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Full title: Effects of childhood-onset SLE on academic achievements and employment in adult life

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ABSTRACT

Objective: Long-term outcome data in adults with childhood-onset SLE are limited. Here, we report the effects of cSLE on education, vocation and employment in a large cohort of adults with cSLE.

Methods: Patients were seen for a single study visit containing a structured history and physical examination. Medical records were retrieved to supplement information obtained during the study visit. Education and employment status were assessed by questionnaires. Health-related quality of life (HRQOL) was measured with the SF36.

Results: 106 cSLE patients (93% female, 73% white), with a median disease duration of 20 years, completed the visit and questionnaires. Almost all patients stated that cSLE had influenced their education, but level of completed education was similar to the general Dutch population. Half of the patients had adjusted their vocational choice due to the disease. Still, 44% of patients who had finished education did not have a paid job. Of the employed patients, 61% worked part-time. Disease damage was equally prevalent in patients with and without paid employment. A high percentage of patients (51%) were declared work disabled, which was related to damage. Patients who did not have paid employment were often work disabled. Both had a negative influence on HRQOL.

Conclusion: The effect of cSLE on academic achievements and employment is substantial, despite adjusting educational and vocational choices to the disease. Ongoing support, not only to help patients find suitable education and vocation, but also to offer guidance regarding potential adjustments during their career, is necessary to optimise participation in the community.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease with an unpredictable disease course. In 10-20% of cases, SLE presents in childhood or adolescence (1). Childhood-onset SLE (cSLE) patients have an additional burden, having to cope with the disease during adolescence, an important period in their intellectual and physical development (2-5). Aside from missing school due to hospital visits, disease-specific features such as arthritis, fatigue and central nervous system involvement can attribute to a deviation from their original academic and vocational goals.

Poor childhood health affects education, career and employment (6). Children with SLE have poorer school performance and meet fewer educational milestones than their healthy peers (4). In children with juvenile idiopathic arthritis (JIA), poor school functioning was associated with disease activity, functional disability and depressive symptoms (7). Young adults with JIA achieved similar educational levels as their healthy peers, but took longer to complete their education (8, 9).

Higher academic achievements are correlated with higher frequencies of employment in the general population (10). One cohort study of adults with cSLE reports that patients are less likely to be employed compared to patients with adult-onset SLE, despite similar educational levels (3). In adults with JIA, associations between functional disabilities, disease duration, medication use and educational and employment status were suggested (11, 12).

Chronic diseases can affect work productivity. Patients may call in sick (absenteeism), or may not be able to work as efficiently (presenteeism) due to their disease. Work productivity of patients with adult-onset SLE is often compared to the healthy working population, but has not yet been studied in adults with childhood-onset rheumatic diseases (13-15).

Health-related quality of life (HRQOL) of (c)SLE patients is impaired compared to the general population (16-18). No studies regarding the effect of employment status on HRQOL of adults with cSLE have been performed. In adults with JIA and in adult-onset SLE patients, being employed is associated with higher HRQOL (19). Receiving a disability allowance in JIA was associated with lower physical HRQOL (20).

The Childhood-onset SLE in the NetherLands (CHILL-NL) study aims to assess the burden of disease in adults with cSLE in the Netherlands. Here, we report on education, vocation and current employment status of adults with cSLE compared to the general Dutch population, and the association of employment status and work disability with HRQOL of cSLE patients.

Methods

Patients

All patients diagnosed with SLE prior to their 18th birthday, who were > 18 years and met the ACR criteria for SLE (21) were eligible for inclusion. The study was designed by the CHILL-NL study team together with a panel of 5 adult cSLE patients. Details regarding enrolment and data collection have been described previously (22). In short, all patients were seen for a single study visit. Information collected during this visit was verified and supplemented with information from medical records. Only data which could be verified in the medical records are reported. The Research Ethics Board of the Erasmus Medical Centre, Erasmus University approved this study (MEC-2013-163), written informed consent was obtained from all patients. This article focuses on educational and job histories among patients with cSLE. Data from our cohort is compared to the general Dutch population (77% white, 13% non-white)

matched for age group (23). If available, data from the female Dutch general population was used for comparison (23).

Clinical characteristics and HRQOL

Demographics, medication use, disease activity (SLEDAI-2k, (24)) and damage (Systemic Lupus Erythematosus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) (25)) at study visit were registered. High disease activity was defined as a SLEDAI-score≥8. Damage was defined SDI≥1. SLEDAI-2k domains 'ongoing inflammatory rash' and/or 'alopecia' were defined as factors affecting physical appearance (22). HRQOL was measured with the SF36 and compared to SF36 scores of the general female Dutch population (23, 26).

Education and employment

Completed level of education was categorized according to the International Standard Classification of Education (ISCED) 2011 by primary, secondary or tertiary education (27). Secondary education was defined as having finished secondary school (e.g. high school or vocational school) and tertiary education included academic education as well as advanced vocational or professional education. Patients still attending secondary or tertiary education, were classified as having finished primary or secondary education respectively. Patients were defined as students when they were currently following secondary or tertiary education. Additionally, patients were asked what the completed level of education of their parents was. Level of education was compared to the general Dutch population (23, 28). Patients were asked whether their disease had affected their educational achievements with a 'yes' or 'no' answer option and if yes, to give a comment to explain the reason(s) for this.

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Patients were asked which categories described them best: having paid employment, looking for work, doing volunteer work, homemaker (with/without children), work disabled, student, or retired. These categories were not mutually exclusive. If categories were conflicting, patients were asked to clarify. The number of hours patients with paid employment worked weekly was used to define full time (>36 hours) or part-time (≤35 hours) jobs, as in the Netherlands, a full-time job is defined as working > 36 hours (23). Employment status in our cohort was compared to the Dutch female population (23, 29).

In the Netherlands, work disability of individuals aged 18 or older is assessed during an objective process regulated by the Dutch government (30). Individual capabilities are evaluated by a physician specialized in occupational medicine. The extent to which a patient is able to work, determines the height of the disability allowance. Patients who reported to be work disabled and had a (part-time) paid job were classified as (partially) work disabled. Work disability was compared to the Dutch female population (31).

Patients were asked whether their disease had affected their career choice or working hours, and if they had to adjust work activities or change job type due to their disease. This was asked via questions with a 'yes' or 'no' answer option and the request comment to explain the reason(s). Questions from the Work Ability Index were used to assess work impairment (32, 33). Presenteeism on the most recent working day (33) and absenteeism of the last three months prior to study visit (32) due to their disease or to other circumstances were assessed.

Statistical analysis

Descriptive statistics were used to describe patient characteristics. Regarding educational achievements, employment status and work disability, data was compared to the Dutch population using χ^2 tests. Between-groups comparisons to compare HRQOL-scores in work

disability and employment, were made using the Mann-Whitney-U test (MWU). Analyses regarding the presence of damage in association with employment and work disability were done using the χ^2 test. All analyses were performed in IBM SPSS Statistics v22 (SPSS Inc, Chicago, IL, USA). Unless referenced otherwise, all data regarding the Dutch general population has been extracted from Statline, the database of the Dutch Central Bureau of Statistics (23).

Results

Patients

Of the 111 adults with cSLE were included in the national CHILL-NL study (22), 106 (96%) completed questionnaires regarding education, work participation and quality of life. Characteristics of the 5 patients who did not complete the questionnaires are described in supplementary table 1. Patient characteristics of the 106 adults with cSLE are described in table 1. Most patients were female (93%), and white (73%). Notably, the general Dutch population data to which we refer, reflects a population with 13% non-white ethnicity (23, 34). The median disease duration was 20 years. Patients generally had low disease activity (median SLEDAI 4), 61% had developed damage (SDI ≥1). Musculoskeletal, renal and neuropsychological damage were the most common items scored on the SDI. HRQOL in the CHILL-NL cohort was lower compared to the general Dutch population. Lower HRQOL was associated with high disease activity (SLEDAI-2k≥8) and changes in physical appearance. The presence of damage (SDI≥1) negatively affected HRQOL in the physical functioning domain only (22).

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Effect of cSLE on education

Almost all patients (91%) reported their education to be affected by the disease (figure 1A). Absence from school (69%) was most commonly reported, 29% of the patients were held back a year and 22% of the patients had to go to a lower level of education. Of the 11% (n=12) of patients who specified other effects of cSLE on education, three reported that education was affected by fatigue and arthralgia, two others by hospital admissions and the last five of 12 patients reported their disease had led to educational delay or they had to quit their study of choice.

Choice of secondary or tertiary education was affected in 58% of patients by the limitations of their disease (figure 1B). Five patients (5%) only completed primary education (figure 1C). Of these five patients, two had followed special education for physically and mentally handicapped children due to the disease, two had started secondary education but were not able to complete their studies. The remaining patient was in high school at the time of study visit. Sixty-seven patients (63%) had completed secondary education (e.g. high school, college, vocational education) and thirty-four (32%) tertiary education (e.g. professional or academic bachelor degree). Compared to the Dutch female population, patients had a similar educational level (χ^2-test 0.701, p=0.4024 for completing secondary education and χ^2-test 0.463, p=0. 4961 for completing tertiary education (figure 1C). An individual's educational level may be related to the educational level of the parents (35). A subset of 51 patients (48%), of whom 23 (45%) had completed tertiary education filled in a questionnaire regarding the education level of their parents. The majority of the patients had an equal (43%) or higher educational level (49%) than their parents. Educational levels of the parents were also similar to those of the general Dutch population (data not shown).

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Twenty-seven patients in the CHILL-NL cohort were students (median age 22 years, range 18-27). They were either following secondary (37%) or tertiary (63%) education. Eleven students (41%) reported to be work disabled.

Vocation

Half of the patients (58%) reported their choice of vocation to be affected by the disease (figure 2). Some specified that their desired profession was not possible due to their disease, while other patients specifically mentioned fatigue or physical complaints to affect the choices. Others reported that their choice of vocation was affected, but that they had adjusted their choice when deciding what to study. Whether patients adjusted their vocation on a similar educational level or changed to a lower level was unknown.

Employment

Students (n=27) and retirees (n=1) were excluded from analyses regarding employment. Of the remaining 78 patients (95% female), 44% (n=34) did not have a paid job. Significantly more patients with a paid job had completed tertiary education (22/44=50%) compared to patients without paid employment (6/34=18%) (χ^2-test 8.724, p=0.003). Of the employed patients (n=44), most (61%) worked part-time, but that is significantly less than the 75% of the Dutch female population (figure 3A, χ^2-test: 11.080 p=<0.001). Notably, part-time employment rate in Dutch women is very high compared to the mean part-time employment rate of 26% for women in Europe (36).The majority of unemployed patients (n=34) reported to have one or more (non-paid) occupation in daily life: 45% was a homemaker, 28% did volunteer work, and 21% took care of their children.

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More than half of the 78 patients reported that the disease had influenced work participation (figure 3B). Thirty percent of employed patients worked less hours (partially) due to their cSLE at a median age of 28 years Twenty-two percent reported to have changed their type of job due to the disease. In total, 28% of all 78 patients had quit their job partially or completely due to cSLE at a median age of 27 years. Work productivity was impaired in 52% of the employed patients, with 43% reporting absenteeism and 25% reporting presenteeism. Of the patients reporting work impairment, 39% reported that this was due to cSLE.

A substantial number of patients had developed damage, which was comparable in the employed and unemployed groups (77% versus 66%, figure 3C, χ^2-test: 1.029, p=0.310).

Work disability

Half of the 78 cSLE patients (53%) were work disabled, compared to the 3.7% work disability rate in the Dutch female population (figure 4A) (31). As expected, the proportion of work disabled patients was higher in the group without paid employment (82% versus 30% figure 4B, χ^2-test: 21.450, p<0.001). Patients who were employed despite being (partially) work disabled (n=13), worked less hours compared to the employed, non-work disabled patients (median of 20 hours versus 31 hours, MWU test: p=0.011, data not shown). Work disabled patients reported that choice of education (68% vs 46%) and vocation (76% vs 35%) had been affected by the disease more often than patients who were not work disabled χ^2-test 3.979, p=0.046 and 12.957, p<0.001 respectively).

Not surprisingly, the number of patients with damage was significantly higher in the work disabled group (81% versus 60% figure 4C, χ^2-test 4.136 p=0.042). Neuropsychiatric damage was overrepresented in the work disabled patients (χ^2-test 4.064 p=0.044). No significant

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difference in musculoskeletal (χ^2-test 2.998 p=0.083) or renal (χ^2-test 0.037 p=0.847) damage between work disabled and not-work disabled patients was found.

Influence of employment and work disability on HRQOL

Patients without paid employment reported lower HRQOL in all SF-36 domains (figure 5A, supplemental table 2). Patients who were work disabled also reported lower HRQOL in all SF-36 domains compared to patients who were not work disabled (figure 5B, supplemental table 2). As work disability is closely related to employment status, the effect of the combination of both is shown in figure 5C. Interestingly, HRQOL of work disabled patients was lower in the majority of the domains, irrespective of having a paid job or not.

Discussion

This is the first study that not only addresses academic achievement and employment in adults with cSLE, but also the self-reported influence of the disease on education and career.

Education

Almost all adults with cSLE reported that their education was hindered by the disease. Indeed, a cross-sectional study in children with cSLE showed that school attendance of most patients was negatively affected by the disease (5). Additionally, patients struggled with schoolwork, which is associated with disease activity and treatment (4, 5). Academic outcomes of patients in the CHILL-NL cohort however, were similar to the general Dutch population. In the only other cohort of adults with cSLE reporting on educational outcomes, educational levels of adults with cSLE patients were similar to patients with adult-onset SLE (3). Comparing

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educational outcomes of cSLE patients with adult-onset SLE is difficult, as adult-onset SLE patients are generally diagnosed after finishing their academic career. Although parental educational level was known for only half the cohort, level of education of patients and their parents was similar or higher. Patients may take longer to finish their education, which has been reported in adults with JIA and other chronic childhood-onset diseases as well (8, 37).

Effect of cSLE on vocation

Finding suitable education and vocation is part of the preparation of young people with chronic diseases for adult-oriented health-care systems, where they need skills to manage their disease independently. Many patients in this cohort reported that their choice of education and vocation was affected by their disease. Patients who struggle with these choices during the transition process in adolescence, need optimal support to give them the best chance to get a paid job in future (38, 39).

Recommendations for a successful transition to adult-centred care of Young People with rheumatic diseases have been formulated by the European League Against Rheumatism (EULAR) and Paediatric Rheumatology European Society (PReS) (38). Disabilities, strengths and abilities should be assessed by patients, parents and paediatrician together. Career exploration should be embedded in this transition (38).

Employment

In the CHILL-NL cohort, 44% of patients did not have a paid job. This is lower compared to the reported percentage (59%) of patients without paid employment in a Dutch adult-onset SLE cohort (93% female, mean age 38.4 years) (40). This might be because cSLE patients have had the opportunity to adjust their vocational choice. As this was reported by many patients in

the CHILL-NL cohort, they may therefore be better prepared when entering the work force. When diagnosed with SLE in adulthood, career choice is often already made and disease manifestations may prevent patients from continuing their job (3). The only other study available looking into employment in cSLE, shows conflicting data; adults with cSLE had a higher risk of not having paid employment compared to adult-onset SLE patients (3). This study was performed in the USA, local circumstances may contribute to this difference. For instance, the opportunities to work part-time and receive (partial) disability allowance may be more easily available in the Netherlands (36).

Another factor accounting for the differences in employment rate may be the educational level. Employed patients in the CHILL-NL study had completed tertiary education more often than patients without a paid job. That higher education can partly counteract the adverse effects of disease on paid employment has also been shown in adults with JIA and patients with adult-onset SLE (19, 41).

Work productivity was affected by the disease, which has also been reported in patients with adult-onset SLE (15, 42). High autonomy regarding work activities is important for maintaining paid employment (43). This holds true for SLE as well, as it has an unpredictable course. A flexible workplace with autonomy regarding working activities and opportunities to work part-time should support adults with childhood-onset chronic illnesses to remain employed (3).

Work disability and related factors

Work disability in the CHILL-NL cohort was very high compared to the general population. Although the majority of the work disabled patients did not have paid employment, several work disabled patients had a paid job. No studies of work disability in adults with cSLE are

available. In a systematic review of 26 studies in adult-onset SLE with a mean disease duration of up to 14 years, work disability was estimated to be 34%, which is lower than the 51% in the CHILL-cohort (41). Several risk factors affecting work disability have been identified in adult-onset SLE, such as presence of damage, and neuropsychiatric and musculoskeletal damage specifically (40, 44, 45). Indeed, in our cohort, damage and neuropsychiatric damage was more prevalent in work disabled patients.

HRQOL

Patients without paid employment had lower HRQOL, which is also seen in adult-onset SLE patients (15, 40). Employment status may facilitate higher HRQOL due to higher financial rewards and feelings of independence and self-worth (19). A negative effect on HRQOL was seen in work disabled patients. Being work disabled appeared to overrule the positive effect of employment on HRQOL in this group. Patients who were work disabled had damage more often. So although damage on its own hardly affected HRQOL in the CHILL-NL cohort, we speculate that specific damage may affect work disability and thereby also HRQOL. For example, cerebral infarction is more likely to affect the capacity to work than having cataract. However, our study was underpowered to perform sub-analyses on damage type and association with work disability and/or HRQOL.

Limitations

The number of patients who were not aware or not interested in the study was unknown. All included patients were cSLE survivors, patients with current high disease activity and/or damage may have found the study too taxing to participate. Our results might be an underrepresentation of the severity of cSLE and its impact on education and work

participation (46, 47). A selection bias towards patients with a high level of education cannot be excluded. As higher educational levels have been associated with higher employment rates (12), it is possible that our results are an underrepresentation of unemployed adults with cSLE. Although all data was verified with clinical records, it is possible that information was missed as data was collected retrospectively. In the questionnaires we asked whether SLE affected education, vocation and employment, and if yes, we asked for the reason why as an open question. We did not specifically ask for other (confounding) factors that could influence employment and education outcomes besides SLE.

This is a cross-sectional study in which data regarding employment is limited to current work status. Prior studies have demonstrated that SLE patients move in and out of work based on their disease status (44), which cannot be assessed for cSLE patients in this study. The intended follow-up of this cohort will help our understanding of the employment status of cSLE patients over time.

The percentage of inhabitants of the Netherlands with a non-Western background is 13% (23), which is lower than the 27% found in our cohort. Our study was underpowered to assess the effect of ethnicity on educational and vocational achievements.

The statistical tests were performed without correction for multiple testing, so it is possible that some significant results may be due to chance. Additionally, our study lacked power to perform regression analysis to adjust for possible confounders and to assess predictors of disability and unemployment.

Conclusion

Despite the large perceived effect of cSLE on education, academic achievements in adults with cSLE were similar compared to the general population. Although vocational choices were

often adjusted due to the effects of the disease, 44% of patients did not a have paid job. A high percentage of patients (51%) were work disabled, which was related to not having paid employment and the presence of damage, specifically neuropsychiatric damage. Employed patients had a higher HRQOL, but being work disabled outweighed the positive effect of employment on HRQOL. Ongoing support, to help patients find suitable education and vocation and to offer guidance regarding potential adjustments during their career is necessary, to facilitate independence and participation in our community.

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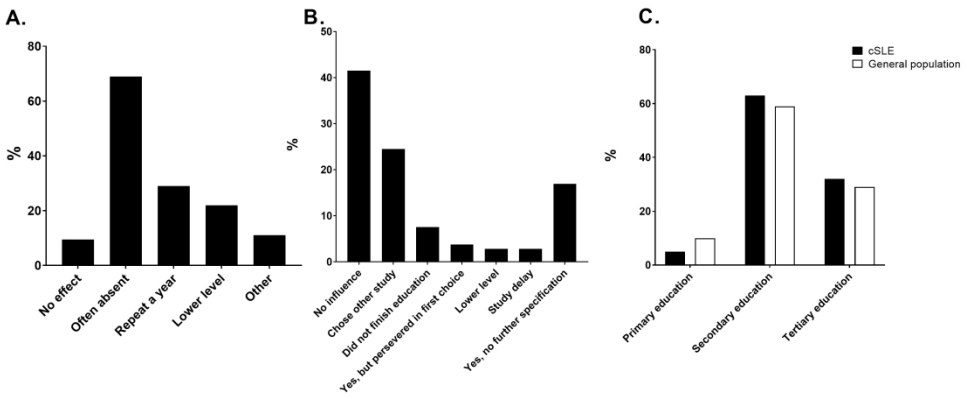

Figure 1. Effect of cSLE on education (n=106).
A: Patient-reported effects of cSLE on education in general. B: Patient-reported effects of cSLE on decision-making regarding choice of secondary/tertiary education. C: Completed level of education of cSLE patients and general population. Completed education level was classified according to the International Standard Classification of Education (ISCED) 2011 (primary, secondary or tertiary education).

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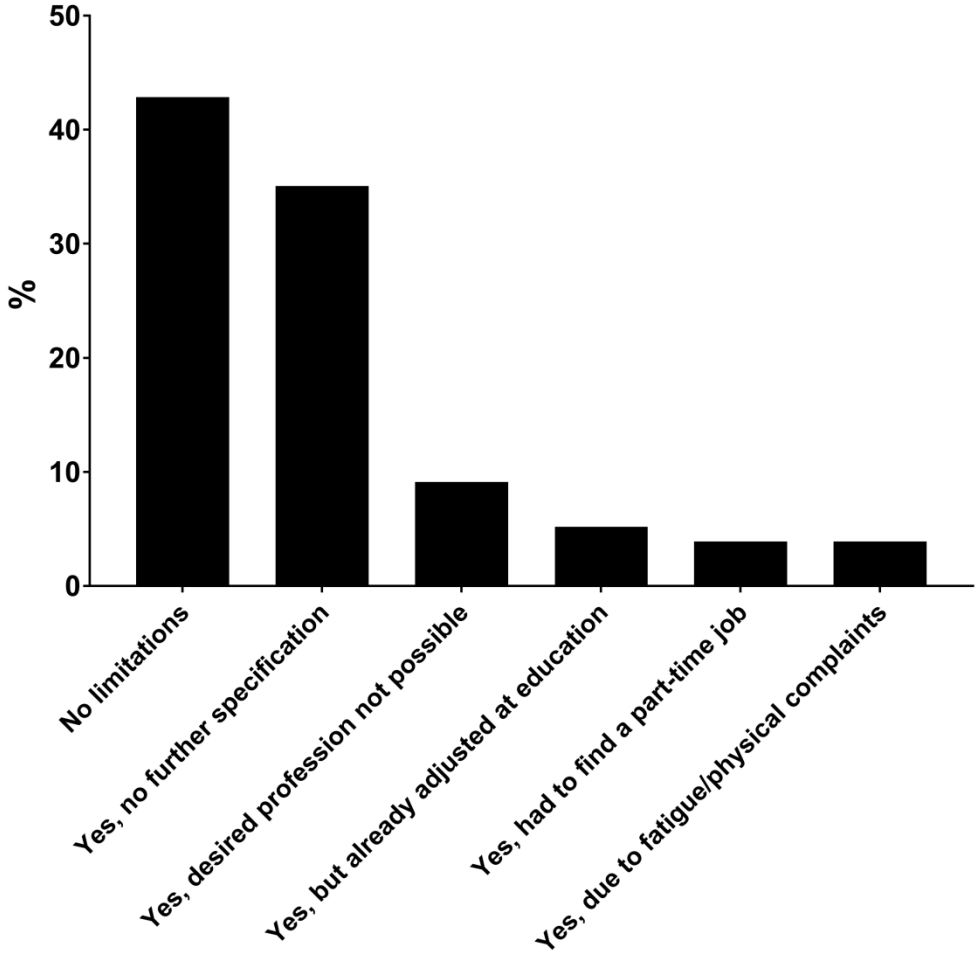

Figure 2. Patient-reported effects of cSLE on choice of vocation (n=106).
Patients were asked whether their disease affected their choice of vocation, with an option to specify in what way this was affected.

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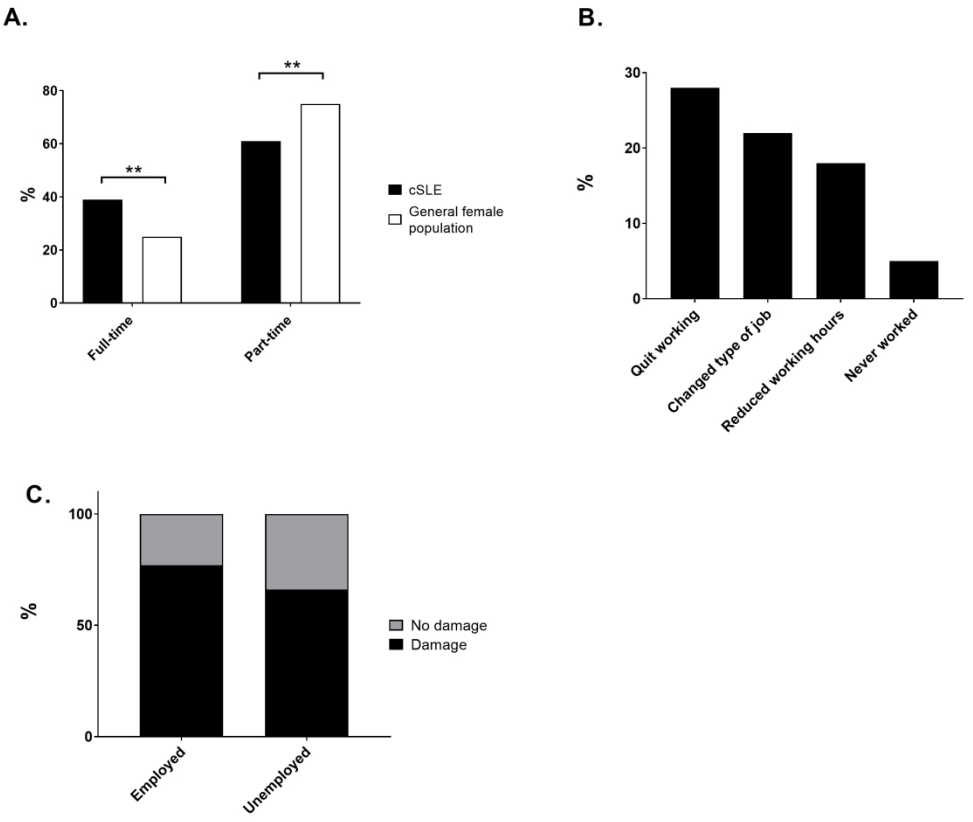

Figure 3. Effects of cSLE on employment.
A: Percentages of full-time and part-time working cSLE patients (n=44) and general female population. B. Patient-reported effects of the disease on employment (n=78). C: Presence of damage in patients with and without paid employment (n=78).
**p<0.01 with χ^2-test

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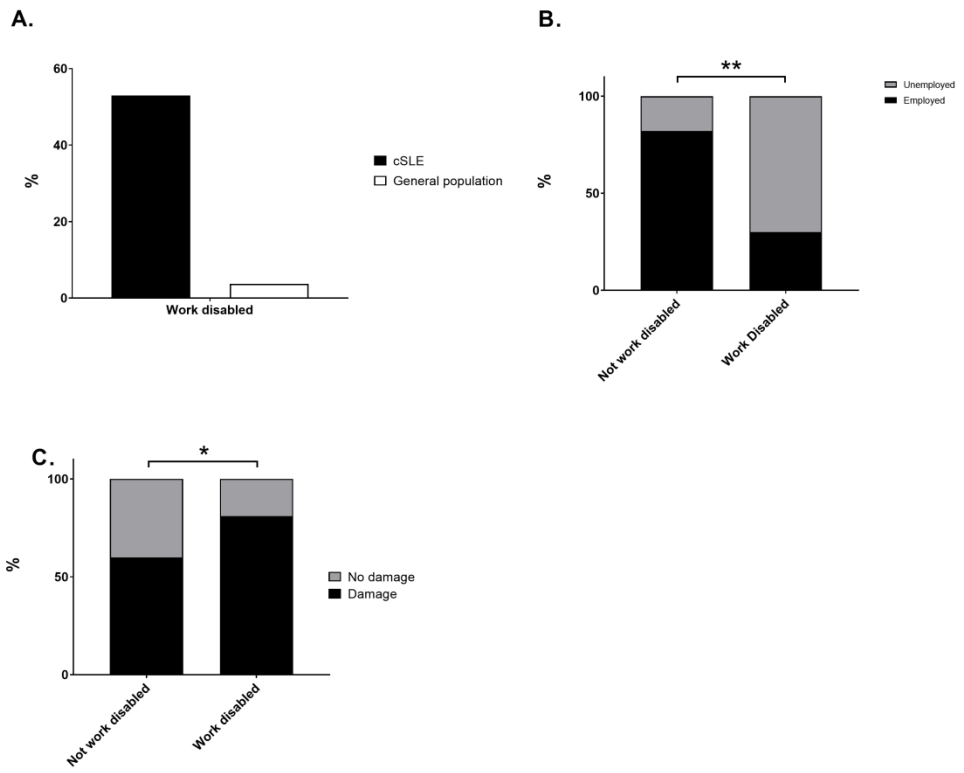

Figure 4. Work disability in cSLE patients and the relation with employment status and disease damage (n=78).
A. Work disability in patients compared to the general Dutch population. B Employment status of not work disabled (n=37) and work disabled (n=41) patients. C. Presence of damage in not work disabled (n=37) and work disabled (n=41) patients.
*p<0.05; **p<0.01 with χ^2-test

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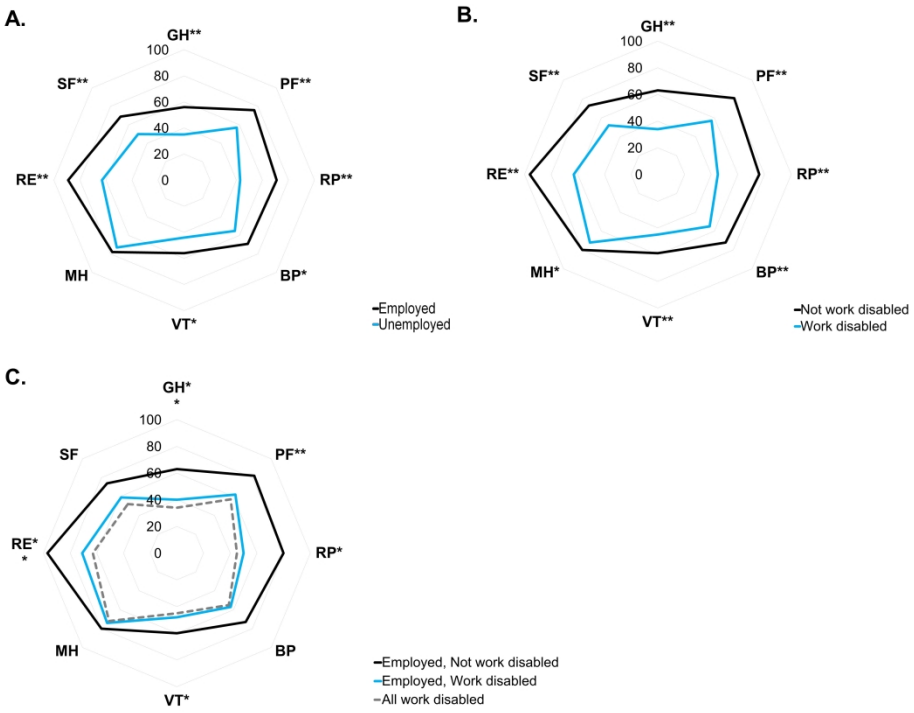

Figure 5. HRQOL in cSLE patients related to employment and work disability (n=78).
HRQOL is expressed as mean Short Form 36 (SF-36) health survey scores per domain. Spiderplots show mean scores within each domain of the SF-36, ranging from 0 (worst) to 100 (best).
A: SF-36 scores of unemployed and employed cSLE patients. B: SF-36 scores of work-disabled cSLE patients and non-work disabled patients. C: SF-36 scores L of employed cSLE patients who were work disabled, compared to SF-36 scores of employed patients who were not work disabled.
*p<0.05; **p<0.01 with Mann-Whitney U test
Abbreviations: GH: General Health Perception; PF: Physical Functioning; RP: Role limitations due to Physical problems; BP: Bodily Pain; VT: Vitality; MH: Mental Health; RE: Role limitations due to Emotional problems; SF: Social Functioning; cSLE: childhood-onset Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

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Table 1. Cohort characteristics

Patient characteristics (n=106)	
Female (n, %)	98 (93%)
Ethnicity *(n, %)*	
White	77 (73%)
Non-white	29 (27%)
Age at study visit *(median, range in years)*	33 (18 – 65)
Age at diagnosis *(median, range in years)*	14 (4 – 17)
Disease duration *(median, range in years)*	20 (1 – 55)
Current corticosteroid and DMARD use *(n, %)*	71 (67%)
Corticosteroids + DMARD *(n, %)*	38 (36%)
Corticosteroids only *(n, %)*	16 (15%)
DMARD only *(n, %)*	17 (16%)
Current HCQ use *(n, %)*	72 (68%)
HCQ + DMARD/corticosteroid *(n, %)*	51 (48%)
HCQ only *(n, %)*	21 (20%)
SLEDAI-score *(median, range)*	4 (0-16)
SDI-score *(median, range)*	1 (0 – 8)
SDI ≥1 *(n, %)*	65 (61%)

Abbreviations and definitions: DMARDs: disease-modifying anti-rheumatic drugs (i.e. azathioprine, ciclosporine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, rituximab, tacrolimus); HCQ: hydroxychloroquine; SLEDAI:

Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (36)