Health-related Quality of Life and Its Relationship to Patient Disease Course in Childhood-onset Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To (1) estimate the health-related quality of life (HRQOL) of children with childhood-onset systemic lupus erythematosus (cSLE) and compare it to that of normative cohorts; (2) assess the relationship of HRQOL with cSLE disease activity and damage; and (3) determine the effects of changes of disease activity on HRQOL.

Methods. Patients with cSLE (n = 98) followed every 3 months completed HRQOL measures, the Pediatric Quality of Life Inventory Generic Core scale (PedsQL-GC), the Rheumatology Module (PedsQL-RM), and the Child Health Questionnaire (CHQ). The British Isles Lupus Activity Group Index (BILAG) was used to measure organ-system-specific disease activity. Physicians rated the course of cSLE between visits.

Results. At baseline, mean (standard deviation, SD) score [parent report] of the PedsQL-GC and the PedsQL-RM was 75 (17) and 79 (14), respectively; the mean (SD) of the CHQ physical summary score (CHQ-PHS) was 49 (7) and that of the CHQ psychological summary score was 42 (12). Higher BILAG scores, especially in the general, musculoskeletal, neurological, and vascular, but not the mucocutaneous, renal, cardiovascular, or hematological BILAG domains, were associated with a significantly lower HRQOL. Patients with damage had lower HRQOL than those without damage. All HRQOL measures included were at most modestly responsive to clinically important changes with cSLE.

Conclusion. HRQOL with cSLE is significantly lower than that reported in healthy populations. Organ-specific involvement with cSLE has a differential effect on HRQOL. Higher disease activity and damage are associated with significantly lower HRQOL as measured by the PedsQL-RM and the CHQ-PHS, and worsening of cSLE leads to a further decline. (J Rheumatol First Release June 1 2009; doi:10.3899/jrheum.081164)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS CHILDREN PEDIATRIC SLE
CHILDHOOD-ONSET SLE QUALITY OF LIFE HEALTH-RELATED QUALITY OF LIFE

Systemic lupus erythematosus (SLE) is a complex, chronic multisystem autoimmune inflammatory disease that targets young women and men (females:males = 7:1)[1,2]. Up to 20% of patients with SLE are diagnosed in childhood, that is, prior to the age of 16 years (childhood-onset SLE, cSLE), and the disease is more severe, particularly with regard to kidney involvement, when diagnosed early in life[3-5]. Research in adults with SLE suggests that the disease has an important negative effect on the patients' health-related quality of life (HRQOL)[6], especially when permanent disease damage, disease activity, and fatigue are present[7]. Similar research in children with cSLE is lacking in that there are few studies examining the HRQOL in current cSLE cohorts using standardized instruments. Additionally,

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the effects of the worsening of cSLE and specific disease symptoms on HRQOL in cSLE have not been well studied.

The revised International Classification of Functioning, Disability and Health, recently published by the World Health Organization, is an effort to standardize the language and framework for the description of "functioning," "health," and "disability." In this framework, the umbrella term "functioning" refers to all body functions, activities, and participation. Similarly, "disability" serves as an umbrella term for impairments, activity limitations, and participation restrictions, whereas HRQOL constitutes the valuation of a certain level of health that results from the interplay of functioning and disability[8].

The objectives of our study were to (1) estimate the HRQOL of patients in a multicenter North American cohort of patients with cSLE and compare it to that of normative cohorts; (2) assess the relationship of disease activity and HRQOL in cSLE; and (3) determine the effects of changes in the disease course of cSLE on HRQOL.

MATERIALS AND METHODS

Patients with cSLE. Children (n = 98) fulfilling American College of Rheumatology (ACR) classification criteria for SLE[2], prior to the age of 16 years, were recruited consecutively during routine visits to the pediatric rheumatology and lupus clinics at 7 pediatric rheumatology centers in the United States. Study visits occurred every 3 months for up to 18 months. Age, sex, height, weight, and findings on examination of all patients were recorded, and information on their medication regimens was obtained. Disease activity and HRQOL were measured at each study visit. Disease damage was only measured every 6 months.

SLE disease measures of disease activity and damage. Disease activity: The British Isles Lupus Activity Group (BILAG) Index has been developed with the goal of assessing organ-system-specific disease activity with SLE. For each of the 8 organ systems or domains considered (general, mucocutaneous, neurological, musculoskeletal, cardiovascular and respiratory, vasculitis, hematology, and renal) an alphabetical value is derived that can be transformed into a numerical score as follows: A = 9; B = 3; C = 1; D or E = 0. Higher scores signify higher disease activity, and domain scores of 0 are indicative of inactive cSLE in the specific organ system. Global disease activity in cSLE can be defined as the average of the 8 domain scores of the BILAG. This measure has been validated for use in children[9] and contains items addressing patient symptoms, that is, SLE features that cannot be objectively measured including, but not limited to, fatigue, arthralgias, or myalgias[10].

Based on the summary scores of the BILAG during the study period, patients were grouped in 1 of 3 groups: (1) those with inactive or minimally active disease, defined as scores ≤ 25th percentile, e.g., ≤ 1; (2) somewhat active disease, defined as scores between the 26th and 75th percentile, e.g., ≤ 5; and (3) very active disease, defined as scores > 75th percentile, e.g., ≥ 5. This categorization was based on previous experience of the investigators when assessing cSLE.

To allow the comparison with a previously reported large cSLE cohort, the 2000 version of the SLE Disease Activity Index (SLEDAI-2K; range 0 to 105; 0 = inactive disease) was completed, which has been validated for use in children with cSLE as well[9,11].

Disease damage: Irreversible scarring or damage of organs and tissues since the diagnosis with SLE was measured by the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI). SDI scores range between 0 and 47, with SDI scores of 0 representing the absence of damage[12]. The SDI has been validated for use in children with cSLE[13]. As has been done by others, for the purpose of our study, minimal disease damage was defined as an SDI score of ≤ 1.

Measures of change in cSLE course. The disease course of cSLE was measured in 3 ways: (1) the managing pediatric rheumatologist rated the change in disease course on a Likert scale in response to the question, "Compared with the last study visit 3 months ago and the patient's overall disease, the patient experienced..." as follows: a worsening of disease, no change in disease, or an improvement of disease; (2) the managing pediatric rheumatologist rated changes in lupus nephritis on a comparable Likert scale; (3) in response to the question, "Compared to the last study visit 3 months ago, when considering your lupus, how would you rate your health," parents or patients completed a Likert scale with the following 3 response options: worsening of health, no change of health, or improvement of health.

HRQOL measures. Available HRQOL questionnaires can be classified as being generic or disease-specific. Generic measures are used to quantify HRQOL in both healthy children and those with various types of illness, and can be used to compare the HRQOL of ill children with those who are healthy. Disease-specific measures are thought to be more responsive to change in a specific disease, or group of diseases, compared to generic measures[14]. In an effort to comprehensively describe the effects of cSLE on HRQOL, we used 2 well validated HRQOL inventories, 1 disease-specific and 1 generic[15].

(1) The Child Health Questionnaire (CHQ™) is a generic HRQOL inventory whose parent-completed version (CHQ PF-50) has been culturally cross-validated for use in cSLE[7,16,17]. Besides a rating of global health on a 5-point Likert scale, the CHQ measures health over 12 domains: Physical Functioning (PF); Role/Social Limitations–Emotional/Behavioral (REB); Role/Social Limitations–Physical (RP); Bodily Pain (BP); Behavior (BE); General Health Perceptions (GH); Mental Health (MH); Self Esteem (SE); Parent Impact–Emotional (PE); Parent Impact–Time (PT); Family Activities (FA); and Family Cohesion (FC). Domain raw scale scores are calculated by computing the arithmetic mean of the items for each domain. Scores for the domains are then transformed on a scale from 0 (worst health) to 100 (best health). In addition, summary scores can be derived to measure Physical Health (CHQ-PHS) and Psychosocial Health (CHQ-PSS). These summary scores have a mean of 50 and a standard deviation (SD) of 10. The CHQ-P50 has been subjected to rigorous validation in parents of children ages 5 to 18.2 years of age. Normative data on a population of healthy children have been published[18].

(2) The Pediatric Quality of Life Questionnaire Inventory (PedsQL™) comprises a parallel child self-report and a parent proxy-report with formats for various age ranges. Besides the PedsQL Generic Core scale, version 4 (PedsQL-GC), there are several disease-specific HRQOL modules, 1 of which is the PedsQL Rheumatology Module (PedsQL-RM).

The PedsQL-RM is a disease-specific HRQOL measure, designed to measure health dimensions that are particularly relevant for children with rheumatic diseases[19]. The PedsQL-RM is a 22-item scale that encompasses the following 5 domains for the preceding 4 weeks: Pain and Hurt, Daily Activities, Treatment, Worry, and Communication. Items are scored using a 5-point Likert scale (never, almost never, sometimes, often, always). From the raw scores of the PedsQL-RM, a summary score of 0 to 100 can be calculated, with higher scores indicating higher HRQOL. For our study, we used PedsQL-RM ratings of a contemporary cohort of children diagnosed with juvenile idiopathic arthritis (JIA; formerly juvenile rheumatoid arthritis)[20] as a comparative population[21]. In this comparison group, the mean ± SD of joints involved with JIA was 3.4 ± 6.1 [median 1; interquartile range (IQR) 4], and 10% of the patients had systemic JIA.

The PedsQL-RM is used in combination with the PedsQL-GC, a generic HRQOL scale, encompassing 4 health domains: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. Items are scored on a 5-point Likert scale identical to that used for the PedsQL-RM. From the sum of the raw scores of the 23 items, a total health summary score ranging from 0 to 100 can be calculated, with higher scores indicating higher HRQOL. Reference scores for healthy children are also

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available. For both the PedsQL and the CHQ, the same parent (mostly mothers) completed each of the questionnaires throughout the study.

Statistical analysis. Numerical variables were summarized by mean ± standard error (SE) or SD; binary and categorical variables were summarized by frequency (percentage). In cross-sectional studies, analysis of variance (ANOVA) tests and Pearson chi-squared tests were used to assess the group effects for numerical and categorical variables, respectively. Spearman correlation analysis was done, using cross-sectional data of the enrollment visit only, to assess the relationship between HRQOL domain scores and SLE features. Scores of study patients were compared to published population norms using a 2-sided unpaired t-test under consideration of population variances.

In the longitudinal analyses, mixed-effect models were used to assess associations of HRQOL (primary outcome) and fixed effects of interest. Primary outcomes considered were the summary scores or changes of the summary scores, of the PedsQL-GC and PedsQL-RM from patients and children, scores of the CHQ General Health domain, the CHQ-PSS, and the CHQ-PhS, respectively. The fixed effects of interest were 3-level categorical variables assessing (1) the disease course as rated by the physician (improved, no change, worse); (2) parent/patient-rated change in health (better, no change, worse); (3) levels of global disease activity as measured by the BILAG summary score (inactive or minimally active disease: BILAG scores ≤ 1; somewhat active disease: 1 < BILAG ≤ 5; very active disease: BILAG > 5); 2-level fixed effects were (4) organ-specific disease activity as measured by the BILAG ("present" for domain score at A, B, or C; "not present" for domain score at D or E); and (5) disease damage (no or minimal damage: SDI ≤ 1; more than minimal damage: SDI > 1).

In each mixed-effect model, a primary measure was assessed for its association to one of the fixed effects of interest, adjusting for patient's demographics. A random effect, e.g. patients, was included in the models to account for within-patient correlation caused by repeated observations in the longitudinal dataset. Post hoc comparisons of means were adjusted using Tukey multiple comparison methods under the mixed-effect model framework.

To support the assessment of responsiveness to change, standardized response means (SRM) were determined as follows: SRM = mean score change/SD of score change, where SD of change score = SE of change score × square root [degree of freedom/(number of repeated observations – 1)], all estimated from mixed-effect models. Statistical computations were performed using SAS version 9.1 software (SAS, Cary, NC, USA). p values < 0.05 were considered statistically significant.

Ethics review. Our study was approved by the institutional review boards of the participating pediatric rheumatology centers. Informed consent was obtained from all parents and, as appropriate, assent was given by the participants, prior to the study procedures.

RESULTS

Characteristics and disease course of patients with SLE. The demographics and disease features of the cSLE patients are summarized in Table 1. A total of 98 children (F:M = 84:14) were included in the analysis. The population consisted of 60 Caucasian, 32 African American, 4 Asian, and 2 mixed-race patients (88 non-Hispanic, 10 Hispanic). A total of 549 visits were available for analysis and the mean ± SD duration of patients' followup was 5.34 ± 8.8 months. Twelve children had renal damage due to longstanding proteinuria (in one patient GFR was < 50% of normal).

At baseline, the scores of the General domain of the BILAG were given for fevers (number of events = 5), involuntary weight loss (3), splenomegaly (1), fatigue (36), and anorexia (1). In all but 1 patient, fatigue was present when other general symptoms were scored. The scores of the Musculoskeletal domain resulted mostly from arthritis (10), arthralgias (21), and myalgias (14); those in the Vasculitis domain were in the majority due to Raynaud's phenomenon (13), and livedo reticularis (4).

Table 1. Demographics and SLE features at baseline.

Measure	n	Arithmetic Mean (SD)
Age, yrs	98	14.7 (0.5)
Disease duration, yrs	98	1.5 (2.0)
Current medications		
Prednisone (mg/day)	81	15.1 (1.8)
Azathioprine, mycophenolate mofetil, methotrexate	47	
Cyclophosphamide	6	
Hydroxychloroquine	73	
NSAID	24	
At least 1 antihypertensive medication	38	
Biopsy-proven lupus nephritis†	54	
Disease activity		
SLEDAI-2K score	98	4.8 (4.4)
BILAG score*		4.9 (5.2)
Disease damage		
SDI score**	98	0.42 (0.1)

† WHO Class 2, 3, 4, 5, 6 was present in 4, 12, 28, 9, and 1 patient, respectively. * British Isles Lupus Activity Group index; alphabetical scores converted as follows: A = 9; B = 3; C = 1; D or E = 0. ** Systemic Lupus International Collaborating Clinics/ACR Damage Index. NSAID: nonsteroidal antiinflammatory drugs; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index, 2000.

Neurological domain scores were given almost exclusively for headaches or migraines (78) and depression (10). There were no strokes or thrombotic events. Details on SLE features and the cSLE disease course during the study are shown in Table 2. When physicians rated patients as better, the same, or worse, the mean ± SE of the BILAG summary score changed as follows: –3.3 ± 0.45, –0.2 ± 0.2, and 1.8 ± 0.41, respectively. When using the SLEDAI-2K, the respective changes were –1.4 ± 0.7, 0.0 ± 0.3, and 0.5 ± 0.7.

Cross-sectional HRQOL in cSLE. Using data from the initial study visit only, the mean ± SD of the HRQOL scores with cSLE are shown in Table 3. In an effort to compare patients with cSLE to healthy children, the respective means ± SD published for normative healthy populations are presented as well[18,22]. Because the PedsQL-RM has been developed for children with rheumatic diseases, comparison is made to a current JIA cohort[21].

CHQ-P50: cSLE was associated with significantly lower scores in the PF, REB, BP, GH, PE, and FA domains when compared to healthy cohorts. Both the CHQ-PHS and the CHQ-PSS were significantly lower in the patients with cSLE compared to controls.

Although, on average, patients with cSLE had lower CHQ-P50 domain scores than the normative healthy con-

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Table 2. Average disease activity and damage and number of events during the study.

Measure score	No. Visits with Event	No. Patients with Score = 0	Mean (SD)	Median (IQR)	No. Visits with Score = 0	No. Visits with Score > 0
Disease activity						
BILAG Summary Score*		13	5.3 (5.4)	4 (6)	79	469
BILAG General domain		61	0.6 (1.4)	0 (1)	171	377
BILAG Mucocutaneous domain		68	0.8 (1.7)	0 (1)	418	130
BILAG Neurological domain		81	0.4 (1.4)	0 (0)	460	88
BILAG Musculoskeletal domain		67	0.5 (1.2)	0 (1)	200	348
BILAG Cardiovascular & Respiratory domain		85	0.3 (1.0)	0 (0)	501	47
BILAG Vasculitis domain		81	0.2 (0.6)	0 (0)	461	87
BILAG Hematology domain		41	0.9 (1.4)	1 (1)	247	301
BILAG Renal domain		55	1.6 (2.6)	0 (3)	356	191
SLEDAI-2K Score		12	5.2 (5.2)	4 (4)	91	458
Disease damage — SDI**						
No or minimal damage (SDI ≤ 1)	265	71	0.5 (1.0)	0 (1)	221	88
More than minimal damage (SDI > 1)	44					
Disease course						
Patient/parent-rated change in health						
Improved	176					
Same	213					
Worse	49					
Physician assessment of overall disease						
Improved	62					
Same	305					
Worse	76					

* British Isles Lupus Activity Group index; alphabetical scores converted as follows: A = 9; B = 3; C = 1; D or E = 0. ** Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI). SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index, 2000. IQR: interquartile range.

trols, these differences did not reach statistical significance for the following domains: RP, PT, MH, SE, BE, and FC.

PedsQL-GC: For both parent proxy-report and patient self-report, the PedsQL-GC summary scores were significantly lower in cSLE than in healthy children. Compared to healthy children, Physical Functioning and School Functioning domain scores were significantly lower for the cSLE sample, while Social Functioning was similar in cSLE and healthy children.

PedsQL-RM: For both parent proxy-report and child self-report, the PedsQL-RM Worry domain scores were lower in cSLE, compared to children with arthritis. For proxy-report, the Treatment domain score was higher and the Communication domain score was lower for cSLE compared to JIA. Neither Pain and Hurt nor Daily Activity scores differed significantly between the 2 groups of patients.

Disease activity and disease damage — effects on HRQOL. Disease activity: Based on the summary scores of the BILAG during the study period, patients were grouped in 1 of 3 groups (inactive or minimally active disease, somewhat active disease, very active disease). As shown in Figure 1A, higher disease activity was associated with lower overall HRQOL, irrespective of the HRQOL inventory (PedsQL, CHQ) considered.

However, the CHQ-PSS did not differ significantly between groups of patients with different levels of disease activity, and the differences in scores between the somewhat active and very active disease groups did not reach significance for the PedsQL-RM patient self-report and the CHQ-PHS.

Disease damage: Patients with minimal or absent disease damage (SDI ≤ 1) had significantly higher HRQOL scores than those with more pronounced damage (Figure 1B). An exception was the CHQ-PSS, which did not differ between groups of patients with different level of disease damage (SDI ≤ 1 vs SDI > 1).

Relationship between specific cSLE features and HRQOL. In mixed models, correcting for disease activity in domains other than the target BILAG organ domain under consideration, only the presence of BILAG general symptoms, musculoskeletal symptoms, vasculitis, or neurological symptoms was related to the HRQOL domain scores. Figure 2A depicts the differences in HRQOL depending on the presence or absence of disease activity in the BILAG General domain. Irrespective of the HRQOL inventory, the presence of general symptoms (mostly fatigue) was associated with significantly lower scores than when such symptoms were absent. Patients with musculoskeletal symptoms (mostly arthralgia and arthritis not limiting function) also had significantly lower HRQOL scores than those without such disease involvement (Figure 2B). Similar relationships between BILAG domain scores were only seen with Vasculitic domain scores (mostly for Raynaud's phenome-

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Table 3. Health-related quality of life (HRQOL) and well-being at baseline (n = 98).

HRQOL Measure	Normative Population Mean (SD)	SLE Mean (SD)	p††
Child Health Questionnaire P50*			
Physical functioning	96.1 (13.9)	81.3 (24.2)	0.0001
Role/social-physical	93.60 (18.6)	90 (17.5)	NS
General health perception	73.0 (17.3)	53.0 (17.4)	0.0001
Bodily pain	81.70 (19.0)	70.4 (25.8)	0.0001
Role/social-emotional/behavioral	92.50 (18.6)	88 (20.6)	0.0367
Parental impact-time	87.80 (19.9)	84.2 (24)	NS
Parental impact — emotional	80.30 (19.1)	47.2 (14.4)	0.0001
Self-esteem	79.80 (17.5)	77.2 (19.7)	NS
Mental health	78.50 (13.2)	77.6 (14.5)	NS
Behavior	75.60 (16.7)	78.4 (14.4)	NS
Family activities	89.70 (18.6)	79.8 (19.9)	0.0001
Family cohesion	72.3 (21.6)	71.3 (23.1)	NS
Physical summary score	53.00 (8.8)	41.8 (12)	0.0001
Psychosocial summary score	51.20 (9.1)	49.2 (6.6)	0.0414
Pediatric Quality of Life Inventory — Generic Score Scale[31]			
Parent proxy-report†			
Physical function	84.1 (19.7)	73.3 (25)	0.0001
Emotional function	81.2 (16.4)	70.1 (21.2)	0.0001
Social function	83.1 (19.7)	80 (23.6)	NS
School function	78.3 (19.6)	70 (20.2)	0.0002
Summary Score	82.3 (15.6)	74.6 (16.7)	0.0001
Child self-report			
Physical function	87.8 (13.2)	77.3 (21.9)	0.0001
Emotional function	79.2 (18.0)	75.9 (20.5)	NS
Social function	85.0 (16.7)	87.7 (15.6)	NS
School function	81.3 (16.1)	71.5 (19.6)	0.0001
Summary Score	83.9 (12.5)	78.1 (15)	0.0001
Pediatric Quality of Life Inventory — Rheumatology Module**			
Parent proxy-report†			
Pain & hurt	73.1 (22.7)	70.6 (24.4)	NS
Daily activity	88.5 (17.1)	90.9 (17.3)	NS
Treatment	70.8 (18.6)	82.7 (15.3)	0.0001
Worry	89.6 (13.9)	72.5 (24.3)	0.0001
Communication	87.9 (16.3)	79.5 (19.6)	0.0032
Summary Score	82.0 (17.7)	79.4 (14.3)	NS
Child self-report			
Pain & hurt	77.8 (24.2)	75.6 (24.2)	NS
Daily activity	95.6 (11.1)	94.1 (11.6)	NS
Treatment	82.1 (16.3)	85.8 (14.8)	NS
Worry	83.6 (18.5)	70.9 (25)	0.0011
Communication	82.9 (19.7)	77.4 (22.6)	NS
Summary Score	84.4 (18.0)	80.8 (14.1)	NS

* Source for CHQ-PF50: Table 18.1: CHQ-50 Scale Scores: National norm for a population sample of U.S. children (n = 391)[18]. ** Source for PedsQL Rheumatology Module norms in 56 children and 85 parents of children with juvenile rheumatoid arthritis[21]. † Available from only 79 caregivers of children with cSLE. †† Double-sided unpaired t-test for unequal and equal variances as applicable. NS: not significant.

non) and Neurological domain scores (mostly for headaches and migraines; Figure 2C and 2D).

Presence of disease activity in other BILAG organ domains (Cardiovascular and Respiratory; Hematological, Mucocutaneous, and Renal domains) did not affect HRQOL ratings systematically.

Physician-rated disease course and change of family-rated health — effects on HRQOL. The mean scores of the HRQOL measures (PedsQL and CHQ-P50) did not change significantly when the disease course between visits was rated as "no change" by the physicians. The same held true for patients with cSLE whose health was rated "no change" or "stable" between visits based on parent/patient ratings of health.

With physician-rated worsening of disease or improvement of disease, the scores of the PedsQL-RM (parent proxy-report and patient self-report: both $p < 0.02$), and the CHQ-PHS ($p < 0.0005$) changed significantly, while those of the PedsQL–GC and the CHQ-PSS did not (Table 4).

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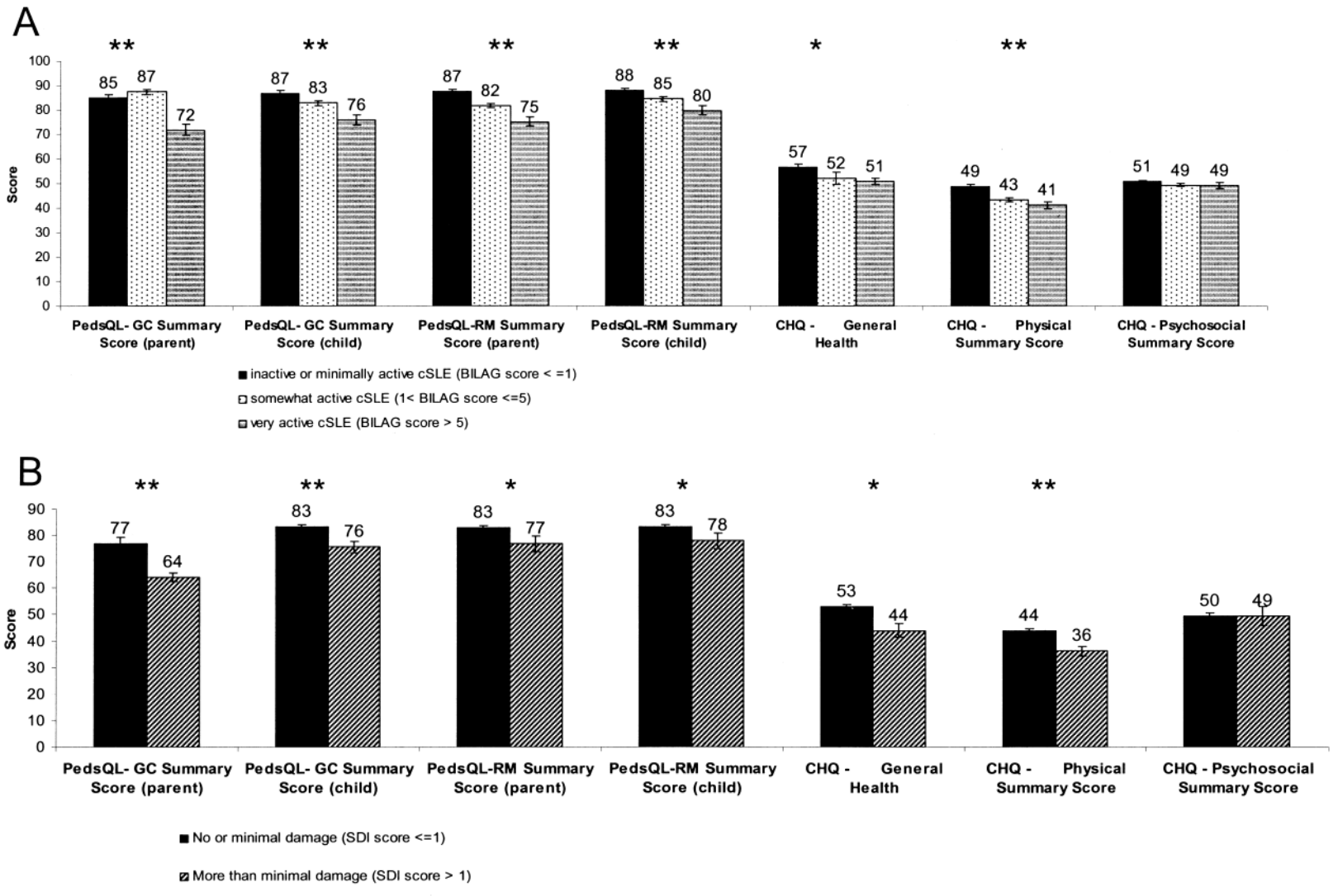

Figure 1. HRQOL — Degree of disease activity and disease damage. Histograms represent means and bars are standard errors (SE). Mixed-model analysis considering repeated measures from 98 patients with cSLE was done to determine significant differences between groups. Significant differences in scores across the 3 categories are marked: **p ≤ 0.006, *p < 0.05. For additional legend see Tables 1 and 2. A: Patients were classified according to BILAG summary score into 1 of 3 groups: inactive or minimally active disease (BILAG ≤ 1); somewhat active disease (1 < BILAG < 5); and very active disease (BILAG ≥ 5). Patients with no or minimal disease activity had higher HRQOL as measured by the PedsQL-GC, PedsQL-RM, General Health, and CHQ-PF50 physical function summary scores than patients with more pronounced disease activity. No differences in CHQ-PF50 psychosocial summary scores were noted for groups of patients with different levels of disease activity. B: Patients were classified according to their disease damage into those with no or minimal damage (SDI scores ≤ 1) and those with more pronounced damage (SDI scores > 1). HRQOL with cSLE as measured by the PedsQL-GC, PedsQL-RM (parent-rating only), and CHQ Physical Summary Score (CHQ-PHS) was significantly higher in the group of patients without or with only minimal disease damage than in those with more pronounced damage.

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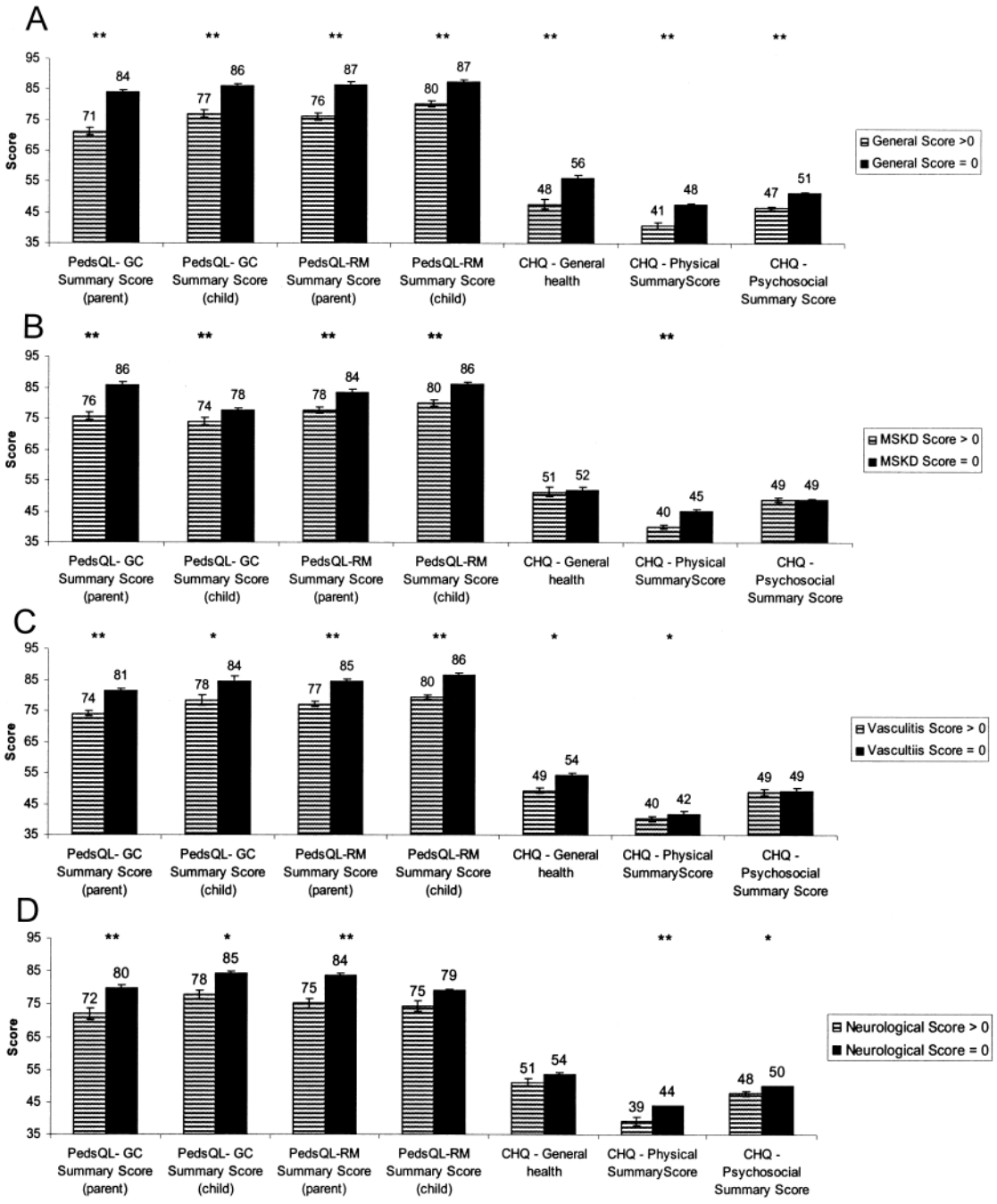

Figure 2. HRQOL — SLE organ involvement. Histograms represent means and bars are standard errors (SE). Patient were grouped for each of the 8 BILAG organ-system domains into 1 of 2 groups: those with disease activity in a certain organ system (BILAG organ-system domain score = A or B or C); and those without disease activity (BILAG organ-system domain score = D or E). Mixed-model analysis considering repeated measures from 98 patients with cSLE was done, correcting for residual disease activity in other than the target BILAG organ system domain under consideration. Significant differences in HRQOL scores between each of the 2 groups are marked: **p ≤ 0.006, *p < 0.05. Additional legend is provided under Tables 1 and 2.

When families (patients or parents) reported a worsening of health or improvement of health, changes in the score of the CHQ-GH also reached statistical significance.

SRM were calculated to further assess the responsiveness of the HRQOL measures to changes of physician-rated cSLE disease course and parent/patient-rated change in health, respectively. With physician-rated worsening or improvement of disease, the SRM of all of the HRQOL measures considered were < 0.4. Similarly, SRM of the HRQOL measures did not exceed 0.4 with improvement or

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worsening of parent/patient-rated health (exception, CHQ-PHS 0.57 with patient/parent-rated worsening of health). This suggests that the PedsQL and the CHQ-P50 are no more than moderately responsive to physician-rated important change in cSLE or family-rated change in health with cSLE.

DISCUSSION

Despite improved survival over the past decade, children with cSLE often continue to have significantly lower HRQOL than their healthy peers. Our results indicate that active disease, the worsening of disease, and the presence of disease damage are all risk factors for poor HRQOL in cSLE. Additionally, there are important differences in how disease activity in different organ systems affects HRQOL in cSLE.

Our study confirms the results of a large multinational cSLE cohort, that children with cSLE have markedly lower CHQ-P50 scores than healthy children[7,23]. Compared to the study by Ruperto *et al*[23], the patients with cSLE enrolled in our study often had higher CHQ-P50 domain scores. This could be because the disease activity in the earlier cohort was somewhat higher (mean SLEDAI-2K score 7.2 vs 4.8; data not shown) as was the amount of disease damage present (mean SDI score 1.1 vs 0.42).

For our study, we also evaluated the usefulness of the PedsQL Inventory for measuring HRQOL in cSLE. Consistent with the results of the CHQ-P50, patients with cSLE have much lower scores on the PedsQL-GC than healthy children. Additionally, when considering the PedsQL-RM, cSLE appears to have a detrimental effect on HRQOL similar to that found in JIA, confirming again the results of the multinational study[7]. Of note, we chose to use PedsQL-RM norms from a recent local JIA cohort instead of other published data[19]. Since JIA therapy has changed, and disease control has improved markedly over the preceding decade, due to the widespread access to biologic medications, comparisons with published historic cohorts would not have been as meaningful.

An important reason for measuring HRQOL is to find ways to improve the HRQOL of children with cSLE. In order to increase HRQOL, modifiable factors need to be identified. Higher levels of disease activity, and increase in disease activity as well as damage, have been found to be associated with worse HRQOL[6,7], and our study supports these earlier data. Our results strongly suggest that control of disease is an important way to improve HRQOL in cSLE. We repeated the same analysis using other validated disease activity measures for cSLE (ECLAM, Systemic Lupus Activity Measure, Safety of Estrogens in Lupus Erythematosus: National Assessment-SLEDAI) and found similar relationships between HRQOL and cSLE disease activity (data not shown).

Using the BILAG to measure organ-specific disease activity, we found that disease activity has a differential effect on HRQOL in cSLE, depending on the organ system involved. Similar to results from the LUMINA cohort of adults with SLE[24], which showed that fibromyalgia and fatigue are associated with low HRQOL, we found that fatigue, joint symptoms, and headaches had a markedly detrimental effect on the HRQOL of children with cSLE. Fatigue is a difficult to treat disease feature and, together with (subjective) joint symptoms and headaches, is part of the fibromyalgia spectrum; however, in the BILAG, they are only scored if thought to be due to cSLE activity rather than from another cause, such as fibromyalgia.

Renal disease activity and renal damage (but not end-stage renal disease) were relatively common in this cohort,

Table 4. Statistically significant changes in HRQOL scores with physician or family-rated changes in cSLE disease course.

Mean + SE of Change Score*	PedsQL-GC Summary Score (parent)	PedsQL-GC Summary Score (child)	PedsQL-RM Summary Score (parent)	PedsQl-RM Summary Score (child)	CHQ–General Health	CHQ–Physical Summary Score	CHQ–Psychosocial Summary Score
Physician-rated disease course**							
Worsening			–2.6 ± 1.5	–1.4 ± 1.1		–3.5 ± 1.2	
No change			0.8 ± 0.7	0.9 ± 0.6		0.5 ± 0.6	
Improvement			4.3 ± 1.6	2.7 ± 1.2		1.4 ± 1.3	
p†	NS	NS	0.0191	0.02	NS	0.0005	NS
Parent/patient-rated change in health***							
Worsening	–2.2 ± 1.9	–3.0 ± 1.3	–2.8 ± 1.8	–2.8 ± 1.8	–2.4 ± 2.0	–6.2 ± 1.4	
No change	0.7 ± 0.9	0.3 ± 0.6	0.5 ± 0.9	0.5 ± 0.9	–1.2 ± 1.0	0.5 ± 0.7	
Improvement	2.2 ± 1.0	2.2 ± 0.7	2.3 ± 1.0	2.3 ± 1.0	1.1 ± 1.1	0.9 ± 0.8	
p	0.052	0.003	0.0441	0.0028	0.0053	0.0064	NS

cSLE: childhood-onset systemic lupus erythematosus; HRQOL: health-related quality of life; SE: standard error. For other abbreviations, see Table 3. * Only values with significant differences between groups are shown. ** Disease course between visits was rated by the treating pediatric rheumatologist as worsening, no change, or improvement of disease activity. *** Change in health between visits was rated by the patients or parent as worsening, no change, or improvement of health. † Values of mean ± SE were estimated from mixed-effect models using a random effect to account for within-subject correlation. Significance was determined across the 3 categories based on F-test.

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but neither active lupus nephritis nor renal damage was associated with importantly decreased HRQOL. These observations are well in line with clinical observations, and might be explained by the fact that neither renal disease activity nor renal damage is associated with pain or fatigue, features we have shown had a negative effect on the HRQOL with cSLE. Thus, although the presence of lupus nephritis is of great concern to physicians in terms of overall morbidity and mortality, non-endstage renal disease has a modest effect, at most, on HRQOL.

We found an association of lower HRQOL with the presence of Raynaud's phenomenon. Only 1 patient had concomitant minor ulcerations on the fingertips. This result was unexpected and will require further investigation. The effect of Raynaud's phenomenon on HRQOL is, to our knowledge, only reported for adults with systemic sclerosis and no comparative data are available for children with rheumatic diseases.

Both the PedsQL and the CHQ-P50 can help provide insight about the health domains most profoundly affected by cSLE. Consistent with qualitative and quantitative research in both adults and children with cSLE[6,7,25], our results show that particular activities of daily living, concerns about therapies, and bodily pain are negatively influenced by SLE, and that this effect can be measured by the CHQ-P50 and PedsQL. Our data, and those previously published[23], support the notion that the CHQ-P50 and the PedsQL have both concurrent as well as construct validity, and are responsive to clinically important changes in cSLE disease activity. In our study, both the CHQ-PHS and the PedsQL-RM scores significantly changed with relevant changes in the course of cSLE, irrespective of whether the physician or the patient/parent are considered as the external standard. Both instruments (CHQ-PF50, PedsQL inventory) have been cross-culturally validated and appear similarly suitable for use in clinical practice and research. Nonetheless, the responsiveness to change (SRM) of the CHQ-PF50 and the PedsQL was relatively low, raising the possibility that a cSLE-specific tool might be needed.

Different from adults with SLE[26], disease activity has not had an important effect on the psychosocial aspects of HRQOL (CHQ-PSS). Although reasons for this observation are not entirely clear, one factor might have been that the CHQ questionnaire we used provided a parent-proxy assessment, rather than a patient self-report.

Limitations to our study include that we did not collect ratings of the change in cSLE patients' health consistently from the parent or the patient. Thus, for the analysis these ratings were simply combined. However, combining the ratings is unlikely to have changed the principal finding that changes in health are associated with changes in HRQOL scores because parents are moderately good proxy reporters of their children's HRQOL[27].

Additionally, most patients were adolescents, and findings may therefore not be applicable to younger children with cSLE, as is suggested by previous research. This, however, has likely only underestimated the effect of cSLE on the HRQOL, as previous research suggests that the effect of cSLE on HRQOL may even be more substantial in younger children[28].

There are numerous confounders of HRQOL, including socioeconomic status (SES), that have not been considered in our study. However, there are no widely accepted measures of SES, and one cannot assume that the perceived SES of an adolescent is the same as that of the parent[29,30]. Further research on the effect of SES will be needed to address the relationship of HRQOL and SES in cSLE.

Our study in a contemporary cohort of North American children and adolescents with cSLE confirms the ongoing detrimental effects of cSLE on HRQoL, especially when disease damage and high disease activity are present. In children with SLE, particular attention should be paid to disease control, musculoskeletal and neurological involvement, and the presence of fatigue, because these features all have a large effect on HRQoL.

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