

# Long-Term Clinical Outcomes in a Cohort of Adults With Childhood-Onset Systemic Lupus Erythematosus

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**Objective.** Childhood-onset systemic lupus erythematosus (SLE) is a severe, lifelong, multisystem autoimmune disease. Long-term outcome data are limited. This study was undertaken to identify clinical characteristics and health-related quality of life (HRQoL) of adults with childhood-onset SLE.

**Methods.** Patients participated in a single study visit comprising a structured history and physical examination. Disease activity (scored using the SLE Disease Activity Index 2000 [SLEDAI-2K]), damage (scored using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index [SDI]), and HRQoL (scored using the Short Form 36 Health Survey) were assessed. Medical records were reviewed.

**Results.** In total, 111 childhood-onset SLE patients were included; the median disease duration was 20 years, 91% of patients were female, and 72% were white. Disease activity was low (median SLEDAI-2K score 4), and 71% of patients received prednisone, hydroxychloroquine (HCQ), and/or other disease-modifying antirheumatic drugs. The vast majority of new childhood-onset SLE-related manifestations developed within 2 years of diagnosis. Damage such as myocardial infarctions began occurring after 5 years. Most patients (62%) experienced damage, predominantly in the musculoskeletal, neuropsychiatric, and renal systems. Cerebrovascular accidents, renal transplants, replacement arthroplasties, and myocardial infarctions typically occurred at a young age (median age 20 years, 24 years, 34 years, and 39 years, respectively). Multivariate logistic regression analysis showed that damage accrual was associated with disease duration (odds ratio [OR] 1.15,  $P < 0.001$ ), antiphospholipid antibody positivity (OR 3.56,  $P = 0.026$ ), and hypertension (OR 3.21,  $P = 0.043$ ). Current HCQ monotherapy was associated with an SDI score of 0 (OR 0.16,  $P = 0.009$ ). In this cohort, HRQoL was impaired compared to the overall Dutch population. The presence of damage reduced HRQoL scores in 1 domain. High disease activity (SLEDAI-2K score  $\geq 8$ ) and changes in physical appearance strongly reduced HRQoL scores (in 4 of 8 domains and 7 of 8 domains, respectively).

**Conclusion.** The majority of adults with childhood-onset SLE in this large cohort developed significant damage at a young age and had impaired HRQoL without achieving drug-free remission, illustrating the substantial impact of childhood-onset SLE on future life.

## INTRODUCTION

Systemic lupus erythematosus (SLE) is a lifelong, multisystem autoimmune disease, known for its highly heterogeneous clinical presentation and waxing–waning disease

course. Childhood-onset SLE, defined as SLE with onset at age  $< 18$  years (1), represents 10–20% of all SLE cases and has a mean age at onset of 11–12 years (2,3). Childhood-onset SLE is a rare disease, with an incidence rate of 0.3–0.9 per 100,000 patient-years and a prevalence of 1.89–25.7 per

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100,000 children worldwide (4–6). Similar to SLE in adults, childhood-onset SLE is seen more often in nonwhite individuals and girls (female:male ratio 4–5:1). Disease manifestations differ among ethnicities, but clinical outcomes such as disease activity and damage tend to be similar among patients when data are corrected for socioeconomic status (7–10).

Although survival rates for childhood-onset SLE patients have greatly improved, morbidity is still high, and questions from children and parents regarding the future course of the disease are difficult to answer (7,11). Long-term follow-up studies of childhood-onset SLE are limited and often have low patient numbers and/or include patients with relatively short disease duration; thus, detailed evidence regarding development of new organ involvement and damage over time is lacking (7,12–17). Overall, these studies show that the majority of adolescents and young adults with childhood-onset SLE still have active disease, receive immunosuppressive drugs, and steadily accrue damage during their disease (7,11,12,18,19).

Only 1 North American cohort study of both childhood-onset SLE and adult-onset SLE patients has included a large number of childhood-onset SLE patients ( $n = 90$ ) with a long disease duration (mean 16.5 years) and compared outcomes of the 2 diseases (18). In that study, structured telephone interviews were used to collect patient-reported clinical outcomes, of which only significant renal outcomes could be validated by chart review. At the time of interview, childhood-onset SLE patients had lower disease activity and were more likely to have ever received and currently receive glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) when compared to adult-onset SLE patients (18). This was also observed in a cohort in which outcomes were compared between childhood-onset SLE patients, adult-onset SLE patients, and late-onset SLE patients with a disease duration of 12 years (19). In the North American cohort of adult-onset and childhood-onset SLE patients, the latter was shown to be an independent risk factor for mortality (11). Due to the nature of that cohort study (which relied primarily on patient-reported clinical outcomes), data regarding development of damage could not be included.

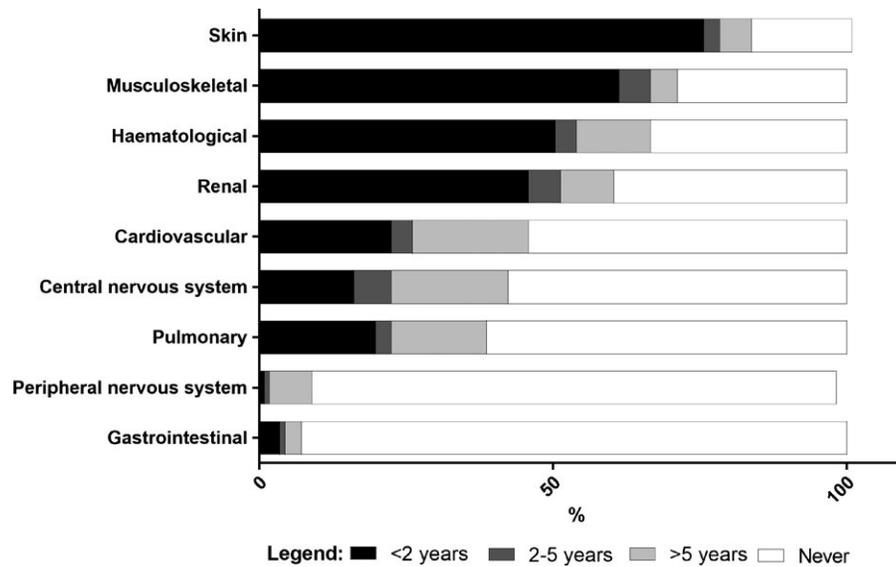
In children with childhood-onset SLE, health-related quality of life (HRQoL) has been shown to be impaired compared to healthy peers, which has been at least partially attributed to disease activity and damage (20,21). There were no data available regarding HRQoL in adult patients with childhood-onset SLE or pertaining to the specific factors that could influence HRQoL in these patients.

In the present study (the Childhood-Onset SLE in The Netherlands [CHILL-NL] study), we aimed to assess the disease burden of childhood-onset SLE in The Netherlands. In this report, we describe the clinical characteristics of adults with childhood-onset SLE, focusing on disease course and damage accrual over time, in association with HRQoL.

## PATIENTS AND METHODS

**Patients.** All childhood-onset SLE patients who were >18 years old, had been treated in any Dutch hospital, and met the American College of Rheumatology (ACR) criteria for SLE (22,23) were eligible for inclusion in the CHILL-NL study. Rheumatologists, immunologists, nephrologists, hematologists, and neurologists in all 88 Dutch hospitals were contacted. Private practices were not contacted, as there are very few in The Netherlands. Moreover, as SLE is a systemic disease and hospital diagnostics are essential for optimal treatment, rheumatologists in private practices do not typically treat SLE patients. All medical specialists in secondary or tertiary hospitals were contacted via email and informational flyers. They were asked to identify SLE patients in their care who were diagnosed as having childhood-onset SLE prior to their 18th birthday, and to ask if these patients were interested in participating in a study on long-term outcomes. The study was also promoted by the Dutch SLE patient organization (the National Association for Lupus, APS, Scleroderma, and MCTD [NVLE]) both in their magazine and on their web site (24). Due to the study design, data regarding mortality in childhood-onset SLE or clinical characteristics of deceased patients could not be retrieved reliably; therefore, we only report data on surviving patients. The Research Ethics Board of the Erasmus University Medical Center approved the study (MEC-2013-163), and written informed consent was obtained from all patients.

**Data collection.** The CHILL-NL team designed the study with the help of a patient panel ( $n = 5$ ). Patients were seen for a single 1.5-hour study visit at the Erasmus University Medical Center. If patients were unable to travel, the study visit was performed at the hospital of their choice. During the study visit, an extensive medical history was obtained using structured data collection forms and (validated) questionnaires. Data regarding demographics, current health, disease activity, damage, disease onset and progression over time, and current and previous medication use were collected. A physical examination was performed, blood and urine were collected, and patients completed questionnaires regarding HRQoL, effects of medication use (on physical appearance, physical health, or mental health [with a yes/no option and a request for elaboration]), education and employment, fertility and family planning, fatigue, depression, and coping and resilience (25–30). For this report, a selection of the data (i.e., disease activity, medication use, disease manifestations over time, damage, and HRQoL) was used. Medical information was requested from all hospitals where patients had previously received care. Clinical data collected during the study visit were supplemented and verified through the retrieved medical history. Only data that could be verified in medical records were reported.



**Figure 1.** First occurrence of disease manifestations (by organ system) over time since diagnosis of childhood-onset systemic lupus erythematosus (SLE). Skin category includes malar rash, discoid rash, ulcers, photosensitivity, cutaneous vasculitis, and other ongoing inflammatory SLE-related rashes. Musculoskeletal category includes arthritis and myositis. Hematologic category includes hemolytic anemia, thrombocytopenia, leukopenia, lymphopenia, neutropenia, and thrombotic thrombocytopenic purpura. Renal category includes persistent proteinuria and lupus nephritis. Cardiovascular category includes pericarditis, myocarditis, endocarditis, myocardial infarction, angina pectoris, cerebrovascular accident, transient ischemic attack, arterial thrombosis, venous thrombosis, and embolus. Central nervous system category includes aseptic meningitis, cerebrovascular disease, demyelinating disease, lupus headache, myelopathy, chorea, convulsions, acute confusional state, anxiety disorder, mood disorder, and psychosis. Pulmonary category includes pleuritis, pneumonia, fibrosis, shrinking lung, pulmonary arterial hypertension, and interstitial lung disease. Peripheral nervous system category includes autonomous nervous system disorder, mononeuropathy, myasthenia gravis, Guillain-Barré syndrome, cranial nerve neuropathy, plexopathy, and polyneuropathy. Gastrointestinal category includes peritonitis, pancreatitis, autoimmune hepatitis, and liver cirrhosis.

**Demographics.** Data regarding demographic characteristics such as age, sex, self-reported ethnicity, and area of residence were collected by structured questionnaires. Categories of ethnicity included African/Caribbean, Arabic, Asian, Hispanic, white, and mixed.

**Diagnosis, disease manifestations, and damage over time.** Data on which components of ACR SLE criteria and/or SLE International Collaborating Clinics (SLICC) SLE criteria patients met were recorded, in addition to any childhood-onset SLE-related manifestations at diagnosis (22,23,31). Definitions of disease manifestations are described in Figure 1. Disease duration was defined as years between date of diagnosis (as reported in medical records) and study visit. Based on findings in previous studies, disease manifestations of childhood-onset SLE over time were recorded according to 6 predefined time frames: 1) never, 2) prior to diagnosis, 3) at diagnosis, 4) <2 years since diagnosis, 5) 2–5 years since diagnosis, and 6) >5 years since diagnosis (7,32,33). Age at first myocardial infarction, renal transplantation, cerebrovascular accident (CVA), and/or replacement arthroplasty was obtained from medical records. Specific disease manifestations such as antibody positivity were recorded as positive or negative if found in medical records and as unknown if not mentioned in the records. Nephrotic syndrome was recorded as present if clinical manifes-

tations (edema, proteinuria [3–3.5 gm/24 hours], and hypoalbuminemia [ $<25$  gm/liter]) were present, or if medical records included a nephrotic syndrome diagnosis. Hypertension was recorded as present if blood pressure was  $>140/90$  mm Hg on repeated examinations, or if medical records included a hypertension diagnosis.

**Disease activity and medication use.** Disease activity was assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K) (34). High disease activity was defined by a SLEDAI-2K score of  $\geq 8$  (35,36). Additionally, patients were asked to rate their disease activity on a visual analog scale (VAS), ranging from 0 (no disease activity) to 100 (very high disease activity). Medication use was classified as current use, previous use, and never used. Glucocorticoids and hydroxychloroquine (HCQ) were considered separately. Non-HCQ DMARDs included azathioprine, cyclosporine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, rituximab, and tacrolimus. All other medication use, including antiepileptic medication, antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), and coumarins was also recorded. During the study visit, patients were asked if there were any medications that had affected them in terms of their physical appearance, physical health, or mental health, and in what ways they were affected.

**Damage assessment.** Disease damage was assessed using the SLICC/ACR Damage Index (SDI) (37). Presence of damage was defined by an SDI score of  $\geq 1$ . For damage that had a specific temporal component (i.e., cognitive impairment or renal impairment present for  $\geq 6$  months), it was recorded if the item was found in 2 consecutive reports from the medical records.

**Assessment of health-related quality of life.** HRQoL was assessed using the Short Form 36 (SF-36), which includes 36 questions about 8 health domains: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, vitality, bodily pain, and general health perception (25). Patient HRQoL scores were compared to those from the general population in The Netherlands. Effects on HRQoL from the following factors were assessed: disease activity (low [SLEDAI-2K score  $\leq 4$ ], intermediate [5–7], or high [ $\geq 8$ ]) (35), SLEDAI-2K items concerning changes in physical appearance (i.e., ongoing inflammatory rash and/or alopecia), and damage.

**Statistical analysis.** Group comparisons were made using the Mann-Whitney U test or the Kruskal-Wallis test, where applicable. One-sample *t*-tests were used for comparisons with normative data from the Dutch population. Logistic regression analysis was performed to assess associations of individual variables and the development of damage. Selection of these variables was based on a literature review (38). Presence of damage was defined as the outcome of interest, and predetermined variables were covariates in the model. Variables with an individual *P* value of  $< 0.1$  were used to build the multivariable model, using a hierarchical entry method. In the final, most parsimonious model, variables with associations at a *P* value of  $< 0.05$  were considered to contribute. To assess goodness of fit, the Hosmer-Lemeshow test was used, and residual statistics (i.e., Cook's distance for standardized residuals, deviance, and leverage) were analyzed. All analyses were performed using IBM SPSS Statistics version 22.

## RESULTS

**Patient inclusion.** Patients were enrolled in the CHILL-NL study from November 2013 until April 2016. Eighty-eight secondary and tertiary hospitals were contacted. Doctors from 18 hospitals confirmed having adult patients with childhood-onset SLE under their care and sent contact information for 121 patients to the study team. An additional 15 patients contacted the study team via NVLE. Of these 136 patients, 111 patients (82%) were seen for a single study visit (see Supplementary Figure 1, on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40697/abstract>). Most study participants (69%) were treated in a tertiary center (Supplementary Figure 1). As an example of the proportion of patients treated at a certain site

who participated in the study, 17 of the 23 current patients with childhood-onset SLE (74%) at the Erasmus University Medical Center participated in the CHILL-NL study. Forty percent of patients in the study lived within the vicinity of the Erasmus University Medical Center; residences of the remaining patients were equally distributed over the rest of the country.

**Demographic and disease characteristics of the patients.** The median age at study visit was 33 years, with a median disease duration of 20 years (Table 1). Patients were divided into 3 diagnostic eras according to year of diagnosis, which ranged from 1959 to 2013. The number of patients among the 3 groups was evenly distributed, with 33% of patients diagnosed before 1990. The most common elements of the ACR criteria met by patients at diagnosis were anti-nuclear antibody positivity, immunologic features, and arthritis (see Supplementary Figure 2, <http://onlinelibrary.wiley.com/doi/10.1002/art.40697/abstract>). Almost all participants were female (91%). The majority of patients were white (72%), while 10% were African/Caribbean, 7% Asian, 3% Hispanic, 1% Arabic, and 7% of mixed heritage. Due to the majority of patients being white, ethnicity was presented as a binary category: white and nonwhite. Age at onset and disease duration were similar across these ethnic groups.

**Treatment.** The vast majority of patients (68%) were taking glucocorticoids and/or non-HCQ DMARDs at the time of the study visit (Table 1). Fifty-six patients (51%) were taking glucocorticoids (with or without non-HCQ DMARDs), and 76 patients (68%) were taking HCQ (of whom 29% were being treated with HCQ monotherapy). Sixty-five percent of patients were taking other non-antiinflammatory medications, including antihypertensive drugs (such as ACE inhibitors and ARBs) (51%), statins (14%), coumarins (14%), acetylsalicylic acid (12%), antidepressants (8%), antiepileptic drugs (5%), and erythropoietin (5%). When asked about the effects of medication use on physical appearance, physical health, or mental health, the majority of patients reported negative effects. The largest impact reported was physical appearance (89% of patients), which was perceived negatively by 93% of patients. Patients also reported a negative impact on physical health (36%) and mental health (28%). Effects on physical appearance (e.g., weight gain) and on mental health (e.g., mood swings) were mostly attributed to prednisone use. Effects on physical health (e.g., nausea) were mostly attributed to non-HCQ DMARDs.

**Disease activity.** At the study visit, recorded disease activity was relatively low (median SLEDAI-2K score 4 and median VAS score 13). Low complement levels (32%), skin rashes (14%), and proteinuria (13%) were the most commonly recorded SLEDAI-2K items. No difference was found between

**Table 1.** Patient characteristics at the study visit\*

Female	101 (91)
Ethnicity	
White	80 (72)
Nonwhite	31 (28)
Age at diagnosis, median (range) years	14 (4–17)
Age at study visit, median (range) years	33 (18–65)
Disease duration, median (range) years	20 (1–55)
Era of diagnosis	
Prior to 1990	37 (33)
Between 1990 and 2000	38 (34)
After 2000	36 (32)
Disease activity	
SLEDAI-2K, median (range) score	4 (0–16)
SLEDAI ≤4	72 (65)
SLEDAI 5–7	23 (21)
SLEDAI ≥8	16 (14)
Patient-reported VAS, median (range) score	13 (0–95)
Current glucocorticoids/non-HCQ DMARDs use†‡	75 (68)
Glucocorticoids with non-HCQ DMARDs	40 (53)
Glucocorticoids only	16 (21)
Non-HCQ DMARDs only	15 (20)
2 non-HCQ DMARDs with or without glucocorticoids	4 (5)
Current HCQ use‡	76 (68)
HCQ with non-HCQ DMARDs/glucocorticoids	54 (71)
HCQ monotherapy	22 (29)
No HCQ, glucocorticoids, or non-HCQ DMARDs	14 (13)§
SDI, median (range)	1 (0–8)
SDI ≥1	69 (62)
Infections requiring IV antibiotics (ever)‡	50 (45)
1 occurrence	26 (52)
>1 occurrence	24 (48)

\* Except where indicated otherwise, values are the number (%) of patients. SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; VAS = visual analog scale; HCQ = hydroxychloroquine; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

† More information regarding specific disease-modifying antirheumatic drug (DMARD) use can be found in Supplementary Table 3, on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40697/abstract>.

‡ Percentages below are based on the number of patients receiving the treatment ( $n = 75$  or  $76$ ) or the number of patients with infections requiring intravenous (IV) antibiotics ( $n = 50$ ), rather than the full cohort of 111 patients.

§ More information regarding these 14 patients can be found in Supplementary Table 4.

the SLEDAI-2K scores of patients receiving glucocorticoids and/or non-HCQ DMARDs, patients receiving HCQ monotherapy, and patients not receiving glucocorticoids, non-HCQ DMARDs, or HCQ monotherapy ( $P = 0.177$  by Kruskal-Wallis test).

**Infections.** During their disease course, almost half of the patients (45%) had been admitted to the hospital due to infections that required intravenous antibiotic therapy. Forty-eight percent of these patients were admitted more than once (Table 1).

#### Disease manifestations and damage over time.

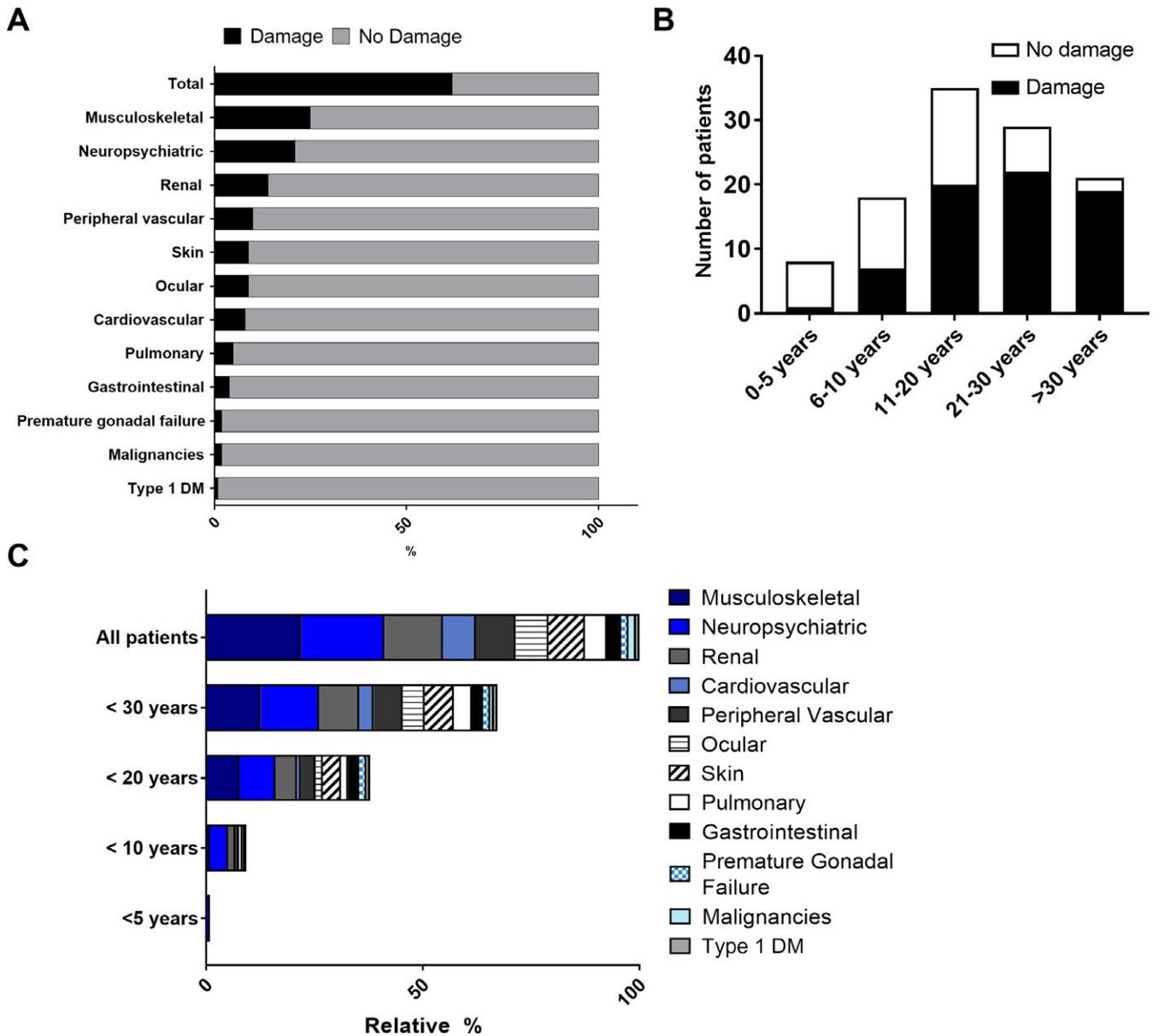
The organ systems that were most frequently involved were the skin (e.g., malar or discoid rash, cutaneous vasculitis), musculoskeletal system (primarily arthritis), hematologic system (e.g., hemolytic anemia, leukopenia), and renal system (e.g., lupus nephritis). The vast majority of new manifestations in these organ systems developed within 2 years of diagnosis (Figure 1). Cardiovascular, pulmonary, and central nervous system (CNS) manifestations occurred in the short term and long term. Within 2 years of diagnosis, pericarditis, pleuritis, and epilepsy were the most common manifestations within these organ systems, while 5 years after diagnosis damage was most prevalent (e.g., myocardial infarction and CVA). Manifestations in the peripheral nervous system and gastrointestinal system were uncommon and mainly occurred ≥5 years after diagnosis.

**Disease damage.** Renal, neuropsychiatric, and musculoskeletal damage were the most prevalent types of damage (Figure 2A). In total, 62% percent of patients had developed disease damage, and the percentage of patients with damage increased over time (Figure 2B). Musculoskeletal damage (e.g., avascular necrosis, deforming/erosive arthritis), neuropsychiatric damage (primarily cognitive impairment, often combined with seizures requiring treatment of >6 months), and renal damage (e.g., end-stage renal disease) were the most prevalent types of damage across disease duration categories (Figure 2C and Supplementary Table 1, <http://onlinelibrary.wiley.com/doi/10.1002/art.40697/abstract>).

Notably, after 10–20 years, when childhood-onset SLE patients were in their 20s and 30s, more than half experienced significant damage (Figure 2C, and Supplementary Table 1). Seven childhood-onset SLE patients (5%) experienced a CVA (at a median age of 20 years). Sixteen patients (24%) who had renal involvement during their disease subsequently developed damage (Supplementary Table 2, <http://onlinelibrary.wiley.com/doi/10.1002/art.40697/abstract>). Of these 16 patients, 38% received a renal transplant (median age 24 years), and 1 patient was undergoing dialysis. Six patients underwent replacement arthroplasty in 1 joint, and 4 patients received >1 joint replacement; the median age at first joint replacement was 34 years (Supplementary Table 2). Five patients experienced a myocardial infarction (at a median age of 39 years), and 3 of them underwent coronary bypass surgery.

#### Factors related to the development of damage.

Logistic regression analysis was performed, and odds ratios (ORs) and 95% confidence intervals (95% CIs) were calcu-



**Figure 2.** Childhood-onset systemic lupus erythematosus–related damage defined by a Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index score of  $\geq 1$ . **A**, Percentage of patients with damage according to organ system. **B**, Number of patients with and without damage, by disease duration category. **C**, Percentage of cumulative specific organ damage relative to the sum of damage scores in all organ systems, displayed by disease duration category. DM = diabetes mellitus.

lated to assess associations between individual variables and development of damage (Table 2). The univariate analysis showed longer disease duration; additionally, antiphospholipid antibody (aPL) positivity, infections requiring hospitalization (ever), the presence of hypertension (ever), and the presence of nephrotic syndrome (ever) were associated with the presence of damage. Neither sex nor ethnicity showed a significant association with the presence of damage. Current HCQ monotherapy was associated with the absence of damage. In the multivariate analysis, disease duration (OR 1.147 [95% CI 1.077–1.227],  $P < 0.001$ ), hypertension (OR 3.214 [95% CI

1.040–9.932],  $P = 0.043$ ), and aPL positivity (OR 3.559 [95% CI 1.161–10.908],  $P = 0.026$ ) were significantly associated with presence of damage, and current HCQ monotherapy (OR 0.162 [95% CI 0.042–0.633],  $P = 0.009$ ) was again associated with the absence of damage. No differences in number or type of organ systems involved or in antiinflammatory medication use were found between patients currently receiving HCQ monotherapy and other patients.

**Health-related quality of life.** HRQoL as measured by the SF-36 at study visit was lower in adults with childhood-

**Table 2.** Binary logistic regression analysis of variables associated with damage as the outcome measure\*

Predictor (no. of patients)	Univariate analysis			Multivariate analysis		
	$\beta$ †	OR (95% CI)	<i>P</i>	$\beta$ †	OR (95% CI)	<i>P</i>
Disease duration (111)	0.107	1.113 (1.057–1.171)	<0.001	0.139	1.147 (1.077–1.227)	<0.001
No. of ACR criteria elements met at diagnosis (111)	0.036	1.037 (0.786–1.367)	0.798	–	–	–
Age at diagnosis (111)	–0.70	0.933 (0.811–1.072)	0.322	–	–	–
Use of DMARDs/gluco-corticoids with or without HCQ (75)						
Compared to HCQ monotherapy (22)	–1.259	0.283 (0.103–0.776)	0.014	–1.818	0.162 (0.042–0.633)	0.009
Compared to no HCQ, glucocorticoids, or non-HCQ DMARDs (14)	–0.185	0.831 (0.251–2.747)	0.761	–0.942	0.390 (0.085–1.787)	0.225
White (80) compared to nonwhite (31)	0.754	2.215 (0.847–5.329)	0.108‡	–	–	–
Female (101) compared to male (10)	–0.964	0.381 (0.077–1.888)	0.237‡	–	–	–
aPL negativity (44)						
Compared to aPL positivity (48)	0.990	2.692 (1.130–6.417)	0.025	1.269	3.559 (1.161–10.908)	0.026
Compared to unknown aPL status (19)	0.539	1.714 (0.569–5.169)	0.338	0.264	1.302 (0.333–5.092)	0.704
No renal involvement ever (44)						–
Compared to renal involvement within 2 years of diagnosis (50)	0.663	1.94 (0.839–4.490)	0.121‡	–	–	–
Compared to renal involvement after 2 years (17)	0.784	2.191 (0.660–7.268)	0.200‡			
No CNS involvement ever (78)						
Compared to CNS involvement within 2 years of diagnosis (9)	1.023	7.515 (1.595–35.423)	0.214‡			
Compared to CNS involvement after 2 years of diagnosis (24)	0.266	2.088 (0.826–5.276)	0.591‡			
Nephrotic syndrome (24) compared to no nephrotic syndrome ever (87)	1.738	5.687 (1.578–20.488)	0.008	0.932	–	0.242§
Hospitalization (50) compared to no hospitalization due to infection ever (61)	0.505	1.656 (1.098–2.500)	0.016	0.393	–	0.456§
Hypertension (71) compared to no hypertension ever (40)	1.522	4.583 (1.792–11.715)	0.001	1.167	3.214 (1.040–9.932)	0.043

\* OR = odds ratio; 95% CI = 95% confidence interval; ACR = American College of Rheumatology; DMARDs = disease-modifying antirheumatic drugs; HCQ = hydroxychloroquine; aPL = antiphospholipid antibody; CNS = central nervous system.

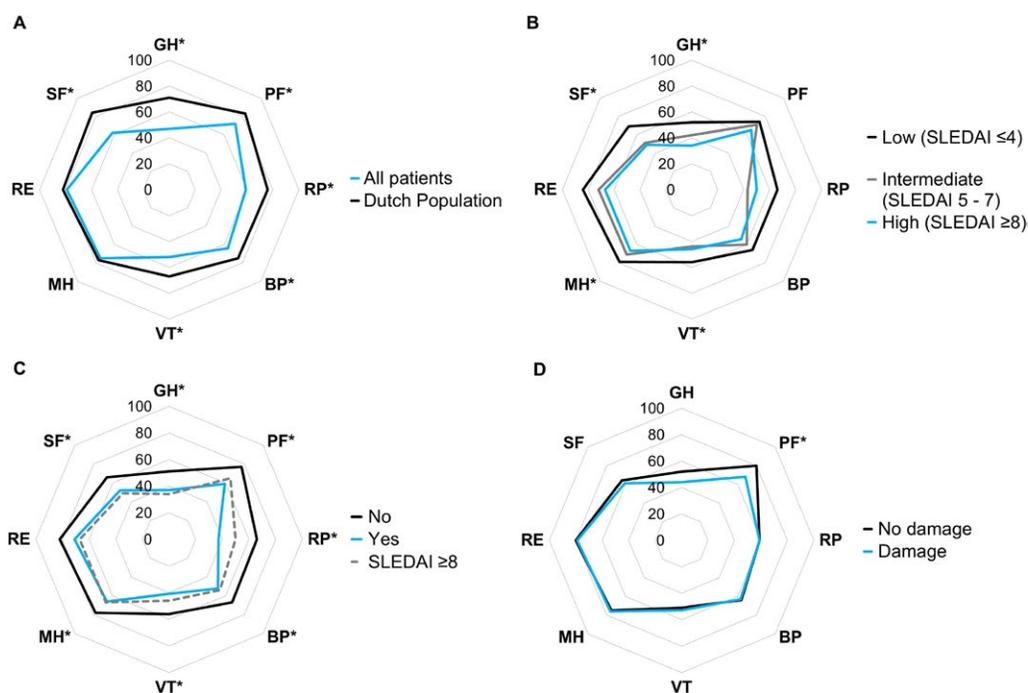
† Regression coefficient.

‡ A cutoff of *P* < 0.100 was set to select the variables for multivariate logistic regression. As such, these covariates were not incorporated in the multivariate model.

§ These covariates did not improve the fit of the model and were therefore not used for the final multivariate model.

onset SLE in 6 of the 8 assessed domains when compared to the Dutch population (Figure 3A). Low disease activity, defined as a SLEDAI score of  $\leq 4$ , positively affected HRQoL (Figure 3B). A more detailed evaluation of SLEDAI-2K items concerning changes in physical appearance (e.g., ongoing inflammatory rash and/or alopecia [*n* = 25]) revealed a clearly negative impact on HRQoL in 7 of 8 domains (Figure 3C). Notably, HRQoL scores in these patients were similar to or even lower than those of patients with high disease activity (SLEDAI-2K  $\geq 8$ ), even though only 24% of patients with changes in physical appearance had high disease activity. An active renal component as defined by the SLEDAI-2K (*n*

= 14) did not affect HRQoL. No differences in HRQoL scores were observed between white and nonwhite patients (data not shown). Notably, in 7 of the 8 domains, HRQoL scores did not differ between patients with damage and those without; significantly lower scores in patients with damage were observed only in the physical functioning domain (Figure 3D). Additionally, physical functioning domain scores of patients with very long disease durations (>30 years) were worse compared to those of patients with short disease durations (<10 years). On the other hand, mental health domain scores improved over time, with higher scores in patients with a long disease duration (data not shown).



**Figure 3.** Health-related quality of life expressed as mean Short Form 36 (SF-36) health survey scores per domain. Spidergrams (63) show mean scores within each domain of the SF-36, ranging from 0 (worst) to 100 (best). **A**, SF-36 scores of childhood-onset systemic lupus erythematosus (SLE) patients versus those of the overall Dutch population. **B**, SF-36 scores of patients with low SLE Disease Activity Index 2000 (SLEDAI-2K) scores ( $\leq 4$ ), intermediate scores (5–7), and high scores ( $\geq 8$ ). **C**, SF-36 scores of patients with affirmative responses to questions about effects on physical appearance (e.g., ongoing inflammatory rash and/or alopecia) versus patients without these symptoms and patients with SLEDAI-2K scores  $\geq 8$ . **D**, SF-36 scores of patients with damage (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index [SDI] score  $\geq 1$ ) versus patients without damage (SDI score 0). GH = general health perception domain; PF = physical functioning domain; RP = role limitations due to physical problems domain; BP = bodily pain domain; VT = vitality domain; MH = mental health domain; RE = role limitations due to emotional problems domain; SF = social functioning domain. \* =  $P < 0.05$ . Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/art.40697/abstract>.

## DISCUSSION

This is the first study to report data on disease manifestations over time, damage, and HRQoL in a large cohort of predominantly white adult patients with childhood-onset SLE with very long disease duration. Most patients had low disease activity but still took DMARDs and/or glucocorticoids 20 years after diagnosis. More than half of the patients also took medications to treat noninflammatory disease or damage-related symptoms. Clearly, drug-free remission remains difficult to achieve, and current DMARDs are not effective enough to be taken without glucocorticoids in many patients. Indeed, half of the patients in our cohort were still taking glucocorticoids with or without DMARDs, which was also reported in cohorts that included patients with childhood-onset SLE or adult-onset SLE patients with a mean disease duration of 12–16 years (18,19). This is concerning, as glucocorticoids are associated with the development of damage (39). Patients in the CHILL-NL cohort were eager to limit glucocorticoid use, as nearly all reported negative experiences with prednisone, especially with regard to their physical appearance and/or

mental well-being. Although our findings may be influenced by recall bias, they illustrate the perceived impact of glucocorticoid use on a patient's well-being, emphasizing the need for the development of new treatment strategies that can limit or even eliminate glucocorticoid use.

Most organ systems became involved within the first 2 years of diagnosis, and thereafter hardly any new childhood-onset SLE-related manifestations occurred in organ systems not previously affected. This finding was also reported in 2 childhood-onset SLE cohorts, but these cohorts had a mean disease duration of only 4 years (32,40). After 5 years of disease, our study demonstrated that the nature of disease manifestations shifts to damage (such as myocardial infarction) instead of primary disease-related manifestations (such as pericarditis or epilepsy). This shift has also been observed in adult-onset SLE patients (41–44), and there has been a push for preventative screening measures for cardiovascular damage and healthy lifestyle advice (i.e., guidance on healthy diet, regular exercise, abstinence from smoking). A study that examined laboratory markers of cardiovascular risk in adolescents with childhood-onset SLE showed that disease duration and signs of renal injury (e.g., proteinuria, history of hypertension)

were associated with these markers (45). As has also been shown by others (12,18), we found in the present study that cardiovascular damage begins when childhood-onset SLE patients are in their 20s and early 30s, so prevention strategies must be considered during transition to adult care, especially in patients with renal involvement. Because infections are common and related to mortality in childhood-onset SLE patients (46,47), infection prevention by vaccination should be encouraged (48,49).

The majority of our patients had developed damage by their mid-20s, and this percentage increased with longer disease duration. The musculoskeletal system, kidneys, and CNS were the most frequently affected, as in other childhood-onset SLE studies, though those studies involved patients with limited disease duration (5–10 years) (13,15,16,19,50). The only available studies of damage in patients with a mean disease duration of  $\geq 20$  years were performed in adult-onset SLE (50,51). Reported frequency and characteristics of damage in these cohorts were similar to the results in the CHILL-NL cohort. However, the mean age at diagnosis in the adult-onset SLE cohorts was 31 years (50,51), versus 14 years in our study, which likely explains why most patients with childhood-onset SLE began to develop significant damage in their early 20s. This is further supported by reports from 2 North American childhood-onset SLE cohorts (mean disease durations of 5 years and 16.5 years) that described myocardial infarction in childhood-onset SLE patients in their 20s and 30s (12,18).

Disease duration was the main variable associated with the development of damage in the CHILL-NL cohort, followed by aPL positivity and hypertension (Table 2), and this has been consistently demonstrated in many other childhood-onset SLE studies (13,15,50–53). Presence of damage did not differ between white and nonwhite patients in our study, but other studies have shown conflicting results regarding ethnicity and development of damage (7,9,12). Similar socioeconomic status among white and nonwhite patients could possibly explain the lack of association of ethnicity with damage (7–11). Due to the low number of men included, this study was underpowered to assess associations of sex with damage.

Current HCQ monotherapy was associated with the absence of damage, although no information regarding the duration of HCQ monotherapy was recorded. Therefore, we cannot be sure of a causal relationship between current HCQ monotherapy and mild disease. This is further highlighted by the lack of association of organ involvement and antiinflammatory medication use (ever) between the patients currently receiving HCQ monotherapy and other patients. Longitudinal cohort studies are necessary to further clarify this issue.

Notably, the association of damage with disease duration also reflects past and current treatment modalities. Patients with long disease duration may have developed more damage over time due to treatment strategies that are now uncommon, and more recently diagnosed patients may have had the benefit of improved treatment strategies that led to less damage. The cross-

sectional design of this study does not allow us to isolate the positive effects of improved treatment modalities from the negative effects of disease duration on the development of damage.

This is the first study assessing HRQoL in childhood-onset SLE patients after they have reached adulthood. HRQoL was reduced in most domains when compared to the overall Dutch population. Other studies in children with childhood-onset SLE and adult-onset SLE patients also showed that patients had an impaired HRQoL (21,54–56), and HRQoL scores were similar or even lower when compared to patients with other chronic illnesses (54–57). A possible explanation for the similar mental and emotional health scores of the CHILL-NL cohort as compared to those of the overall Dutch population (Figure 3) might be the development of resilience at a young age to the emotional impact of the disease, as perceived HRQoL can be affected by different styles of coping (58).

High disease activity (SLEDAI-2K  $\geq 8$ ) had a significant negative effect on HRQoL, which is supported by other studies (20,21,57,59). Interestingly, an even larger negative effect was seen with regard to factors affecting physical appearance. Indeed, 2 other studies showed that changes in physical appearance (e.g., obesity, skin involvement) were associated with reduced HRQoL (60,61). Surprisingly, in the CHILL-NL cohort, the presence of damage barely affected HRQoL, with only scores in the physical functioning domain significantly reduced. However, other studies showed a negative association of damage with HRQoL (21,52). This discrepancy might be explained by the heterogeneous nature of damage that can differ between cohorts, but also by the development of coping styles in childhood-onset SLE patients, who may have learned at an earlier age to adjust their lifestyle according to damage.

The CHILL-NL study has several strengths. It is a large cohort, and all patients were seen in person, providing the opportunity to verify disease activity and damage by laboratory analysis and physical examination. Medical records were retrieved for all patients, by which all reported outcomes were verified. The lack of studies in adults with childhood-onset SLE demonstrates the challenge in identifying patients after they transfer to adult care. Even in a report from a North American cohort that included outcomes in adult childhood-onset SLE patients, the study was not designed to specifically recruit adults with childhood-onset SLE (62). The present study describes verified disease characteristics and HRQoL in the largest cohort of childhood-onset SLE patients with very long disease duration.

The limitations of the CHILL-NL study must also be addressed. First, the number of patients who were not interested in participating in the study (and as such were not referred to the study team) was unknown. It must be noted that the patients included in this study are not a random selection of the total childhood-onset SLE population in The Netherlands. Patients from both ends of the severity spectrum (i.e. those with severe disease and those with mild disease) who do not visit a physician regularly will be missed in this cross-sectional study. Patients with high disease activity or severe damage may not have partic-

ipated in the study due to participation being seen as too taxing. To overcome this limitation, we offered to travel to the patient if they indicated that travel distance was seen as a barrier. Of the patients who were referred to the study team, the vast majority participated in the study. Second, due to the cross-sectional nature of the study, deceased patients were not included. As disease severity is a risk factor for mortality (11,50), it is possible that our study had a bias toward less severe disease. Third, data for this study were collected retrospectively, and information may have been missed. We chose only to report disease characteristics that could be verified with medical records, and no data could be collected from deceased patients. Consequently, it is likely that the results from the CHILL-NL study will underrepresent the severity of the disease. These limitations illustrate the need for longitudinal cohorts in which childhood-onset SLE patients are followed up even after they transfer to adult care (12).

In conclusion, the CHILL-NL study shows that childhood-onset SLE has a major impact on adult life. This is the first study to provide insight into the HRQoL and the development of disease manifestations and damage over time in adults with childhood-onset SLE. Childhood-onset SLE-related manifestations developed mostly within 2 years of diagnosis, with a shift to development of damage 5 years after diagnosis. Major medical complications (i.e., renal transplants, CVA, myocardial infarction) occurred at a young age. These results demonstrate the need for optimal control over disease activity and preventative screening measures (particularly cardiovascular) beginning before age 30 to facilitate a better disease prognosis. HRQoL scores of adults with childhood-onset SLE are affected by factors other than disease activity or damage alone. By identifying and addressing these factors, such as physical appearance and coping styles, HRQoL may be improved.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Ms Groot had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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