominator atherosclerotic plaque build-up in the arteries [1, 2]. Atherosclerosis is a chronic inflammatory disease, with involvement of both innate and adaptive immunity in response to infiltration of apolipoprotein B-containing lipoproteins within the vessel intimal space [3–7]. Evidence has shown that management of dyslipidemia alone is not sufficient for preventing cardiovascular events, and biomarkers of inflammation—such as C-reactive protein—are now recognized as independent predictors of cardiovascular risk [8, 9]. Furthermore, targeting inflammation through the administration of the IL-1β monoclonal antibody Canakinumab to post myocardial infarction patients who were also receiving high-dose statins proved to reduce the occurrence of major adverse cardiovascular events. Similar results have been obtained with the use of colchicine in the setting of an acute or chronic coronary syndrome [10–13].

Systemic autoimmune/inflammatory diseases (SAD), though considered rare, have an strong impact in both morbidity and mortality, significantly affecting the productive years of the population affected [14]. The prevalence of these conditions is 3–5% in the general population [14, 15], with specific prevalence and incidence varying according to gender, ethnicity, age and other demographic factors [16]. Interestingly, the frequency of autoimmune diseases is higher in women, though the reason behind such sex bias remains unknown [16]. The recognition of atherosclerosis

as a chronic inflammatory disease, rather than just a disease caused by the passive accumulation of lipid in the vessel wall, has highlighted the potential association between systemic inflammation and atheromatous disease, positioning inflammation as a plausible explanation for the residual risk observed [17–20]. Systemic inflammation is a staple in SAD and, along with traditional cardiovascular (CV) risk factors [21, 22], might increase CV morbidity and mortality in this group of patients [23, 24]. In this systematic review, we seek to assess whether patients with SAD present with higher rates of CV events when compared to the general population, exploring the effects of systemic inflammatory diseases upon CVD risk.

Methods

A systematic review and meta-analysis of observational studies (cohort and case–control studies) were carried out. People with and without SAD were compared based on the incidence of CV events. This study was developed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist [25]. The protocol for this systematic review was registered in PROSPERO (CRD42021266933).

Search

A structured and comprehensive literature search was performed on MEDLINE (via PubMed) to identify relevant articles. The following questions were addressed: Do patients with systemic autoimmune diseases (SAD) have higher rates of CV events? We searched the references list of articles selected for further relevant studies.

The search strategy was carried out combining the search term "arthritis, rheumatoid"[MeSH]; "Lupus Erythematosus, Systemic"[Mesh]; "Psoriasis"[Mesh]; "Arthritis, Psoriatic"[Mesh]; "Spondylitis, Ankylosing"[Mesh] with each of the following keywords: Coronary Artery Disease"[Mesh], Myocardial Infarction"[MeSH], "Stroke"[MeSH], Percutaneous Coronary Intervention"[MeSH], cardiovascular mortality [TXT]; major adverse cardiovascular events (MACE) [TXT]; coronary revascularization [TXT] using the Boolean logical operators AND, OR. The search was limited to articles in English or Spanish up to May 2021. For studies based on the same patient's cohort, only the most recent and complete report was selected to avoid data duplication.

Selection criteria

This review included observational studies (prospective and retrospective cohort studies, case–control studies) that reported a measure of association (i.e., OR, RR, HR, IRR) and variability (SE or 95% CI) for effects of SAD on incident Cardiovascular Events (CV mortality, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization), adjusted at least for age and sex, in participants 16 years and older. Of note, studies with participants that experienced CV events before SAD diagnosis were excluded.

Exposure (Prognostic factor): The SAD assessed in this review were the following: (1) Rheumatoid Arthritis (RA); (2) Psoriasis (Ps) and Psoriatic Arthritis (PsA); (3) Systemic Lupus Erythematosus (SLE); (4) Ankylosing Spondylitis (AS). SAD diagnosis had to be defined by established clinical criteria, patient self-report, medical chart review, or medical codes. Studies with participants with concomitant SAD or other inflammatory conditions and studies where the temporal line between prognostic factor and outcome was not clear were excluded.

Outcomes

The primary outcomes included Cardiovascular Events such as death due to cardiovascular causes (CV mortality), all cause of death and non-CV-death, non-fatal myocardial infarction (MI), non-fatal stroke (including ischemic and hemorrhagic stroke), and coronary revascularization (including percutaneous coronary intervention and coronary artery bypass graft surgery). The association between SAD and the first occurrence of Cardiovascular Events after the SAD diagnosis was assessed.

The secondary outcome was the composite Major Adverse Cardiovascular Events (MACE) as defined by individual studies, including defined primary outcomes and other events, e.g., heart failure and chest angina, among others. Venous thromboembolism events were also assessed.

Selection and data extraction

Two reviewers working independently screened the titles and abstracts of all articles for appropriateness. Full-text articles of potentially eligible studies were obtained and reviewed. Disagreements in study selection were resolved through discussion, and when it was necessary, a third reviewer was included to facilitate consensus. Three reviewers extracted data independently using a standardized form that was piloted on a small number of included studies. Any differences between reviewers were discussed until a consensus was reached.

Risk of bias (quality) assessment

Three independent reviewers assessed the quality and risk of bias of the selected studies using the QUIPS* (Quality in Prognostic Factor Studies) tool [26] across six domains:

study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, and statistical analysis and reporting. A judgment was made of 'High, 'Low, or 'Unclear/moderate' risk of bias for each domain. The risk of bias was presented in a color-coded table: red for high, yellow for unclear/moderate, and green for low. Discrepancies were resolved by consensus.

The review and meta-analysis procedures were conducted following published guidelines for developing reviews of prognostic factors [27].

Sub-group analysis

A sub-group analysis was performed by sex, to explore potential gender differences for the association between SAD and CV events.

Data synthesis and analysis

A narrative synthesis of the findings from the included studies was developed assessing systematically and comprehensively the studies' results, highlighting the relevant similarities or differences among them.

The extracted data were combined for meta-analysis using STATA 17/SE software (College Station, TX: StataCorp LLC). The overall pooled HRs were obtained using the Hartung–Knapp–Sidik–Jonkman method for random effects meta-analysis. Forest Plots were built to summarize the overall HR estimated and their 95% CIs, comparing the risk of patients with SAD with the risk in people from the general population without SAD, for each type of measured outcome. Heterogeneity between studies was assessed using I^2. When the primary studies provided separate analysis and data according to disease severity, a subgroup analysis was carried out to examine whether this factor was a potential source of heterogeneity between the studies included.

We conducted a sensitivity analysis to assess the impact of trial sample size on the outcomes, using quarters within each outcome (from quarter 1 including 25% of the smallest trials, to quarter 4 including 25% of the largest trials) excluding quarters sequentially to observe if the overall effects of the meta-analysis change or if it is affected by sample size.

Results

The flowcharts summarizing the selection process of included studies for each SAD are shown in supplementary material online, Supplementary Fig. 1.

Fifty-four studies were included (RA = 15, Ps = 17, SLE = 11, and AS = 11), with a total of 24,107,072 participants (RA N = 7,466,969; Ps N = 14,337,496; SLE N = 556,251; and AS N = 1,746,356). The characteristics of the studies that fulfilled the selection criteria and thus were included in the meta-analysis are summarized in the supplementary material online, Supplementary Tables 1–4.

All selected studies followed a cohort design (RA: 14 prospective and 1 retrospective; Ps: 14 prospective and 2 retrospectives; SLE: 10 prospective and 1 retrospective; and AS: 10 prospective and 1 retrospective). The studies included were carried out in a variety of countries: Sweden (RA: 3, Ps: 1, SLE: 2, AS: 2); Denmark (RA: 2, Ps: 3, SLE: 1); Australia (A: 1); Spain (RA: 1, Ps: 1, AS: 1); Germany (Ps: 1); Taiwan (RA: 2, Ps: 1, SLE: 4, AS: 4); Korea (Ps: 1, LES: 1, EA: 1); United Kingdom (RA: 2, Ps: 4, AS: 1); USA (RA: 3, Ps: 2, SLE: 1); Canada (RA: 1, SLE: 2, AS: 1), The Netherlands (Ps: 2) and Wales (AS: 1).

Most studies reported Hazard Ratios (HR), with few exceptions including the SLE study by Hak 2009 [28]; the RA studies by Solomon 2003 [29], Holmqvist 2010 [30], Solomon 2006 [31], Watson 2003 [32]; and the Ps studies by Ahlehoff 2011[33] and Koch 2015 [34], all of which reported relative risk (RR). Additionally, the RA studies by Del Rincón 2001 [35] and Lindhardsen 2011 [36] reported Incidence Rate Ratios (IRR). The RR data were analyzed separately; however, the IRR data were not possible to meta-analyze due to the few studies (Del Rincon 2011 [35] and Lindhardsen 2011 [36]) reporting such measure.

Assessment of bias in selected studies

Figure 1 shows the consensus reached by three independent reviewers regarding the risk of bias, with the use of the QUIPS tool. The predominant evaluation for risk of bias in all studies was moderate. The main categories considered to be a source of bias in the included studies were frequently associated with the lack of information regarding attrition rates and the prognostic factor measurement.

Mortality

The presence of SAD was associated with a 49% increase in CV mortality, with RA, SLE and AS presenting the highest risk (HR 1.43 IC 95% 1.28–1.59, HR 2.58 IC 95% 1.08–6.17 and HR 1.36 IC 95% 1.13–1.64, respectively, Fig. 2). The meta-analysis of the pooled RR data reported in Ps [33] and RA [30, 32] studies showed the same trend of increased risk in patients exposed to the prognostic factor, when compared to the general population (RR 1.33 IC 95% 1.12–1.58).

Only two studies in RA and one in Ps reported all-cause mortality. For this reason, conducting a meta-analysis for this specific outcome was not possible. These studies showed an increased risk of mortality associated with these SAD (refer to data in Supplementary Table 5).

A

Study ID	1	2	3	4	5	6
Holmqvist 2013	low	unclear	low	moderate	high	low
Lindhardsen 2012	moderate	unclear	moderate	low	moderate	low
Van Doornum 2006	low	unclear	moderate	low	low	low
Solomon 2003	moderate	unclear	moderate	moderate	low	moderate
Del Rincón 2001	moderate	unclear	moderate	moderate	low	moderate
Holmqvist 2010	low	unclear	low	low	high	low
Solomon 2006	low	unclear	moderate	low	high	low
Maradit-Kremers 200	low	unclear	low	low	moderate	low
Løgstrup 2018	moderate	unclear	low	low	high	low
Chen 2018	moderate	unclear	moderate	low	low	low
Watson 2003	low	unclear	moderate	moderate	high	moderate
Ogdie 2015	moderate	low	low	low	low	moderate
Eriksson 2017	low	unclear	moderate	low	high	moderate
Liou 2014	low	unclear	low	low	low	low
Martin-Martínez 201	low	unclear	low	low	low	low

B

Study ID	1	2	3	4	5	6
Ahlehoff 2011	low	unclear	moderate	low	moderate	moderate
Dowlatshahi 2013	moderate	unclear	low	low	low	low
Dregan 2014	low	unclear	moderate	low	low	low
Egebert 2015	low	unclear	low	low	moderate	low
Jung 2019	low	unclear	low	low	low	low
Koch 2015	low	unclear	moderate	moderate	moderate	low
Leisner 2018	low	unclear	moderate	low	high	moderate
Parisi 2015	low	unclear	moderate	moderate	high	moderate
Wu 2015	low	unclear	moderate	low	moderate	low
Lin 2011	low	unclear	low	low	low	low
Kaye 2008	low	unclear	moderate	moderate	high	moderate
Maradit-Kremers	moderate	unclear	moderate	low	high	low
Wakke 2010	low	unclear	moderate	moderate	low	low
Mehta 2010	low	low	moderate	moderate	high	low
Ogdie 2015	moderate	low	low	low	low	moderate
Bengtsson 2017	low	unclear	low	low	high	low
Martín-Martínez	low	unclear	low	low	low	low

C

Study ID	1	2	3	4	5	6
Tornwall 2021	low	unclear	moderate	low	low	low
Lim 2018	low	unclear	low	low	low	moderate
Goldberg 2009	moderate	low	moderate	low	high	moderate
Chou 2014	moderate	unclear	moderate	high	low	high
Arkema 2017	low	unclear	moderate	low	moderate	low
Wang 2012	low	unclear	low	low	moderate	low
Chiu 2012	low	unclear	low	low	moderate	moderate
Hak 2009	moderate	unclear	moderate	moderate	low	low
Liou 2014	low	unclear	low	low	low	low
Aviña Zubieta 2017	low	unclear	low	low	high	high
Hermansen 2017	low	unclear	low	low	high	high

D

Study ID	1	2	3	4	5	6
Martín-Martínez 201	low	unclear	low	low	low	low
Park 2018	low	unclear	moderate	low	low	low
Bengtsson 2017	low	unclear	low	low	high	low
Hung 2016	moderate	unclear	low	low	low	moderate
Haroon 2015	low	unclear	low	low	low	low
Essers 2016	low	unclear	moderate	moderate	low	low
Lin 2014	moderate	unclear	low	low	low	low
Keller 2014	low	unclear	low	low	low	moderate
Chou 2014	low	unclear	moderate	low	low	low
Brophy 2012	moderate	moderate	moderate	low	high	moderate
Eriksson 2017	low	unclear	moderate	low	high	moderate

1 = Study participation, 2 = Study attrition, 3 = Prognostic factor measurement, 4 = Outcome measurement, 5 = Adjustment for other prognostic factors, 6 = Statistical Analysis and Reporting. A. QUIPS for Rheumatoid Arthritis. B. QUIPS for Psoriasis. C. QUIPS for Systemic Lupus Erythematosus. D. QUIPS for Ankylosing Spondylitis.

Fig. 1 Risk of bias evaluation using QUIPS (Quality in Prognosis Studies) tool

Non-fatal myocardial infarction

Patients with SAD showed an increased risk of developing myocardial infarction (HR 1.42 IC 95% 1.23–1.62). SLE was associated with a significantly higher risk (HR 2.30 IC 95% 1.85–2.86), whereas AS did not show statistically significant differences with the general population (Fig. 3). RA [29, 30, 32] and Ps [33, 34] studies reporting RR were pooled and analyzed and showed consistent results with the HR meta-analysis (RR 1.42 IC 95% 1.20–1.66).

Non-fatal stroke

The pooled analysis of SAD showed an increased risk of developing a stroke (HR 1.47 IC 95% 1.28–1.70). This risk was particularly prominent in SLE with a 129% increase (HR 2.29 IC 95% 1.90–2.77, Fig. 4). Ps only showed a statistically significant risk association when present in the form of psoriatic arthritis (HR 1.34 IC 95% 1.22–1.47); RA and AS also showed a significant risk of stroke (HR 1.33 IC 95% 1.22–1.44 and HR 1.52 IC 95% 1.13–2.04, respectively). The pooled RR of SLE, Ps and RA showed the same trend (RR 1.35 IC 95% 1.09–1.68).

The subgroup analysis by stroke type (ischemic and hemorrhagic) showed that SAD is associated with higher risk of ischemic, but not hemorrhagic, stroke (HR 1.69 IC 95% 1.20–2.38, Fig. 5).

Coronary revascularization

Only RA and Ps studies reported coronary revascularization. Holmqvist 2010 [30] showed increased risk for the need of coronary revascularization in subjects with RA (RR 1.6 IC 95% 1.2–2.1), similar to the reports of Logstrup 2018 [37] (coronary angioplasty HR 1.24 IC 95% 1.0–1.4; and bypass graft surgery HR 1.2 IC 95% 1.03–1.41). Conversely, Maradit-Kremers 2005 [38] did not report any association between RA and coronary revascularization procedures.

Regarding Ps, Ahlehoff 2011 [33] assessed whether patients with mild and severe psoriasis were at higher risk of needing coronary revascularization, finding that both groups showed an increased RR, a risk that was slightly higher in subjects with the severe form of disease (severe: RR 1.77 IC 95% 1.35–2.32) vs (mild: RR 1.37 IC 95% 1.26–1.49).

Composite of major adverse cardiovascular events (MACE) according to study definition

Both SLE and RA were significantly associated with a major risk for composite MACE as reported in individual studies (CV death, non-fatal MI, non-fatal stroke, revascularization, chest angina, among others) (SLE HR 2.56 IC 95% 1.54–4.28; and RA HR 1.67 IC 95% 1.24–2.25). The meta-analysis of the complete data showed that, overall, SAD was associated with a 45% increase in risk (HR 1.45 IC 95% 1.16–1.83, Fig. 6).

Venous thromboembolism

Venous thromboembolism (VTE) events were scarcely reported; however, all studies addressing this outcome demonstrated a significant association between SAD and VTE. Eriksson 2017 [39] found a statistically significant increased risk of VTE in individuals with AR with a RR

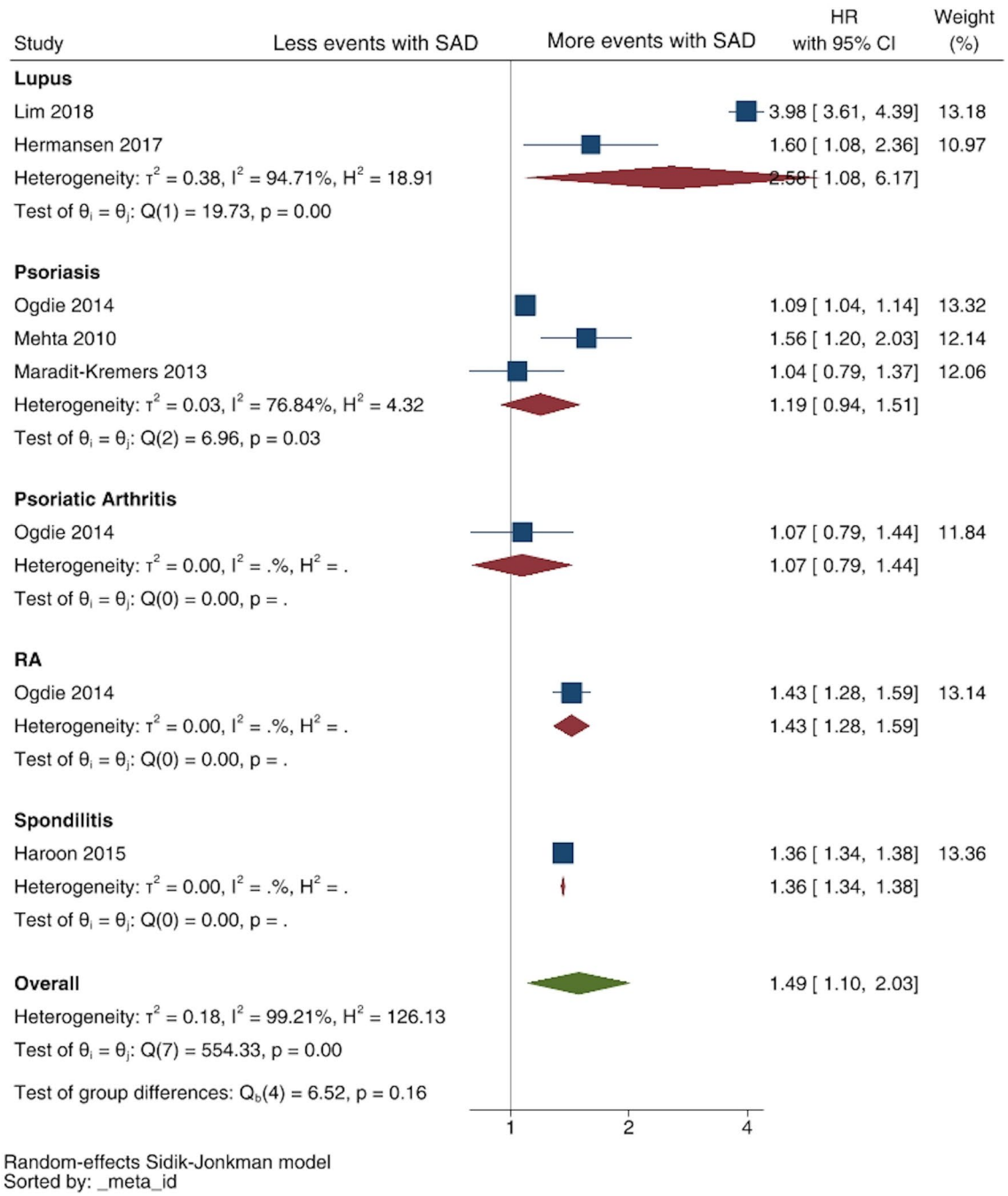


Fig. 2 Forest plot of the effect of SAD on Cardiovascular Mortality risk

of 1.8 (IC 95% 1.5–2.1). Bengtsson 2017 [40] reported an HR of 1.46 (IC 95%1.29–1.87) for VTE in individuals with PsA.

Furthermore, two studies showed a significant association between AS and VTE. Bengtsson 2017 [40] reported an HR of 1.53 (CI 95%1.25–1.65) and Eriksson 2017 [39] an HR of 1.4 (CI 95% 1.1–1.9) for developing VTE.

Sub-group analysis by gender

The analyses were repeated for the available studies that presented data according to gender. Although these analyses were limited and depending on the outcome did not include all the studied SAD, they help to further understand their effect. Forest plot can be found in Supplementary Figs. 2–6.

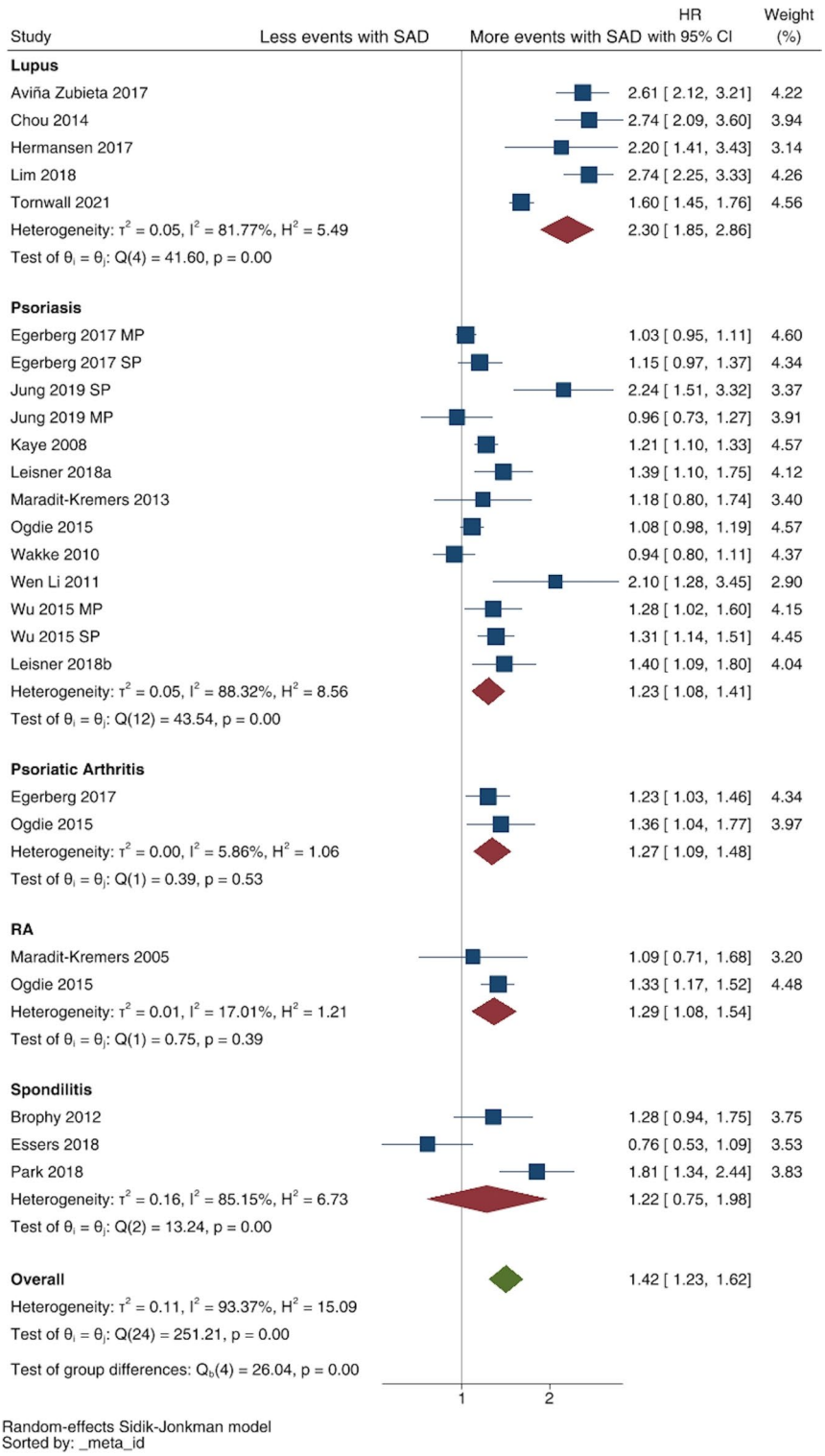


Fig. 3 Forest plot of the effect of SAD on non-fatal myocardial infarction risk

Overall, it seems that the presence of SAD affected both women and men, although the magnitude of risk varied.

In terms of CV mortality, women and men presented a similarly increased risk. However, this was driven by SLE in women, and by AS in men, most probably reflecting sex disparities in disease presentation. For non-fatal MI, the risk was significantly higher in women with SAD, whereas it did not reach conventional levels of significance in men, although SLE seemed to increase the risk for both women and men.

For all strokes, women and men showed increased events, although the risk was more pronounce in the

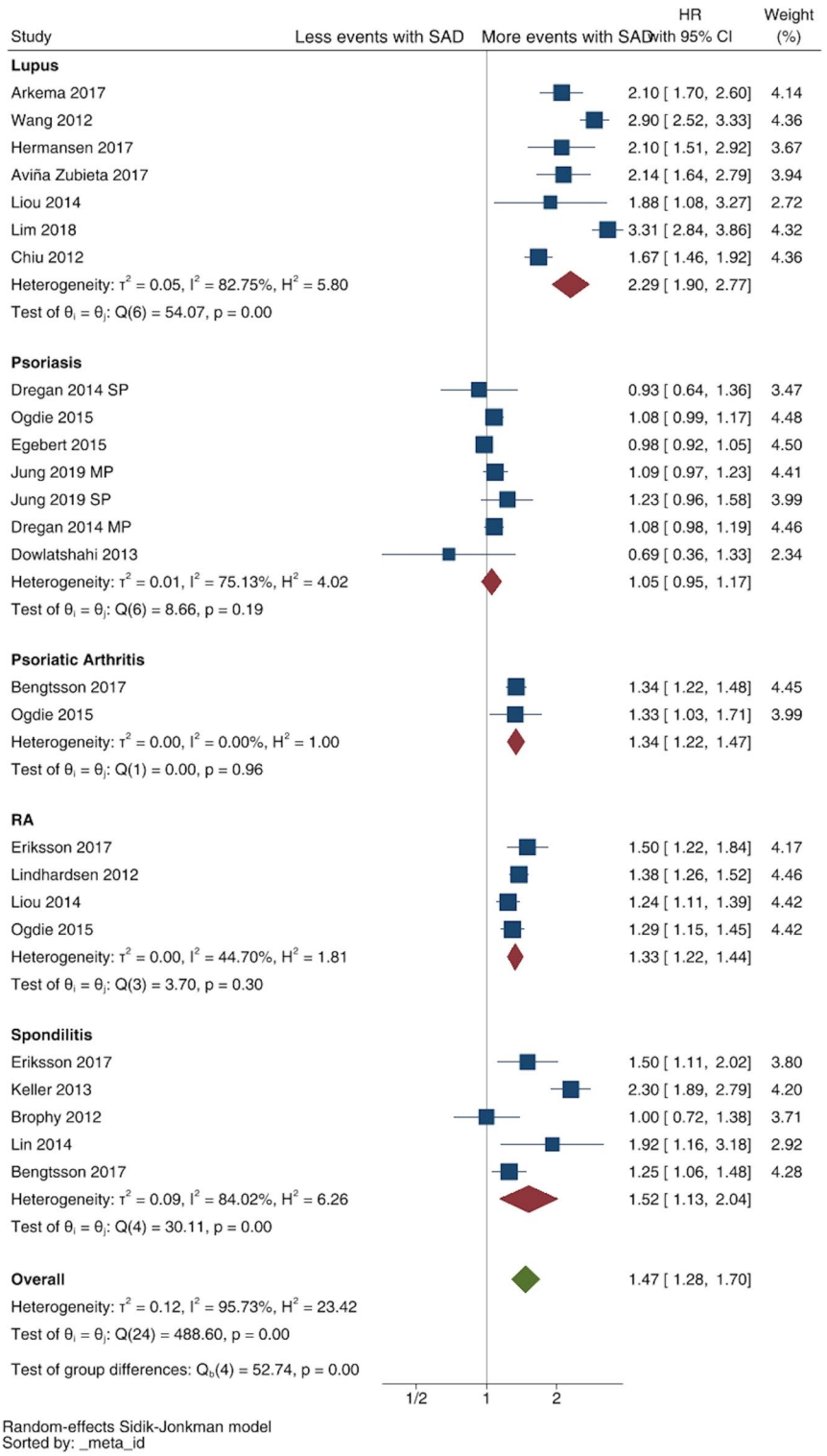


Fig. 4 Forest plot of the effect of SAD on non-fatal stroke risk

former, with an 88% greater risk than in women without SAD. When considering stroke subtypes, the risk of ischemic stroke was 91% higher in women with SAD than the control. Men with SAD also showed a trend for an increased risk (22% higher than control), but it was not statistically significant. Conversely, the risk of hemorrhagic stroke was not affected by the presence of SAD, although in the one study of SLE that could be included, the risk was substantially increased for both women and men.

Finally, the risk of MACE was higher in both women and men with SAD.

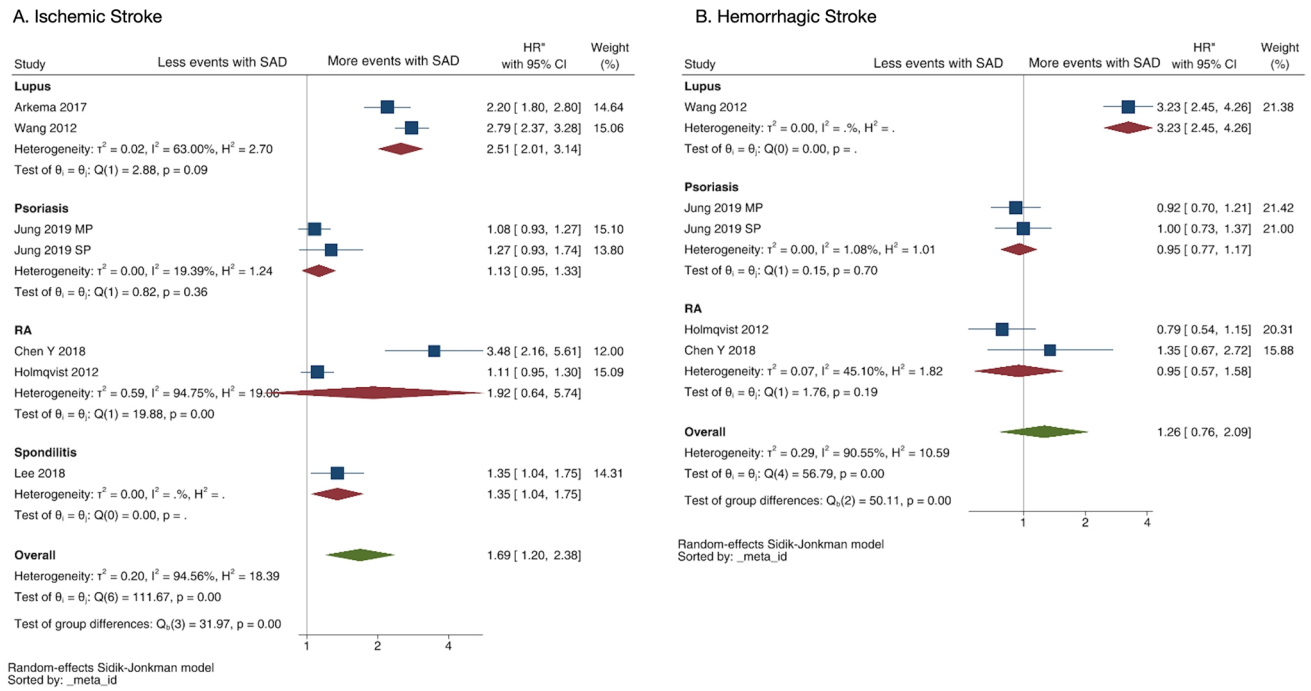


Fig. 5 Forest plot of the effect of SAD on subgroup of stroke

Sensitivity analysis

Upon sequentially excluding smaller studies from the analysis, the association strength decreased for non-fatal MI and all strokes; it increased for cardiovascular mortality and remained mostly unchanged for MACE. However, the overall risk trend remained consistent. The findings of the sensitivity analysis are available in the supplementary material online, Supplementary Table 6.

Discussion

The main finding of this systematic review is that the presence of SAD is associated with a significant increase in the probability of the first occurrence of Cardiovascular Events when compared to the general population. Of note, increased CV mortality was detected in patients with SAD, particularly in those with RA, SLE and Ps.

The increased CV risk in patients with SAD has biological plausibility. In the pathogenesis of atherosclerosis, the accumulation of sub-endothelial low-density lipoprotein (LDL) is recognized as an initial event, followed by a maladaptive and self-perpetuating inflammatory response with involvement of both innate and adaptive immunity [3–7]. In addition, it has been recently postulated that the peripheral nervous system interacts with diseased vessels at the adventitia level—the neuroimmune cardiovascular interfaces, NICIs—to assemble a structural artery–brain circuit, which modulates atherosclerosis progression [41]. In this cross-talk between plaques, immune cells and nerves, the presence of systemic inflammation, as in SAD, could result in accelerated or premature atherosclerosis [42], which has been named *autoimmune atherosclerosis* by some authors [43]. Supporting this, several cell types (Th1 and Th17 lymphocytes) and cytokines (TNF-a, IL-1, IL-6)—key to the inflammatory response of several SAD—are also involved in the pathogenesis of atherosclerosis [44–46]. Likewise, it has been shown that classic SAD autoantibodies (e.g., rheumatoid factor, anti-cyclic citrullinated peptide antibodies and antinuclear antibodies) contribute to athero-inflammation and are associated with increased CV event risk [47, 48]. It is also important to recognize the contribution of classical CV risk factors, including hypertension, diabetes, smoking, and dyslipidemia, to the increased risk of MACE observed in SAD patients [49, 50]. The prevalence of classical risk factors can be higher in SAD patients compared to the general population [51], due to both organ damage caused by the disease itself (e.g., hypertension secondary to glomerulonephritis, obesity caused by restricted mobility), and therapies used for disease control (e.g., dyslipidemia induced by corticoids, cyclosporin or azathioprine) [52, 53]. Nevertheless, most studies included in this systematic review adjusted for traditional risk factors; hence, chronic inflammation remains as a plausible explanation for the increased CV risk seen in SAD patients in our study. In fact, distant inflammation (for example in the skin or joints) can modulate vascular responses through the action of neutrophil extracellular

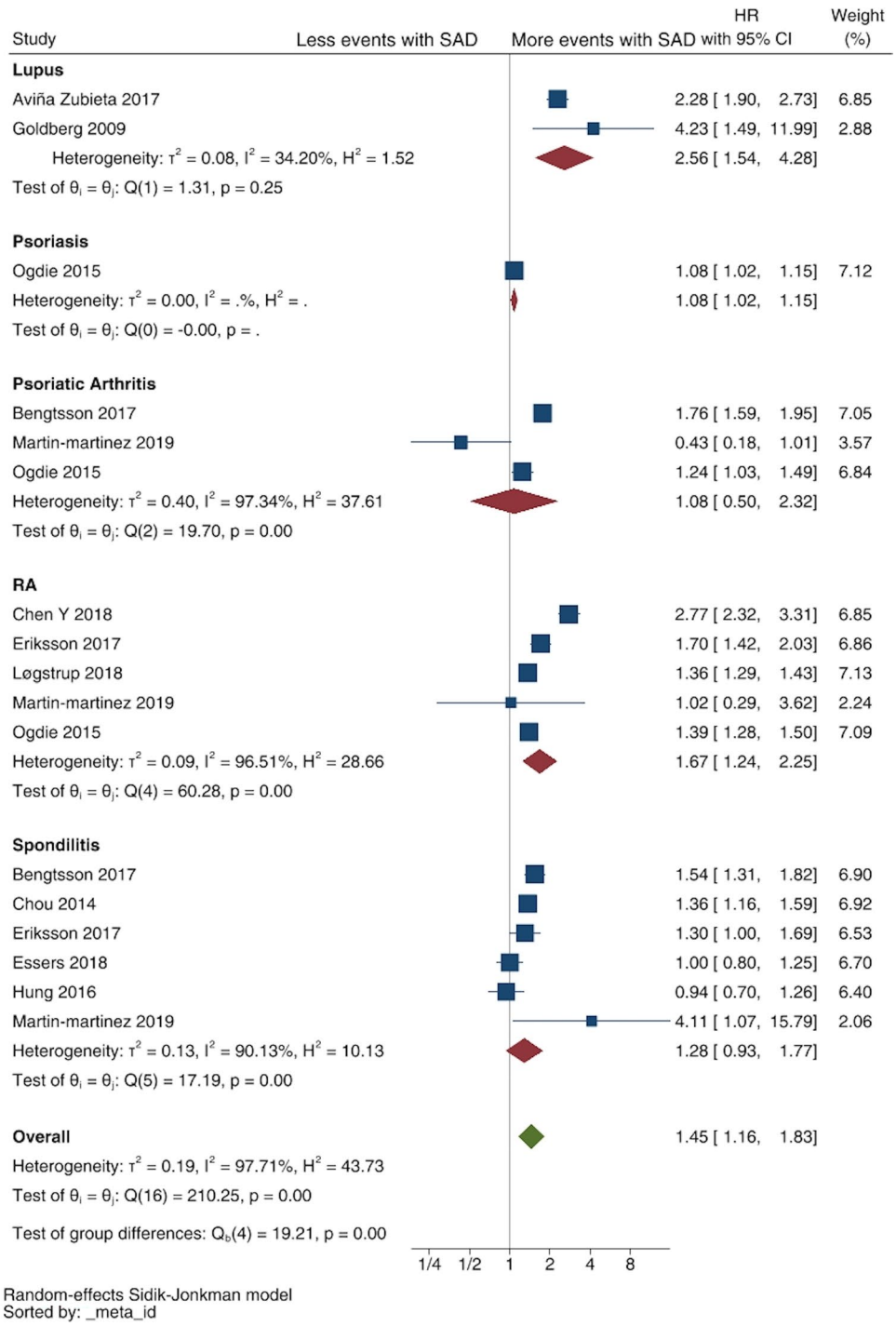


Fig. 6 Forest plot of the effect of SAD on composite Major Adverse Cardiovascular Events (as defined by individual studies)

traps (NETs), which are considered key in the inflammatory response associated with atherosclerosis—particularly in the context of plaque erosion and resulting acute CV events [54, 55]—a phenomenon known as *inflammatory echo.*

The magnitude of increase in CV risk in each individual SAD was not homogeneous. SLE was associated with the highest risk, followed by RA; and both were associated with an increase in risk in all individual outcomes. Although Ps did not show a significant increase in some of the measured CV events, it showed a significant effect on non-fatal MI. On the other hand, PsA—a more complex type of Ps—showed an increased risk for non-fatal stroke and MI. Finally, AS showed less association with CV events; however, it did show a higher incidence in non-fatal stroke and CV mortality. Although the reasons behind such differences between individual SAD are unknown, one can hypothesize that more

extensive and thus systemic involvement, as seen in SLE and RA compared to AS and Ps, can have more impact on the vascular wall. Another possible explanation is the frequent occurrence of vasculitis in SLE and RA, as opposed to AS or Ps, which could further accelerate the development of atherosclerosis [49].

Importantly, we only assessed clinical events. Recent findings support the need for advance imaging to further increase our awareness of cardiovascular involvement in patients with SAD [56]. Accordingly, the expected prevalence, and thus the potential for event prevention, can be much larger if specific diagnostic tools are correctly employed, including both imaging and laboratory biomarkers [57].

This study has several advantages. The major strength is that the risk of CV events was assessed in a large group of SAD, including over 20 million patients. Although systematic reviews on this field are available, most are limited to one SAD or focus on one cardiovascular outcome. Second, the observed results are robust, and the increase in the risk of CV events can be attributed to the presence of the SAD analyzed, since most of the studies adjusted for traditional risk factors, as well as age and sex. Moreover, different from previous reports, we only evaluated incident events, thus precluding the possibility of having patients with a CV event before the SAD had been diagnosed. Additionally, patients with previous events were also excluded. This point is critical, as the history of a previous CV event by itself increases the risk of a new event, therefore is a potential source of bias, not always recognized in some of the key studies on this topic. Third, the results presented are consistent in a wide variety of ethnic groups. Patients from European, Asian, and North American origin, with diverse socioeconomic situations, were included. Unfortunately, as it has been recognized previously [58], Latin America and Africa remain underrepresented regions. Fourth, it provides both information for individual entities and SAD as a group, thus allowing for a comprehensive assessment of current available information.

Recently, a large-scale population-based study in the United Kingdom was published [59]. This brilliant work showed that the presence of any autoimmune disease increased the risk of cardiovascular diseases by roughly 50% during a 6-year follow-up. These results are consistent with our findings, although the aforementioned study also included conditions not related to atherosclerosis-driven diseases, such as infective endocarditis, myo/pericarditis and conduction system diseases. Moreover, some of the autoimmune diseases included present an inherent increased CV risk due to its pathobiological mechanisms (i.e., type 1 diabetes), further complicating results interpretation. Therefore, we believe our results complement those from Conrad et al. and help clarify the landscape on this topic.

One limitation of this work is the heterogeneity of the studies included, due to differences in the definition of the prognostic factor (individual SAD) and outcome, the adjustment for confounding variables and the inherent bias of observational studies. However, this diversity along with the large number of studies available is, indeed, the main reason justifying the need for a meta-analysis. Although such heterogeneity demands a careful interpretation of the results, the existence of a clear trend that is clinically relevant appears to be robust. Second, even though duplicated studies were excluded, residual overlapping of the populations studied is still possible. Nonetheless, we think that the effect of such overlapping would not be significant, considering the number of studies and patients included in the analysis and the consistency of the results obtained. Third, the different studies included in this meta-analysis were conducted during a large time span; therefore, differences throughout time in diagnostic tools and treatments options might have influenced outcome assignment.

These findings are clinically relevant. They stress the importance of implementing effective strategies for cardiovascular risk management in SAD patients, both in primary and secondary prevention. Along with traditional risk factors, the existence of SAD should be considered when estimating the individual cardiovascular risk. The results of this systematic review support the concept that optimal control of traditional risk factors is of paramount importance in these patients. Keeping this in mind and considering that inflammation might play an essential role in the increased cardiovascular risk attributed to SAD, the effect of targeted anti-inflammatory therapies in the reduction in such events is worth exploring. This is even more promising when considering the results of therapies targeting inflammation in patients with atherosclerosis but without SAD. In patients with a previous MI and persistent inflammation, the administration of the IL-1β antibody Canakinumab showed a reduction in MACE, cancer, and gout attacks, although it slightly increased fatal infections [10]. Regarding the use of Colchicine, a meta-analysis including the five main randomized controlled trials showed a significant reduction in MACE, an effect that was consistent in both acute and chronic coronary syndromes [60]. Of note, the magnitude of the benefit obtained with Colchicine in patients with CAD was comparable to that achieved by each of the mainstay therapies for the secondary prevention of CAD—such as antiplatelet agents and statins—and was achieved against a background of optimal treatment with these therapies. Other agents targeting inflammation have been tested, but without convincing results. Tocilizumab, an IL-6 receptor antibody, reduced troponin release in a group of patients with acute coronary syndrome [61], and a trial of methotrexate administered to a group of chronic coronary syndrome patients

with evidence of inflammation had to be halted prematurely because of futility [62].

On the other hand, the available evidence regarding the use of targeted anti-inflammatory therapies or biologic disease modifying antirheumatic drugs (bDMARDs) in patients with SAD is obtained from observational studies or limited to intermediate cardiovascular outcomes. A systematic review evaluating the effect of the treatment with TNF-α antagonists in RA patients showed reduction in arterial wall stiffness and other markers of subclinical atherosclerosis [54]. The largest meta-analysis focusing on clinical outcomes—which included mainly observational studies—showed that in patients with RA, treatment with TNF inhibitors or methotrexate was associated with a 30% and 28% reduction in the risk of MACE, respectively; and that in patients with Ps or AS, use of systemic therapy achieved a comparable benefit of 25% reduction in MACE [63]. Likewise, in an observational study including 18,754 RA patients, some bDMARDs (Abatacept and TNF inhibitors) showed a more favorable CV profile than traditional RA therapies, including methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide, as well as systemic steroids. However, it is not possible to confirm if these findings were a result of bDMARDs risk reduction or an increased CV risk determined by traditional therapies [64]. Hence, although these results are promising, there is an unmet need for properly designed studies evaluating the effects of immunomodulatory therapies on CV events in patients with SAD.

In conclusion, according to our meta-analysis, the presence of SAD is associated with a significant increase in the risk for CV events, including cardiovascular mortality, non-fatal MI, coronary revascularization, and stroke. These findings support the role of systemic inflammation in the development of atherosclerosis and should promote strategies to optimize the management of cardiovascular risk in SAD patients.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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