OPEN ACCESS

EXTENDED REPORT

Clinical associations of the metabolic syndrome in systemic lupus erythematosus: data from an international inception cohort

Ben Parker,[1] Murray B Urowitz,[2] Dafna D Gladman,[2] Mark Lunt,[1,3] Sang-Cheol Bae,[4] Jorge Sanchez-Guerrero,[5] Juanita Romero-Diaz,[5] Caroline Gordon,[6] Daniel J Wallace,[7] Ann E Clarke,[8] Sasha Bernatsky,[8] Ellen M Ginzler,[9] David A Isenberg,[10] Anisur Rahman,[10] Joan T Merrill,[11] Graciela S Alarcón,[12] Barri J Fessler,[12] Paul R Fortin,[13] John G Hanly,[14,15] Michelle Petri,[16] Kristjan Steinsson,[17] Mary-Anne Dooley,[18] Susan Manzi,[19] Munther A Khamashta,[20] Rosalind Ramsey-Goldman,[21] Asad A Zoma,[22] Gunnar K Sturfelt,[23] Ola Nived,[23] Cynthia Aranow,[24] Meggan Mackay,[24] Manuel Ramos-Casals,[25] Raymond F van Vollenhoven,[26] Kenneth C Kalunian,[27] Guillermo Ruiz-Irastorza,[28] Sam Lim,[29] Diane L Kamen,[30] Christine A Peschken,[31] Murat Inanc,[32] Ian N Bruce[1,3]

ABSTRACT

Background The metabolic syndrome (MetS) may contribute to increased cardiovascular risk in systemic lupus erythematosus (SLE). We aimed to examine the association of demographic factors, lupus phenotype and therapy exposure with the presence of MetS.
Methods The Systemic Lupus International Collaborating Clinics Registry for Atherosclerosis inception cohort enrolled recently diagnosed (<15 months) SLE patients from 30 centres across 11 countries from 2000. Clinical, laboratory and therapeutic data were collected according to a standardised protocol. MetS was defined according to the 2009 consensus statement from the International Diabetes Federation. Univariate and backward stepwise multivariate logistic regression were used to assess the relationship of individual variables with MetS.
Results We studied 1686 patients, of whom 1494 (86.6%) had sufficient data to determine their MetS status. The mean (SD) age at enrolment and disease duration was 35.2 years (13.4) and 24.1 weeks (18.0), respectively. MetS was present at the enrolment visit in 239 (16%). In backward stepwise multivariable regression analysis, higher daily average prednisolone dose (mg) (OR 1.02, 95% CI 1.00 to 1.03), older age (years) (OR 1.04, 95% CI 1.03 to 1.06), Korean (OR 6.33, 95% CI 3.68 to 10.86) and Hispanic (OR 6.2, 95% CI 3.78 to 10.12) ethnicity, current renal disease (OR 1.79, 95% CI 1.14 to 2.80) and immunosuppressant use (OR 1.81, 95% CI 1.18 to 2.78) were associated with MetS.
Conclusions Renal lupus, higher corticosteroid doses, Korean and Hispanic ethnicity are associated with MetS in SLE patients. Balancing disease control and minimising corticosteroid exposure should therefore be at the forefront of personalised treatment decisions in SLE patients.

Open Access
Scan to access more free content

INTRODUCTION

Women with systemic lupus erythematosus (SLE) have a greater than fivefold increased risk of clinical coronary heart disease (CHD) events, rising to a 50-fold increase in younger patients.[1] Patients with SLE also have an increased burden of subclinical atherosclerosis, as measured by coronary calcium, carotid plaque, arterial stiffness and endothelial dysfunction.[2–5] Although classic Framingham risk factors are more prevalent in SLE,[6] they do not fully explain this excess CHD risk.[7]

The metabolic syndrome (MetS) is a clustering of related CHD risk factors that reflects central obesity and insulin resistance. MetS is associated with an increased risk of developing both type 2 diabetes mellitus and atherosclerosis in the general population.[8] While there have been several historical definitions,[9] a recent consensus statement proposed a harmonised definition to aid research and permit comparisons between cohorts and populations to be made.[10] The precise role of the MetS in CHD risk prediction remains subject to intense debate;[11–14] however, it is recognised to be a useful clinical tool to identify patients who may warrant more focused CHD risk assessment.[15]

In small cross-sectional studies, MetS is more common in SLE patients,[16] and as such may contribute to the CHD risk in SLE. In addition, the actual MetS phenotype in SLE may also differ.[17–20] Similar rates of central obesity in SLE compared to controls have been observed, but differences in the prevalence of hypertension and hypertriglyceridaemia suggest that lupus may drive a more inflammatory MetS phenotype. Lupus features implicated in MetS include inflammatory disease activity, disease damage and therapeutic exposures, particularly to corticosteroids, although studies to date have been inconsistent.[16] Determining the contribution of the SLE phenotype and therapeutic exposures to the development of MetS in SLE would yield important insights into the pathophysiology of cardiovascular risk and guide better stratification of CHD risk in these patients.

The Systemic Lupus International Collaborating Clinics (SLICC) group has developed an international registry of patients with newly diagnosed SLE to facilitate prospective, longitudinal studies of risk factors for the development of atherosclerosis in SLE. The aim of the present cross-sectional study was to investigate the prevalence of, and factors associated with, MetS in patients with SLE at enrolment into the SLICC inception cohort.

METHODS
SLICC registry for atherosclerosis
SLICC comprises 30 centres from 11 countries in North America, Europe and Asia. An inception cohort was recruited between 2000 and 2009 to investigate risk factors for atherosclerosis in SLE. Data were submitted to the coordinating centre at the University of Toronto at enrolment, and patients were reviewed annually in their local centre. Laboratory tests (fasting or non-fasting) necessary to evaluate disease activity, CHD risk factors, and to define MetS were performed locally. The study was approved by the University Health Network Research Institute, Research Ethics Committee, Toronto, Canada and by the institutional research ethics boards of participating centres in accordance with the Declaration of Helsinki's guidelines for research in humans.

Patients
Patients were enrolled when four or more American College of Rheumatology (ACR) classification criteria for SLE[21] were recognised. All patients were enrolled within 15 months of the date of their diagnosis. There were no specific exclusion criteria other than failing to meet four or more ACR criteria and being more than 15 months since diagnosis. Clinical and laboratory features, including CHD risk factors and therapeutic exposures, were recorded according to a standard protocol. SLE disease activity and damage were assessed using the SLE disease activity index (SLEDAI-2K)[22] and the SLICC/ACR damage index (SLICC-DI),[23] respectively. Active nephritis was defined as: haematuria greater than five red blood cells/high power field, excluding other causes; pyuria greater than five white blood cells/high power field, excluding infection; new/recent increase of more than 500 mg/24 h protein; casts including granular or red blood cells; or consistent renal biopsy. Nephrotic syndrome was defined as proteinuria greater than 3 g/24 h, oedema and increased blood pressure (BP). All patients provided written informed consent.

Definition of MetS
MetS was defined according to the 2009 definition in the joint interim statement from the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society and International Association for the Study of Obesity.[10] This harmonising statement requires three or more of the following five criteria to be present: (1) elevated waist circumference (MetS WC) using population/country-specific thresholds; (2) elevated triglycerides (MetS TG) of 1.7 mmol/l or greater ($\geq$150 mg/dl) or drug therapy for hypertriglyceridaemia; (3) reduced high-density lipoprotein (HDL) cholesterol (MetS HDL) less than 1.3 mmol/l (<50 mg/dl) in women and less than 1.0 in men or drug therapy for reduced HDL-cholesterol; (4) elevated BP (MetS BP) of 130/85 mm Hg or greater or drug therapy for hypertension; and (5) elevated fasting glucose (MetS Glu) of 5.6 mmol/l or greater ($\geq$100 mg/dl) or drug therapy for hyperglycaemia.

Statistical analysis
SLE factors implicated in MetS development in SLE were defined a priori. These represented inflammatory disease activity (SLEDAI-2K), disease phenotype including active renal disease, low complement or high anti-double-stranded DNA antibodies and therapeutic exposures including several measures of corticosteroid exposure. All corticosteroid doses were converted to milligrams (mg) of prednisolone equivalent. The cumulative oral prednisolone dose received before enrolment (g) was calculated for each individual. A comparison of continuous data was performed using Wilcoxon's rank sum test, and of categorical data using the χ^2 test. Univariate logistic regression was used to assess the relationship between the presence of MetS at enrolment into the SLICC registry for atherosclerosis (RAS) and individual variables. Results presented are adjusted OR and 95% CI. Analysis was adjusted for age, ethnicity and gender. Those factors associated with MetS on univariate analysis (p<0.2) were entered into a multivariable model. Backward stepwise multivariate logistic regression was performed with significance set at 5%, resulting in a final model. All statistical analyses were performed using STATA 10.0.

RESULTS
Patients
By 2009, 1686 patients were enrolled into SLICC–RAS. Sufficient data were available to define the presence or absence of MetS in 1494 (88.6%) patients, of whom 1336 (89.4%) were women. The mean (SD) age at enrolment into the study was 35.2 years (13.4) and the mean (SD) disease duration was 24.1 weeks (18.0). There was a wide ethnic variation, reflecting the participating centres; 660 (44.2%) were Caucasian, 240 (16.1%) were Hispanic, 228 (15.3%) were black African, African-American or Afro-Caribbean and 303 (20.3%) were south-east Asian. At enrolment the mean (SD) SLEDAI was 5.5 (5.4) and 287 (19.3%) had very active disease with a SLEDAI of 10 or greater (table 1).

There were 192 (11.4%) patients with insufficient data to determine the MetS status. This group had similar demographics and SLICC-DI to the rest of the cohort. However, they had a lower mean SLEDAI, a lower prevalence of renal disease, less immunosuppressant use and were more likely to be receiving antimalarial therapies. This subset also had a lower frequency of corticosteroid exposure (see supplementary table S1, available online only).

Prevalence of MetS
MetS was present in 239/1494 (16%) patients. The individual MetS criteria met were: MetS WC (686/1334, 48.4%), MetS BP (686/1491, 46%), MetS TG (619/1342, 46.1%), MetS HDL (486/822, 59.1%) and MetS Glu (271/1344, 20.2%). MetS was more common in men than women (22.2% vs 15.2%; p=0.03) and those with MetS were older than those without (mean (SD) age 36.9 years (13.3) vs 34.9 years (14.7); p<0.04). Patients of Hispanic and Korean ethnicity had the highest prevalence of MetS, compared to the rest of the cohort (31.3% and 30.1% vs 10.3%; p<0.0001).

Factors associated with MetS at enrolment
In an age, ethnicity and gender-adjusted analysis we assessed the strength of the relationship between the presence of MetS and our predefined variables related to inflammation, disease

Table 1 Characteristics of patients at enrolment into SLICC–RAS

No of patients	1494
Age, years (mean (SD))	35.2 (13.4)
Gender (%)	
Female	1336 (89.4)
Male	158 (10.6)
Ethnicity (%)	
Caucasian	660/1492 (44.2)
Black African/Afro-Caribbean	228/1492 (15.3)
SE Asian	303/1492 (20.3)
Hispanic	240/1492 (16.1)
Other	61/1492 (4.1)
Region (%)	
Canada	358/1477 (24.2)
Mexico	194/1477 (13.1)
USA	374/1477 (25.3)
Asia	168/1477 (11.4)
Europe	383/1477 (25.3)
CHD risk factors (mean (SD))	
BP systolic, mm Hg	119.5 (16.8)
BP diastolic, mm Hg	75.3 (11.0)
On AHT medication, %	435 (29.1)
Total cholesterol, mmol/l	4.93 (1.49)
Triglyceride, mmol/l	1.79 (1.19)
HDL-cholesterol, mmol/l	1.39 (0.60)
On lipid-lowering medication, %	171 (11.5)
Glucose, mmol/l	5.03 (1.63)
Diabetes, %	50 (3.4)
Smoker current, %	225 (15.1)
Premenopausal, %	1244 (83.3)
BMI	25.1 (5.9)
WC, cm	82.9 (14.0)
5-Year % Framingham risk	
Women	0.57
Men	5.03
Disease duration, weeks (mean SD)	24.1 (18.0)
SLEDAI (mean SD)	5.5 (5.4)
SLICC/ACR-DI=0	528 (81.9%)
Disease phenotype (%)	
Active renal disease	314 (22.9)
Anti-dsDNA positive	541/1347 (40.2)
Low complement	519/1349 (38.5)
Thrombocytopenia	44/1313 (3.4)
Oral CS use (median (IQR))	1043 (69.8)
Average CS dose, mg	20 (10, 30)
Highest CS dose, mg	40 (20, 60)
Cumulative CS dose, g	2.6 (1.1, 5.0)
Pulse IV CS (%)	70/1423 (4.9)
Immunosuppressant use (%)	599/1491 (31.0)
Azathioprine	262 (43.7)
Methotrexate	104 (17.4)
Mycophenolate mofetil	98 (16.4)
IV cyclophosphamide	95 (15.9)
Ciclosporin	21 (3.5)
Other	19 (3.2)
Antimalarial use (%)	971 (65.0)

ACR, American College of Rheumatology; AHT, antihypertensive; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CS, corticosteroid; DI, damage index; HDL, high-density lipoprotein; IV, intravenous; RAS, Registry for Atherosclerosis; SLEDAI, systemic lupus erythematosus disease activity index; SLICC, Systemic Lupus International Collaborating Clinics; WC, waist circumference.

phenotype and therapeutic exposure (table 2). SLE features associated with MetS included active renal lupus (OR 2.87, 95% CI 2.05 to 4.02), SLEDAI-2K greater than 10 (OR 1.73, 95% CI 1.22 to 2.44) and thrombocytopenia (OR 2.10, 95% CI 1.03 to 4.29). Several corticosteroid variables showed an association, including current oral (OR 1.53, 95% CI 1.05 to 2.25) and past intravenous (OR 3.22, 95% CI 1.35 to 7.68) corticosteroid use. SLE patients with MetS received oral corticosteroids at higher average daily doses and with higher cumulative and peak doses compared to those without MetS. The use of immunosuppressive agents was also associated with MetS (OR 2.21, 95% CI 1.63 to 3.00), and a negative association with antimalarial use was observed (OR 0.51, 95% CI 0.38 to 0.67).

In a backward stepwise multivariable regression analysis, factors independently associated with MetS were higher average daily oral prednisolone dose (mg) (OR 1.02, 95% CI 1.00 to 1.03), older age at study entry (years) (OR 1.04, 95% CI 1.03, 1.06), Korean (OR 6.33, 95% CI 3.68 to 10.86) and Hispanic (OR 6.2, 95% CI 3.78 to 10.12) ethnicity, active renal lupus (OR 1.79, 95% CI 1.14 to 2.80) and immunosuppressant use (OR 1.81, 95% CI 1.18 to 2.78). These remained unchanged when overlapping variables (such as proteinuria and active renal disease) were excluded. When active renal involvement was removed from the multivariable model in favour of the renal components scored on SLEDAI, the presence of haematuria became significant (OR 1.70, 95% CI 1.03 to 2.82) (with other variables in the final model unchanged).

Exploratory analyses
We further examined the two highest risk ethnicities to explore potential differences in SLE features or therapeutic exposures that may influence the presence of MetS. One hundred and sixty-five of 169 (97.6%) patients of Korean ethnicity resided in South Korea; 192 of 240 (80%) patients of Hispanic ethnicity resided in Mexico and 16.3% in the USA. Korean and Hispanic patients demonstrated distinct and contrasting MetS phenotypes compared to each other and the rest of the cohort (table 3). Patients of Korean ethnicity had a lower prevalence of central obesity (MetS WC 20.1% vs 51.3%; p<0.0001) and lower mean (SD) body mass index (BMI) (21.6 (4.3) vs 25.8 (6.1) kg/m², p=<0.0001), but a significantly increased prevalence of hyperglycaemia and dyslipidaemia. Korean patients also had more active laboratory features in the SLEDAI, such as positive anti-dsDNA antibodies (66% vs 36.0%; p<0.001), hypocomplementaemia (75.2% vs 33.1%; p<0.001) and thrombocytopenia (11.2% vs 2.7%; p<0.001). Oral corticosteroid use in the Korean cohort was almost universal (95.3%), although the average daily, peak and cumulative doses were similar or lower than the rest of the cohort.

In the Hispanic cohort, MetS was contributed to by significantly more dyslipidaemia (MetS TG 64.3% vs 40.3%; p<0.0001); MetS HDL (65.1% vs 52.7%; p<0.0001), despite a similar prevalence of central obesity. Hispanic patients also had more active renal disease at enrolment (40.4% vs 15.5%; p<0.0001) but similar rates of both hypertension and active serological indicators (ie, elevated anti-dsDNA antibodies and low complement) to other ethnicities. Hispanic patients were also exposed to higher average, peak and cumulative doses of corticosteroids but less antimalarial agents than the rest of the SLICC–RAS cohort (table 4).

To test whether the effect of corticosteroids was dose dependent, the multivariable model was run using only current oral cor-

Table 2 Significant factors associated with MetS at enrolment into SLICC–RAS in age, ethnicity and gender-adjusted analyses

	MetS			
	Yes	No	p Value	OR (95% CI)
Current CS (%)	193/239 (80.8)	8250/1255 (67.7)	<0.001	1.53 (1.05 to 2.25)
Average CS dose, mg (median (IQR))	30 (15, 45)	20 (10, 30)	<0.001	1.02 (1.01 to 1.04)
Highest CS dose, mg (median (IQR))	50 (30, 60)	30 (20, 50)	<0.001	1.00 (1.00 to 1.01)
Cumulative CS dose, g (median (IQR))	3.1 (1.5, 5.4)	2.3 (1.0, 4.0)	0.006	1.05 (1.00 to 1.09)
Past IV CS (%)	18/230 (7.8)	52/1193 (4.4)	0.03	3.22 (1.35 to 7.68)
Antimalarial (%)	123/239 (51.5)	848/1255 (67.6)	<0.001	0.51 (0.38 to 0.67)
Immunosuppressant (%)	140/238 (58.8)	459/1253 (36.6)	<0.001	2.21 (1.63 to 3.00)
SLICC-DI ≥1 (%)	26/95 (27.4)	91/550 (16.6)	0.01	1.99 (1.16 to 3.40)
SLEDAI-2K (mean (SD))	6.79 (6.19)	5.24 (5.25)	<0.001	1.05 (1.02 to 1.07)
SLEDAI ≥10 (%)	66/239 (27.6)	221/1252 (17.7)	0.001	1.73 (1.22 to 2.44)
High anti-dsDNA (%)	101/216 (46.8)	440/1131 (38.9)	0.03	1.32 (1.00 to 1.82)
Thrombocytopenia (%)	14/206 (6.8)	30/1107 (2.7)	0.003	2.10 (1.03 to 4.29)
Leucopenia (%)	7/203 (3.5)	92/1108 (8.3)	0.02	0.33 (0.14 to 0.75)
Active renal disease (%)	94/239 (39.3)	220/1255 (17.5)	<0.001	2.87 (2.05 to 4.02)
Past renal disease (%)	22/239 (9.2)	69/1255 (5.5)	0.03	1.67 (1.00 to 2.88)

Variables reflect current exposures, recorded at enrolment.
CS, corticosteroid; DI, damage index; IV, intravenous; MetS, metabolic syndrome; RAS, Registry for Atherosclerosis; SLEDAI, systemic lupus erythematosus disease activity index; SLICC, Systemic Lupus International Collaborating Clinics.

Table 3 Characteristics of patients of Korean and Hispanic ethnicity compared to all other ethnicities

	Korean	p Value*	Hispanic	p Value†	Other ethnicities
No of patients	169		240		1085
Age, years (mean (SD))	28.8 (9.7)	<0.0001	29.2 (10.3)	<0.0001	37.5 (14.0)
Gender (%)					
Female	150 (88.8)	0.90	218 (90.8)	0.45	968 (89.2)
Male	19 (11.2)	0.90	22 (9.2)	0.45	117 (10.8)
MetS (%)	52 (30.8)	<0.0001	72 (31.3)	<0.0001	112 (10.3)
MetS phenotype (%)					
MetS WC	33/164 (20.1)	<0.0001	129/228 (56.6)	0.15	483/942 (51.3)
MetS BP	74 (43.8)	0.63	117 (48.8)	0.40	495/1082 (45.8)
MetS TG	100/153 (65.4)	<0.0001	108/168 (64.3)	<0.0001	411/1021 (40.3)
MetS HDL	110/144 (76.4)	<0.0001	97/149 (65.1)	0.007	279/529 (52.7)
MetS Glu	45/168 (26.8)	0.04	41/236 (17.4)	0.42	185/940 (19.7)
BMI (mean(SD))	21.6 (4.3)	<0.0001	24.5 (5.0)	0.002	25.8 (6.1)
WC, cm (mean (SD))	74.7 (8.1)	<0.0001	82.9 (10.9)	0.17	84.3 (14.9)
Disease duration, weeks (mean SD)	18.5 (15.9)	<0.0001	23.2 (16.9)	0.15	25.1 (18.4)
SLEDAI (mean SD))	7.45 (6.09)	<0.0001	6.46 (5.75)	<0.0001	5.0 (5.2)
SLICC/ACR-DI (mean (SD))	0.24 (0.69)	0.50	0.28 (0.69)	0.87	0.30 (0.74)
Disease phenotype (%)					
Active renal disease	49 (29.0)	<0.0001	97 (40.4)	<0.0001	168 (15.5)
Anti-dsDNA positive	105/159 (66.0)	<0.0001	84/211 (39.8)	0.30	352/977 (36.0)
Low complement	121/161 (75.2)	<0.0001	74/208 (35.6)	0.46	324/980 (33.1)
Thrombocytopenia	16/143 (11.2)	<0.0001	2/210 (1.0)	0.13	26/960 (2.7)
Medication (median (IQR))					
Oral CS, %*	161 (95.3)	<0.0001	211 (87.9)	<0.0001	671 (61.8)
Average CS dose, mg	20 (10, 35)	0.26	30 (15, 42.5)	<0.0001	20 (10, 30)
Highest CS dose, mg	30 (15, 55)	0.07	50 (30, 60)	<0.0001	40 (20, 60)
Cumulative CS dose, g	1.4 (0.4, 3.1)	<0.0001	3.9 (1.8, 6.2)	<0.0001	2.5 (1.2, 4.8)
Pulse intravenous CS, %	26 (15.4)	<0.0001	5/223 (2.2)	0.26	39/1031 (3.8)
Immunosuppressant (%)	86 (50.9)	<0.0001	146 (60.8)	<0.0001	367/1082 (33.9)
Antimalarial (%)	120 (71.0)	0.29	125 (52.1)	<0.0001	705 (65.0)

*Korean versus all other (non-Hispanic) ethnicities.
†Hispanic versus all other (non-Korean) ethnicities.
ACR, American College of Rheumatology; BMI, body mass index; BP, blood pressure; CS, corticosteroid; DI, damage index; Glu, glucose; HDL, high-density lipoprotein; MetS, metabolic syndrome; SLEDAI, systemic lupus erythematosus disease activity index; SLICC, Systemic Lupus International Collaborating Clinics; TG, triglycerides; WC, waist circumference.

Table 4 Multivariable model of predictors of MetS at enrolment

Variable	OR (95% CI)
Average corticosteroid dose, mg/day	1.02 (1.00 to 1.03)
Age, years	1.04 (1.03 to 1.06)
Korean ethnicity	6.33 (3.68 to 10.86)
Hispanic ethnicity	6.20 (3.78 to 10.12)
Active renal disease	1.79 (1.14 to 2.80)
Immunosuppression use*	1.81 (1.18 to 2.78)

Variables reflect current exposures, recorded at enrolment.
Includes azathioprine, mycophenolate mofetil, cyclophosphamide, ciclosporin, methotrexate.
MetS, metabolic syndrome.

ticosteroid use (yes/no), with dose-related variables excluded. In this model, current corticosteroid use was not significantly associated with MetS although past intravenous corticosteroid use was (OR 2.45, 95%CI 1.01 to 5.97), suggesting that increasing corticosteroid doses have a greater impact on MetS susceptibility than simple exposure status. Immunosuppressive therapies were not predicted a priori to be mechanistically involved in MetS development but rather act as a marker of disease severity, higher disease activity and/or corticosteroid use. The majority of patients receiving immunosuppressive therapies were also receiving oral corticosteroids (91.5%), and at higher doses than those not on immunosuppressive the-rapies. Immunosuppressant users also had higher SLEDAI and SLICC-DI indices (see supplementary table S2, available online only). However, use of immunosuppressive therapies remained a significant predictor of MetS even after adjusting for all clinically correlating factors, such as SLEDAI, renal disease and corticosteroid use/dose (fully adjusted OR 2.15, 95%CI 1.15 to 4.00).

Finally, those with renal involvement had more hypertension (MetS BP 72.9% vs 38.8%; p<0.0001) and hypertriglyceridae-mia (MetS TG 74.1% vs 38.8%; p<0.0001) than those without renal lupus. Central obesity parameters (BMI and MetS WC) were, however, lower in those with renal disease, despite significantly higher corticosteroid exposures (eg, median (IQR) average oral prednisolone dose 30 mg (20, 50) vs 16 mg (10, 30)) (see supplementary table S3, available online only).

DISCUSSION

We report that MetS was common (16%) in SLE despite our cohort being young, predominantly female and early in the course of their disease. The relatively high prevalence of MetS at enrolment suggests that the metabolic derangements that contribute to long-term CHD risk characterised by MetS appear early in the course of the disease. Smaller studies of established lupus cohorts have reported MetS rates of 18–32%, which were consistently higher than control populations.[16] For example, Parker et al[17] found a prevalence of 30% in a UK SLE cohort, compared to 20% in controls, and Sabio et al[18] reported a prevalence of 20%, compared to 13% in controls. These results support the hypothesis that rapid control of inflammatory disease activity with the lowest doses of corticosteroid possible is likely to be beneficial to long-term cardiovascular risk. The role of inflammation in the development of atherosclerosis has been increasingly recognised,[24] and SLE is associated with higher circulating levels of high sensitivity C-reactive protein, interleukin 18 and tumour necrosis factor α, which are associated with insulin resistance and endothelial dysfunction and have been implicated in the development of CHD in the general population.[16 25] Long-term and high-

dose corticosteroid use is associated with the pro-atherogenic metabolic disturbances characterised by MetS,[26 27] and the weight of evidence in SLE suggests they are pro-atherogenic. Others have, however, suggested that their anti-inflammatory activity in lupus may exert an atheroprotective role.[4] The present study suggests that in early disease, higher doses of corticosteroids play a pivotal role in the development of MetS.

The strong association of MetS with Korean and Hispanic ethnicities partly reflects a higher background population prevalence of MetS. In 2006 a Mexican study found the prevalence of MetS in adults was 37–50%, depending on the definition used,[28] and 24–36% in adults aged 20–39 years. Similarly, the San Antonio Heart Study demonstrated that people of Mexican Hispanic descent had a higher prevalence of MetS than Caucasian individuals, an observation especially pronounced in women (30.9% vs 16.8%).[29] A recent study of South Korean adults described a MetS prevalence in women of 16–31% depending on the definition used, with low levels of central obesity, as we found in our study.[30] While there is therefore variability in the background prevalence of MetS, MetS remains more prevalent in SLE than controls.[16] The ethnic gradient may therefore reflect an increased susceptibility to MetS and enhanced sensitivity to the adverse effects of inflammation and corticosteroid exposure in Korean and Hispanic patients. There were, however, important differences in the MetS pheno-type observed in these two subsets, as well as differences in the clinical and inflammatory pattern of disease observed to be associated with MetS. Whether these differences translate into a differential effect on future cardiovascular endpoints is the subject of prospective study.

Antimalarial agents showed a significant negative association with MetS on univariate analysis; however, this did not remain significant in our multivariable model. A protective effect of antimalarial use against MetS has been demonstrated by other groups with more stable, mild disease.[18 31] Our study included recently diagnosed patients with a shorter exposure to the drug in the context of a more severe, active disease. It will be of interest to observe how longer exposure to antimalarial agents in the context of disease stabilisation will influence the MetS phenotype over time in this cohort. The significant association between immunosuppressant use and MetS may represent confounding, an indication of disease severity rather than mediating metabolic derangement. However, the relationship persists even after adjusting for all measured potential confounders (such as SLEDAI and corticosteroid use). This suggests that either immunosuppressive therapies have direct adverse metabolic effects, or there is residual confounding related to inadequately measured exposures, such as disease activity. Apart from ciclosporin A, immunosuppressive therapies commonly used in SLE are not associated with metabolic derangements,[32] and may play a role in preventing atherosclerosis.[33 34] Therefore, immunosuppressant use is likely to reflect residual confounding, and additional biomarkers and/or indices of disease activity may improve the estimation of exposure to systemic inflammation.

This is the largest study to date examining MetS in SLE and has many advantages over previous studies. The cohort is young, with a range of disease activity that allows us to explore more effectively the impact of inflammation on MetS development. We also studied an international cohort recruited from 11 countries with a range of ethnicities, and therefore the results can be generalised to a range of populations. Our data also included a breadth of corticosteroid data, allowing us to

explore their effects in more detail. Finally, the prospective nature of the cohort limits many potential sources of bias associated with retrospective studies.

The analysis does, however, have several limitations. First, there are missing MetS data on 11.4% of the cohort. While the demographics of this cohort are broadly similar they appear to have less severe disease, which may bias the analysis towards disease severity markers. Our data may therefore overestimate the true prevalence of MetS in this population. The most common missing variable was HDL-cholesterol, which was not universally performed locally in all centres. Second, a cross-sectional study is not the ideal study design to dissect the interplay between inflammation, corticosteroid exposure and MetS, although it can provide important data with which to inform prospective studies. Future work will examine how these factors influence MetS over time and investigate the influence of genetic factors on MetS prevalence and susceptibility. Finally, the use of MetS as a CHD risk prediction tool for adverse cardiovascular events has yet to be validated in SLE and the SLICC–RAS cohort is an ideal setting in which to examine this further.

Our study confirms that MetS is common in young patients with recently diagnosed SLE. This clustering of CHD risk factors and the observed ethnic variation in MetS susceptibility should help inform risk stratification in the management of early disease. MetS is associated with a more severe disease phenotype and higher doses of corticosteroids, therefore balancing disease control while minimising corticosteroid exposure should be at the forefront of personalised treatment decisions in these patients.

Author affiliations
[1]Arthritis Research UK Epidemiology Unit, Institute of Inflammation and Repair, Manchester Academic Health Sciences Centre, The University of Manchester, Manchester, UK
[2]Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital and University of Toronto, Toronto, Ontario, Canada
[3]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
[4]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea
[5]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Medicas y Nutrición, Mexico City, Mexico
[6]Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
[7]Department of Rheumatology, Cedars-Sinai/David Geffen School of Medicine at UCLA, Los Angeles, California, USA
[8]Divisions of Clinical Immunology/Allergy and Clinical Epidemiology, Montreal General Hospital, McGill University Health Centre, Montreal, Quebec, Canada
[9]Department of Medicine, SUNY Downstate Medical Center, Brooklyn, New York, USA
[10]Centre for Rheumatology Research, University College London, London, UK
[11]Department of Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA
[12]Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA
[13]Division of Rheumatology, Centre Hospitalier Universitaire de Québec et Université Laval, Quebec City, Quebec, Canada
[14]Division of Rheumatology, Department of Medicine, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Nova Scotia, Canada
[15]Department of Pathology, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Nova Scotia, Canada
[16]Department of Rheumatology, Johns Hopkins University, Baltimore, Maryland, USA
[17]Center for Rheumatology Research, Landspitali University Hospital, Reykjavik, Iceland
[18]University of North Carolina, Chapel Hill, North Carolina, USA
[19]Department of Medicine, West Penn Allegheny, Pittsburgh, Pennsylvania, USA
[20]Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, King's College London School of Medicine, London, UK
[21]Northwestern University and Feinberg School of Medicine, Chicago, Illinois, USA
[22]Lanarkshire Centre for Rheumatology, Hairmyres Hospital, East Kilbride, Scotland, UK
[23]Department of Rheumatology, University Hospital Lund, Lund, Sweden
[24]Center for Autoimmune and Musculoskeletal, Feinstein Institute for Medical Research, Manhasset, New York, USA
[25]Josep Font Autoimmune Diseases Laboratory, IDIBAPS, Department of Autoimmune Diseases, Hospital Clínic, Barcelona, Spain
[26]Department of Rheumatology, Karolinska Institute, Stockholm, Sweden
[27]UCSD School of Medicine, La Jolla, California, USA
[28]Autoimmune Disease Unit, Department of Internal Medicine, Hospital Universitario Cruces, University of the Basque Country, Barakaldo, Spain
[29]School of Medicine, Emory University, Atlanta, Georgia, USA
[30]Medical University of South Carolina, Charleston, South Carolina, USA
[31]Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
[32]Division of Rheumatology, Department of Internal Medicine, Istanbul University, Istanbul, Turkey

REFERENCES
1. **Manzi S,** Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol* 1997;**145**:408–15.
2. **Petri MA,** Kiani AN, Post W, et al. Lupus Atherosclerosis Prevention Study (LAPS). *Ann Rheum Dis* 2011;**70**:760–5.
3. **Ahmad Y,** Shelmerdine J, Bodill H, et al. Subclinical atherosclerosis in systemic lupus erythematosus (SLE): the relative contribution of classic risk factors and the lupus phenotype. *Rheumatology* 2007;**46**:983–8.
4. **Roman MJ,** Shanker BA, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;**349**:2399–406.
5. **El-Magadmi M,** Bodill H, Ahmad Y, et al. Systemic lupus erythematosus: an independent risk factor for endothelial dysfunction in women. *Circulation* 2004;**110**:399–404.
6. **Bruce IN,** Urowitz MB, Gladman DD, et al. Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto Risk Factor Study. *Arthritis Rheum* 2003;**48**:3159–67.
7. **Esdaile JM,** Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2001;**44**:2331–7.
8. **Alberti KG,** Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006;**23**:469–80.

9. **Cornier MA,** Dabelea D, Hernandez TL, et al. The metabolic syndrome. Endocr Rev 2008;**29**:777–822.

10. **Alberti KG,** Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and international association for the Study of Obesity. Circulation 2009;**120**: 1640–5.

11. **Gami AS,** Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007;**49**:403–14.

12. **Kahn R,** Buse J, Ferrannini E, et al. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2005;**28**:2289–304.

13. **Wannamethee SG,** Shaper AG, Lennon L, et al. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med 2005;**165**:2644–50.

14. **Grundy SM.** Does the metabolic syndrome exist? Diabetes Care 2006;**29**:1689–92.

15. **Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.** Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III). JAMA 2001;**285**:2486–97.

16. **Parker B,** Bruce IN. The metabolic syndrome in systemic lupus erythematosus. Rheum Dis Clin North Am 2010;**36**:81–97.

17. **Parker B,** Ahmad Y, Shelmerdine J, et al. An analysis of the metabolic syndrome phenotype in systemic lupus erythematosus. Lupus 2011;**20**:1459–65.

18. **Sabio JM,** Zamora-Pasadas M, Jimenez-Jaimez J, et al. Metabolic syndrome in patients with systemic lupus erythematosus from Southern Spain. Lupus 2008;**17**:849–59.

19. **Chung CP,** Avalos I, Oeser A, et al. High prevalence of the metabolic syndrome in patients with systemic lupus erythematosus: association with disease characteristics and cardiovascular risk factors. Ann Rheum Dis 2007;**66**:208–14.

20. **El-Magadmi M,** Ahmad Y, Turkie W, et al. Hyperinsulinemia, insulin resistance, and circulating oxidized low density lipoprotein in women with systemic lupus erythematosus. J Rheumatol 2006;**33**:50–6.

21. **Hochberg MC.** Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;**40**:1725.

22. **Gladman DD,** Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;**29**:288–91.

23. **Gladman D,** Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;**39**:363–9.

24. **Ross R.** Atherosclerosis is an inflammatory disease. Am Heart J 1999;**138**: S419–20.

25. **Tso TK,** Huang WN, Huang HY, et al. Elevation of plasma interleukin-18 concentration is associated with insulin levels in patients with systemic lupus erythematosus. Lupus 2006;**15**:207–12.

26. **Petri M,** Spence D, Bone LR, et al. Coronary artery disease risk factors in the Johns Hopkins Lupus Cohort: prevalence, recognition by patients, and preventive practices. Medicine 1992;**71**:291–302.

27. **Posadas-Romero C,** Torres-Tamayo M, Zamora-Gonzalez J, et al. High insulin levels and increased low-density lipoprotein oxidizability in pediatric patients with systemic lupus erythematosus. Arthritis Rheum 2004;**50**:160–5.

28. **Rojas R,** guilar-Salinas CA, Jimenez-Corona A, et al. Metabolic syndrome in Mexican adults: results from the National Health and Nutrition Survey 2006. Salud Publica Mex 2010;**52**(Suppl. 1):S11–18.

29. **Lorenzo C,** Williams K, Hunt KJ, et al. The National Cholesterol Education Program—Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. Diabetes Care 2007;**30**:8–13.

30. **Park HS,** Park CY, Oh SW, et al. Prevalence of obesity and metabolic syndrome in Korean adults. Obes Rev 2008;**9**:104–7.

31. **Bellomio V,** Spindler A, Lucero E, et al. Metabolic syndrome in Argentinean patients with systemic lupus erythematosus. Lupus 2009;**18**:1019–25.

32. **Claes K,** Meier-Kriesche HU, Schold JD, et al. Effect of different immunosuppressive regimens on the evolution of distinct metabolic parameters: evidence from the Symphony study. Nephrol Dial Transplant 2012;**27**:850–7.

33. **van Leuven SI,** van Wijk DF, Volger OL, et al. Mycophenolate mofetil attenuates plaque inflammation in patients with symptomatic carotid artery stenosis. Atherosclerosis 2010;**211**:231–6.

34. **Choi HK,** Hernan MA, Seeger JD, et al. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet 2002;**359**:1173–7.

Correction

Parker B, Urowitz MB, Gladman DD, *et al*. Clinical associations of the metabolic syndrome in systemic lupus erythematosus: data from an international inception cohort. *Ann Rheum Dis* 2013;72:1308–14.

A statistical error occurred in the above manuscript. On routine review of the analysis, the authors have uncovered a statistical error in their original baseline analysis that has resulted in an error in the attribution of metabolic syndrome (MetS) status to individuals in the cohort, such that a number of individuals have been misclassified by the algorithm reported. The error relates to how the authors used the coding commands in Stata for handling missing data. The authors' intention was to count the total number of MetS variables present in each individual and to allow patients with missing data to be included if they had sufficient data points to make a determination of their status. Instead, the command the authors originally used ('total') resulted in patients with any missing data being erroneously assigned a zero total for MetS components present (instead of the true number (if ≥3) or a missing status (if ≤2). This resulted in both an underestimation of the true prevalence and individuals being erroneously included in the experimental group when they should have been excluded, and thus a larger denominator group. The authors' initial manual checks of the data failed to identify this error.

Correction of this error (using the command 'rowtotal') has resulted in a reduced cohort size and an overall increase in the number of patients classified as having MetS in the cohort (now 38.2% as opposed to 16% as originally reported). The prevalence estimates in all racial/ethnic subsets are therefore higher and the estimate for patients of African ancestry is particularly affected, such that the authors now report a high prevalence in this population (55.7%). Although the point estimates in the multivariate analysis of factors associated with MetS have changed, the actual factors remain very similar to the published multivariate model (see table A) and the authors' discussion of the impact of disease activity and exposure to steroids remains unchanged.

In summary, the estimated prevalence of MetS in this cohort is now higher than that originally reported. The multivariate model has as a result of this changed, but remains similar to the authors' original report. Overall the key message of this paper remains the same in that "the observed ethnic variation in MetS susceptibility should help inform risk stratification in management of early disease. MetS is associated with a more severe disease phenotype and higher doses of corticosteroids, therefore balancing disease control while minimising corticosteroid exposure should be at the forefront of personalised treatment decisions in these patients".

Updated tables and supplementary tables, as well as a revised abstract that summarises the corrected results accurately, are available online as a data supplement.

The authors profoundly apologise for this error and feel it is important to communicate this to the research community in the interests of accuracy and scientific validity.

Table S1: Characteristics of patients with missing MetS status

	MetS assigned	MetS missing	p
No. of patients	1494	193	-
Age (years) (mean (SD))	35.2 (13.4)	35.1 (12.1)	1.00
Gender (%)			
Female	1336 (89.4)	169 (88.5)	0.70
Male	158 (10.6)	22 (11.5)	
Ethnicity (%)			
Caucasian	660/1492 (44.2)	100/191 (52.4)	<0.001
Black	228/1492 (15.3)	44/191 (23.0)	<0.001
SE Asian	303/1492 (20.3)	24/191 (12.6)	<0.001
Hispanic	240/1492 (16.1)	17/191 (8.9)	<0.001
Other	61/1492 (4.1)	6/191 (3.1)	0.9
Region (%)			
Canada	358/1477 (24.2)	27/178 (15.2)	<0.001
Mexico	194/1477 (13.1)	9/178 (5.1)	<0.001
USA	374/1477 (25.3)	97/178 (54.5)	<0.001
Asia	168/1477 (11.4)	1/178 (0.6)	<0.001
Europe	383/1477 (25.3)	44/178 (24.7)	0.9
CHD Risk Factors (mean (SD))			
BP systolic (mmHg)	119.5 (16.8)	118.7 (16.8)	0.54
BP diastolic (mmHg)	75.3 (11.0)	73.0 (10.9)	0.01
On AHT medication (%)	435 (29.1)	49 (25.4)	0.28
Triglyceride (mmol/l)	1.79 (1.19)	1.50 (0.93)	0.31
HDL-cholesterol (mmol/l)	1.39 (0.60)	1.51 (0.29)	0.79
On lipid-lowering medication (%)	171 (11.5)	0 (0)	<0.001
Glucose (mmol/l)	5.03 (1.63)	5.39 (1.81)	0.25
Diabetes (%)	50/1475 (3.4)	6/184 (3.3)	0.90
Smoker current (%)	225/1491 (15.1)	27/191 (14.1)	0.70
BMI	25.1 (5.9)	26.3 (6.3)	0.02
WC (cm)	82.9 (14.0)	84.2(14.2)	0.38
Disease duration weeks (mean SD))	24.1 (18.0)	27.6 (19.5)	0.01
SLEDAI (mean SD))	5.5 (5.4)	3.78 (4.20)	<0.001
SLICC/ACR-DI (mean(SD))	0.29 (0.72)	0.18 (0.46)	0.15
Disease Phenotype (%)			
Active renal disease	314 (22.9)	21 (10.8)	0.001
Anti-dsDNA positive	541/1347 (40.2)	38/161 (23.6)	<0.001
Low Complement	519/1349 (38.5)	50/164 (30.5)	0.05
Thrombocytopenia	44/1313 (3.4)	2/158 (1.3)	0.20
Medication (median (IQR))			
Oral CS (%)	1043 (69.8)	122 (63.2)	0.06
Average CS dose(mg)	20 (10, 30)	15 (7, 30)	0.001
Highest CS dose(mg)	40 (20, 60)	30 (20, 50)	0.08
Cumulative CS dose (g)	2.6 (1.1, 5.0)	1.7 (0.7. 4.3)	0.02
Pulse intravenous CS (%)	70/1423 (4.9)	4/184 (2.2)	0.10
Immunosuppressant (%)	599/1491 (31.0)	58/187 (40.1)	0.02
Antimalarial (%)	971 (65.0)	144 (74.6)	0.008

CHD coronary heart disease; BP blood pressure; AHT anti-hypertensive; WC waist circumference; SLEDAI Systemic Lupus Erythematosus Disease Activity index; SLICC Systemic Lupus Erythematosus; ACR American College of Rheumatology; CS corticosteroid.

Table S2: Characteristics of patients of by immunosuppressant use

	Not On Immunosuppressive	On Immunosuppressive	p
No. of patients	892	599	
Age (years) (mean (SD))	36.6 (13.7)	33.3 (13.1)	<0.001
Gender (%)			
Female	809 (90.7)	524 (87.5)	0.05
Male	83 (9.3)	75 (12.5)	0.05
MetS (%)	98 (11.0)	140 (23.4)	<0.001
MetS Phenotype (%)			
MetS WC	370/786 (47.1)	274/546 (50.2)	0.26
MetS BP	331/889 (37.2)	352 (58.8)	<0.001
MetS TG	319/808 (39.5)	297/531 (55.9)	<0.001
MetS HDL	261/453 (57.6)	224/366 (61.2)	0.30
MetS Glu	140/791 (17.7)	130/550 (23.6)	0.008
BMI (mean(SD))	25.2 (5.9)	24.9 (5.8)	0.25
WC (cm) (mean (SD))	82.7 (14.2)	83.0 (13.5)	0.70
Disease duration (wks) (mean SD))	22.7 (17.9)	25.9 (17.9)	0.001
SLEDAI (mean SD))	4.72 (4.90)	6.65 (6.00)	<0.001
SLICC/ACR-DI (mean(SD))	0.22 (0.66)	0.39 (0.79)	0.004
Medication (median (IQR)			
Oral CS (%)*	492 (55.2)	548 (91.5)	<0.001
Average CS dose(mg)	15 (10, 30)	25 (15, 40)	<0.001
Highest CS dose(mg)	30 (15, 50)	50 (30, 60)	<0.001
Cumulative CS dose (g)	1.6 (0.6, 3.4)	3.5 (1.8, 6.1)	<0.001
Pulse intravenous CS (%)	26/838 (3.1)	44/583 (7.5)	<0.001
Antimalarial (%)	654 (73.3)	316 (52.8)	<0.001

Table S3: Characteristics of patients of with and without active renal disease

	No Active Renal Disease	**Active Renal Disease**	**p**
No. of patients	1180	314	
Age (years) (mean (SD))	36.5 (13.7)	30.3 (11.9)	<0.001
Gender (%)			
Female	1078 (91.4)	258 (82.2)	<0.001
Male	102 (8.6)	56 (17.8)	<0.001
MetS (%)	145 (12.3)	94 (29.9)	<0.001
MetS Phenotype (%)			
MetS WC	524/1049 (50.0)	121/285 (42.5)	0.03
MetS BP	457/1177 (38.8)	229 (72.9)	<0.001
MetS TG	413/1064 (38.8)	206/278 (74.1)	<0.001
MetS HDL	352/615 (57.2)	134/207 (64.7)	0.06
MetS Glu	211/1048 (20.1)	60/296 (20.3)	1.00
BMI (mean(SD))	25.4 (6.1)	23.9 (4.7)	<0.001
WC (cm) (mean (SD))	83.2 (14.4)	81.6 (12.4)	0.09
Disease duration (wks) (mean SD))	24.9 (18.0)	20.8 (17.4)	<0.001
SLEDAI (mean SD))	4.09 (3.98)	10.8 (6.8)	<0.001
SLICC/ACR-DI (mean(SD))	0.26 (0.69)	0.42 (0.85)	0.03
Medication (median (IQR)			
Oral CS (%)*	750 (63.6)	293 (93.3)	<0.001
Average CS dose(mg)	16 (10, 30)	30 (20, 50)	<0.001
Highest CS dose(mg)	30 (15, 50)	50 (30, 60)	<0.001
Cumulative CS dose (g)	2.2 (0.9, 4.7)	3.1 (1.5, 5.7)	<0.001
Pulse intravenous CS (%)	33/1120 (12.2)	37/303 (3.0)	<0.001
Immunosuppressant (%)	372/1178 (31.6)	227/313 (72.5)	<0.001
Antimalarial (%)	834 (70.7)	137 (43.6)	<0.001

New Prevalence Data

MetS was present in 439/1150 patients (38.2%). The individual MetS criteria met were: MetS WC (686/1334 - 48.4%), MetS BP (491/1150 – 42.7%), MetS triglycerides (508/1099 – 46.2%), MetS HDL (470/792 – 59.3%) and MetS glucose (204/1077 – 18.9%). MetS was more common in men than women (55.3% vs. 36.3%; p = 0.03) and those with MetS were older than those without (mean (SD) age 36.9 (13.3) years vs. 34.9 (14.7) years; p <0.04). Patients of Hispanic, Korean and African Ancestry race/ethnicity had the highest prevalence of MetS (41.3% and 48.4% vs. 55.7%)

Table A: New, revised multivariable model of predictors of MetS at enrolment

Variable	Adjusted Odds Ratio (95% CI)
Age (years)	1.05 (1.04, 1.07)
Hispanic race/ethnicity	1.79 (1.13, 2.87)
Korean race/ethnicity	2.07 (1.31, 3.25)
African Ancestry race/ethnicity	2.73 (1.46, 5.12)
Active Renal Disease (yes/no)	2.70 (1.83, 3.99)
Peak CS dose (mg)	1.02 (1.01, 1.03)
Cumulative CS dose (g)	1.07 (1.01, 1.12)
Current Anti-malarial use (yes/no)	0.53 (0.37, 0.75)

Amended Abstract

Background:

The metabolic syndrome (MetS) may contribute to increased cardiovascular risk in SLE. We aimed to examine the association of demographic factors, lupus phenotype and therapy exposure with the presence of metabolic syndrome.

Methods:

The Systemic Lupus International Collaborating Clinics Registry for Atherosclerosis inception cohort enrolled recently diagnosed (<15 months) SLE patients from 30 centres across 11 countries since 2000. Clinical, laboratory and therapeutic data were collected according to a standardised protocol. MetS was defined according to the 2009 Consensus Statement from the International Diabetes Federation. Univariate and backward stepwise multivariate logistic regression were used to assess the relationship of individual variables with MetS.

Results:

We studied 1686 patients of whom 1150 (68.2%) had sufficient data to determine their MetS status. The mean (SD) age at enrolment and disease duration was 34.8 (13.6) years old and 24.2 (18.0) weeks respectively. MetS was present at the enrollment visit in 439 (38.2%). In backward stepwise multivariable regression analysis, higher peak oral prednisolone dose (mg) (OR [95% CI] 1.02 [1.01, 1.03]), cumulative corticosteroid dose (g) (1.07 [1.01, 1.12]), older age (years) (1.05 [1.04, 1.07]), Korean (2.07 [1.31, 3.25]), Hispanic (1.79 [1.13, 2.87]) and African Ancestry (2.73 [1.46, 5.12]) race/ethnicity, and current renal disease (2.70 [1.83, 3.99]) were associated with MetS. Antimalarial use was associated with a reduced risk of MetS (0.53 [0.37, 0.75]).

Conclusions:

Renal lupus, higher corticosteroid doses, Korean, Hispanic and African Ancestry race/ethnicity are associated with MetS in SLE patients whilst antimalarials appear 'protective'. Balancing disease control and minimizing corticosteroid exposure should therefore be at the forefront of personalised treatment decisions in SLE patients.

Amended Table 1: Characteristics of patients at enrolment into SLICC-RAS

No. of patients	1150
Age (years) (mean (SD))	34.8 (13.6)
Gender (%)	
Female	1036 (90.1)
Male	114 (9.9)
Ethnicity (%)	
Caucasian	516/1148 (44.9)
African Ancestry	153/1148 (13.3)
SE Asian	237/1148 (20.6)
Hispanic	182/1148 (15.9)
Other	59/1148 (5.1)
Region (%)	
Canada	358/1134 (27.1)
Mexico	194/1134 (13.5)
USA	374/1134 (22.6)
Asia	168/1134 (13.4)
Europe	383/1134 (23.5)
CHD Risk Factors (mean (SD))	
BP systolic (mmHg)	118.5 (16.4)
BP diastolic (mmHg)	74.7 (10.7)
On AHT medication (%)	328 (28.5)
Total cholesterol (mmol/l)	4.89 (1.50)
Triglyceride (mmol/l)	1.78 (1.21)
HDL-cholesterol (mmol/l)	1.39 (0.60)
On lipid-lowering medication (%)	168 (14.6)
Glucose (mmol/l)	5.02 (1.71)
Diabetes (%)	43 (3.7)
Smoker current (%)	169 (14.7)
Pre-menopausal (%)	813 (78.3)
BMI	24.9 (5.9)
WC (cm)	82.0 (14.0)
5 year % Framingham Risk	
Females	0.57
Males	5.03
Disease duration (weeks) (mean SD))	24.2 (18.0)
SLEDAI (mean SD))	5.4 (5.2)
SLICC/ACR-DI = 0	407/504 (80.8%)
Disease Phenotype (%)	
Active renal disease	243/1115 (21.1)
Anti-dsDNA positive	427/1034 (41.3)
Low Complement	419/1038 (40.4)
Thrombocytopenia	34/1313 (3.4)
Oral CS use (median (IQR))	796 (69.2)
Average CS dose(mg)	20 (10, 35)
Highest CS dose(mg)	40 (20, 60)
Cumulative CS dose (g)	2.5 (1.1, 5.0)
Pulse IV CS (%)	52/1095 (4.8)
Immunosuppressant use (%)	464/1147 (40.5)
Azathioprine	196 (42.2)
Methotrexate	84 (18.1)
Mycophenolate Mofetil	77 (16.6)
IV cyclophosphamide	78 (16.8)
Cyclosporin	17 (3.7)
Other	12 (2.6)
Antimalarial use (%)	759(66.0)

SD standard deviation; CHD coronary heart disease; BP blood pressure; AHT anti-hypertensive; HDL high density lipoprotein; BMI body mass index; WC waist circumference; SLEDAI Systemic Lupus Erythematosus Disease Activity index; SLICC Systemic Lupus Erythematosus; ACR American College of Rheumatology; CS corticosteroid; IV intravenous.

Amended Table 2: Significant factors associated with MetS at enrolment into SLICC-RAS in age, ethnicity and gender adjusted analyses

	MetS Yes	Mets No	p	Odds Ratio (95% CI)
Current CS (%)	340/439 (77.4)	456/711 (64.1)	<0.001	2.01 (1.47, 2.74)
Average CS dose (mg) (median (IQR))	25 (15, 40)	16.9 (10, 30)	<0.001	1.03 (1.02, 1.04)
Highest CS dose (mg) (median (IQR))	50 (30, 60)	30 (15, 50)	<0.001	1.03(1.02, 1.04)
Cumulative CS dose (g) (median (IQR))	3.24 (1.5, 5.9)	1.98 (0.8, 4.0)	<0.001	1.13 (1.07, 1.18)
Past IV CS (%)	14/439 (3.2)	6/711 (0.8)	0.03	4.33 (1.60, 11.74)
Antimalarial (%)	239/439 (54.5)	520/711 (73.1)	<0.001	0.43 (0.33, 0.56)
Immunosuppressant (%)	232/437 (53.1)	232/710 (32.7)	<0.001	2.55 (1.94, 3.34)
SLICC-DI ≥ 1 (%)	57/198 (28.8)	40/306 (13.1)	<0.001	2.35 (1.46, 3.79)
SLEDAI-2K (mean (SD))	6.29 (5.76)	4.91 (4.82)	0.001	1.07 (1.04, 1.10)
SLEDAI ≥ 10 (%)	110/439 (25.1)	107/708 (15.1)	<0.001	2.26 (1.64, 3.13)
Thrombocytopenia (%)	19/389 (4.9)	15/615 (2.4)	0.003	1.95 (0.93, 4.11)
Leucopenia (%)	14/383 (3.7)	57/619 (9.2)	0.001	0.35 (0.19, 0.67)
Active renal disease (%)	152/439 (34.6)	91/711 (12.8)	<0.001	4.60 (3.29, 6.43)
Past renal disease (%)	39/439 (8.9)	29/711 (4.1)	0.001	2.43 (1.43, 4.13)

CS corticosteroid; IV intravenous;

Variables reflect current exposures, recorded at enrolment

Amended Table 3: Multivariable Model of predictors of MetS at enrolment   5

Variable	Adjusted Odds Ratio (95% CI)
Age (years)	1.05 (1.04, 1.07)
Hispanic race/ethnicity	1.79 (1.13, 2.87)
Korean race/ethnicity	2.07 (1.31, 3.25)
Black African race/ethnicity	2.73 (1.46, 5.12)
Active Renal Disease (yes/no)	2.70 (1.83, 3.99)
Peak CS dose (mg)	1.02 (1.01, 1.03)
Cumulative CS dose (g)	1.07 (1.01, 1.12)
Current Anti-malarial use (yes/no)	0.53 (0.37, 0.75)

* includes azathioprine, mycophenolate mofetil, cyclophosphamide, ciclosporin, methotrexate

Variables reflect current exposures, recorded at enrolment

Amended Table 4: Characteristics of patients of Korean and Hispanic ethnicity compared to all other ethnicities

	Korean	p *	Hispanic	p **	Other ethnicities
No. of patients	151		182		738
Age (years) (mean (SD))	29.3 (14.5)	<0.0001	28.9(10.3)	<0.0001	37.5 (14.5)
Gender (%)					
Female	134 (88.7)	0.47	162 (89.0)	0.5	669 (90.7)
Male	17 (11.3)	0.47	20 (11.0)	0.5	69 (9.4)
MetS (%)	63 (41.7)	<0.0001	88 (48.4)	<0.0001	244 (33.1)
MetS Phenotype (%)					
MetS WC	32/149 (21.5)	<0.0001	92/178 (51.7)	0.14	303/666 (45.5)
MetS BP	63 (41.7)	0.63	89/182 (48.9)	0.02	289 (39.2)
MetS TG	94/146 (64.4)	<0.0001	99/156 (63.5)	<0.0001	275/722 (38.1)
MetS HDL	107/141 (75.9)	<0.0001	94/146 (64.4)	0.01	246/468 (52.6)
MetS Glu	37/150(24.7)	0.07	27/179 (15.1)	0.33	124/681 (18.2)
BMI (mean(SD))	21.7 (4.5)	<0.0001	24.3 (4.8)	0.02	25.4 (5.9)
WC (cm) (mean (SD))	75.0 (8.1)	<0.0001	82.0 (11.0)	0.56	82.7 (14.9)
Disease duration (wks) (mean SD))	18.0 (15.7)	<0.0001	23.4 (16.5)	0.27	25.1 (18.4)
SLEDAI (mean SD))	7.23 (6.32)	<0.0001	6.41 (5.75)	<0.0001	4.93 (5.2)
SLICC/ACR-DI (mean(SD))	0.19 (0.44)	0.31	0.29 (0.72)	0.95	0.28 (0.68)
Disease Phenotype (%)					
Active renal disease	45 (29.8)	<0.0001	78 (42.9)	<0.0001	99 (13.4)
Anti-dsDNA positive	92/141 (65.3)	<0.0001	62/164 (37.8)	0.89	245/658 (37.2)
Low Complement	109/143 (76.2)	<0.0001	54/163 (33.1)	0.57	234/659 (33.1)
Thrombocytopenia	15/125 (12.0)	<0.0001	2/164 (1.2)	0.29	17/646 (2.6)
Medication (median (IQR)					
Oral CS (%)*	146 (96.7)	<0.0001	159 (87.4)	<0.0001	425 (57.6)
Average CS dose(mg)	20 (10, 35)	0.03	30 (15, 42.5)	<0.0001	15.9 (10, 30)
Highest CS dose(mg)	30 (15, 55)	0.50	50 (30, 60)	<0.0001	30 (20, 50)
Cumulative CS dose (g)	1.4 (0.4, 3.1)	<0.0001	3.9 (1.8, 6.2)	<0.0001	2.27 (1.1, 4.6)
Pulse intravenous CS (%)	22 (14.5)	<0.0001	5/169 (3.0)	0.90	22/700 (3.1)
Immunosuppressant (%)	78 (51.7)	<0.0001	114 (52.2)	<0.0001	236 (32.0)
Antimalarial (%)	107 (71.0)	0.69	95 (62.6)	<0.0001	511 (69.0)

* Korean vs. all other (non-Hispanic) ethnicities; ** Hispanic vs. all other (non-Korean) ethnicities

Amended Supplemental Table S1: Characteristics of patients with missing MetS status

	MetS assigned	MetS missing	p
No. of patients	1150	537	-
Age (years) (mean (SD))	34.9 (13.6)	35.9 (12.9)	1.00
Gender (%)			
Female	1036 (90.1)	469 (87.3)	0.0.13
Male	114 (9.9)	66 (12.7)	
Ethnicity (%)			
Caucasian	516 (44.9)	244 (45.6)	<0.001
African Ancestry	154 (13.4)	118 (22.1)	<0.001
SE Asian	251 (21.9)	76 (14.2)	<0.001
Hispanic	182 (15.9)	75 (14.0)	<0.001
Other	45 (3.9)	22 (4.1)	0.9
Region (%)			
Canada	307/1134 (21.1)	78/521 (15.0)	<0.001
Mexico	153/1134 (13.5)	50/521 (9.6)	<0.001
USA	256/1134 (22.6)	215/521 (41.3)	<0.001
Asia	152/1134 (13.4)	17/521 (3.3)	<0.001
Europe	266/1134 (23.5)	161/521 (30.9)	0.9
CHD Risk Factors (mean (SD))			
BP systolic (mmHg)	118.5 (16.4)	121.4 (17.2)	0.001
BP diastolic (mmHg)	74.7 (10.7)	75.7 (11.6)	0.08
On AHT medication (%)	328 (28.5)	156 (29.1)	0.82
Triglyceride (mmol/l)	1.78 (1.21)	1.81 (1.09)	0.72
HDL-cholesterol (mmol/l)	1.39 (0.61)	1.35 (0.52)	0.72
On lipid-lowering medication (%)	168 (14.6)	3 (0.6)	<0.001
Glucose (mmol/l)	5.02 (1.71)	5.10 (1.31)	0.44
Diabetes (%)	43/1138 (3.8)	13/521 (2.5)	0.18
Smoker current (%)	169/1147 (14.7)	83/535 (15.5)	0.70
BMI	25.1 (5.9)	26.0 (6.0)	0.004
WC (cm)	82.0 (14.0)	85.7 (13.6)	<0.001
Disease duration weeks (mean SD))	24.2 (18.0)	25.0 (18.6)	0.38
SLEDAI (mean SD))	5.4 (5.2)	5.05 (5.58)	0.17
SLICC/ACR-DI (mean(SD))	0.30 (0.74)	0.21 (0.60)	0.09
Disease Phenotype (%)			
Active renal disease	243 (21.1)	92 (17.1)	0.06
Anti-dsDNA positive	427/1034 (41.3)	152/474 (32.1)	0.001
Low Complement	419/1038 (40.4)	150/475 (31.5)	0.001
Thrombocytopenia	34/1004 (3.4)	12/467 (2.6)	0.40
Medication (median (IQR))			
Oral CS (%)	796 (69.2)	369 (68.7)	0.84
Average CS dose(mg)	20 (10, 30)	15 (10, 30)	0.16
Highest CS dose(mg)	40 (20, 60)	40 (20, 60)	0.27
Cumulative CS dose (g)	2.6 (1.0, 5.0)	2.4 (1.1, 4.7)	0.74
Pulse intravenous CS (%)	52/1095 (4.8)	22/512 (4.3)	0.69
Immunosuppressant (%)	464/1147 (40.5)	193/531 (36.4)	0.11
Antimalarial (%)	759 (66.0)	356 (66.3)	0.91

CHD coronary heart disease; BP blood pressure; AHT anti-hypertensive; WC waist circumference; SLEDAI Systemic Lupus Erythematosus Disease Activity index; SLICC Systemic Lupus Erythematosus; ACR American College of Rheumatology; CS corticosteroid.

Amended Supplemental Table S2: Characteristics of patients of by immunosuppressant use

	Not On Immunosuppressive	On Immunosuppressive	p
No. of patients	683	464	
Age (years) (mean (SD))	36.3 (13.6)	32.6 (13.4)	<0.001
Gender (%)			
Female	629 (92.1)	524 (87.1)	0.005
Male	54 (7.9)	75 (12.9)	0.005
MetS (%)	205 (30.0)	232 (50.0)	<0.001
MetS Phenotype (%)			
MetS WC	266/628 (42.4)	209/438 (47.7)	0.08
MetS BP	221/683 (32.4)	267/464 (57.5)	<0.001
MetS TG	247/651 (37.9)	257/445 (58.0)	<0.001
MetS HDL	251/435 (57.7)	218/354 (61.6)	0.27
MetS Glu	104/635 (16.4)	99/435 (22.6)	0.01
BMI (mean(SD))	25.0 (6.0)	24.7 (5.6)	0.41
WC (cm) (mean (SD))	81.7 (14.2)	82.5 (13.6)	0.38
Disease duration (wks) (mean SD))	22.8 (17.8)	26.0 (18.0)	0.003
SLEDAI (mean SD))	4.68 (4.65)	6.57 (5.85)	<0.001
SLICC/ACR-DI (mean(SD))	0.21 (0.62)	0.43 (0.85)	0.006
Medication (median (IQR)			
Oral CS (%)*	369 (54.0)	424 (91.4)	<0.001
Average CS dose(mg)	15 (10, 30)	25 (15, 40)	<0.001
Highest CS dose(mg)	30 (15, 50)	50 (30, 60)	<0.001
Cumulative CS dose (g)	1.5 (0.6, 3.2)	3.4 (1.8, 6.0)	<0.001
Pulse intravenous CS (%)	19/640 (3.0)	33/453 (7.3)	<0.001
Antimalarial (%)	510 (74.7)	248 (53.4)	<0.001

Table S3: Characteristics of patients of with and without active renal disease

	No Active Renal Disease	Active Renal Disease	p
No. of patients	907	243	
Age (years) (mean (SD))	36.2 (13.8)	29.9 (11.8)	<0.001
Gender (%)			
Female	836 (92.2)	200 (82.3)	<0.001
Male	71 (7.8)	43 (17.7)	<0.001
MetS (%)	287 (31.6)	152 (62.6)	<0.001
MetS Phenotype (%)			
MetS WC	380/842 (45.1)	96/226 (42.5)	0.48
MetS BP	318/907 (35.1)	173/243 (71.2)	<0.001
MetS TG	329/863 (38.1)	179/236 (75.9)	<0.001
MetS HDL	339/590 (57.5)	131202 (64.9)	0.07
MetS Glu	154/846 (18.2)	50/231 (21.7)	0.24
BMI (mean(SD))	25.2 (6.1)	23.8 (4.5)	0.001
WC (cm) (mean (SD))	82.2 (14.5)	81.4 (12.0)	0.43
Disease duration (wks) (mean SD))	25.2 (18.1)	20.4 (17.1)	0.002
SLEDAI (mean SD))	4.1 (3.9)	10.6 (6.3)	<0.001
SLICC/ACR-DI (mean(SD))	0.27 (0.71)	0.45 (0.86)	0.04
Medication (median (IQR)			
Oral CS (%)*	570 (62.8)	226 (93.30	<0.001
Average CS dose(mg)	15 (10, 27.5)	31 (23.5, 50)	<0.001
Highest CS dose(mg)	30 (15, 50)	50 (40, 60)	<0.001
Cumulative CS dose (g)	2.2 (0.8, 4.6)	3.2 (1.6, 5.7)	<0.001
Pulse intravenous CS (%)	23/861 (2.7)	29/234 (12.4)	<0.001
Immunosuppressant (%)	285/905 (31.5)	179/242 (74.0)	<0.001
Antimalarial (%)	653/907 (72.0)	106/243 (43.6)	<0.001