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Systemic Lupus Erythematosus

The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: A systematic review

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ABSTRACT

Objective: To perform a systematic review of the literature regarding the epidemiology of the association between systemic lupus erythematosus (SLE) and atherosclerotic cardiovascular disease (CVD), including the increased risk for CVD, as well as the risk factors responsible for development of CVD in patients with SLE.

Methods: We followed the PRISMA guidelines to systematically search the PubMed database from inception to June 2012. Studies were selected using predefined eligibility criteria, and 2 authors independently extracted data. The risk of bias was measured for each study using a domain-based assessment.

Results: We report on 28 studies that met criteria for inclusion in our analysis. We found strong epidemiologic evidence that SLE patients have an increased relative risk of CVD compared to controls. There is limited information regarding relative CVD mortality risks among SLE patients. Traditional CVD risk factors, including age, male sex, hyperlipidemia, smoking, hypertension, and CRP, are associated with CVD risk among SLE patients. Several SLE-specific factors, including disease activity and duration, and possibly specific manifestations and therapies, further increase risk. Several risk factors, such as disease activity and glucocorticoid use, are closely associated, making it difficult to disentangle their effects.

Conclusions: CVD risk among SLE patients compared to the general population is at least doubled. While older SLE patients appear to have the highest absolute risks of CVD, young women have alarmingly high relative risks, given the rarity of CVD in the comparison general population. Both traditional and SLE-specific risk factors are important, although there are discrepancies within the literature.

Cardiovascular disease (CVD) is a well-recognized complication of systemic lupus erythematosus (SLE). Urowitz et al. first described a bimodal mortality pattern among SLE patients in 1976, with an early peak in the first 3 years after diagnosis due to active disease, infections and glomerulonephritis, and later deaths, 4–20 years after SLE diagnosis, due to CVD [1]. Since then, there has been a growing interest in both the epidemiology and pathophysiology of CVD among SLE patients. Although overall mortality for patients with SLE has improved over the past 30 years with advances in treatment and better understanding of disease mechanisms, mortality due to CVD has remained the same [2]. The biology and mechanisms underlying accelerated atherosclerosis in SLE are complex and remain areas of active investigation. Although traditional risk factors such as hyperlipidemia and smoking have been shown to predict cardiovascular disease in patients with SLE, SLE itself is an independent risk factor for CVD, and a number of SLE-specific risk factors for CVD have been studied [3].

Several types of 'cardiovascular disease' are observed among individuals with SLE, including pericarditis, myocarditis, conduction system disease, vasculitis and valvular disease. In this review, we concentrate upon atherosclerotic CVD including coronary artery disease (CAD), cerebrovascular disease (cerebrovascular accidents, CVAs; and transient ischemic attacks, TIAs), congestive heart failure (CHF) and peripheral vascular disease (PVD). We also review the body of evidence on both traditional and disease-specific risk factors, highlighting some discrepancies within the literature.

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; CVA, cerebrovascular accident; MI, myocardial infarction; PVD, peripheral vascular disease; SLE, systemic lupus erythematosus

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Methods

Search strategy and selection criteria

We used the PRISMA guidelines for conducting a systematic review as a basis for our search protocol [4]. We searched the PubMed database from inception to June 2012, restricted to the English language with the following search terms: "lupus AND"; "angina"; "atherosclerosis"; "cardiovascular"; "cardiovascular mortality"; "cerebrovascular accident"; "congestive heart failure"; "coronary artery disease"; "coronary heart disease"; "myocardial infarction"; "peripheral vascular disease"; and "stroke." We excluded review articles, nonhuman studies, case reports, basic science studies pertaining to the mechanism of atherosclerotic disease, and studies related to non-atherosclerotic cardiovascular disease such as pericarditis, myocarditis, conduction system disease, vasculitis and valvular disease. We also excluded articles that focused only on the antiphospholipid antibody syndrome without concomitant SLE. We limited our search to studies that examined clinical endpoints such as CAD, CHF, CVA, PVD or CVD mortality and excluded studies that had subclinical atherosclerosis as an endpoint. We also conducted hand searches of reference lists to ensure that we did not miss any articles.

We aimed to address the following questions: [1] what is the risk of cardiovascular disease, specifically CAD, CHF, CVA, PVD and CVD related mortality among SLE patients compared to the general population? and [2] what are the risk factors for the development of CVD among SLE patients?

Data extraction

SS screened all abstracts and applied the eligibility criteria in order to identify studies that were appropriate for inclusion. SS and SK then independently extracted data using predefined criteria, which included date of publication, population, language, study design, duration, participant data, outcome definition, results, funding and risk of bias (Appendix Table A1–A4). Risk of bias was broken down into 3 domains including selection bias, measurement bias and confounders, as adapted from Cochrane Database guidelines (Appendix Tables A2 and A4) [5]. Any disagreements were reconciled by consensus and by KC. This data extraction process was done for the studies involving the risk of CVD in SLE patients as well as for the papers that looked at risk factors for CVD in SLE patients.

Results

Through our screening process, we identified 28 studies that met the criteria for inclusion in our analysis. Seven of these studies pertained to the risk of symptomatic atherosclerotic disease in SLE patients compared to the general population; 1 study examined the risk of CV related death among SLE patients; and 20 studies related to the risk factors for symptomatic atherosclerotic disease among SLE patients (Fig. 1).

Risk of symptomatic atherosclerotic disease in SLE patients compared to the general population

Coronary artery disease (CAD)

The increased risk of myocardial infarction (MI) and angina among SLE patients has been well characterized in a number of population-based studies. The 6 papers examined in this review include 4 cohort and 2 case-control studies comprising 15,822 SLE patients with 1232 events related to CAD (Appendix Table A1) [6–11]. Most studies reported a 2–10 fold increase in the risk of MI among SLE patients, with a greater increase in relative risk generally observed in younger patient groups (Fig. 2). The most striking of these studies was conducted by Manzi et al. who

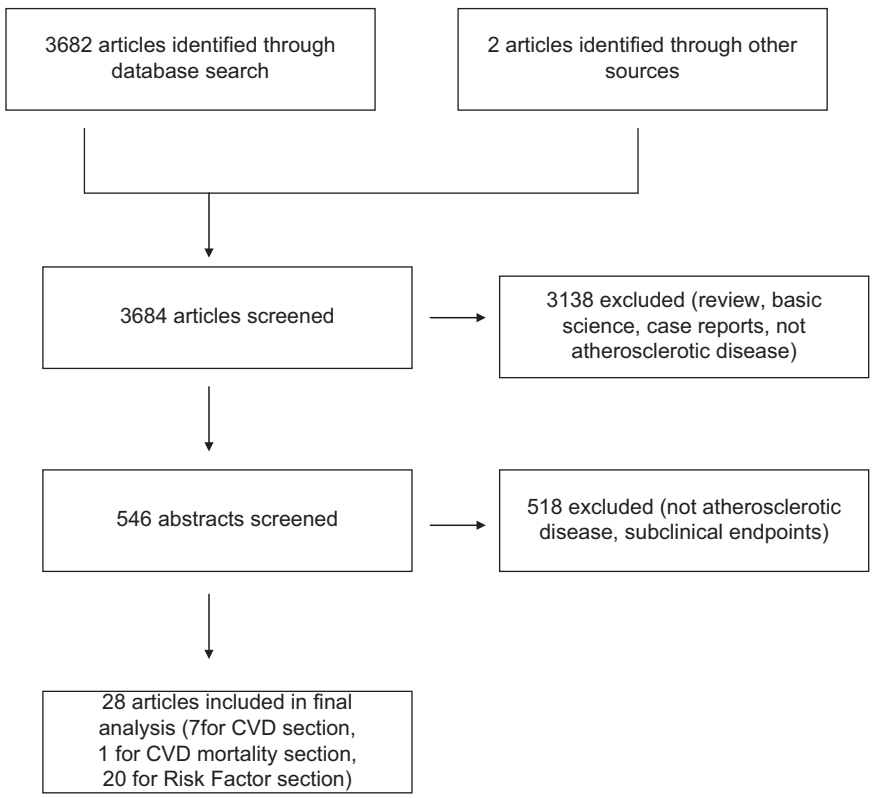

Fig. 1. Flow diagram of literature search strategy.

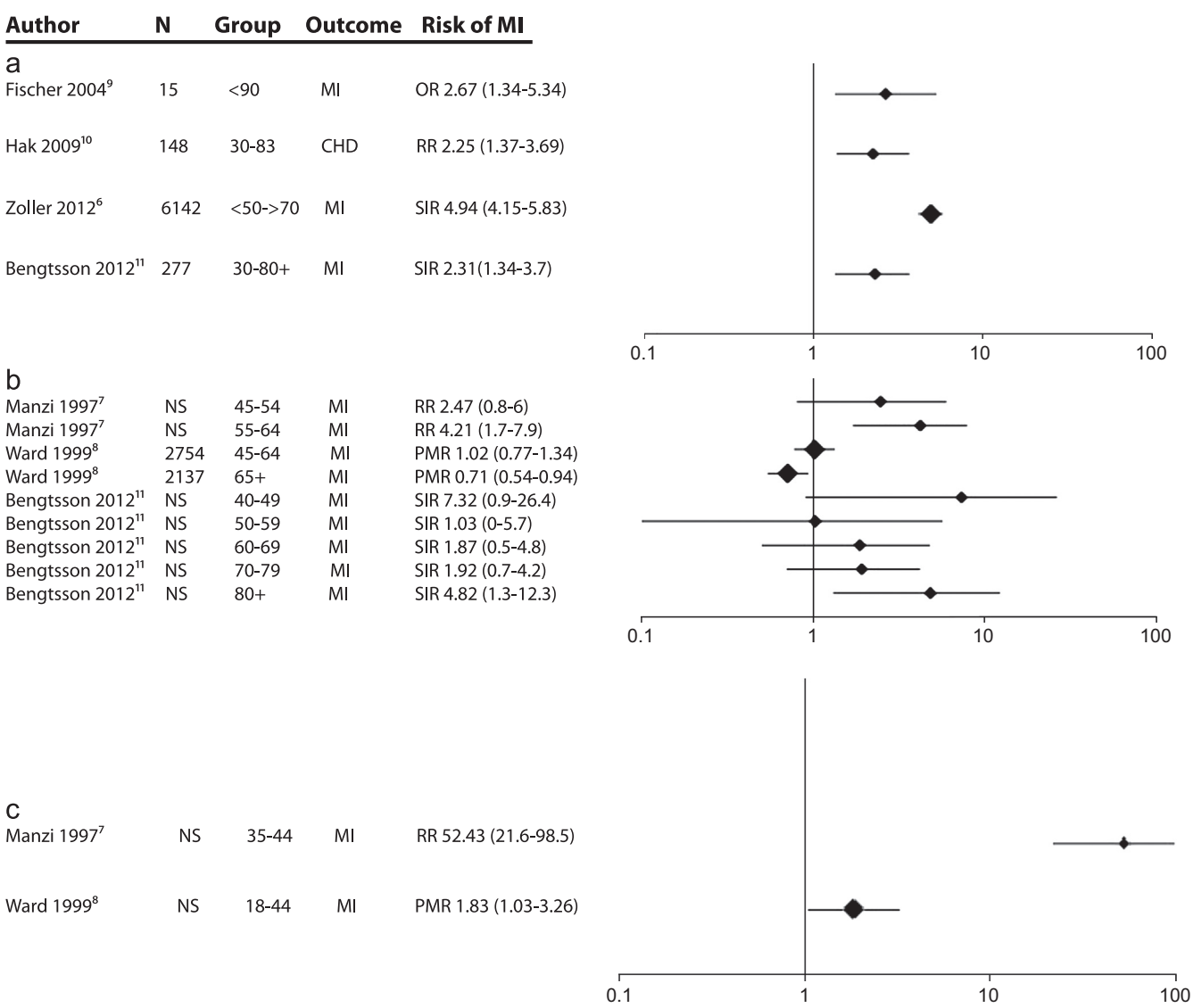

Fig. 2. Forest plots of study effect estimates and population sizes for epidemiologic studies investigating the risk of MI among SLE patients compared to the general population by age group. (a) Studies with all age groups combined. (b) Studies stratified by age group for older SLE patients. (c) Studies stratified by age group for younger SLE patients. *The size of the diamond reflects the size of the study population. *The position of the diamond reflects the risk estimate and the length of the bars reflects the 95% confidence interval. *OR = odds ratio, CHD = coronary heart disease (MI, CABG, and angioplasty), RR = relative risk, SIR = standardized incidence ratio, NS = not specified how many patients in each subgroup, PMR = proportionate morbidity ratio.

compared 498 SLE patients in the University of Pittsburgh cohort to age-matched controls from the Framingham Heart Study in a retrospective cohort analysis [7]. They found that young women aged 35–44 with SLE had a staggering 52.4 (95% CI 21.6–98.5) times increased relative risk of MI over an average of 6.7 years of observation compared to their aged-matched controls, a group with a very low absolute risk of MI. Older women with SLE also had an elevated relative risk of MI, although this risk was only 2–5 fold higher than controls. The strength of this study was the relatively large number of SLE patients examined, while limitations included that CV events were initially identified by self-reporting and many confounders were not controlled for in the statistical analysis (Appendix Table A2).

Studies in other populations have also found that the greatest increase in relative risk for MI is among younger patients, suggesting that SLE patients have premature and accelerated atherosclerosis and cardiac events compared to their healthy peers. In a retrospective analysis of patients admitted to California hospitals between 1991 and 1994, Ward used billing codes to demonstrate that SLE patients were approximately twice as likely to be admitted to the hospital for acute MI compared to age-matched controls, again with the most important increase in relative risk among those patients under 44 years of age [8]. In patients older than 45, there was no difference in the rate of hospitalization for acute MI between those with and without SLE. Ward's findings are particularly significant as he examined the data of over 8000 SLE patients, but are biased by the fact that he looked exclusively at patients who were hospitalized, thus focusing on a more ill subset of the population.

More recently, a population-based study from Sweden by Bengtsson et al. identified SLE patients from rheumatology, internal medicine and dermatology practices as well as all 140 national healthcare centers and 1 private practitioner office in 4 counties in Northern Sweden and compared them to the general population in the same region, specifically evaluating incidence rates of MI and stroke in a 7-year follow-up period [11]. SLE patients had a greater than 2-fold increased risk of MI when compared to the general population over the 7-year follow-up period. Again, the most strikingly elevated relative risk was seen among likely premenopausal female patients, aged 40–49, among

whom there was an 8.7-fold increased risk of MI during the same follow-up period. This study, like that of Ward, looked only at events that required hospitalization and may have missed subacute CV events, but was unique in looking at all SLE patients within a defined geographic region.

Three large population-based studies, 1 in Sweden, 1 in the UK and 1 in the US, found an overall 2- to 3-fold increase in CVD events in SLE patients compared to the general population [6,9,10]. In a 2012 nationwide retrospective study by Zoller et al., all individuals in Sweden hospitalized with a main diagnosis of autoimmune disease without previous or coexisting CVD were followed for first hospitalization for MI or angina [6]. In over 6000 patients hospitalized for SLE between 1964 and 2008, the likelihood of hospitalization for new CVD in the first year after discharge was nearly 5 times that of patients without SLE who were matched for age, socioeconomic status, and multiple medical comorbidities. This relative risk dropped to about 1.6 after 10 years had elapsed from initial hospitalization. As this study only looked at hospitalized patients it may overestimate CVD incidence.

A 2004 study by Fischer et al. employed data from the United Kingdom General Practice Research Database in a case-control analysis [9]. They found that SLE patients, identified through billing codes, had 2.67-times overall relative risk of developing an acute MI compared to patients without SLE. This study included a slightly older group of patients, as greater than 90% of the study population was older than 50 years of age and 50% were 70–89 years of age. In addition, the study was limited by its size, examining only 15 patients with SLE with an inadequate number of controls. In a large prospective population-based study using the Nurses' Health Study, Hak et al. compared rates of CV events among incident SLE patients to rates among participants who were not diagnosed with SLE [10]. They demonstrated a 2- to 3-fold increase in cardiovascular events in the women with SLE compared to the rest of the cohort during the 28-year study period. After adjusting for a number of potential confounding factors including age, hypertension, diabetes, hypercholesterolemia, parental history of CAD before age 60, BMI, physical exercise, smoking status, alcohol consumption, menopause status, use of hormone replacement therapy, race, use of aspirin, NSAIDS and glucocorticoids, they found that the relative risk for any coronary heart disease was slightly greater than 2, with a higher relative risk for coronary artery bypass grafting (CABG) or angioplasty than for MI. The average age of the study participants was 56, again slightly older than in other SLE studies, and the patient population was not necessarily representative of the general SLE population as all participants in the cohort were female nurses and predominantly white (95% of the cohort).

In the 3 studies that performed age-stratified analyses, several of the CAD-risk estimates were not statistically elevated for older SLE populations [7,8,11] (Fig. 2). The heterogeneity among these studies may stem from the different epidemiologic methods employed. For example Ward's study estimated proportionate morbidity ratios for hospitalized patients, while the study by Manzi et al. compared SLE patients followed in an academic cohort study to healthy individuals followed in another community-based cohort study. Additionally, the small sizes of some of the subgroups were likely underpowered to detect risk elevations. The lack of a reproducible risk estimate for CAD in older SLE populations likely also reflects a lower relative risk, due to the increased prevalence of CAD in the general population.

Congestive heart failure (CHF)

Epidemiologic data also suggest that SLE patients have an increased risk of CHF compared to the general population. Our review found only 1 study that compared the risk of CHF among SLE patients to healthy controls [8]. Using the California Hospital Discharge Database, Ward reported that SLE patients were 1-to 3-times more likely to be admitted to the hospital with CHF compared to age- and sex-matched non-SLE counterparts [8]. SLE patients aged 18–44 were 2.61 times more likely to be hospitalized for CHF, whereas 45–64 year old patients had no statistically significant increase in CHF admissions and the oldest age group, over 65 years old, was only 1.26 more likely to be admitted for CHF. Given the low absolute risk of CHF among young healthy individuals, this study highlights the increase in relative risk of CHF in young SLE patients. The underlying cause of CHF (i.e. due to ischemia, hypertension, or valvular heart disease) could not be obtained from this administrative database. However, data from a separate large multicenter cohort of 1249 patients followed over 8 years demonstrated that only 21% (5/24) of the cases of CHF were attributable to atherosclerosis, suggesting that CHF among SLE patients is likely multifactorial in etiology [12].

Cerebrovascular disease

SLE patients have an increased risk of stroke when compared to control populations, similar to that seen for MI and CHF. Our review examined four studies comprising 9657 SLE patients and 177 cerebrovascular events (Fig. 3) [8,10,11,13]. Ward found that in the 18–44 year old age group of SLE patients, the risk of stroke was 1.75 times that of age-matched controls [8]. The increased relative risk diminished with age such that SLE patients over age 65 actually had a somewhat lower overall risk of stroke than controls. Hak et al. reported a 2.29-fold increased risk of stroke among older incident SLE patients compared to other population-based women in the Nurses' Health Study Cohort [10]. Mok et al. similarly found a 2-fold increase in the risk of CVAs among all SLE patients over an 8-year period at a single institution in Hong Kong; this risk was 22-fold higher for the youngest group of SLE patients [13]. Bengtsson et al. further corroborated these results in their population-based Swedish study where they demonstrated that the risk of stroke and/or MI in the total SLE population was 1.27 fold higher than the general population, but among women with SLE aged 40–49 it was 8-fold higher over the 7-year follow-up period [11].

As with the risk estimates of CAD, CVA risk estimates were most strikingly increased for younger SLE patients, but less consistently elevated among older SLE patients (Fig. 3). Again, the small sizes of the subgroups and the different study designs may account for some of the variation in findings [8,11,13]. A major limitation to most of these studies, and certainly to all of the administrative database studies, is the lack of data concerning SLE-related comorbidities, such as hypertension, antiphospholipid syndrome, renal failure, and valvular heart disease in particular.

Peripheral vascular disease (PVD)

Our review found no data regarding the relative risk of PVD among SLE patients compared to population-based controls. Several research groups have reported prevalence rates in SLE cohorts. In the Systemic Lupus International Collaborating Clinics-Registry for Atherosclerosis (SLICC-RAS) cohort, there were 8 cases of PVD among 1249 patients during a 2-year period [12]. In the Lupus in Minorities: Nature vs. Nurture study (LUMINA), a large multicenter, multiethnic inception cohort, 5.3% of 637 patients developed PVD over a mean follow-up of 4.4 years [14]. The average age of this population was young (36.5 years) and, strikingly, a significantly greater percentage of patients with PVD died during this time compared with patients who did not have PVD (32% vs.

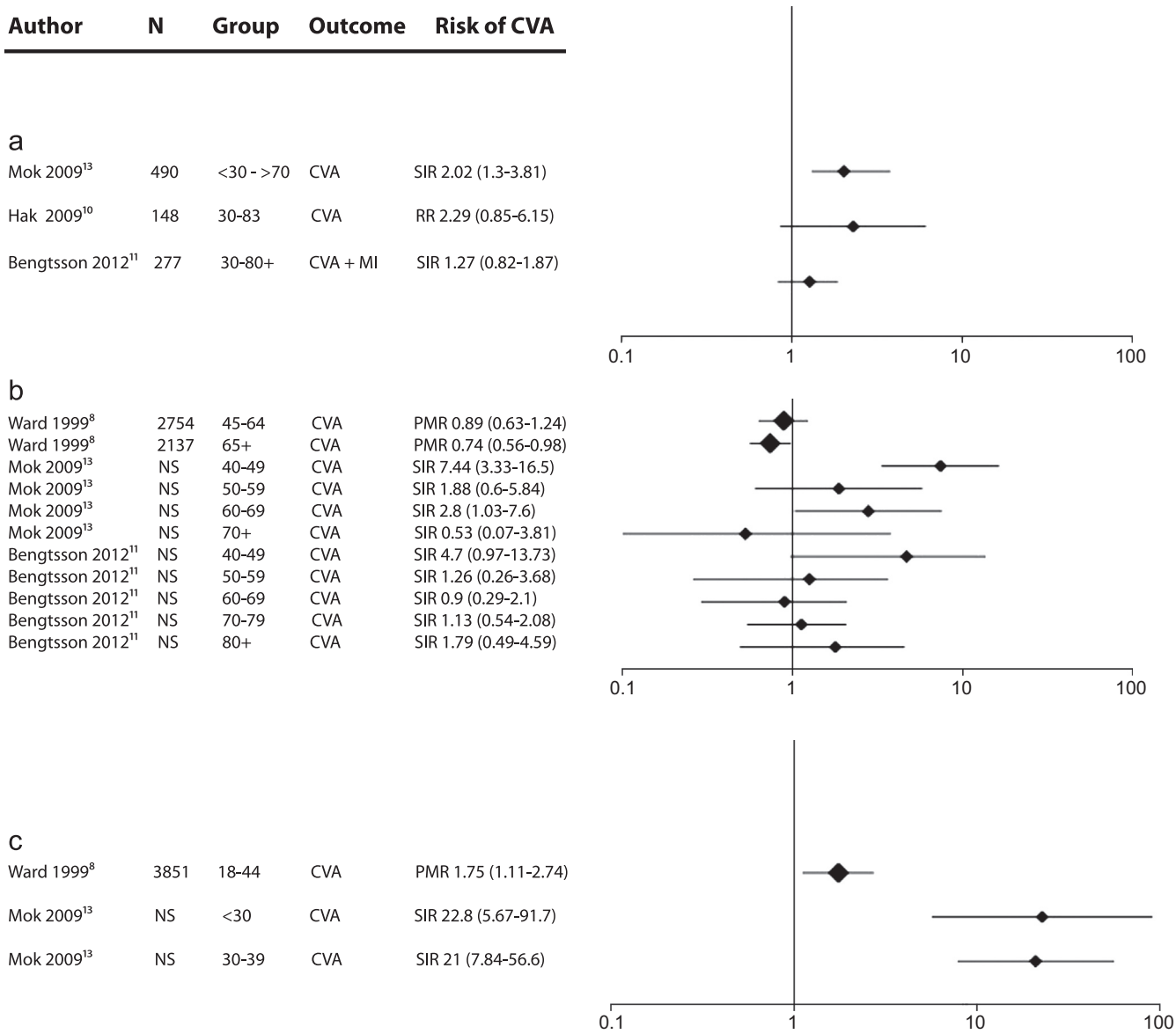

Fig. 3. Forest plots of study effect estimates and population sizes for epidemiologic studies investigating the risk of CVA among SLE patients compared to the general population by age aroup. (a) Studies with all age groups combined. (b) Studies stratified by age group for older SLE patients. (c) Studies stratified by age group for younger SLE patients. *The size of the diamond reflects the size of the study population. *The position of the diamond reflects the risk estimate and the length of the bars reflects the 95% confidence interval. *CVA = cerebrovascular accident, SIR = standardized incidence ratio, RR = relative risk, MI = myocardial infarction PMR = proportionate morbidity ratio, NS = not specified how many patients in each subgroup.

14%, $p = 0.0043$). PVD likely predicts either more severe SLE activity or more widespread atherosclerotic disease.

Risk of CVD mortality in SLE patients

Although there have been multiple studies addressing the increased risk of CVD in SLE patients, the risk of death from CVD among SLE patients compared to controls has not been well described. In the 1 study to address this question, Bjornadal et al. used the Hospital Discharge Register and Cause of Death Register in Sweden [2]. They included 4737 patients with a diagnostic code for SLE discharged from the hospital for the first time between 1964 and 1994 and compared the causes of death to those of the general Swedish population. Although the authors estimated that their study encompassed approximately 80% of the SLE patients in Sweden, their results likely overestimated the increased risk of death from CVD among patients with SLE, given that they included only hospitalized and more severely ill SLE patients. The overall standardized mortality ratio (SMR) for SLE patients compared to the general Swedish population was 3.63. When cause of death was examined, the SMR for any CVD cause of death was 2.97, while for CAD alone it was 3.03. Younger patients were again at higher relative risk for CVD death compared to age-matched controls; patients aged 20–39 at the time of discharge had a 16-fold increased risk of dying from a CVD event compared to controls. As this study spanned 30 years, it was able to track overall and specific causes of death. There was a reduction in all-cause mortality, in particular from infections and renal failure, among SLE patients over time but there were no changes in death rates due to CVD. It could be that, in recent years, as fewer SLE patients succumb to the early complications of disease, they are now living to experience CVD outcomes, despite increasing recognition and better treatment of CVD risk factors.

In summary, we have found strong epidemiologic evidence of at least 2- to 3-fold elevated risks of MI, CHF, cerebrovascular

disease and overall CVD mortality among patients with SLE compared to the general population. There are no epidemiologic studies of PVD risk among patients with SLE. The preponderance of the epidemiologic data point to particularly elevated relative risks of CVD among young patients who have low background CVD risk. However, the risks are also elevated among older SLE patients.

Risk factors for atherosclerosis among SLE patients

Considerable research has focused on identification of SLE patients who are at highest risk for CVD, and specifically on the identification of potentially modifiable risk factors. Both traditional and SLE-related risk factors have been examined (Tables 1 and 2). Through our review process, we identified 20 studies that met criteria for inclusion in our analysis for this section. These included 17 cohort studies and 3 case-control analyses, comprising 10,426 SLE patients (Appendix Table A3).

Traditional CVD risk factors (Table 1)

Hyperlipidemia

The inflammatory milieu of SLE leads to dysregulation of lipid metabolism pathways, which contributes to the increased risk of atherosclerotic disease among SLE patients [15,16]. Five large cohort studies have shown hypercholesterolemia to be a significant risk factor for CVD in SLE patients [7,17–20]. On average, total cholesterol was associated with a 1- to 2-fold increased risk of CVD events in these studies. Goldberg et al. and Touma et al. also found that elevated triglycerides were predictive of CAD, defined as MI or angina [17,21]. Although Touma et al. had a large cohort and was therefore one of the bigger studies, their outcome definition and measurement methods were not clearly defined, making it possible that there would be high risk of bias in these categories (Appendix Table A4). Manzi et al. had a well-established and clearly defined cohort, but they only controlled for age in their multivariable analysis, putting their study at higher risk for potential confounding.

Smoking

Three large cohort studies and 2 smaller Swedish studies have found that smoking acts as an independent risk factor for CVD in SLE patients [22–26]. As part of the LUMINA study, Toloza et al. prospectively followed SLE patients over a median follow-up of 73.8 months and compared those who had a CVD event to those who did not [25]. All patients had been diagnosed with SLE within 5 years of the start of the study and approximately 7% of patients had a CVD event (defined as MI, angina, vascular procedure for ischemic heart disease, stroke or PVD) within the study period. Current cigarette use was significantly associated with a 3.7-times increased risk of having a CVD event. This was a well-designed study made up of a relatively large cohort that controlled for a number of variables in the multivariable analysis, putting their findings at a relatively low risk of bias (Appendix Table A4). Urowitz et al. also found that smoking was associated with a greater than 3-times increased risk of CVD events over an approximately 8-year period in their study of 561 SLE patients from the Toronto inception cohort [26]. This study, too, had an overall low risk of bias by our assessment (Appendix Table A4). In the PROFILE population, another multicenter, multiethnic study population, Bertoli et al. found that smoking acted as an independent risk factor associated with a 2-fold decrease in time to a

Table 1
Traditional Risk Factors Associated with CVD Among SLE patients.

Author	Hyperlipidemia	Smoking	Hypertension	Sex	Age	Diabetes	Family History	BMI	CRP	Homocysteine	Others
Bengtsson et al. [11]	N/A	–	–	–	–	–	N/A	N/A	–	N/A	
Gustafsson et al. [24]	–	+	–	–	–	–	N/A	N/A	+	–	High soluble VCAM1 +, anti-beta2 glycoprotein 1 +, warfarin +
Touma et al. [17]	+	–	+	–	+	–	N/A	N/A	N/A	N/A	Triglycerides +
Yang et al. [42]	–	–	–	–	–	–	–	N/A	N/A	N/A	Creatinine +, proteinuria +, decreased C4 +, anti-Sm +
Nikpour et al. [20]	+	–	+	–	+	–	N/A	N/A	N/A	N/A	
Urowitz et al. [12]	–	–	–	+	+	–	–	–	N/A	N/A	
Haque et al. [28]	–	–	+	–	+	–	+	–	N/A	N/A	
Gustafsson et al. [23]	–	+	–	–	+	–	–	N/A	–	–	Absence of thrombocytopenia +
Burgos et al. [14]	–	–	–	–	+	–	N/A	–	–	–	Warfarin +
Goldberg et al. [21]	–	–	–	–	+	–	–	–	–	–	Triglycerides +
Bertoli et al. [22]	N/A	+	–	–	+	N/A	N/A	N/A	N/A	N/A	CRP genes +
Pons-Estel et al. 2009 [30]	–	–	–	+	+	–	N/A	–	+	N/A	# Years education −
Mikdashi et al. [19]	+	–	+	–	–	–	N/A	–	–	–	
Urowitz et al. [26]	–	+	–	N/A	N/A	–	N/A	N/A	N/A	N/A	
Bessant et al. [29]	–	–	+	N/A	–	N/A	–	N/A	N/A	N/A	
Ruiz-Irastorza et al. [36]	N/A	–	–	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Previous thrombosis +
Toloza et al. [25]	–	+	–	–	+	–	–	–	+	N/A	Follow-up time +
Manzi et al. [7]	+	–	–	N/A	N/A	–	–	N/A	N/A	N/A	Disease duration +, older age at SLE dx +
Petri et al. [34]	–	N/A	–	–	+ (arterial thrombosis, not stroke)	–	N/A	–	N/A	+	
Petri et al. [18]	+	–	+	–	–	–	–	+	N/A	N/A	Age at SLE dx +

Abbreviations: + = statistically significant correlation in multivariate analysis, − = no statistically significant correlation in multivariate analysis, N/A = did not examine variable, BMI=body mass index, CRP=C-reactive protein.

Table 2
SLE-Related Risk Factors Associated with CVD Among SLE Patients.

Author	Disease Activity	Antiphospholipid Abs	Glucocorticoids	Hydroxychloroquine	Azathioprine	Neuropsychiatric Disease
Bengtsson et al. [11]	+	+	−	−	−	N/A
Gustafsson et al. [24]	−	+	−	−	−	−
Touma et al. [17]	+	N/A	−	−	+	N/A
Yang et al. [42]	−	−	−	+	N/A	−
Nikpour et al. [20]	+	−	+	+	−	−
Urowitz et al. [12]	−	N/A	−	−	−	N/A
Haque et al. [28]	−	−	−	−	+	−
Gustafsson et al. [23]	−	+	−	−	−	−
Burgos et al. [14]	−	−	−	−	+	−
Goldberg et al. [21]	−	N/A	−	−	−	N/A
Bertoli et al. [22]	N/A	−	−	−	−	+
Pons-Estel et al. [30]	−	−	−	−	−	−
Mikdashi et al. [19]	+	−	−	N/A	N/A	N/A
Urowitz et al. [26]	−	−	−	−	−	+
Bessant et al. [29]	−	N/A	−	−	N/A	N/A
Ruiz-Irastorza et al. [36]	N/A	+	−	+	−	−
Toloza et al. [25]	−	+	−	−	−	N/A
Manzi et al. [7]	N/A	N/A	−	N/A	N/A	N/A
Petri et al. [34]	N/A	−	N/A	N/A	N/A	N/A
Petri et al. [18]	N/A	−	+	−	N/A	N/A

Abbreviations: + = statistically significant correlation in multivariate analysis, − = no statistically significant correlation in multivariate analysis, N/A = did not examine variable.

cardiovascular event among 1333 SLE patients over a 6.4-year follow-up period [22]. The outcome definitions and measurement methods were not clearly defined in this study, making it difficult to assess the exact methodology. More recently, in a smaller study, Gustafsson et al. found that smoking was a risk factor for CVD mortality (RR 3.4, 95% CI 1.3–9.2) among 208 SLE patients, a conclusion which was consistent with their earlier findings that smoking was predictive of MI, CVA, PVD or CV mortality among the same patient population [23,24]. Both of these studies had a relatively low risk of bias by our domain-based bias assessment. Certainly, smoking cessation should be an important goal for physicians caring for SLE patients.

Hypertension

In the Toronto Lupus Cohort, 33% of 250 SLE patients were hypertensive compared to 13% of 250 age-matched controls ($p = 0.001$) [27]. In the Hopkins Lupus cohort, the presence of hypertension or use of antihypertensive medications were independent risk factors for CVD (RR not defined) [18]. Two smaller retrospective case-control studies have also reported that hypertension or treatment for hypertension were associated with a greater than 2-fold increased risk of CVD [28,29], and 2 recent studies using data from the Toronto Lupus Cohort found that hypertension was associated with a 1- to 2-fold risk of CAD among SLE patients [17,20]. Mikdashi et al. also found that hypertension predicted a greater than 2-fold risk of stroke in SLE patients [19]. A potential concern regarding the study by Haque et al. is that data about participants' lipid status, family history and ethnicity was missing in nearly 20% of the cases.

Sex

While most SLE cohorts are comprised predominantly of women, the risk of CVD events, as in the general population, appears higher among men. In each of the 2 large cohort studies, SLICC and LUMINA, male SLE patients had a nearly 4-fold increased risk of experiencing a CVD event compared to females [12,30]. Although both studies were comprised of large databases and were well conducted, it should be noted that nearly 90% of the patients were females in both studies. Similarly, in a population-based study by Nikpour et al., males had a nearly 2-fold increased risk of MI, angina and sudden cardiac death, although again the cohort was comprised of only 10% males [20]. A strength of the study by Nikpour et al. was that all outcomes were validated by a cardiologist, making the risk of bias for outcome measurement relatively low (Appendix Table A4).

Age

Older age is a relatively consistent independent predictor of CVD events among SLE patients. Gustafsson et al. found the strongest correlation between age and cardiovascular events, with age predicting a 2- to 3-fold increase in CVD events and CVD death [23]. A number of other studies have found a weaker correlation between age and CVD among SLE patients [7,12,14,17,20–22,25,30].

C-reactive protein (CRP)

Unlike in the general population, where high sensitivity CRP has clearly been shown to be associated with increased risk of CVD [31], this finding is less consistent among SLE patients. In the LUMINA study [25,30], as well as in a smaller study involving 208 Swedish SLE patients [24], elevated CRP levels were associated with anywhere between a 1.5 and 3.3 increased CVD risk. However, most of the other large SLE cohorts have not examined CRP in their analyses [7,12,18,26]. Although the 3 studies that found CRP to be associated with CVD were all well designed and executed, it is difficult to draw conclusions about the role of CRP in CVD among SLE patients given the inconsistency in the literature.

Homocysteine

Elevated homocysteine levels may act as an independent risk factor for atherosclerotic CVD in the general population [32,33] and among those with SLE [34]. Petri et al. studied 337 SLE patients and compared homocysteine levels in those patients who had a stroke or thrombotic event versus those who did not over a mean follow-up period of 4.8 years [34]. Twenty-nine patients had a stroke during the follow-up time and 31 patients had an

arterial thrombotic event including thromboembolic stroke, MI, gangrene of the fingers or other arterial thrombosis. After adjusting for age, sex, race, obesity, hypercholesterolemia, hypertension, diabetes, renal insufficiency and presence of the lupus anticoagulant, homocysteine remained an independent predictor of stroke and arterial thrombotic events. One of the strengths of this study lies in the fact that it controlled for a number of important variables in the multivariable analysis.

Diabetes mellitus

None of the studies we identified found that diabetes or treatment for diabetes was an independent risk factor for CVD among SLE patients. Many of the cohort studies have not examined diabetes as a risk factor, again highlighting their heterogeneity [22,29]. Those studies that did include diabetes had small numbers of diabetic patients [26,30].

Obesity

Similarly, obesity has not been frequently examined in relation to CVD risk in SLE populations [7,26,29]. Only 1 study in the early 1990s has reported that obesity was correlated with an increased risk of CVD events (RR not reported) [18]. In summary, there is strong epidemiologic evidence that traditional CVD risk factors also elevate CVD risk among SLE patients.

Disease-specific factors

While traditional CVD risk factors, in particular hypertension, smoking and hyperlipidemia, are undoubtedly important in increasing the CVD risk among SLE patients, studies have shown that these risk factors do not fully account for the elevated risk of CVD in this patient population [3]. Several CVD risk factors related to inflammation and SLE have been identified in epidemiologic studies and are summarized here, although there are inconsistencies in the literature as to which of these are the most predictive (Table 2).

SLE disease activity

The importance of disease activity in predicting CVD outcomes has been variable among different studies. For example, the SLICC cohort found that SLE disease activity, as measured by SLEDAI-2K, was not an independent predictor of CVD events [12]. It is important to note, however, that this study involved an inception cohort of patients who enrolled in the study within 15 months of diagnosis. Given the early stage of disease of these patients, SLE disease-related factors or treatments may not have played as large a role. Other studies have indeed found disease activity to be an important predictor of CVD events [11,17,19,20]. In a recent study of 269 SLE patients in Northern Sweden, Bengtsson et al. found that a higher SLEDAI score predicted both stroke and MI among SLE patients followed over 7 years [11]. It should be noted that this study used information from an inpatient database and would therefore miss events not requiring hospital admission. Nikpour et al. and Touma et al. similarly found that disease activity, as measured by SLEDAI-2K was predictive of a modest increase risk of CAD during a 6- and 37-year follow-up period, respectively. Mikdashi et al. reported that baseline SLEDAI-2K scores were associated with a 2-fold increased risk of stroke within 8 years [17,19,20]. Measures of SLE disease activity, including the SLEDAI, BILAG and SLAM, used in many of the studies we reviewed, have been criticized as being insensitive and may not accurately capture systemic inflammation that could drive atherosclerosis.

SLE disease duration

We identified only 2 studies that examined duration of SLE as a risk factor for incident CVD event and they arrived at no clear consensus. Manzi et al. found that longer disease duration appeared to be protective for CVD (rate ratio 0.82, 95% CI 0.74–0.92) among women in the Pittsburgh SLE Cohort [7]. Toloza et al., however, reported that increasing duration of SLE was associated with increased risk of all types of vascular events in the LUMINA cohort study [25]. Not only is accurately defining SLE disease duration a challenge, but several variables, including age itself, as well as SLE-related damage and total cumulative-steroid dose, all parallel increases in SLE disease duration.

Neuropsychiatric disease

Although likely a proxy for more severe disease and potentially for increased glucocorticoid use, a number of studies have demonstrated a correlation between neuropsychiatric SLE and an increased risk of cardiovascular events. In particular, Urowitz et al. found that neuropsychiatric disease predicted a nearly 4-fold increased risk of cardiovascular events including MI, angina, TIA, stroke, PVD and sudden death [26]. In another large study, Bertoli et al. found that both psychosis and seizure were independent predictors of time to a CVD event, although again it should be noted that it was not clear how these outcomes were assessed in this study [22].

Antiphospholipid antibodies

The antiphospholipid antibody syndrome is characterized by an increased risk of stroke and MI [35], and many studies have therefore tried to determine whether the presence of antiphospholipid antibodies may be an independent risk factor for CVD among SLE patients. In the LUMINA study, the presence of a positive antiphospholipid antibody was significantly associated with 4-times increased risk of having a CVD event over a median of approximately 6 years [25]. The presence of antiphospholipid antibodies was also associated with a greater than 4-fold increased risk of first time MI, stroke or PVD in a study of 182 SLE women followed for a mean of 8.3 years, and a later study by the same group again demonstrated that a positive antiphospholipid antibody titer predicted a greater than 2-fold increased risk of CVD related mortality [23,24]. Bengtsson et al. found that anticardiolipin IgG predicted a 3-fold increased risk of stroke, but not MI, in their study of 269 SLE patients [11]. Finally, in a Spanish study by Ruiz-Irastorza et al. the presence of a positive antiphospholipid Ab was associated with a nearly 3-fold risk of thrombosis or death, but it should be noted that DVT and PE were included in this analysis as well as atherosclerotic vascular events [36]. In addition, this study controlled for relatively few factors in their multivariable analysis, placing their findings at a higher risk of bias.

Glucocorticoids

In general, the examination of medications and risk of CVD is problematic in that there may be much confounding by indication. More severely ill SLE patients are more likely to receive glucocorticoids and other immunosuppressants, while those with milder disease may be more likely to receive hydroxychloroquine alone. The relationship between glucocorticoid use and CVD risk among SLE patients is difficult to fully elucidate as increasing

glucocorticoid dose is strongly correlated with increased disease activity [37]. While glucocorticoids decrease systemic inflammation, thereby having the potential to decrease atherogenesis, their use correlates with exacerbation of multiple traditional risk factors, including total cholesterol, blood glucose, body mass index and systolic blood pressure [37]. Petri et al. demonstrated that longer duration of glucocorticoid use was independently associated with incident CVD events although the relative risk was not quantified in that study [18]. Nikpour et al. also found that glucocorticoid use independently predicted a 2-fold increase in the risk of MI, angina and sudden cardiac death (RR 2.01, 95% CI 1.19–3.41) [20], but other studies have not replicated these findings [7,12,25,26,29,30]. Part of the discrepancy among studies may stem from the different ways in which glucocorticoid use has been quantified, including duration of use and maximum, current or total dose [11,12,18,20,23,26,30], and the difficulty of separating disease activity from glucocorticoid use.

Hydroxychloroquine

It has been clearly demonstrated that hydroxychloroquine has a favorable effect on lipid profiles and glycemic control among SLE patients [38–40]. Whether hydroxychloroquine has an effect on CVD outcomes is less clear, although it has been associated with increased survival among patients with SLE [41]. Nikpour et al. and Ruiz-Irastorza et al. both found that hydroxycholoroquine use conferred a 50–60% decrease in risk of CVD events [20,36]. Similarly, a small retrospective case-control study in China found that hydroxychloroquine use was protective against the development of CVD, although there were only 28 SLE patients in this analysis and the authors controlled for few variables in their multivariable analysis [42].

Azathioprine

Finally, 2 studies have reported that azathioprine use is an independent risk factor for CVD among SLE patients, predicting a 3-fold increased risk of PVD in 1 study [14] and of MI and angina in another [28]. In a study by Touma et al., immunosuppressive medications including azathioprine were associated with an increased risk of CAD [17]. Most studies have not examined azathioprine as an independent predictor; and azathioprine, like glucocorticoid use, is correlated with more severe SLE. In summary, SLE-related factors that have been demonstrated to be associated with increased CVD risk include physician's assessment of SLE activity, neuropsychiatric lupus, antiphospholipid antibodies, and potentially glucocorticoid and azathioprine therapy [11,14,17–20,22–26,28,36,42]. The discrepancies between studies as to the relative importance of the factors may be due to different methodologies and study designs. In addition, most of these factors are highly correlated. Increasing age and longer duration of SLE are strongly associated, for example, as are SLE disease activity measures and use of glucocorticoids and immunosuppressants [37]. Despite the variability in study design and covariates, it is clear that while young patients have the most profound increase in CVD risk, relative to the low absolute risk for their age group, both SLE disease activity and glucocorticoid use increase the absolute risk of CVD for an SLE patient.

A number of other traditional and disease-specific risk factors have been shown in single studies to be predictors of CVD among SLE patients. These include number of years of education, family history of CVD, warfarin use, cystatin C level, absence of thrombocytopenia, proteinuria, anti-Smith Ab, soluble VCAM level, B2GP1 and the CPR2C allele [14,22–24,30,42]. While many of these variables may represent true risk factors, we do not feel that these can be classified as definitive risk factors at this time given the paucity of reproducible data.

Discussion

The epidemiologic data strongly support that SLE patients are at elevated relative risk of CVD. The risks of MI, CHF, CVA and CVD mortality are all increased among SLE patients compared to general population risks. Younger patients with SLE have the greatest relative risk compared to their healthy counterparts, but the absolute risk of CVD among SLE patients increases with advancing age.

From the epidemiologic studies to date, it appears that traditional CVD risk factors, including hyperlipidemia, cigarette smoking, advancing age, hypertension, male sex, and elevated C-reactive protein are all associated with increased CVD risk among SLE patients. However, past studies have not simultaneously examined all of these risk factors in the same populations, so comparisons of the relative risk associated with each are not possible. In addition to traditional CVD risk factors, several SLE-associated factors have also been predictive of CVD risk in past cohort studies. These include increased SLE disease activity, potentially neuropsychiatric SLE manifestations in particular, and use of azathioprine and glucocorticoids (which are inextricably linked to disease severity). Antiphospholipid antibodies in SLE patients are clearly related to increased risk of CVAs, but less clearly to increased risk of atherosclerotic CVD. The variability regarding the relative importance of risk factors for CVD among SLE patients in past epidemiologic studies is likely due in part to different design methods and different patient and comparison groups. In addition, there are inconsistencies with regard to which factors are considered simultaneously in multivariable models, and it is difficult to separate inherently related factors. Unfortunately, many SLE-related factors, such as disease activity, organ damage and antiphospholipid antibodies are not included in administrative data.

It has been proposed that SLE should be treated as a "CVD equivalent" such as diabetes mellitus is, with lower lipid goals, more aggressive aspirin use and potentially more aggressive monitoring [43]. For the physician caring for a patient with SLE, the implications of the studies reviewed here include that aggressive screening and management of traditional CVD risk factors should be the goal. All modifiable risk factors, in particular hyperlipidemia, hypertension and smoking, should be addressed in an effort to reduce CVD risk. It has not yet been proven, however, that this effort will reduce CVD risk to the same extent as in the general population. Recent studies have started to address whether traditional treatment regimens may prevent or slow atherosclerosis in SLE patients. The recent randomized controlled Lupus Atherosclerosis Prevention Study by Petri et al. suggests that atorvastatin did not in fact slow progression of subclinical atherosclerosis in 200 SLE patients over 2 years [44]. A similar trial in a pediatric SLE population also did not show any effect of atorvastatin on the progression of carotid IMT [45].

Another implication for treating physicians is that SLE disease activity contributes to CVD risk and treating it to reduce disease-related inflammation should also be an objective. There is an expanding field of literature suggesting that antiinflammatory and SLE-specific agents may modulate CVD risk factors in rheumatic diseases. A recent study examining whether mycophenolate mofetil use was correlated with a reduction in subclinical atherosclerotic progression did not show an effect, although this was a small study with a relatively short period of follow-up [46]. As further biomarkers and molecular pathways of atherogenesis among SLE patients are identified, the hope is that we will be able to better stratify patients to prevent and treat complications of atherosclerosis in this population.

Table A1
Data Extraction Sheet for Studies Investigating Risk of CVD Among SLE Patients Compared to the General Population.

Author	Date Published	Population	Language	Study Design	Duration	Gender	Age	Race	Country	Outcome Definition	Results	Funding Source
Bengtsson et al. [11]	2012	277 SLE cases, Northern Sweden; 554 controls, Northern Sweden	English	Prospective cohort	7 years	84.5% F	51.2 (mean)	Not specified	Sweden	SIR for CVE (MI and MI/stroke); time to event	CVE = 1.27 (95% CI 0.82–1.87); CVE for F aged 40–49 = 8.00 (95% CI 1.65–23.38); MI = 2.31 (95% CI 1.34–3.7); MI for F = 1.75 (95% CI 0.84–3.22); MI for M 2.9 (05% CI 1.16–5.98); MI for F aged 40–49 = 8.7 (95% CI 1.1–31.4).	County council for Northern Sweden, Umea, Sweden and Research Development Department, Jamtland County Council, Sweden
Zoller et al. [6]	2012	6142 SLE cases hospitalized for SLE w/o h/o CHD, Sweden; controls total population of Sweden	English	Retrospective cohort	45 years	60.3% F (IMD); 42.7% F (controls)	50 to >70, age stratified	Not specified	Sweden	SIR for CHD (MI, angina)	1 year f/u = 4.94 (95% CI 4.15–5.83); for all years f/u = 2.27 (95% CI 2.14–2.42)	Swedish Research Council, Swedish Council for Working Life and Social Research, Formas, and Region Skane
Hak et al. [10]	2009	148 SLE cases, Nurses Health Study; 119,184 controls, Nurses Health Study	English	Prospective cohort	28 years	100% F	56 (mean)	SLE: 95% White, 4% Black; Non-SLE: 97% White, 2% Black	USA	RR for total CVD, CHD (MI, CABG, angioplasty), CVA	CVD = 2.26 (95% CI 1.45–3.52); CHD = 2.25 (95% CI 1.37–3.69); CVA = 2.29 (95% CI 0.85–6.15)	NIMH, NIAID, NICHHD, NIH
Mok et al. [13]	2009	490 SLE cases, rheumatol-ogy and lupus clinic Tuen Mun Hospital, Hong Kong; controls hospitalized for CVA at same hospital	English	Retrospective cohort	8 years	92% F	46.4 (mean)	Not specified	Hong Kong	SIR for CVA	Total = 2.02 (95% CI 1.3–3.81); age <30 = 22.8 (95% CI 5.67–91.7); age 30–39 = 21 (95% CI 7.84–56.5); age 40–49 = 7.44 (95% CI 3.33–16.6); age 50–59 = 1.88 (95% CI 0.6–5.84); age 60–69 = 2.8 (1.03–7.6); age >70 = 0.53 (95% CI 0.07–3.81)	Not specified

Fischer et al. [9]	2004	15 SLE cases with first time AMI, GPRD UK; 26 controls same database	English	Case control	7 years	46.6% F (SLE); 73% F (controls)	≤ 89	Not specified	UK	OR of 1st time MI	MI = 2.67 (95% CI 1.34–5.34)	Study not directly funded (support from Swiss NSF, EU grant, Bundesamt fur Bildung und Wissenschaft)
Ward [8]	1999	8742 SLE cases hospitalized for CVD, California Hospital Discharge Database; 43,710 controls, same database	English	Case control	4 years	100% F	18 to > 65, age stratified	SLE: 56% White, 18% Black, 17% Hispanic; Controls: 65% White, 12% Black, 16% Hispanic	USA	PMR for MI, CHF, and CVA as reason for hospitalization	For MI: age 18–44 = 1.83 (95% CI 1.03–3.26), age 45–64 = 1.02 (95% CI 0.77–1.34), age > 65 = 0.71 (95% CI 0.54–0.94); for CHF: age 18–44 = 2.61 (95% CI 1.74–3.92), age 45–64 = 1.24 (0.95–1.61), age > 65 = 1.26 (1.03–1.54); for CVA: age 18–44 = 1.75 (95% CI 1.11–2.74), age 45–64 = 0.89 (0.63–1.24), age > 65 = 0.74 (0.56–0.98)	Unknown
Manzi et al. [7]	1997	498 SLE cases, UPMC; 2208 controls, Framingham Offspring Study	English	Retrospective cohort	14 years	100% F	15–74, age stratified	SLE: 76% Caucasian, 22% African American, 2% American Indian, Asian American, and Eastern Indian: Control: 100% Caucausian	USA	Rate ratio for CVE (MI or angina pectoris)	For MI: age 35–44 = 52.43 (95% CI 21.6–98.5), age 45–54 = 2.47 (95% CI 0.9–3.6), age 55–64 = 4.21 (95% CI 0.6–4.6); for angina: age 35–44 = 2.35 (95% CI 0.4–11.1)	Commonwealth of Pennsylvania (Department of Health); Lupus Foundation of America, Western Pennsylvania Chapter; and Pennsylvania Lupus Foundation, Inc.

Abbreviations: SIR = standardized incidence ratio, CVE = cardiovascular event, MI = myocardial infarction, CI = confidence interval, CHD = coronary heart disease, CVD = cardiovascular disease, RR = relative risk, CABG = coronary artery bypass grafting, CVA = cerebrovascular accident, OR = odds ratio, PMR = proportionate morbidity ratio.

Table A2
Risk of Bias for Studies Investigating Risk of CVD Among SLE Patients Compared to the General Population.

Author	Population	Study Design	Selection Bias		Measurement Bias			Control for Confounders	Comments
			Representative of Population	Participation Rate	Recall Bias	Outcome Definition	Outcome Measurement Method		
Bengtsson et al. [11]	277 SLE cases, Northern Sweden; 554 controls, Northern Sweden	Prospective cohort	L	L	N/A	L	L	L	Database for inpatient admissions and death; would miss events not requiring hospitalization
Zoller et al. [6]	6142 SLE cases hospitalized for SLE w/o h/o CHD, Sweden; controls total population of Sweden	Retrospective cohort	H	L	N/A	L	L	L	Only hospitalized patients with SLE, so likely studying a sicker population
Hak et al. [10]	148 SLE cases, Nurses Health Study; 119,184 controls, Nurses Health Study	Prospective cohort	H	L	H	L	L	L	All women cohort, all nurses, slightly higher SES; for CABG and angiography relied on participant recall of event
Mok et al. [13]	490 SLE cases, rheumatology and lupus clinic Tuen Mun Hospital, Hong Kong; controls hospitalized for CVA at same hospital	Retrospective cohort	L	L	L	L	L	H	Control group was only patients hospitalized for CVA; do not describe baseline characteristics of control group or which variables they control for
Fischer et al. [9]	15 SLE cases with first time AMI, GPRD UK; 26 controls same database	Case control	H	L	N/A	L	L	L	Small number of patients with SLE; over 50% male without adequate number of controls
Ward [8]	8742 SLE cases hospitalized for CVD, California Hospital Discharge Database; 43,710 controls, same database	Case control	H	L	N/A	L	L	L	All women and only hospitalized patients
Manzi et al. [7]	498 SLE cases, UPMC; 2208 controls, Framingham Offspring Study	Retrospective cohort	L	L	H	L	L	H	Relied on self-reporting and reviewed charts only of self-reported events

Abbreviations: H = high risk that methodology may have resulted in bias in the specified domain, L = low risk that methodology may have resulted in bias in the specified domain, N/A = not applicable.

Table A3
Data Extraction Sheet for Studies Investigating Risk Factors for CVD Among SLE Patients.

Author	Date of Publication	Population	Language	Study Design	Duration	Gender	Age	Race	Country	Outcome Definition	Results	Funding Source
Bengtsson et al. [11]	2012	277 SLE cases, Northern Sweden	English	Prospective cohort	7 years	85% F	51.2 (mean)	Not specified	Sweden	Time to CVE (MI, stroke)	aCL IgG Ab 3.08 (95% CI 1.32–7.17); high SLEDAI 1.16 (1.06–1.26)	County council for Northern Sweden, Umea, Sweden and Research Development Department, Jamtland County Council, Sweden
Gustafsson et al. [24]	2012	208 SLE cases, Karolinska University Hospital	English	Prospective cohort	12 years	89% F	47 (mean)	94% Caucasian	Sweden	Overall mortality, nonvascular mortality,CVD mortality	For CVD mortality adjusted for age, previous arterial disease, cystatin C: Smoking 3.4 (95% CI 1.3–9.2); aB2GP1 3.4 (95% CI 1.2–9.7); any aPL medium titer 2.8 (95% CI 1.0–8.2); warfarin use 3.4 (95% CI 1–10.4); hsCRP 1.6 (95% CI 1.1–2.3); soluble VCAM1 5.3 (95% CI 1.3–19.3). Controlled only for age: Cystatin C 5.3 (95% CI 2–13), arterial disease 5.4 (95% CI 2.1–13.6)	Swedish Heart-Lung Foundation, Stockholm County Council and Karolinska Institutet (ALF), Swedish Rheumatism Association etc
Touma et al. [17]	2012	1289 SLE cases, University of Toronto	English	Prospective cohort	37 years	90% F	39 (mean fasting), 35 (mean nonfasting)	Not specified	Canada	CAD (MI, angina)	TG (nonfasting and fasting) 1.15 (95% CI 1.02–1.29); age 1.06 (95% CI 1.04–1.08); SLEDAI-2K 1.07 (95% CI 1.03–1.11); hypertension 1.7 (95% CI 1.07–2.7); elevated total cholesterol 1.64 (95% CI 1.05–2.55); in stepwise, Immunosuppressive meds 1.71 (95% CI 1.09–2.66)	Lupus Ontario Geoff Carr Fellowship,University of Toronto Arthritis Centre of Excellence Fellowship, The Lupus Flare Foundation, Arthritis and Autoimmune Centre Foundation, Toronto General-Toronto Western Hospital Foundation and Smythe Foundation

Table A3 (*continued*)

Author	Date of Publication	Population	Language	Study Design	Duration	Gender	Age	Race	Country	Outcome Definition	Results	Funding Source
Yang et al. [42]	2012	139 SLE cases, Union Hospital, Tongji Medical College, China; 139 controls, same hospital	English	Retrospective case control	N/A	84% F	34 (mean)	Not specified	China	CVD (MI, angina, PAD, pulmonary HTN, valvular disease, cerebral ischemia)	Elevated serum creatinine 2.126 (95% CI 2.004–5.325); presence of proteinuria 2.416 (95% CI 1.736–7.516); anti-Sm antibody 4.727 (95% CI 1.136–21.336); decreased C4 0.008 (95% CI 0.002–0.337); hydroxychloroquine 0.067 (95% CI 0.014–0.735)	National Natural Science Fund Program from National Natural Science Foundation of China
Nikpour et al. [20]	2011	991 SLE cases, University of Toronto	English	Prospective cohort	6.4 years	89% F	37 (mean)	70% Caucasian; 11% Black, 11% Asian	Canada	CAD events (MI, angina, sudden cardiac death)	Time dependent model: older age 1.13 (95% CI 1.06–1.20); male sex 1.83 (95% CI 1.01–3.29); SLEDAI-2K 1.10 (95% CI 1.06–1.14); corticosteroid use 2.01 (95% CI 1.19–3.41); total cholesterol 2.07 (1.28–3.36). Time constant model: also hydroxychloroquine 0.50	Centre for Prognosis Studies in The Rheumatic Diseases, The Smythe Foundation, Lupus Flare Foundation, Ontario Lupus Association, and The Lupus Society of Alberta
Urowitz et al. [12]	2010	1289 SLE cases, SLICC Cohort	English	Prospective cohort	8 years	89% F	Not specified	White 49%, African American 15%, Hispanic 16%, Asian 16%	Multinational (11 countries in North America, Asia, Europe)	Atherosclerotic vascular event (CVA, CHF, TIA, PVD, MI, angina, PPM insertion)	Older age at diagnosis 1.08 (95% CI 1.05–1.11); male sex 3.67 (95% CI 1.41–9.52)	Multiple
Haque et al. [28]	2010	53 SLE cases, centers from BILAG and British Society of Rheumatology Lupus Special Interest Group; 96 controls, same centers	English	Retrospective case control	N/A	80% F (cases); 93% F (controls)	53 (cases mean)	Not specified	United Kingdom	CHD (MI or angina)	HTN 2.56 (95% CI 1.05–6.25); family history 3.62 (95% CI 1.15–11.34); azathioprine 3.18 (95% CI 1.33–7.59)	Lupus UK

Gustafsson et al. [23]	2009	182 SLE cases, Karolinska University Hospital	English	Prospective cohort	8.3 years	90% F	45 (mean)	94% Caucasian, 6% Asian	Sweden	CVE (MI, angina, CVA, TIA, PVD, or death due to CVD)	Age 2.39 (95% CI 1.71–3.32); thrombocytopenia 0.35 (95% CI 0.08–0.77); positive aPL 4.23 (95% CI 1.56–14.83); von Willebrand factor 1.97 (95% CI 1.16–3.33)	Swedish Heart-Lung Foundation, Swedish Rheumatism Association, Centre of Gender related Medicine at Karolinska Institute etc.
Burgos et al. [14]	2009	637 SLE cases, LUMINA Cohort	English	Prospective cohort	4.4 years	90% F	36.5 (mean)	Texan-Hispanic 18%, Puerto Rican-Hispanic 16%, African-American 37% and Caucasian 28%	USA	Peripheral vascular damage by SDI	Age 1.05 (95% CI 1.01–1.08); damage Index 1.3 (95% CI 1.09–1.56); azathioprine 3.2 (95% CI 1.34–7.64); warfarin 6.16 (95% CI 2.43–15.59); statin 0.2 (95% CI 0.05–0.8)	National Institute of Arthritis and Musculoskeletal and Skin Diseases, NCRR/HIH, RCRII, STELLAR
Goldberg et al. [21]	2009	241 SLE cases, University of Toronto SLE Clinic	English	Prospective cohort	7.2 years	100% F	44.2 (mean)	SLE: 77% White, 10% Black, 6% Chinese, 7% Other; Controls: 89% White, 3% Black, 5% Chinese, 3% Other	Canada	CAD (MI and angina)	Age 1.08 (95% CI 1.04–1.12); total TG 7.96 (95% CI 2.65–23.97); SLE 4.23 (95% CI 1.49–11.97)	Heart and Stroke Foundation, The Ontario Lupus Association, and the Lupus Flare Foundation
Bertoli et al. [22]	2009	1333 SLE cases, PROFILE Cohort	English	Prospective cohort	6.4 years	90% F	35.7 (mean)	10.4% Texan Hispanics; 7.7% Puerto Rican Hispanics; 35.4% African-Americans; 46.5% Caucasians	USA	Time to CVE (MI, angina, vascular procedure for MI, CVA, claudication, gangrene or tissue loss)	Current smoking 2.2 (95% CI 1.4–3.46); CRP2*C alleles 1.91 (95% CI 1.04–3.49); age at cohort enrollment 1.04 (95% CI 1.03–1.06); arthritis 0.32 (95% CI 0.18–0.58); psychosis 2.21 (95% CI 1.18–4.44); seizures 1.85 (95% CI 1.05–3.24); SDI 1.1 (95% CI 1.0–1.22); anemia 1.83 (95% CI 1.02–3.31)	National Institute of Arthritis and Musculoskeletal and Skin Diseases; National Center for Research Resources/National Institutes of Health RCMI Clinical Research Infrastructure Initiative; Bristol Myers Squibb educational grant; General Clinical Research Centers
Pons-Estel et al. [30]	2009	637 SLE cases, LUMINA Cohort	English	Prospective cohort	6.6 years	90% F	36.8 (mean)	Texan-Hispanic 18%, Puerto Rican-Hispanic 16%, African-American 37% and Caucasian 28%	USA	CVE (angina, CABG, MI, CHF)	Age 1.06 (95% CI 1.03–1.09); male sex 3.57 (95% CI 1.35–9.09); highest tertile CRP 2.63 (95% CI 1.17–5.91); disease damage (SDI excluding CV domain) 1.28 (95% CI 1.09–1.5); # years education 0.84 (95% CI 0.74–0.94)	National Institute of Arthritis and Musculoskeletal and Skin Diseases, General Clinical Research Centers, National Center for Research Resources (NCRR/NIH) RCMI Clinical Research Infrastructure Initiative (RCRII), STELLAR

Table A3 (*continued*)

Author	Date of Publication	Population	Language	Study Design	Duration	Gender	Age	Race	Country	Outcome Definition	Results	Funding Source
Mikdashi et al. [19]	2007	232 SLE cases, Maryland Lupus Clinic	English	Prospective cohort	8 years	90% F	Not specified	66% Black	USA	Ischemic stroke, severe ischemic stroke (NIHSS ≥ 6)	Any stroke: HTN 2.31(95% CI 1.15–4.65); cholesterol 1.09 (95% CI 1.02–1.16); baseline SLEDAI 2.09 (95% CI 1–4.6). Severe stroke: HTN 3.17 (95% CI 1.38–7.32); cholesterol 1.12 (95% CI 1.04–1.21); baseline SLEDAI 2.56 (95% CI 1.0–6.4)	Office of Research and Development, Medical Research Service, the Baltimore Research Enhancement Award Program in Stroke and the Baltimore Geriatrics Research, Education, and Clinical Center of the Department of Veterans Affairs; NINDS; NIH ORWH; NIA
Urowitz et al. [26]	2007	1087 (total), 561 (inception) SLE cases, University of Toronto	English	Prospective cohort	8.4 years	96% F	31.9 (mean)	79% Caucasian, 8% Blacks, 7% Chinese, and 6% Other	Canada	Atherosclerotic vascular events (MI, angina, PVD, TIA, stroke, sudden death)	Inception Cohort: Neuropsychiatric disease 3.7 (95% CI 1.33–10.32); smoking 3.28 (95% CI 1.14–9.43). Total cohort: Neuropsychiatric disease 2.19 (95% CI 1.05–4.59); vasculitis 2.26 (95% CI 1.22–4.17); # of CAD-risk factors 1.76 (95% CI 1.26–2.47)	The Arthritis Society, Canadian Institutes for Health Research, and the Krembil Foundation
Bessant et al. [29]	2006	29 SLE cases w/o CVD, Birmingham Lupus Cohort; 58 SLE cases w/o CVD, same cohort	English	Retrospective Case Control	N/A	83%F	48 (mean)	72% White, 17% Asian, 10% African Caribbean	United Kingdom	CVD (MI, angina, cerebral infarction, PVD)	Age matched controls: Treatment for HTN (no OR reported). Duration matched controls: treatment for HTN (no OR reported)	Lupus UK, Arthritis Research Campaign, and the Wellcome Trust Clinical Research Facility
Ruiz-Irastorza et al. [36]	2006	232 SLE cases, IM Department Hospital de Cruces, University of the Basque Country, Spain	English	Prospective cohort	10.6 years	88% F	36.2 (mean)	99% White	Spain	Thrombosis (DVT, PE, MI, PVD, stroke, TIA), death from any cause	Antimalarials 0.28 (95% CI 0.08–0.90); aPL Ab positive 3.16 (95% CI 1.45–6.88); previous thrombosis 3.85 (95% CI 1.50–9.91)	Not specified

Toloza et al. [25]	2004	546 SLE cases, LUMINA Cohort	English	Prospective cohort	73.8 months (median)	90% F	36.5 (mean)	35.1% Hispanic, 36.6% African American, 28.4% Caucasian	USA	CVE (MI, angina, vascular procedure, CABG, CVA, TIA, PVD)	Age 1.075 (95% CI 1.037–1.114); current smoking 3.731 (95% CI 1.391–10.000); follow-up time 1.452 (95% CI 1.223–1.725); CRP 3.356 (95% CI 1.264–8.929); aPL Ab 4.717 (95% CI 1.675–13.158); azathioprine 1.452 (95% CI 1.215–10.378)	NIH etc
Manzi et al. [7]	1997	498 SLE cases, UPMC	English	Retrospective cohort	14 years	100% F	15–74, age stratified	SLE: 76% Caucasian, 22% African American, 2% American Indian, Asian American, and Eastern Indian: Control: 100% Caucausian	USA	CVE (MI/angina)	Disease duration 0.83 (95% CI 0.74–0.92); hypercholesterolemia 3.35 (95% CI 1.34–8.36); older age at diagnosis 1.21 (95% CI 1.09–1.35)	Commonwealth of Pennsylvania (Department of Health); Lupus Foundation of America, Western Pennsylvania Chapter; and Pennsylvania Lupus Foundation, Inc.
Petri et al. [34]	1996	337 SLE cases, Johns Hopkins Lupus Cohort	English	Prospective cohort	4.8 years	93% F	34.9 (mean)	54% African American, 45% White	USA	Stroke, arterial thrombotic events (thromboembolic stroke, MI, gangrene of fingers, other), venous thrombotic events (DVT, Budd Chiari)	Stroke: homocysteine 2.44 (95% CI 1.04–5.75)	National Institutes of Health, American Heart Association; the Arthritis Foundation; General Clinical Research Center, USDA
Petri et al. [18]	1992	229 SLE cases, Johns Hopkins Lupus Cohort	English	Prospective cohort	3 years	93% F	34.9 (mean)	54% African American, 45% White	USA	CAD (MI, angina, sudden death)	HTN, hyperlipidemia, obesity, age at SLE diagnosis, duration of glucocorticoid use	NIH

Abbreviations: CVE = cardiovascular event, MI = myocardial infarction, CI = confidence interval, CVD = cardiovascular disease, MI = myocardial infarction, PAD = peripheral vascular disease, HTN = hypertension, CAD = coronary artery disease, CVA = cerebrovascular disease, CHF = congestive heart failure, TIA = transient ischemic attack, PVD = peripheral vascular disease, PPM = permanent pacemaker, CHD = coronary heart disease, CABG = coronary artery bypass grafting, DVT = deep vein thrombosis, PE = pulmonary embolism.

Table A4
Risk of Bias for Studies Investigating Risk Factors for CVD Among SLE Patients.

Study	Population	Study Design	Selection Bias		Measurement Bias			Control for Confounders	Comments
			Representative pop	Participation Rate	Recall Bias	Outcome Definition	Outcome Measurement Method		
Bengtsson et al. [11]	277 SLE cases, Northern Sweden	Prospective cohort	L	L	N/A	L	L	L	Database for inpatient admissions and death; would miss events not requiring hospitalization
Gustafsson et al. [24]	208 SLE cases, Karolinska University Hospital	Prospective cohort	L	UTD	N/A	L	L	L	Unclear how population was chosen from the hospital
Touma et al. [17]	1289 SLE cases, University of Toronto	Prospective cohort	L	L	UTD	UTD	UTD	L	Unclear how outcomes and measurement are defined
Yang et al. [42]	139 SLE cases, Union Hospital, Tongji Medical College, China; 139 controls, same hospital	Retrospective case control	L	UTD	H	L	L	H	Relied on patient reporting of outcomes; only patient reported events were confirmed by medical record review
Nikpour et al. [20]	991 SLE cases, University of Toronto	Prospective cohort	L	L	L	L	L	L	Outcomes validated by a cardiologist
Urowitz et al. [12]	1289 SLE cases, SLICC Cohort	Prospective cohort	L	L	N/A	L	H	L	Relied on physician judgment of SLE vs. atherosclerotic event; did use imaging in cases to confirm
Haque et al. [28]	53 SLE cases, centers from BILAG and British Society of Rheumatology Lupus Special Interest Group; 96 controls, same centers	Retrospective case control	H	L	N/A	L	H	H	Missing up to 20% of information regarding hyperlipidemia, FH, ethnicity
Gustafsson et al. [23]	182 SLE cases, Karolinska University Hospital	Prospective cohort	L	L	L	L	L	L	
Burgos et al. [14]	637 SLE cases, LUMINA Cohort	Prospective cohort	L	L	N/A	L	L	L	
Goldberg et al. [21]	241 SLE cases, University of Toronto SLE Clinic	Prospective cohort	L	L	H	L	L	L	Controls only followed through telephone interviews; potential for high recall bias for controls
Bertoli et al. [22]	1333 SLE cases, PROFILE Cohort	Prospective cohort	L	L	UTD	L	UTD	L	Unclear how outcomes are measured
Pons-Estel et al. [30]	637 SLE cases, LUMINA Cohort	Prospective cohort	L	L	N/A	L	L	L	
Mikdashi et al. [19]	232 SLE cases, Maryland Lupus Clinic	Prospective cohort	L	L	N/A	L	L	L	Conducted at potential referral center for neuropsychiatric SLE
Urowitz et al. [26]	1087 (total), 561 (inception) SLE cases, University of Toronto	Prospective cohort	L	L	N/A	L	L	L	
Bessant et al. [29]	29 SLE cases w/ CVD, Birmingham Lupus Cohort; 58 SLE cases w/o CVD, same cohort	Retrospective Case Control	L	L	L	L	L	L	
Ruiz-Irastorza et al. [36]	232 SLE cases, IM Department Hospital de Cruces, University of the Basque Country, Spain	Prospective cohort	H	L	N/A	L	L	H	8% lost to follow-up; included PE and DVT as thrombosis end points
Toloza et al. [25]	546 SLE cases, LUMINA Cohort	Prospective cohort	L	L	N/A	L	L	L	
Manzi et al. [7]	498 SLE cases, UPMC	Retrospective cohort	L	L	H	L	L	H	Relied on self-reporting of events, then confirmed with medical record review; only controlled for age in multivariate analysis
Petri et al. [34]	337 SLE cases, Johns Hopkins Lupus Cohort	Prospective cohort	L	L	N/A	L	L	L	
Petri et al. [18]	229 SLE cases, Johns Hopkins Lupus Cohort	Prospective cohort	L	L	L	L	L	L	

Abbreviations: H = high risk that methodology may have resulted in bias in the specified domain, L = low risk that methodology may have resulted in bias in the specified domain, N/A = not applicable, UTD = unable to determine risk of bias from methodology.

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Appendix A

See Tables A1–A4

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