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Systemic lupus erythematosus and risk of cardiovascular disease Results from the Nurses' Health Study

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Abstract

Background—Systemic lupus erythematosus (SLE) has been associated with an increased risk of cardiovascular disease. However, prospective population-based data addressing this association have been lacking.

Methods—We conducted a prospective cohort study among 119,332 women participating in the Nurses' Health Study who were free of cardiovascular disease and SLE at baseline in 1976. Incident SLE was confirmed by medical record review. Cardiovascular events included fatal and nonfatal myocardial infarction, stroke, coronary artery bypass grafting and angioplasty. The relative risk of cardiovascular events among participants with SLE as compared to those without was estimated using Cox proportional hazards models.

Results—Over 28 years of follow-up (2.9 million person-years) 8,169 cardiovascular events occurred and 148 women developed incident SLE. Mean age at SLE diagnosis was 52.6 years, and 20 participants with SLE developed a subsequent cardiovascular event. After adjusting for potential confounding factors, including age, race, cardiovascular risk factors and medication use, the relative risk (RR) of a cardiovascular event in women with SLE compared with those without was 2.26 (95% CI 1.45–3.52). When endpoints were analyzed separately, the RR for coronary heart disease was 2.25; 95% CI 1.37–3.69, and the RR for stroke was 2.29; 95% CI 0.85–6.15.

Conclusion—In this prospective population-based study, we found a statistically significant over 2-fold increased risk of cardiovascular disease among participants with SLE. The risk was not as high as has been previously reported, which may be due to the relatively high age at diagnosis of SLE in this cohort.

Keywords

cardiovascular diseases; epidemiology; immunology; systemic lupus erythematosus; women

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Disclosures

None of the authors have any conflict to disclose.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder occurring predominantly in women.¹ Despite improved life expectancy in the past few decades,² increased cardiovascular mortality and morbidity among SLE patients has been documented in several studies.^{3–7} Estimates of the magnitude of the increased cardiovascular disease risks among women with SLE range from a fifty-fold increased risk of myocardial infarction among premenopausal women,³ to no increase in risk above that of the general population among elderly women.^{4, 7} This broad range in risk estimates may reflect the biology of cardiovascular disease among SLE patients, but may also reflect selection of SLE case populations and controls. Thus far, no population-based study has prospectively examined the association between SLE and cardiovascular disease.

We investigated the association between SLE and incident cardiovascular disease among women participating in the Nurses' Health Study, the largest cohort of women followed prospectively for rheumatic disease.

Subjects and Methods

Study Population

The Nurses' Health Study (NHS) is a cohort study of 121,700 female U.S. nurses aged 30–55 years in 1976 at study inception.⁸ The cohort was designed to prospectively examine relationships between lifestyle factors and chronic diseases, particularly cancer and cardiovascular disease. Information regarding diseases, lifestyle, and health practices is collected via biennial mailed questionnaires. More than ninety percent of the NHS participants have remained in active follow-up.

Identification of SLE

As previously described,⁹ we employed a two-stage procedure in which nurses were asked whether they had developed a physician diagnosed connective tissue disease on the biennial questionnaires. Nurses who reported they had such a diagnosis were sent a connective tissue disease screening questionnaire¹⁰ (response rate after five mailings 80%)⁹, and if this was positive, medical records were requested (response rate 74%) and reviewed. Two rheumatologist trained in chart abstraction independently conducted a medical record review examining the charts for the 11 American College of Rheumatology (ACR) classification criteria for SLE.^{11, 12} SLE cases were confirmed if they met ACR criteria (≥ 4 criteria) and reviewers had consensus regarding definite SLE diagnosis. The case confirmation rate was 69% of the medical records reviewed and 7% of the original self-reports of any connective tissue disease,⁹ which is nearly identical to the self-reported rheumatoid arthritis confirmation rate of 6% reported for the Iowa Women's Health Study, another large, prospective, female cohort study.¹³ Furthermore, the rate of confirmed SLE in our cohort of approximately 0.1%⁹ is in line with recent estimates of the prevalence of SLE in the U.S.¹⁴

Cardiovascular End Points

The endpoint for the current analyses was a composite endpoint¹⁵ of fatal and nonfatal myocardial infarction, stroke, coronary artery bypass grafting and angioplasty that occurred after the return of the 1976 questionnaire, but before May 31, 2004. We also investigated the outcomes separately. We requested permission to review medical records from women who reported having a nonfatal myocardial infarction or stroke on a follow-up questionnaire. Study physicians with no knowledge of risk factor status reviewed the medical records. Nonfatal myocardial infarction was confirmed if it met the criteria of the World Health Organization for symptoms plus either diagnostic electrocardiographic changes or elevated cardiac enzyme levels.¹⁴ Stroke was classified according to criteria established by the National Survey of Stroke, which required onset of a neurological deficit with sudden or

rapid onset that persisted for >24 hours or until death.¹⁵ We used self-reports for coronary artery bypass grafting and angioplasty because a validation in a subgroup indicated that self-reports from these nurse-participants were virtually perfectly accurate.

Deaths were reported by the next of kin and the postal system or were ascertained by through the national Death Index. Follow-up for the deaths was more than 98% complete in the NHS.¹⁶ Fatal myocardial infarctions and strokes were coded using the same criteria as nonfatal cases, but for both we additionally accepted autopsy evidence.

Covariates

Information on diagnosis of hypertension, diabetes, and hypercholesterolemia was ascertained on each questionnaire. At baseline, participants reported parental history of coronary heart disease before the age of 60 years. Body mass index was computed for each two-year time interval using the most recent weight in kilograms divided by height in meters squared. Hours per week spent in physical activities were assessed seven times during the follow-up. Information on smoking status (never, past, or current) was assessed at baseline and updated every 2 years. Alcohol consumption was reported on the self-administered semi-quantitative food frequency questionnaires (SFFQ).^{17, 18} The baseline SFFQ was completed in 1980, and updated every four years. On each questionnaire, participants were asked about their menopausal status and whether they used postmenopausal hormone therapy. From 1980 onwards, information on use of aspirin was collected, and from 1990 and 1994 onwards, respectively, information on use of non-steroidal anti-inflammatory drugs and oral corticosteroids was collected. In 1992, participants were asked to report their race, which was categorized as white, black, or other (Asian, American Indian and Hawaiian).

Population for Analysis

At baseline, we excluded women with incomplete data on identification (n=126), prevalent cardiovascular disease (n=712) or connective tissue disease (n=114). In addition, women who reported cardiovascular disease (n=1,033) or connective tissue disease (n=383) during follow-up and had unconfirmed disease with missing date of diagnosis were excluded at the start of the cohort. Thus, 119,332 women were followed from 1976 until 2004. Women who reported myocardial infarction or stroke that was not subsequently confirmed by medical record review were censored at the time of this report, as were women who reported any connective tissue disease other than confirmed SLE.

Statistical Analysis

We compared the presence of potential confounding factors and covariates among women diagnosed with SLE after the initial questionnaire in 1976 and the remainder of the cohort in 1990, the approximate midpoint of follow-up, as a representative time-point (n=103 women with incident SLE at that time). To prevent underrepresentation of cardiovascular disease risk factors, women already diagnosed with cardiovascular disease up to 1990 were included in these analyses.

We calculated person-time of follow-up for each woman as the interval between the date of return of the 1976 questionnaire until the report of cardiovascular disease, death, or May 31, 2004, whichever came first. Women who developed SLE contributed exposed person-time from the questionnaire cycle following the date of confirmed SLE diagnosis. Relative risk, the measure of association, was defined as the incidence rate of cardiovascular disease among women after the onset of SLE, divided by the incidence rate among women without SLE. We used Cox proportional hazards models to determine the independent association between SLE and risk of incident cardiovascular disease while simultaneously adjusting for

other risk factors. The Anderson-Gill data structure was used to handle time-varying covariates efficiently,¹⁹ where a new data record is created for every questionnaire cycle at which a participant is at risk, with covariates set to their values at the time that the questionnaire is returned. In these analyses, we used time-varying information from each two-year interval to analyze the risk of cardiovascular disease in the next two-year cycle

Known or suspected risk factors for cardiovascular disease included in the multivariable proportional hazards models were hypertension, diabetes, hypercholesterolemia, parental history of coronary heart disease before the age of 60, body mass index (five categories), physical exercise (hours per week), smoking status (never, past, or current), alcohol consumption (six categories), menopausal status and use of postmenopausal hormone therapy, aspirin, non-steroidal anti-inflammatory drugs and oral corticosteroids (yes/no) and race (white, black or other).

Because of limited power, we were not able to study the potential effect of SLE disease duration on the risk of cardiovascular disease through stratification by disease duration. Instead, we created a variable for disease duration using the baseline of each two year time period minus year of diagnosis for women with SLE. Because SLE and SLE disease duration are highly correlated, we substituted SLE disease duration for SLE in separate regression models with cardiovascular disease as dependent variable.

In our main analyses, only women with definite SLE contributed to exposed person-time (4 or more ACR criteria and reviewers had consensus regarding definite SLE diagnosis). The use of ACR criteria for diagnosing SLE biases against including milder or atypical cases or patients who do not fulfill criteria early in their disease,²⁰ potentially underestimating the true incidence of the disease. Therefore, we examined the sensitivity of these analyses to the definition of SLE in secondary analyses using a broader definition of at least 3 ACR criteria and the reviewers' consensus on the diagnosis of SLE (probable SLE). Furthermore, as SLE may develop insidiously over several years, we conducted a sensitivity analysis in which we subtracted 4 years from the definitive SLE diagnosis date (which is synonymous with adding 4 years to exposure time) to potentially capture cardiovascular events that occurred close to but before the definitive diagnosis. All analyses were performed using SAS software (SAS Statistical Software, Inc). The Partners Health Care System Institutional Review Board (IRB) approved this study.

Results

In this study involving 119,332 women and 28 years of follow-up (2.9 million person-years), 8,169 cardiovascular events occurred and we confirmed a diagnosis of incident SLE in 148 women. At SLE diagnosis the mean age of the women was 52.6 years and the mean number of ACR criteria was 4.8 (Table 1).

The distribution of potential cardiovascular risk factors among participants with SLE and those without in 1990 is presented in Table 2. The mean ages were similar in the two groups. Women with SLE were more likely to have a history of hypertension and diabetes and to report a parental history of coronary heart disease before the age of 60 years. Participants with SLE exercised more, smoked less, but were more likely to have smoked in the past, and consumed less alcohol than those without SLE. Compared with women without SLE, women with SLE were more likely to be postmenopausal and to use postmenopausal hormone therapy. As expected, a much higher percentage of women with SLE than those without reported regular use of steroids and non-steroidal anti-inflammatory drugs. The majority of the participants were of white race, reflecting this cohort's racial composition, although a slightly higher proportion of the participants with SLE were of black race. In the

middle of follow-up in 1990, the mean disease duration among women with SLE was 6.6 years.

We calculated the age- and multivariable-adjusted relative risk of the composite cardiovascular end point for women with SLE (Table 3). The age-adjusted risk of any cardiovascular event was >2-fold higher for participants with SLE than those without (relative risk (RR) 2.75; 95% CI 1.77 to 4.27). After adjusting for potential confounding factors, the relative risk of any cardiovascular event for women with SLE decreased somewhat. When endpoints were analyzed separately, the multivariable-adjusted relative risk for coronary heart disease was 2.25; 95% CI 1.37 to 3.69. The number of incident strokes among the women with incident SLE was low (n=4), and correspondingly the confidence interval for the relative risk was wide (RR 2.29; 95% CI 0.85 to 6.15). When coronary heart disease events were analyzed separately, the multivariable-adjusted relative risk for myocardial infarction was 1.81; 95% CI 0.75 to 4.37 (n=5) and the corresponding relative risk for coronary artery bypass grafting or angioplasty was 2.54; 95% CI 1.40 to 4.62 (n=11).

When studying the effect of disease duration, we found that one year increase of SLE disease duration was associated with a RR of 1.08 (95% CI 1.04 to 1.11) for cardiovascular disease. This corresponds to a $RR\ of\ 1.08^5 = 1.47$ for SLE disease duration of 5 years. Multivariate adjustment did not materially change this risk (RR for one year disease duration 1.06; 95% CI 1.03 to 1.09).

Secondary analyses, using a broader definition of at least 3 ACR criteria and the reviewers' consensus on the diagnosis of SLE, included 152 women with probable SLE and produced results quantitatively similar to the main analyses (20 cardiovascular events, multivariable-adjusted RR for the composite cardiovascular end point 2.25; 95% CI 1.44 to 3.49). Starting SLE-exposed person-time 4 years prior to the date of SLE diagnosis from the medical records captured just one additional cardiovascular event (coronary artery bypass grafting/angioplasty) among the exposed, with a multivariable-adjusted RR for the composite cardiovascular end point of 2.14; 95% CI 1.39 to 3.29.

Discussion

In this prospective population-based study of 119,332 mainly Caucasian women with 28 years of follow-up, we found that women with SLE with mean age at diagnosis of 53 years had a more than 2-fold increased risk of cardiovascular disease compared with women without SLE. Furthermore, we found that longer SLE disease duration was associated with an increased risk of cardiovascular disease.

The relative risk of cardiovascular disease in our study is lower than has been reported in several previous studies investigating the risk of cardiovascular disease among SLE patients.^{3, 5, 6} Several factors may explain these different results. First, SLE patients included in our cohort were generally older and had an older age at diagnosis than those included in previous studies. Since the absolute cardiovascular disease risk increases with age among all women, the relative cardiovascular disease risk among elderly SLE patients is proportionally lower. Furthermore, younger age at SLE onset is generally associated with more severe disease,²¹ which may be associated with a higher risk of cardiovascular disease among younger SLE patients.^{22, 23} Second, unlike our study, none of the previous studies enrolled SLE patients from the general population. Either SLE patients from tertiary referral centers were included,^{3, 5} or hospital discharge data were employed,⁶ potentially leading to the selection of more severe SLE cases. Third, comparing cardiovascular disease rates among SLE cases from referral populations with cardiovascular disease rates among controls from

the general population^{3, 5} may have overestimated the magnitude of previously reported associations. Furthermore, the relatively high socioeconomic status of our population might have decreased the overall cardiovascular disease risk compared to other populations.

Our results are comparable with results from a population-based case-control analysis using general practice database data, which found a relative cardiovascular disease risk of 2 for women with SLE.⁷ When stratified by age, women in younger age groups were found to be at increased cardiovascular disease risk, whereas elderly women (≥ 70 years) were not.⁷ Also, in the Framingham Offspring Heart Study, in which a fifty-fold increased risk of myocardial infarction among premenopausal women was reported, women aged 45–54 years had a relative risk of myocardial infarction of 2.47, which is comparable with our results.³ This decrease of risk with age most likely reflects the increase in absolute cardiovascular disease risk with age, but may also represent a selection phenomenon. Young women with SLE and vascular disease may have high mortality rates, and therefore not live long enough to become older women with cardiovascular disease.² We restricted the analyses to incident SLE cases occurring after baseline in 1976 when the women in our study were ages 30–55 and followed the cohort for 28 years. Our results may therefore not apply to women with younger age at SLE diagnosis. Although the mean age at SLE onset in this cohort was 53 years, these relatively older patients still had a more than 2-fold increased risk of cardiovascular disease. When endpoints were analyzed separately, the relative risk for coronary artery bypass grafting or angioplasty was somewhat higher than the relative risk for myocardial infarction. This might reflect increased cardiovascular surveillance among SLE patients. However, the number of incident myocardial infarctions among SLE patients in our population was limited and correspondingly the confidence interval for the relative risk was wide. Therefore, we can not infer that results for coronary artery bypass grafting or angioplasty are significantly different from those for myocardial infarction.

The increased cardiovascular disease risk in SLE patients is likely to be caused by a combination of factors.²⁴ Traditional cardiovascular disease risk factors, such as hypertension and diabetes, are more prevalent among SLE patients,²⁵ but do not fully explain the risk in other studies,⁵ nor in our population. Whether SLE itself and/or its treatment increase cardiovascular disease risk is unclear. The inflammatory and immune mechanisms of SLE are considered to be of paramount importance in the pathogenesis of cardiovascular disease among SLE patients.^{26–28} Additionally, procoagulant factors such as homocysteine and antiphospholipid antibodies, may be involved in cardiovascular disease risk.^{29–31} Medications used to treat SLE may induce or protect from thrombotic events or atherogenesis. The widely held opinion that prolonged administration of corticosteroids accelerates atherosclerosis³² has recently been challenged.^{22, 23} Furthermore, more frequent use of hydroxychloroquine and cyclophosphamide is associated with a lower risk of atherosclerosis,²³ suggesting that control of disease activity with these medications might help prevent cardiovascular disease. Hydroxychloroquine may also favorably influence cardiovascular disease risk through lipid-lowering and anti-thrombotic effects.^{31, 33, 34} However, depending on the type used, both traditional non-steroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors may increase the risk of cardiovascular disease.^{35, 36}

The strengths of our study include the large number of incident SLE cases, the prospective repeated assessment of exposures allowing for time-varying covariates, and the long duration of follow-up. We performed thorough medical record reviews in validating all cases of self-reported SLE and only definite cases of SLE (4 or more ACR criteria) contributed to exposed person-time. Since the use of ACR criteria for diagnosing SLE biases against including milder or atypical cases or patients who do not fulfill criteria early in their disease,²⁰ we examined the sensitivity of our analyses to the definition of SLE in secondary

analyses using a definition of at least 3 ACR criteria and the reviewers' consensus on the diagnosis of SLE and by beginning follow-up among SLE cases 4 years prior to the definitive SLE diagnosis date. These analyses produced results quantitatively similar to the main analyses, supporting the robustness of our results.

The results of our study must be interpreted within the limitations of the methodology used. Although the NHS is the largest population-based cohort of women who have been followed prospectively for rheumatic disease, the number of incident cardiovascular events among SLE patients was limited. Also, any misclassification of SLE cases as non-cases due to nonresponse to the request for information or insufficient data in medical records could have biased our study towards the null. However, the incidence rate of SLE in this study is comparable to rates reported in the literature, suggesting minimal misclassification. In our study, information on use of medication was limited to glucocorticoids and non-steroidal anti-inflammatory drugs with data collected since 1994 and 1990 only, respectively. Neither precise information on dosage or duration of use nor data on use other medications used to treat SLE was available. Since we did not review the updated medical records for each participant with SLE we could not determine the cumulative disease severity over time. In addition, to maintain the prospective design, we excluded women who developed SLE at a younger age, prior to the start of the cohort, who likely have more disease activity. Participants in the NHS are a select group of mainly Caucasian, educated women, and are not among the group at highest risk of severe SLE; hence, the generalizability of our findings to other racial and ethnic groups and those of lower socioeconomic status may be limited.^{37, 38}

In our prospective, population-based study we found a more than 2-fold increased risk of cardiovascular disease among women with SLE. The risk was not as high as has been previously reported, which may be due to the relatively high age at diagnosis of SLE in this cohort. Furthermore, our findings support the importance of cardiovascular disease prevention and surveillance in SLE patients.

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Table 1

Disease characteristics* of the incident systemic lupus erythematosus (SLE) cases in the Nurses' Health Study at initial diagnosis

	n=148
Age at SLE diagnosis, years (mean $\pm$ SD)	52.6 $\pm$ 8.6
Arthritis, n (%)	115 (78%)
Serositis (pleuritis or pericarditis), n (%)	52 (35%)
Renal involvement (persistent proteinuria or cellular casts), n (%)	28 (19%)
Hematologic involvement (hemolytic anemia, leucopenia, lymphopenia or thrombocytopenia), n (%)	72 (49%)
Immunologic disorder [†] , n (%)	59 (40%)
Anti-nuclear antibody $\geq$ 1:40, n (%)	141 (95%)
Number of ACR criteria [‡] , (mean $\pm$ SD)	4.8 $\pm$ 1.0
Diagnosed by American College of Rheumatology (ACR) member, n (%)	106 (72%)

* Manifestations of SLE from medical record review

[†] Anti-double stranded DNA antibody (anti-dsDNA), antibody to Sm nuclear antigen (anti-Sm) and/or positive anti-phospholipid antibody positive

[‡] 4/11 criteria required for diagnosis of SLE by ACR criteria

Table 2

Age-standardized characteristics among participants in the Nurses' Health Study in 1990 according to history of validated incident systemic lupus erythematosus (SLE)*

	SLE	No SLE
Age (years, mean $\pm$ SD)	56.2 $\pm$ 6.7	56.2 $\pm$ 7.2
History of hypertension (%)	42.8	29.6
History of diabetes (%)	8.8	5.0
History of hypercholesterolemia (%)	34.0	34.2
Parental history of coronary heart disease before 60 years of age (%)	22.2	15.6
BMI (kg/m ²)	25.4	25.6
Physical exercise (hours per week)	3.7	3.1
Cigarette use (%)		
Never	44.1	43.2
Past	43.2	36.4
Current	12.4	16.9
Alcohol consumption (gram/day)	2.5	5.1
Postmenopausal (%)	73.7	66.6
Postmenopausal hormone therapy among postmenopausal women (%)	42.2	30.0
Aspirin use (%)	42.1	38.3
Nonsteroidal anti-inflammatory drug use (%)	36.1	12.6
Steroid use (%) [†]	29.8	1.3
Race (%)		
White	95.1	96.8
Black	3.6	2.2
Other [‡]	1.3	1.0
SLE disease duration (years)	6.6	not applicable

* Variables were assessed at the 1990 questionnaire for participants who had previously been diagnosed with SLE (n=103) and those without SLE (n=108,968)

[†] 1994 data are shown

[‡] Asian, American Indian and Hawaiian

Table 3

Age- and multivariate adjusted relative risks (RR) * for cardiovascular disease according to presence of incident systemic lupus erythematosus (SLE) in the Nurses' Health Study, 1976 to 2004

	SLE	No SLE	P-value
Person-years of follow-up	2,082	2,932,407	
All cardiovascular end points[‡]			
Incidence/100,000 person-years	961	278	
No. of cases	20	8,149	
Age-adjusted RR (95% CI)	2.75 (1.77 – 4.27)	1.0 (ref)	<0.001
Multivariable RR (95% CI) [†]	2.26 (1.45 – 3.52)	1.0 (ref)	<0.001
Coronary heart disease[§]			
Incidence/100,000 person-years	769	214	
No. of cases	16	6,284	
Age-adjusted RR (95% CI)	2.81 (1.72 – 4.59)	1.0 (ref)	<0.001
Multivariable RR (95% CI) [†]	2.25 (1.37 – 3.69)	1.0 (ref)	0.001
Stroke^{//}			
Incidence/100,000 person-years	192	64	
No. of cases	4	1,865	
Age-adjusted RR (95% CI)	2.51 (0.94 – 6.69)	1.0 (ref)	0.07
Multivariable RR (95% CI) [†]	2.29 (0.85 – 6.15)	1.0 (ref)	0.10

* Relative risks represent hazard ratio's computed using Cox proportional hazard regression analyses

[†] Adjusted for age in years, history of hypertension, diabetes, and hypercholesterolemia, parental history of coronary heart disease before the age of 60, body mass index, physical exercise, smoking status, alcohol consumption, menopausal status and use of hormone replacement therapy, aspirin, non-steroidal anti-inflammatory drugs and oral corticosteroids and race

[‡] Fatal and nonfatal myocardial infarction or stroke, coronary artery bypass grafting or angioplasty

[§] Fatal and nonfatal myocardial infarction, coronary artery bypass grafting or angioplasty

^{//} Fatal and nonfatal stroke