Longitudinal Evolution of Risk of Coronary Heart Disease in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To produce evidence on the longitudinal evolution of risk factors for coronary heart disease (CHD) in patients with systemic lupus erythematosus (SLE).

Methods. Based on data for 115 patients from the Montreal General Hospital Lupus Clinic (1971-2003) and for 4367 control subjects from the Framingham Offspring Study (1971-1994), we investigated the temporal evolution of total serum cholesterol, systolic blood pressure (SBP), body mass index (BMI), blood glucose, and estimated risk for CHD (reflecting the balance of changes in different risk factors). In analyses limited to patients with SLE, we assessed the effect of SLE duration on each risk factor, adjusting for age, calendar time, sex, baseline level of the risk factor, and medication use. Next, we assessed how the adjusted difference in the values of the risk factors between SLE and controls changes over time.

Results. Among patients with SLE, longer disease duration was independently associated with higher SBP and blood glucose levels. Compared with controls, these patients appeared to have accelerated rates of increase in total cholesterol, blood glucose, and overall estimated CHD risk. The rate of increase in BMI was lower in patients with SLE than in controls.

Conclusion. Elevated CHD risk in patients with SLE appears to be at least partially mediated by accelerated increases in some CHD risk factors, longitudinal trajectories of which increasingly diverge over time from those of population controls. (First Release April 1 2012; J Rheumatol 2012;39:968–73; doi:10.3899/jrheum.111127)

Key Indexing Terms:
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The dramatically elevated risk of coronary heart disease (CHD) in patients with systemic lupus erythematosus (SLE) has been well documented and is recognized as an important feature of this disease[1]. However, the etiology and pathogenesis of the accelerated atherosclerosis underlying the development of CHD in SLE are not well understood[2,3]. In the general population, atherosclerosis, which develops with aging, is commonly associated with increases in levels of traditional CHD risk factors, such as total cholesterol, systolic blood pressure (SBP), body mass index (BMI), and blood glucose. Yet initial values of traditional CHD risk factors measured at or soon after the SLE diagnosis cannot explain the highly increased risk in subjects with SLE[4]. However, the hypothesis that these risk factors increase over time in SLE at a higher rate than in the general population has not been adequately addressed.

We reported that the risk of CHD is affected more by the recent values of risk factors than by their baseline values[5].

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Further, findings from our recent study suggest that both corticosteroid therapy and SLE disease activity affect the levels of several traditional CHD risk factors in patients with SLE[6]. In our current study, we have attempted to assess whether the accelerated atherosclerosis in SLE could be partially mediated by an accelerated rate of increase in traditional CHD risk factors. Specifically, we investigated the longitudinal evolution of these risk factors in patients with SLE. We also compared the longitudinal trajectories in the levels of particular CHD risk factors, and in the resulting estimated global coronary risk, between patients with SLE and controls from the general population-based Framingham Offspring Study[7]. We hypothesized that with increasing disease duration, the trajectories of CHD risk factors in patients with SLE would increasingly diverge from those in comparable population controls.

MATERIALS AND METHODS

Data sources. We used 2 data sources to investigate longitudinal trajectories of CHD risk factors in patients with SLE and the influence of SLE disease duration on these factors.

Montreal General Hospital SLE Cohort. We used data from the Montreal General Hospital (MGH) Lupus Clinic (1971-2003). Only patients first seen in the clinic within 1 year of SLE diagnosis were included in this study. A trained research nurse reviewed patients' records at each visit to the clinic and abstracted data on medication use and physical and laboratory measurements. Details of data collection are described elsewhere[8]. Each patient was followed from the entry into the cohort, i.e., the time of SLE diagnosis or first clinic visit, whichever came last, until development of a cardiovascular (CV) event, the end of the study (December 31, 2003), or loss to followup, whichever came first. Each subject contributed to the analyses only during the time interval when her/his age was between 18 and 80 years. In addition, because the followup in the Framingham Offspring Study database (described below) was limited to 24 years, the longitudinal data for the patients with SLE in the MGH Lupus Clinic cohort were also limited to the first 24 years after the patient's entry into the cohort.

Framingham Offspring Cohort. To enable comparisons of SLE patients with control subjects, the Framingham Offspring Study database was used. In the Offspring Study, assessments of risk factors and outcomes were conducted every 4 to 6 years; detailed procedures of data collection were as reported[9]. In our study, all analyses were limited to person-moments at which the subject's age was between 18 and 80 years.

At each visit (for patients with SLE) or examination (for controls), the current use of lipid-lowering, antihypertensive, and blood glucose-lowering medication was documented, and time-varying binary indicators of the current use of the medications were created.

Outcomes. In separate analyses, the repeated measures of the following CHD risk factors were used as outcome variables: total serum cholesterol level, SBP, nonfasting blood glucose level, and BMI. BMI was computed as weight (kg) divided by height (m) squared. If the height measurement was missing at a given visit, a value from the nearest previous available measurement was used. Only visits when a given risk factor was recorded were used in the analysis.

Overall CHD risk. To assess the overall effect of changes in selected risk factors, the estimated risk of having a CHD event (defined as myocardial infarction, angina pectoris, coronary insufficiency, or CHD death[10]) in the next 2 years was calculated for each SLE and control subject, at each visit/examination. The risk estimate was based on estimated regression coefficients from a multivariable logistic model (Appendix; see also Karp, *et al*[6]), using the corresponding set of current values of the following traditional CHD risk factors: total serum cholesterol, SBP, and glucose intolerance, defined as positive if a nonfasting blood glucose level was ≥ 6.7 mmol/l or if a glucose-lowering medication was being prescribed. Thus, the estimated risk of a CHD event in the 2 years after a given visit/examination, for a given subject, was calculated by multiplying the regression coefficients from the estimated multiple logistic model by the actual individual values, observed at a given visit, of 3 modifiable risk factors: total serum cholesterol, SBP, and glucose intolerance[6]. In addition, to make the estimated risk for all subjects more comparable, regardless of individual differences in age, sex, smoking, and BMI, for all subjects and at all visits/examinations, the sample mean values of age, sex (i.e., the proportion of men), number of cigarettes smoked, and BMI were multiplied by the corresponding logistic regression coefficients. In other words, the risk estimates were standardized with respect to the distribution of age, sex, number of cigarettes smoked, and BMI in the overall study population. Accordingly, longitudinal changes in the estimated risk of a CHD event represented the effect that the actual changes in a given subject's total serum cholesterol, SBP, and blood glucose levels would have on a hypothetical subject with average values of the other risk factors.

Statistical analysis. As the distributions of blood glucose and the estimated 2-year coronary risk were highly positively skewed, these variables were log-transformed for the analyses. We used multivariable linear mixed-effects models[11,12] to analyze the longitudinal changes in risk factors. These models incorporated a random intercept term to account for the correlation among repeated measures from individual subjects, which was estimated assuming the variance components covariance structure of residuals[13].

The next 2 sections describe 2 different types of mixed-model analyses used in our study.

(1) Internal comparisons: These analyses were limited to SLE subjects and focused on the independent influence of SLE duration on CHD risk.

Disease duration was dynamically updated during the followup, and was defined as the difference between the current date (at each visit) and the date of SLE diagnosis according to American College of Rheumatology (ACR) classification criteria[14]. Conventional risk factors of interest included total serum cholesterol, SBP, BMI, and blood glucose. Because few patients had their risk factor values measured at the time of diagnosis, the baseline level of the risk factors was operationalized as the average value during the first year after the SLE diagnosis. At each visit, the proportions of days during the past year when a lipid-lowering, antihypertensive, and blood glucose-lowering medication was taken were computed.

Separate models were fitted to estimate the effect of a continuous variable indicating time since SLE diagnosis on repeated measures of each of the risk factors while adjusting for current age, calendar time, and the baseline level of the given risk factor. In addition, the models with total cholesterol, SBP, and blood glucose as the outcomes were adjusted for a binary indicator of past-year use of, respectively, lipid-lowering, antihypertensive, and blood glucose-lowering medications. The model with the estimated 2-year coronary risk was adjusted for past-year use of lipid-lowering and antihypertensive medications. Because baseline risk factor values reflected measurements during the first year after the SLE diagnosis, only values observed more than 1 year since the diagnosis were used to represent dependent variables in the analysis.

Because age at SLE diagnosis varied considerably across patients, current age and disease duration were not collinear. Therefore, by adjusting one for the other, we could separate the "natural" effects of aging from the specific effect of SLE duration. In other words, the estimated effect of disease duration reflects its effect on a given risk factor among subjects with the same current age. Potential nonlinear effects of age were explored by adding the quadratic term and testing its statistical significance.

(2) External comparisons: These analyses compared the longitudinal changes in the level of the selected risk factors in the SLE cohort with those in the Framingham Offspring Cohort. The main focus of these analyses was to estimate the differential effect of duration of followup on the level of the risk factors between SLE and control subjects, and to test the hypothesis that SLE is associated with an accelerated rate of increase in the CHD risk factors.

At each assessment, current duration of followup was computed as the difference between the current date and: (i) the date of SLE diagnosis according to ACR classification criteria[14] for patients with SLE, and (ii) the date of

cohort entry (examination 1) for controls. The baseline level of the risk factor was defined as (i) the average of all available values within 1 year after the diagnosis for SLE subjects, and (ii) the value at the first examination for controls.

Separate multivariable mixed-effects linear models[11,12] were estimated for the same set of the dependent variables as in the internal comparisons. The models included a binary indicator of SLE status (1 for patients with SLE, 0 for Framingham controls), duration of followup, which in patients with SLE corresponded to disease duration, and the 2-way interaction terms between the 2. The statistical significance of the interaction terms would lend support to the hypothesis that the rates of change over time in the risk factor's levels in the 2 populations differ systematically, i.e., that the mean trajectories in the 2 cohorts diverge gradually with increasing duration of followup. All the models were adjusted for age at baseline, sex, calendar time, and the baseline level of the given risk factor. As in the internal comparisons, the models with total serum cholesterol, SBP, and blood glucose as the outcomes were, in addition, adjusted for current use of lipid-lowering, antihypertensive, and blood glucose-lowering medications, respectively. The model for the overall 2-year coronary risk as the outcome was, in addition, adjusted for current use of lipid-lowering and antihypertensive medications. Because the variable representing the baseline risk factor level in patients with SLE could incorporate the values up to 1 year after time of SLE diagnosis, only measurements made more than 1 year after the diagnosis were included in analysis.

In these analyses, we adjusted for baseline values of both age and the level of the corresponding risk factor. Therefore, in the presence of interaction between SLE status and duration of followup, the estimated regression coefficients for duration of followup indicate the rate of change over time in the corresponding risk factor in SLE-free subjects, i.e., they represent the "natural effect" of aging. The coefficient for the interaction term between the SLE status and duration of followup estimates the difference between the yearly rate of the changes in the SLE versus the control subjects, with the same baseline value of the risk factor and the same age. Thus, the interaction coefficient estimates by how much the expected "natural" longitudinal change in the particular risk factor is affected by increasing SLE duration.

RESULTS

In the MGH SLE cohort, 115 patients who were first seen within 1 year after SLE diagnosis contributed a total of 3802 observations. In the Framingham Offspring Study cohort, 4367 subjects contributed 14,411 observations during the study followup. Baseline characteristics of subjects in the 2 cohorts are summarized in Table 1. As expected, the Framingham Offspring cohort included a considerably higher proportion of men than the MGH SLE cohort. Further, the mean baseline values of the other CHD-relevant risk factors (age, total serum cholesterol, SBP, BMI, and blood glucose) were also slightly higher in the Framingham Offspring cohort, likely reflecting the older age (Table 1).

Table 1. Baseline characteristics of the subjects in the Montreal General Hospital (MGH) Lupus Clinic cohort and Framingham Offspring cohort.

Characteristic, mean (SD) or %	MGH Cohort	Framingham Cohort
Age, yrs	38.8 (14.5)	44.4 (10.1)
Male sex	10	47
Prednisone-equivalent dose, mg	9.4 (11.9)	NA
SLEDAI score	5.2 (3.3)	NA
Total serum cholesterol, mmol/l	5.2 (1.5)	5.4 (1.0)
Systolic blood pressure, mm Hg	120.5 (13.7)	122.4 (16.9)
Body mass index, kg/m^2	23.8 (5.1)	25.9 (4.6)
Blood glucose, mmol/l	5.3 (2.3)	5.5 (1.1)

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; NA: not applicable.

Table 2 summarizes the results of "internal" analyses of the MGH SLE cohort, with each row corresponding to a different risk factor considered as the dependent variable. The left part of the table focuses on the effects of SLE disease duration and the right part on the effects of age. Adjusted estimates show that, independent of aging and other characteristics, increasing SLE disease duration was associated with statistically significant increases in SBP and blood glucose levels. In particular, among subjects with the same age, each additional year of SLE disease duration was associated with a 0.3-mm Hg (95% CI 0.1, 0.6) increase in SBP and a 0.7% (95% CI 0.1%, 1.7%) relative increase in blood glucose level. Conversely, among subjects with the same disease duration, with each additional year of age there was a 0.3 mm Hg (95% CI 0.1, 0.4) increase in SBP and a 0.3% (95% CI 0.1, 0.5) relative increase in blood glucose level. In contrast, the independent effects of SLE disease duration on total cholesterol and BMI were very weak and not statistically significant (Table 2). Finally, whereas the point estimate suggested that a 1-year increase in disease duration was associated with a 0.7% relative increase in the aggregate 2-year CHD risk, the association was not statistically significant (Table 2).

Table 3 summarizes the results of "external" comparisons, with each row corresponding to a separate dependent variable. The adjusted estimated regression coefficients for duration of followup (the middle part of Table 3) indicate the expected independent effect of the natural process of aging on the longitudinal changes in the levels of the coronary risk factors, or their aggregate overall score (the last row of Table 3), estimated from the population "controls" in the Framingham Offspring cohort. Not unexpectedly, even among subjects with the same baseline age and the same baseline level of a corresponding factor, the levels of each of the 4 individual risk factors as well as the aggregate CHD risk score show statistically significant increases with increasing duration of followup, which reflects the influence of aging on these risk factors.

The left part of Table 3 shows that, at baseline, SLE patients had significantly higher BMI and significantly lower overall CHD risk than Framingham subjects of the same age and sex. In turn, the adjusted estimated regression coefficients for the interaction between SLE status and duration of followup (shown in the right part of Table 3) indicate how having SLE modifies the aforementioned "natural effect" of aging on longitudinal changes in the levels of coronary risk factors. In particular, the results suggest that each additional year of followup in subjects with SLE is associated with an additional increase by 0.01 (95% CI 0.00, 0.02) mmol/l in total serum cholesterol and relative increase by 0.5% (95% CI 0.1, 0.9) in the overall 2-year CHD risk, over and above the expected "natural" aging-related changes in these factors. In other words, the rates of within-subject longitudinal increases in

Table 2. Results from 5 sets of linear mixed regression models (Montreal General Hospital Lupus Clinic cohort): "internal comparisons".

Outcome	No. Persons, Person-moments	Predictor: SLE Duration, yrs		Predictor: Age, yrs	
		Crude†	Adjusted††	Crude†	Adjusted††
Total cholesterol, mmol/l	93, 1109	0.03*** (0.01, 0.04)	0.00 (–0.03, 0.04)	0.02*** (0.01, 0.02)	0.01 (0.00, 0.03)
SBP, mm Hg	116, 2887	0.4*** (0.4, 0.5)	0.3* (0.1, 0.6)	0.4*** (0.3, 0.5)	0.3*** (0.1, 0.4)
BMI, kg/m^2	72, 584	0.03 (0.00, 0.06)	0.01 (–0.09, 0.12)	0.02 (0.00, 0.05)	0.01 (–0.03, 0.06)
Ln-blood glucose, mmol/l	104, 1725	0.006*** (0.003, 0.009)	0.007* (0.001, 0.017)	0.004*** (0.002, 0.006)	0.003** (0.001, 0.005)
Ln-2-year CHD risk, %	80, 756	0.019*** (0.012, 0.025)	0.007 (–0.008, 0.023)	0.013*** (0.008, 0.017)	0.008* (0.002, 0.013)

† All models are adjusted for baseline level of the outcome at issue. †† All models are adjusted for sex, current age, SLE duration, calendar year, and baseline level of the outcome at issue. In addition, the model with total cholesterol as the outcome is adjusted for use of lipid-lowering medications in past year, the model with SBP as the outcome is adjusted for use of blood pressure-lowering medications in past year, the model with blood glucose as the outcome is adjusted for use of antidiabetic medications in past year, and the model with 2-year CHD risk as the outcome is adjusted for use of lipid-lowering and blood pressure-lowering medications in past year. * $0.01 < p \le 0.05$; ** $0.001 < p \le 0.01$; *** $p \le 0.001$. SLE: systemic lupus erythematosus; SBP: systolic blood pressure; BMI: body mass index; CHD coronary heart disease.

Table 3. Results from 5 sets of linear mixed regression models (MGH Lupus Clinic Cohort and Framingham Offspring Cohort): "external comparisons".

Outcome	No. Persons, Person-moments	Predictor: SLE Status (yes/no)		Predictor: Duration Followup, yrs		Predictor: SLE Status * Duration of Followup	
		Crude†	Adjusted††	Crude†	Adjusted††	Crude†	Adjusted††
Total cholesterol, mmol/l	4330, 11,831	–0.40*** (–0.53, –0.27)	–0.28 (–0.58, 0.01)	0.01*** (0.01, 0.01)	0.02** (0.01, 0.04)	0.01*** (0.01, 0.02)	0.01** (0.00, 0.02)
SBP, mm Hg	4491, 17,707	0.0 (–2.1, 2.2)	0.9 (–3.3, 5.2)	0.5*** (0.4, 0.5)	0.6*** (0.3, 0.8)	0.0 (–0.1, 0.1)	0.0 (–0.1, 0.1)
BMI, kg/m^2	4438, 14,904	1.8*** (1.2, 2.5)	2.3** (0.7, 3.8)	0.1*** (0.1, 0.2)	0.2*** (0.1, 0.3)	–0.1*** (–0.2, –0.1)	–0.1*** (–0.2, –0.1)
Ln-blood glucose, mmol/l	4306, 15,629	–0.039** (–0.064, –0.014)	0.029 (–0.020, 0.077)	0.001** (0.000, 0.001)	0.005** (0.002, 0.007)	0.003*** (0.001, 0.005)	0.001 (–0.015, 0.017)
Ln-2-year CHD risk, %	4192, 10,991	–0.169*** (–0.232, –0.105)	–0.131*** (–0.190, –0.072)	0.012*** (0.011, 0.013)	0.012*** (0.010, 0.013)	0.005* (0.001, 0.009)	0.005* (0.001, 0.009)

† All models are adjusted for SLE status and baseline level of the outcome at issue. †† All models are adjusted for SLE status, age at baseline, sex, calendar year, and baseline level of the outcome at issue. In addition, the model with total cholesterol as the outcome is adjusted for current use of lipid-lowering medications, the model with SBP as the outcome is adjusted for current use of blood pressure (BP)-lowering medications, the model with blood glucose as the outcome is adjusted for current use of antidiabetic medications, and the model with 2-year CHD risk as the outcome is adjusted for current use of lipid-lowering and BP-lowering medications. * $0.01 < p \le 0.05$; ** $0.001 < p \le 0.01$; *** $p \le 0.001$. SLE: systemic lupus erythematosus; MGH: Montreal General Hospital; SBP: systolic blood pressure; BMI: body mass index; CHD: coronary heart disease.

total cholesterol and overall CHD risk are statistically significantly higher in patients with SLE than in the population controls of the same age and sex and with the same baseline values of the respective outcome variable. While the point estimate from the regression model suggested that blood glucose level may also increase at an accelerated rate in patients with SLE, the corresponding interaction did not reach statistical significance (Table 3). On the other hand, the results for the model with the BMI as the dependent variable suggested that BMI in patients with SLE increases over time at a slower rate than that observed in controls (0.1 kg/m^2 per year vs 0.2 kg/m^2 per year, respectively). The results for SBP suggested that the rate of longitudinal progression in patients with SLE was the same as among control subjects (Table 3).

DISCUSSION

Our results suggest that the increasing duration of SLE is associated with increases in "traditional" CHD risk factors. These increases were independent of the effects of aging, and thus suggested that CHD risk elevation observed in patients with SLE could be driven, at least in part, by accelerated longitudinal increases in the values of "traditional" CHD risk factors that seem specific to SLE.

On the other hand, the results regarding the effect of disease duration on BMI were more difficult to interpret. Although both internal and external analyses suggest that BMI in patients with SLE increased with time, the "internal" analyses failed to show the added effect of disease duration over and above that of natural aging (Table 2). Moreover, the "external" analyses suggested that the rate of increase in BMI over time in patients with SLE could in fact be slower than that in control subjects (Table 3). The only other report on this issue[15] also suggested that BMI decreases with increasing duration of SLE, although this association was not statistically significant. One explanation may be related to the findings of Garcia-Gonzalez, *et al*[16], who reported that patients with

SLE had higher levels of leptin, a powerful body-fat suppressant, compared with controls matched for age and BMI. However, interpretation of the findings in that study is limited by its cross-sectional design, precluding establishment of the temporal relation between the BMI and leptin levels.

Several previous studies attempted to investigate the influence of duration of SLE on CV risk. Manzi, *et al*[17] reported that among women with SLE, those who had a CV event after the SLE diagnosis had, on average, a statistically significantly longer SLE duration than those who did not develop a CV event. Further, positive statistically significant associations of SLE disease duration were found with the risk of combined CV, cerebrovascular, and peripheral vascular events[18] and the presence of carotid plaque (indicated by ultrasonography)[19]. Similarly, Urowitz, *et al*[20] followed an inception cohort of 935 patients with SLE and found that the rates of hypertension, hypercholesterolemia, smoking, and diabetes all increased statistically significantly over the 3 years of followup. Roman, *et al*[21] followed 158 outpatients with SLE over an average of 34 months and found that SLE duration was a statistically significant independent predictor of progression of atherosclerosis. In contrast, Vlachoyiannopoulos, *et al*[22] found no statistically significant association between SLE duration and the presence of arterial atherosclerotic lesions in premenopausal women diagnosed with either antiphospholipid syndrome or SLE. In the analysis of baseline data on 221 adolescents (mean age 16 yrs) enrolled in the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) Trial, no statistically significant independent association was observed between SLE duration and low-density lipoprotein (LDL)-cholesterol and triglyceride levels[23]. Finally, Nikpour, *et al*[24] reported that in 1260 patients with SLE followed for an average of 9 years, no statistically significant independent association was found between disease duration and either total cholesterol or SBP levels in the overall sample (whereas upon restriction of the sample to female patients, a statistically significant but negative correlation was found with total cholesterol). However, except for the study by Nikpour, *et al*[24], none of these studies accounted for the well-known effect of aging on CV risk. This limits the interpretability of the reported findings, as age is naturally correlated with disease duration (i.e., as disease duration increases, age-related CV risk increases), and thus is an important potential confounder for its association with CV risk.

The results of our "internal" comparisons are consistent with the results of Bruce, *et al*[25], who reported an increased risk of hypertension and diabetes mellitus in patients with SLE, with the average disease duration of 14 years, compared with age-matched controls. Nevertheless, in that study, the mean values of the aggregate 10-year CHD risk scores, estimated by a Framingham equation, were similar in the 2 groups[25].

Some limitations of our study must be recognized. First, data from many visits had to be excluded from analyses because of missing values of some of the relevant variables, and the accuracy of our results could be affected if these data were not missing at random. On the other hand, the amount of retained data was sufficient to ensure statistical significance of the associations of SLE duration with some individual coronary risk factors as well as with the overall CHD risk score. Second, we were not able to examine the associations with such important CHD determinants as LDL cholesterol, high-density lipoprotein cholesterol, triglycerides, and apolipoprotein B, as the data on these variables were too sparse to ensure meaningful investigation. Third, the risk factor measurements used in the MGH SLE cohort and the control Framingham Offspring population were not mutually standardized, thus creating a possibility of systematic bias in the comparative analyses of the 2 cohorts. However, after adjustment for age and sex, the mean baseline values of most risk factors were quite similar in the 2 cohorts (Table 1). Moreover, by adjusting for the baseline levels of the respective outcomes and focusing on the within-individual longitudinal changes in the values of these outcomes, as opposed to their absolute values, we have minimized the possibility of systematic bias in our investigation of the associations of interest. The reason is that any systematic difference between measurement procedures used in the 2 cohorts should be largely accounted for by the differences in the baseline values.

Our results suggest that development of accelerated atherosclerosis in patients with SLE could be at least partly due to accelerated progression of some traditional CHD risk factors, over and above the "natural effect" of aging. This helps explain, at least in part, why baseline values of traditional risk factors do not account for a dramatic CHD risk increase associated with SLE[4], and emphasizes the importance of longitudinal changes in these risk factors. As previously suggested, both the activity of SLE itself and the corticosteroid therapy could be underlying these changes[6,26]. Thus, our findings suggest that there may be a role for CHD prevention in patients with SLE through interventions targeting traditional modifiable CHD risk factors[27,28]. Given that the etiology of CHD in SLE appears to be multifactorial and complex, research in this area should continue, with a view to establishing and quantifying the role of SLE-specific CHD risk factors[1,6,29].

APPENDIX. Estimated regression coefficients from a logistic regression model predicting the occurrence of a coronary heart disease event within the next 2 years. Framingham Heart Study (1948–1978) population.

Variable	Regression Coefficient
Intercept	–12.1284
Age, yrs	0.0540
Blood cholesterol, mmol/l	0.2431
Systolic blood pressure, mm Hg	0.0149
Current smoking, cigarettes/day	0.0142
Glucose intolerance, 1 if yes, 0 if no	0.3944
Body mass index, kg/m^2	0.0374
Sex, 1 if male, 0 if female	0.8069

REFERENCES

1. Schattner A, Liang MH. The cardiovascular burden of lupus. A complex challenge. Arch Intern Med 2003;163:1507-9.
2. Lockshin MD, Salmon JE, Roman MJ. Atherosclerosis and lupus: A work in progress [editorial]. Arthritis Rheum 2001;44:2215-7.
3. Abusamieh M, Ash J. Atherosclerosis and systemic lupus erythematosus. Cardiol Rev 2004;12:267-75.
4. Esdaile JM, Abrahamowicz M, Grodzicky T, Li Y, Panaritis C, de Berger R, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001;44:2331-7.
5. Karp I, Abrahamowicz M, Bartlett G, Pilote L. Updated risk factor values and the ability of the multivariable risk score to predict coronary heart disease. Am J Epidemiol 2004;160:707-16.
6. Karp I, Abrahamowicz M, Fortin PR, Pilote L, Neville C, Pineau CA, et al. Recent corticosteroid use and recent disease activity: Independent determinants of coronary heart disease risk factors in systemic lupus erythematosus? Arthritis Rheum 2008;59:169-75.
7. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: The Framingham Offspring Study. Am J Epidemiol 1979;110:281-90.
8. Fortin PR, Abrahamowicz M, Danoff D. Small changes in outpatient lupus activity are better detected by clinical instruments than by laboratory test. J Rheumatol 1995;22:2078-83.
9. Kannel W, Wolf P, Garrison R, editors. The Framingham Study: An epidemiological investigation of cardiovascular disease. Washington, DC: US Department of Commerce; 1988.
10. Wilson PW, Castelli WP, Kannel WB. Coronary risk prediction in adults (the Framingham Heart Study). Am J Cardiol 1987;59:91G-94G.
11. Littell RC, Milliken GA, Stroup WW, Wolfinger RD. SAS system for mixed models. Cary, NC: SAS Institute Inc.; 1996.
12. Raudenbush SW, Bryk AS. Hierarchical linear models. Applications and data analysis methods. Thousand Oaks, CA: Sage Publications; 2002.
13. Searle SR, Casella G, McCulloch CE. Variance components. New York: Wiley; 1992.
14. Hochberg MC. Update of the 1982 revised criteria for the classification of SLE. Arthritis Rheum 1997;40:1725.
15. Kipen Y, Strauss BJG, Morand EF. Body composition in systemic lupus erythematosus. Br J Rheumatol 1998;37a:514-9.
16. Garcia-Gonzalez A, Gonzalez-Lopez L, Valera-Gonzalez IC, Cardona-Munoz EG, Salazar-Paramo M, Gonzalez-Ortiz M, et al. Serum leptin levels in women with systemic lupus erythematosus. Rheumatol Int 2002;22:138-41.
17. Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr, Jansen-McWilliams L, 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.
18. Toloza MA, Uribe AG, McGwin G Jr, Alarcon GS, Fessler BJ, Bastian HM, et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA). XXIII. Baseline predictors of vascular events. Arthritis Rheum 2004;50:3947-57.
19. Roman MJ, Shanker BE, Davis A, Lockshin MD, Sammaritano L, Simantov R, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N Engl J Med 2003;349:2399-406.
20. Urowitz MB, Gladman DD, Ibanez D, Fortin PR, Sanchez-Guerrero J, Bae SC, et al. Accumulation of coronary artery disease risk factors over three years: Data from an international inception cohort. Arthritis Rheum 2008;59:176-80.
21. Roman MJ, Crow MK, Lockshin MD, Devereux RB, Paget SA, Sammaritano L, et al. Rate and determinants of progression of atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2007;56:3412-9.
22. Vlachoyiannopoulos PG, Kanellopoulos PG, Ioannidis JP, Tektonidou MG, Mastarakou I, Moutsopoulos HM. Atherosclerosis in premenopausal women with antiphospholipid syndrome and systemic lupus erythematosus: A controlled study. Rheumatology 2003;42:645-51.
23. Ardoin SP, Schanberg LE, Sandborg C, Yow E, Bamhart HX, Mieszkalski KL, et al. Laboratory biomarkers of cardiovascular risk in pediatric SLE: The APPLE baseline cohort. Lupus 2010;19:1315-25.
24. Nikpour MN, Gladman DD, Ibanez D, Harvey PJ, Urowitz MB. Variability over time and correlates of cholesterol and blood pressure in systemic lupus erythematosus: A longitudinal cohort study. Arthritis Res Ther 2010;12:R125.
25. Bruce IN, Urowitz MB, Gladman DD, Ibanez D, Steiner G. Risk factors for coronary heart disease in women with systemic lupus erythematosus: The Toronto Risk Factor Study. Arthritis Rheum 2003;48:3159-67.
26. Doria A, Shoenfeld Y, Wu R, Gambari PF, Puato M, Ghirardello A, et al. Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. Ann Rheum Dis 2003;62:1071-7.
27. Salmon JE, Roman MJ. Accelerated atherosclerosis in systemic lupus erythematosus: Implications for patient management. Curr Opin Rheumatol 2001;13:341-4.
28. Wajed J, Ahmad Y, Durrington PN, Bruce IN. Prevention of cardiovascular disease in systemic lupus erythematosus — proposed guidelines for risk factor management [review]. Rheumatology 2004;43:7-12.
29. Costenbader KH, Liang MH. Practical and theoretical barriers to the prevention of accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Res Ther 2003;5:178-9.