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Cardiovascular Complications of Systemic Lupus Erythematosus: Impact of Risk Factors and Therapeutic efficacy--a Tertiary Centre Experience in an Appalachian State

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Cardiovascular complications of systemic lupus erythematosus: impact of risk factors and therapeutic efficacy—a tertiary centre experience in an Appalachian state

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ABSTRACT

Objectives Cardiovascular complications became a notable cause of morbidity and mortality in patients with lupus as therapeutic advancements became more efficient at managing other complications. The Appalachian community in Kentucky has a higher prevalence of traditional cardiovascular risk factors, predisposing them to cardiovascular events. Namely, the mean body mass index of the members of the Kentucky Appalachian community was reported at 33 kg/m^2 and 94.3% of male members of this community use tobacco. We sought to identify risk factors that predispose patients with lupus to cardiovascular morbidities and examine the effect of immunomodulatory drugs.

Methods We identified 20 UKHS patients having both a lupus diagnosis and experienced at least one cardiovascular event. We chose three controls matched for birth-year ±5 years to each case. In a case–control design, we analysed lupus manifestations, cardiovascular risk factors and immunosuppressive therapies. We collected Systemic Lupus Erythematosus Disease Activity Index 2000 disease activity index during the cardiovascular event.

Results We identified 308 patients with lupus from among all University of Kentucky Health System patients. 20 (6.5%) of such patients with lupus were confirmed to cardiovascular complication. Of those 20, 7 (35%) had experienced myocardial infarction, 10 (50%) had experienced stroke and 4 (20%) had peripheral ischaemia. Tobacco use and male gender were the only traditional cardiovascular risk factors higher in the cases group. Hydroxychloroquine and steroids were less utilised in the cases than in the controls (70% vs 100% in hydroxychloroquine, 30% vs 82% in steroids). Venous thrombosis was found to be significantly higher in the cases. On multivariate analysis, venous thrombosis remained significant.

Conclusion Despite tobacco use partially explaining the increased risk of cardiovascular disease among the cases group, the higher prevalence of venous thrombosis in the cases group suggests lupus as a potential additional risk factor of cardiovascular morbidity among patients with lupus in this Appalachian community.

Key messages

What is already known about this subject?

- Lupus is a known contributor to increased risk of cardiovascular morbidity.

What does this study add?

- Traditional cardiovascular risk factors, especially tobacco use, should be addressed in patients with lupus .

How might this impact on clinical practice or future developments?

- Among patients with lupus with venous thrombosis, clinicians should be alert to the higher risk of cardiovascular complications, particularly stroke.
- Among patients with arterial thrombovascular disease, venous thrombosis should alert clinicians to consider the presence of underlying lupus.

INTRODUCTION

SLE is a multisystem autoimmune disease with high morbidity.[1] Classically, disease mortality was attributed to renal involvement.[1] As immunomodulatory therapy improved, renal-related mortality was reduced.[1–3] Cardiovascular mortality has become a more prominent cause of mortality,[4] making up 30% of mortality in the first 5 years after diagnosis.[5–7] Both stroke and myocardial infarction were noted to occur more often in premenopausal lupus women compared with their counterparts.[1 5–10] Average age at which such events occurred in comparison to general population was younger (49 vs 69 years).[6] The risk of cardiovascular disease in lupus is not completely accounted for by traditional cardiovascular risk factors.[8 11] The increased risk is not restricted to myocardial infarctions and stroke but also includes peripheral arterial disease.[12]

In Appalachian communities, cardiovascular events are increased compared with the rest of the USA. Particularly, Kentucky ranked sixth in 2003 on total cardiovascular age-adjusted death rate.[13] According to the American Heart Association, the state of Kentucky has one of the highest death rates in both stroke and coronary artery disease. Kentucky is ranked 42nd in the nation, with first ranked state reflecting lowest death rate from stroke and coronary artery disease.[14]

It is noteworthy that traditional cardiovascular risk factors are increased in this population, with overall average body mass index (BMI) of 33 kg/m^2 and tobacco use reaching up to 94.3% in male members of the population.[15] Therefore, addressing all potential risk factors of cardiovascular disease among Kentucky Appalachian patients with lupus is imperative. Among traditional cardiovascular risk factors in patients with lupus, several studies have demonstrated important associations. Namely, peripheral arterial disease was associated with higher risk of cardiovascular endpoints.[16] Additionally, dyslipidaemia,[17] metabolic syndrome,[18] older age at diagnosis and longer duration of cardiovascular disease were also associated with high risk of cardiovascular adverse events.[9 19] In contrast, among other studies, particularly in Europe[10 20] and Canada,[18] lupus itself and its manifestations were identified as risk factors for cardiovascular disease in patients with lupus. Namely, arthritis, pleuritis, venous thrombosis, neuropsychiatric disease manifestations and antiphospholipid antibodies were identified as important predictors.[6 20]

Response to immunosuppressive treatments differed among studies and medications. In a study on peripheral ischaemia in lupus, Erdozain *et al*[12] noted that patients with lupus with normal ankle-brachial index had a higher chance of being on cyclophosphamide. This raised the question that perhaps cyclophosphamide may have been protective of peripheral arterial disease in this studied population. However, hydroxychloroquine did not show this potential beneficial effect.[12] Yet, other studies have shown a reduction of cardiovascular disease in hydroxychloroquine users.[21] In regard to steroids, a study on all cardiovascular end points, mean duration of steroid use was correlated with higher risk.[9]

Cardiovascular disease pathogenesis in lupus was explained by either atherosclerosis and/or subclinical vasculitis. Ultrasonographic carotid intima-media thickness, as a proven predictor of myocardial infarction events in lupus, was used as surrogate of atherosclerosis.[22–29] A multination study, utilising angiography as a surrogate for atherosclerosis, did not show atherosclerosis as predictor of cardiovascular disease in patients with lupus.[30] In autopsy-based studies, both accelerated atherosclerosis and vasculitis were noted on histopathology of coronary vasculature.[31 32] These findings might partially justify why studies differ in the type of risk factors (traditional cardiovascular vs lupus manifestations) and response to immunosuppressive therapies. Therefore, further studies need to delineate the magnitude of contribution of cardiovascular risk factors and atherosclerosis versus lupus disease activity and subclinical vasculitis in different populations.

METHODS

Patient population

Through search of the University of Kentucky Health System (UKHS) database, including inpatient and outpatient medical records for the years 2004 through 2020, we identified 308 patients having diagnosis codes of ICD-9 (710-Connective tissue disease, unspecified) or (Lupus erythematosus 695.4) or ICD-10 (M32 Systemic lupus erythematosus) or (L93 Lupus erythematosus). Among these patients, only those who received treatment with hydroxychloroquine and/or had two or more visits with University of Kentucky Rheumatology Clinic were selected for further study. The hydroxychloroquine treatment criteria was added to capture newly added UKHS patients who had previously received outpatient rheumatology treatment outside of that system. Since some relevant individuals might not have been captured if treatment with hydroxychloroquine had been contraindicated, we elected to expand the search by including individuals who were provided at least one follow-up visit with the UKHS Rheumatology Clinic as a more reliable indicator of a true diagnosis of systemic autoimmunity. All patients included in this study fulfill the American College of Rheumatology classification criteria by reviewing documentation in medical records.[33]

We screened the 308 UKHS patients with lupus for atherosclerosis (ICD-9 440.2, ICD-10 I70), coronary artery disease (ICD-9 414.01, ICD-10 I20-I25, I00-I99) and peripheral arterial disease (ICD-9 443.9, ICD-10 I73.9), which identified 20 patients as our cases group of patients with lupus having cardiovascular complications. Three of the UKHS patients with lupus that had not exhibited any cardiovascular complications were matched with each member of the cases group by birth year ±5 years as controls to increase the power of the study. The codes encompassed events occurring within the University of Kentucky or historically, particularly when events occurred in external systems. Follow-up post lupus diagnosis ranged between 1 year and 41 years, as earliest diagnosis was 1979 and latest was 2019.

We searched the medical records of the cases and control groups for traditional cardiovascular risk factors including tobacco use, diabetes mellitus, hypertension, dyslipidaemia and obesity. We recorded lupus manifestations at baseline and at the time of cardiovascular events. These included malar rash, arthritis, other lupus rashes, alopecia, mucocutaneous ulceration, pleuritis, pericarditis, neuropsychiatric manifestations, renal involvement, Raynaud's phenomenon and sicca symptoms. We collected information regarding laboratory test results for these patients, including leucopenia, thrombocytopenia, lymphopenia, leukouria, haematuria, proteinuria, red cell casts, C3 and C4 complements levels, anti-double-stranded

DNA antibodies, anti-Smith antibodies, anti-RNP antibodies, anti-SSA antibodies, anti-SSB antibodies, lupus anticoagulant, anti-cardiolipin antibodies and anti-β2 glycoprotein antibodies. Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) was collected at the time of event for the cases.

We also collected information regarding any immunomodulatory disease-modifying agents that had been administered to patients of the study cohort (with such administration being before the occurrence of cardiovascular events for patients of the cases group). Such agents included steroids, azathioprine, mycophenolate mofetil, rituximab, cyclophosphamide, belimumab and hydroxychloroquine.

Statistical analysis

χ^2 test was used for categorical variables, while the Shapiro-Wilks test was used when the assumption of normality was not fulfilled. Equal variance t-tests for continuous variables were used to compare case versus control at baseline. We evaluated the association between the cardiovascular outcomes (stroke, myocardial infarction and peripheral ischaemic event) and aforementioned lupus clinical manifestations, serological testing and traditional cardiovascular risk factors using univariate analysis. Multivariate logistic regression was done using all variables and their two-way interactions as possible predictors for forward selection using the rFSA R package to check for interactions. Throughout the analyses, a p value<0.05 was considered statistically significant.

RESULTS

We identified 308 UKHS patients with lupus fulfilling aforementioned ICD-9/10 code at the University of Kentucky in addition to either use of hydroxychloroquine and/or having two or more visits with Rheumatology between the years 2004 and 2020. Among the 308 patients with lupus identified, we found 20 (6.7%) patients who had cardiovascular complications. In comparison, the University of Pittsburgh Registry demonstrated that 23/498 (4.7%) patients developed myocardial infarction.[8] Among these 20 individuals, 7 (35%) had myocardial infraction, 10 (50%) had stroke and 4 (20%) had peripheral ischaemia. One patient had both a cardiovascular complication and stroke. Out of the 20 patients with SLE with cardiovascular disease, 15 (75%) were Caucasian and 5 (25%) were African American (table 1). The mean SLEDAI-2K score among the cases group at the time of cardiovascular event was 11.15±9.25, with most common associated manifestation being thrombocytopenia at 6 (30%), followed by low complements at 5 (25 %) and elevated dsDNA at 4 (20%). Excluding neuropsychiatric manifestations, SLEDAI score would be reduced to 9.35±5.68.

Among the seven patients who developed coronary artery disease, three of these patients, all of which were tobacco users, underwent Coronary Artery Bypass Graft. The average age at lupus diagnosis of all the individuals developing myocardial infarction was 45.4 years. Among the patients with single-vessel disease involvement, two had right coronary artery involvement and one had left anterior descending artery involvement. Tobacco use was a risk factor in 4/7 (57%) myocardial infarction patients (online supplemental table 1). The mean age at diagnosis of myocardial infarction was 51.43±8.43.

Table 1 Active lupus manifestations prior to cardiovascular end event

Active features	Frequency	Percentage
SLEDAI-2K score	11.15±9.25	
Any lupus rash	1	5
Arthritis	2	10
Serositis	1	5
Renal disease	2	10
Neuropsychiatric	2	10
Leucopenia	3	15
Thrombocytopenia	6	30
Low complements	5	25
Elevated anti-dsDNA	4	20

dsDNA, double stranded DNA; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Among patients who had a stroke, average age in patients with lupus was 30.9 years, which is around 15 years younger than lupus diagnosis in the myocardial infarction group. Tobacco use was a risk factor present in 4 (40%) of the 10 patients who had a stroke. Two patients had multi-infarct disease, both of whom were diagnosed with lupus in their 20's and neither of whom was a tobacco user. The mean of age of stroke diagnosis was 38±11.97, which is 13 years younger than the mean age of occurrence of myocardial infarction. (p=0.0297) (online supplemental table 2).

Among the individuals who had suffered a myocardial infarction, three patients suffered that event prior to their lupus diagnosis. Per records, these were initially attributed to traditional risk factors such as obesity (online supplemental table 1). Among the individuals who had experienced one or more strokes, one patient was diagnosed with lupus after stroke diagnosis and this was initially attributed to traditional risk factors of hypertension and obesity (online supplemental table 2). A prior study at University of Toronto noted myocardial infarction occurred early at onset of lupus or prior to diagnosis.[8]

Among patients with peripheral ischaemic vascular disease, only one was a tobacco user. Two of the peripheral ischaemia patients were diagnosed with lupus in their teenage years, one of whom was diagnosed with both lupus and peripheral ischaemia at a young age (online supplemental table 3).

We controlled for baseline therapy by focusing on the therapies given to the cases group prior to occurrence of a cardiovascular event. All patients of the control group

Table 2 Treatments given prior to cardiovascular events versus treatments given in control group

Treatment	Cases (n=20)	Controls (n=60)	OR (CI)	P value
Steroids	6/20	49/60	0.10 (0.03 to 0.31)	**<0.001***†
Hydroxychloroquine	14/20	60/60	Not applicable	**<0.001**†
Azathioprine	6/20	17/60	1.08 (0.36 to 3.29)	0.89
Mycophenolate mofetil	5/20	18/60	0.78 (0.25 to 2.46)	0.67
Cyclophosphamide	3/20	6/60	1.59 (0.36 to 7.04)	0.54
Rituximab	3/20	3/60	3.35 (0.62 to 18.16)	0.14
Belimumab	1/20	4/60	0.74 (0.08 to 7.01)	0.79

*Remained significant in multivariate analysis.
†Bold indicates statistical significance.

had been treated with hydroxychloroquine, while only 70% (14/20) of the cases group had been treated with hydroxychloroquine. Steroid use was also lower in the cases group. None of the other disease-modifying agents were found to have protective effect or different utilisation between the cases and the controls (table 2).

On univariate analysis, the cases group had less arthritis reported (table 3). Among the other lupus risk factors, only venous thrombosis was higher in the cases group, which persisted through multivariate analysis (table 4). Among the traditional cardiovascular risk factors, tobacco use was higher in the cases group, but did not persist into multivariate analysis.

Among the six patients who had venous thrombosis, four had strokes and two had peripheral ischaemia. Four of the six venous thrombosis patients were diagnosed with lupus at an age below 45 years and two of such patients were diagnosed after 45 years of age. Three of the six venous thrombosis patients were tobacco users (online supplemental table 4).

DISCUSSION

SLE has been associated with an increased risk of adverse cardiovascular events. However, the risk of cardiovascular events among a high-risk population such as the Appalachian population is not well understood. To our knowledge, this is the first study on cardiovascular morbidity risk factors among Appalachian patients with lupus. In a prospective lupus cohort, several risk factors were found to be predictive of a first cardiovascular event including arthritis, pleuritis and venous thrombosis.[20] We found similar correlation in venous thrombosis and association with cardiovascular morbidity. As we analysed our cases with venous thrombosis, they were mainly patients who developed strokes and peripheral ischaemia rather than myocardial infarction. Generally, we show in our study trends towards higher traditional cardiovascular risk factors in the cases group, particularly using tobacco showing statistical significance (only on univariate analysis). Similarly, results from the University of Toronto lupus cohort identified tobacco as a risk factor for cardiovascular end points (myocardial infarction (MI), stroke and peripheral ischaemia).[6] Appalachian communities are at higher risk of cardiovascular morbidity.[34] For instance, a 2020 study noted an average BMI of 33 kg/m^2 in the Kentucky Appalachian community with a concerning 94.3% tobacco use among men.[15]

Beyond showing the contribution of traditional cardiovascular risk factors, we were able to identify venous thrombosis as significantly higher in cases with adverse cardiovascular events compared with controls.[35] In view of this result, we believe it is important that clinicians be vigilant in regarding a new diagnosis of lupus as a risk factor for stroke and regard lupus as a potential risk factor for early stroke, particularly in patients with history of venous thrombosis.[6 20 36] Nonetheless, we show some cases who developed myocardial infarction or stroke prior to lupus diagnosis in our study. Initially, those events were attributed to traditional risk factors. Prior study from the University of Toronto showed myocardial infarction prior to or early on after diagnoses of lupus.[37]

Our cases had mean SLEDAI-2K score of 11.15 prior to the event. A prospective study evaluating stroke in lupus found an SLEDAI-2K of 12.6 on average in comparison with 8.4 in control group.[38] Hinting that even in the Appalachian community, which has high level of traditional cardiovascular risk factors, lupus activity remains a contributing factor for stroke. Prior studies supported our findings, namely the Framingham score, fell short of predicting cardiovascular morbidity in patients with lupus indicating lupus-related risk.[8 11]

Our study shows lower steroid use in cases with adverse cardiovascular events compared with controls in contrast to a prior study which showed higher steroid use.[9] However, we measured steroids use as a dichotomous value in comparison with the Hopkins cohort who utilised duration of steroid use.[9] Steroid use is a risk of cardiovascular disease but can lead to lower lupus disease activity. A possible explanation is that, at initial doses, steroid use reduces disease activity but when such use is excessive the benefit of disease control is offset by steroid side effects such as obesity. Additionally, our study is in 2020 in comparison with the 1992 study.[9] The use of steroids could possibly be higher in 1992 compared with 2020, as rheumatologists are becoming more aggressive with disease-modifying agents. In relation to immunosuppression, a

Table 3 Comparison of patients with cardiovascular events and the control group (univariate analysis)

Historical features	Cases (n=20)	Controls (n=60)	OR (CI)	P value
Malar rash	2/20	11/60	0.49 (0.10 to 2.45)	0.38
Any lupus rash	9/20	28/60	0.94 (0.34 to 2.58)	0.90
Mucocutaneous ulcers	2/20	11/60	0.49 (0.10 to 2.45)	0.38
Sicca	6/20	17/60	1.08 (0.36 to 3.29)	0.89
Alopecia	4/20	11/60	1.11 (0.31 to 3.99)	0.87
Arthritis	5/20	34/60	0.25 (0.08 to 0.79)	**0.01**†
Serositis	4/20	7/60	1.89 (0.49 to 7.30)	0.35
Pericarditis	3/20	5/60	1.94 (0.42 to 8.98)	0.39
Pleuritis	1/20	2/60	1.53 (0.13 to 17.79)	0.73
DAH	1/20	0/60	Not applicable	0.08
Renal disease	7/20	19/60	1.16 (0.40 to 3.38)	0.78
Neuropsychiatric	1/20	1/60	3.10 (0.19 to 52.08)	0.40
Raynaud's	5/20	16/60	0.92 (0.29 to 2.93)	0.88
Leucopenia	11/20	32/60	1.07 (0.39 to 2.96)	0.90
Thrombocytopenia	9/20	25/60	1.15 (0.41 to 3.18)	0.79
Haemolysis	3/20	2/60	5.12 (0.79 to 33.17)	0.06
Low complement	12/20	29/60	1.60 (0.57 to 4.48)	0.37
Anti-dsDNA	6/18	32/59	0.42 (0.14 to 1.27)	0.12
Anti-SSA	12/16	25/50	3 (0.85 to 10.58)	0.08
Anti-SSB	2/15	10/50	0.62 (0.12 to 3.18)	0.56
Anti-Smith	4/15	8/52	2 (0.51 to 7.87)	0.32
Anti-RNP	7/14	21/53	1.52 (0.47 to 4.98)	0.48
Venous thrombosis	6/20	4/60	6 (1.49 to 24.19)	**0.006***†
Pregnancy loss	1/17	2/58	1.75 (0.15 to 20.56)	0.65
Livedo reticularis	0/20	1/60	Not applicable	0.56
Seizure	5/20	5/60	3.67 (0.94 to 14.35)	0.05
Anti-β_2GPI IgG	0/12	0/32	Not applicable	0.00
Anti-β_2GPI IgM	2/12	1/32	6.2 (0.51 to 75.84)	0.11
Cardiolipin IgG	2/14	2/34	2.67 (0.34 to 21.12)	0.34
Cardiolipin IgM	1/14	1/34	2.54 (0.15 to 43.67)	0.51
Lupus anticoagulant	4/13	5/32	2.4 (0.53 to 10.93)	0.25
BMI>30	11/20	22/60	2.11 (0.76 to 5.89)	0.15
Diabetes	2/20	3/60	2.11 (0.33 to 13.64)	0.42
Dyslipidaemia	8/20	15/60	1.83 (0.63 to 5.30)	0.26
Hypertension	10/20	28/60	1.14 (0.42 to 3.15)	0.80
Tobacco	11/20	14/60	4.01 (1.38 to 11.65)	**0.008**†
Female gender	13/20	58/60	0.064 (0.01 to 0.34)	**0.0001***†

*Remained significant in multivariate analysis.
†Bold indicates statistical significance.
BMI, body mass index; DAH, diffuse alveolar haemorrhage; dsDNA, double-stranded DNA; β_2GPI, β-2 glycoprotein I; RNP, ribonucleoprotein; SSA, Sjögren syndrome A; SSB, Sjögren syndrome B.

Table 4 Logistic regression predicting case

Term	Estimate	P value	OR (95% CI)
Female	−1.61	0.0016	0.034 (0.003 to 0.371)
Steroids	−1.42	0.0003	0.063 (0.012 to 0.342)
Venous clot	1.51	0.0032	18.690 (2.250 to 155.243)

study focused on peripheral ischaemia showed potential correlation between cyclophosphamide as protective against peripheral vascular disease, but this was not demonstrated with hydroxychloroquine.[12] In contrast, we have found that hydroxychloroquine use was significantly lower in the cases group indicating possible

protective effect that was not found in other immunosuppressive disease-modifying agents. A possible reason for this discrepancy is that we analysed stroke, MI and peripheral ischaemic vascular disease, while the Erdozain *et al*[12] focused on peripheral ischaemia in their study. Additionally, the reason behind patient cardiovascular morbidity could have been atherosclerosis and/or subclinical coronary vasculitis.[31 32] Another possible explanation is that most of our cases, particularly among patients that had experienced a stroke, experienced the cardiovascular event and were diagnosed with lupus at a young age. Also, we need to keep in mind the possibility of skewed data due to the selection methodology. As pointed out in Methods, we chose patients with lupus based on lupus ICD codes with additional criteria of having had two or more visits with University of Kentucky Rheumatology Clinic and/or being treated with hydroxychloroquine, wherein the hydroxychloroquine treatment criteria was intended to catch patients with lupus who were followed at Rheumatology clinics outside the University of Kentucky Rheumatology Clinic.

In summary, our study highlights the significance of tobacco use and venous thrombosis in lupus cardiovascular morbidity, also in agreement with the similar findings in the University of Toronto cohort.[6] In contrast to prior studies in the USA, we were able to show the effect of lupus manifestations, namely venous thrombosis.[9] Statistical significance of this manifestation was found despite the high prevalence of cardiovascular risk factors in our cases, particularly using tobacco, and overall higher cardiovascular risk factors in Appalachian communities.[15] In regard to medications, we showed the potential benefit of hydroxychloroquine on reducing cardiovascular events as seen in prior analyses.[21] We showed a lower steroid use in the cases which contrasts with higher mean duration use of steroids in a prior study among individuals with cardiovascular events.[9]

Therefore, rheumatologists should be vigilant with cessation of tobacco use counselling in patients with lupus. Neurologists and clinicians caring for new patients who had a stroke should consider lupus as risk factors, especially in younger patients, even in the presence of other risk factors. We further note that, despite being generally regarded as a mainstay of therapy in all patients with lupus, hydroxychloroquine is still not prescribed consistently in clinical practice. In view of the potential benefit of hydroxychloroquine in reducing cardiovascular events, hydroxychloroquine initiation threshold should be lowered, particularly in patients who have other traditional risk factors or had venous thrombosis.

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Contributors EDM, AB and NMK contributed to formulation of original idea, collecting information, statistical analysis and writing and review of the manuscript. AA-L contributed to the original idea and writing and review of the manuscript. AS contributed to statistical analysis as statistician of the project and contributed to writing and review of manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol complies with the Declaration of Helsinki and was approved by the University of Kentucky's Institutional Review Board and Ethics Committees under number 57062.

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Data availability statement Data are available upon reasonable request. After data collected, they were stored on secure drive. Deidentified data were statistically analysed. Excel sheets with deidentified data and statistical analysis would be available for journal upon reasonable request till 5 years after publication. Proposals to request data should be directed to abdel-latif@uky.edu to gain access. Data requestors will need to sign a data access agreement.

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REFERENCES

1 Gustafsson JT, Svenungsson E. Definitions of and contributions to cardiovascular disease in systemic lupus erythematosus. *Autoimmunity* 2014;47:67–76.
2 Jacobsen S, Petersen J, Ullman S, *et al*. A multicentre study of 513 Danish patients with systemic lupus erythematosus. II. disease mortality and clinical factors of prognostic value. *Clin Rheumatol* 1998;17:478–84.
3 Chambers SA, Allen E, Rahman A, *et al*. Damage and mortality in a group of British patients with systemic lupus erythematosus followed up for over 10 years. *Rheumatology* 2009;48:673–5.
4 Björnådal L, Yin L, Granath F, *et al*. Cardiovascular disease a hazard despite improved prognosis in patients with systemic lupus erythematosus: results from a Swedish population based study 1964-95. *J Rheumatol* 2004;31:713–9.
5 Urowitz MB, Bookman AA, Koehler BE, *et al*. The bimodal mortality pattern of systemic lupus erythematosus. *Am J Med* 1976;60:221–5.
6 Urowitz MB, Ibañez D, Gladman DD. Atherosclerotic vascular events in a single large lupus cohort: prevalence and risk factors. *J Rheumatol* 2007;34:70–5.
7 Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;42:338–46.
8 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.
9 Petri M, Perez-Gutthann S, Spence D, *et al*. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med* 1992;93:513–9.
10 Fernández-Nebro A, Rúa-Figueroa Íñigo, López-Longo FJ, *et al*. Cardiovascular events in systemic lupus erythematosus: a nationwide study in Spain from the RELESSER registry. *Medicine* 2015;94:e1183.
11 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.

12 Erdozain JG, Villar I, Nieto J, *et al*. Peripheral arterial disease in systemic lupus erythematosus: prevalence and risk factors. *J Rheumatol* 2014;41:310–7.
13 Rugg SS, Bailey AL, Browning SR. Preventing cardiovascular disease in Kentucky: epidemiology, trends, and strategies for the future. *J Ky Med Assoc* 2008;106:149-61; quiz 149, 162-3.
14 Thom T, Haase N, Rosamond W, *et al*. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006;113:e85–151.
15 Abraham CM, Kelly S, Wantland D, *et al*. Factors influencing cardiovascular risk factors and health perception among Kentuckians living in Appalachia. *J Cardiovasc Nurs* 2020;35:E1–8.
16 Leng GC, Lee AJ, Fowkes FG, *et al*. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1996;25:1172–81.
17 Bhatt SP, Handa R, Gulati GS, *et al*. Peripheral vascular disease in systemic lupus erythematosus. *Lupus* 2007;16:720–3.
18 Bultink IEM, Turkstra F, Diamant M, *et al*. Prevalence of and risk factors for the metabolic syndrome in women with systemic lupus erythematosus. *Clin Exp Rheumatol* 2008;26:32–8.
19 Bruce IN, Gladman DD, Urowitz MB. Premature atherosclerosis in systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000;26:257–78.
20 Gustafsson J, Gunnarsson I, Börjesson O, *et al*. Predictors of the first cardiovascular event in patients with systemic lupus erythematosus - a prospective cohort study. *Arthritis Res Ther* 2009;11:R186.
21 Liu D, Li X, Zhang Y, *et al*. Chloroquine and hydroxychloroquine are associated with reduced cardiovascular risk: a systematic review and meta-analysis. *Drug Des Devel Ther* 2018;12:1685–95.
22 Manzi S, Selzer F, Sutton-Tyrrell K, *et al*. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;42:51–60.
23 Roman MJ, Salmon JE, Sobel R, *et al*. Prevalence and relation to risk factors of carotid atherosclerosis and left ventricular hypertrophy in systemic lupus erythematosus and antiphospholipid antibody syndrome. *Am J Cardiol* 2001;87:663–6.
24 Svenungsson E, Jensen-Urstad K, Heimbürger M, *et al*. Risk factors for cardiovascular disease in systemic lupus erythematosus. *Circulation* 2001;104:1887–93.
25 Roman MJ, Shanker B-A, Davis A, *et al*. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;349:2399–406.
26 Souza AWSde, Hatta FS, Miranda F, *et al*. Atherosclerotic plaque in carotid arteries in systemic lupus erythematosus: frequency and associated risk factors. *Sao Paulo Med J* 2005;123:137–42.
27 Telles RW, Lanna CCD, Ferreira GA, *et al*. Carotid atherosclerotic alterations in systemic lupus erythematosus patients treated at a Brazilian university setting. *Lupus* 2008;17:105–13.
28 Eder L, Gladman DD, Ibañez D, *et al*. The correlation between carotid artery atherosclerosis and clinical ischemic heart disease in lupus patients. *Lupus* 2014;23:1142–8.
29 Kao AH, Lertratanakul A, Elliott JR, *et al*. Relation of carotid intima-media thickness and plaque with incident cardiovascular events in women with systemic lupus erythematosus. *Am J Cardiol* 2013;112:1025–32.
30 Urowitz MB, Gladman D, Ibañez D, *et al*. Atherosclerotic vascular events in a multinational inception cohort of systemic lupus erythematosus. *Arthritis Care Res* 2010;62:881–7.
31 Panchal L, Divate S, Vaideeswar P, *et al*. Cardiovascular involvement in systemic lupus erythematosus: an autopsy study of 27 patients in India. *J Postgrad Med* 2006;52:5-10; discussion 10.
32 Kazzaz NM, Wilson AM, Kado R, *et al*. A 37-year-old man with primary antiphospholipid syndrome presenting with respiratory distress and worsening toe ischemia. *Arthritis Care Res* 2017;69:1253–9.
33 Hochberg MC. Updating the American College of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
34 Esch L, Hendryx M. Chronic cardiovascular disease mortality in mountaintop mining areas of central Appalachian states. *J Rural Health* 2011;27:350–7.
35 Bertolaccini ML, Amengual O, Andreoli L, *et al*. 14Th international Congress on antiphospholipid antibodies Task force. Report on antiphospholipid syndrome laboratory diagnostics and trends. *Autoimmun Rev* 2014;13:917–30.
36 Bessant R, Duncan R, Ambler G, *et al*. Prevalence of conventional and lupus-specific risk factors for cardiovascular disease in patients with systemic lupus erythematosus: a case-control study. *Arthritis Rheum* 2006;55:892–9.
37 Urowitz MB, Gladman DD, Anderson NM, *et al*. Cardiovascular events prior to or early after diagnosis of systemic lupus erythematosus in the systemic lupus international collaborating clinics cohort. *Lupus Sci Med* 2016;3:e000143.
38 Mikdashi J, Handwerger B, Langenberg P, *et al*. Baseline disease activity, hyperlipidemia, and hypertension are predictive factors for ischemic stroke and stroke severity in systemic lupus erythematosus. *Stroke* 2007;38:281–5.

Supplemental:

Table 1 Supplemental: Myocardial infarction cases

Age during event	Age at Lupus Diagnosis	Coronaries involved and/or intervention	Traditional risk factors
48	51	CABG	Tobacco user and obese
43	*39*	*Not documented*	*Dyslipidemia, HTN, and obese*
50	52	RCA	Dyslipidemia and Obese
39	30	LAD, CABG	Tobacco user, diabetes, and HTN
62	64	Not documented, CABG	Dyslipidemia, tobacco user, and HTN
55	32	RCA	Dyslipidemia, tobacco user and obese
63	50	Not documented	Dyslipidemia, tobacco user and HTN

LAD, Left anterior descending; RCA, right coronary artery; PDA, posterior descending artery; CABG, coronary artery bypass graft
Italic: also had stroke

Table 2 supplemental: Stroke cases

Age during event	Age at Lupus Diagnosis	Vessels involved	Traditional risk factors
26	23	Unknown	Tobacco user, HTN, and obese
27	*39*	*Right MCA*	*HTN and obese*
58	46	Right PCA	HTN
28	28	Right MCA	Tobacco user
44	44	Unknown	HTN and obese
24	24	Right occipital & thalamic	Diabetic, HTN, and Obese
58	27	MCA	Tobacco user, HTN, and obese
37	20	Multi-cerebellar & thalamic	Nil
35	35	Unknown	Obese
43	21	Left PCA	Tobacco user and obese

HTN, Hypertension; PCA, posterior cerebral artery; MCA, Middle cerebral artery
Italic: also had myocardial infarction

Table 3 supplemental: Peripheral ischemic disease cases

Age during event	Age at Lupus Diagnosis	Blood vessels involved	Traditional risk factors
55	17	Left posterior tibial artery	NIL
70	49	Unknown	Hypertension
22	18	Feet digits	Tobacco user and obese

Table 4 supplemental: Individuals who had venous thrombosis

Age at Lupus Diagnosis	Age at first event	Events	Tobacco user
46	58	Stroke	No
18	22	Peripheral Ischemia	Yes
17	55	Peripheral Ischemia	No
27	58	Stroke	Yes
35	35	Stroke	No
21	43	Stroke	Yes

Table 5 supplemental: Demographics of cases vs controls

Parameter	Cases	Controls
Mean age at lupus Diagnosis	36.3	37.43
Female gender	13/20 (65%)	58/60 (97%)
Caucasian	15/20 (75%)	42/60 (70%)
Black	5/20 (25%)	17/60 (28%)
Asian	0/20 (0%)	1/60 (2%)
Hispanic	1/20 (5%)	0/20 (0%)