

Determinants of health-related quality of life across the spectrum of connective tissue diseases using latent profile analysis

Dyball, Sarah; Reynolds, John; Herrick, Ariane; Haque, Sahena; Chinoy, Hector; Bruce, Ellen; Naz, Sophia; Parker, Ben; Bruce, Ian

DOI:

[10.1093/rheumatology/keac680](https://doi.org/10.1093/rheumatology/keac680)

License:

Creative Commons: Attribution (CC BY)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Dyball, S, Reynolds, J, Herrick, A, Haque, S, Chinoy, H, Bruce, E, Naz, S, Parker, B & Bruce, I 2022, 'Determinants of health-related quality of life across the spectrum of connective tissue diseases using latent profile analysis: results from the LEAP cohort', *Rheumatology*. <https://doi.org/10.1093/rheumatology/keac680>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Clinical science

Determinants of health-related quality of life across the spectrum of connective tissue diseases using latent profile analysis: results from the LEAP cohort

Sarah Dyball ^{1,2}, John A. Reynolds ^{3,4}, Ariane L. Herrick ^{5,6}, Sahena Haque⁷, Hector Chinoy ^{1,5,6}, Ellen Bruce², Sophia Naz⁸, Ben Parker^{2,5}, Ian N. Bruce ^{1,2,5*}

¹Centre for Epidemiology Versus Arthritis, Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

²Kellgren Centre for Rheumatology, Manchester University Hospitals NHS Foundation Trust, Manchester, UK

³Rheumatology Research Group, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

⁴Rheumatology Department, Sandwell and West Birmingham NHS Trust, Birmingham, UK

⁵National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, University of Manchester, Manchester, UK

⁶Department of Rheumatology, Salford Care Organisation, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK

⁷Department of Rheumatology, Manchester University Foundation Trust, Wythenshawe Hospital, Manchester, UK

⁸Department of Rheumatology, Pennine Acute Hospitals NHS Trust, Manchester, UK

*Correspondence to: Ian N. Bruce, Centre for Epidemiology Versus Arthritis, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PL, UK. E-mail: ian.bruce@manchester.ac.uk

Abstract

Objectives: Poor health-related quality of life (HRQoL) is well recognized in patients with CTD. We hypothesized that subgroups of patients across the spectrum of CTD experience different HRQoL patterns and aimed to determine patient-level characteristics associated with these different subgroups.

Methods: Using the eight continuous domains of the Medical Outcomes Study 36-item Short Form (SF-36) questionnaire we performed data-driven clustering to derive latent profiles (LPs) of patients with distinct HRQoL patterns. Multivariable ordinal logistic regression was used to determine patient-level characteristics associated with each HRQoL subgroup identified.

Results: A total of 309 CTD patients completed the SF-36 questionnaire. The most impaired SF-36 domains in each disease group were vitality, general health and bodily pain. The physical component of the SF-36 was consistently more impaired compared with the mental component, with similar scores across disease groups. Three LPs were identified with poor [$n = 89$ (29%)], average [$n = 190$ (61.4%)] and excellent [$n = 30$ (9.7%)] HRQoL. LPs were not associated with diagnostic grouping or autoantibody profiles. Black background [odds ratio (OR) 0.22 (95% CI 0.08, 0.63)], Indo-Asian background [OR 0.39 (95% CI 0.19, 0.78)], concomitant fibromyalgia [OR 0.40 (95% CI 0.20, 0.78)], sicca symptoms [OR 0.56 (95% CI 0.32, 0.98)] and multimorbidity [Charlson Comorbidity Index; OR 0.81 (95% CI 0.67, 0.97)] were associated with the 'poor' HRQoL LP.

Conclusion: Distinct HRQoL subgroups exist that are not primarily driven by a specific diagnosis or autoantibody profiles. We identified a number of key demographic and clinical factors associated with poor HRQoL. These factors need to be addressed across the whole CTD spectrum as part of a holistic management approach aimed at improving overall patient outcomes.

Keywords: QoL, SLE, UCTD, PROMS, SF-36

Rheumatology key messages

- CTD patients can be clustered into distinct HRQoL subgroups that are not driven by diagnosis.
- Ethnicity, smoking, multimorbidity and sicca syndrome are key clinical predictors of poor HRQoL.
- These factors should be addressed across the whole CTD spectrum as part of holistic management.

Introduction

Health-related quality of life (HRQoL) is a multidimensional concept representing an individual's perception of health,

encompassing spiritual, functional, physical, emotional and social well-being. Reduced HRQoL in CTDs, also known as systemic autoimmune rheumatic diseases, is likely

Received: 12 September 2022. Accepted: 24 November 2022

© The Author(s) 2022. Published by Oxford University Press on behalf of the British Society for Rheumatology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

multifactorial and may relate to organ damage and physical disability, medication adverse events, mental health and pain, as well as impaired work-related productivity and social functioning. Major goals of managing patients with a rheumatic disease are to minimize functional loss and damage, maintain independence and preserve HRQoL [1, 2].

Poor HRQoL is recognized in patients with established CTDs, however, it is unclear how it affects patients with UCTD, which has traditionally been associated with a 'mild' or more benign profile [3, 4]. The Medical Outcomes Study 36-item Short Form (SF-36) questionnaire is the most commonly used, comprehensive and generic HRQoL measure and has been validated in rheumatic diseases including SLE, SSc, idiopathic inflammatory myopathies (IIMs) and primary SS (pSS) [5–9].

Latent profile analysis (LPA) is an exploratory, data-driven, statistical method for grouping individuals based on shared features, but it is a novel approach in research of HRQoL in rheumatic diseases. Current research into HRQoL among patients with CTDs has predominately looked at factors associated with HRQoL in a single disease or performed a comparison of several rheumatic diseases; however, there have been no studies investigating whether across CTDs there are subgroups of patients who have shared HRQoL profiles. LPA can identify subpopulations within a group of individuals based on a number of variables [10]. This method lends itself to the multidimensional nature of HRQoL by allowing us to identify whether there are distinct groups of people with similar patterns of QoL responses in terms of the domains affected. This can identify those individuals who are most in need of intervention or areas to target to improve HRQoL.

We hypothesized that subgroups of patients across the spectrum of CTDs experience different HRQoL patterns, irrespective of their clinical diagnosis. Our objectives were to investigate HRQoL in patients affected with a variety of CTDs (including UCTD) using the SF-36, to identify subgroups of patients who experience shared HRQoL patterns across a CTD diagnosis and to determine patient-level characteristics associated with different subgroups of HRQoL identified.

Patients and methods

Study population

Between May 2014 and June 2019, adult patients were recruited into the Lupus Extended Autoimmune Phenotype (LEAP) cohort from Manchester University NHS Foundation Trust (three sites) and the Northern Care Alliance NHS Foundation Trust (two sites). Patients with an established CTD diagnosis and clinically stable disease were eligible for inclusion if they had one or more clinical feature of a CTD and one or more antibody within the ANA spectrum. Autoantibodies were measured historically, according to physician discretion, but all included the BioPlex 2200 ANA Screen [11]. Rheumatologist diagnosis was used to classify patients into four groups: SLE, pSS, UCTD and those with IIM, SSc or an overlap syndrome including MCTD (combined due to low numbers in these CTD subtypes).

Ethical approval was obtained from the Greater Manchester East Research Ethics Committee (13/NW/0564), all patients signed written informed consent and the study was conducted in accordance with the Declaration of Helsinki.

Measurement of HRQoL

The SF-36 version 2 QoL questionnaire was completed at enrolment and includes eight domains: physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH), with scores ranging from 0 to 100, with higher scores reflecting better HRQoL. The physical component summary (PCS) and mental component summary (MCS) scores were calculated for each group, with a score <50 representing a worse HRQoL compared with the general UK population [12]. All patients completed the SF-36 questionnaire and missing values were imputed using methodology suggested by the SF-36 manual [13].

The European Quality of Life 5-dimension 3-level (EQ-5D-3L) questionnaires were completed in a subgroup of the cohort (those recruited after 20 June 2016) concurrently with the SF-36 questionnaire. The EQ-5D-3L is a generic HRQoL measure that can be used for cost-effectiveness studies across diseases [14, 15]. The EQ-5D-3L index score ranges from 1 (full health) to <0 (worse than being dead) and is calculated from five descriptive questions that encompass five domains of HRQoL: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EuroQol visual analogue scale (EQ-VAS) reports self-rated health (score range 0–100) from 'worst imaginable health state' to 'best imaginable health state'.

Covariates

Demographic factors, smoking status, medical records-confirmed comorbid conditions and previous rheumatic therapies were recorded. Comorbidities were categorized using the Charlson Comorbidity Index (CCI) [16]. Missing data were collected where possible from patient records.

IFN-stimulated gene (ISG) scores

ISG scores were calculated as previously described using a six-gene reverse transcription quantitative polymerase chain reaction (RT-qPCR) analysis [17]. The mean ISG was calculated using data from healthy controls, with scores >2 s.d. above the mean calculated and scores above this value (>2.466) designated as positive.

Statistical analysis

Descriptive statistics were calculated using Stata version 14 (StataCorp, College Station, TX, USA) and R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria) using Kruskal–Wallis or chi-squared testing to compare across the four disease groups, unless specified otherwise. Spearman's r was used to assess correlation. Univariate linear and logistic regression models were used with SLE as the referent group. Multivariable models included all covariates with a P -value <0.1 unless otherwise specified. A P -value <0.05 was considered statistically significant.

LPA models

LPA is a statistical method for identifying homogeneous subgroups of individuals based on a set of continuous measured variables. Classification of individuals into latent classes is probabilistic and LPA allows for selection of the optimum numbers of classes, through comparison of model fit indices. Using the eight continuous domains of the SF-36 questionnaire, we used the *mclust* model-based clustering package in

R version 4.0.4 to implement a more generalized version of LPA to identify clusters of patients who experienced distinct HRQoL patterns [18]. In all models, variances were equated and covariances fixed to zero. We used the Bayesian Information Criteria (BIC), Integrated Completed Likelihood (ICL) criterion and bootstrap sequential likelihood ratio test (LRT) to compare fits of models with different covariance structures and numbers of LPs. Demographic, clinical and serological variables were compared between clusters. Further details of LPA methods are given in [Supplementary Data S1](#), available at *Rheumatology* online.

Predicting LP membership

Multivariable ordered logistic regression models were used to determine whether patient-level characteristics were significantly associated with LP membership, with the lowest HRQoL LP (LP1) as the referent group. The proportional odds assumption was tested using the Brant test and maximum likelihood ordered logit estimation [19]. Multicollinearity was tested using the variance inflation factor (VIF).

Results

Baseline demographics

Data were collected from 309 patients {280 (90.6%) women, median age 51 years [interquartile range (IQR) 40–59]}: 237 (76.7%) patients were Caucasian, 46 (14.9%) were of Black background and 18 (5.8%) were of Indo-Asian background. By rheumatologist diagnosis, 115 (37.2%) had SLE, 56 (18.1%) had pSS, 72 (23.3%) had UCTD and 66 (21.4%) had SSc-IIM spectrum disorder; this fourth group consisted of 25 patients with SSc, 28 with an overlap syndrome and 13 with IIM. [Supplementary Table S2](#), available at *Rheumatology* online, reports the demographic data of patients with SSc, IIM and overlap syndromes.

Patients with an SSc-IIM spectrum disease or pSS were older than those with SLE. Disease duration differed across diagnostic groups (kwallis, $P < 0.001$), with the longest disease duration being in patients with SLE [median 11.0 years (IQR 5.4–18.0)]. There were 101 (32.7%) patients with a CCI score of zero, 150 (48.5%) patients with a score of 1–2 and 58 (18.8%) patients with a score >3 . The most common chronic comorbidities included reflux disease [$n = 48/309$ (15.5%)] thyroid disease [46/309 (14.9%)] and respiratory disease [42/309 (13.6%)]. Peptic ulcer disease and respiratory disease were most common in SSc-IIM spectrum disease [14/66 (21%) and 16/66 (24%), respectively] as shown in [Supplementary Table S3](#), available at *Rheumatology* online. There were 42 (13.6%) patients with coexisting fibromyalgia, 25 (8.1%) with hypermobility and 20 (6.5%) with anxiety or depression. The rate of fibromyalgia was highest in pSS [$n = 11/56$ (20%)] and hypermobility was greatest in UCTD [$n = 10/72$ (15%)]. Patients with SSc-IIM disease had the lowest rates of anxiety and depression [$n = 2/66$ (3%)].

Prior oral steroid and immunosuppressant use was highest in SLE (82% and 59%, respectively) and SSc-IIM spectrum disease (59% and 52%, respectively). A proportion of patients from all disease groups had been prescribed biologic therapies, but this was highest in SLE and SSc-IIM spectrum disease (12% and 6%, respectively). Antihypertensive use was similar across diseases in approximately one-third of patients [$n = 101/309$ (33%)], whereas statin use was most

common in SLE [$n = 21/103$ (18%)] and least common in SSc-IIM disease [$n = 6/66$ (9%)]. [Table 1](#) shows the main demographic, clinical and therapeutic characteristics by disease group.

HRQoL scores by diagnosis

The eight domains of the SF-36 questionnaire are shown by diagnostic group in [Fig. 1](#) and the most impaired domains in each disease group were VT, GH and BP. When comparing medians across groups ([Supplementary Table S4](#), available at *Rheumatology* online), VT was significantly lower in patients with UCTD and pSS compared with SLE and IIM/SSc (kwallis, $P = 0.005$) and BP, which was higher in SLE, UCTD and pSS compared with IIM/SSc (kwallis, $P = 0.047$).

The PCS and MCS scores (calculated from the eight SF-36 domains) by diagnosis group are shown in [Fig. 2A and B](#). The PCS was more impaired compared with the MCS, with similar scores across disease groups. There was wide variation in both the PCS and MCS scores across diseases. In particular, there were a significant number of patients from each disease group exhibiting MCS scores that were higher, in line or lower than the general population. The majority of patients had a PCS score lower than the average UK population.

EQ-5D scores by diagnosis

EQ-5D scores were available in 174/309 (56.3%) patients in this cohort and are summarized in [Fig. 2C and D](#). Pain, usual activity and mobility were the most significantly impaired domains of the EQ-5D, shown in [Supplementary Fig. S7](#), available at *Rheumatology* online. The EQ-5D index score was lower in the pSS group compared with SLE [$\beta = -0.14$ (95% CI $-0.26, -0.01$), $P = 0.038$] but was otherwise similar between groups. The EQ-VAS was not significantly different between disease groups. The SF-36 PCS correlated well with EQ-5D index score ($r = 0.689$, $P < 0.0001$) and less strongly with the EQ-VAS ($r = 0.420$, $P < 0.0001$). The MCS also correlated more strongly with the EQ-5D index score ($r = 0.601$, $P < 0.0001$) than with the EQ-VAS ($r = 0.396$, $P < 0.0001$).

LPA

HR-QoL did not differ significantly across diagnostic groups ([Fig. 2](#)), however, there was wide intragroup variation, suggesting hidden groups across diseases. An LP approach was taken that identified three HRQoL LPs ([Fig. 3](#)). The profiles had mean overall MCS scores of 34.8 (s.d. 9.0), 50.3 (s.d. 8.4) and 56.5 (s.d. 5.1), respectively, and mean PCS scores of 21.7 (s.d. 9.0), 31.6 (s.d. 11.3) and 51.5 (s.d. 4.2), respectively. LP1 [$n = 89$ (29%)] had the poorest HRQoL scores across all domains and was considered the 'poor' HRQoL profile. LP3 [$n = 30$ (10%)] had the highest HRQoL scores across domains and is considered the 'excellent' HRQoL LP. LP2 [$n = 190$ (61%)] had intermediate physical and mental well-being and was considered the 'average' HR-QoL profile. LPs were not associated with diagnostic groupings ([Table 2](#)).

The LP matched the EQ-5D index and VAS scores. The median EQ-5D index score was 0.52 (IQR -0.02 – 0.65) in LP1, 0.69 (0.62–0.80) in LP2 and 1.0 (0.80–1.0) in LP3. The median VAS was 50 (IQR 35–65), 70 (46.5–80) and 89 (82–90) in each LP, respectively.

Predicting latent profile membership

An ordinal logistic regression model was used, as the proportional odds assumption was met (Brant test $P = 0.474$,

Table 1. Baseline demographics of the four diagnostic groups

Characteristics	SLE (<i>n</i> = 115)	pSS (<i>n</i> = 56)	UCTD (<i>n</i> = 72)	SSC/IIIM/overlap (<i>n</i> = 66)
Age, years, median (IQR)	47 (34–54)	55.5 (44.5–60.5)	47.5 (37–58)	57.5 (50–64)
Female, <i>n</i> (%)	106 (92.2)	53 (94.6)	61 (84.7)	60 (90.9)
Disease duration, years, median (IQR) (<i>N</i> = 298)	11.0 (5.4–18.0)	3.7 (2.5–8.0)	3.8 (1.8–7.3)	6.1 (2.9–14.0)
Ethnicity, <i>n</i> (%)				
Caucasian	88 (76.5)	47 (83.9)	48 (66.7)	54 (81.8)
Indo-Asian	7 (6.1)	5 (8.9)	4 (5.6)	2 (3.0)
Black	17 (14.8)	3 (5.4)	17 (23.6)	9 (13.6)
Other	3 (2.6)	1 (1.8)	3 (4.2)	1 (1.5)
BMI, kg/m ² , median (IQR) (<i>N</i> = 304)	26.9 (22.6–32.0)	29 (25.4–32.0)	28.5 (23.8–32.4)	28 (23.6–32.8)
Currently smoke, <i>n</i> (%) (<i>n</i> = 306)	10 (8.7)	4 (7.1)	8 (11.1)	4 (6.1)
Fibromyalgia, <i>n</i> (%)	14 (12.2)	11 (19.6)	9 (12.5)	6 (9.1)
Anxiety, <i>n</i> (%)	6 (5.2)	2 (3.6)	3 (4.2)	1 (1.5)
Depression, <i>n</i> (%)	8 (7.0)	4 (7.1)	3 (4.2)	1 (1.5)
CCI, mean (s.d.)	1.2 (1.3)	1.4 (1.1)	1.2 (1.4)	1.8 (1.2)
Medications (ever), <i>n</i> (%)				
Oral steroids (<i>N</i> = 306)	94 (81.7)	19 (33.9)	25 (34.7)	34 (51.5)
Immunosuppressants (<i>N</i> = 300)	68 (59.1)	15 (26.8)	22 (30.6)	34 (51.5)
Biologic therapy (<i>N</i> = 302)	14 (12.2)	1 (1.8)	3 (4.2)	4 (6.1)

N represents the total number of patients with data for this variable if complete data not available.

likelihood ratio test $P=0.539$) and multicollinearity was deemed to not be an issue (VIF range 1.02–1.15).

Gender, age and disease duration were not associated with the HRQoL LP subgroup (Table 3). The poor HRQoL subgroup was associated with Black and Indo-Asian background, multimorbidity (defined using the CCI) and smoking. Sicca symptoms, but not a diagnosis of pSS or anti-Ro/La antibodies, were associated with being in the poor HRQoL LP subgroup. Steroid, immunosuppressant and biologic therapies were not associated with LP membership.

ISGs

ISG analysis was performed in 159/309 (51.5%) patients; 58/159 (36.5%) patients had a positive ISG score. There was no association between the ISG score and either the MCS or PCS. There was no association between the ISG score and LP group.

Discussion

In this mixed cohort of patients with CTD, there were no clear differences in HRQoL between different CTD diagnoses. Patients with UCTD had comparable HRQoL to patients with other CTDs. Overall, the physical components of HRQoL were consistently more impaired than the mental components. Due to the wide variation in scores across CTD diagnoses, we hypothesised that HRQoL subgroups exist independently of CTD diagnosis. Our LP analysis identified three LPs that we termed poor, average and excellent HRQoL LP; again, these LPs were not associated with diagnostic grouping. As far as we are aware, this study is the first to apply LP analysis to HRQoL outcomes in patients with a CTD.

It is clinically pertinent to rheumatologists who review the full spectrum of patients to recognize that similar factors drive HRQoL irrespective of diagnosis. Patients who were of Black or Indo-Asian background, had sicca syndrome, smoked or had multimorbidity were more likely to be in a lower HRQoL LP. Understanding which patient-level characteristics might be most associated with poor HRQoL LP membership across CTD diagnoses may help stratify patients most likely to benefit from HRQoL management strategies. Furthermore, some

modifiable patient factors such as obesity and smoking status were identified as being associated with membership in a poorer HRQoL LP and could be addressed to potentially improve HRQoL.

HRQoL measurements are used in randomized controlled trials (RCTs) to determine treatment efficacy, in observational studies, as well as increasingly in clinical practice to understand the impairment in an individual patient. In landmark RCTs enrolling CTD patients, patient-reported outcome measures (PROMs), including the SF-36 and EQ-5D, are commonly used secondary outcomes [20–23], and in pSS the EULAR Sjögren's Syndrome Patient Reported Index has been used as a primary outcome measure [24]. The US Food and Drug Administration recommends that PROMs should be used to assess efficacy in clinical trials [25], and the OMERACT group has recommended that HRQoL assessments should be considered a core measurement in RCTs [26].

Previous studies have shown that patients with a CTD have a lower HRQoL compared with the general population, as well as other chronic diseases such as diabetes and congestive heart failure [27, 28]. A major contributor to reduced HRQoL compared with the general public is the CTD diagnosis itself; in RA, worry about the consequences of illness has been shown to be a stronger correlate of physical HRQoL than pain [29]. HRQoL is complex and multifactorial. In CTDs, both physical health (e.g. disability, loss of function, pain and fatigue) and psychosocial health (e.g. fear for the future, depression and anxiety, loss of role and reduced participation in social and work-related activities) may be affected. This is the first study to show that UCTD has a PCS and MCS score in keeping with other CTDs. In this cohort, patients with UCTD were more likely to be from a non-White background or to smoke, both of which were associated with reduced HRQoL. Furthermore, we would suggest that the uncertainty around this diagnosis, and lack of understanding from support networks, may also play a role in reducing HRQoL, in line with other CTDs. There may be a disconnect in the agenda between what is important for the patient and what is important for the clinician, e.g. fatigue, pain and cognitive dysfunction are commonly reported as the most



Figure 1. Radar diagrams of the SF-36 score in each CTD diagnostic group ranging from 0 (worst) to 100 (best) in each of the eight HRQoL domains

disabling symptoms for patients with a CTD, which are highly prevalent in patients with UCTD and may in part explain their poor HRQoL [30–35]. Furthermore, the invisibility of these symptoms to healthcare professionals, as well as society more widely, generates an additional challenge of feeling ‘disbelieved’ [36].

There were differences in the ethnic backgrounds of patients in each HRQoL profile but no difference in other demographic variables. The relationship between ethnicity and HRQoL is complex. Patients with Black and Indo-Asian ethnicity are more likely to have more severe disease and worse outcomes [37–39]. Furthermore, HRQoL is influenced by health inequalities, which disproportionately affect patients from ethnic minority groups, including secure employment, education level and economic status [40].

Fibromyalgia commonly manifests with non-specific pain and fatigue, and often coexists in patients with CTDs, making it difficult to disentangle from damage and CTD-related disease activity [41–43]. Furthermore, chronic pain and fatigue are often a barrier to exercise, which can improve mood and HRQoL. Further work is required to understand how early intervention with physical therapy, in conjunction with psychological and pharmacotherapies where appropriate, may improve HRQoL in these groups.

Comorbidity, in particular multimorbidity, has previously been shown to be associated with poorer HRQoL [44, 45]. As we move toward managing an ageing, multimorbid population, we should be aware of the complex health needs of this population and the link between multimorbidity and HRQoL.

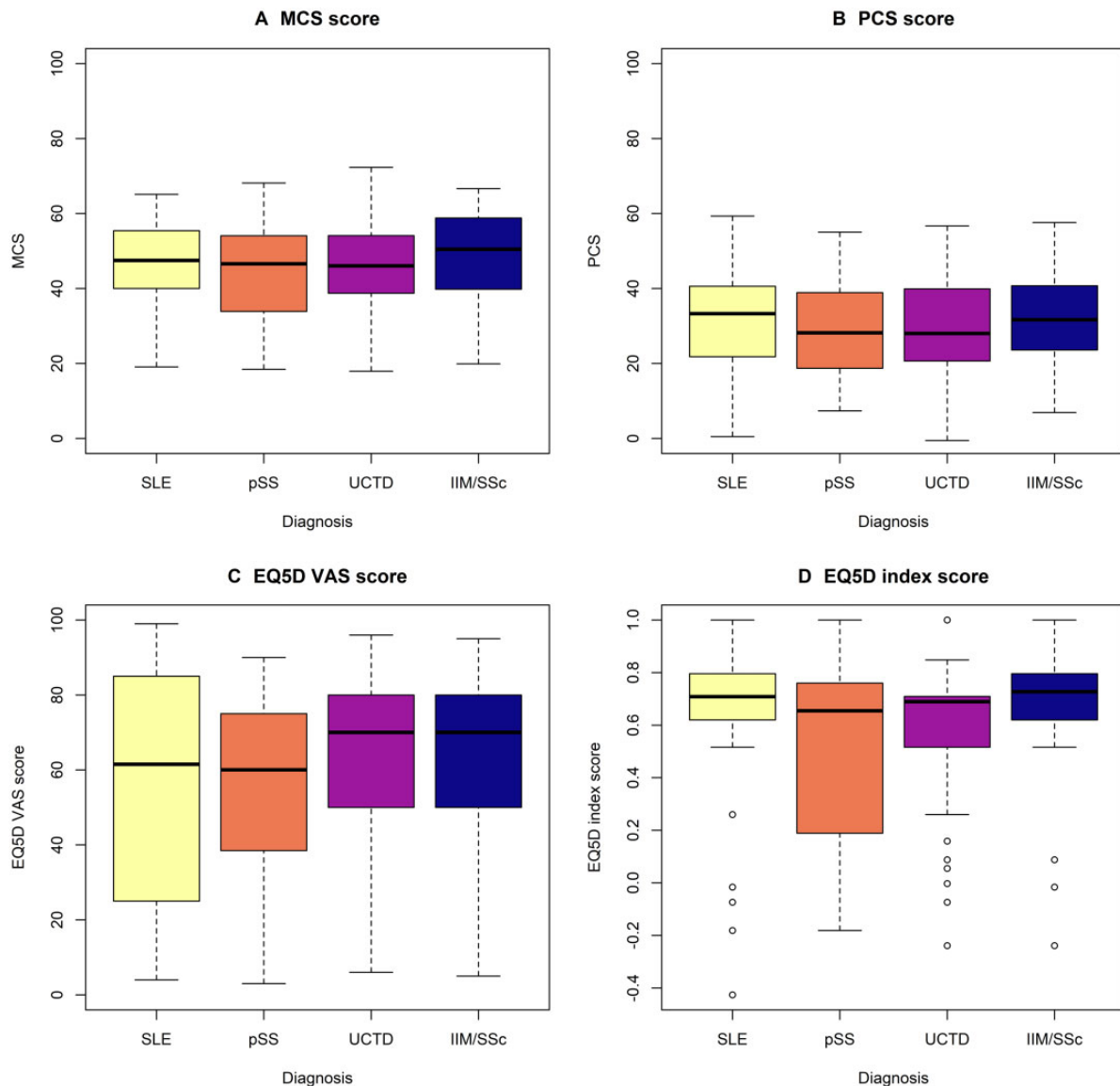


Figure 2. (A) MCS, (B) PCS, (C) EQ-VAS and (D) EQ-5D index score across four diagnostic groups

All pSS patients and one-third of patients with other clinical diagnoses exhibited sicca syndrome in this cohort, which includes a proportion of patients from each diagnostic group. Sicca syndrome, but not pSS or anti-Ro antibodies, were associated with poor HRQoL. Both xerophthalmia and xerostomia may be underappreciated by clinicians, in part because they are difficult to treat, however, they can be disabling to patients and associated with negative health outcomes [30, 46]. Xerostomia is associated with a susceptibility to dental caries and periodontal disease, increases the incidence of oral candidiasis and ulceration and causes difficulties in chewing and swallowing and changes in taste perception that contribute to impaired HRQoL [47, 48]. Interestingly, although HRQoL is reduced in SS patients when compared with healthy controls, no difference was seen when compared with non-SS sicca patients [49–51], suggesting that dryness itself plays an important role in HRQoL.

Due to the ‘mixed’ nature of this cohort, no formal disease activity scores were collected. Anti-dsDNA and low complement are serological indicators of high disease activity in SLE

and may be associated with a higher HRQoL LP. The ISG was measured as a molecular biomarker and potential treatment target that is prevalent across patients with CTDs, however, it did not correlate with HRQoL scores. This is in line with previous studies that showed fatigue severity does not correlate with inflammatory cytokines, including IFN [33].

CTDs frequently share common clinical manifestations, immunopathology and medications; e.g. type 1 IFN has previously been implicated across all diagnostic groups in this cohort [17]. Directly targeting molecular pathology in biomarker-positive patients could revolutionize drug development by improving response to therapy, and if regulatory approval was sought across diseases, it would benefit overlap conditions or undifferentiated diseases that would be traditionally excluded from clinical trials. A limitation of a basket trial approach includes the difficulty of measuring disease-specific outcomes in a mixed population. This analysis has demonstrated that outcomes can be measured across CTDs with distinct profiles of patients existing beyond their

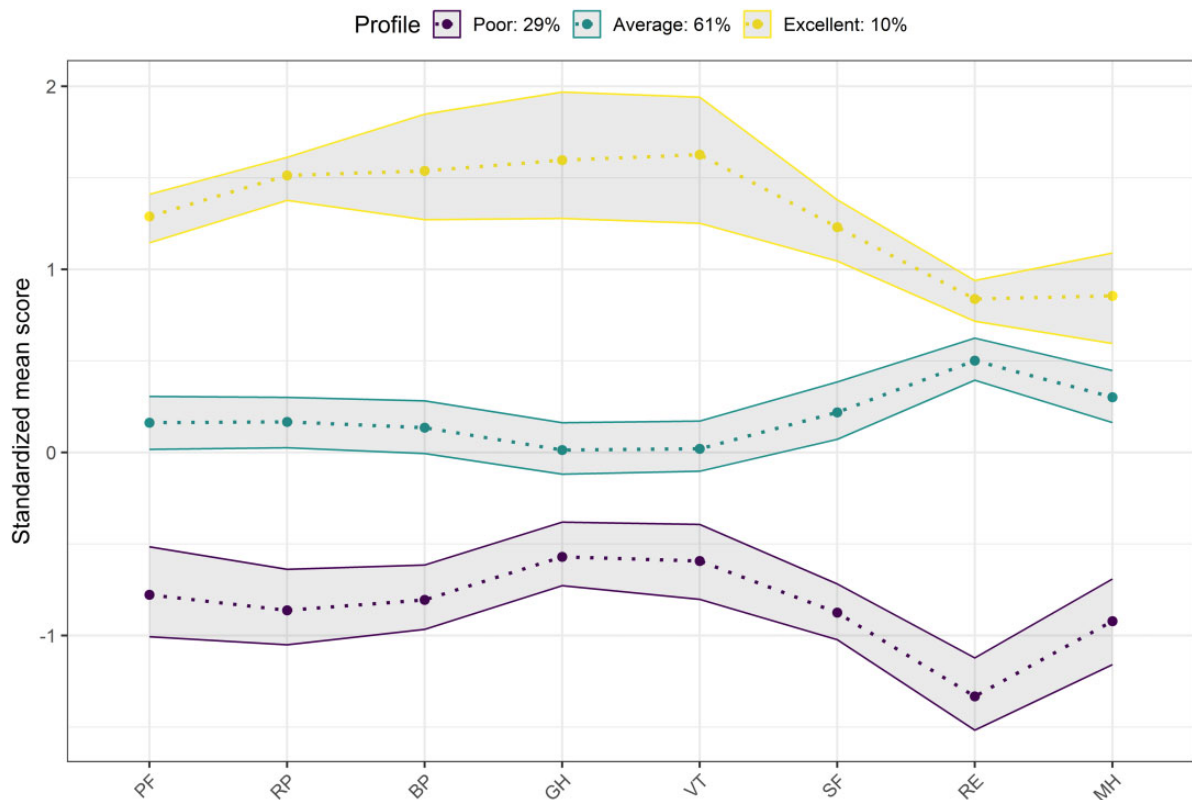


Figure 3. The three LPs graphically represented by mean SF-36 domain scores and 95% CI. LP1 (poor, *n* = 89 (29%); LP2 (average), *n* = 190 (61%); LP3 (excellent), *n* = 30 (10%)

Table 2. Membership of the three LPs by each clinical diagnostic group

Diagnosis	Poor (LP1) [<i>N</i> = 89 (29%)]	Average (LP2) [<i>N</i> = 190 (61%)]	Excellent (LP3) [<i>N</i> = 30 (10%)]	Overall [<i>N</i> = 309 (100%)]	<i>P</i> -value
SLE	29 (32.6)	76 (40.0)	10 (33.3)	115 (37.2)	0.440
pSS	21 (23.6)	30 (15.8)	5 (16.7)	56 (18.1)	0.281
UCTD	19 (21.3)	47 (24.7)	6 (20.0)	72 (23.3)	0.744
SSc	11 (12.4)	11 (5.8)	3 (10.0)	25 (8.1)	0.159
MCTD/overlap	5 (5.6)	18 (9.5)	5 (16.7)	28 (9.1)	0.180
IIM	4 (4.5)	8 (4.2)	1 (3.3)	13 (4.2)	0.963

Data are presented as *n* (%).

diagnostic groups. This approach could be employed as an outcome measure in novel trial designs such as molecular pathology-driven and/or holistic management trials.

This study has several strengths. It compares HRQoL across several diseases recruited in the same cohort, thus reducing sampling and recruitment bias. The SF-36 HRQoL LPs were corroborated with EQ-5D scores in a subset of the cohort. This is a free and widely available tool that can be adopted in the clinical setting to measure HRQoL. Although disease-specific HRQoL scores incorporate components of HRQoL that are distinct to a given disease, the SF-36 is widely used and validated in CTDs and is a reliable measure of HRQoL that can be used across diseases [5–9].

This study has a number of limitations. First, there are no validated scoring systems to measure cross-disease activity in CTDs and disease-specific disease activity measures were not collected. In general, the patients in this cohort have relatively stable disease activity, therefore the external validity of these results in a more active cohort is unclear, as disease activity is likely to negatively impact HRQoL. Second, the data analysed

in this study is cross-sectional, however, follow-up is presently under way. Prospective longitudinal data will address whether patient’s HRQoL may be improved by intervention in modifiable risk factors associated with a poor HRQoL LP, such as smoking cessation or weight reduction. Furthermore, the SSc-IIM spectrum group was composed of patients with SSc, IIM and overlap syndromes, due to the small numbers of patients with these diseases, which limits precision. In this analysis, patients were initially categorized by their physician diagnosis, which we chose as our ‘gold standard’. This was because all classification criteria sets come with the qualifier that they are not diagnostic criteria. It would be interesting in future analyses to consider what the optimal classification criteria for UCTD would be, and test this against the physician diagnosis in future studies of molecular taxonomy and clinical outcomes. Finally, we acknowledge that associates of HRQoL are multifactorial and many important covariates were not measured in this study, including damage scores and social factors (e.g. employment status, marital status and level of social support).

Table 3. Univariate and multivariable ordinal logistic regression comparing patient characteristics across LPs, with LP1 (poor HRQoL) used as the reference category

Characteristics	Univariate, OR (95% CI)	P-value	Multivariable, OR (95% CI) ^a	P-value
Demographics				
Age	0.99 (0.97, 1.00)	0.131		
Female	0.56 (0.24, 1.25)	0.157		
Disease duration	0.99 (0.95, 1.04)	0.754		
Black ethnicity	0.28 (0.11, 0.74)	0.010	0.12 (0.04, 0.37)	<0.001
Indo-Asian ethnicity	0.53 (0.28, 1.01)	0.056	0.27 (0.13, 0.57)	0.001
Obesity	0.56 (0.35, 0.88)	0.013	0.62 (0.38, 1.03)	0.064
Cigarette smoker	0.55 (0.34, 0.87)	0.012	0.55 (0.32, 0.84)	0.038
Clinical diagnosis				
pSS	0.64 (0.34, 1.22)	0.176		
UCTD	0.95 (0.53, 1.71)	0.861		
SSc-IIM spectrum	0.96 (0.52, 1.78)	0.900		
Comorbidities				
Fibromyalgia	0.40 (0.21, 0.77)	0.006	0.49 (0.23, 1.05)	0.065
Anxiety or depression	0.38 (0.16, 0.94)	0.037	0.37 (0.10, 1.38)	0.065
CCI	0.82 (0.69, 0.98)	0.026	0.78 (0.63, 0.97)	0.024
Medication use (ever)				
Steroids	0.78 (0.49, 1.23)	0.280		
Immunosuppressants	1.11 (0.70, 1.76)	0.644		
Disease-related factors				
Sicca syndrome	0.55 (0.35, 0.88)	0.013	0.53 (0.30, 0.94)	0.031
Anti-Ro positive	0.90 (0.56, 1.44)	0.667		
Anti-dsDNA positive	1.91 (1.11, 3.26)	0.019	1.61 (0.79, 3.27)	0.190
Low complement	1.63 (0.98, 2.70)	0.059	0.98 (0.51, 1.88)	0.955
Positive ISG score	1.03 (0.99, 1.08)	0.179		

^a Multivariate analysis adjusted for variables in univariate analysis with $P < 0.1$ (ethnicity, fibromyalgia, anxiety or depression, CCI, sicca syndrome, anti-dsDNA antibodies, low complement, obesity and cigarette smoking).

Significant values in bold.

The OR is the odds of being in a higher LP (i.e. a better HRQoL) for a unit increase in each variable. For disease group, SLE was the reference; for ethnicity, white was the reference.

In conclusion, poor HRQoL is common in patients with CTDs and CTD patients can be clustered into distinct HRQoL subgroups that are not primarily driven by their specific diagnosis or autoantibody profile. We identified a number of key demographic, lifestyle and clinical factors associated with poor HRQoL in this population. These factors need to be addressed across the whole CTD spectrum as part of a holistic management approach aimed at improving overall patient outcomes.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability

The LEAP Study is an ongoing prospective study and no data are available.

Authors' contributions

S.D., J.A.R., B.P. and I.N.B. contributed to the design of the study. All authors made substantial contributions to the acquisition of data. S.D. and J.A.R. analysed the data and performed statistical analyses. All authors read and approved the final manuscript.

Funding

S.D. is an MRC Clinical Training Fellow based at the University of Manchester supported by the North West England Medical Research Council Fellowship Scheme in

Clinical Pharmacology and Therapeutics, which is funded by the Medical Research Council (award MR/N025989/1), Roche Pharma, Eli Lilly, UCB Pharma, Novartis, the University of Liverpool and the University of Manchester. H.C. and A.H. are supported by the National Institution for Health Research Manchester Biomedical Research Centre Funding Scheme. I.N.B. is a National Institute for Health Research (NIHR) Senior Investigator Emeritus and is funded by the NIHR Manchester Biomedical Research Centre. B.P. is supported by the NIHR Manchester Biomedical Research Centre and NIHR Manchester Clinical Research Facility.

Disclosure statement: S.D. has received grant support from UCB and Eli Lilly. A.L.H. has received grant support from Gesynta; consultancy fees from Arena, Boehringer-Ingelheim, Camurus, CSL-Behring, and Gesynta and speaker fees from Janssen. H.C. has received grant support from Eli Lilly and UCB; consulting fees from Novartis, Eli Lilly, Orphazyme and AstraZeneca and has been a speaker for UCB and Biogen. I.N.B. has received grant support from Genzyme/Sanofi, GlaxoSmithKline, Roche and UCB; consulting fees from AstraZeneca, Eli Lilly, GlaxoSmithKline, Merck Serono and UCB and was a speaker for AstraZeneca, GlaxoSmithKline and UCB. B.P. has received grant support from Genzyme/Sanofi and GlaxoSmithKline, honoraria from Fresenius-Kabi and AbbVie and was a speaker for Eli Lilly and Roche.

References

- van Vollenhoven RF, Mosca M, Bertias G *et al.* Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis* 2014;73:958–67.

2. Smolen JS, Breedveld FC, Burmester GR *et al.* Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016;75:3–15.
3. Sciascia S, Roccatello D, Radin M *et al.* Differentiating between UCTD and early-stage SLE: from definitions to clinical approach. *Nat Rev Rheumatol* 2022;18:9–21.
4. Greenfield J, Hudson M, Vinet E *et al.* A comparison of health-related quality of life (HRQoL) across four systemic autoimmune rheumatic diseases (SARDs). *PLoS One* 2017;12:e0189840.
5. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
6. Cossutta R, Zeni S, Soldi A *et al.* [Evaluation of quality of life in patients with systemic sclerosis by administering the SF-36 questionnaire]. *Reumatismo* 2002;54:122–7.
7. Sultan SM, Ioannou Y, Moss K, Isenberg DA. Outcome in patients with idiopathic inflammatory myositis: morbidity and mortality. *Rheumatology (Oxford)* 2002;41:22–6.
8. Strömbeck B, Ekdahl C, Manthorpe R, Wikström I, Jacobsson L. Health-related quality of life in primary Sjogren's syndrome, rheumatoid arthritis and fibromyalgia compared to normal population data using SF-36. *Scand J Rheumatol* 2000;29:20–8.
9. Stoll T, Gordon C, Seifert B *et al.* Consistency and validity of patient administered assessment of quality of life by the MOS SF-36; its association with disease activity and damage in patients with systemic lupus erythematosus. *J Rheumatol* 1997;24:1608–14.
10. Spurk D, Hirschi A, Wang M, Valero D, Kauffeld S. Latent profile analyses: a review and “how to” guide of its application within vocational behavior research. *J Vocat Behav* 2020;120:103445.
11. Desplat-Jego S, Bardin N, Larida B, Sanmarco M. Evaluation of the BioPlex 2200 ANA screen for the detection of antinuclear antibodies and comparison with conventional methods. *Ann N Y Acad Sci* 2007;1109:245–55.
12. Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Commun Health* 1999;53:46–50.
13. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide. Boston: Health Institute, New England Medical Center, 1993.
14. EuroQol. G. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
15. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making* 2006;26:410–20.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
17. Reynolds JA, Briggs TA, Rice GI *et al.* Type I interferon in patients with systemic autoimmune rheumatic disease is associated with haematological abnormalities and specific autoantibody profiles. *Arthritis Res Ther* 2019;21:147.
18. Scrucca L, Fop M, Murphy TB, Raftery AE. mclust 5: clustering, classification and density estimation using gaussian finite mixture models. *R J* 2016;8:289–317.
19. Scott Long J, Freese J. Regression models for categorical dependent variables using Stata. 3rd ed. College Station, TX: Stata Press, 2014.
20. Navarra SV, Guzman RM, Gallacher AE *et al.* Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011;377:721–31.
21. Brown S, Navarro Coy N, Pitzalis C *et al.* The TRACTISS protocol: a randomised double blind placebo controlled clinical trial of anti-B-cell therapy in patients with primary Sjogren's syndrome. *BMC Musculoskelet Disord* 2014;15:21.
22. Tjarnlund A, Tang Q, Wick C *et al.* Abatacept in the treatment of adult dermatomyositis and polymyositis: a randomised, phase IIb treatment delayed-start trial. *Ann Rheum Dis* 2018;77:55–62.
23. Tashkin DP, Elashoff R, Clements PJ *et al.* Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006;354:2655–66.
24. Bowman SJ, Everett CC, O'Dwyer JL *et al.* Randomized controlled trial of rituximab and cost-effectiveness analysis in treating fatigue and oral dryness in primary Sjogren's syndrome. *Arthritis Rheumatol* 2017;69:1440–50.
25. U.S. Department of Health and Human Services. Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims. 2009. <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf> (12 August 2022, date last accessed).
26. Boers M, Kirwan JR, Wells G *et al.* Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol* 2014;67:745–53.
27. Petri M, Kawata AK, Fernandes AW *et al.* Impaired health status and the effect of pain and fatigue on functioning in clinical trial patients with systemic lupus erythematosus. *J Rheumatol* 2013;40:1865–74.
28. Schmeding A, Schneider M. Fatigue, health-related quality of life and other patient-reported outcomes in systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2013;27:363–75.
29. Kotsis K, Voulgari PV, Tsifetaki N *et al.* Anxiety and depressive symptoms and illness perceptions in psoriatic arthritis and associations with physical health-related quality of life. *Arthritis Care Res (Hoboken)* 2012;64:1593–601.
30. Cornet A, Andersen J, Myllys K, Edwards A, Arnaud L. Living with systemic lupus erythematosus in 2020: a European patient survey. *Lupus Sci Med* 2021;8:e000469.
31. Strombeck B, Ekdahl C, Manthorpe R, Jacobsson LT. Physical capacity in women with primary Sjogren's syndrome: a controlled study. *Arthritis Rheum* 2003;49:681–8.
32. Basta F, Afeltra A, Margiotta DPE. Fatigue in systemic sclerosis: a systematic review. *Clin Exp Rheumatol* 2018;36:150–60.
33. Hafiz W, Nori R, Bregasi A *et al.* Fatigue severity in anti-nuclear antibody-positive individuals does not correlate with pro-inflammatory cytokine levels or predict imminent progression to symptomatic disease. *Arthritis Res Ther* 2019;21:223.
34. Morgan C, Bland AR, Maker C, Dunnage J, Bruce IN. Individuals living with lupus: findings from the LUPUS UK Members Survey 2014. *Lupus* 2018;27:681–7.
35. Sloan M, Naughton F, Harwood R *et al.* Is it me? The impact of patient-physician interactions on lupus patients' psychological well-being, cognition and health-care-seeking behaviour. *Rheumatol Adv Pract* 2020;4:rkaa037.
36. Sloan M, Harwood R, Sutton S *et al.* Medically explained symptoms: a mixed methods study of diagnostic, symptom and support experiences of patients with lupus and related systemic autoimmune diseases. *Rheumatol Adv Pract* 2020;4:rkaa006.
37. Maningding E, Dall'Era M, Trupin L, Murphy LB, Yazdany J. Racial and ethnic differences in the prevalence and time to onset of manifestations of systemic lupus erythematosus: the California Lupus Surveillance Project. *Arthritis Care Res (Hoboken)* 2020;72:622–9.
38. Jaeger VK, Tikly M, Xu D *et al.* Racial differences in systemic sclerosis disease presentation: a European Scleroderma Trials and Research group study. *Rheumatology (Oxford)* 2020;59:1684–94.
39. Phillippi K, Hoeltzel M, Byun Robinson A, Kim S, Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry Investigators. Race, income, and disease outcomes in juvenile dermatomyositis. *J Pediatr* 2017;184:38–44.e1.
40. Geryk LL, Carpenter DM, Blalock SJ, DeVellis RF, Jordan JM. The impact of co-morbidity on health-related quality of life in rheumatoid arthritis and osteoarthritis patients. *Clin Exp Rheumatol* 2015;33:366–74.
41. Iudici M, Irace R, Riccardi A *et al.* Longitudinal analysis of quality of life in patients with undifferentiated connective tissue diseases. *Patient Relat Outcome Meas* 2017;8:7–13.
42. Dias LH, Miyamoto ST, Gioielli RA, de Magalhães CIM, Valim V. Pain and fatigue are predictors of quality of life in primary Sjogren's syndrome. *Adv Rheumatol* 2021;61:28.
43. Gladman DD, Urowitz MB, Gough J, MacKinnon A. Fibromyalgia is a major contributor to quality of life in lupus. *J Rheumatol* 1997; 24:2145–8.

44. Fortin M, Lapointe L, Hudon C *et al.* Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes* 2004;2:51.
45. Wang L, Palmer AJ, Cocker F, Sanderson K. Multimorbidity and health-related quality of life (HRQoL) in a nationally representative population sample: implications of count versus cluster method for defining multimorbidity on HRQoL. *Health Qual Life Outcomes* 2017;15:7.
46. Cornec D, Devauchelle-Pensec V, Mariette X *et al.* Severe health-related quality of life impairment in active primary Sjogren's syndrome and patient-reported outcomes: data from a large therapeutic trial. *Arthritis Care Res (Hoboken)* 2017;69:528–35.
47. Kamel UF, Maddison P, Whitaker R. Impact of primary Sjogren's syndrome on smell and taste: effect on quality of life. *Rheumatology (Oxford)* 2009;48:1512–4.
48. Rusthen S, Young A, Herlofson BB *et al.* Oral disorders, saliva secretion, and oral health-related quality of life in patients with primary Sjogren's syndrome. *Eur J Oral Sci* 2017;125:265–71.
49. Milin M, Cornec D, Chastaing M *et al.* Sicca symptoms are associated with similar fatigue, anxiety, depression, and quality-of-life impairments in patients with and without primary Sjogren's syndrome. *Joint Bone Spine* 2016;83:681–5.
50. Cho HJ, Yoo JJ, Yun CY *et al.* The EULAR Sjogren's syndrome patient reported index as an independent determinant of health-related quality of life in primary Sjogren's syndrome patients: in comparison with non-Sjogren's sicca patients. *Rheumatology (Oxford)* 2013;52:2208–17.
51. Champey J, Corruble E, Gottenberg JE *et al.* Quality of life and psychological status in patients with primary Sjogren's syndrome and sicca symptoms without autoimmune features. *Arthritis Rheum* 2006;55:451–7.