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Time to Neuropsychiatric Damage Occurrence in LUMINA: A Multiethnic Lupus Cohort

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Abstract

The aims of this study were to examine the predictors of time-to-neuropsychiatric (NP) damage and its impact on mortality in 632 systemic lupus erythematosus (SLE) African American, Hispanic and Caucasian LUMINA patients, age 16 years and disease duration 5 years at baseline (T0). Time-to-NP damage and its impact on mortality were examined by Cox proportional hazards regressions. One-hundred eighty-five (29.3%) patients developed NP-damage over a mean (SD) disease duration of 5.6 (3.7) years. After adjusting for neuropsychiatric manifestations present, older age [Hazard ratio (HR)=1.02; 95% [Confidence interval (CI) 1.00–1.04]], Caucasian ethnicity (HR=1.87; 95% CI 1.22–2.87), disease activity over the disease course (HR=1.16; 95% CI 1.12–1.21), diabetes (HR=3.47; 95% CI 1.44–8.38) and abnormal illness-related behaviors (HR=1.05; 95% CI 1.02–1.08) were associated with a shorter time to NP-damage. Photosensitivity (HR=0.65; 95% CI 0.44–0.95), anemia (HR=0.56; 95% CI 0.31–0.98), Raynaud's phenomenon (HR=0.49; 95% CI 0.34–0.72), a medium dose of prednisone (HR=0.56; 95% CI 0.35–0.92) and hydroxychloroquine use (HR=0.58; 95% CI 0.36–0.93) were associated with a longer time. NP-damage did not contribute to mortality. Older age, Caucasian ethnicity, disease activity and abnormal illness-related behaviors are associated with a shorter time-to-NP damage; hydroxychloroquine and a medium dose of prednisone with a longer time.

INTRODUCTION

Neuropsychiatric (NP) manifestations of systemic lupus erythematosus (SLE) are frequent and heterogeneous with prevalence figures ranging from 18% to 91 %^{1–5}; this variability is explained by differences in the definitions and ascertainment methods used as well as the demographic and socioeconomic characteristics and the duration of follow-up of the patients studied. Furthermore, the lack of specificity of some NP manifestations makes these studies difficult.

NP-SLE manifestations are an important source of morbidity; cognitive and functional impairment, work disability and poor quality of life may result from their occurrence¹⁻⁴. NP-damage in SLE is relatively common⁵⁻⁷; in fact, in earlier analyses of the LUMINA (LUPus in MINorities: NAture versus Nurture) cohort database⁵, the NP domain was the most frequently involved. Predictors of overall damage accrual in SLE have been examined by several different investigators^{5,6,8,9} but predictors of NP-damage have been infrequently evaluated. For example, Mikdashi and Handwerger identified disease activity, Caucasian ethnicity, older age at disease onset and the presence of anti-Ro/SSA and antiphospholipid (aPL) antibodies as independent predictors of significant NP-damage in patients from the University of Maryland Lupus Cohort¹⁰. In turn, Mok et al found disease activity at diagnosis, the presence of aPL antibodies, the use of intravenous pulse methylprednisolone and cumulative non-NP damage to be independently associated with NP-damage accrual in a Chinese lupus cohort¹¹. However, in contrast to overall damage, a well recognized predictor of mortality¹²⁻¹⁴, NP-damage *per se* was not found to be associated with mortality in either study^{10,11}.

We have now assessed the predictors of time-to-NP damage occurrence and the impact of NP-damage on mortality in patients with SLE from LUMINA, a large multiethnic US cohort. We hypothesized that patient with serious disease manifestations and higher levels of disease activity will experience NP-damage some time in the course of their disease and that NP-damage *per se* may contribute to mortality.

PATIENTS AND METHODS

Patients

LUMINA is a longitudinal study of outcome^{15,16}. Details about this cohort have been previously described; briefly, all LUMINA patients meet the American College of Rheumatology (ACR) revised and updated classification criteria^{17,18}, have disease duration 5 years at enrollment (T0), are 16 years of age, of defined ethnicity (Hispanic from Texas and Puerto Rico, African American and Caucasian) and are living in the geographical enrollment areas of the participating centers [University of Alabama at Birmingham (UAB), The University of Texas Health Science Center at Houston (UTH) and The University of Puerto Rico Medical Sciences Campus (UPR)]. LUMINA recruitment started in 1994 except in Puerto Rico where recruitment started in 2001. The Institutional Review Boards of the participating institutions approved the study; written informed consent was obtained from each patient according to the declaration of Helsinki.

Prior to enrollment all medical records are reviewed to confirm the patient's eligibility, and to gather socioeconomic-demographic information and relevant clinical data from the time of diagnosis (TD) to T0. Every patient is seen at T0, every six months for the first year (T0.5 and T1, respectively), and yearly thereafter. A LUMINA study visit consists of an interview, a physical examination, and laboratory tests. Data for missed study visits are obtained, whenever possible, by review of all available medical records. TD is defined as the time at which patients meet four of the ACR classification criteria. Disease duration is the interval between TD and T0. For those patients who developed NP-damage, their observation time was truncated at the time of its occurrence; thus, last visit (TL) for these patients was the time at which the first NP-damage occurred. For those patients who had developed damage before T0, TL was considered the median value between T0 and TD plus six months. For patients who did not develop NP-damage, TL was the time of the last visit.

Variables

As previously described¹⁶, the LUMINA database includes variables from the socioeconomic-demographic, clinical, immunological, genetic, behavioral and psychological domains. With the exception of the genetic variables which are obtained at T0, all other variables are ascertained at every subsequent visit. Only the variables included in this study will be described.

NP-damage, the dependent variable, was defined per the SDI¹⁹ as the presence, for at least six months, of one or more of the following clinical events: cognitive impairment or major psychosis, seizures, cranial or peripheral neuropathy (excluding optic neuropathy), transverse myelitis; cerebrovascular accident (CVA) or surgical resection for causes other than malignancy are scored regardless of their duration. A second CVA if occurs more than six months apart from the first is also scored. As per the SDI, these events are defined clinically; thus, no formal neuropsychological testing with the exception of a self-reported validated cognitive assessment (the Cognitive Symptom Inventory) was performed²⁰ and assessed at every study visit. As reported before, for a patient to be considered cognitively impaired six of the 21 questions needed to be answered as indicative of having difficulty present most of the time or all the time. Given that we have previously shown that once cognitive impairment is recognized using this instrument, it tends to remain unchanged²¹, we believe it truly assesses permanent cognitive impairment.

Variables from the socioeconomic-demographic domain included were age, gender, ethnicity, marital status, education, poverty (as defined by the US Federal Government adjusted for the number of subjects in the household)²², health insurance and health-related behaviors (smoking, drinking and using recreational drugs). Variables from this domain included in the analyses were from T0, except health insurance which was obtained either at TD or T0 if data at TD were not available; as in previous analyses, socioeconomic-demographic data were found to be quite stable over time.

Clinical variables included were disease duration (TD-T0), disease onset type, number of ACR criteria at TD, disease manifestations, disease activity and damage. Disease onset type was considered acute if clinical manifestations evolved over 4 weeks and insidious, if otherwise. Disease activity was assessed at TD and T0, and subsequently using the Systemic Lupus Activity Measure-Revised (SLAM-R)²³; with the exception of TD, in which disease activity was ascertained using all available medical records, disease activity was assessed during regularly scheduled study visits. The domains and laboratory variables of the SLAM-R were also examined. Damage was measured with the SDI at T0 and at TL and it was examined as a continuous variable (total damage score). The scores for each one the domains of the SDI at both, T0 and TL, were also recorded. For the purpose of these analyses, the NP domain items were excluded from both the SLAM-R and the SDI total score to avoid attributing any disease activity or damage to them; the weighted SLAM-R reflecting disease activity over the course of the disease was used in these analyses.

Cumulative SLE clinical manifestations were assessed as per the ACR classification criteria^{17,18}; NP manifestations due to lupus but not included in the ACR criteria were the following: CVA (transient ischemic attack, stroke and subarachnoid hemorrhage), headaches, neuropathy (cranial neuropathy, peripheral neuropathy or mononeuritis multiplex), myelopathy, mood disorder (depression) and cognitive dysfunction; as previously described, all were clinically defined. Other clinical manifestations attributable to lupus such as Raynaud's phenomenon, livedo reticularis and nephritis were also examined²⁴.

Comorbidities included were diabetes mellitus [fasting plasma glucose at or above 126 mg/dl and/or random (or two-hour value in a oral glucose tolerance test) at or above 200 mg/dl; physician diagnosed and/or patient self-reported intake of pharmacological treatment (requiring either insulin and/or oral hypoglycemic agent)], hypertension [defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg on two or more occasions and/or patient self-reported intake of antihypertensive medications regardless of cause; however, if agents are taken for proteinuria (ACE inhibitors), and/or for Raynaud's phenomenon, hypertension is not recorded], valvular heart disease (including non-infectious endocarditis), coronary artery disease (myocardial infarction or angina), venous or arterial peripheral thrombotic events, hypothyroidism [high serum thyroid stimulating hormone and/or clinical symptoms and/or pharmacological treatment for hypothyroidism] and hypercholesterolemia (serum total cholesterol ≥ 200 mg/dl). Menopausal status was also recorded.

Within the autoantibodies IgG and IgM aPL anti-phospholipid antibodies [(abnormal > 13 IgG phospholipid (GPL) units/ml and/or > 13 IgM phospholipid (MPL) units/ml, by enzyme-linked immunoabsorbents assay (ELISA) technique]²⁵ and the lupus anticoagulant (LAC) (Staclot Test Diagnostica Stago 92600, Asnières-Sur-Seine, France)²⁶ were included in these analyses .

Cumulative exposure to glucocorticoids (as prednisone equivalent), cyclophosphamide, hydroxychloroquine, azathioprine and mycophenolate mofetil was also recorded. Glucocorticoid dose (prednisone) was estimated as a categorical variable as follows: low (< 10 mg/day), medium (10–30 mg/day) and high (> 30 mg/day) and as the weighted average of the maximum glucocorticoid dose from T0 to TL, which was calculated by multiplying the maximum prednisone dose for each individual visit by the number of months in the interval between visits divided by the total follow up time.

Behavioral and psychological variables included were helplessness (ascertained with the Rheumatology Attitude Index)²⁷, social support [assessed with the International Support Evaluation List (ISEL)]²⁸ and abnormal illness-related behaviors [assessed with the Illness Behavior Questionnaire (IBQ)]²⁹.

Statistical Analyses

Disease and patient characteristics (NP-damage or no NP-damage) were examined by the Chi-square and Student's *t*-tests for categorical and continuous variables, respectively; variables with $p \leq 0.10$ in these analyses were examined by univariable Cox proportional hazards regressions in which the dependent variable was the time-to-NP damage occurrence. Variables with a $p \leq 0.10$ in these univariable Cox regressions were entered into Cox proportional hazards multivariable regression models using a computer-driven backward selection procedure until no further variables were found to be significant at $p \leq 0.05$. Because of its potential biological importance, age, gender and ethnicity were also included. Two different models were examined; in the main model, glucocorticoid use was defined as a categorical variable whereas in the alternative model as a continuous variable, the weighted average maximum glucocorticoid dose from T0 to TL (*vide supra*); this was done as we were interested in examining the possible deleterious effect not only of the different glucocorticoid dose categories but also the impact of its continuous use. Finally, a second set of multivariable Cox regressions in which the neuropsychiatric manifestations were omitted as possible explanatory variables of the outcome of interest was examined. These second set of models; however, are clinically less informative since NP damage cannot possibly ensue if neuropsychiatric manifestations do not occur to begin with. In alternative models all variables significant in the univariable analyses were entered into the multivariable analyses. Finally given that neuro-cognitive impairment and/or psychosis are but one joint element of

the NP domain of the SDI, the few (5 or 3.7%) cases of psychosis were removed and the analyses redone. Results of the univariable and multivariable analyses are reported as hazard ratios (HRs) where values ≥ 1 indicate a shorter time to the occurrence of NP-damage while values < 1 indicate a longer time; p values ≤ 0.05 were considered significant in these analyses.

A Kaplan-Meier survival curve with NP-damage being the end-point was also examined.

The contribution of NP-damage to mortality was examined by Cox univariable and multivariable proportional hazards regressions. In the multivariable analyses, age, gender, ethnicity and variables previously found to significantly predict mortality (disease activity, damage and poverty)^{12,13} were included in the model. Statistical significance was defined as a p value ≤ 0.05 .

Analyses were performed using either SAS, version 9.1 (SAS Institute, Cary, NC) or the SPSS program, version 15.0 software (Chicago, IL).

RESULTS

Six-hundred and thirty-two patients were included in these analyses. One-hundred and eighty five (29.3%) developed NP-damage (one or more events) over a mean [Standard Deviation (SD)] total disease duration of 5.6 (3.7) years. There were 117 (18.5%) Texan-Hispanics, 102 (16.1%) Puerto Rican Hispanics, 234 (37.0%) African Americans and 179 (28.3%) Caucasians; as expected, these patients were predominantly women (88.6%) and their mean age and disease duration at T0 were 38.6 (12.6) years and 18.9 (15.8) months, respectively. NP damage occurred in about one third of Texan Hispanics, African Americans and Caucasians but only in about 7% of the Puerto Rican Hispanics ($p < 0.0001$) and a median time of 4 years. Among patients in whom NP-damage had occurred, 135 had developed cognitive impairment and/or major psychosis (5 of them psychosis and 130 cognitive impairment), 45 had developed CVA events (one CVA in 40, two CVAs in five), 30 seizures, 22 cranial/peripheral neuropathy and three transverse myelitis. NP-damage was the most common domain of the SDI involved, followed by the renal (19.6%), ocular (15.7%), integument (14.9%) and musculoskeletal (13.6%) domains.

Survival Analysis

As noted in Figure 1, the cumulative probability of NP-damage occurrence at five and 10 years were 30.7% and 42.1%, respectively. The estimates beyond 10 years are based on relatively few patients exposed to the risk and thus lack precision.

Features Associated with Time-to-NP Damage Occurrence

Univariable Analyses—Among the socioeconomic-demographic features, Texan-Hispanic, African American and Caucasian ethnicities were associated with a shorter time-to-NP damage occurrence as compared to the reference ethnic group (Puerto Rican-Hispanics); similarly, living below the poverty line, having higher levels of illness-related behaviors and of helplessness were associated with a shorter time-to-NP damage occurrence. In contrast, the number of years of education, having health insurance and higher levels of social support were associated with a longer time-to-NP damage occurrence. These data are shown in Table 1.

Among the clinical variables, in addition to the neurological manifestations (seizures, psychosis, CVA and cognitive disorder), hemolytic anemia, aPL antibodies, hypercholesterolemia, disease activity at TD and T0, damage accrual at T0 but not at TL, diabetes, the weighted average maximum prednisone dose and prednisone at a dose > 30

mg/day were associated with a shorter time-to-NP damage occurrence whereas disease duration, malar rash, photosensitivity, lymphopenia, Raynaud's phenomenon, hydroxychloroquine use and prednisone at a dose between 10–30 mg/day were associated with a longer time-to-NP damage occurrence. These data are depicted in Table 2. Other medications were not associated with NP damage occurrence (data not shown). Analyses limited to women failed to find an association between menopausal status and time-to-NP damage (data not shown).

Multivariable Analyses—After adjusting for the presence of neuropsychiatric manifestations, older age at T0 (HR=1.02; 95% CI 1.00–1.04), Caucasian ethnicity (HR=1.87; 95% CI 1.22–2.87), disease activity over the course of the disease (HR=1.16; 95% CI 1.12–1.21), diabetes (HR=3.47; 95% CI 1.44–8.38) and abnormal illness-related behaviors (HR=1.05; 95% CI 1.02–1.08) were associated with a shorter time-to-NP damage occurrence. In contrast photosensitivity (HR=0.65; 95% CI 0.44–0.95), anemia (HR=0.56; 95% CI 0.31–0.98), Raynaud's phenomenon (HR=0.49; 95% CI 0.34–0.72), a medium dose of prednisone (HR=0.56; 95% CI 0.35–0.92) and hydroxychloroquine use (HR=0.58; 95% CI 0.36–0.93) were associated with a longer time-to-NP damage occurrence. These data are depicted in table 3.

The results were comparable in the alternative model; however, glucocorticoid use (as the weighted average maximum prednisone dose) was not found to be associated with a shorter time-to-NP-damage occurrence in this model. Removing the five patients in whom psychosis had occurred from this regression did not alter the results of these models.

In the second set of models in which the neuropsychiatric manifestations were omitted the results were comparable; however, now aPL antibodies were found to be associated with a shorter time-to-the occurrence of NP damage (HR=1.50 to 1.52; 95% CI 1.03 to 1.04 – 2.21 to 2.23).

Given the apparent protective effect of hydroxychloroquine on time to NP-damage, propensity score analyses were performed to adjust for confounding by indication. Although the HR for hydroxychloroquine remained below 1 after adjusting for the propensity score, the 95% CI encompassed the unit, and thus hydroxychloroquine was no longer significant (data not shown).

NP-damage and Mortality—Of the 185 patients who had developed NP-damage 30 (16.2%) were deceased compared to 47 of 447 (10.5%) among these who had not developed NP-damage ($p=0.0462$). In the univariable Cox regression, NP-damage was a predictor of mortality, (HR=1.75; 95% CI 1.09–2.79); however NP damage was not significant after adjusting for age, gender, ethnicity, poverty, disease activity and damage (omitting NP-damage) in the multivariable analysis [HR=1.38; 95% CI 0.79–2.40; $p=0.2546$].

DISCUSSION

NP-SLE manifestations cause substantial morbidity^{1,2} and may lead to permanent damage^{2,5,7,10,30}; thus, understanding the factors predicting it, over and above the occurrence of NP manifestations, has important implications. Utilizing the extensive database of the LUMINA cohort, we have now conducted such a study. Nearly one third of the patients experienced NP-damage after a mean total disease duration of 5.6 years and a median time to the event of 4 years; this rate of NP-damage is higher than the one in the Chinese cohort (18%), but lower than in the Maryland Lupus Cohort (51%)^{10,11}. This variability probably relates to differences in the patients' age (youngest in the Chinese cohort), ethnic origin [larger representation of African Americans in the Maryland cohort

(64% versus 37% in ours)], the enrichment of NP cases in the Maryland cohort and the analytical methods used.

Although we have shown a protective role for hydroxychloroquine, this reflects in part confounding by indication ³¹ as patients with milder disease tend to be treated with this compound. Given the overall anti-inflammatory, anti-thrombotic, anti-platelet, hypolipidemic, glucocorticoid-sparing and immunomodulatory properties of antimalarials coupled with their relatively benign safety profile and the protective effect on overall damage and survival ^{32–34}, this compound should be regarded as a standard element of the treatment of patients with lupus.

We have also found higher disease activity over the course of the disease, older age, Caucasian ethnicity, diabetes and abnormal illness-related behaviors to be associated with a shorter time-to-NP damage occurrence; in contrast, photosensitivity, Raynaud's phenomenon, anemia and a medium dose of prednisone per day, were associated with a longer time-to-NP damage occurrence. As to glucocorticoids, it appears that a medium dose may exert some level of protection in comparison with a low or a high dose; however, lacking precise information about treatment duration it is possible that glucocorticoids offer such a protective effect only if this dose is used for a relatively short time period rather than for a prolonged one.

Older age has been strongly associated with NP-damage ^{5,7,9} probably because of these patients' associated comorbidities such as hypertension, diabetes and atherosclerotic cerebrovascular disease that may predispose them to vascular endothelium damage and strokes and subsequently to NP-damage. This finding is consistent with the data from the Maryland Lupus Cohort. In addition, traditional cardiovascular risk factors, such as hypertension, dyslipidemia and accelerated atherosclerosis are more prevalent in SLE ^{35–37} and may also contribute to NP-damage; however, hypercholesterolemia was not retained in our multivariable models. Abnormal illness-related behaviors, that is inadequate coping mechanisms in dealing with lupus, were also found to be associated with a shorter time-to-NP damage which is consistent with findings we have previously reported relative to overall damage in lupus (8).

In the univariable analyses, we found Texan-Hispanic, African American and Caucasian ethnicities to be associated with a shorter time-to-NP damage occurrence in comparison to the Puerto Rican patients; in the multivariable analyses, only Caucasian ethnicity was associated with a shorter time-to-NP damage occurrence which supports the findings from the Maryland Lupus Cohort ¹⁰. It is conceivable that these patients could have other underlying factors predisposing them to develop NP-damage earlier ¹⁰.

The association of photosensitivity and Raynaud's phenomenon with a longer time-to-NP damage suggests that patients with these manifestations have, overall, a less severe disease. Indeed, Raynaud's phenomenon has been shown to occur in patients with milder disease with frequent integument and musculoskeletal involvement ³⁸. On the other hand, Raynaud's phenomenon has been inconsistently associated with migraine headaches in SLE patients ^{39,40}; but we failed to demonstrate an association between headaches and NP-damage. Anemia was also associated with a longer time-to-NP damage; anemia is an indicator of disease activity and a predictor of overall damage accrual ^{41,42}. Thus, we do not have a plausible explanation for this finding. Their lack of association when the neuropsychiatric manifestations when included, probably reflects that these manifestations are stronger predictors of NP-damage than aPL antibodies, that is they may exert their effect through their association with neuropsychiatric manifestations rather than independently.

Of interest, in the alternative set of multivariable models (neuropsychiatric manifestations excluded), aPL antibodies were found to predispose to the occurrence of NP damage, which is consistent with previous reports, particularly in relation to NP-vascular events ¹¹.

Damage has been shown to be a predictor of mortality ^{8,12–14}; however, and consistent with previous studies ^{10,11}, NP-damage was not found to be an independent contributor to mortality when examined in conjunction with variables known to be associated with this outcome; however, overall damage was found to be an independent contributor. Patients with NP-damage had more frequent involvement and higher damage scores in the cardiovascular and renal SDI domains (data not shown), suggesting that these are more important contributors to mortality than NP-damage *per se*.

Our study has some limitations. Firstly, our assessment of cognitive impairment was based on the patient's self-report of their cognition through a validated instrument, the Cognitive System Inventory, rather than on formal neuropsychological testing; this is, however, consistent with the SDI definition set forth over a decade ago ⁴³; moreover, given that this inventory was applied at every study visit and that we have previously found cognitive impairment to persist over time, we feel that patients categorized as having neuropsychiatric damage based on these assessments were correctly classified. Secondly, additional studies such as electroencephalography, imaging, and biochemical markers of neuronal damage, such as levels of intrathecal neurofilament triplet protein and glial fibrillary acidic protein ⁴⁴ were not systematically performed in all patients. Thirdly, not all elements of the NP-damage domain share the same pathophysiology; by examining them together we may have failed to demonstrate factors that may be related to its specific elements; nevertheless, such information may be quite useful to clinicians caring for lupus patients. Fourthly, Puerto Rican-Hispanics have been followed up for a relative shorter time and thus their contribution to the end-point examined may not have been yet fully realized. Finally, although the SDI is a valid and reliable instrument for the assessment of damage, it is not intended to distinguish the underlying cause of any of the items that constitute this or any other of its domains.

Despite these limitations, this study provides important information for clinicians caring for SLE patients. Firstly, NP-damage is relative common in our patients being the most frequent SDI domain involved. Secondly, higher disease activity over time, diabetes and older age are significantly associated with a shorter time to NP-damage occurrence. Thirdly, Caucasians are at high risk of developing NP-damage within a relatively shorter time. Fourthly, hydroxychloroquine may be associated with a longer time-to-NP damage. Finally, a better control of disease activity is needed to reduce NP-damage and improve the long-term outcome of all SLE patients. Medium doses of glucocorticoids if used for a short time to diminish the probability of long-term side effects, may prevent NP-damage.

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Reference List

1. Hanly JG, McCurdy G, Fougere L, Douglas JA, Thompson K. Neuropsychiatric events in systemic lupus erythematosus: attribution and clinical significance. *J Rheumatol.* 2004 Nov; 31(11):2156–2162. [PubMed: 15517627]
2. Jonsen A, Bengtsson AA, Nived O, Ryberg B, Sturfelt G. Outcome of neuropsychiatric systemic lupus erythematosus within a defined Swedish population: increased morbidity but low mortality. *Rheumatology (Oxford).* 2002 Nov; 41(11):1308–1312. [PubMed: 12422005]
3. Bultink IE, Turkstra F, Dijkman BA, Voskuyl AE. High Prevalence of Unemployment in Patients with Systemic Lupus Erythematosus: Association with Organ Damage and Health-Related Quality of Life. *J Rheumatol.* 2008 Mar 15. [Epub ahead of print].
4. Zhou HQ, Zhang FC, Tian XP, Leng XM, Lu JJ, Zhao Y, et al. Clinical features and outcome of neuropsychiatric lupus in Chinese: analysis of 240 hospitalized patients. *Lupus.* 2008; 17(2):93–99. [PubMed: 18250131]
5. Alarcon GS, McGwin G Jr. Bartolucci AA, Roseman J, Lisse J, Fessler BJ, et al. Systemic lupus erythematosus in three ethnic groups IX Differences in damage accrual. *Arthritis Rheum.* 2001; 44:2797–2806. [PubMed: 11762940]
6. Petri M. Hopkins lupus cohort: 1999 update. *Rheum Dis Clin North Am.* 2000; 26:199–213. [PubMed: 10768209]
7. Zonana-Nacach A, Camargo-Coronel A, Yanez P, de Lourdes Sanchez M, Jiménez-Balderas FJ, Aceves-Avila J, et al. Measurement of damage in 210 Mexican patients with systemic lupus erythematosus: relationship with disease duration. *Lupus.* 1998; 7:119–123. [PubMed: 9580342]
8. Rahman P, Gladman DD, Urowitz MB, Hallett D, Tam LS. Early damage as measured by the SLICC/ACR damage index is a predictor of mortality in systemic lupus erythematosus. *Lupus.* 2001; 10:93–96. [PubMed: 11237132]
9. Alarcon GS, Roseman JM, McGwin G Jr. Uribe A, Bastian HM, Fessler BJ, et al. Systemic lupus erythematosus in three ethnic groups: XXDamage as predictor of further damage. *Rheumatology.* 2004; 43:202–205. [PubMed: 12923289]
10. Mikdashi J, Handwerker B. Predictors of neuropsychiatric damage in systemic lupus erythematosus: data from the Maryland lupus cohort. *Rheumatology (Oxford).* 2004 Dec; 43(12):1555–1560. [PubMed: 15342927]
11. Mok CC, To CH, Mak A. Neuropsychiatric damage in Southern Chinese patients with systemic lupus erythematosus. *Medicine (Baltimore).* 2006 Jul; 85(4):221–228. [PubMed: 16862047]
12. Alarcon GS, McGwin G Jr. Bastian HM, Roseman J, Lisse J, Fessler BJ, et al. Systemic lupus erythematosus in three ethnic groups VII [correction of VIII]. Predictors of early mortality in the LUMINA cohort LUMINA Study Group. *Arthritis Rheum.* 2001 Apr; 45(2):191–202. [PubMed: 11324784]
13. Fernandez M, Alarcon GS, Calvo-Alen J, Andrade R, McGwin G Jr. Vila LM, et al. A multiethnic, multicenter cohort of patients with systemic lupus erythematosus (SLE) as a model for the study of ethnic disparities in SLE. *Arthritis Rheum.* 2007 May 15; 57(4):576–584. [PubMed: 17471524]
14. Mok CC, Mak A, Chu WP, To CH, Wong SN. Long-term survival of Southern Chinese patients with systemic lupus erythematosus: a prospective study of all age-groups. *Medicine (Baltimore).* 2005 Jul; 84(4):218–224. [PubMed: 16010206]
15. Alarcon GS, Roseman J, Bartolucci AA, Friedman AW, Moulds JM, Goel N, et al. Systemic lupus erythematosus in three ethnic groups: II Features predictive of disease activity early in its course. *Arthritis Rheum.* 1998; 41:1173–1180. [PubMed: 9663472]
16. Alarcon GS, Friedman AW, Straaton KV, Moulds JM, Lisse J, Bastian HM, et al. Systemic lupus erythematosus in three ethnic groups: III. A comparison of characteristics early in the natural history of the LUMINA cohort. Lupus in Minority populations: Nature vs Nurture. *Lupus.* 1999; 8:197–209. [PubMed: 10342712]
17. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982; 25:1271–1277. [PubMed: 7138600]

18. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1997; 40:1725. [PubMed: 9324032]
19. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the systemic lupus international collaborating clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum.* 1996; 39:363–369. [PubMed: 8607884]
20. Pincus T, Swearingen C, Callahan LF. A self-report cognitive symptoms inventory to assess patients with rheumatic diseases: Results in eosinophilia-myalgia syndrome (EMS), fibromyalgia, rheumatoid arthritis (RA), and other rheumatic diseases. *Arthritis Rheum.* 1996; 39:S261.
21. Sanchez ML, Zhang J, Vilá LM, Reveille JD, Alarcón GS. Factors associated with the development of cognitive impairment over the course of systemic lupus erythematosus (SLE): Data from a multiethnic cohort. *Arthritis Rheum.* 2007; (56):S826.
22. U.S. Department of Commerce, Bureau of the Census. Current population reports, Series P-23, No. 28 and Series P-60, No. 68 and subsequent years. Washington, DC: Housing and Household Economic Statistics Division; 1995.
23. Liang MH, Socher SA, Larson MG, Schur PH. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. *Arthritis Rheum.* 1989; 32:1107–1118. [PubMed: 2775320]
24. Bastian HM, Roseman JM, McGwin G Jr. Alarcón GS, Friedman AW, Fessler BJ, et al. Systemic lupus erythematosus in three ethnic groups: XIIRisk factors for lupus nephritis after diagnosis. *Lupus.* 2002; 11:152–160. [PubMed: 12004788]
25. Harris EN. Special report The second international anti-cardiolipin standardization workshop/the Kingston anti-phospholipid antibody study (KAPS) group. *Am J Clin Pathol.* 1990; 94(4):476–484. [PubMed: 2220676]
26. Triplett DA, Barna LK, Unger GA. A hexagonal (II) phase phospholipid neutralization assay for lupus anticoagulant identification. *Thromb Haemost.* 1993; 70(5):787–793. [PubMed: 8128436]
27. Engle EW, Callahan LF, Pincus T, Hochberg MC. Learned helplessness in systemic lupus erythematosus: Analysis using the Rheumatology Attitude Index. *Arthritis Rheum.* 1990; 33:281–286. [PubMed: 2306296]
28. Cohen, S.; Mermelstein, R.; Kamarck, T.; Hoberman, HN. Measuring the functional components of social support. In: Sarason, IG.; Sarason, BR., editors. *Social Support: Theory, Research and Applications.* Boston: Martinus Nijhoff; 1985. p. 73-94.
29. Pilowsky I. Dimensions of illness behavior as measured by the Illness Behavior Questionnaire: A replication study. *J Psychosom Res.* 1993; 37:53–62. [PubMed: 8421260]
30. Fragoso-Loyo HE, Sanchez-Guerrero J. Effect of severe neuropsychiatric manifestations on short-term damage in systemic lupus erythematosus. *J Rheumatol.* 2007 Jan; 34(1):76–80. [PubMed: 17143970]
31. Landewe RB. The benefits of early treatment in rheumatoid arthritis: confounding by indication and the issue of timing. *Arthritis Rheum.* 2003; 48(1):1–5. [PubMed: 12528097]
32. Fessler BJ, Alarcon GS, McGwin G Jr. Roseman J, Bastian HM, Friedman AW, et al. Systemic lupus erythematosus in three ethnic groups: XVIAssociation of hydroxychloroquine use with reduced risk of damage accrual. *Arthritis Rheum.* 2005 May; 52(5):1473–1480. [PubMed: 15880829]
33. Alarcon GS, McGwin G Jr. Bertoli AM, Fessler BJ, Calvo-Alen J, Bastian HM, et al. Effect of hydroxychloroquine in the survival of patients with systemic lupus erythematosus. Data from LUMINA, a multiethnic us cohort (LUMINA L). *Ann Rheum Dis.* 2007 Mar 27; 66:1168–1172. [PubMed: 17389655]
34. Ruiz-Irastorza G, Egurbide MV, Ibarra S, Garmendia M, Erdozain JG, Villar I, et al. Effect of antimalarials on long-term survival of patients with systemic lupus erythematosus. *Lupus.* 2005; 14(3):220.
35. Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum.* 1999; 42(2):338–346. [PubMed: 10025929]

36. Esdaile JM, Abrahamowicz M, Grodzicky T, Li Y, Panaritis C, Du Berger R, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum.* 2001; 44:2331–2337. [PubMed: 11665973]
37. Kitagawa Y, Gotoh F, Koto A, Okayasu H. Stroke in systemic lupus erythematosus. *Stroke.* 1990 Nov; 21(11):1533–1539. [PubMed: 2237945]
38. Dimant J, Ginzler E, Schlesinger M, Sterba G, Diamond H, Kaplan D, et al. The clinical significance of Raynaud's phenomenon in systemic lupus erythematosus. *Arthritis Rheum.* 1979 Aug; 22(8):815–819. [PubMed: 465096]
39. Appenzeller S, Costallat LT. Clinical implications of migraine in systemic lupus erythematosus: relation to cumulative organ damage. *Cephalalgia.* 2004 Dec; 24(12):1024–1030. [PubMed: 15566416]
40. Isenberg DA, Meyrick-Thomas D, Snaith ML, McKeran RO, Royston JP. A study of migraine in systemic lupus erythematosus. *Ann Rheum Dis.* 1982 Feb; 41(1):30–32. [PubMed: 7065726]
41. Feletar M, Ibañez D, Urowitz MB, Gladman DD. The impact of the 1997 update of the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus: what has been changed? *Arthritis Rheum.* 2003; 48(7):2067–2073. [PubMed: 12847702]
42. Bertoli AM, Vila LM, Apte M, Fessler BJ, Bastian HM, Reveille JD, et al. Systemic lupus erythematosus in a multiethnic US cohort LUMINA LI: anaemia as a predictor of disease activity and damage accrual. *Rheumatology (Oxford).* 2007 Sep; 46(9):1471–1476. [PubMed: 17650522]
43. ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum.* 1999; 42(4):599–608.
44. Trysberg E, Nylen K, Rosengren LE, Tarkowski A. Neuronal and astrocytic damage in systemic lupus erythematosus patients with central nervous system involvement. *Arthritis Rheum.* 2003 Oct; 48(10):2881–2887. [PubMed: 14558094]

Time (years)	0	2.5	5	7.5	10	12.5	15
Patients at risk	632	412	255	121	57	26	5
Patients developing NP-damage	0	115	160	172	181	185	185

Figure 1.
NP-damage in LUMINA patients by Kaplan-Meier survival curve. Table below shows the number of patients at risk.

Table 1

Socioeconomic-Demographic and Psychological/Behavioral Variables Associated with Time-to-Neuropsychiatric Damage Occurrence in LUMINA^{*} Patients by Univariable Cox Proportional Hazards Regressions

Variable	Hazard Ratio	95% Confidence Interval	p value
Age at baseline, years	1.01	0.99–1.02	0.1035
Gender	0.78	0.50–1.23	0.2826
Ethnicity			
Texan-Hispanic	5.94	2.66–13.27	<0.0001
Puerto Rican-Hispanic		Reference group	
African American	6.12	2.82–13.26	<0.0001
Caucasian	5.25	2.40–11.52	<0.0001
Education, years	0.95	0.91–0.99	0.0310
Health insurance	0.59	0.43–0.81	0.0012
Poverty [†]	1.42	1.04–1.93	0.0268
Smoking	1.28	0.86–1.91	0.2207
Social support [‡]	0.88	0.82–0.96	0.0020
Abnormal illness-related behaviors [‡]	1.04	1.02–1.07	0.0004
Helplessness [‡]	1.04	1.02–1.06	0.0007

^{*} Lupus in Minorities: Nature vs Nurture;

[†] as per US Federal government guidelines, adjusted for the number of persons in the household;

[‡] ascertained with the Interpersonal Support Evaluation List, the Illness Behavior Questionnaire and the Rheumatology Attitude Index, respectively.

Table 2

Clinical Variables Associated with Time-to-Neuropsychiatric Damage Occurrence in LUMINA * Patients by Univariable Cox Proportional Hazards Regressions

Variable	Hazard Ratio	95% Confidence Interval	p value
Disease duration [†]	0.99	0.98–0.99	0.0168
Disease manifestations			
Malar rash	0.58	0.44–0.78	0.0002
Photosensitivity	0.49	0.37–0.65	<0.0001
Seizures	3.48	2.37–5.10	<0.0001
Psychosis	2.53	1.56–4.11	0.0002
Stroke	4.84	2.75–8.53	<0.0001
Neurocognitive disorder	3.82	2.83–5.14	<0.0001
Hemolytic anemia	1.60	1.07–2.41	0.0234
Lymphopenia	0.70	0.52–0.94	0.0181
Raynaud's phenomenon	0.47	0.35–0.63	<0.0001
Comorbidities			
Hypertension	0.84	0.63 –1.13	0.2540
Diabetes	2.71	1.51 – 4.86	0.0009
Laboratory features			
aPL antibodies [‡]	1.34	0.99–1.80	0.0572
Hypercholesterolemia	1.42	1.04–1.95	0.0292
SLAM-R [§] score			
Diagnosis	1.04	1.02–1.06	0.0004
Baseline	1.07	1.04–1.09	<0.0001
SDI [¶] score			
Baseline	1.38	1.23–1.55	<0.0001
Last visit	1.02	0.94–1.10	0.6753
Medications			
Hydroxychloroquine	0.48	0.34–0.66	<0.0001
Glucocorticoids ^{**}			
Weighted maximum dose	1.01	1.00–1.01	<0.0001
Categorical			
Low dose (<10mg/day)		Reference group	
Medium dose (10–30 mg/day)	0.50	0.33–0.76	0.0010
High dose (>30 mg/day)	2.21	1.60–3.05	<0.0001

* LUPus in MINorities: NAture vs Nurture;

[†] interval between diagnosis and baseline;

[‡] IgG and IgM antiphospholipid antibodies and/or the lupus anticoagulant;

[§] Systemic Lupus Activity Measure-Revised and

[¶]Systemic Lupus International Collaborating Clinics/Damage Index (neuropsychiatric domain items excluded from both),

^{**}
As prednisone.

Table 3

Time-to-Neuropsychiatric Damage Occurrence by Multivariable Cox Proportional Hazards Regression Analyses in LUMINA ^{*} Patients [†]

Variable	Hazard Ratio	95% Confidence Interval	p value
Age at baseline, years	1.02	1.00–1.04	0.0233
Ethnicity, Caucasian	1.87	1.22–2.87	0.0041
Disease manifestations			
Photosensitivity	0.65	0.44–0.95	0.0257
Anemia	0.56	0.31–0.98	0.0448
Raynaud's phenomenon	0.49	0.34–0.72	0.0002
SLAM-R [‡] weighted	1.16	1.12–1.21	<0.0001
Diabetes	3.47	1.44–8.38	0.0056
Medications			
Hydroxychloroquine	0.58	0.36–0.93	0.0248
Glucocorticoid [§] , dose mg/d			
Medium dose (10–30 mg/day)	0.56	0.35–0.92	0.0211
Abnormal illness-related behaviors [¶]	1.05	1.02–1.08	0.0011

^{*} Lupus in Minorities: NAture vs Nurture;

[†] Variables included in the model were, in addition to the ones noted in this Table, the following: gender, ethnicity, education, poverty, malar rash, hemolytic anemia, neuropsychiatric manifestations, (seizures, psychosis, cognitive impairment and stroke) damage at baseline (without neuropsychiatric domain items), aPL antibodies, hypercholesterolemia, social support and helplessness;

[‡] Systemic Lupus Activity Measure-Revised;

[§] as prednisone equivalent;

[¶] as per the Illness Behavior Questionnaire.