Title

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Journal

Arthritis Care & Research, 73(10)

ISSN

2151-464X

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Publication Date

2021-10-01

DOI

10.1002/acr.24349

Peer reviewed

HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2022 October 01.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2021 October ; 73(10): 1436–1443. doi:10.1002/acr.24349.

COGNITIVE FUNCTION TRAJECTORIES ARE ASSOCIATED WITH THE DEPRESSIVE SYMPTOMS TRAJECTORIES IN SYSTEMIC LUPUS ERYTHEMATOSUS OVER TIME

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Abstract

Background—Cognitive function may change over time in patients with SLE, and cognitive function trajectories have not well been studied. We aim to: 1) identify cognitive function trajectories in SLE and describe it with depressive symptoms trajectories and 2) identify baseline factors associated with class membership in the dual trajectories.

Methods—Longitudinal data from the University of California San Francisco Lupus Outcomes Study were analyzed. Two outcome trajectories were studied jointly – The Hopkins Verbal Learning Test-Revised (HVLT-R) and the Center of Epidemiologic Studies Depression Scale (CES-D) (administered annually). Univariate/multivariable logistic regression analyses examined baseline factors associated with class memberships.

Results—755 patients were studied. 4 latent classes were identified: 1-low CES-D scores and low cognitive scores (no depression + cognitive impairment; 20%), 2-lowest CES-D scores and highest normal cognitive scores (no depression + normal cognition; 48%), 3-highest CES-D scores and lowest cognitive scores (depression + cognitive impairment; 9%), and 4-high CES-D scores and cognitive score at borderline (depression + borderline cognition; 23%).

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The author declares no conflict of interest, financial or otherwise.

Conclusion—4 distinct classes of dual cognitive function and the depressive symptoms were identified. Persistently low cognitive performance in 28% of patients (Classes 1 and 3) did not significantly improve over 7 years. Cognitive impairment was associated with depression status in 9% of patients (class 3). Other factors also predicted latent class membership; ethnicity, education, disease activity, physical functioning and bodily pain. These results highlight the importance of periodic assessment of cognitive function, and different aspects relevant for assessing and managing cognitive function over time in SLE.

Keywords

lupus; cognitive; trajectory; depression

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with multi-systemic manifestations which include neuropsychiatric SLE (NPSLE) [1]. The American College of Rheumatology (ACR), proposed 19 discrete central and peripheral nervous system syndromes as NPSLE [2]. This includes both cognitive dysfunction and mood disorder. Cognitive impairment (CI) is amongst the most commonly reported neuropsychiatric symptoms amongst patients with SLE, with a prevalence of 33–43% [1–3]. CI can involve any of the following functions as defined by the ACR nomenclature : "*memory (learning and recall), complex attention, simple attention, executive skills (planning, organizing, and sequencing), visual-spatial processing, language (e.g. verbal, fluency), reasoning/problem solving and psychomotor speed*" [2]. Previous studies have shown that patients with SLE perform poorly compared to controls on standardized neuropsychiatric testing with decreased attention, impairment in working memory and executive function [4,5].

Impairment in cognitive function can be subtle and fluctuate over time. Several studies have addressed the longitudinal course of CI, however their results are limited by small sample size and short duration of follow-up. The sample size in these studies ranges between 28–188 patients and the duration of follow up did not surpass 3–5 years [6,7,8]. Furthermore, while studies have shown that cognitive function may fluctuate over time in SLE patients [3], cognitive function trajectories have not been previously studied in SLE.

Comorbid depression is also common in SLE patients [9, 10], with a prevalence of 30% −40% based on the results of a recent systematic review [11]. Depression has been shown to be associated with CI in cross-sectional SLE studies [3,10,12]. These studies have shown that the association of depression and CI in SLE can be independent of baseline demographic factors and disease activity [13]. Despite this, the longitudinal relationship between cognition and depression in SLE patients has not been studied previously.

Our study is the first study to identify joint cognitive function and depressive symptom trajectories in SLE. We used group-based trajectory modelling to determine if cognitive function and depressive symptoms in patients with SLE can be clustered in discrete latent classes [14]. We have used previously validated tools including the Hopkins Verbal Learning Test-Revised (HVLT-R) and Center of Epidemiologic Studies Depression Scale (CES-D) in

generating trajectories [10–12]. In addition, we aimed to identify baseline factors associated with trajectory membership.

METHODS

Patients and Data

Data was obtained from the University of California San Francisco (UCSF) Lupus Outcomes Study (LOS) [15], in which patients are followed longitudinally since 2002 via annual telephone structured surveys conducted by trained interviewers. Patients with physician-diagnosed SLE were confirmed to meet the ACR SLE classification criteria [16]. The annual survey encompasses the following domains: demographics and socioeconomic status, SLE disease activity by Systemic Lupus Activity Questionnaire (SLAQ) [17], bodily pain and physical functioning as reported on the Short Form 36 (SF-36) health questionnaire [18], education and employment, cognitive function and medications use (glucocorticoids, anti-malarials and immunosuppressants). Income was coded as above or below 125% of the US federal poverty threshold, based on income and household size.

All participants provided informed consent for the data collection and the study protocol was approved by the UCSF Committee on Human Research.

Measures—The Hopkins Verbal Learning Test-Revised (HVLT-R; measures verbal memory) was administered annually in years 2–7, providing up to 6 waves of observation (wave 2 is the baseline assessment for cognitive function). Age- and education-adjusted z-scores were derived for HVLT delayed recall. HVLT-R is a word-list learning and memory test that encompasses recall and recognition. This tool provides an assessment of verbal learning efficiency, ability to access newly learned information, and retention [19]. The Center of Epidemiologic Studies Depression Scale (CES-D: score range 0–60; score ≥ 24 represents depression in SLE) was administered yearly [20]. Each CES-D item includes four response categories, with possible scores between 0 and 3. The CES-D score is a sum of the 20 items, which can total between 0 and 60. The Systemic Lupus Erythematosus Activity Questionnaire (SLAQ) is available from the second interview year and then annually. The percentage of missing data for different variables in represented in table 1.

Statistical Analyses

Demographic characteristics were described by mean ± standard deviation (SD) for continuous variables and frequency (percent) for categorical variables. Patients' HVLT-R and CES-D scores over follow up were modeled using dual trajectory analysis [21]. For modeling the trajectory analysis, the study period starts from the first administration of the cognitive tests and extends over 6 waves of observations performed annually. Dual trajectory analysis allows the investigation of the dynamic interrelationship between two outcomes over time. In our study, dual trajectory modelling was used to assess the extent of association between latent patterns of cognitive function (measured by HVLT-R) and latent patterns of depressive symptoms (measured by CES-D). Dual latent class trajectory analysis for HVLT-R and CES-D was performed using group-based trajectory model on 755 patients in SAS procedure PROC TRAJ in version 9.3 [22]. The dual models for HVLT-R and CES-D

with up to 2–6 classes were assessed and the best models were determined by a combination of clinical plausibility [models wherein individual groups were too small, less than 10%, to have clinical significance (where the differences between cognitive trajectories would not be clinically significant) were excluded] and statistical criteria [planning to look for the minimum points of the Bayesian Information Criterion (BIC) and the Akaike information criterion (AIC)]. The model outputs included the identification of the appropriate number of dual trajectories and their shapes, the percentage of patients of each trajectory and the estimated combined and conditional probabilities of group membership of each dual trajectories.

Posterior probability is a parameter of model adequacy when grouping individual into a particular trajectory. Using only members with a dual latent class posterior probability of >0.80 (n=655), we further conducted univariate/multivariable logistic regression analyses to examine baseline factors associated with latent classes memberships, including sex, ethnicity, education, disease duration, treatments, physical functioning, bodily pain, and self-reported disease activity. We first tested for proportionality of clinical variables including education, medication use (glucocorticoids and immunosuppressants), SLE disease activity, physical functioning and bodily pain in between the four latent classes. Under the circumstances of lacking proportionality in predictors, we analyzed the association in two groups with the best and worst trajectories. Logistic regression analysis comparing Class 2 and Class 3, using the latter as a reference was performed. This approach allowed us to determine factors that are associated with normal cognitive function and absence of depression in the studied cohort. Step-down variable selection method was used in variable selection in multivariable analysis – variables with highest p values were dropped one by one until lowest AIC value was reached. The demographics of patients with missing data was compared with the rest of the cohort. All patients had visits or followed in the first two waves (2 and 3), 31 patients had no more follow up data after wave 4 (the third year after wave 2).

RESULTS

Patient Characteristics

Of the 815 participants in the study, 755 had at least two scores recorded for both HVLT and CES-D in the follow-up period and were included in the analysis. The characteristics of the patients are represented in table 1. Demographics and clinical characteristics of the cohort are shown in table 1. The average age of the analytic sample was 50.1 (SD 12.6) years and 92.5 % (n= 698) were females. The mean age at SLE diagnosis and disease duration at first visit in the study were 34.3 (SD 13.4) and 15.5 (SD 8.5) years, respectively. SLE disease activity as measure by SLAQ was 4.1 (SD 2.7) at the baseline assessment. Over 40% of participants reported exposure to oral glucocorticoids in the past 12 months (at baseline visit). In Total, 31 patients had missing data (loss-to-follow-up). There was no statistically significant difference between patients with loss-to follow-up and patients in the first two waves and patients who had more follow up after wave 2 (Supplement 1).

Dual latent classes trajectories for cognitive function and depressive symptoms

We identified the best model (Figure 1) as having 4 latent classes with four trajectories for cognitive function and four trajectories for depressive symptoms over the 6-year follow-up period.

Class 1 was defined as low CES-D and low cognitive scores (no depression + CI; n= 119, 18.6%). Class 2 was comprised by those with the lowest CES-D score and highest normal cognitive scores (no depression + normal cognition; n=334, 51.0%). Class 3 included those with the highest CES-D scores and lowest cognitive scores (depression + CI; n=61, 9.3%). Class 4 consisted of those with high CES-D scores and normal cognitive scores (depression + normal cognition; n=141, 21.5%) (Figure1).

Classes with persistent HVLT-R z-scores of −1 and below reflect persistent low cognition and classes with CES-D of 24 or greater reflect persistent depression. Two classes, 1 and 3, comprised 18.6% and 9.3% of patients respectively, displayed persistently low cognition. Two classes 3 and 4, comprised 9.3% and 21.5% of patients respectively, displayed persistent depression (Figure 2 and Figure 3).

Demographic information and clinical characteristics of each class is shown in table 1. There were no significant differences in age or disease duration between the four latent classes. Ethnic composition varied between latent classes with higher percentage of Caucasians in classes 2 and 4 where cognitive function was graded as normal (70.6% and 74.6%, respectively), and a higher percentage of African-Americans (14.1%) in class 3 were both depressive symptoms and CI are observed. The highest education levels were observed in class 2 with 56.8% having a college degree or higher education. The highest frequency of lower income levels was observed in class 3 and the lowest in class 2 (31.1% and 4.8%, respectively). Patients in class 2 also reported higher quality of life measures with the highest values of SF-36 physical functioning and bodily pain amongst all four classes. Additionally, this group had the lowest disease activity as determined by the SLAQ.

Univariate/multivariable logistic regression analyses (modeling factors at baseline associated with normal cognition and no depression)

The cohort size after removing patients with low posterior probability (< 0.80) was 655 (Patients characteristics are in supplement 2). Caucasian ethnicity and higher levels of education were associated with normal cognitive function and absence of depression (Table 2). Caucasians were found to have OR 2.1 (95% CI 1.9–3.8) and OR 4.3 (95% CI, 1.69–10.86) times the odds of normal cognitive function and low CES-D score in univariate and multivariate regression analysis, respectively. Similarly, higher levels of education were associated with normal cognitive performance and lower depressive symptoms with OR 2.22 (95% CI, 1.75–2.81) and 2.52 (95% CI, 1.73–3.66) in univariate and multivariate analysis, respectively. Higher SF-36 scores in physical function were associated with membership in C2 with OR 1.06 (95% CI, 1.05 – 1.07) and OR 1.04 (95% CI, 1.02 −1.06) in univariate and multivariate regression, respectively. Similarly, higher SF-36 scores in bodily pain were associated with membership in C2 with OR 1.17 (95% CI, 1.12 −1.21) and, OR 1.12 (95% CI, 1.06 −1.18) in univariate and multivariate regression, respectively. Higher disease

activity at baseline and use of disease modifying anti-rheumatic drugs (DMARDs) were not associated with Class 2 membership (normal cognition and absence of depression).

DISCUSSION

Neuropsychiatric SLE manifestations including CI and depression are commonly reported in literature [3]. Our study is the first to describe joint cognitive function and depressive symptom trajectories in patients with SLE. Using group-based trajectory modelling, we were able to identify four distinct dual trajectory patterns for depression and cognitive function in SLE patients over a seven-year period.

Overall, we observed persistently low cognitive scores as determined by poor performance in the HVLT-R in 27.9% of our cohort (Classes 1 and 3). In both latent classes, the cognitive function trajectories did not fluctuate significantly throughout the follow-up period demonstrating a stable trajectory without further decline or improvement. Similarly, cognitive function trajectories did not fluctuate with normal cognition (Classes 2 and 4), again following a stable trajectory without progression to cognitive impairment (CI).

Our study provides a long follow-up period for monitoring cognitive function in SLE patients. Previous longitudinal studies on the course and outcome of cognitive impairment in SLE patients have reported variable findings, and have been limited by small sample size and short duration of follow-up. Hanly et al reported CI in 21% of a small prospective cohort (n=70) of SLE patients and observed resolution of CI in the majority of their cohort after one-year of follow-up with only 12% exhibiting persistent CI [23]. In a 5-year follow-up study of same cohort, persistent CI was only present in only 4% (2 patients) and resolution of CI in 19% of their cohort [8]. In another small prospective cohort (28 patients), Waterloo et al reported stable cognitive function in a 5-year follow-up period with resolution of CI in a small subset of patients who had improvement of underlying psychiatric disorders [24]. In another small prospective cohort (n=43), Ceccarelli et al reported a prevalence of 20.9% of CI at baseline, and 13.9% at follow-up in ten years [25]. Contrary to the aforementioned studies, we did not observe resolution of CI over time in C1 (20%) and C3 (9%). This difference may be accounted for by the differences in follow-up period and sample sizes or because we used a research cohort rather than a clinical sample and individuals with significant levels of CI may have been screened out of the study due to inability to provide informed consent. Furthermore, each study used different neuropsychiatric assessments of cognitive dysfunction. While all of these assessment tools have been previously validated in studying CI in patients with SLE, they vary in specificity and sensitivity, and a direct comparison between the results of these studies may not be possible [26].

Depression, as determined by high scores on CES-D, was observed in 31% of the study cohort (Classes 3 and 4). Similar to our finding of stable cognitive function, trajectories of depressive symptoms did not fluctuate significantly throughout the follow-up period. Previous studies have reported a wide-range in prevalence of depression in SLE, ranging from 30% to 40% [11,26]. Despite this high prevalence, trends of depression in persons with SLE over time have not been consistently reported in literature. Huang et al. [27] reported an incidence of 29.7 per 1000 person-years in a cohort followed over 26 years. However,

incidence of depression was determined based on recorded chart data, diagnostic codes and anti-depressant use, as opposed to validated screening tools.

We compared two latent classes to determine baseline factors associated with membership in each trajectory. We chose class 2 (high cognitive and low depression scores) and class 3 (low cognitive and high depression scores) for this comparison as they represent the most differing classes. In our univariate regression analysis, we found Caucasian ethnicity (OR 2.13, 95% CI 1.19–3.80) and higher education levels (OR 2.22, 95% CI 1.75–2,81) to be associated with normal cognitive function and absence of depression. This association remained significant in the multivariate regression analysis. High baseline SLE disease activity and use of DMARDs, were not associated with normal cognitive function and absence of depression. Demographic differences in CI, including ethnicity and education levels, in SLE have been previously explored in several studies [28–31]. While some did not find any association between ethnicity and cognitive performance in SLE patients, others have reported a higher prevalence of CI among Blacks, and a lower prevalence among Asians. These differences may be related to background socioeconomic factors [28] which may influence access to resources including education. This in turn, can alter cognitive reserve, which has been shown to be increased in those with higher education levels [32]. Indeed, having higher education level, has been linked to higher cognitive reserve and larger hippocampal volumes, allowing individuals to capitalize on greater structural integrity of the brain [33]. Sociodemographic factors, specifically lower income, financial strain and low education have also been associated with depression in those with SLE [9].

There are limitations and strengths to our study. The first limitation is the use of HVLT-R as opposed to the ACR comprehensive neuropsychological battery of tests. While HVLT-R is both time and cost-efficient, it only identifies impairment in episodic verbal learning memory. Several previous studies have shown that CI in SLE can occur in any cognitive domain including decreased attention, impaired working memory, executive function and also overall cognitive slowing [4]. However, the HVLT-R has been previously validated against the ACR-SLE neuropsychological battery and has been shown to have a sensitivity of 81% in identifying CI in patients with SLE [10] and is therefore, a reasonable assessment tool for our study. There is a possibility that those with the cognitive impairment had fewer years of follow-up or were more likely to drop out. In our study, 31 patients were loss-to-follow-up after wave 2. The demographics of patients' loss-to-follow-up did not differ from those who remained in the study. We conducted annual telephone surveys to collect our data as opposed to in-person interviews. While face-to-face assessments are preferred especially for evaluation of depression, our current model allowed collection of a larger pool of data within the limits of resources. Lastly, in interpreting our results, it is important to keep in mind the complex interplay between depression and CI. For instance, CI can reduce occupational productivity and interfere with several domains of social functioning. These emotional and social factors may lead to depression. Conversely, symptoms of depression including poor concentration or psychomotor slowing, may impact performance on cognitive tasks [34,35].

Our study has the advantage of long-term follow-up period with annual reassessment providing continuous monitored data points. However, it is possible that individuals

with severe illness, including those with cognitive impairment, are under-represented. Additionally, our results are based on outcomes from a large cohort and more likely to be reflective of a general lupus patient population. Finally, our study is the first to identify distinct trajectories in combined cognitive function and depressive symptoms in SLE.

CONCLUSION

We have shown that persistently low cognitive performance in 28% of patients (Classes 1 and 3) did not significantly improve over 7 years. Also, normal cognitive performance in 72% (Classes 2 and 4) followed a stable trajectory. This highlight the importance of periodic, yearly, assessment of cognitive function in SLE.

We have identified four distinct classes of combined cognitive function and depressive symptoms in patients with SLE. Overall, low cognitive function is associated with persistent depression in 9.3% of patients. Several factors may be associated with membership in each latent class. These include ethnicity, education level, disease activity, physical functioning and bodily pain. Further studies are needed to determine how to best integrate our understanding of factors related to depression and cognitive impairment, in assessment and management of SLE patients. It is also important to determine if the management of depression would alter cognitive trajectories particularly in patients with low cognitive function and persistent depression (class 3).

Our results have confirmed the complexity of the underlying factors sociodemographic factors, disease activity and comorbidities associated with persistent CI which require further research. There is still however an unmet need to identify patients at high risk of developing of CI, distinguish between different trajectories of CI (persistent CI and normal cognitive function), and to monitor CI progression over time. These results highlight different aspects relevant for assessing and managing cognitive function over time in SLE. This will help facilitate the development of treatments or interventions in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENT AND FINANCIAL SUPPORT

The Lupus Outcomes Study was supported by grant AR053308 from NIH/NIAMS. Dr Z. Touma has received the Arthritis Society Salary support and the Canadian Rheumatology Association (CRA) (CIORA) Arthritis Society Clinician Investigator Salary Award.

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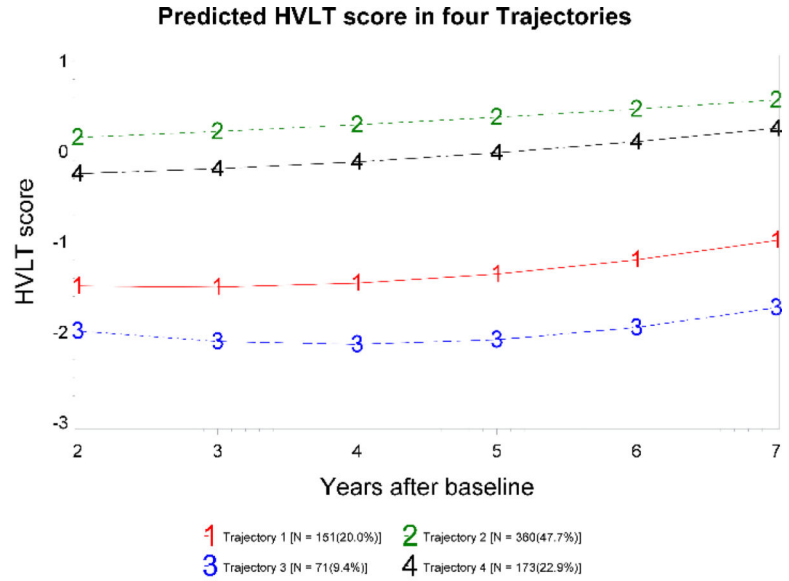
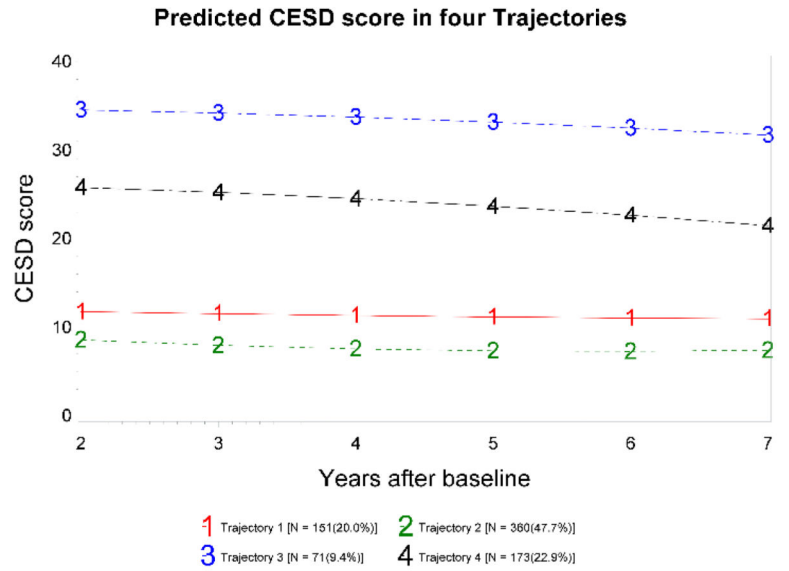
SIGNIFICANCE AND INNOVATION

- Persistently low cognitive performance in 28% of patients (Classes 1 and 3) did not significantly improve over 7 years.
- Normal cognitive performance in 72% (Classes 2 and 4) followed a stable trajectory.
- Four latent classes of dual cognitive function and depressive symptoms are identified.
- Factors associated with latent class membership include ethnicity, education, disease activity, physical functioning and bodily pain.



A-Trajectories of HVLT-R



B-Trajectories of CES-D

Figure 1 –. Dual trajectory model of HVLT-R and CES-D over seven years

A: HVLT-R scores presented at z-scores compared to controls, z-scores ≤−1 indicate cognitive impairment. B: CES-D scores, a score ≥24 represents depression in SLE. Members in each class C1 (red), C2 (green), C3 (blue), and C4 (black) are the same across each figure.

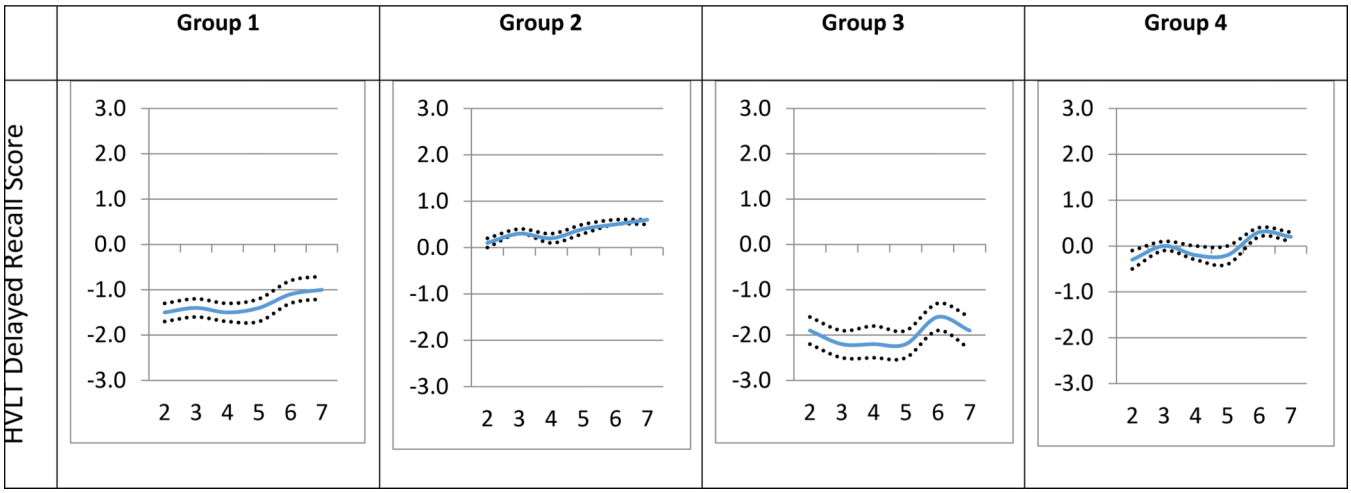


Figure 2 –. Individual trajectories for HVLT scores in latent classes.

HVLT-R scores presented at z-scores compared to controls, z-scores ≤ −1 indicate cognitive impairment.

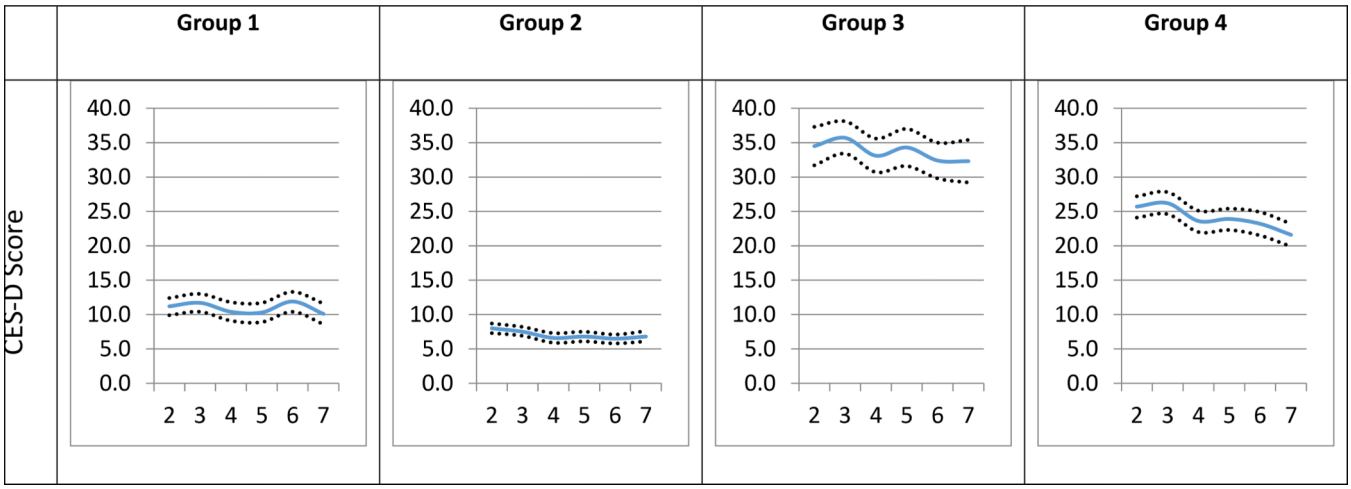


Figure 3 –. Individual trajectories for CES-D scores in latent classes.

CES-D scores, a score ≥24 represents depression in SLE. Group 1 no depression and but cognitive impairment (n= 119), Group 2 no depression and normal cognition (n= 334), Group 3 depression and cognitive impairment (n= 61), Group 4 depression and normal cognition (n= 141)

Table 1-

Characteristics at baseline cognitive assessment for all study participants (n=755)

Subject characteristics at baseline	All study participants (n=755)	Class 1 (n=151)	Class 2 (n=360)	Class 3 (n=71)	Class 4 (n=173)
Female (%)	698 (92.5%)	134 (88.7%)	332 (92.2%)	68 (95.8%)	164 (94.8%)
Age at SLE diagnosis	34.3± 13.4	35.5 ± 14.2	33.2 ± 13.3	35.3 ± 12.5	35.6 ± 11.9
Disease duration	15.5 ± 8.5	15.9 ± 8.7	15.5 ± 8.7	15.6 ± 8.4	15.1 ± 7.8
Ethnicity (%)					
Missing	34 (4.5%)	7 (4.6%)	19 (5.3%)	3 (4.2%)	5 (2.9%)
Caucasian	519 (68.7%)	95 (62.9%)	254 (70.6%)	41 (57.7%)	129 (74.6%)
Hispanic	54 (7.2%)	16 (10.6%)	18 (5.0%)	6 (8.5%)	14 (8.1%)
African-American	47 (6.2%)	11 (7.3%)	15 (4.2%)	10 (14.1%)	11 (6.4%)
Asian	61 (8.1%)	15 (9.9%)	32 (8.9%)	5 (7.0%)	9 (5.2%)
Other	40 (5.3%)	7 (4.6%)	22 (6.1%)	6 (8.5%)	5 (2.9%)
Education					
Less than high school	15 (2.0%)	3 (2.0%)	2 (0.6%)	8 (11.3%)	2 (1.2%)
High school graduate	81 (10.7%)	23 (15.2%)	21 (5.8%)	18 (25.4%)	19 (11.0%)
Some college	214 (28.3%)	56 (37.1%)	85 (23.6%)	18 (25.4%)	55 (31.8%)
Trade or vocational school	136 (18.0%)	23 (15.2%)	55 (15.3%)	20 (28.2%)	38 (22.0%)
College graduate	175 (23.2%)	35 (23.2%)	100 (27.8%)	4 (5.6%)	36 (20.8%)
Post-graduate degree	134 (17.7%)	11 (7.3%)	97 (26.9%)	3 (4.2%)	23 (13.3%)
Employment status					
Unemployed	397 (52.6%)	82 (54.3%)	147 (40.8%)	59 (83.1%)	109 (63.0%)
Employed	358 (47.4%)	69 (45.7%)	213 (59.2%)	12 (16.9%)	64 (37.0%)
Below poverty threshold	83 (11.0%)	19 (12.6%)	19 (5.3%)	23 (32.4%)	22 (12.7%)
Smoking status					
Missing	4 (0.5%)	0 (0.0%)	2 (0.6%)	0 (0.0%)	2 (1.2%)
Current smoker	72 (9.5%)	11 (7.3%)	27 (7.5%)	9 (12.7%)	25 (14.5%)
Former smoker	242 (32.1%)	55 (36.4%)	107 (29.7%)	23 (32.4%)	57 (32.9%)
Never smoker	437 (57.9%)	85 (56.3%)	224 (62.2%)	39 (54.9%)	89 (51.4%)
Glucocorticoid exposure					
Oral	320 (42.4%)	69 (45.7%)	144 (40.0%)	30 (42.3%)	77 (44.5%)
Intravenous	47 (6.2%)	13 (8.6%)	17 (4.7%)	10 (14.1%)	7 (4.0%)
DMARD therapy					
Hydroxychloroquine	384 (50.9%)	86 (57.0%)	179 (49.7%)	40 (56.3%)	79 (45.7%)
Azathioprine	55 (7.3%)	13 (8.6%)	26 (7.2%)	3 (4.2%)	13 (7.5%)
Methotrexate (oral)	51 (6.8%)	10 (6.6%)	21 (5.8%)	6 (8.5%)	14 (8.1%)
Methotrexate (s/c)	23 (3.0%)	3 (2.0%)	7 (1.9%)	2 (2.8%)	11 (6.4%)
Mycophenolate mofetil	73 (9.7%)	12 (7.9%)	34 (9.4%)	8 (11.3%)	19 (11.0%)
Cyclophosphamide	6 (0.8%)	2 (1.3%)	0 (0.0%)	2 (2.8%)	2 (1.2%)
SLE disease activity [SLAQ]					
Mean± SD	4.1 ± 2.7	4.0 ± 2.8	3.1 ± 2.4	6.2 ± 2.3	5.3 ± 2.5
Median (interquartile range)	4 (2–6)	4 (2–6)	3 (1–5)	7 (5–8)	5 (4–7)

Subject characteristics at baseline	All study participants (n=755)	Class 1 (n=151)	Class 2 (n=360)	Class 3 (n=71)	Class 4 (n=173)
SF-36 physical function					
Mean± SD	58.9 ± 29.7	56.5 ± 30.2	71.0 ± 26.7	31.4 ± 19.4	47.3 ± 25.8
Median (interquartile range)	60 (35–85)	60 (30–85)	80 (50–95)	30 (20–45)	50 (25–65)
SF-36 bodily pain					
Mean± SD	41.8 ± 11.0	42.4 ± 10.1	46.4 ± 10.3	31.5 ± 8.3	36.0 ± 8.3
Median (interquartile range)	41 (33–50)	42 (33–50)	46 (37–55)	31 (25–37)	37 (29–42)

Table 2 –

Baseline factors associated with normal cognitive function and absence of depression (class 3 is the reference group as compared to class 2) in 655 patients

Baseline Variable		p-values		p-values
	Univariate Analysis		Multivariate Analysis	
Female gender	0.39 (0.09–1.677)	0.20	-	-
Caucasian ethnicity	2.13 (1.19–3.80)	0.01	4.28 (1.69–10.86)	0.002
Disease duration	0.99 (0.97–1.03)	0.96	-	-
Education	2.22 (1.75–2.81)	<0.001	2.52 (1.73–3.66)	<0.0001
Income below poverty threshold	0.113 (0.05–0.24)	<0.0001		
Smoking status	0.71 (0.41–1.24)	0.23	-	NS
SLE disease activity	0.60 (0.52–0.68)	<0.001	0.77 (0.62–0.94)	0.01
Glucocorticoid (IV)	0.27 (0.12–0.63)	0.002	-	-
Glucocorticoid (oral)	0.83 (0.48–1.44)	0.52	-	-
Any DMARDs *	1.13 (0.58–2.18)	0.73	-	-
Hydroxychloroquine	0.76 (0.44–1.32)	0.33	0.23 (0.09–0.60)	0.002
SF-36 Physical function	1.06 (1.05–1.07)	<0.0001	1.04 (1.02–1.06)	0.0004
SF-36 Bodily pain	1.17 (1.12–1.21)	<0.0001	1.12 (1.06–1.18)	<0.0001

* Any immunosuppressant includes any use of methotrexate oral or subcutaneous, azathioprine, mycophenolate mofetil and cyclophosphamide.

The cohort size after removing patients with low posterior probability (< 0.80) was 655.