Ethnic differences in cardiovascular risk in rheumatic disease: focus on Asians

Kai-Hang Yiu, Hung-Fat Tse, Mo-Yin Mok & Chak-Sing Lau

Abstract | Rheumatic diseases are associated with high cardiovascular morbidity and mortality. Considerable differences exist in the frequency of cardiovascular disease (CVD) risk factors and events among people of different ethnic origins, but little is known of the ethnic variations in the relative distribution of CVD risk factors and the degree of atherosclerosis in patients with rheumatic diseases. Understanding this variation will provide insight into the underlying pathogenesis of CVD in patients with rheumatic diseases, and aid in future studies of the detection and management of this complication. In general, although Asian patients seem to have fewer background CVD risk factors and are less affected by metabolic syndrome (MetS) than their non-Asian counterparts, those with rheumatic disease are equally as susceptible to CVD. Furthermore, it seems that systemic inflammation and mechanisms that do not involve conventional CVD risk factors and MetS have an important role in the development of atherosclerosis in patients with rheumatic diseases. Here we examine the frequency of conventional CVD risk factors and the prevalence of MetS in both Asian and non-Asian patients with selected rheumatic diseases. We also discuss the burden of CVD, as evaluated using various surrogate markers in these patients, and their overall CVD mortality rate.

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Introduction

The epidemiology of cardiovascular disease (CVD)[1] and cardiovascular mortality[2] in the general population varies across different ethnic groups owing to differences in both genetic and host susceptibility factors, dietary practice, and exercise.[3,4] In particular, variation is observed between the frequency of CVD risk factors, such as type 2 diabetes mellitus (T2DM),[5] metabolic syndrome (MetS)[6] and smoking habit,[7] across different ethnic groups. Population-based studies have shown the prevalence of CVD risk factors including hyperlipidemia, hypertension, T2DM and obesity, for example, is greater in patients from the USA than in those from China, although smoking is more prevalent in Chinese populations.[8,9] Indeed, in 2004, the reported 10-year coronary heart disease event rates for Chinese men and women were 1.5% and 0.6%, respectively, in comparison with the corresponding event rates of 8.0% and 2.8% for US men and women.[9] Despite this observation, differences in CVD risk factors and cardiovascular manifestations between Asian and non-Asian patients with rheumatic disease are not known.

Accelerated atherosclerosis leading to premature CVD is recognized as a major cause of long-term morbitiy and mortality in patients with rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc).[10–12] In addition to a high frequency of CVD risk factors, systemic inflammation has a pivotal role in the development of atherosclerosis in these patients.[13]

Competing interests
The authors declare no competing interests.

In this Review, we examine the potential differences in the prevalence of conventional CVD risk factors and MetS, the atherosclerotic burden (as assessed by various surrogate markers), and the epidemiology of CVD in patients with selected rheumatic disease. For the purposes of this Review, we have focused on RA, SLE and SSc in Asian and non-Asian populations; the populations studied and the main data gathered are summarized in Figure 1.

CVD risk factors in rheumatic disease

Rheumatoid arthritis

The conventional CVD risk factors, including T2DM, dyslipidemia and hypertension, were first studied when increased risk of CVD in patients with RA became evident. In a study by Gonzalez *et al.*,[14] the prevalence of CVD risk factors was similar among 603 patients with RA and 603 non-RA controls (all from the USA), including T2DM (7% versus 7%, respectively), dyslipidemia (49% versus 52%) and hypertension (52% versus 49%). In the Nurses' Health Study involving 114,342 US women, of whom 527 had RA, the incidences of T2DM (5% versus 5%), dyslipidemia (35% versus 33%) and hypertension (34% versus 30%) were also similar among patients with or without RA, although patients with RA were more likely to have been smokers in their past (current smokers: 17% versus 20%; past smokers: 49% versus 37%; $P<0.01$).[15] Overall, these studies demonstrated that the prevalence of conventional CVD risk factors was similar in US patients with RA and non-RA controls, although patients with RA were probably more likely

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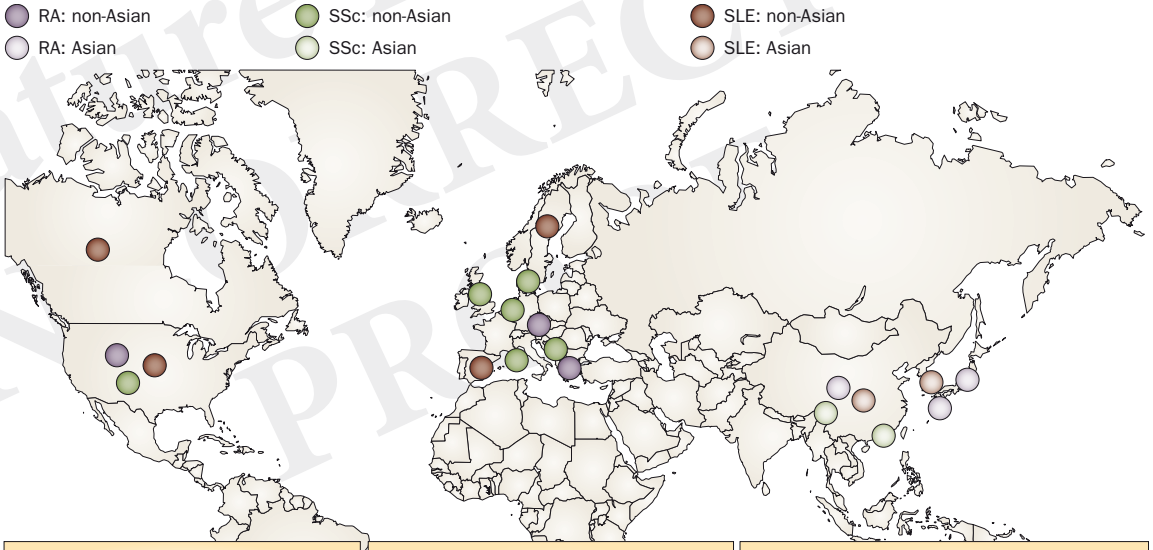
Key points

- Cardiovascular-related death is more prevalent in non-Asian patients than in Asian patients, in whom death owing to infection is more likely, although direct comparison studies are needed
- Conventional cardiovascular disease (CVD) risk factors, such as diabetes mellitus, dyslipidemia and hypertension, are similar between patients with or without rheumatic disease
- The prevalence of metabolic syndrome varies between patients with rheumatic disease of different ethnicity, with Asian patients tending to be less affected than non-Asian patients
- On the basis of calcium score, carotid intima-media thickness and detection of carotid plaque, Asian patients with rheumatic disease are as susceptible to CVD as their non-Asian counterparts
- Systemic inflammation has a prominent role in the development of atherosclerosis in Asian patients, despite their low background risk profiles

than controls to be past smokers.[15,16] However, increased disease duration might be associated with an increase in cardiovascular risk. In a separate US study evaluating 66 patients with long-standing RA, 89 patients with early RA and 85 non-RA controls, several conventional CVD risk factors differed among the three groups (systolic blood pressure: 138 mm Hg versus 128 mm Hg versus 128 mm Hg, respectively, $P = 0.01$; smoking history: 30% versus 21% versus 9%, respectively, $P < 0.01$).[17] In addition, this study also evaluated patients' Framingham risk score—an index to predict cardiovascular risk that includes assessment of age, gender, smoking habit, blood pressure and cholesterol concentrations. The Framingham risk score also estimates the risk of coronary events by stratifying individuals into three risk categories: low (<10% risk of an event in 10 years), intermediate (10% to 20% risk), and high (>20% risk).[18] Overall, patients with long-standing RA had higher Framingham risk scores than patients with early disease or non-RA controls (14 versus 11 versus 12 units; $P < 0.01$).[17] In contrast to non-Asian populations, Mok and colleagues[19] compared Chinese patients with RA with non-RA controls and found that the prevalence of elevated fasting glucose level (≥5.6 mmol/l; 16% versus 22%, $P < 0.01$) and dyslipidemia (high triglyceride level; 12% versus 20%, $P < 0.01$; low high-density lipoprotein level: 17% versus 46%, $P < 0.01$) were lower in those with RA. However, the prevalence of hypertension was highest



SSC	Asians	Non-Asians
DM	8%	4%
IMT (relatiive increase)	N/A	1–31%
CCS	71%	56%

SLE	Asians	Non-Asians
DM	1–2%	5%
Dyslipidemia	N/A	34%
Hypertension	N/A	33%
MetS		
(WHO)	N/A	32%
(NCEP)	16%	16–29%
IMT (relatiive increase)	38–71%	–11–12%
CCS	50%	16–31%
CVS epidemiology (RR)		
CAD	N/A	2.3
Stroke	N/A	2.3

RA	Asians	Non-Asians
DM	N/A	7–15%
Dyslipidemia	17%	35–49%
Hypertension	22%	33–52%
MetS	20–27%	
(WHO) N/A	N/A	42%
(NCEP) N/A	N/A	42–44%
IMT (relatiive increase)	10.3–13.2%	–9.8–28.5%
CCS	41%	61%
MI	N/A	2.0–2.1
Stroke	N/A	1.5–1.7

Figure 1 | Summary of known risk factors for, surrogate markers of, and epidemiology of CVD in Asian and non-Asian populations with RA, SLE or SSc. The countries in which the studies mentioned in this Review were conducted are indicated on the map. Fewer data exist for patients with SSc than for those with SLE or RA, and for Asian populations in comparison with non-Asians. Data on cardiovascular causes of death in Asian patients with rheumatic diseases are scarce, and no direct comparisons have been carried out between Asian and non-Asian populations. In general, Asian patients with SLE or RA seem to have fewer traditional CVD risk factors than their non-Asian counterparts, but (according to surrogate markers of CVD) are as susceptible to development of CVD. Further studies are needed to clarify whether genetic differences and/or diagnosis or treatment related factors boost the CVD risk of Asian patients with rheumatic diseases above the level predicted by traditional risk factors. Abbreviations: CVD, cardiovascular disease; RA, rheumatoid arthritis; SSc, systemic sclerosis; SLE, systemic lupus erythematosus.

in patients with RA (52% versus 45%, $P = 0.01$), similar to non-Asian populations.

The relative effect of conventional CVD risk factors on the development of adverse cardiovascular events seems to be less prominent in patients with RA than in non-RA controls. Gonzalez *et al.*[14] found that the influence of CVD risk factors on combined cardiovascular outcome (myocardial infarction, heart failure and cardiovascular death) was lower in patients with RA than in non-RA controls (T2DM: hazard ratio [HR] 1.62 versus 2.05, $P = 0.16$; dyslipidemia: HR 0.92 versus 1.14, $P = 0.44$; hypertension: HR 1.97 versus 2.75, $P = 0.30$ and smoking history: HR 1.32 versus 2.19, $P < 0.01$). Although there is a paucity of data available for Asian patients with RA in this regard, the evidence suggests that competing mechanisms, including high-grade systemic inflammation might have a more prominent role in the development of CVD in these patients, as opposed to individual CVD risk factors that have more influence in non-Asian populations.

Systemic lupus erythematosus

In a Canadian study comparing 250 patients with SLE with 250 non-SLE controls, T2DM (5% versus 1%, $P < 0.01$) and hypertension (33% versus 13%, $P < 0.01$) were more prevalent in those with SLE. Conversely, dyslipidemia (34% versus 36%) and smoking history (17% vs. 20%) were similar between patients with or without SLE.[20] In comparison with the 5% of US patients with T2DM,[20] a study of 588 Korean patients with SLE reported that the prevalence of T2DM was 1%[21], and in another study of 242 Chinese patients with SLE, T2DM was reported in 2% of the patients.[22] However, no study has directly compared conventional CVD risk factors of Asian patients with SLE with well-matched non-SLE controls. Furthermore, because of different disease characteristics, a valid conclusion of potential differences in conventional CVD risk factors cannot be drawn between non-Asian and Asian SLE populations. Although it is known that the increased incidence of CVD and premature atherosclerosis in SLE cannot be fully accounted for by conventional CVD risk factors, recommendations from the European League Against Rheumatism (EULAR) have suggested the need for monitoring and treating conventional CVD risk factors according to existing guidelines.[23,24]

Systemic sclerosis

In a study performed in the Mediterranean region by Tsifetaki *et al.*,[25] 60 patients with SSc exhibited mild dyslipidemia with lower serum levels of high-density lipoprotein (HDL) and higher triglyceride levels than 51 non-SSc controls. In addition, the atherogenic low density lipoprotein (LDL):HDL ratio was considerably higher in those with SSc.[25] A separate study comparing 49 Dutch patients with SSc with 32 non-SSc controls found that those with SSc had a lower HDL level (1.4 mmol/l versus 1.7 mmol/l, respectively, $P < 0.03$) and a higher triglyceride level (1.4 mmol/l versus 1.2 mmol/l, $P = 0.03$).[26] On the other hand, the prevalence of T2DM (4% versus 0%), systolic blood pressure (120 mmHg versus 120 mmHg) and diastolic blood pressure (75 mmHg versus 75 mmHg) were similar between both patient groups.

In a study by Mok *et al.*,[27] a comparison of 53 Chinese patients with SSc and 106 non-SSc controls found that patients with SSc were more likely to have lower LDL (2.4 ± 0.6 mmol/dl versus 2.8 ± 0.7 mmol/dl, respectively, $P < 0.01$) and HDL (1.4 ± 0.4 mmol/dl versus 1.6 ± 0.4 mmol/dl, $P = 0.01$) levels. Moreover, blood pressure was lower in those with SSc, an observation that could be attributed to a higher frequency of vasodilator use in this patient group (70% versus 23%, $P < 0.01$).[27] Nevertheless, the prevalence of T2DM was similar between patients with or without SSc (7.5% versus 11.3%). Although the combined data suggest that for patients with SSc, those from Asian populations have lower conventional CVD risk factors (such as dyslipidemia and blood pressure) than those from a non-Asian background, larger studies are needed to validate this conclusion.

MetS in rheumatic disease

MetS is a combination of medical disorders (including hypertension, diabetes, dyslipidemia and central obesity) that increases the risk of future cardiovascular events. Two of the most commonly used definitions for the diagnosis of MetS include the WHO criteria[28] and the National Cholesterol Education Program Adult Treatment Panel (NCEP) III criteria, both of which involve the assessment of fasting glucose, dyslipidemia, hypertension and central obesity **[Au: OK?]**.[29] MetS is a common presentation in patients with rheumatic diseases and represents an important risk for developing atherosclerosis. However, variable environmental factors, including the consumption of dairy-related products, might lead to differences in the prevalence of MetS between ethnic groups.

Rheumatoid arthritis

Whereas individual conventional CVD risk factors seem to be similar between patients with RA and non-RA individuals, MetS is more prevalent in US patients with long-standing RA or early RA than in non-RA controls (WHO criteria: 42% versus 31% versus 11%, respectively, $P < 0.001$; NCEPIII criteria: 42% versus 30% versus 22%, $P = 0.03$).[30] In another study, Karvounaris and colleagues[31] evaluated the prevalence of MetS in 200 patients with RA (with a mean age of 63) and 400 age-matched non-RA controls in the Mediterranean region. Although the overall prevalence of MetS was similar between both patient groups (44% versus 41%, respectively), those with RA who had MetS were more likely to have high RA disease activity than those without MetS.

In a study of 699 Chinese patients with RA, Mok *et al.*[19] determined that up to 20% of these patients had MetS, which was not higher than the frequency in the general population. In agreement with this finding, another study by Karimi *et al.*[32] found that the frequency of MetS in patients with RA from Iran was also similar to the frequency in non-RA controls. However, the duration of disease among those with RA was associated with an increased frequency of MetS, suggesting a pivotal role of

chronic inflammation in the development of this disease complex.

Interestingly, a study performed by Dessein *et al.*[33] in 74 patients with RA showed that individual MetS features, including hypertension, insulin resistance and high triglycerides, were more strongly associated with subclinical atherosclerosis than the currently recommended MetS definitions for subclinical atherosclerosis. Similarly, another study involving 631 patients with RA showed that individual CVD risk factors (diabetes, dyslipidemia, hypertension and smoking) contributed to carotid intima-media thickness (IMT) and the presence of carotid plaque.[34] Data from the Consortium of Rheumatology Researchers of North America (CORRONA) registry, which involves over 10,000 US patients with RA, demonstrated that increased markers of severity of RA, in addition to conventional CVD risk factors, were associated with an increase in cardiovascular risk. In particular, patients with no risk factors or markers of RA severity had an incidence rate of zero (95% CI 0–5.98) cardiovascular events per 1,000 person-years, whereas patients with at least two traditional CVD risk factors and three or more markers of RA severity had an incidence rate of 7.47 (95% CI 4.21–10.73) per 1,000 person-years.[35] Therefore, these data suggest that conventional CVD risk factors and MetS both contribute to the development of premature atherosclerosis in RA.

Systemic lupus erythematosus

Similarly to studies in patients with RA, previous reports have demonstrated that patients with SLE have a higher prevalence of MetS than non-SLE controls. Chung *et al.*[36] reported a higher prevalence of MetS in 102 US patients with SLE than in 101 non-SLE controls (WHO criteria: 32.4% versus 10.9%, respectively, $P<0.001$), although this difference was not significant according to NCEPIII criteria (29.4% versus 19.8%). That these latter criteria do not include assessment of insulin resistance, which is associated with systemic inflammation, might explain why their use finds a lower prevalence of MetS than use of the WHO criteria **[Au:OK?]**. A Spanish study also reported that 160 young patients with SLE patients had a higher prevalence of MetS compared with 245 age-matched non-SLE controls (NCEP-ATPIII criteria: 15.8% vs. 4.2%, respectively, $P<0.001$).[37]

Few relevant studies have been carried out in Asian patients with SLE. However, in another study by Mok *et al.*[38] evaluating 123 Chinese patients with SLE, the prevalence of MetS was higher in these individuals than in 492 non-SLE controls (16.3% versus 9.5%, respectively $P<0.05$). In addition, patients with MetS had higher levels of high-sensitive C-reactive protein, homocysteine and soluble thrombomodulin than those without MetS.

Systemic sclerosis

To our knowledge, no direct studies have evaluated MetS in patients with SSc in both non-Asian and Asian populations. Overall, although ethnic studies on the prevalence of MetS in patients with various rheumatic diseases have not been conducted, the incidence of MetS in the general population seems to be lower among Asian populations than in non-Asian populations, a finding that might be related to ethnic differences in dairy-related product consumption and the incidence of obesity.[39,40] This phenomenon suggests that Asian patients with rheumatic disease might be at a lower risk of developing CVD than their non-Asian counterparts. Further studies are required, however, for a more detailed evaluation of the incidence of MetS in patients with rheumatic diseases across different ethnicities.

CVD markers in rheumatic disease

Large, long-term cohort studies are required to determine the true prevalence of CVD in patients of different ethnicities with rheumatic disease. In the absence of these studies (many of which are underway), the detection of surrogate markers of CVD enables clinicians to evaluate the burden of cardiovascular complication in these patients.

Coronary artery calcification

The advent of multi-detector computed tomography (MDCT) allows rapid, effective and noninvasive detection of the extent and severity of atherosclerosis in vascular beds by imaging arterial calcification to reflect the presence of calcified atherosclerotic plaques. Previous studies have shown that the presence of coronary and aortic calcification detected by MDCT is predictive of major cardiovascular events.[41,42]

Rheumatoid arthritis

In a report by Chung *et al.*,[43] US patients with early RA or established RA had a higher prevalence of coronary calcification compared with non-RA controls (42.9% versus 60.6% versus 38.4%, respectively, $P=0.016$). Moreover, severe coronary calcification (as defined by an Agatston coronary calcification score [CCS]>109) was 3.4-fold higher in patients with established RA than in non-RA controls. The presence of coronary calcification in RA patients has also been shown to be associated with longer disease duration.[44]

Similar to non-Asian patients, our group has recently demonstrated that 85 patients with RA from Hong Kong, when compared with 85 non-RA controls, had a fivefold higher prevalence (CCS >0) and extent (CCS 63 ± 197 versus 11 ± 39, $P<0.01$) of coronary calcification as detected by MDCT.[45] Moreover, our study has further described that the presence and extent of arterial calcification in patients with RA was not only limited to the coronary vessel but was found across the whole vascular bed including the aorta and the carotid artery.

Systemic lupus erythematosus

In a 2002 report by Von Feldt *et al.*[46] studying 13 US patients with SLE, it was revealed that five of these patients had a CCS in the 70th percentile compared with historic age-matched women without known coronary artery disease and without SLE. This finding of high coronary calcification has been further confirmed by a study comparing 65 US patients with SLE with 69

non-SLE controls, which demonstrated up to a 10-fold higher risk of coronary calcification (CCS >0) in those with SLE as detected by MDCT.[47] Moreover, the mean CCS was higher in patients with SLE than in non-SLE controls (69 ± 244 versus 9 ± 42, respectively, $P<0.01$).

We have also demonstrated that the presence of coronary calcification (CCS >0) was 30-fold higher in 50 Chinese patients with SLE when compared with 50 non-SLE controls.[48] Moreover, the prevalence and extent of vascular calcification in the rest of the systemic vascular tree including the thoracic aorta and the carotid arteries were higher in those patients with SLE. These findings suggest that for patients with SLE, Chinese patients are as susceptible to CVD as their non-Asian counterparts. It must be stressed, however, that since only a few MDCT studies have been performed so far in patients with SLE, and the number of included patients is low, caution is needed when comparing the frequency of CVD between Asian and non-Asian patients on the basis of MDCT studies. Indeed, much larger studies are required.

Systemic sclerosis

In a study comparing 17 US patients with SSc with 17 non-SSc controls, coronary calcification (CCS >0) was more prevalent in those with SSc (56.2% versus 18.8%, respectively, $P = 0.03$).[49] Moreover, the severity of CCS was also greater in these patients (126.6 ± 251.0 versus 14.7 ± 52.2, $P = 0.003$).

Similarly, we studied 53 Chinese patients with SSc and found that up to 57% of them had severe coronary calcification (CCS ≥101), which was higher than the observed coronary calcification in non-SSc controls.[27] Multivariate analysis demonstrated that SSc was an independent risk factor for severe coronary calcification. This study has further suggested that SSc was associated with coronary atherosclerosis in Asian patients, similar to non-Asian patients, even after the data was controlled for conventional CVD risk factors.

Carotid intima-media thickness

Carotid IMT is a well-validated surrogate marker for preclinical atherosclerosis and a predictor of future cardiovascular events.[50] The ability to measure arterial intima-media wall thickness enables early detection of atherosclerosis and allows quantification of atherosclerotic burden. By contrast, an invasive angiogram might only detect the late stages of atherosclerosis that cause significant luminal obstruction. A number of studies have been carried out in patients with rheumatic disease using carotid IMT and the prevalence of carotid plaque as surrogate markers for premature atherosclerosis (Table 1). In addition, a meta-analysis of data from 25 studies of RA, 24 studies of SLE and six studies of SSc has shown that patients from all three groups of rheumatic disease have a higher carotid IMT than nonrheumatic controls.[51]

Rheumatoid arthritis

Carotid IMT and the prevalence of carotid plaque are among the most commonly evaluated surrogate markers of CVD in patients with RA. In a Swedish trial, 39 patients with RA had a greater carotid IMT than 39 non-RA controls.[52] Furthermore, carotid IMT correlated positively with abnormal lipid profile and tissue plasminogen activator antigen, a marker of thrombotic activity. Another study evaluating 84 patients with RA from Greece demonstrated that the carotid IMT and the prevalence of carotid plaque were both higher when compared with non-RA controls.[53] Moreover, patients with RA had a similar carotid IMT and prevalence of carotid plaque when compared with age-matched and gender-matched patients with T2DM, suggesting that both diseases contribute equally to the development of preclinical atherosclerosis. On the other hand, in a large study performed in the USA, carotid IMT was not found to be similar in patients with or without RA.[54] Carotid IMT, however, correlated positively with inflammatory markers both in patients with RA and in non-RA controls, a finding that is consistent with the hypothesis that systemic inflammation has a significant role in the development of atherosclerosis. Other studies in non-Asian patients with RA have also demonstrated that the prevalence of carotid IMT and the presence of carotid plaque were both higher in these patients than in non-RA controls (Table 1).[55–57]

Studies involving Asian populations have consistently demonstrated a similar increase in carotid IMT in those with RA compared with non-RA controls.[58–61] In a Japanese study by Kumeda *et al.*,[58] carotid IMT in patients with RA was higher than in non-RA controls. Moreover, high carotid IMT was associated with an increased disease duration and disease activity. In another report published by the same group,[60] it was shown that female Japanese patients with RA had a greater increase in carotid IMT than their non-RA counterparts (0.027 ± 0.046 mm/year versus 0.001 ± 0.059 mm/year, respectively, $P = 0.0074$), which was positively correlated with disease activity. In a separate study carried out in Korea, postmenopausal female patients with RA had increased carotid IMT when compared with non-RA controls.[59] Furthermore, no differences in carotid IMT were observed in this study between patients who were or were not receiving methotrexate or steroids.

Systemic lupus erythematosus

A study of female Swedish patients with SLE found that carotid IMT was increased in the subgroup who developed CVD, in comparison either with the patients without CVD or with non-SLE controls.[62] Patients with SLE but without CVD had a similar carotid IMT thickness to non-SLE controls, but with a higher prevalence of carotid plaque. In a study involving 197 US patients with SLE, Roman and colleagues[63] demonstrated that patients with SLE had a higher prevalence of carotid plaque than non-SLE controls (multivariate adjusted odds ratio 4.8). Similarly, Thomsom *et al.*[64] demonstrated a higher prevalence of carotid plaque in US patients with SLE than in non-SLE controls, further suggesting that early onset of premature atherosclerosis occurs in patients with SLE.

In a study comparing 32 Chinese patients with SLE with 32 non-SLE controls, carotid IMT was found to be

Table 1 | Studies of carotid IMT in patients with RA, SLE or SSc from different ethnic backgrounds

Study population			Carotid IMT (mm)			Carotid Plaque (%)		
Ethnicity	Controls	Patients	Controls	Patients	Relative increase (%)/ (*P*-value)	Controls	Patients	*P*-value
RA								
Swedish[52]	*n*=39; mean age 52; 30% male	*n*=39; mean age 52; 30% male	0.70±0.03*	0.79±0.04*	12.8 (0.05)	ND	ND	ND
US[54]	*n*=102; mean age 60; 11% male	*n*=204; mean age 60; 12% male	0.98±0.45‡	1.03±0.43‡	5.1 (0.30)	25	30	0.28
US[57]	*n*=105; mean age 47; 2% male	*n*=80; mean age 45; 2% male	0.71±0.17‡	0.64±0.17‡	–9.8 (0.01)	15	44	<0.01
Greek[53]	*n*=84; mean age 63; 29% male	*n*=84; mean age 64; 29% male	0.65±0.15‡	0.75±0.15‡	15.3 (<0.01)	9.5	47.6	<0.01
Slovenian[56]	*n*=40; mean age 42; 0% male	*n*=70; mean age 42; 0% male	0.47	0.59	25.5 (<0.01)	ND	ND	ND
Mexican[55]	*n*=20; mean age 41; 0% male	*n*=55; mean age 44; 0% male	0.58±0.10‡	0.67±0.18‡	15.5 (0.01)	ND	ND	ND
Japanese[58]	*n*=138; mean age 55; 12% male	*n*=94; mean age 52; 10% male	0.58±0.12‡	0.64±0.13‡	10.3 (<0.01)	ND	ND	ND
Korean[59]	*n*=53; mean age 55; 0% male	*n*=53; mean age 55; 0% male	0.68±0.14‡	0.77±0.09‡	13.2 (<0.01)	0	1.9	>0.05
SLE								
Swedish[62]	*n*=26; mean age 52; 0% male	*n*=26; mean age 52; 0% male	0.59±0.12‡	0.66±0.15‡	11.9 (0.03)	11.5	65.4	<0.05
US[63]	*n*=197; mean age 44; 6% male	*n*=197; mean age 44; 6% male	0.61±0.16‡	0.67±0.14‡	–11.4 (<0.01)	15.2	37.1	<0.01
American[64]	*n*=104; mean age 44; 0% male	*n*=217; mean age 45; 0% male	0.63±0.08‡	0.63±0.13‡	0 (0.71)	17	31	<0.01
Chinese[66]	*n*=40; mean age 36; 0% male	*n*=111; mean age 34; 0% male	0.45 (IQR 0.38-0.48)	0.62 (IQR 0.55-0.67)	37.7 (<0.01)	0	14.4	<0.01
Japanese[61]	*n*=22; mean age 57; 0% male	*n*=25; mean age 58; 0% male	0.7±0.2	1.3±0.7	71.4 (<0.01)	ND	ND	ND
SSc								
Dutch[26]	*n*=32; mean age 51; 9% male	*n*=49; mean age 55; 16% male	0.68 (IQR 0.56-0.75)	0.69 (IQR 0.62-0.79)	1.4 (0.07)	ND	ND	ND
Greek[25]	*n*=54; age and gender unclear[Au: OK?]	*n*=54; age and gender unclear	0.59±0.14‡	0.77±0.2‡	30.5 (<0.01)	ND	ND	ND

*Standard error of mean. ‡Standard deviation. Abbreviations: IMT, intima media thickness; IQR, interquartile range; ND, not determined; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

greater in those with SLE.[65] Moreover, patients with a high disease activity (as defined by an SLE disease activity index [SLEDAI] score ≥3) had greater carotid IMT than patients with stable disease (SLEDAI <1). Moreover, Zhang *et al.*[66] found that carotid IMT was higher and the prevalence of carotid plaque was more frequent in 111 premenopausal Chinese patients with SLE than in 40 non-SLE controls. These studies highlight that in Asian populations, carotid IMT is greater and the presence of plaque is more frequent in patients with SLE than in non-SLE controls, suggesting that the rate of accelerated atherosclerosis in SLE might be similar to that observed in non-Asian populations.

Systemic sclerosis

In a European study, Hettema *et al.*[26] showed that the carotid IMT was similar in patients with or without SSc (0.69 mm versus 0.68 mm, respectively. On the other hand, in a study of 60 patients with SSc from Greece, carotid IMT was found to be higher in these patients than in non-SSc controls (0.77 mm versus 0.59 mm, $P<0.0001$).[25] The reason for the discrepancy between these findings is unknown and will require exploration in future studies.

To our knowledge, no studies to date have evaluated carotid IMT in Asian SSc populations, and no major studies have assessed other surrogate markers of CVD risk in such cohorts [Au:OK?]. An effort to examine the degree of carotid atherosclerosis in this group of patients is needed and will highlight any potential ethnic differences between Asian and non-Asian populations with SSc.

CVD epidemiology in rheumatic disease

Rheumatoid arthritis

CVD represents a major cause of morbidity and mortality in patients with RA. Community-based studies in the USA have consistently found that patients with RA have an increased risk of cardiovascular events (Table 2).[15,67] In

Table 2 | Studies of cardiovascular risk in patients with RA or SLE

Ethnicity	Study type	Controls	Patients	Follow-up (years)	Adjusted relative risk (CI)
RA					
US[15]	Prospective cohort study	*n*=113,815; mean age 56, 0% male	*n*=527; mean age 58, 0% male	21	MI, 2.0 (1.2–3.3), *P*<0.01; stroke, 1.5 (0.7–3.1), *P*=0.31
US[67]	Cross-sectional study	*n*=2,479; mean age 66, 18% male	*n*=9,093; mean age 60, 23% male	NA	MI, 2.1 (1.5-2.9), *P*<0.05; stroke, 1.7 (1.3-2.4), *P*<0.05
US[68]	Retrospective cohort study	*n*=603; mean age 58; 27% male	*n*=603; mean age 58; 27% male	NA	Unrecognized MI, 2.13 (1.13-4.03), *P*<0.05; sudden death, 1.94 (1.06–3.55), *P*<0.05
SLE					
US[71]	Prospective cohort study	*n*=119,184; mean age 56; 0% male	*n*=148; mean age 53; 0% male	28	CAD, 2.25 (1.37–3.69), *P*<0.01; stroke, 2.29 (0.85–6.15), *P*=0.10
Swedish[72]	Retrospective cohort study	SMR of the general population	*n*=4,737; age 20–39 (27%), 40–59 (35%), >60 (38%), 22% male	≤31	CAD SMR, 3.0 (2.8–3.1), *P*<0.05; stroke SMR, 2.1 (1.7–2.4), *P*<0.05

Abbreviations: CAD, coronary artery disease; MI, myocardial infarction; NA, not applicable; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SMR, standardized mortality rate.

addition, a retrospective study by Maradit-Kremers *et al.*[68] showed that US patients with RA were twice as likely to have unrecognized myocardial infarctions, even before the diagnosis of RA, and sudden deaths compared with non-RA controls. Currently, no data are available concerning the exact risk of cardiovascular events in Asian patients with RA compared with non-RA controls. A study by Mok and colleagues,[69] however, showed that the standardized mortality rate (SMR) in Chinese patients with RA was 1.7 (95% CI 1.6–1.8), with infection being the most common cause of death, followed by cardiovascular events and stroke (34% versus 12% versus 7%, respectively). An accurate evaluation of ethnic differences in cardiovascular causes of death in RA requires future exploration.

Systemic lupus erythematosus

Similarly to individuals with RA, patients with SLE have a higher risk of cardiovascular events than non-SLE controls. A 1976 study by Urowitz *et al.*[11] identified a bimodal mortality pattern in patients with SLE. On the basis of the Framingham Offspring Study carried out in the USA, young women with SLE were particularly more likely to have a myocardial infarction than age-matched non-SLE controls (35–44 year age group relative risk [RR] 52.4, 95% CI 21.6–98.5; 45–54 year age group RR 2.47, 95% CI 0.8–6.0; 55–64 year age group RR 4.21, 95% CI 1.7–7.9).[70] In the Nurses' Health Study, US patients with SLE had a RR of 2.25 for coronary artery disease and a RR of 2.29 for stroke, after adjustment for confounding factors and ethnicities (95% white, 4% black and 1% others) (Table 2).[71] In another European study involving over 4,000 patients with SLE, the major cause of death was attributable to CVD, with up to a 16-fold increased risk of death from coronary heart disease in young patients with SLE (aged 20–39 years) in comparison with the general population.[72] Although the overall all-cause mortality in SLE has declined over the past 20 years, the risk of mortality associated with ischemic heart disease remains unchanged.

Data comparing cardiovascular causes of death between Asian patients with or without SLE are scarce. A study comparing 5,243 Chinese patients with SLE with the general population found a higher SMR in those with SLE (5.25, 95% CI 4.79–5.70), of which the most likely cause of death was infection, followed by cardiovascular and cerebrovascular events (22% versus 10% versus 6%, respectively).[69] Similarly, another prospective study involving 285 Chinese patients with SLE who were assessed for up to 15 years showed that the major cause of death was attributable to infections, followed by CVD and cerebrovascular complications (55% versus 17% versus 14%).[73] Although the study population was small compared with other studies conducted in non-Asian populations, the potential discrepancies in the causes of mortality between ethnicities, particularly those that are CVD-related, require further exploration.

Systemic sclerosis

In patients with SSc, the major causes of mortality are disease-related complications, including interstitial lung disease, pulmonary hypertension and renal crisis. To our knowledge, no studies have specifically evaluated the cardiovascular risk in patients with SSc compared with non-SSc controls, in either Asian or non-Asian populations. A previous report suggested a possible increase in CVD or cerebrovascular disease in SSc,[74] and other studies have demonstrated that the rate of CVD is increased in patients with SSc. A UK cohort study involving 283 patients with SSc demonstrated a fourfold increase in mortality in SSc (female SMR 4.6, 95% CI 3.2–6.2; male SMR 3.2, 95% CI 1.8–5.0) and almost 30% of these deaths were attributable to CVD-related events.[75] In a Danish trial involving 344 patients with SSc, 30% of the mortalities were cardiovascular in origin.[76] A study of

the EULAR Scleroderma Trials and Research (EUSTAR) cohort, a multinational, prospective cohort involving 5,860 European patients with SSc, demonstrated that up to 5% of all-cause mortalities were attributable to myocardial infarction and 3% to stroke.[77] This comparatively lower prevalence of CVD mortality might be explained by the multi-ethnic nature of the EUSTAR registry, and potentially by changes in the pattern of mortality (due to advances in the treatment of SSc) being reflected in this more recent study **[Au:OK?]**.[77]

Data concerning cardiovascular-related mortality in Asian patients with SSc are limited. A study involving 449 Chinese patients with SSc found that the SMR compared with the general population was 3.9 (95% CI 3.2–4.7).[69] The most common cause of death was due to infection, closely followed by cardiovascular cause and stroke (17% versus 16% versus 3%, respectively).

Considering the potential differences in CVD risk factors between non-Asian and Asian patients with rheumatic disease, a difference regarding cardiovascular-related mortality might be expected. Unfortunately, such data in Asian populations are sparse, and any conclusions must be drawn with caution. While we await the implementation and reporting of large long-term cohort studies—some of which are underway—on the frequency of CVD and its associated risk factors in Asian rheumatic disease populations, it is worth noting that surrogate markers of CVD are similarly increased in Asian and non-Asian patients in comparison with nonrheumatic controls.

Possible causes of ethnic differences

Factors that might explain ethnic differences in the cardiovascular risk in patients with rheumatic disease include differences in epidemiologic transition, psychosocial stress burden and genetic make-up between Asian and non-Asian patients. For example, it has been shown that in European patients with SLE, low-expression genotypes for mannose-binding lectin gene (*MBL2*), and hence low levels of MBL, were correlated with carotid IMT, independent of conventional CVD risk factors.[78] Furthermore, in the PROFILE study involving a multiethnic prospective cohort of patients with SLE, the incidence of overall vascular events (myocardial infarction ± vascular procedures, stroke, claudication or significant gangrene of extremities) were similar between different ethnic groups, but the presence of *CRP2*C* allele (rs1800947) was associated with a shorter time to the occurrence of arterial vascular events (HR = 1.75, 95% CI 1.00–3.07).[79] The implications of these factors require further studies. In addition, certain rheumatic diseases, such as SLE, have anecdotally been reported to be more active and severe in Asia.[80] For example, the incidence of severe nephritis is believed to be higher in Asian patients with lupus. The associated excessive inflammatory response and the use of high-dose steroids and cytotoxic agents have been shown to accelerate the development of CVD**[Au: ref?]**. Further, although prompt effective control of underlying rheumatic disease is key to the prevention of cardiovascular events, the management of rheumatic diseases in many Asian countries is suboptimal as a result of inadequate resources. Indeed, many countries in the Asia Pacific have failed to have rheumatology established as a subspecialty in medicine. In the early 1990s, with the exception of developed countries such as Australia, Japan and New Zealand, there were probably fewer than 100 fully trained and accredited rheumatologists for the whole of the Asia-Pacific region, with a population of nearly 3 billion people. Delay in the diagnosis and treatment of rheumatic diseases might explain the development of CVD complications in Asian patients despite a lower incidence of conventional CV risk factors.

Conclusions

Patients with rheumatic diseases are known to be at increased risk of the development of CVD, the mechanism of which is thought to be related to excess inflammation. The contribution of inflammation towards CVD development can be evaluated by studying patients of different ethnicities with rheumatic diseases. General population studies have shown that Asians, on the whole, are exposed to fewer CVD risk factors and are less susceptible to CVD deaths than their non-Asian counterparts. Indeed, studies have so far shown that Asian patients with RA or SLE possess fewer traditional CVD risk factors such as T2DM, dyslipidemia and MetS than non-Asian patients. However, using surrogate markers such as carotid IMT and CCS, Asian patients with RA and SLE seem to be as susceptible to CVD development as their non-Asian counterparts. Fewer and less comprehensive studies on CVD in SSc have been carried out so far. Nevertheless, Asian and non-Asian patients with SSc probably have a similarly increased frequency of CVD, based on CCS measurement. These observations suggest that inflammation and other immune mediated responses are important in CVD development in patients with rheumatic diseases, and that these factors have proportionately more influence in Asian patients than their non-Asian counterparts. It should, however, be noted that CVD epidemiology studies in Asia are scarce and that direct comparisons of cardiovascular causes of death between Asian and non-Asian patients with rheumatic disease have not been conducted so far. These studies should be encouraged. Future studies should also focus on the relationship between the cumulative burden of inflammation and CVD development, and the effects of aggressive treatment on the long-term cardiovascular outcome of rheumatic diseases.

Review criteria

A systematic literature search for full-text papers in the English language was performed using MEDLINE, Embase and the Cochrane library through to May 2011. In the search phrases used, the following terms were combined with the phrase "AND rheumatoid arthritis [OR lupus] [OR systemic sclerosis]": "cardiovascular disease"; "cardiovascular risk"; "metabolic syndrome"; "carotid intima media thickness"; "coronary calcium score"; "myocardial infarction"; "stroke"; "cardiovascular epidemiology". Papers selected and cited in this Review were based on the authors' view of their direct relevance to the topics discussed.

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Author contributions
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