Health related quality of Life, Perceptions and experiences of female patients with Systemic Lupus Erythematosus in South Africa: Exploring Unmet needs using a mixed methods approach.

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A thesis submitted in fulfilment of the requirements for the degree

Doctor of Philosophy

Medicine

Department of Medicine

Faculty of Health Sciences

University of Cape Town

February 2020

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Declarations

I, Angel Phuti, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. Ethical approval was obtained from the University of Cape Town and University of Witwatersrand. Ethical approval letters are available in Appendix IV.

I confirm that permission to include the four publications (listed below) in this PhD thesis was granted by the University of Cape Town's Doctoral Degrees Board (Appendix VII). Furthermore, a statement of originality, authors' contribution and declarations from co-authors to include these publications are included in Appendix VII.

For consistency throughout the thesis, kindly note each full original publication or manuscript was used as an attachment to every relevant chapter. The abstract of each publication was slightly edited and used as an overview in each relevant chapter.

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Chapter 2

Phuti A, Schneider M, Tikly M, Hodkinson B. *Living with systemic lupus erythematosus in the developing world.* Rheum. International 2018; 38:1601 1-13.

Chapter 4

Phuti A, Schneider M, Makan K, Tikly M, Hodkinson B. *Living with systemic lupus erythematosus in South Africa: a bitter pill to swallow.* Health Qual Life Outcomes 2019; 17:65.

Chapter 5

Phuti A, Hodkinson B, Tikly M, Schneider M. *'The feeling of not being entitled to something': Fertility, pregnancy and sexuality among women with systemic lupus erythematosus in South Africa.* Scand J Rheumatol 2019; 00:1–7.

Chapter 6

Phuti A, Schneider M, Tikly M, Hodkinson B. *Fatigue and functioning among women living with systemic lupus erythematosus in South Africa: Validation of narratives using FACIT-Fatigue, FAI and SF-36 tools.* (manuscript-2019)

In these publications, I was the main researcher whose tasks involved planning, data collection, data analysis, writing the manuscript first drafts. In the thesis, I refer to 'we' or 'the researchers' because of the contribution of my supervisors in my PhD process, and the co-authors support and involvement. I, Angel Phuti remain solely the primary researcher.

SIGNATURE: Signed by candidate DATE: 10 February 2020

List of Presentations

South African Rheumatism and Arthritis Association

2019, Durban; South Africa: *Living with Systemic Lupus Erythematosus in South Africa-A study of women attending two tertiary hospitals in South Africa*. Phuti A, Schneider M, Makan K, Tikly M and Hodkinson B.

2018, Cape Town; South Africa: *Living with Systemic Lupus Erythematosus in South Africa- "A Misunderstood burden."* Phuti A, Schneider M, Makan K, Tikly M and Hodkinson B.

European Congress of Rheumatology

2018, Amsterdam; Holland: A Misunderstood burden- living with Systemic Lupus Erythematosus in South Africa (Abstract published on the Annals of the Rheumatic Diseases- BMJ Journals) Phuti A, Schneider M, Tikly M and Hodkinson B. http://dx.doi.org/10.1136/annrheumdis-2018-eular.7254

2017, Johannesburg; South Africa: Living with Systematic Lupus Erythematosus in South Africa- "A Bitter Pill to Swallow." Phuti A, Tikly M, Kalla A, Makan K, Schneider M and Hodkinson B.

2017, Johannesburg; South Africa: *Applying Questionnaires in Systematic Lupus Erythematosus.* Phuti A, Tikly M, Kalla A, Makan K, Schneider M and Hodkinson B.

2nd Africa Lupus Genetics Network (ALUGEN Workshop

2016, Cape Town; South Africa: *Health Related Quality of Life (HRQoL), experiences and perceptions of females living with SLE study.* (oral presentation) Phuti A, Schneider M and Hodkinson B. https://vula.uct.ac.za/access/content/group/25f04c1d-1bf4-497a-bdb5-e12357b066ef/test/2nd%20UCT%20LUPUS%20WORKSHOP-FINAL%20PROGRAM.pdf

Abstract

Objective

Systemic Lupus Erythematosus (SLE) is a multi-system disease that predominately affects women. Considering the lack of data on health related quality of life (HRQoL) especially in sub-Saharan Africa, we undertook a literature review on HRQoL of SLE patients in developing countries to collate the existing evidence and identify information gaps. A mixed methods qualitative and quantitative study of lived experiences of South African women with SLE was performed.

Methods

A literature search was conducted on medical databases using MeSH terms pertaining to HRQoL amongst SLE patients in the developing or low income countries to identify articles published between January 1975 and February 2018.

The main study included 25 consenting SLE patients attending two tertiary hospitals in Johannesburg and Cape Town. Individual in-depth interviews, using a topic guide, were conducted and analysed using NVivo software. In addition, participants completed the Short Form-36 (SF-36), Functional Assessment Instrument (FAI) and functional assessment of chronic illness therapy (FACIT) for fatigue questionnaires. The questionnaires were analysed per each tool's scoring method and SPSS software was used to calculate mean, standard deviations and correlations.

Results

The review of 31 articles, from 11 countries indicated that SLE women have a poor general HRQoL. In addition, we found relationships between disease factors including disease activity, organ damage, functioning, and mental health. Poor socioeconomic status worsened SLE outcomes by limiting patients' access to health care and psychosocial services.

In the main study, the majority (72.0%) were black Africans, unemployed (76.0%), with low formal educational level and singlehood status (72.0%). The mean (SD) mental and physical composite

SF-36 scores were poor (50.9 (22.1) and 49.1 (20.5) respectively), and 68.0% of women had FACIT scores of severe fatigue. The mean (SD) FAI was 1.33 (0.8), showing that activities of daily living (ADL) were performed with difficulty. Major themes expressed were fatigue, pain, impaired functioning, depression, pregnancy, aesthetic concerns and sexuality issues. Disease chronicity, fatigue and pain were described by many participants as ‘taking over life’ and impacting on performing ADL and career opportunities contributing to indigence. Negative pregnancy outcomes were frequently exacerbated by poor sexual relationships and miscommunication between patient and health care workers. Lack of understanding of SLE by patients, community and family as well as suicidal ideations and depressive symptoms were expressed. Although the quantitative tools measured these aspects, they were unable to explore complexities such as limitations in job acquisition, suicidal ideations, disease understanding and support systems.

Conclusion

This study underscores the complex, chronic and challenging life experiences, often exacerbated by poverty, of SA women with SLE. Quantitative tools may be inadequate in capturing important aspects of HRQoL that emerged from the qualitive interviews. Awareness of these limitations, together with psycho-social support and education, might improve HRQoL. This thesis recommends multi-centred, interventional longitudinal studies that incorporate mixed methods and focus on strategies to improve the negative outcomes in SLE.

Acknowledgements

This work is dedicated to all the lupus patients and to the women who poured not only their hearts but their tears for their struggles to be heard, the women who smiled through those tears I shall never forget, showing that despite any storms, there are rays of hope. Through you, I saw the face of strength. Let's continue to voice the struggle, hold our hands together and find a way. Never forget that you are not alone in this!

My supervisors thank you for the immense support, for walking alongside me throughout this journey! It feels like yesterday when we had our first meeting, and afterwards, when my concept note came back red with a well-done note. I remembered these Tswana words "Morogo wa ngwana ga o tlhotswe ditlhokwa". My co-authors Prof Tikly for the mentorship and Dr Makan for the support.

To the funders: Thuthuka grant and the Harry Crossley Foundation for financial support.

I would like to thank the staff in Groote Schuur Hospital and Chris Hani Baragwanath Academic Hospital for being there, your assistance and your everyday commitment to caring for those in need. Angels do indeed exist!

My countless family members and friends, writing about each one of you is a PhD thesis on its own, I am sure you would advise me to rather stick to these few lines. To you all, you are such a dosage of love. To Joern, thank you for all the love, support and being there for our daughter when I was so busy.

Dear Lelani 'Llani'- My everytime words "Ngiyini nje ngaphandle kwakho?" (What am I without you?), are really true. Thank you for encouraging me to take chances which I always considered risky and to never fear. You taught me that without these, the best is often missed.

To Suryavati-Masa, through you I discovered the meaning of true love. Your small finger next to mine as we pressed confirm and send buttons, picking up a loud timer clock and asking if that meant PhD is finally over, bringing the artwork and asking for a real dog drawing is imprinted in my brain forever. You really shaped my time skills which I plan to take further, and art too- with you of course!

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Nomenclature (excluding those in published papers)

ACR	American College of Rheumatology
ADL	activities of daily living
AIDS	acquired immune deficiency syndrome
ALUGEN	African Genetics Lupus Network
ANA	anti-nuclear antibodies
APLS	anti-phospholipid syndrome
ARA	American Rheumatism Association
ARV's	antiretroviral therapy
BILAG	British Isles Lupus Assessment Group
COREQ	Consolidated criteria for Reporting Qualitative research
dsDNA	double-stranded DNA
ECLAM	European Consensus Lupus Activity Measurement
FACIT-Fatigue	functional assessment of chronic illness therapy for fatigue
FAI	functional assessment instrument
FSFI	Female Sexual Function Index
HCWs	health care workers
HIV	human immune deficiency virus
HRQoL	health-related quality of life
ICF	International Classification of Functioning, Disability and Health
IVIGs	Intravenous immune-globulins
LN	lupus nephritis
MCS	mental component score
NPSLE	neuropsychiatric SLE
PCS	physical component score
PGA	physician global assessment
PROs	patient reported outcomes
SES	socio-economic status

SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SF-36	Medical Outcomes Short Form-36
SLAM	Systemic Lupus Activity Measure Index,
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLE-DAS	SLE Disease Activity Score
SLE	systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
Sm	Smith antigen
SRQ-20	self-reporting questionnaire
WHO	World Health Organisation
WHOQoL	World Health Organisation Quality of Life

Introduction

The thesis is based on three publications and one manuscript under review focusing on health-related quality of life (HRQoL) amongst Systemic Lupus Erythematosus (SLE) patients attending Chris Hani Baragwanath Hospital in Soweto or Groote Schuur Hospital in Cape Town. The published papers include a review pertaining to HRQoL of SLE patients living in the developing world, and two data-based qualitative papers, one on the general experiences of living with SLE and another on sexual and reproductive health aspects of women living with SLE. The fourth article (currently under review) collates and compares quantitative and qualitative results.
Authors' contributions are described in each certificate of agreement by each co-author and are available on the appendix. Chapter 2, 4, 5, 6 are all based on these papers which together provide an exploration of what it means to be a woman living with SLE.

Chapter 1 gives an overview of the literature pertaining to SLE. The current and existing knowledge and conceptions on SLE are defined. This includes the disease history, pathophysiology, its diagnosis, presentation, and a general overview on the management of SLE. Moreover, this chapter highlights the knowledge gaps, the main aim of this research work, research questions that subsequent chapters aim to address and anticipated outcomes.

Chapter 2 is a published review investigating the existing published literature on HRQoL in SLE in developing or low and middle income countries (LMIC).

Chapter 3 discusses the methodology of the study in detail. This chapter describes how I used a mixed methods approach, with focused individual interviews and self-reported outcome questionnaires to collect the data.

Chapter 4 is based on qualitative data collected during the interviews, and answers one of the thesis's research objectives: To explore women living with SLE's experiences. Themes explored and presented were pain, fatigue, emotional, social and work function, fertility, aesthetic concerns, coping mechanisms and medication adherence.

Chapter 5 is the second qualitative paper whose objective is specific to sexual and reproductive health experiences. Findings from the women's narratives show the controversy that surrounds fertility, pregnancy, puerperium, postnatal and sexuality for women living with SLE. Gaps in practice are identified, discussed and a few recommendations are presented on this chapter.

Chapter 6 explores fatigue, pain and functioning. A publication, currently under review, uses both qualitative and quantitative methods to understand and explore the phenomenon of fatigue and functioning amongst SLE women. The aim is to correlate both sets of findings to give a more in-depth understanding of these aspects investigated and explored using assessment tools and interviews.

Chapter 7 discusses and links the results of all the papers giving a broader understanding of the findings and demonstrating how HRQoL in SLE patients is compromised. I use the World Health Organization's International Classification of Functioning, Disability and Health framework (WHO-ICF) developed in our published review. Recommendations, novel strategies and implications of care and practice, future research priorities in developing countries are discussed, together with the limitations of this research.

Chapter 8 summarises and concludes the thesis.

CHAPTER 1: Background

1.1 History of SLE

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disorder of unknown indefinite course [1]. Due to its cutaneous manifestations, it was first known as herpes esthiomenos (gnawing dermatosis) by Hippocrates [2]. It was first documented in 855 AD as 'lupus' in reference to the illness that consumed the Bishop of Liège by Hebernus, the Archbishop of Tours, France. In the fifteen century, a well-known and insightful Swiss-German physician re-used the name 'lupus' to describe the cutaneous manifestations of the illness or "a hungry wolf eating flesh", and further defining it as an illness with "greater blood supply" resulting in "bloodletting" as a treatment of choice which was popular at that time [3].

Other prominent scientists made classical discoveries and definitions explaining its clinical presentations. Paracelsus in the sixteenth century and Mainardi (1530 AD) who used the term 'lupus' to describe ulcers and boils in the lower extremities [4]. A German scientist Rudolf Virchow (1821-1902) was the first scientist to systematically review the history of SLE dating it back to the thirteen century when it was being referred to as 'lupus or a wolf-bite' disease by superstitious people which could be linked to current day stigma and misunderstanding [5]. In 1872 Moritz Karposi further documented the nature of the disease. Between 1895 and 1904 Sir William Olsoer became the first scientist to document the quiescent and relapsing nature of lupus [6]. Initial understanding on the pathogenesis of lupus dates back to 1948 by Malcolm Hargraves who examined lupus erythematosus cells and in 1963 Heyler & Howie describing the first murine model for lupus [7]. In 1961, Morteo et al and Leohardht (1964) did family studies in SLE influencing more understanding on disease treatment and management modalities [8, 9]. Rheumatologist Edmund L. Dubois's professional dedication (1950-1985) through numerous publications to date and his clinical practice led to more insight on the pathophysiology, clinical manifestations, treatment and management of SLE including setting up the first lupus clinic in the United states of America (USA) [10, 11].

Although this disease can affect individuals from neonatal stage, and is more aggressive in adolescent stage, it is most prevalent amongst females between the ages of 20-30 years [12, 13]. Since its early discovery, the clinical manifestations of this disease were described mainly from the skin involvement. However, SLE is now classified as a multi-system disorder which can affect any organ system in the body [14].

1.2 Classification of SLE

In 1971, the then American Rheumatism Association (ARA) developed a classification framework for diagnosing a patient with SLE which required fulfilling at least four of the 14 criteria. This was later revised in 1982 as the American College of Rheumatology (ACR) [15] and subsequently in 1997 [16]. In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) validated criteria for diagnosis of SLE requiring patients to meet ≥4 of 17 of both clinical and immunological criteria [17, 18]. Both the SLICC and ACR criteria are widely used by clinicians in most settings for diagnosis and classification of SLE. Because of the protean manifestations of SLE, the diagnosis is often missed and a late diagnosis is frequently encountered [1].

Table 1.1: 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion *1. OR* 2. Pericarditis--documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed *1. OR* 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements e.g., uremia, ketoacidosis, or electrolyte imbalance *1. OR* 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic	1. Hemolytic anemia--with reticulocytosis

Criterion	Definition
	2. Leukopenia--< 4,000/mm^3 on; 2 occasions 1. *OR* 3. Lyphopenia--< 1,500/ mm^3 on; 2 occasions 1. *OR* 4. Thrombocytopenia--<100,000/ mm^3 in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer 1. *OR* 2. Anti-Sm: presence of antibody to Sm nuclear antigen 1. *OR* 3. Positive finding of antiphospholipid antibodies on: 1. 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. 2. a positive test result for lupus anticoagulant using a standard method, or 3. 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

*The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation [15, 16].

1.3 Diagnosis of SLE

Various genetic predispositions as causative factors of SLE have been described. Individuals with this susceptibility, in the setting of a “trigger”, produce auto-antibodies, resulting in the clinical and biochemical features of the disease. Tissue and organ injury in SLE results from inflammation with antibody-antigen complex deposition. Auto-antibodies are produced by B-lymphocyte cells [1, 19]. The majority of SLE patients have a high titre of anti-nuclear antibodies (ANA), and may have other auto-antibodies including double-stranded DNA (dsDNA), and anti- Smith (Sm) antigen. In addition, low levels of complement (particularly C3 and C4) suggest high activity of the immune system [20].

Environmental triggers include ultraviolet rays from sunlight, heavy metals or chemicals, pathogenic organisms and lifestyle [1, 19, 21]. In addition, oestrogen seems to play an important role in the pathogenesis of the disease, perhaps explaining why females are affected more commonly than males. Between 1999-2012, a retrospective cohort study in a UK reported a female-male ratio of 6:1. Over the years this ratio has varied across published literature [22-24]. Occasionally medication causes drug-induced lupus erythematosus. This type of lupus may be reversible once the suspected drug is withdrawn. Though there are at least 38 drugs that have been implicated, the most common are procainamide, isoniazid, hydralazine, quinidine and phenytoin [25].

This illness is usually characterised by “flares” of inflammation in one or more organ system, interspersed with quiescent periods. The most commonly involved organs are the skin and mucous membranes (with rashes and scarring of sun-exposed areas, hair loss, and mouth ulcers), the joints (resulting in painful arthritis), the kidneys (causing inflammation and renal failure if untreated), the blood (low white cell, haemoglobin and platelet levels) and the central nervous system (resulting in numerous complications including strokes, headaches, cognitive dysfunction, psychosis and depression) [14]. Figure 1.2 shows the protean organ involvement encountered in this illness.

1.4 Skin Involvement

Skin involvement in SLE diagnosis is the second commonest symptom after joint involvement [26]. A study in India reported 30% of patients presenting with skin lesions, and by the end of a 5 year follow up period, all patients had all developed skin manifestations [27]. Diagnosis of skin disease requires clinical evaluation, possibly including the use of a dermoscope and histopathological assessment of a skin biopsy [28]. A thorough evaluation of skin lesions to determine if they are lupus-specific or not is important for efficient management [27].

Patients may have chronic DLE, acute cutaneous lupus (ACLE) and subacute cutaneous lupus (SCLE) [29]. Acute lupus lesions are characterized by butterfly rash with erythematous macules (red and inflamed patches), with a patchy, scaly and crusty appearance [1]. In contrast, DLE lesions are hyperpigmented macules with follicular plugging that occur on sub-exposed areas. The face, being the most sun exposed body part is particularly prone to DLE, but other areas can also be affected including the scalp [28].

Alopecia (hair falling out) can be either scarring (due to DLE) or non-scarring (due to SLE disease flare, medication, or stress). Alopecia as a result of DLE has been described as a frequent feature in lupus and it has been reported that about more than 50% of the patients suffer from this feature during the disease course [30]. The irreversibility of scarring alopecia due to DLE may cause distress [31]. Figure 1.1 below shows scarring alopecia in an SLE patient, a result of DLE.

Not all patients with discoid lupus erythematosus (DLE) skin lesions have systemic features in keeping with SLE, with only 1-5% patients presenting with DLE develop SLE. On the other hand, about 25% of SLE patients tend to develop discoid lesions [29]. Patients of African ancestry with DLE have been found to have a four-fold risk of developing lupus erythematosus compared to American-Caucasians [29, 32].

Figure 1.1: Scarring alopecia from an SLE patient as a result of DLE

Image obtained from journal with permission for re-use electronically and imprint [27].

Morbidity, such as pain, can result from painful skin lesions, alopecia, and disfigurement [27]. One study has found that almost 50% of patients with skin disease including SLE also suffer from vocational disability. Disease manifestations, such as pain, were the main causes of inability to fulfill job roles [33].

Limited research has been conducted on aesthetic concerns such as alopecia and facial disfigurements, but the limited studies have highlighted that these play a pivotal role in HRQoL in particular emotional, social and mental well-being [31, 34].

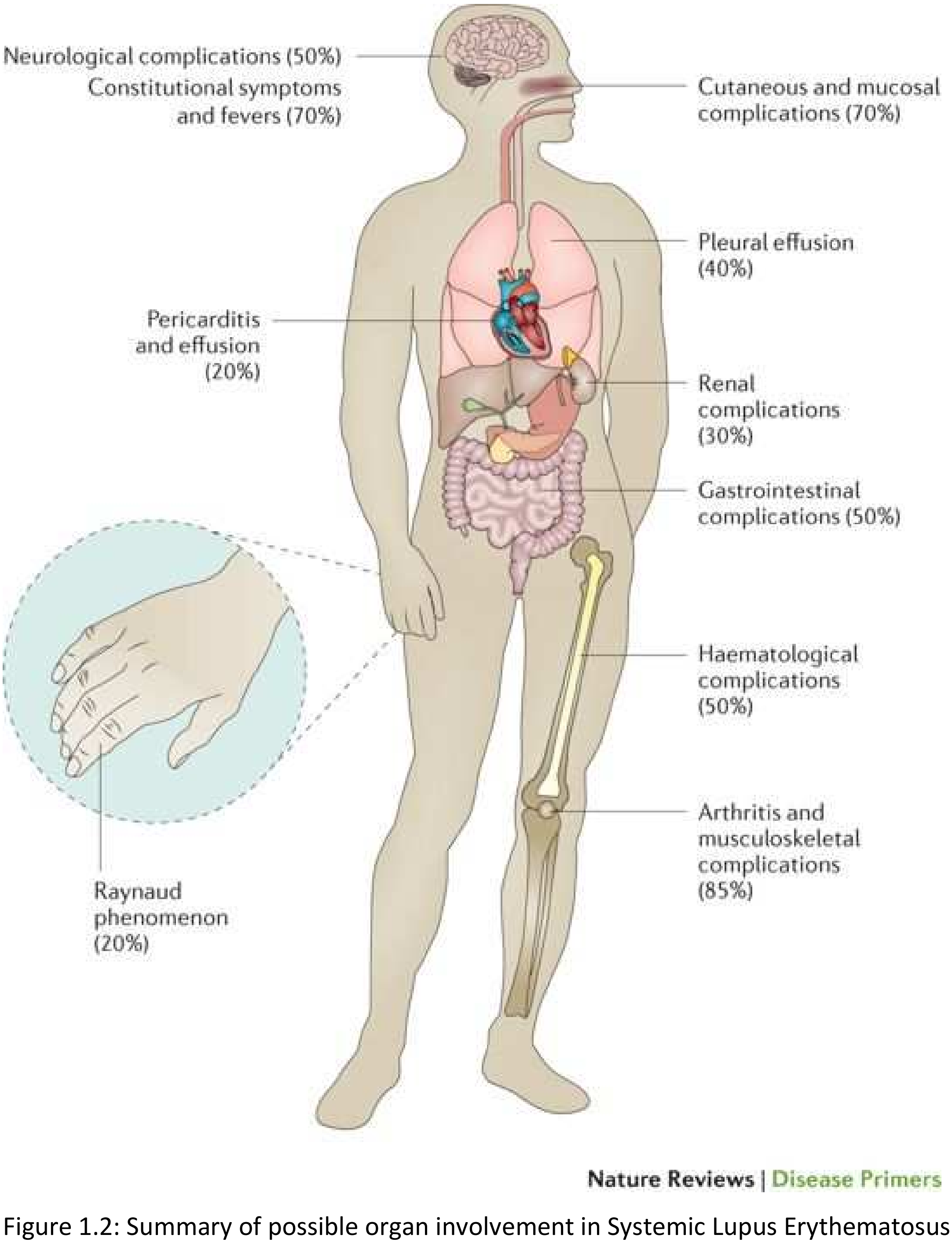

Figure 1.2: Summary of possible organ involvement in Systemic Lupus Erythematosus

Image obtained from journal with permission for re-use electronically and imprint [14].

1.5 Physical concerns in SLE

Pain, fatigue and functioning and related outcomes

Pain

In SLE, physical concerns such as pain, poor physical functioning, fatigue, fibromyalgia and poor sleep are a daily challenge for patients and have been reported to overlap with each other [35]. At diagnosis or first clinical visit, pain is usually the first symptom that patients will present with, which is either classified as arthralgia, arthritis or myalgia [35]. Arthritis, as the commonest presenting feature of SLE, is a common cause of pain amongst SLE patients [35]. Headache may be due to neuropsychiatric SLE (NPSLE), stress, medication, or infection, has been recorded in up to 70% of SLE patients [36, 37]. Other causes of pain commonly reported are neurological problems causing neuropathic pain, skin lesions, abdominal pain, Raynaud's phenomena and fibromyalgia causing chronic widespread pain [35, 38].

A study in the USA investigating psychosocial adaptation to chronic pain compared SLE patients, patients with chronic lower back pain and temporomandibular disorders and found that SLE patients' scores were similar to those with temporomandibular disorders, and showed that 87.5% of SLE patients had dysfunctionality, interpersonal distress and maladaptive coping [38].

Pain in SLE has negative outcomes including psychosocial distress, disability or loss of functioning in daily tasks such as job roles and household chores [31]. Clinicians need to rely on patients for information pertaining to the nature, extent and patterns of pain. This can be challenging for the patients and clinicians [39]. A review of pain in SLE has stressed the importance of accurate diagnosis of pain as either musculoskeletal, inflammatory (SLE- related) or fibromyalgia-associated in order to optimise management. This focussed approach may avoid over-treatment and unnecessary drug side effects [35].

Physical functioning

Poor physical functioning has a number of consequences for SLE patients including unemployment, especially those with limited or no formal education. Living with SLE may be a major hindrance to financial stability. Other studies have found that, lack of education correlated with poor socio-economic status (SES) including lack of home ownership [40, 41]. Low SES has also been associated with low physical functioning, depression and high disease activity [42]. Complete work-disability after SLE diagnosis was seen in about 16% of Chinese patients while those employed generally had physically undemanding jobs or holding part-time jobs. In this study, there was a strong inter-relationship between work impairment, a low level of education and reduced functioning associated with pleurisy, pain, and longer disease duration [43].

The majority of studies have found that disease activity is also strongly associated with a poor SF-36 physical component score [44-48]. A cross sectional study in South Africa (SA) amongst black South Africans demonstrated a globally reduced HRQoL due to functional disability as a result of high disease activity and body pains amongst SLE and rheumatoid arthritis patients [40]. The findings from another study indicated that the more active the SLE, the greater the risk of physical and psychological deterioration [44]. A Swedish study amongst different age groups concluded that HRQoL in SLE is generally lower for people with SLE but that working ability can be associated with a better HRQoL [49]. However, the authors suggested that more research on this field is needed to substantiate this evidence. In the same setting, fifty percent of the participants self-reported fatigue, musculoskeletal distress and pain as the most dominating features in their lives and those reporting only fatigue had better physical and mental aspects of HRQoL [50].

Fatigue

Similar to pain and poor functioning, fatigue is multifactorial and may be related to SLE disease activity itself, SLE treatment as well as deconditioning with long term decrease in physical activity due to body pains, cardiac dysfunction, muscle weakness, insomnia, renal dysfunction or depression [51, 52]. This notable feature of SLE needs to be carefully considered in any assessment and treatment plans as it could hinder optimum patient care and management [52, 53].

Fatigue is now recognised as a major problem experienced by a large percentage of SLE patients and is best measured by patient reported outcomes (PROs). A Swedish qualitative study using semi-structured focus group discussions together with two self-administered questionnaires exploring fatigue, concluded that fatigue in SLE is complex and overwhelming for SLE sufferers [54]. The main themes in this Swedish study included the nature of fatigue which controlled the participant's individual lives and was beyond explanation, unpredictable harsh occurrences, and paralysing fatigue sensations. In addition, fatigue had a negative impact on social activities, family life and work for these participants. Ninety-five percent of SLE patients enrolled in a USA qualitative study self-reported fatigue as a severe negative experience impacting on their cognition, occupation, family and social life [55].

1.6 Lupus Nephritis

Renal involvement in SLE, known as lupus nephritis, is a complicated and frequent feature of SLE. Nephritis is diagnosed by renal biopsy or clinically (proteinuria and urine red cell casts) in contexts with resource constraints [18, 56, 57]. In its most severe state, lupus nephritis can lead to end stage renal failure requiring dialysis or kidney transplant [57]. It is estimated that about 40% of SLE patients are diagnosed with lupus nephritis. Despite established and emerging treatment regimes, nephritis is a predictor of poor outcomes including mortality, especially in patients from a poor socio-economic background [56, 58, 59].

Availing renal services, timely diagnosis and management of nephritis, encouragement of patients to adhere to therapy and monitoring serum drug levels for adherence are some of the strategies that have been recommended [56].

1.7 Mental health and Neuropsychiatric SLE (NPSLE)

Undesirable physical changes, pain, fatigue, challenges in fertility, pregnancy and limitations in physical activities can cause depressive and anxiety symptoms in SLE affected individuals leading to psychosocial distress and affecting their HRQoL [54, 60, 61]. Recent research in the USA showed that African-Americans and Hispanics experienced higher levels of depression and anxiety levels compared to other ethnic groups [60]. These patients lived in low SES and described lack of control over their SLE, physical limitations due to muscle and body pain, body changes and uncertainty about the future as their major concerns. In addition, they indicated needing psychosocial interventions to cope with such feelings.

Neuropsychiatric SLE (NPSLE) affects 14 to 90% of SLE patients [62, 63]. The clinical manifestations range from diffuse to focal and from mild to life threatening states and are therefore associated with high morbidity and mortality [64, 65]. Central nervous system (cognitive dysfunction, headaches, psychosis, acute confusion status, mood disorders such as depression and anxiety) and peripheral nervous system (neuropathies, demyelinating polyneuropathies and myasthenia gravis) involvement are described [65]. NPSLE remains challenging to diagnose and manage and therefore requires multi-modal clinical care and management [64, 65].

1.8 SLE and pregnancy

In women of child-bearing age, SLE can complicate contraception choices, challenge fertility, or flare during pregnancy, requiring complex management during pregnancy and the postnatal period. Anti-phospholipid syndrome (APLS) has been described as the main causative factor of negative pregnancy outcomes. This autoimmune thrombotic disorder is characterised by the presence of antibodies that attack anti-phospholipid protein binding instead of the phospholipid itself leading to vascular thrombosis [66, 67]. In pregnancy, negative maternal outcomes and complications resulting from APLS range from recurrent miscarriages, placental insufficiency, premature delivery, oligohydramnios, prematurity, intrauterine growth restriction, fetal distress, fetal to neonatal thrombosis, pre-eclampsia/eclampsia, HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome, arterial or venous thrombosis [67].

Although SLE does not alter fertility specifically, there is an increased risk of spontaneous abortions and premature deliveries amongst SLE patients [23]. A retrospective cohort of Saudi Arabian women with SLE reported significantly low live births, increased risks of fetal deaths and preterm births. In this study, disease manifestations such as lupus nephritis, antiphospholipid syndrome, hypertension and high disease activity were the main contributing factors to these unfavourable outcomes [68]. This finding was supported by a systematic review which meta-analysed 37 articles featuring outcomes of 2751 pregnancies and it was concluded that for SLE patients, both lupus nephritis and APL increase the risk of maternal hypertension and premature deliveries [69].

Management of pregnancy in patients with lupus nephritis can be complicated as drugs of choice targeting disease remission could be detrimental to the foetus or baby [70, 71]. A retrospective review of 61 pregnancies at Groote Schuur Hospital, SA, found that women with lupus nephritis experienced more flares, pre-eclampsia, long hospital duration and low birth weight compared to SLE patients without nephritis [72]. Though pregnancy outcomes can be successful in SLE, according to a Chinese retrospective cohort, fetal echo investigating all the heart structures and functionality is essential as this cohort revealed significantly higher congenital malformations compared to the general population [73]. While some studies encouragingly state that, in cases where pregnancy is viable, maternal disease status does not affect the infant, there is conflicting evidence in other studies citing higher congenital malformations in pregnant SLE patients compared to the general population and advocating for more research on this issue [23, 73].

Furthermore, women with SLE suffer from a wide range of issues that surrounds childbearing. These important factors, such as aesthetic concerns and fatigue affecting both physical and emotional health and in turn affecting intimate relationships and chances of conception, remain under-published concepts that need attention.

1.9 Assessment of outcomes in SLE

Disease Activity

In addition to accurate SLE diagnosis, monitoring disease activity and assessment of accrual damage, is crucial throughout the disease course [74]. In clinical practice, different tools have been designed and validated to measure disease activity. The SLE Disease Activity Index (SLEDAI), which comprises of the SLEDAI 2000 (SLEDAI-2K) and Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI versions is widely used in clinical settings [75, 76]. The physician global assessment tool (PGA) score is also important in determining disease activity [77]. Recently, other authors have advocated for the use of SLE Disease Activity Score (SLE-DAS) due to its higher sensitivity and accurate recognition of clinically meaningful changes over time [78]. Other validated tools used across settings are the British Isles Lupus Assessment Group (BILAG) Index, Systemic Lupus Activity Measure (SLAM) Index, European Consensus Lupus Activity Measurement (ECLAM).

Damage

The Systemic Lupus International Collaborating Clinics (SLICC), also known as the SLICC/ ACR Damage Index after its validation by the ACR, is a standardized tool to measure irreversible organ damage [74].

Patient reported outcomes

PROs are health outcome measures that take the patient's impressions and experiences of their disease into account and allow a broader understanding of the patients' health status from their own self-reported perspective. They include measures of functioning, disability, quality of life or general perceptions of health [79]. These questionnaires are used to compliment the clinical assessment. Considering the complexity and heterogeneric nature of SLE, assessing patient's daily personal experiences and perceptions play a vital role in holistic management of the disease.

1.10 Co-morbidities in SLE

Patients diagnosed with SLE frequently have a burden of living with more than one illness. The main comorbidities of SLE are osteoporosis, infections, malignancies and cardiovascular diseases [80]. In the developing world, some of these comorbidities, in particular infections, are more common, and SLE carries a higher mortality in these countries [81]. A study in SA found that overall, almost 80% of SLE patients experienced more than one co-morbidity. The commonest were hypertension (42%), serious infections (36.6%) and tuberculosis (18.8%) [82]. Tuberculosis [82] and serious infections were the main causes of deaths. This is in keeping with SA's high TB and human immune deficiency virus (HIV) prevalence [83]. Other studies in SA conducted amongst participants from a poor socio-economic background affirm these results [84, 85]. One study in Durban, found that infections were the main cause of death in 14% of patients who in addition had high SLEDAI scores [84]. Infections, accounting for about 33% of deaths, followed by renal failure (16.4%) were common as reported by a retrospective cohort analysis at Chris Hani Baragwanath Academic Hospital, Johannesburg.

A review published in 2017 assessing the incidence and prevalence of co-morbidities particularly cardiovascular diseases, malignancies and osteoporosis in SLE patients recommended that in addition to targeting remission stage of SLE, it is vital to apply effective approaches in managing co-morbidities [86]. These should be a combination of preventative strategies and drug therapies, such as screening and managing risk factors and specific treatment for coronary heart diseases.

Assisting patients to quit smoking to decrease the risks of cardiovascular diseases, and implementing cancer screening programmes to exclude cervical cancer or early detection of cervical dysplasia and timely management can increase survival in SLE patients [87, 88]. When assessing risk for cardiovascular disease, traditional risk factors, such as age, male sex, arterial hypertension, dyslipidaemia and smoking, in addition to disease-related risk factors such as disease activity and duration, accrual damage, anti-phospholipid profiles, and the presence of nephritis need to be taken into account [89]. This highlights the complexity of caring for SLE patients, requiring a considerable resources and expertise which could be challenging to achieve in poor settings [90].

In addition, due to lack of sun exposure and constant use of sunscreen, SLE patients may have low vitamin D levels [70]. Osteoporosis risks should be minimized and approaches aiming at increasing bone strength, its mass and fracture risks should be integrated in SLE management [86]. This might include weight-bearing exercise, use of bisphosphates, vitamin D supplementation and minimising corticosteroid dosages [70, 71]. Constant health education and ensuring the patient stays well informed is critical to avoid confusion during therapy changes [91, 92].

1.11 Quality of Life in SLE patients

According to the World Health Organisation, HRQoL can be defined as a “multi-dimensional aspect in individuals which involves their experiences and perceptions of physical, psycho-social and mental states including their satisfaction of life’s goals, achievements and concerns” [93]. These concerns are measured best by either PRO questionnaires, or by qualitative interviews. In comparison to the general population, HRQoL is poor in SLE due to the multifactorial nature of SLE and high disease activity [94].

An extensive literature review by Schmeding et al [95] focused on published research reflecting on ≥100 patients with SLE. They reviewed HRQoL, function/disability, patient perceptions/experience of their illness, physical/psychological/social impact, unmet needs and work disability/employment status or specific signs/symptoms expected to impact on HRQoL and activities of daily living (ADL). The main findings were that, compared to other chronic illnesses or the general population, SLE patients have the worst HRQoL and highest rate of disability. In addition, the main predictors of poor undesirable HRQoL were old age, fatigue, high disease activity, organ damage and the presence of co-morbid neurological or mental disorders, particularly depression or anxiety. Despite these detailed findings, a research emphasising primarily on HRQoL in SLE was recommended for clarity on and confirmation of most of the findings [95].

1.12 Disease management and adherence to treatment

This disease remains incurable, and despite improved therapy over the last few decades, still carries a mortality two to five fold that of the general population [96, 97]. There is clearly a need for better medical and non-medical interventions to manage the many manifestations of SLE [1, 22]. A holistic pharmacological and non-pharmacological approach is required in the management of an SLE patient, and a multidisciplinary team approach is the most successful [22]. Early treatment of SLE may result in better HRQoL. In the USA, the results of a multi-centre, double blinded controlled trial involving patients with arthritis showed significant improvement of quality of life with early therapy initiation [98]. In SLE, treatment of lupus nephritis particularly within the first year has shown to improve HRQoL [99]. In addition, special conditions, such as pregnancy and post-partum, require safe drug choices and careful monitoring to preserve the health of both the baby and mother [70].

Patients need to be on chronic therapy, and this medication is prescribed to manage acute life threatening disease manifestations, and to reduce the risk of flares and co-morbidities [70, 71].

Patients’ experiences of flare-up and remission trends can affect their adherence to therapy, and patients in remission are frequently tempted to stop therapy, triggering a disease flare [70]. Table 1.2 summarises SLE management [1, 70, 71, 100, 101].

Evaluations of adherence to SLE medication has been reported to be very challenging and studies show a wide range of 3 to 78% adherence rate [91, 102]. A qualitative study involving interviews and medical record review of SLE patients in the USA showed a maximum of 61% adherence, substantially lower than the ≥ 80% recommended therapeutic response rate [91]. In this study, significant risk factors for poor adherence included limited understanding by physicians, illiteracy, being single, busy schedules, existing co-morbidities and dislike of chronic medication [91].
A study in the USA investigating the relationship between morbidity and socioeconomic status and race found a strong association between high morbidity due to renal failure among patients that were poorly adhering to the medication. Although race did not play any independent significant role as a contributing factor to morbidity, a large proportion of black patients, who mostly had poor medical insurance, were prone to poor medication adherence, complications of renal disease and hypertension [103]. A focus group discussion amongst SLE and rheumatoid arthritis patients in Texas-USA, exploring determinants of treatment adherence, found that patients with financial challenges were unable to purchase medications [104]. Generally, the higher the disease activity, the more medications are needed, hence the higher the purchase price. In addition, some patients expressed doubts about treatment efficacy as a reason for not taking prescribed medications. Other contributing factors to adherence were distance and transport costs to hospitals, physical limitations due to disease complications and failure to keep hospital appointments [102, 104, 105].

Clinicians depend on patient reports, records of pharmacy script purchases and laboratory drug levels to evaluate adherence, but sometimes this information cannot be obtained. Inaccurate assessment of adherence could lead to misinterpretation of response to treatment, leading to incorrect decisions about disease management which might be detrimental to the patient’s health. Therefore, better tools are needed to measure adherence [106].

Table 1.2: Pharmacological and non-pharmacological management of SLE

	Class	Medication	Comments
Pharmacological (Drugs)	Antimalarial	Hydroxychloroquine	Regular eye test due to retinal damage.
		Chloroquine	
	Corticosteroids	Methylprednisolone	Aim for lowest and short term use. Avoid betamethasone and dexamethasone in pregnancy.
		Prednisone	
	Non-steroids anti-inflammatory drug and aspirin		Use with caution especially last trimester in pregnancy. Carries risks of gastrointestinal ulcer (use with proton-pump-inhibitor).
	Immunosuppressants	Azathioprine	
		Cyclophosphamide	Teratogenic in pregnancy. Aim for low dosages.
		Mycophenolate	Teratogenic in pregnancy also avoid during breastfeeding.
		Cyclosporin	Avoid in pregnancy/ postpartum.
	Biologics	Rituximab	TNF inhibitors, Abatacept and Tocilizumab available for off-label use. Belimumab contradicted in lupus nephritis while Rituximab may be used in severe renal and central nervous system diseases.
		Belimumab	
		TNF inhibitors	
		Tocilizumab	
	Other	Intravenous immuno-globulins (IVIGs)	Effective in treating severe hematologic manifestations.
		Plasmapheresis	Associated with patient's discomfort, costly and technical.
		Isoniazid prophylaxis	To avoid tuberculosis.
		Omeprazole/lansoprazole	To avoid gastrointestinal ulcers.
		Safe contraception	To target pregnancy at remission.
		Vitamin D	Due to less sun-exposure.
Non-pharmacological	Recommended	Diet	Fish oil may be beneficial. Healthy balanced diet
		Sunscreen ≥ SPF 50. Avoid direct sunlight.	

	Class	Medication	Comments
		Screening for comorbidities co-morbidities and infections screening	Annual ophthalmological assessments (screening for early antimalarial maculopathy) Annual pap smear (screening for cervical cancer), Vigilance for infections. Treat and manage any condition according to relevant protocol.
		Psychosocial counselling	For mental and emotional support.
		Regular exercise	To improve metabolism and associated diseases such as diabetes, cardiovascular diseases, obesity, improves mental health, improves bone and muscle strength. Also has a positive impact on general health.

1.13 Lupus around the world

SLE occurs world-wide, and over the last 50 years there has been a significant increase in incidence, especially in developed contexts [107]. In 2017, a systematic review of epidemiological studies on the incidence and prevalence of SLE worldwide was published [108]. North America showed the highest incidence of about 23.2/100 000 person-years and prevalence of around 241/100 000 people compared to other continents, with people of African origin accounting for the highest prevalence. In Northern Australia, no SLE cases were found in a sample of 847 participants, while in Zimbabwe (Africa) and Ukraine (Europe) had the lowest rates, (both 0.3/100 000 person years available only in Ukraine data). Figure 1.3 shows the incidence and prevalence of SLE [109]. Map A shows the global incidence while Map B shows the global prevalence of SLE.

For decades SLE was reported as rare in Africa, and in SA, the incidence of SLE in 1990 was reported to be 12.2/100 000 amongst black South Africans [108, 110]. Recent surveys and clinical reports suggest that SLE is not as uncommon on the African continent as previously reported, and that diagnostic delays due to poor access to health care, poor awareness and limited number of specialist physicians might underlie the apparent low prevalence of the disease [90]. On the map below, countries such as SA, Egypt, Kenya have no data but a few studies on SLE patients have been published [40, 42, 84, 111] indicating a lack of epidemiological data in the continent accounting for the underestimated or non-estimated prevalence and incidence. Research focusing on SLE and ethnicity has shown that the individuals with African ancestry in North America had the highest prevalence [1, 18, 107, 112]. Although people with African ancestry have the highest incidence and prevalence, the 2017 review included only one study from the African continent, reflecting a lack of epidemiological studies and data in this region [108].

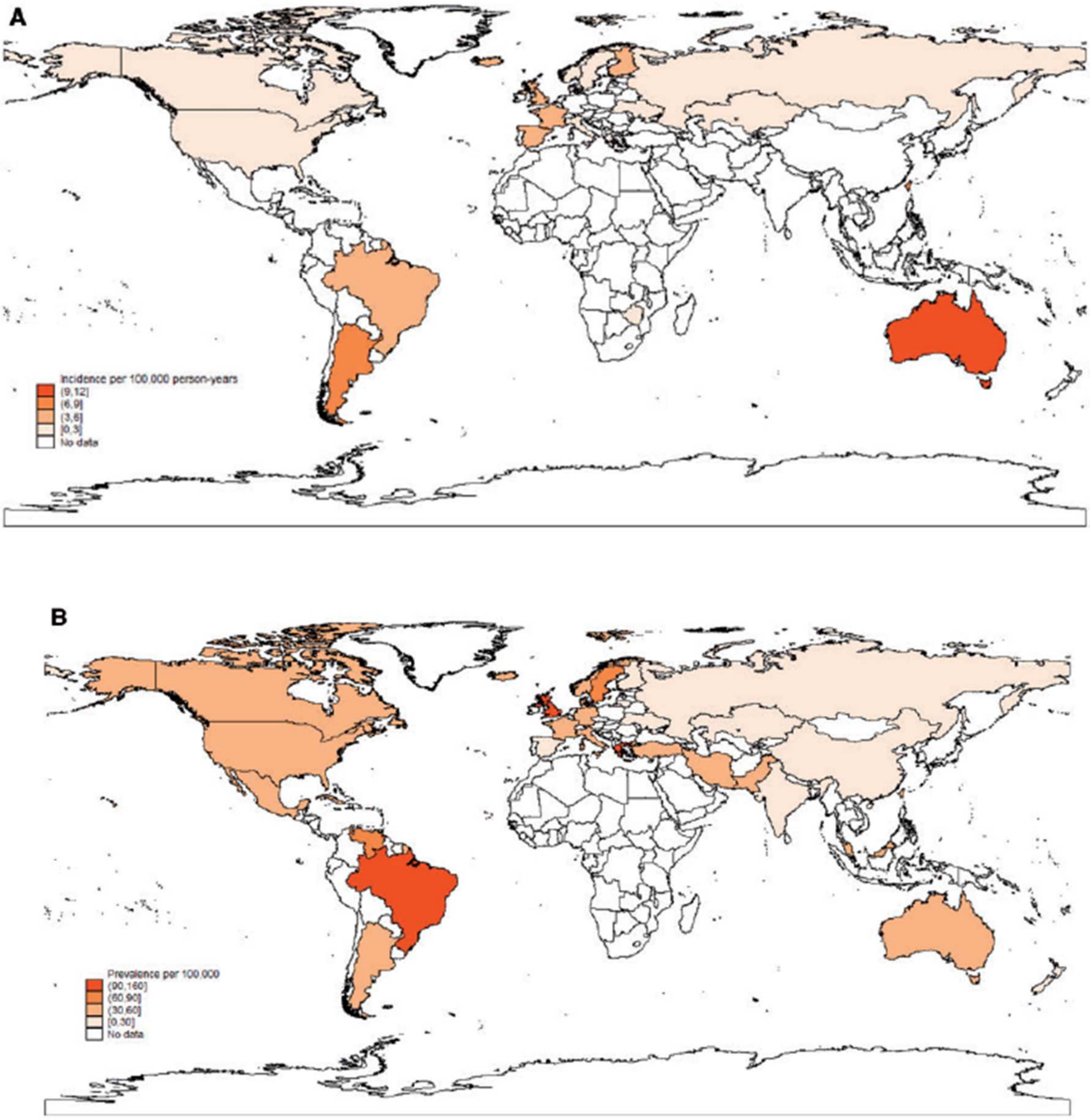

Figure 1.3: World map showing the incidence and prevalence of SLE in 2017

Image obtained from journal with permission for re-use electronically and imprint [108].

1.14 Poverty and SLE in the developing world

The World Bank describes LMICs as the ones in which the population have either one of the following characteristics: poor basic public services such as education or health; collapsed government rule through conflicts; unsustainable, poor turnover in agriculture with low and unstable income [81, 113]. The three regions with the majority of developing countries are Africa, Asia and South America.

Poverty is an important predictor of poor outcomes in any chronic illness. Multi-ethnic cohorts have demonstrated that SES affects SLE outcomes more than ethnic background [114, 115]. In a review of SLE in LMICs, survival rates of SLE patients was shown to be as low as 65% compared to the over 90% 5-year survival seen in high income countries (HICs) [81]. The factors behind this higher mortality were late prognosis, delayed or poor intervention and co-morbidities of infections [81]. The findings of a qualitative study with women living with rheumatoid arthritis in SA indicated that poverty worsened women's experiences which included pain, decreased level of functioning, social interaction, access to facilities and earning a living [116]. A paediatric SA study found that transport costs to seek medical care was the main obstacle for SLE patients to access care which increased SLE disease progression leading to irreversible organ damage in children [105]. To date, data on HRQoL or the direct and indirect medical costs of SLE from LMICs, and sub-Saharan Africa in particular are scarce.

In summary, despite recent advances, SLE remains complex and incurable and therefore carries a high mortality rate. Its unpredictable, relapsing and remitting course can have devastating consequences for the patient and her community, and particularly in the resource-constrained African continent where we have little data on the disease [60, 117]. In 2005, Benitha and Tikly advocated for a South African large scale, longitudinal study on HRQoL and SLE in order to facilitate health management planning [40]. This study is in part a response to that call.

1.15 Gaps to be addressed and Thesis Rationale

In the post-apartheid era, SA's health system is either public (state) or private, with the majority of the population relying on state services which is accessible at low or no cost. To date, the state health system remains resource-constrained.

The literature presented above has shown that compared to developed or HICs, research on SLE in developing countries is limited. There are no published prospective studies on HRQoL in SLE patients from sub-Saharan Africa, and no research has yet been done to explore and investigate functional status, depression, illness perceptions, or the impact of the illness on social life and self-confidence, fertility issues or indeed other outcomes that are important to SLE patients. This study aims to enrich our understanding of SLE patients' lives through this mixed methods approach. This information should contribute to refining the focus of future health interventions for SLE patients.

1.16 Aim

This study was designed and conducted to explore the HRQoL, perceptions and experiences of female patients with SLE living in two metropolitan areas of SA. It focuses on each participant's experience of the disease and how it has and still is affecting their daily experiences and various aspects of their lives. Using both qualitative and quantitative methods, we explored physical concerns and functioning at diverse levels, fertility and pregnancy, psycho-social wellbeing, adherence and coping skills. In addition, different PROs were used to determine HRQoL amongst these individual women living with SLE.

This thesis comprises of publications derived from data collected using these methods, and a review on the studied subject pertaining to developing countries - contexts with similar characteristics as those in this study's setting.

1.17 Objectives

The overall objective of this thesis is to explore and determine the HRQoL, perceptions and experiences of SLE patients. The specific objectives are detailed below.

1. To map the existing literature on HRQoL in SLE patients living in developing countries, collating all the findings for dissemination, and to identify the gaps for the focus of future research.

The first paper 'Living with Systemic Lupus Erythematosus in the developing world', was conducted to determine any existing information on HRQoL amongst SLE patients living in the developing world or LMIC, such as SA. This review forms part of the thesis's background reflected in Chapter 2. It gives comprehensive published data from 31 studies conducted in 11 developing countries on HRQoL and it offers a model derived from WHO-ICF to describe HRQoL in women living with SLE (Figure 3.1).

2. To explore in depth women's experiences of living with SLE's.

This is addressed in Chapter 4 which is based on publication 2. The results give an overview of the "lived experiences" of SLE as described by the women included in the study.

3. To understand women living with SLE's experiences and perceptions on sexuality and reproduction.

This is addressed in Chapter 5 which is based on publication 3. This study's objective is specific to reproductive health. The women's narratives show the controversy that surrounds this. Gaps in practice are identified, discussed and recommendations are presented.

4. To explore and investigate fatigue, pain and functioning in SLE female patients.

In Chapter 6 (based on paper 4 currently under review). The aim is to correlate findings derived from a mixed methods approach to give a more in-depth understanding of the aspects explored. We used the Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue tool to measure fatigue, the Short Form (SF-36) as a general measure of HRQoL and Functional Assessment Instrument (FAI) as a measure of an individual's ability to perform daily activities and responsibilities at home and work.

5. To seek prognostic factors or "red flags" for poor HRQoL outcomes and indicators for good outcomes.

Chapter 7 discusses this objective through summarizing the results of the study. Through linking all the results, it gives a broader understanding on living with SLE in a resource-constrained setting and recommendations for better outcomes.

CHAPTER 2: Living with Systemic Lupus Erythematosus in the developing world- A narrative review

2.1 Overview

Most of our understanding of SLE and its negative impact originates from developed countries. We undertook a literature review on HRQoL among SLE patients living in developing countries for more understanding and to identify the gaps for the focus of future research.

Author's declarations and contributions: Appendix VII

Rheumatology International (2018) 38:1601–1613
https://doi.org/10.1007/s00296-018-4017-1

Rheumatology
INTERNATIONAL

REVIEW

Living with systemic lupus erythematosus in the developing world

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Received: 2 January 2018 / Accepted: 19 March 2018 / Published online: 26 March 2018

Abstract

Most of our understanding of SLE and its negative impact originates from developed countries. This review aims to collate existing literature on Health-Related Quality of Life (HRQoL) in SLE patients living in developing countries to identify the gaps for the focus of future research. A narrative literature review was compiled using selected MeSH terms to search EBSCOHOST for articles published between January 1975 and February 2018 pertaining to HRQoL in SLE patients in developing countries. 31 studies from 11 countries were included for analysis. Only one longitudinal, one randomized controlled trial (RCT), one qualitative study, and two intervention studies were found. High disease activity and organ damage were associated with poor functional ability, mental health and low socio-economic status (SES). Poor SES is a recurring theme in developing countries, and worsens all SLE outcomes by reducing access to healthcare, mental, social and emotional support systems. In developing countries, SLE has a globally negative impact on patients' HRQoL, similar to that seen in developed countries. There is an urgent need for more HRQoL studies, and in particular, longitudinal, qualitative and interventional studies in these countries to investigate unmet needs, and to explore novel strategies to improve patient outcomes.

Keywords Systemic lupus erythematosus · Health-Related Quality of Life · Developing world

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disorder that commonly affects the skin, joints, kidney and central nervous system. Many patients experience "flares" of inflammation in one or more organ system, interspersed with quiescent periods [1, 2]. This unpredictable course makes SLE frustrating for both patients and their clinicians. Uncontrolled inflammation, or the therapy used to control active SLE, may result in irreversible damage. Despite improved therapy over the last few decades, SLE still carries a mortality 2- to 5-fold that of the general population [1, 2]. Uncontrolled disease with nephritis or severe neurological involvement, in addition to co-morbid conditions such as infections and cardiovascular events, are frequent causes of death [3, 4]. In addition, studies show that SLE patients have significant unmet needs, in particular in the areas of uncontrolled skin and neurological disease, fertility and pregnancy, fatigue, adherence to therapy, and mental health [5].

According to the World Health Organization (WHO) [6], Health-Related Quality of Life (HRQoL) can be defined as a "multi-dimensional aspect in individuals which involves their experiences and perceptions of physical, psychosocial and mental states". In 2001, the WHO initiated the International Classification of Functioning, Disability and Health (ICF) with the intention of standardizing measurement and interpretation of health statuses, functioning and disability in individuals [7]. Various Patient Reported Outcome questionnaires have been developed, validated and used to quantitatively measure HRQoL, and qualitative interviews offer further in-depth insights [8–12]. Many tools offer a general score, but also measure different domains, allowing the clinician or researcher insight into the most severely affected HRQoL aspects.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00296-018-4017-1) contains supplementary material, which is available to authorized users.

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Examples are the 36-item short-form health survey (SF-36) which comprises the Mental Component Scores (MCS) and Physical Component Scores (PCS) [13], the WHOQoL-100 which gives a general HRQoL score from six domains: physical health, psychological, independence, social relations, environmental and spirituality [10, 14]. Other tools have been to specifically measure mental well-being [15–19].

A systematic review including participants from Europe, North America and Australia has shown that compared to other chronic illnesses or to the general population, SLE patients have the worst HRQoL and highest rate of disability [20]. Poor HRQoL was associated with older age, fatigue, high disease activity, organ damage and the presence of co-morbid neurological or mental disorders, particularly depression or anxiety. Future research focusing primarily on HRQoL in SLE was recommended [20].

SLE occurs worldwide, but for decades was reported as rare in Africa [21]. Recent surveys and clinical reports suggest that SLE is not as uncommon on the African continent as previously reported, and that diagnostic delays due to poor access to health care, poor awareness and limited number of specialist physicians might underlie the apparent low prevalence of the disease [22]. Most published research on SLE is from developed countries. However, certain clinical features of SLE, such as renal and skin disease, together with comorbidities, in particular infections, are more common in the developing world, and SLE carries a higher mortality in these countries [23].

To date, there are no published reviews that focus on HRQoL amongst SLE patients in developing or lower and middle-income countries. This review aims to map the existing literature to collate findings for dissemination, and to identify the gaps for the focus of future research.

Methods

This narrative review was conducted using recommendations by Gasparyan et al. and Green et al. [24, 25]. A narrative rather than a systematic or scoping review was selected to get a broader perspective on SLE and HRQoL regardless of the bias or quality of studies rather than determine the effect sizes of interventions [26].

A literature search was conducted through EBSCOHOST including CINAHL and PsycINFO, PubMed, MEDLINE and SCOPUS, using the keywords: Health Related Quality of Life/HRQoL/QoL and/Systemic Lupus Erythematosus/SLE/lupus, HRQoL in SLE patients, in least developed/underdeveloped/developing countries (by listing every developing country). The "Appendix" shows the search engine used during this review. More articles were sought by a snowballing method where references of all included papers were scrutinized, and relevant papers were assessed for suitability and included when they met the inclusion criteria [4]. The timeline of published articles ranged from 1975 to February 2018. Inclusion criteria were articles which included participants who were diagnosed with SLE according to the American College of Rheumatology (ACR) [27] or Systemic Lupus International Collaborating Clinics (SLICC) criteria [28]. English-language studies which reported any dimension of Quality of Life or HRQoL as defined by WHO [6], using either quantitative or qualitative methodology, with participants recruited from developing countries as classified by the United Nations were included [29].

Data analysis

NVivo 11 software was used to sort, arrange and map the data from included studies. The following information was extracted from each eligible article by AP: author and year of publication, study aim, design, population, location, SLE disease duration, HRQoL measurement instruments, outcomes and their associations. An independent assessor (BH) subsequently reviewed all studies and extracted data for data validation to reduce the risk of bias and errors.

Results

The search brought up 6364 records (Fig. 1). Duplicates or multiple publications from the same databases were eliminated. Irrelevant titles were excluded yielding a total of 1972 archives. A further 1806 studies from developed countries were eliminated. Articles not reporting HRQoL, editor's reports and interviews not related to the context studied were excluded but those comparing other illnesses with SLE were included, leaving 166 full-text articles. These articles were further scrutinized and 135 were excluded due to not reporting the review's outcomes of interest such those reporting only on illnesses other than SLE. In total, 31 studies were included in analysis. These comprised 30 quantitative studies, 28 of which were cross-sectional (C/S), and one longitudinal study, one randomized controlled trial and one qualitative study. Table 1 shows a summary of included studies according to continent and country. Each included study used a validated tool to measure a specific HRQoL outcome, as summarized in Table 2. The majority of studies used the SF-36 (Mental Component Scores and Physical Component Scores), World Health Organization Quality of Life (WHOQoL), Center for Epidemiological Studies Depression scale (CES-D), Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS).

The analysis of the outcomes and associations identified in the 31 studies were pooled into seven categories: general well-being (disease activity, severity and age), physical concerns (pain, functional disability and fatigue),

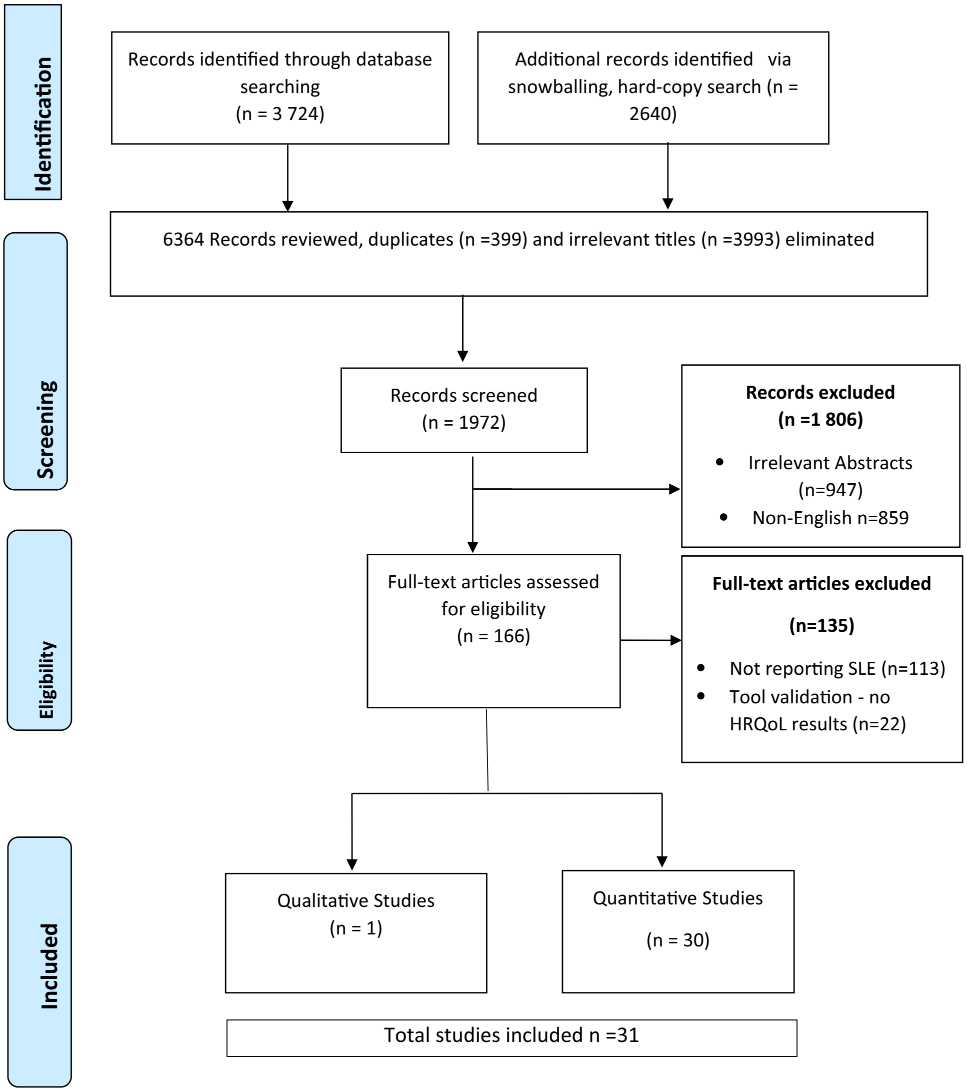

Fig. 1 Flow diagram showing selection of studies for the review

socio-economic status, mental health status (emotions and aesthetic concerns), health and the environment, social impact, spirituality and sexual well-being.

General well-being (disease duration, severity and age)

Conflicting results were reported across different studies regarding an association between disease duration and its impact on general HRQoL. A Chinese study showed that the longer duration of illness exposure, the better the HRQoL of SLE patients [40]. Patients with recent-onset SLE (≤ 2; mean 1.2 ± 0.6 years duration) had worse HRQoL scores compared to those with longer disease duration [(>2; mean 8.5 ± 5.2 years duration) ($p = 0.07$)]. The authors speculated that improved disease perceptions and coping mechanisms were some of these reasons for the changes [40]. However, a Brazilian study reported better HRQoL scores amongst participants with shorter disease duration compared to an SLE diagnosis of more than 5 years [87.3 vs 82.2% on the total WHOQoL score, ($p = 0.05$)] [10]. In an Iranian study, a larger percentage of participants (62.3%) with a disease duration of less than 3 months self-reported no depression compared to 37.7% among those with disease duration of more than 3 months. Though there were no associations with age, mild to moderate depression was associated with severe SLE [19]. A Kenyan study did not find any relationship between disease duration and HRQoL, but age significantly influenced certain domains. The older (age unspecified; range 14–71 years, mean 37.3) patients scored better in the physical ($r = 0.306$, $p = 0.016$), dependency on others ($r = 0.272$, $p = 0.032$) and emotional ($r = 0.315$, $p = 0.013$) HRQoL domains [31].

Table 1 Studies included in the review according to continent and country

Continent	Country	Year	Study	Aim	Study design, number of patients and controls	Outcome
Africa	Egypt	2015	Rafaat et al. [30]	Relationship between DA and depression	C/S (50 SLE 50 controls)	Major depression was more common in patients than controls
	Egypt	2014	Abdul Sattar et al. [15]	Role of neighborhood characteristics, on health status	C/S (80 SLE)	Rural residency was associated with higher depression symptoms and DA scores
	Kenya	2014	Odhiambo et al. [31]	Assess and correlate HRQOL with duration of illness, drugs used and age	C/S (62 SLE)	Advanced age was associated with better HRQOL
	Egypt	2014	Kotb et al. [32]	Prevalence of sleep disturbance and correlation with disease parameters	C/S (30 SLE)	Poor sleep was associated with longer disease duration and high DA
	Egypt	2012	Rizk et al. [33]	Effect of obesity on QoL	C/S (60 SLE 30 controls)	In SLE there is an association of BMI with dyslipidemia and decreased QoL
	Egypt	2010	Sliem et al. [34]	Impact of DA on QoL	C/S case–control study (59 SLE 20 controls)	The QoL of SLE patients with renal involvement was poorer than controls
	South Africa	2006	Benitha et al. [9]	FD and HRQOL	C/S (50 SLE 50 RA, 50 controls)	Physical function and general HRQOL are severely affected by SLE
Asia	Iran	2017	Solati et al. [35]	Efficacy of MBCT on psychological symptoms and QoL	RCT (23 experimental SLE, 23 controls SLE)	MBCT could improve patient’s psychological QoL, but not physical symptoms
	Iran	2016	Mirbhager et al. [36]	Sleep quality, its contributors and effects on HRQoL	C/S (77 SLE)	57% had poor sleep quality
	Taiwan	2011	Tseng et al. [37]	Impact of SLE on sexual functioning	C/S case-control design (279 SLE 1 580 controls)	Patients and controls had similar rates of sexual dysfunction
	Iran	2011	Zakeri et al. [19]	Prevalence of depression symptoms	C/S (85 SLE)	Depression was highly prevalent (60%) in SLE patients
	China	2011	Zhu et al. [12]	Prevalence and risk factors for loss of productivity	C/S (125 SLE)	Profound impact of SLE on patients’ labor and non-labor market productivity
	India	2017	Muhammed et al. [38]	Prevalence of neuropsychiatric manifestations and their impact on QoL	C/S (101 SLE)	Neuropsychiatric manifestations significantly affect QoL
	India	2009	Chadrasekara et al. [17]	Analyze sleep complaints, prevalence and associations	C/S (56 SLE)	Poor sleep quality was associated with DA, pain severity, FD and depression
	China	2008	Zheng et al. [39]	Examine HRQOL and social support	C/S (202 SLE 207 controls)	SLE have significant impairment of their HRQOL and less social support
	China	2008	Mok et al. [40]	Effect of DA and damage on HRQoL	Longitudinal case–control (155 SLE)	Organ damage is associated with poor HRQoL
	India	2004	Khanna et al. [41]	Assess the QOL	C/S (73)	Physical and psychological QOL are impaired
	Taiwan	2004	Huang et al. [42]	Explore disability, health-promoting lifestyle, and QoL	C/S (129 SLE)	Fatigue and pain were predicting factors of poor QOL

Table 1 (continued)

Continent	Country	Year	Study	Aim	Study design, number of patients and controls	Outcome
South America	Peru	2018	Elera-Fitzcarrald et al. [43]	Define factors associated with HRQoL	C/S (277 SLE)	High SES, disease duration, and use of antimalarials were positively associated with HRQoL
	Mexico	2017	Etchegaray-Morales et al. [44]	Assess DA, damage, depression and fibromyalgia and HRQOL	C/S (138 SLE)	SLE DA, damage, FM and depression were associated with poor HRQOL
	Mexico	2015	Mendoza-Pinto et al. [45]	SES and organ damage	C/S (143 SLE)	Low income may be associated with organ damage in Mexican SLE patients
	Brazil	2015	da Silver et al. [10]	Evaluate QoL of SLE patients	C/S (39 SLE)	Continuous specialized medical care could improve HRQoL
	Mexico	2015	Saavedra et al. [46]	Identify risk factors associated with flare during pregnancy	C/S (124 pregnancies in 120 SLE women)	First pregnancy associated with flare
	Mexico	2013	Garcia-Carrasco et al. [16]	IBS-type symptoms, their impact on HRQOL	C/S (105 SLE)	IBS-type symptoms are highly prevalent among women with SLE
	Mexico	2012	Garcia-Carrasco et al. [47]	Evaluate HRQOL	C/S (127 SLE)	Low HRQOL in SLE patients
	Ecuador	2010	Miles [48]	Understand the lived experiences	C/S (qualitative) (20 SLE women)	Women with lupus face structural constraints emotional burdens
	Brazil	2010	dos Reis et al. [14]	Evaluate the QoL	C/S (59 SLE)	The higher the DA, the worse the QOL
	Brazil	2007	Medeiros et al. [49]	Examine QoL	C/S (30 SLE 30 controls)	Poor HRQoL in SLE patients
	Brazil	2005	Ferraz et al. [50]	Translate the DLQI	C/S (71 SLE)	Active cutaneous lesions impaired scores
	Mexico	2004	Ruperto et al. [51]	HRQL and damage	C/S (297 JSLE)	DA and damage impair HRQL, particularly in the physical domain
	Mexico	1999	Valencia-Flores et al. [18]	Assess sleep disorders Correlate with DA and depression	C/S (14 SLE)	SLE patients reported to be sleepier during the day due to DA, restlessness and fatigue

BMI body mass index, *C/S* cross-sectional, *CP* cyclophosphamide, *DA* disease activity, *DLQI* dermatology life quality index, *FD* functional disability, *FM* fibromyalgia, *HRQoL* Health-Related Quality of Life, *IBS* irritable bowel syndrome, *SES* socio-economic status, *SLE* systemic lupus erythematosus, *JSLE* juvenile systemic lupus erythematosus, *SLEDA* systemic lupus erythematosus disease activity index, *RA* rheumatoid arthritis, *QoL* quality of life

Table 2 Tools used to assess Health-Related Quality of Life in included studies

HRQoL aspect reported	Studies utilizing tool to measure HRQoL
General well-being	WHOQoL-100 [10], Lupus QoL [31], SF-36 [40], BDI [19], CHQ [51], GHQ-28 [35]
Physical concerns	1991 (ACR) revised criteria for classification of functional status [44], VAS [17, 32, 42], CHQ [51], HPLP [42], DLQI [50], MSLT [18], SDQ [49], FSS [33]
	SF-36 domains: PCS, body pain, role physical, physical function and general health [9, 15, 16, 34, 35, 40, 46, 47, 49], WHOQoL-100 [10, 41].Semi-structured interview guide [48], Lupus QoL [31, 36, 44, 47], mHAQ-DI [9, 17, 30, 32, 33], PSQI [17, 32, 36, 42]
Socio-economic status	SES scale for health research [15], Economic demographics [9], Health-Promoting Lifestyle Profile [42], Semi-structured interview guide [48]. Socio-economic data questionnaire [40, 43], Graffar method and monthly household income [45], EQ-5D [12], SSRS [39]
Mental Health	SF-36 domains: MCS, mental health, vitality, social functioning and role emotional [35, 40, 49, 50], EuroQol-5D [38] Lupus QoL [43] WHOQOL-Bref [41], Semi-structured interview guide [48]. BDI [18, 19, 30], SRQ-20 [49], CES-D [15–17, 32, 44], HADS [36, 42]
Health and the Environment	Aesthetic environment and safety scales [15], WHOQoL [10, 14, 41]
Social status	SF-36: social functioning domain [9, 49], Social cohesion tool [15], WHOQoL -Social QoL domain [41], Interview guide [48]
Spirituality	WHOQoL [10, 14]
Sexual well-being	FSFI [37], Interview guide [48], WHOQoL Social; sexual activity domain [14]

ACR American College of Rheumatology, *BDI* beck depression inventory, *CES-D* Center for Epidemiological Studies Depression scale, *CHQ* Child Health Questionnaire, *DLQI* dermatology life quality index, *EQ-5D* Euroqol 5 dimensions, *FSFI* female sexual function index, *FSS* fatigue severity score, *GHQ-28* general health questionnaire, *HADS* hospital anxiety and depression scale, *HPLP* health-promoting lifestyle profile, *MCS* mental component score, *mHAQ-DI* modified health assessment questionnaires disability index, *MSLT* multiple sleep latency test, *SDQ* sleep disorders questionnaire, *PCS* physical component score, *PSQI* Pittsburgh sleep quality index, *SDI* systemic lupus collaborative clinics damage index, *SLICC* systemic lupus international collaborating clinics, *SF-36* short form 36, *SES* socio-economic status, *SSRS* social support rate scale questionnaire, *SRQ* self-reporting questionnaire, *VAS* visual analogue scale, *WHOQoL-100* World Health Organization quality of life-100

Only one study reported on HRQoL in juvenile or pediatric SLE [51]. In this multi-centered study conducted primarily in developed countries, Mexico was the only developing country [52]. The CHAQ-parent questionnaire scores were worse on the physical and psychosocial domains among the Mexican participants compared to other sites.

Eight studies included in this review reported on the effects of therapeutic interventions, including the effect of immunosuppressant drug therapy on HRQoL [10, 17, 19, 31, 43, 44, 46, 49]. In one study, antimalarials had a positive impact on HRQoL [43], but no other study reported a significant change in HRQoL outcome due to medication.

Physical concerns (pain, functional disability and fatigue)

Generally, SLE patients were described as having poor physical health scores, with physical functioning, pain, fatigue, and poor sleep as the main features. Disease activity was the driver of the poor SF-36 PCS in the majority of studies [9, 10, 17, 34, 41, 43, 44, 49]. An Egyptian study found a poor mean score of 51.4 on PCS domain of the SF-36, which was associated with high disease activity, and worse perception of their neighborhood, aesthetics and social cohesion [15]. In an Indian study, fibromyalgia was associated with high disease activity and poor HRQoL [17]. A study from China found no association between disease activity and general HRQoL, possibly because 67.0% of the participants had low disease activity. In comparison to their healthy controls, however, these participants had a low SF-36 PCS [53.0 ± 19.2 vs 81.8 ± 8.8 ($p < 0.001$)] [40].

A South African study compared SLE and rheumatoid arthritis (RA) patients, and showed that compared to healthy controls, both groups had significantly impaired HRQOL across all SF-36 domains, with RA patients having worse physical functioning, disability and pain than SLE patients. Disease activity in SLE patients was associated with pain, poor vitality, mental and global health [9]. In China, physical disability due to pain and pleurisy led to dependency on other people for activities of daily living when disease duration was an average of 46 days [12]. In addition, about 36.8% of these participants were reported to have disability hindering them from carrying out any employment, studies or leisurely activities.

Co-existing medical conditions have been associated with low HRQoL [16, 33, 46]. Irritable bowel syndrome (IBS) was associated with fibromyalgia and depression in a study from Mexico. These participants displayed poor HRQoL compared to other SLE patients without IBS using an SF-36 score [49.65 ± 18.57 vs 62.67 ± 18.14 ($p = 0.02$)] [16]. Obese patients were found to be at significant risk of nephritis and hypertension with a globally poor HRQoL

[33]. In Mexico, primigravid patients were shown to be at higher risk for lupus flares than multiparas [OR 2.3, 95% CI 0.99–5.52, ($p = 0.05$)] [46]. None of the included studies assessed loss of functioning in SLE due to cardiovascular involvement.

High pain scores were associated with higher disease activity and substantial risk of developing fibromyalgia, fatigue and poor mental health [17, 40, 42]. In China, poor physical function was significantly associated with older age, low educational level, high pain intensity and poor MCS in the Chinese version of the SF-36 [12]. Comparable results from a Mexican cohort highlighted that poor physical function due to pain forced individuals to seek social assistance [44]. In a Brazilian cohort of 39 women, disease remission was significantly associated with high mobility and better overall HRQoL (86.1%) compared to patients with high disease activity (80.5%) as measured by the WHOQoL-100 instrument and an unspecified clinical questionnaire [10].

Fatigue has been highlighted as an important predisposing factor to poor HRQoL. In Mexico, 138 women with SLE reported a mean score of 60.0% on the fatigue domain of the LupusQoL, and fatigue was mentioned as one of the most affected aspects of HRQoL [44]. Similar reports were found in a Peruvian study [43]. Fatigue was associated with both mental and physical impairment in a Taiwanese study. The participant's self-reported fatigue mean scores of (37.4 ± 26.6) were noted as the main markers for HRQoL. The authors conclude that treatment of fatigue is vital in general health promotion amongst SLE patients and suggested that health promotion strategies such as exercise, good diet, nurturing skills, positive outlook on life and stress management might have an indirect or direct effect on fatigue. A health-promoting lifestyle tool was developed to assess SLE patient's behavior towards promoting their own health indicating a low score of 61.5 (SD = 17.2) [42].

Five quantitative studies [17, 18, 32, 36, 42] investigated the impact of SLE on sleep among patients and the results were consistent across the settings, showing that SLE patients generally have poor sleep. In studies from Egypt and China, a high number of patients, (77.0 and 72.0%, respectively) reported poor sleep quality [32, 42]. Of patients reporting poor sleep disturbances in Egypt and India, 70.0 and 90.0% were not on sleep enhancement therapy, suggesting that many patients with poor sleep are undiagnosed, and untreated [17, 32]. Sleep disorders were associated with depression, disease activity and poor functional status but not with pain or prednisone use. Sleep disorders were found to be present in 57.1% of female SLE patients in Iran, and were associated with anxiety, depression, older age and increased body mass index [36]. The SRQ-20, electrocardiogram and poly sonographic data were used to assess sleep outcomes among Mexican SLE patients; restlessness, sleep disturbances and fatigue were the main findings associated with respiratory and general movement abnormalities. Poor sleep scores correlated significantly with disease activity [18].

Socio-economic status

Retaining employment is a major challenge amongst women suffering from SLE, with negative impact on socio-economic status (SES). Eight quantitative studies and one qualitative study reported on SES, and most showed a strong relationship between disease activity, organ damage and functional disability. The higher organ damage and disease activity scores, the lower the functional or work ability of an SLE patients. In one study, the longer the duration of high disease activity, the higher the risk of losing employment [42]. Low educational levels amongst SLE patients are strongly associated with low household income, unemployment and with greater organ damage [9, 42, 45]. Poor physical function as measured by the SF-36 was significantly associated with unemployment amongst patients with little or no formal education [9]. Similar findings are reported in a study from Egypt where poor SES was associated with low physical functioning, depression and high disease activity [15]. Poor overall HRQoL on the SF-36 amongst Hong Kong SLE patients had a strong correlation with low educational level and no home ownership [40]. The availability of social support was associated with better SF-36 scores overall, particularly in the social functioning domain in Chinese SLE patients [39].

A Chinese study reported that 44.8% of employed SLE patients had physically undemanding jobs, and 25.6% of these had part-time jobs [12]. A further 16.0% had complete work disability since SLE diagnosis. In this population, work impairment, a low level of education and reduced function associated with pleurisy, pain, and longer disease duration were interrelated [12]. In Miles's qualitative study from Ecuador, informants described the burden of SLE on employment with the majority reporting overwhelming medical and household expenses together with loss of work due to SLE. In addition, they explained that the possession of health insurance, together with the high costs of medical care influenced the treatment they could afford and thus affected their disease control [48].

Mental health status (emotions and aesthetic concerns)

Mental health was a focus in 17 articles included in this review. Amongst the quantitative studies which used the SF-36 tool, the MCS had poor scores ranging between 34.0 and 62.0% and these scores were worse with longer disease duration [40, 41, 49, 50]. There was a strong link between mental illness, high disease activity and low educational status amongst Brazilian patients who generally had a low HRQoL as measured with a SRQ-20 tool [49]. Similarly, a study from India had 32.7% participants presenting with neuropsychiatric manifestations and was associated with high SLEDAI scores [38]. Women with SLE interviewed in Ecuador described living with confusion, self-judgment. Furthermore, they expressed that dealing with the unpredictable nature of the disease and stigmatization by the community led to a very stressful life [48]. Other studies highlighted that the main predictors of poor mental health are loss of physical functioning due to high disease activity, comorbidities and low SES [16, 39, 40, 49].

Patients generally had low role-emotional scores in studies from Mexico and Brazil [44, 49]. Participants in a qualitative study expressed feelings of being a burden to others, deep sadness, unfulfilled intimate relationships and sense of failure and emptiness due to fertility struggles [48]. Depressive symptoms were very prevalent amongst SLE patients. In a cross-sectional study in Egypt, 64.0% of SLE patients vs 36.0% controls had major depression as measured by the BDS instrument [30]. The prevalence of major depression was 38% in Mexico and 40.0% in Iran SLE cohorts [18, 19]. Severe anxiety and emotional distress as measured by the HADS instrument was seen in 32.0% and 20.0%, respectively, in a Taiwanese study [42]. Chandrasekhara et al. in India used the CES-D score and showed that 70.0% of patients had depressive symptoms, and only 60.0% of patients were prescribed anti-depressive medication [17]. The authors concluded that depression is underestimated in SLE. Depressive symptoms were associated with low SES, higher disease activity, lower physical health, organ damage and co-existing medical condition resulting in general poor HRQoL [15, 16, 44].

The feelings of being a burden to others, with poor emotional scores as measured by the LupusQoL, were described amongst Mexican and Peruvian patients [43, 44]. In another Mexican study assessing the effects of cyclophosphamide therapy on HRQoL in SLE, patients with active disease scored significantly lower on the SF-36 role-emotional domain compared to patients with inactive disease, regardless of treatment type [49]. Qualitative interviews showed that SLE had a complex impact on the lives of Ecuadorian patients [48]. In addition to managing the disease, long-term relationships with men were challenging. These women frequently remained single and childless, leading to unhappiness, loneliness, lack of fulfillment and emotional distress. Modern interventions for infertility including artificial insemination evoked moral and social acceptance issues. Many of these women experienced feelings of guilt due to extreme adjustments done by their families to accommodate their illness.

Aesthetic concerns, when measured, were an important component of SLE patients' HRQoL. A translation and validation of Brazilian-Portuguese version of DLQI study further assessed HRQoL and found that alopecia had a significant negative impact on HRQoL [50]. Similarly, this aspect was an emerging theme in the qualitative study of Ecuadorian SLE patients. In addition, weight gain and general body appearance, particularly facial changes due to corticosteroid use influenced patient's emotional, social and mental well-being [48, 50]. An Iranian randomized controlled study found that a Mindfulness-Based Cognitive Therapy (MBCT) could improve patient's mental health [35].

Health and the environment

A patient's surroundings, including safety and security, comfort and contentment with living space is an important aspect in their well-being. Negative perception of the environment was associated with high disease activity in three studies [10, 14, 15].

Patient's perception of the environment was influenced by their values together with their interaction with their community. A Brazilian study found that participants with high disease activity had a tendency to have better scores on safety and security domain of the WHOQoL-100 scale. The authors speculated that this could be due to immense social support that their participants received at this critical stage of the illness [10]. Interestingly, a few studies reported different results. In an Egyptian study, negative perception of the environment in terms of safety, aesthetics, and social cohesion as measured by the aesthetic environment and safety scales was associated with lower physical role functioning and higher disease activity [15]. An Indian study found no associations between high disease activity and environmental HRQoL while in Brazil authors found very poor HRQoL scores among participants on the environmental domain of the WHOQoL-100 tool [14, 41].

Social impact

Research from India showed a good HRQoL for the social component of the WHOQoL-Bref with a mean (SD) of 15.4 (3.5) [41], and good scores were also shown in the Mexican social functioning aspect of the SF-36 [49]. Societal expectations can be an added burden to SLE patients. The Ecuadorian qualitative study [48] reported the unpredictability of SLE as an issue affecting informant's social well-being in relation to the people around them. Lack of disease awareness by other people led to the legitimacy of the patients' hospitalization and suffering being questioned by work colleagues and family members, especially because they appeared well and healthy on some days [48]. Similar experiences were reported in a quantitative study from Egypt, and in particular, single, female patients reported a poor sense of belonging and feelings of exclusion from society [15]. A South African study reported low and worse social functioning scores among SLE patients compared to RA patients and healthy controls [9].

Spirituality

Spirituality emerged as a theme in two studies that investigated HRQoL in SLE patients using the WHOQOL-100 questionnaire [10, 14]. These studies highlight a strong correlation between participant's belief systems and a positive outlook on life circumstances, suggesting that spirituality strengthened their ability to cope with their unpredictable disease and flares.

Sexual well-being

Sexuality is a very important HRQoL aspect for an SLE patient, and may be the most challenging to measure and treat [14, 37, 48]. These studies show that the multi-system nature of SLE affects not only intimacy between partners, but also fertility and pregnancy. The emotional burden of these issues is a struggle for many patients to cope with. In the qualitative study, women with SLE expressed feelings of guilt for the lack of intimacy with their husbands. Additionally, the shift in household roles, where husbands had to take on new roles because of SLE patient's reduced function, led to some patients questioning their sexuality as women, causing feelings of sadness [48]. A Taiwanese study found a higher prevalence of sexual dysfunction in SLE patients compared to healthy controls, and SLE was found to have an impact on the lubrication domain of the FSFI, due to secondary Sjögren's syndrome. Depression-related low libido together with vascular disease, pain, amenorrhea and menopause had a negative impact on the sexual health [37].

Discussion

Numerous studies have been conducted to investigate the impact of SLE in developed countries, and they demonstrate that SLE has a profound negative impact on numerous facets of life [8, 53]. This review identified 31 studies that focused on the HRQoL of SLE patients in developing countries in Africa, Asia and South America. These reports emphasize that, similar to patients in developed countries, SLE patients have interconnected and overlapping concerns which impact on their daily lives and functioning.

A systematic review from developed countries found conflicting results regarding a clear relationship between disease activity, organ damage and general HRQoL. Differences in physicians and patient assessments were cited as the contributing factors to this poor clarity [20]. Our review found that SLE is multi-faceted; disease activity and organ damage interact with a range of factors both within the person with SLE and external to them. These factors include perception of the mental health, social status, sexual health and the ability to function physically. This complex interaction leads to overall poor HRQoL. The ICF describes functioning and correlate disability as an outcome of the interaction between the person with a health condition and the context in which the person lives. Impairments and activity limitations interacting with a range of contextual factors lead to difficulty in doing various activities of daily life [7]. The HRQoL features of women living with lupus can be explained using a framework (Fig. 2).

Worldwide, poorer communities are more frequently and more severely affected by acute, chronic, communicable and non-communicable diseases [54]. This review highlights that SLE and its complications and comorbidities are heavily influenced by SES. Numerous studies including participants in poorer communities from developed countries have shown that socio-economic status (SES) and psychological well-being are strong independent predictors of outcomes in SLE; poor SES were associated with poor physical health and mental health status [8, 53, 55]. A multi-ethnic cohort, LUMINA, from Texas and Puerto Rico, showed that patients with poor SES, living below the poverty line or with low level of education, and lack of social support or poor sense of coherence tended to have low physical and mental health scores. In addition, participants who generally had poor HRQoL at initial assessment were likely to have poor HRQoL repeatedly at follow up visits [8]. In another multi-ethnic cohort from the USA, younger or old age, inadequate social support and poverty were associated with higher disease activity leading to poor mental status in SLE patients [53]. In a large USA cohort, good social support positively influenced participant's perceptions of their mental and physical health, leading to the "stress buffer concept" [55]. Amongst Canadian SLE patients, the intrusion of illness together with educational level were the most important predictors of psychosocial statuses across races. Black SLE women who had the lowest educational level had a high perception of illness interference in their lives and poor psychosocial well-being [56].

Up to half of SLE patients in developed countries are unemployed with gender, educational level, mental well-being, co-existing diagnoses, disease duration, and type of job influencing employment status [20]. The current review of developing countries shows that lack of facilities, limited infrastructure and the dearth of social security together with low levels of formal education, high unemployment rates, and dire economic circumstances for households affected by SLE are recurring themes. Poor SES worsens all SLE outcomes by reducing access to medical and mental healthcare, as well as social and emotional support systems. This limits

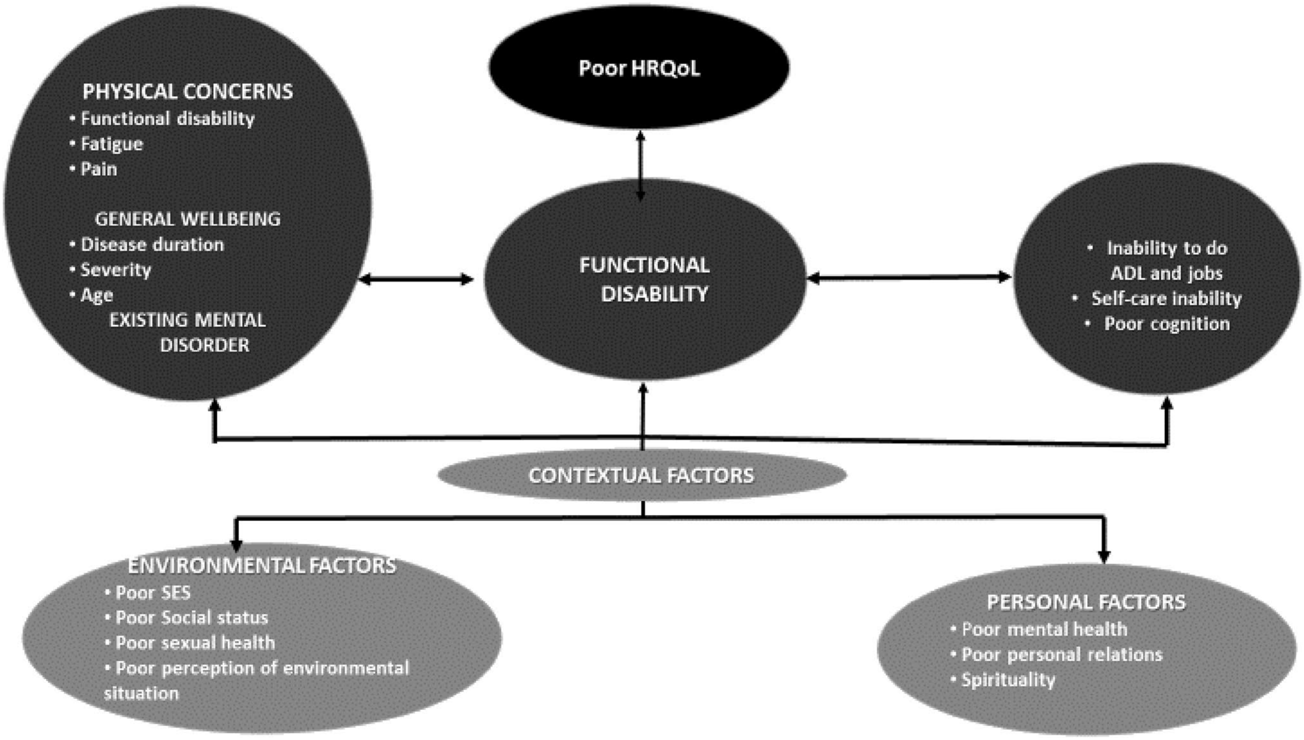

Fig. 2 Interactions between aspects of Health-Related Quality of Life in SLE patients using the International Classification of Functioning, Disability and Health (ICF) framework. *ADL* activities of daily living, *SES* socio-economic status, *HRQoL* Health-Related Quality of Life, *SLE* systemic lupus erythematosus

lifestyle options that can reduce the burden of pain and disability. In addition, in developed countries, there are accommodations for patients with chronic illnesses which might include assistive technology, health care insurance, social security, disability benefits, public transport, and labor policies, which mitigate the effect of SLE on employment. One study from a developed country showed that higher income and possession of medical insurance had a positive influence on the mental health of SLE patients [55]. In developing countries, low education levels often mean employment opportunities are restricted to physically demanding jobs, which may be a challenge for many SLE. Unemployment due to physical disability is associated with poor SES and poor mental health status.

The vast majority of SLE patients from eight studies in this narrative review were found to be living with depression. The general poor mental well-being of these SLE patients was multi-factorial with strong associations with poor physical and emotional health, socio-economic depravity, and poor coping mechanisms.

In this review, SLE patients had good scores in social functioning compared to other domains [41, 49]. However, the Ecuadorian qualitative study gave in-depth insights of the social struggles that SLE women face while a South African and an Egyptian study reported generally low social functioning scores. Summative conclusions from these authors suggest that a holistic approach to tackle poor scores on health perceptions in SLE patients could improve general HRQoL. Similarly, research from developed countries described that recognition, proper diagnosis and management of patient's negative health perceptions are contributors to good HRQoL [56, 57].

This review revealed that some important aspects of HRQoL were not measured or only to a limited extent, such as aesthetic concerns, fatigue, and environment and safety. Apart from the DLQI study, no research has been conducted in developing countries to explore the impact of discoid lupus and other SLE skin manifestations on HRQoL [50]. This facet is relatively well researched in developed countries using validated tools, and may be of high importance to dark-skinned patients in developing countries [58, 59]. Fatigue was investigated by only one study, yet has been widely explored in developed studies and is recognized as a major problem experienced by a significant percentage of SLE patients [42]. There is a strong need to validate the environment and safety scales in developing countries. Various non-Western cultural beliefs prevalent in developing countries including spirituality, superstition and the use of traditional or herbal medicines and their impact on HRQoL, adherence, and coping skills have not yet been explored amongst SLE patients, and are likely to be enrich our understanding of patient's experience of SLE specifically in this setting.

In addition, qualitative studies draw attention to opinions and problems of patients that would not otherwise have been measured by quantitative research [60, 61]. This review highlights that there are relatively few publications from developing countries addressing HRQoL, and of these there is only one longitudinal, one RCT and one qualitative study. In addition, only two intervention studies to improve HRQoL were found in this literature search [35, 42].

Limitations

Most of the studies included were cross-sectional studies, and outcomes and associations are difficult to interpret. Further, we were unable to assess the quality of each study. Only articles published in English were considered due to costs and time that are involved in translation. Thus, important studies from developing countries published in foreign languages might have been excluded. In addition, we acknowledge that the choice and use of search terms may not be adequate to extract all potentially eligible studies.

Conclusion

This review summarizes published evidence on HRQoL in developing countries, demonstrating that, similar to reports from the developed world, SLE has a global and complex negative impact on HRQoL. There is an urgent need for more studies to investigate HRQoL and its associations in developing countries. In particular, longitudinal, qualitative and interventional studies need to be undertaken to explore attitudes and unmet needs, and to test the effectiveness of novel strategies to improve patient outcomes.

Acknowledgements The authors acknowledge financial support from the South African National Research Fund.

Author contributions AP, MS, MT and BH were involved in the conceptualization, planning and execution of this review. All authors contributed to data synthesis and interpretation, simultaneous draft review and the final version of the manuscript.

Compliance with ethical standards

Conflict of interest Angel Phuti (AP), Marguerite Schneider (MS) and Mohammed Tikly (MT) received no research grants and each declare no conflict of interest. This study was funded by the National Research Fund (NRF); South Africa—Thuthuka Grant no: 443812. Bridget Hodkinson (BH) received this research grant and declares that she has no conflict of interest.

Informed consent This narrative review includes research studies that enrolled human subjects who had individually given an informed consent.

Research involving human participants All procedures performed in the studies (included in this review) involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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CHAPTER 3: Participants and Methods

3.1 Thesis overall design

Data were collected, analysed and presented using both qualitative and quantitative study methods.

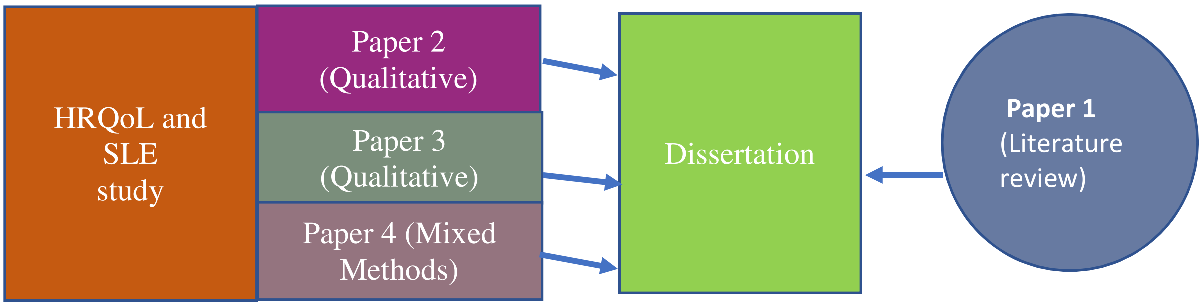


Figure 3.1: Illustration of thesis design

3.1.2 The importance of using qualitative and quantitative methods in SLE

Qualitative studies with in-depth interviews allow patients to “tell their stories”, and provide a rich and deep understanding of patients’ lives and the impact of a chronic illness [116, 118]. Individuals respond to and cope with interventions differently, and qualitative research captures important experiences that might otherwise be overlooked or missed in quantitative research, giving insights into cultural and socio-economic aspects of therapy [119]. Quantitative studies in health research focus on empirical investigations of an observed condition of interest in a group of people or a population rather than individual responses. In health research this method is useful in studying population and disease trends through quantifying data and drawing conclusions using inferential or descriptive statistics [120, 121].

Referred as the ‘third methodological movement’, Mixed Methods Research (MMR) has been proven to be the most effective and efficient aspect of conducting research that requires to be embraced by all researchers [122]. In addition, MMR ensures that through using both methods, information gaps are reduced and findings with good validity produced. This method can be applied at various stages of research: during study design, during the data collection process, at analysis level and integrated during data interpretation [122, 123].

The aim was to compile a thesis with MMR comprehensive data on HRQoL in SLE and for this reason, a review based on published work from contexts similar to ours is also included in Chapter 2. Figure 3.1 above illustrates the thesis structure.

3.2 Contribution to the research study

The PhD candidate (AP), who was not part of the clinical teams in Cape Town or Soweto, led in designing the research proposal for this study, ethics application, data collection, analysis, manuscript drafts and leading the publication processes. AP worked in paediatric rheumatology as a researcher and as a data capturer for the adult SLE registry and has a background in nursing and midwifery both as a researcher and clinician for approximately 10 years. The candidate is multilingual, and this skill was useful during data collection. The full details of contributions to all the papers and manuscript included in this thesis are elaborated in Appendix VII.

3.3 Participants

SLE Participants:

The study was conducted in two state-funded hospitals. Patients from the adult rheumatology outpatient clinic of Groote Schuur Hospital were recruited into the **A**frican **L**upus **G**enetics **N**etwork (ALUGEN) project, an established prospective multi-centred registry of SA SLE patients [124]. Other participants were recruited from the adult rheumatology clinic at Chris Hani Baragwanath Academic Hospital, Soweto. These Lupus clinics run on a weekly basis at Groote Schuur Hospital in Cape Town and Chris Hani Baragwanath Academic Hospital in Soweto, Johannesburg. Figure 3.2 below shows the cities where the research sites were situated. Qualitative and quantitative data was collected from all participants from both sites. We included only women in this study to narrow the scope to allow for more in-depth exploration of women's experiences without confounding it by gender. Furthermore, the FAI tool was developed specifically to explore the function of women with regards to child-care and household chores, and might be less applicable to men.

All SLE participants fulfilled the following criteria:

1. met the 2010 SLICC classification criteria for SLE [17]
2. Female gender
3. Age 18 years or older
4. Signed informed consent to participate.

Participants were excluded if:

1. They had been diagnosed with or showed symptoms of severe mental illness or were critically ill.

Healthy Controls:

Thirty healthy controls were recruited to complete the PRO questionnaires. These were age-matched healthy adult females (≥ 18 years) were recruited from the outpatient clinics of Groote Schuur Hospital.

3.3.1 Study Settings: Cape Town and Soweto (Johannesburg)

The study hospitals based in Cape Town and Soweto are tertiary referral hospitals, and are relatively poorly resourced. They serve indigent residents of the formerly segregated townships together with residents from distant rural areas of SA. Groote Schuur Hospital is situated close to Cape Town's city centre, requiring most patients to commute [125]. Chris Hani Baragwanath Academic Hospital, situated in Soweto, is the third largest hospital in the world. The daily challenges of indigent SA residents include unemployment, poor education, lack of proper housing and poor access to transport services [126]. Table 3.1 below shows the socio demographics in the studied population [127].

Johannesburg had the highest population of Black African ancestry (80%) compared to Cape Town which had more residents of mixed ancestry origin (47.5% vs 3.3% seen in Johannesburg). While 20% of study participants lived in informal dwellings, an equal number had insufficient income to buy food in Johannesburg compared to the 10% in Cape Town. Figure 3.3 shows a part of Soweto township were most of the study participants in Johannesburg lived.

Figure 3.2: Map of SA showing Cape Town and Soweto (near Johannesburg) were the two study sites were situated

Table 3.1: Socio-demographics and characteristics of people living in the city of Cape Town and Johannesburg highlighting the sociodemographic background of the study population (Statistics SA 2016).

	Cape Town	Johannesburg (GP)
Population size (n)	4 005 016	13 399 724
Gender (per province: WP & GP) %		
Females	50.7	49.6
Males	49.3	50.4
Race (per province: WP& GP) %		
White	16.0	13.6
Mixed ancestry	0.8	2.7
Coloured	47.5	3.3
Black African	35.7	80.4
Marital Status 18 years and older %		
Never married	43.1	47.8
Legally/ traditionally married	41.1	33.2
Cohabiting	6.0	11.4
Divorced	3.9	2.6
Separated but still lawfully married	0.9	0.8
Widowed	5.0	4.3
Highest education level among adults aged 20 years or more (%) (for GP, totals excludes those who answered ‘other, don’t know/unspecified’		
No education at all	2.1	7.8
Incomplete primary schooling	6.7	ND
Primary schooling	4.2	6.2
Incomplete secondary schooling	37.1	ND
Completed secondary school	35.0	76.1
Higher (tertiary) education	14.8	10.8
Food access (%)		
Households running out of income to buy food	12.7	17.1
Housing (%)		
Formal dwellings	81.6	81.3
Flush toilet in dwelling	92.8	88.6
Access to safe drinking water	93.7	94.1
Electricity	97.8	91.9

Abbreviations- WP: Western Cape, GP: Gauteng Province.

Figure 3.3: A part of Soweto with government funded houses and the informal houses known as shacks

3.3.2 Participant recruitment

Participants were recruited, screened and enrolled between September 2016 and February 2017. The sample size was dependent on the saturation level of the qualitative data collected and therefore, by the 25th participant, recruitment was stopped. In addition to the narratives, quantitative data was collected from these participants and from the 30 age-matched controls. The clinical co-authors identified potential participants and AP approached them privately and introduced the study. A private, quiet room in the clinic with a neutral environment was used during screening and enrolment. The purpose of the study was explained and all participants fulfilling the criteria signed the informed consent (Appendix VI).

3.4 Data collection process: use of tools and interviews in research

In the field of rheumatology, PROs in addition to clinical and laboratory measures of the disease are becoming increasingly important. These measures take the patient's impressions and experiences of their disease into account, and allow for a broader understanding of the patient's life [79]. Patients are the central core in the health system; therefore, their disease-specific, self-reported outcomes are vital in the final diagnosis, treatment and management [128].

PROs are largely structured lists of questions with little room for open-ended questions. According to Calvert et al [129], these questions are designed by researchers and clinicians and often lack patient's input. This can lead to exclusion of important information that could have been helpful to assess the patient's quality of life. Often patients have difficulties in understanding questions, or these are not culturally diverse, making the question irrelevant to the participant. That could lead to a patient either giving an irrelevant or no answer. This stresses the importance of using tools validated in a relevant setting [129].

Clinicians and researchers need to be aware that the tools are also disease or condition specific to gather relevant information [129, 130]. Some researchers argue that the role of PRO measures in maximizing patient care has not been fully established while others raise ethical concerns of inflicting the burden of completing numerous questions on patients for insignificant reasons. The design, interpretation and analysis of some PRO measures have also been reported to be difficult therefore needing a certain level of expertise on the part of the clinician [131-133].

For these reasons, we chose to take a more detailed qualitative look at the women's perceptions and experiences. In addition to conducting in-depth interviews, we then used relevant standard PRO tools to collect data pertaining to functioning and this was analysed as per the different tools' scoring system. These tools are described later in the chapter. Furthermore, the combined use of PROs and the interviews in Chapter 5 allowed us to explore how the two sources of information complement each other.

Qualitative interviews

Interviews were conducted in the language suitable for each patient. These were either English, Tswana, Sotho, Zulu or Pedi or a combination these languages, a common dialectal occurrence in SA urban areas.

The rooms used ensured privacy. In addition, a note was placed on the door to indicate that interviews were in progress to avoid noise and intrusions. The interview took place during clinic times at the convenience of the patient: either before consultation, if the waiting period before a patient to see a clinician was long, or after consultation while waiting for their medication at the pharmacy.

A topic guide (Appendix V) was used to elicit narratives on a range of themes such as experiences of the disease, particularly highlighting fatigue, pain, functioning, fertility and pregnancy issues, and aesthetic concerns of patients with disfiguring skin lesions, coping mechanisms and adherence to therapy. The study's aim and objectives were used as a guide to formulate the topics to be explored. A pilot version of this interview guide was tested on 4 participants before being finalised.

The interview started with the researcher welcoming the interviewee and introducing the study. The interviewee was given the opportunity to introduce herself. This varied from one interview to the next, with most relating the diagnosis journey and all the challenges earlier and some talking about their families and children. The researcher allowed the participants to do this to make them more comfortable while taking pointers on what the participant had included or not from the interview guide, and what could be explored further for in-depth information. While using the existing guide the researcher ensured all points stipulated were posed to the participant in an open-ended manner.

After each interview was transcribed, the researcher and supervisors (BH and MS) reviewed the transcript before further interviews were conducted to determine if additional topics should be included. One prominent adjustment was to explore the pain and fatigue phenomena further. The researcher asked the participants to give a visual picture of these experiences, including the frequency to give the researcher more understanding of the extent of the phenomena and to elicit further narratives. By the fourth pilot interview, questions were posed in a modified manner and few additional changes were made to the topics in the remaining interviews.

Adjustments to the interview guide were made when necessary prior to the main study to ensure relevancy to the all the participants. Questions and answers that were irrelevant to the study's aim and objectives were excluded in the analysis.

Quantitative data collection

All 25 participants with SLE were able to read and write sufficiently to self-complete the Functional Assessment Instrument (FAI) and the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue tool and the Short Form 36 (SF-36). The control participants who were also able to read and write completed the SF-36. The tools used are available on Appendix II, III and IV. Where necessary, the researcher assisted in clarifying questions participants did not understand. These were done on the day of the interview before the qualitative interview to avoid sensitization of the participants to the issues that may be discussed in the interview. In addition, we anticipated that after the interviews, participants might be tired or emotional, and therefore completing the questionnaire first would reduce biased responses. No repeat questionnaires were completed. The 30 healthy controls who were recruited from outpatients' department completed the SF-36 questionnaire while waiting for consultation or accompanying a patient to the consultation. They were consented in a private room and self-completed the questionnaire.

Functional Assessment Instrument

The FAI was developed as part of a randomised controlled trial testing an intervention for pregnant women with depressive symptoms in Cape Town. It is a measure of women's ability to perform daily activities and responsibilities at home. This includes a range of domains of functioning such as exercise, social interactions and community participation, taking care of self and others, and domestic activities [134].

The FAI was developed to complement the World Health Organization Disability Schedule (WHODAS 2.0) to assess functional difficulties in relation to everyday activities and tasks particularly relevant to women living in a low resources' peri-urban context like that of many of the women recruited in this study [134]. It consists of 10 questions covering self-care, care of others and social activities. Responses are graded on a scale range of 0-5 where 0 is *"No difficulty"* 1 - "*A little difficulty"* 2 - "*A lot of difficulty (but can still do task)",* 3 - "*Often can't do task or activity at all",* 4 - "*Can never do a task or activity"* and 5 is *"Not Applicable".* A response of 5 is not included in the overall scoring of functioning. A mean score of a sum of all the responses is compiled to give the overall level of functioning of a patient.

FACIT-fatigue score

The Functional Assessment of Chronic Illness Therapy (FACIT)- Fatigue Scale measures fatigue related experiences in the past 7 days for people with chronic illness; for example, feeling weak, listless, tired, washed out, energy levels, inability to execute and complete activities, abilities to do usual activities, sleep, eating habits, requiring assistance, frustrations due to limitations to do desired tasks and limitations to social activities [135]. The tool has been validated and used across a number of studies including participants with SLE and other chronic illnesses [61, 136-138]. A validation study in Iran including cancer patients found the tool to be relevant in assessing fatigue among these patients living in a LMIC. The FACIT instrument has 13 questions with responses ranging from 0-4 with 0 being "not all", 1 being "A little bit", 2 being "somewhat", 3 being "Quite a bit" and 4= "Very much" responses. Examples of questions are "I feel tired" and an answer to 0 means not at all. If the same participant is asked question 7 "I have energy" and selects 3 it means she/he has quite a bit of energy. The scoring reversal is done in a FACIT-fatigue instrument. The score ranges between 0-52. The higher the score in a FACIT-fatigue assessment the lower the level of fatigue experienced by a person and, therefore, the better the quality of life [136].

Short Form 36 (SF-36)

The SF-36 tool measures the health status in patients to determine their HRQoL [139]. It has 36 items of which 35 reflect 8 dimensions of health – vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health. This instrument also includes one item on how patients perceive their health. The eight domains are scored on a scale from 0-100 of which 100 indicates the best health status or HRQoL. A standardised scoring tool with set percentages is used to compile aggregate scores for each question that is relevant to a specific domain. The mean average of the scores in each domain is calculated to give a percentage measure of the health status of the patient. Unanswered questions are not considered [139]. This validated tool, proven to be reliable, is applicable in clinical or research settings and has been used across studies in various chronic diseases in both HIC and LMIC contexts [40, 140].

3.5 Data Analysis

3.5.1 Qualitative interviews

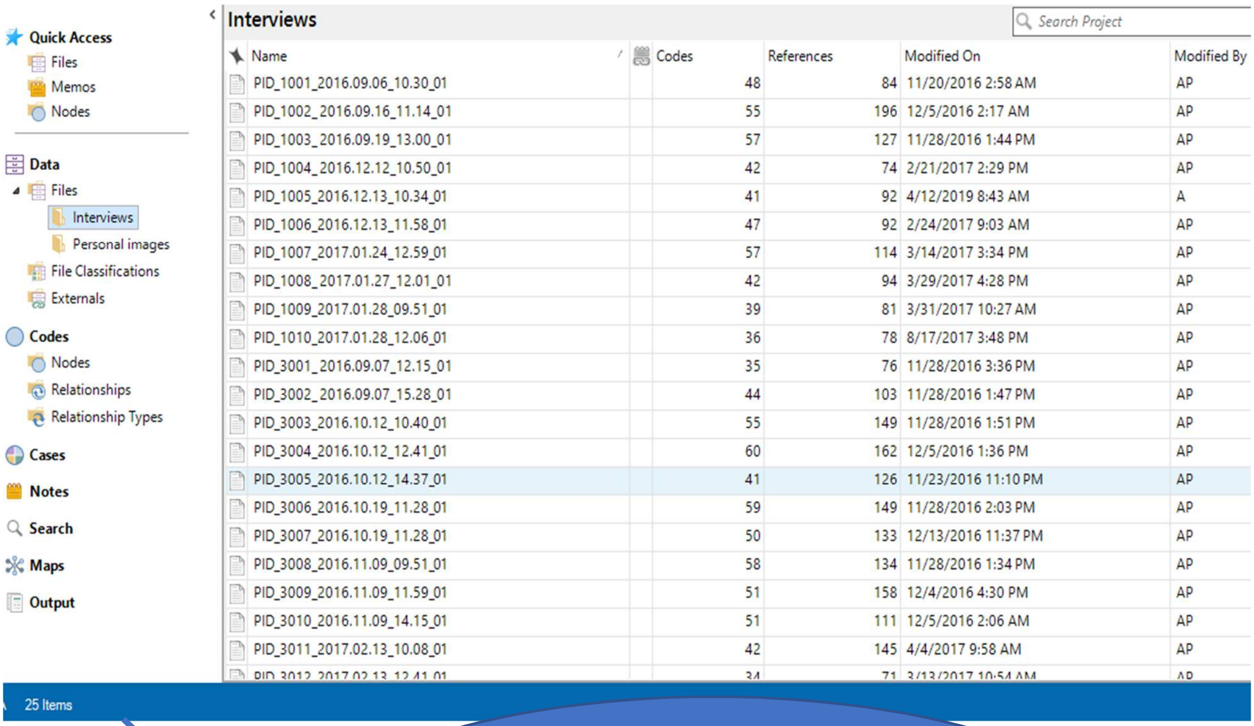
The phenomenology approach was used to conceptualize and develop theories which were later analysed. This inductive qualitative method is the best in 'rooting up' or bringing up issues that are taken for granted, misunderstood, biased or even assumptions that might have a negative impact on care and management of patients [141, 142]. Individual subjectivity is the essence of understanding and getting a picture of what these participants go through on daily basis, therefore, such information could challenge existing practices and fill in all the knowledge gaps where it is needed [141, 142].

Audio recorded interviews were transcribed and those in dialect were translated into English during the transcription process. To ensure validity and reliability of the transcripts, the researcher listened to the audio recorder and read through the text and made corrections where necessary. Themes were identified by AP and were discussed and refined together with the two supervisors. Major themes were physical concerns (fatigue, pain, functioning), socio-economic status (SES) (work function), mental health (aesthetic concerns and emotional health), social impact, sexuality and reproduction, and spirituality.

Narratives were sorted into themes using a coding system on the NVivo 12 software. To articulate the true experiences and perceptions of the participants during the analysis phase, the interviewer ensured that she excluded her own perception and emotions and interpreted the data using the themes or codes identified with ongoing discussion with supervisors. Data were arranged and categorised and all related themes were grouped into parent or child nodes to extract as much information as possible pertaining to experiences and perceptions of living with SLE. Parent node/ main node is normally 'the general information' and the child node are more 'specific'. Figure 3.4 shows the project on NVivo and the coding system. The researchers AP, BH and MS reviewed, discussed and refined the coding system. The Consolidated criteria for Reporting Qualitative research (COREQ) guidelines were used to report the results.

3.5.2 Quantitative data analysis

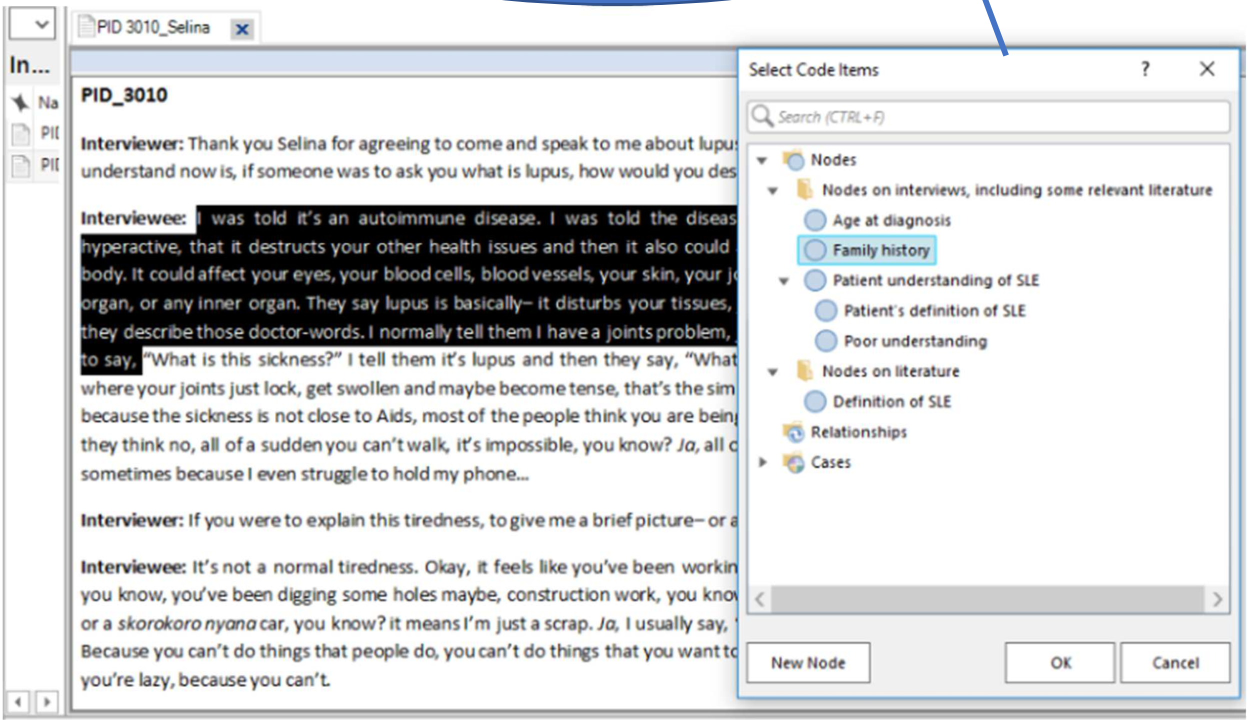
For all the 3 tools used in this study, the researchers followed each tool's standard scoring system. Descriptive statistics were calculated including Spearman correlations which were used to find associations between the variables within the tools. SPSS software was used for the analysis. A p-value of <0.05 was considered significant.



Interviews

Name	Codes	References	Modified On	Modified By
PID_1001_2016.09.06_10.30_01	48	84	11/20/2016 2:58 AM	AP
PID_1002_2016.09.16_11.14_01	55	196	12/5/2016 2:17 AM	AP
PID_1003_2016.09.19_13.00_01	57	127	11/28/2016 1:44 PM	AP
PID_1004_2016.12.12_10.50_01	42	74	2/21/2017 2:29 PM	AP
PID_1005_2016.12.13_10.34_01	41	92	4/12/2019 8:43 AM	A
PID_1006_2016.12.13_11.58_01	47	92	2/24/2017 9:03 AM	AP
PID_1007_2017.01.24_12.59_01	57	114	3/14/2017 3:34 PM	AP
PID_1008_2017.01.27_12.01_01	42	94	3/29/2017 4:28 PM	AP
PID_1009_2017.01.28_09.51_01	39	81	3/31/2017 10:27 AM	AP
PID_1010_2017.01.28_12.06_01	36	78	8/17/2017 3:48 PM	AP
PID_3001_2016.09.07_12.15_01	35	76	11/28/2016 3:36 PM	AP
PID_3002_2016.09.07_15.28_01	44	103	11/28/2016 1:47 PM	AP
PID_3003_2016.10.12_10.40_01	55	149	11/28/2016 1:51 PM	AP
PID_3004_2016.10.12_12.41_01	60	162	12/5/2016 1:36 PM	AP
PID_3005_2016.10.12_14.37_01	41	126	11/23/2016 11:10 PM	AP
PID_3006_2016.10.19_11.28_01	59	149	11/28/2016 2:03 PM	AP
PID_3007_2016.10.19_11.28_01	50	133	12/13/2016 11:37 PM	AP
PID_3008_2016.11.09_09.51_01	58	134	11/28/2016 1:34 PM	AP
PID_3009_2016.11.09_11.59_01	51	158	12/4/2016 4:30 PM	AP
PID_3010_2016.11.09_14.15_01	51	111	12/5/2016 2:06 AM	AP
PID_3011_2017.02.13_10.08_01	42	145	4/4/2017 9:58 AM	AP
PID_3012_2017.02.13_12.41_01	34	71	3/13/2017 10:54 AM	AP

The top figure shows a list of Interviews imported to NVivo software and the bottom figure shows an open transcript during the coding process. The text was highlighted, and with a right click and selecting 'code to', the researcher coded it to the relevant node.



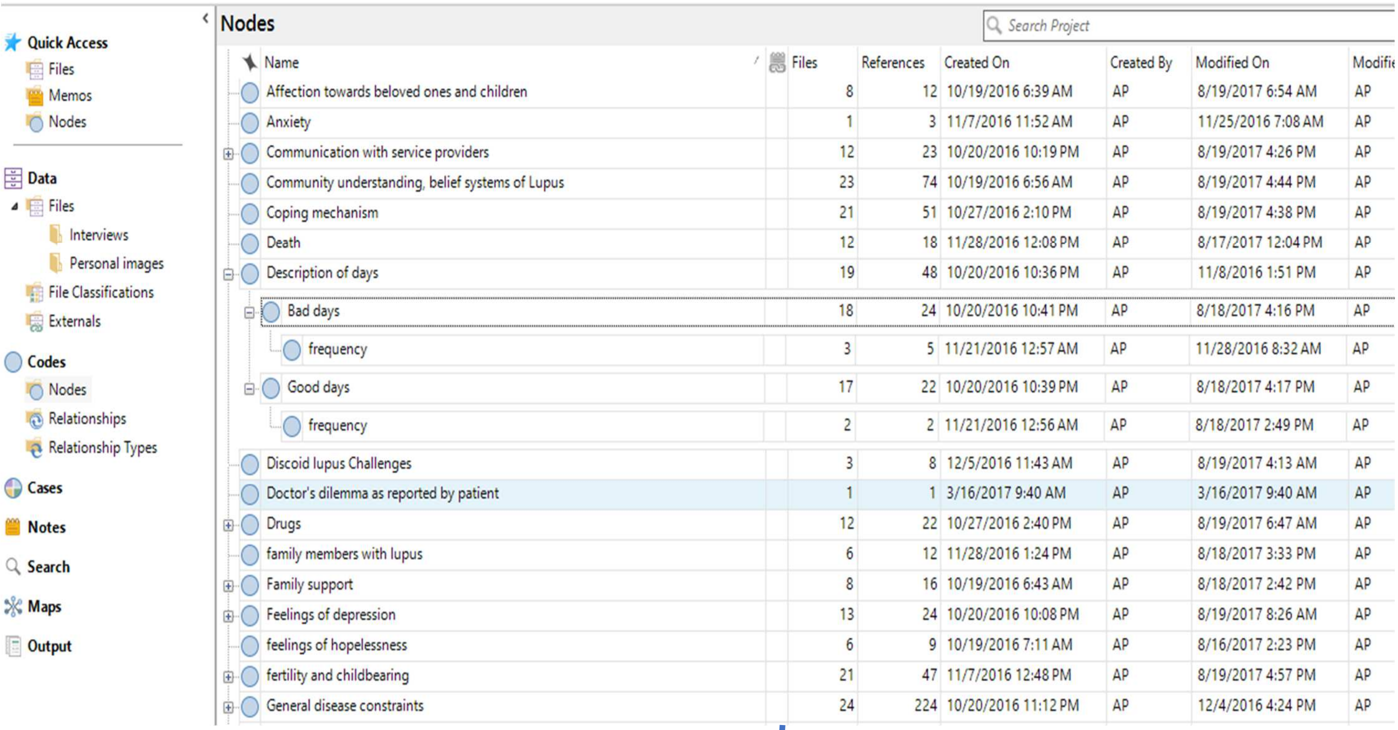
PID_3010

Interviewer: Thank you Selina for agreeing to come and speak to me about lupu
understand now is, if someone was to ask you what is lupus, how would you des

Interviewee: I was told it's an autoimmune disease. I was told the diseas
hyperactive, that it destructs your other health issues and then it also could
body. It could affect your eyes, your blood cells, blood vessels, your skin, your j
organ, or any inner organ. They say lupus is basically– it disturbs your tissues,
they describe those doctor-words. I normally tell them I have a joints problem,
to say, "What is this sickness?" I tell them it's lupus and then they say, "What
where your joints just lock, get swollen and maybe become tense, that's the sim
because the sickness is not close to Aids, most of the people think you are bein
they think no, all of a sudden you can't walk, it's impossible, you know? *Ja*, all c
sometimes because I even struggle to hold my phone...

Interviewer: If you were to explain this tiredness, to give me a brief picture– or a

Interviewee: It's not a normal tiredness. Okay, it feels like you've been workin
you know, you've been digging some holes maybe, construction work, you kno
or a *skorokoro nyana* car, you know? it means I'm just a scrap. *Ja*, I usually say,
Because you can't do things that people do, you can't do things that you want t
you're lazy, because you can't.



Name	Files	References	Created On	Created By	Modified On	Modifie
Affection towards beloved ones and children	8	12	10/19/2016 6:39 AM	AP	8/19/2017 6:54 AM	AP
Anxiety	1	3	11/7/2016 11:52 AM	AP	11/25/2016 7:08 AM	AP
Communication with service providers	12	23	10/20/2016 10:19 PM	AP	8/19/2017 4:26 PM	AP
Community understanding, belief systems of Lupus	23	74	10/19/2016 6:56 AM	AP	8/19/2017 4:44 PM	AP
Coping mechanism	21	51	10/27/2016 2:10 PM	AP	8/19/2017 4:38 PM	AP
Death	12	18	11/28/2016 12:08 PM	AP	8/17/2017 12:04 PM	AP
Description of days	19	48	10/20/2016 10:36 PM	AP	11/8/2016 1:51 PM	AP
Bad days	18	24	10/20/2016 10:41 PM	AP	8/18/2017 4:16 PM	AP
frequency	3	5	11/21/2016 12:57 AM	AP	11/28/2016 8:32 AM	AP
Good days	17	22	10/20/2016 10:39 PM	AP	8/18/2017 4:17 PM	AP
frequency	2	2	11/21/2016 12:56 AM	AP	8/18/2017 2:49 PM	AP
Discoid lupus Challenges	3	8	12/5/2016 11:43 AM	AP	8/19/2017 4:13 AM	AP
Doctor's dilemma as reported by patient	1	1	3/16/2017 9:40 AM	AP	3/16/2017 9:40 AM	AP
Drugs	12	22	10/27/2016 2:40 PM	AP	8/19/2017 6:47 AM	AP
family members with lupus	6	12	11/28/2016 1:24 PM	AP	8/18/2017 3:33 PM	AP
Family support	8	16	10/19/2016 6:43 AM	AP	8/18/2017 2:42 PM	AP
Feelings of depression	13	24	10/20/2016 10:08 PM	AP	8/19/2017 8:26 AM	AP
feelings of hopelessness	6	9	10/19/2016 7:11 AM	AP	8/16/2017 2:23 PM	AP
fertility and childbearing	21	47	11/7/2016 12:48 PM	AP	8/19/2017 4:57 PM	AP
General disease constraints	24	224	10/20/2016 11:12 PM	AP	12/4/2016 4:24 PM	AP

List of codes showing main and child nodes. Figure also shows the number of women who reflected on the theme under files and the number of times a theme or node was cited under References.

Figure 3.4: Coding system showing coded data including parents and child nodes

CHAPTER 4: Living with systemic lupus erythematosus in South Africa: A bitter pill to swallow.

4.1 Overview

A qualitative study exploring living experiences, perceptions and unmet needs of South African patients with SLE.

Author's declarations and contributions: Appendix VII

Phuti *et al. Health and Quality of Life Outcomes* (2019) 17:65
https://doi.org/10.1186/s12955-019-1132-y

Health and Quality of Life Outcomes

RESEARCH Open Access

Living with systemic lupus erythematosus in South Africa: a bitter pill to swallow

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Abstract

Background: Systemic lupus erythematosus (SLE) often has a profound negative impact on health-related quality of life (HRQoL). In the absence of any qualitative studies in sub-Saharan Africa, we undertook a study to explore living experiences, perceptions and unmet needs of South African patients with SLE.

Methods: Twenty-five women with SLE consented to participate in the study. They underwent individual in-depth interviews exploring their physical concerns, emotional health, sexual well-being and fertility. NVivo software was used for analysis.

Results: Participants were either of black ancestry or mixed racial ancestry, mainly indigent with only a quarter gainfully employed. Living with pain was the most common complaint, negatively impacting on activities of daily living (ADL), family expectations, social life, sleep and intimacy. Most participants expressed challenges of living with fatigue, and many felt their fatigue was misconstrued as being 'simply lazy'. This pernicious fatigue had negative consequences on many facets of ADL, including caring for dependants, job sustainability and sexual well-being. All participants experienced low emotional states, often associated with suicidal ideations. Many experienced difficulties with fertility and childbearing and these were exacerbated in many instances by the pessimism of health care providers, resulting in confusion and depression. Physical disfigurements resulting from lupus-associated alopecia and rashes and corticosteroid-induced weight fluctuations were a major concern. These changes often affected self-image and libido, leading to strained personal relationships. Coping mechanisms that participants adopted included intense spiritual beliefs, 'pushing through the difficult times' and use of alternative therapies to relief symptoms was common. A poor understanding of SLE on the part of participant's family and the community, coupled with the unpredictable course of the disease, exacerbated frustration and social exclusion. For most, limited income, lack of basic services, family dependencies, and comorbid diseases, such as human immune deficiency virus (HIV), exacerbated the daily negative SLE experiences.

Conclusion: In this study of mainly indigent South African women, SLE is associated with complex, chronic and challenging life experiences. The chronic relapsing and unpredictable nature of the disease, poor understanding and acceptance of SLE, compounded by a background of poverty, inadequate social support structures, negatively impact on a range of personal, social and vocational daily life experiences. Improved access to psychosocial services and SLE education might result in better outcomes.

Trial registration: (Ethics Project identification code: 275/2016 and M160633 registered 10 & 29 August 2016).

Keywords: Systemic lupus erythematosus, Experiences, Perceptions, Health related quality of life, Qualitative, Africa

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Background

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder predominantly affecting young women. This disease normally affects a broad spectrum of organs, most commonly the skin and mucous membranes, joints, kidneys, blood and the central nervous system [1, 2]. The disease is associated with reduced life expectancy and high morbidity, related to both active disease and therapies used to treat the disease. The chronic relapsing and unpredictable nature of the disease results in significant unmet needs affecting various spheres of health-related quality of life (HRQoL). Pain, fatigue and adverse effects of medications impact negatively social functioning, mental health and moreover complex in the case of fertility and pregnancy [3–7].

The World Health Organisation (WHO) defines HRQoL as a "multi-dimensional aspect in individuals which involves their experiences and perceptions of physical, psycho-social and mental states" [8]. HRQoL is a function of both the personal and socio-economic support structures in which the individual lives and the interaction of these with the context in which a person lives resulting in good functioning or limited functioning (disability) which in turn affects HRQoL. This is the conceptualization of functioning represented by the World Health Organization's International Classification of Functioning, Disability and Health (ICF) (2001) [9]. This is a useful framework that could describe and understand the lives of SLE women.

SLE occurs world-wide, but for decades was reported as rare in Africa but common and severe in individuals of African ancestry living in Europe, America and Asia [10, 11]. Diagnostic delays due to poor access to health care, low awareness and limited number of specialist physicians are explanations for the underestimated prevalence of the disease on the African continent itself [12]. Data on HRQoL are scarce in developing countries, including much of the African continent [13, 14]. Poverty is an important predictor of poor outcome in any chronic illness [5, 6]. Patients living with SLE in the Low and Middle Income Countries have a lower survival rates than those living in High Income Countries [15]. The factors that contribute to this higher mortality are late diagnosis, delayed or poor intervention and infectious co-morbidities [16]. A recent narrative review of HRQoL in developing countries included 31 studies and highlighted that adverse SLE outcomes are exacerbated by poor socioeconomic contexts which affect physical and mental well-being [17].

Given the lack of research on HRQoL of women living with SLE in Africa, we undertook a qualitative study by interviewing individual women with SLE to explore their "lived experience" of SLE as a chronic illness. The study was based on the phenomenology approach. We aimed to obtain understanding of issues that may be underexplored or misunderstood in routine clinical care.

Methods

Participants were enrolled from two tertiary academic centers - Groote Schuur Hospital, Cape Town and Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto. Participants from the Cape Town site were identified from the African Genetics Lupus Network (ALUGEN), a prospective registry of SLE [18]. Patients from CHBAH were recruited from the Lupus Clinic. The study was approved by the Human Research Ethics Committee at the University of Cape Town and the University of Witwatersrand.

Participants were purposively sampled to include younger (< 30 years) and older (> 30 years) age groups, those with skin involvement, fertility issues, and those with high disease activity versus those with quiescent disease, and participants with poor adherence to treatment. The study was conducted from September 2016–February 2017. All participants met the 2010 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE [19], were females of 18 years or older and signed informed consent to participate. Socio-demographics including self-reported ethnic background, and disease features were documented before the individual interviews were conducted. Lupus disease activity was determined using the Physician Global Assessment (PGA) score from the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [20].

An interview guide reflecting the main themes of pain, fatigue, emotional, social and work function, fertility, aesthetic concerns, coping mechanisms and medication adherence was developed to facilitate the process. This was based on the general issues faced by SLE women reported in other literature that we wanted to explore further. The interview process was based on the phenomenology approach to explore women's "lived experience" of SLE as a chronic illness and in addition to give the researcher a clear and in-depth understanding of this phenomena [21, 22]. A pilot study of this interview guide was tested on four participants which were later included in the analysis. The transcripts were discussed, and adjustments were done where necessary by all authors.

Interviews were conducted in a language selected by the participant: English, Xhosa, Zulu, Tswana, Sotho, and Pedi. The interviewer and first author (AP) is a registered nurse and midwife fluent in all the languages. Interviews were conducted in a private, neutral room of the respective outpatient clinics, where noise and intrusion were avoided. Though most participants expressed the desire to be known, rather than to remain anonymous, in light of how much they suffer in silence, there was an agreement to choose a pseudonym and these have been used throughout the text. The interviewer was not at any stage involved in the care of participants.

All interviews were audio recorded, had an average duration of 70 min and were transcribed and translated into English. In addition, field notes were taken particularly on the individual each participant's body language. No repeat interviews were done. Data saturation was reached by the 20th participant, but after discussion between the authors, five more participants were included to consolidate the existing themes.

Data analysis

The project was set up on NVivo 11 software, and themes were identified during the pilot phase, data collection and processing [21, 22]. All participants were given individual feedback after the interview and were referred for further services if required. Thematic analysis with co-authors by going through a number of transcripts to ensure validity of the coding was done. To control for bias and data trustworthiness a number of measures were implemented. Firstly, at the time of the interview clinical data were available, and these were used to cross check critical medical information provided by informants. Secondly, the interviewer took field notes including on body language and these were compared with themes that came up from the interviews. Thirdly, to ensure consistency, Participants were asked to clarify some concepts or explain what was not clear to the interviewer. In addition, the interviewer summarised the main themes arising from participants' narrative at the end of the interview which they either agreed with, corrected or re-worded. Fourthly, during the analysis the themes were continuously compared and were discussed early in the analysis process with all the authors to make sure that they reflected what the participants were expressing as described further below.

AP was involved in the translation process. Interviews needing translation were a mix of native languages and English in one recording, a typical communication strategy in the South African context. An accuracy check on every translation through repeated listening to the recorded interview was done while re-reading the transcription and translation and any errors rectified. AP was close to the data and the nuances required in the translation. Verbatim translation and transcription were done. AP did the initial coding using themes that emerged from the first 5 interviews. This was presented to co-authors MS and BH and they assessed the audios, translations and discussed the coding. Codes were further reviewed by all authors where it was decided that a further 5 participants were to be recruited to consolidate the existing themes. Without any disagreements, pointers on probing strategies and more codes were discovered.

The Consolidated criteria for Reporting Qualitative research (COREQ) [23] was used to prepare this paper.

Results

Twenty-five consenting participants were interviewed. Their mean age was 30.9 years (range: 22–45) and mean disease duration was ≥5 years (range 1-5 years). Most were black Africans (72%), the remaining were of mixed racial ancestry (Table 1). Eighteen were single, 3 separated/divorced and 4 were married. Ten participants completed secondary school of 12 years, and the remainder stopped school below secondary level (5), were still at college (5) or completed formal training (5). Six participants were employed, 2 were students and the remaining were unemployed. Only 6 were recipients of state disability grants. All participants had arthritis as a presenting feature of SLE and about a quarter each had skin lesions or lupus nephritis. Eight participants were assessed to have active disease by the PGA score, and the mean score was 1.9 (range 0–4).

The major themes arising from the interviews are detailed below:

Body function

Physical impairments

Pain Living with pain was the most complex and consistent grievance, and nineteen participants expressed living with pain almost every day. Pain was cited as the cause of "constant bad days". The source of pain was from arthritis, and skin lesions, and 3 participants explained that they did not understand the origin of their pain. They slept on a stack of pillows or sitting position while 1 participant admitted to using large quantities of painkillers. Joint pain frequently restricted women from doing their activities of daily living.

> *It [pain] is on my hands and knees mostly, sometimes I can't even dry out my washing. If I wash, I can't fold my hands, like this [attempting to make fists without success]. It's painful but then it's swollen also (Chan; 35 years, unemployed).*

Younger participants were worried about the chronicity of pain and how it affected their ability to function, their sleep and their present and future life expectations. Several factors aggravated their pain including erratic adherence to medication, a cold environment and physical activity. The pain was often coupled with muscle stiffness especially in the mornings. Despite the pain, many still had to care for dependants.

The nature of pain was described in diverse ways and all participants expressed that they struggled to explain the nature of the pain to their families, employers,

Table 1 Summary of the 25-participant's socio-demographics, clinical features and themes explored

	n = 25	%
Age (years)		
> 30	15	60
< 30	10	40
Ethnicity (self-reported)		
Mixed Ancestry	7	28
Black African	18	72
Educational level		
Below Secondary level	5	20
Secondary level	10	40
At college/university/job training	5	20
Completed college/university/job training	5	20
Job status		
Employed	6	24
Unemployed	17	68
Student	2	8
Disability grant recipients	6	24
Marital status		
Married	4	16
Separated	3	12
Single	18	72
SLE features		
Lupus nephritis	6	24
Skin/discoid lupus	6	24
Arthritis	25	100
Disease Activity[a]		
High disease activity	8	32
Quiescent disease	17	68
Themes explored		
Physical Impairment:		
Pain	19	76
Fatigue	17	68
Emotional Health	25	100
Employment	25	100
Social functioning	8	32
Sexuality	22	88
Aesthetic concerns	20	80
Fertility issues	14	56
Adherence to treatment	11	44
Coping mechanisms	21	84

[a] The Physicians Global assessment of SLEDAI is a score of 1 to 4 in categories of 0 = No activity, 1 = Mild, 2 = Moderate, 3 = Severe [20]

community and health care providers (HCPs). Furthermore, many felt that the concept of "pain" did not describe their experience adequately.

> *It's as if you are tied in wires around the joints! (Neelo; 25 years-old former domestic worker, unemployed due to severe arthritis).*

> *It feels like somebody's chipping away at your bones with a nail and a hammer especially when it's cold! (Larona; 23-year-old university student).*

Fatigue Seventeen participants disclosed living with fatigue which they described as "severe loss of energy" and "a strong need to sleep". They expressed it as the most emotionally draining experience that no one, including HCPs, understood fully. Participants reported being viewed as 'simply lazy' by most family members. One participant expressed frustration at being told by her doctor that fatigue was "normal". Fatigue impaired activities of daily living (ADL), including taking care of dependents and employment.

> *I will not iron the laundry. I leave it. But I would wake up tired, feeling that today, I am doing nothing. I do not clean, I do nothing. I sit. I do not have strength. There is nothing I can do. I cannot even go to the shop (Tumi; 43-year old, unemployed).*

One participant described a day without fatigue as a 'happy day' which occurred 'seldom'. While some participants succumbed to the feelings of fatigue, a few stood up against it.

> *Even if I'm tired, I keep on doing what I'm supposed to be doing. So, I can't really say it stopped me to do anything, as I said to you I'm strong, I'll just force myself to do things. I feel everything is only in the mind. If you say, "Today I'm tired", then you'll stay in bed and you'll stay tired the whole day. So, I'm not that kind of a person. I'll wake up in the morning and I'll feel tired and I'll say, "Today I told myself that I'm going to do this," and I'm going to do it tired or not. So, I'm that kind of a person. Even if I feel tired, still it doesn't stop me (Kiswa; 40 years old, separated mother of three).*

One participant (37-year-old Lizzie, unemployed) described her tiredness as a feeling of being in a very long distance race. Furthermore, it was coupled with weakness and dizziness and struggling with sitting for extended periods of time. Like most participants, despite not being physically active at all, she felt as though she had just carried out a very heavy task.

Three participants struggled with fatigue in the workplace and often found themselves sleeping while on duty and feared losing their jobs. Participant Olivia expressed her gratitude for the interview opportunity as it gave her a platform to voice that fatigue is not normal.

Most participants suspected that fatigue could be from SLE and in 1 case, severe fatigue was the leading symptom that led to the diagnosis of SLE. However, most participants did not associate fatigue with disease activity, while some associated it with sun exposure, body pain or evil spirits.

One participant (Tumi; 43 years old, unemployed) blamed supernatural powers:

> *On Sunday at church, I was so tired, I know that it is the spirits from there because when I arrived… mmh!... fatigue came. It's the evil spirits! [patting her shoulders, slouching on the chair, shaking her head vigorously and displaying signs of being defeated].*

Emotional function

Poor emotional and mental health All 25 participants expressed various kinds of emotional problems due to the SLE diagnosis and its complications. These included dealing with the anonymity of SLE, job and career loss, aesthetic concerns, struggles with fertility and pregnancy, pain, fatigue, poor memory, sexual dysfunction and loss of intimate relationships. Feelings of sadness, anger, anxiety and symptoms of depression were voiced. Most participants expressed feeling emotional 'out of nothing' and having extremely bad days full of negative emotions.

The most striking interview was with 25-year-old Olivia, employed, mother of one, who had several suicidal attempts without anyone's knowledge.

> *When I started, I would take ten pills, drink them. The second time when I get to that position I thought, okay, the last time I had ten pills and they didn't work, meaning this time I must drink more than that. Afterwards, I feel weak, sleepy, sweaty, but I don't say, and nobody knows - you are the first person, the first person to know about this. (sobbing uncontrollably).*

Only 3 participants had been diagnosed with depression. One was diagnosed with depression after being diagnosed with human immune deficiency virus (HIV) infection. She admitted to weaning herself off the anti-depressants as they made her feel out of touch with reality. In one case, the participant was adherent to her anti-depressant but showed poor coping skills while in another case, the participant stopped her medication because she believed she was not crazy. The latter participant later relapsed and needed to restart her antidepressants. One participant showed features of undiagnosed post-traumatic stress disorder (PTSD) after a miscarriage. After their interviews, 5 participants were referred, with their consent, back to their respective clinicians for further management of the depression.

Environmental factors

Poor socio-economic status (education and jobs)

Most participants believed they deserved a social grant due to their body limitations, and 16 reported SLE-related joint pain together with fatigue as the cause of their unemployment. They struggled with work conditions such as cleaning, doing laundry, sitting for a prolonged time, a cold environment and carrying plates in a restaurant. Those who had resigned from their formal employment, cited challenges like SLE-related role limitations, together with employer dissatisfaction for the multiple hospital visits and admissions or being more at home than at work. All the 6 formally employed participants had completed tertiary education. Those without higher qualifications struggled to find or continue work. More than half of the participants had either left school before completing secondary education or had obtained inadequate grades and had abandoned tertiary education. For most, further education was impossible without financial means.

> *Jobs are also not [there] because I am not educated, it's not easy to get a job. When I found out I have the Lupus disease I was working as a domestic worker. That's what affected me [job nature], because of the water I was doing the laundry with hands, not with a laundry machine. It's so difficult. It's hard (Neelo; 25-year-old former domestic worker, unemployed due to severe arthritis).*

> *This arthritis, my wrists would get sore, one side of the wrist would get sore then I couldn't work. Maybe I could work with one hand (Phumlani; 28-year-old previous chef).*

On a change in lifestyle, 33-year-old Sinethemba (former domestic worker and mother of two living with lupus nephritis) disclosed that she had no choice but to sit and do nothing due to the pains and could not force herself to do anything.

Limited household income was a major concern for most participants. This coupled with a poor understanding of the chronicity of SLE affected adherence to medication and attendance of follow-up visits to the Lupus clinic. Lack of transport money was also a main contributor to poor access to care amongst these indigent women.

> *I am now feeling better. It's not like in the beginning when I was very sick. I had decided to quit due to circumstances. This year I was telling her that "mom, I am quitting treatment because we don't have money. You [mother] are supporting the family and I also require money for travel" (Neelo; 25-year-old former domestic worker, unemployed due to severe arthritis).*

Poor social health

The unpredictable course of the disease and limitations to physical activities forced many women not to socialize at all. They explained that the South African social system requires attendance at funerals, weddings and parties. For one participant on peritoneal dialysis for chronic renal failure, food and drinks at social events were a challenge given her dietary and fluid restrictions. In addition, these events required a lot of physical activity that most participants could not cope with.

> *"You must do something madam! (imitating a third person)", and when you are busy peeling potatoes; peel potatoes pain, peel potatoes pain, pain, pain, pain, pain; the whole night! (Selina; 24 years old, employed).*

Many participants described feelings of being drained by interacting with new people and struggling to explain their diagnosis. Hence, they resorted to being alone.

When asked about what the community understood about SLE, nine participants explained that SLE was confused with HIV, cancer, death or witchcraft.

> *When I lost weight, the community said I have HIV, it was depressing! When I gained weight, they said "she's starting to be fresh, she is on ARV's (antiretroviral therapy)" (Trisha; 29 years old, jewellery designer trainee).*

Thuswa (37 years old, IT consultant) described the reasons for her cleansing ceremony in church as arising from the community's comments about her illness:

> *No, there's something wrong with you! You have a demon. We [church] have to get that demon out!*

Activity limitations

Poor sexual health

Problems with sexuality became one of the major themes expressed. For most, a woman's image is her sexuality, and aesthetic concerns were a main hindrance to fulfilled intimacy as they lacked the confidence and courage to engage.

> *I don't feel that I want to be sexually active or intimate. At night I don't sleep with a wig; with this bald head, I am shy and uncomfortable (Nino; 27 years old, unemployed, newly-wed).*

Fatigue and pain were also listed as contributors to poor sexual health causing tensions in intimate relationships. The majority of single and separated participants disclosed that poor sexual health was the main cause of their failed relationships and felt that their partners did not understand their condition.

Aesthetic concerns Participants expressed distress at a range of the SLE-related or treatment-related body changes including moon-shaped face, weight gain, weight loss, alopecia, discoid skin lesions and scars. Most felt they could not dress the way they desired. The participants who were single or separated felt their single status was mostly due to aesthetic concerns, which in turn affected self-image and libido.

> *…because of my body, my husband left me because he's not attracted to me. I'm not cute enough for him anymore. So those are the things that make me feel so down (Kiswa; 40 years old, separated mother of three).*

Skin lesions Living with discoid skin lesions did not cause only excruciating physical pain, but raised emotional, social and economic issues due to the change in appearances, for about a quarter of the participants. One of them was quoted saying:

> *When the discoid lupus started, that's when I stopped going out, oh my goodness they (everyone) were staring at me (Phumlani; 28 years old, previous chef).*

Perceptions on how they were seen by their society caused feelings of sadness, anger and discomfort. Most participants had low self-esteem and explained that the looks from the community or workplace colleagues were driving them to stay behind closed doors.

Personal factors

Fertility concerns

Childbearing was one of the important concerns and some expressed the stresses and trauma of pregnancy and fertility experiences. Many participants were put-off by the pessimism of their HCPs regarding prospects of having a family, and cited this as a cause of confusion and depression.

> *Two years, no child. Some of them [in-laws] are going to say, "You must take this one out, this is a barren [woman]" (28-year-old Zayo, unemployed).*

> *The doctor is not God, so he can't say that. I want to experience to be a mother. He said I won't be able to have children and I didn't believe him. I prayed and now I have two. They told me the children won't be normal. Both are normal (Chan; 35 years old, unemployed).*

Adherence to treatment issues

Eleven participants admitted to poor adherence to medication. The reasons they offered included the overwhelming number of tablets they were expected to take every day, a belief that they were not sick especially when the illness was inactive, forgetfulness and side effects of the medications such as weight gain, unpleasant taste, nausea, and loss of a sense of reality (felt to be due to antidepressant medication):

One participant blamed her lupus flares on the tablets:

> *Too many tablets are not good, they all clash with one another. I even stopped the anti-depressant because I am not mentally sick. I'm full of side effects, that's why I'm so sick (Inn; 40 years old, unemployed).*

While most participants had branded chloroquine "the bitter pill" as it has a bitter taste when swallowing it, they felt that their lives were bitter just like the taste of the chloroquine.

Despite their reluctance to take many tablets, lupus flares following poor adherences had forced most participants to take all their medication, making use of daily pill boxes or reminders from a phone alarm or family member.

Participants understanding of SLE

Twenty participants had a reasonably good understanding of SLE, while five could neither explain nor accept the diagnosis:

> *I don't get what Lupus is, I just take my medications and come for check-ups (Neelo; 25-year-old former domestic worker, unemployed due to severe arthritis).*

Many found the disease mysterious and unpredictable, often with a malicious intent, a silent killer that has been there for years. Some described the SLE outcomes, especially the excruciating pain, as something they would not wish for anyone, even their worst enemy.

> *Lupus is a very sneaky disease. It attacks you at a time that you are dumbstruck. It just slaps you in your face and you're down. I don't know what causes the flare-ups or what triggers it (Debbie; 43-year-old teacher).*

> *A disease that one would never really know it until one gets it, one would never know what pain and tiredness is until they get it; an irritating and frustrating disease (Tina; 29-year-old call center employee).*

> *It's not like AIDS (acquired immune deficiency syndrome) - this one is still undercover. "We only know about it when we are here at the clinics" (Selina; 24 years old, employed).*

Coping strategies

Family support and alternative medicine

> Despite most participants describing problems socializing, family support was one of the most important tools that helped them cope with SLE. All participants reported that having either a family member, friends or partner support gave them strength to cope with the unpredictable nature of the disease. Some revealed that their supporters went as far as arranging alternative medicines for them. Moreover, participants felt that patient-led support groups, better education by HCPs, and public awareness of SLE would help them cope better with the disease. Two participants explained that their medications consistently helped prevent fatigue. Strong disease acceptance and the drive to care for oneself or a dependant was helpful. Some described their feelings as follows:

> *"I hold my head high and I have a reason to live; my young son- he needs me" (Tina; 29-year-old, call center employee).*

> *I'm a strong woman, I've fought with HIV to hell and back, I'm going to beat this SLE. I'm going to take medication as I'm doing with my HIV medication and I'm going to look after myself as I always did (Kiswa; 40 years old, separated mother of three).*

Many participants explained that alternative therapies helped contain the symptoms of SLE. These included drinking 'blessed' water from church, strong spiritual beliefs in God, traditional herbal remedies, and soothing elephant tree leaves or pressure bandage applications to painful joints.

The three levels of functioning in Fig. 1 interrelate, are intertwined with each other and are affected and

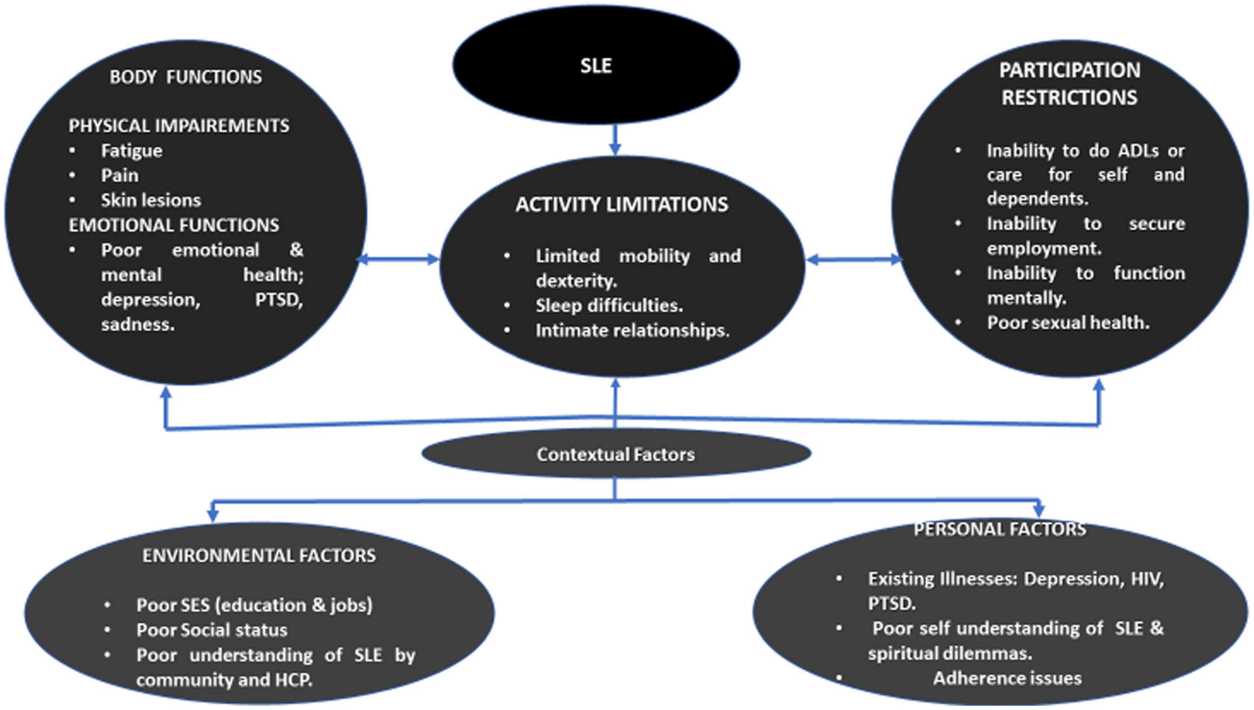

Fig. 1 Interactions between experiences of SLE women and their general health outcome using the International Classification of Functioning, Disability and Health (ICF) framework. Abbreviations: *ADL*: activities of daily living, *HIV*: Human immune deficiency virus, *HCP*: Health care provider, *PTSD*: Post traumatic stress disorder, *SES*: socio-economic status, *SLE*: Systemic lupus erythematosus

influenced by the contextual factors of a patient living with SLE. The individual body structure and function impairments (pain, skin lesions, fatigue and existing illnesses such as HIV, depression, and post-traumatic stress disorder) negatively affected activities executed by the participants, specifically limited mobility and dexterity, sleep and engaging in intimate relationships. The activity limitations interacting with the external environmental factors and personal factors resulted in difficulties in caring for themselves or dependants, carrying out household tasks, securing employment, functioning effectively mentally or having intimate relationships. The environmental and personal factors that interacted with the activity limitations included poor economic status (education and jobs), poor social status, poor understanding of SLE by community and HCPs**,** poor self-understanding of SLE, and existing illnesses and spiritual dilemmas and adherence issues.

Discussion

This qualitative study reflects on the challenges of women living with SLE in poorly resourced communities of South Africa. We explored activity limitations that were exacerbated by lack of understanding and negative attitudes of family, friends and employers, costs of transport, and other factors resulting in restricted participation in work, social life and intimate relationships. Women living with SLE reported on some of the obstacles and factors which may negatively impact their HRQOL. The ICF framework demonstrates a level of disability which is an outcome of complex interactions between the SLE, activity limitations and contextual factors as shown in Fig. 1 [8, 9]. Strikingly, SLE remained mysterious to the participants and their communities, and this poor understanding exacerbated frustration and life uncertainties.

The confusion of HIV with lupus was a common experience amongst the participants. This is not a surprising finding as the symptoms of the two illnesses overlap [24]. In the South African context both illnesses affect mainly young women and the overlapping features of the two conditions not infrequently lead to either in misdiagnosis or delay in diagnosis of SLE. In our study, living with both these diagnoses caused major distress amongst the women.

Our study shows that SLE has a severe impact on social lives resulting in self-imposed isolation from society at large, and impaired sexual health leading to either separation or singlehood status. These findings are similar to those described amongst Ecuadorian women with SLE were the majority of young women expressed unhappiness at not being married [25].

Two previous South African studies have explored HRQoL - a quantitative study showed poorer social functioning amongst SLE compared to rheumatoid arthritis (RA) patients [14], and a qualitative study in RA highlighted social exclusion and lack of independence exacerbated by poverty [26]. In our study aesthetic concerns dominated the narratives on how it affected self-esteem and, in turn, affected both social participation, intimate relationships and work opportunities.

Family support was a key element that assisted participants to cope with the disease. Their responsibility towards their dependants and conversely, family members offering support, gave them greater strength to cope with the illness. Moreover, spiritual beliefs were an important component of the coping strategies for many participants. Two Brazilian quantitative studies have similarly highlighted that SLE patients with strong spiritual beliefs had a positive outlook on life and coped better with the diagnosis [27, 28]. Unlike the participants in a study from the United Kingdom who expressed some positive aspects of living with SLE [29], none of the women in our study felt upbeat about their diagnosis.

Much work is needed in developing and testing of local coping strategies to overcome pain, fatigue and mental health challenges associated with SLE. These might include patient-led support groups and improved access to psychosocial services. Ongoing training for HCPs together with community awareness programmes might result in better understanding of SLE. In addition, considering the high rate of unemployment and lack of formal training amongst these women, better disability support and training opportunities are vital to alleviate the poverty that complicates the lives of patients with SLE.

Whilst our results are a good reflection of the experiences of women with SLE attending the tertiary level facilities, unknown biases could have arisen during the analysis process. As the themes were presented by the first author to the co-authors for discussion, the themes were further refined. During this process, some important themes might have been excluded. In addition, variations in the moods of participants at the time of interview, might have affected their responses.

Conclusion

In conclusion, notwithstanding these limitations, our study highlights the many complex, chronic and challenging life experiences of indigent South African women with SLE. A poor understanding, perception and acceptance of SLE by both patients and the community at large, coupled with unpredictable and mysterious nature of the disease has a profound negative impact on multiple dimensions of SLE patients. Physical disability due to pain and fatigue together with aesthetic concerns have a strong negative effect impact on mental health, social functioning, job acquisition and sexual health. Family support and spirituality are major coping strategies but stigma and lack of understanding by others also negatively affects their participation in major life activities such as employment. As mentioned above, comprehensive, multi-pronged approaches are likely to improve the overall lived experience of women with SLE.

Abbreviations

ADL: Activities of daily living; AIDS: Acquired immune deficiency syndrome; ALUGEN: African Genetics Lupus Network; ARV's: Antiretroviral therapy; COREQ: Consolidated criteria for Reporting Qualitative research; HCPs: Health care providers; HIV: Human immune deficiency virus; HRQoL: Health-related quality of life; ICF: International Classification of Functioning, Disability and Health; PGA: Physician Global Assessment; PTSD: Post-traumatic stress disorder; RA: Rheumatoid arthritis; SES: Socio-economic status; SLE: Systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics; WHO: World Health Organisation; WHOQoL: World Health Organisation Quality of Life

Acknowledgements

The authors wish to extend their heartfelt thanks to all the women who opened their hearts to share their intimate and private experiences. Our sincere gratitude to the research assistants and hospital staff for assistance during the fieldwork.

Funding

This study was funded by the South African National Research Fund (NRF)-Thuthuka grant no: 443812 and the Harry Crossley Foundation through the University of Cape Town, South Africa.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the regulating ethics committee and participants.

Authors' contributions

AP was involved in the conception, coordination and fieldwork process. All authors were involved in data synthesis, interpretation, review of drafts and the definitive version of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethical clearance was obtained from the Human Research Ethics Committee at the University of Cape Town (275/2016) and University of Witwatersrand (M160633). All participants signed the consent form to participate.

Consent for publication

The signed informed consents were informative to participants regarding the use of their narratives and personal data (names in pseudonym format) for publications in journals.

Competing interests

The authors declare that they have no competing ineterests.

Publisher's Note

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Received: 18 July 2018 Accepted: 29 March 2019

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CHAPTER 5: ‘The feeling of not being entitled to something’: Fertility, pregnancy and sexuality among women with systemic lupus erythematosus in South Africa.

5.1 Overview

With the background that fertility, pregnancy and the postpartum period can pose many challenges for patients with systemic lupus erythematosus (SLE), we explored the perceptions and experiences of South African women relating to fertility and pregnancy.

Author’s declarations and contributions: Appendix VII

Scandinavian Journal of Rheumatology

ISSN: 0300-9742 (Print) 1502-7732 (Online) Journal homepage: https://www.tandfonline.com/loi/irhe20

‘The feeling of not being entitled to something’: fertility, pregnancy, and sexuality among women with systemic lupus erythematosus in South Africa

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To cite this article: A Phuti, B Hodkinson, M Tikly & M Schneider (2019): ‘The feeling of not being entitled to something’: fertility, pregnancy, and sexuality among women with systemic lupus erythematosus in South Africa, Scandinavian Journal of Rheumatology, DOI: 10.1080/03009742.2019.1657492

To link to this article: https://doi.org/10.1080/03009742.2019.1657492

Scand J Rheumatol 2019;00:1–7

'The feeling of not being entitled to something': fertility, pregnancy, and sexuality among women with systemic lupus erythematosus in South Africa

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Objective: Fertility, pregnancy, and the postpartum period can pose many challenges for patients with systemic lupus erythematosus (SLE) in sub-Saharan Africa. We explored the perceptions and experiences of South African women relating to fertility and pregnancy.
Method: In-depth interviews were conducted with 25 consenting women with SLE. We explored their perceptions and experiences on conception, pregnancy, and sexuality. Data were analysed using Nvivo software.
Results: Participants had a mean age of 30.9 years (range 22–45 years) and mean disease duration of 4.5 years (range 1–5 years). The majority were black Africans, and the remainder were of mixed racial ancestry. Unemployment, low educational level, and singlehood status were the most predominant sociodemographic features. Most participants had been pregnant and a few reported being sexually inactive. Participants described many negative pregnancy outcomes including lupus flares, miscarriages, premature deliveries, prolonged hospitalization, and unexpected caesarean sections. Conflicting medical advice on conception, together with conflicting personal, cultural, and societal pressures to procreate, resulted in emotional turmoil and pessimism. Participants frequently described intimacy problems, loss of libido, and infidelity by partners leading to sexually transmitted infections. Aesthetic and physical concerns were perceived as the main causes of infidelity. Most participants felt confined to these relationships as they were financially dependent on their partners, which added to their stress.
Conclusion: A combination of patient-centred care focusing on safe, effective contraception and medication targeting remission state, constant counselling, consistent information, and a pregnancy managed jointly by an obstetrics and rheumatology team could achieve optimum results.

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that predominantly affects young women. While overall life expectancy has improved over the past few decades, the disease continues to have a profound effect on health-related quality of life (HRQoL) (1–3). In women of child-bearing age, SLE poses many challenges regarding contraception, fertility, pregnancy, and the postnatal period (4, 5). The undesirable outcomes of the diagnosis can negatively impact social interactions and sexual health, resulting in singlehood status (6). In addition, aspects such as aesthetic concerns and fatigue affecting both physical and emotional health are under-researched concepts that affect intimate relationships and the chances of childbearing (3).

The negative relationship of pregnancy with SLE is often bidirectional, with pregnancy increasing the risk of lupus flares, and SLE, in turn, often having an adverse effect on foetal pregnancy outcomes (5). Several manifestations of SLE, such as lupus nephritis, antiphospholipid syndrome, hypertension, and high disease activity, are associated with an increased risk of foetal deaths and preterm births (5, 7, 8). In general, environmental factors such as lower socioeconomic status and a history of foetal loss have been associated with nephritis in SLE (9). The disease is associated with a higher rate of spontaneous abortions, pre-eclampsia, and premature deliveries, and there is an increased risk of congenital malformations compared to the general population (5, 8, 10). While some studies show that there is an increased risk of maternal flares in pregnancy (11, 12), others report unclear results (13, 14). The risk of ovarian failure associated with cyclophosphamide therapy, the teratogenicity of some immunosuppressant drugs, and the clear evidence that pregnancy outcomes are better when SLE is in remission highlight the importance of communication between patients and healthcare workers (HCWs) (15, 16).

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Accepted 15 August 2019

DOI: https://doi.org/10.1080/03009742.2019.1657492

Given that there are few published data on fertility, pregnancy, and the postnatal period in women with SLE in sub-Saharan Africa, and the added burden of poverty hindering access to the already limited healthcare services, we undertook a phenomenological qualitative research study. As part of a larger project on social aspects of living with SLE, we allowed women with SLE to tell their stories, particularly pertaining to SLE, investigating their perceptions and experiences of conception, pregnancy, and sexuality.

Method

Qualitative in-depth interviews, which involved exploring and capturing women's narratives on their lived experiences of SLE as a chronic illness to give the researcher a clear and deeper understanding, were conducted between September 2016 and February 2017. Using a phenomenological approach, participants' narratives of fertility, pregnancy, puerperium, postnatal period, childbearing, and sexuality were explored (17, 18). Twenty-five consenting women aged 18 years and older, diagnosed with SLE according to the 2010 Systemic Lupus International Collaborative Clinics (SLICC) classification criteria for SLE and living with SLE for at least 1 year, were included. All participants were diagnosed with SLE by a rheumatologist and were regularly attending the lupus clinic at either of two state tertiary hospitals in South Africa. Participants from Cape Town were recruited at the Groote Schuur Hospital Lupus Clinic, as part of the African Lupus Genetics Network (ALUGEN), a prospective registry of SLE patients (19). In Soweto, Johannesburg, patients were recruited from the Lupus Clinic, Chris Hani Baragwanath Academic Hospital. The study was approved by the Human Research Ethics Committees of the University of Cape Town and University of the Witwatersrand. Signed informed consent was sought from all participants.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration.

The lead author, AP, a registered nurse and midwife, who was not involved in participants' care, conducted the interviews in the absence of the participants' healthcare providers in a non-intrusive, quiet, and private clinic room in the outpatient clinic. The interviews were conducted while participants were waiting for their doctor's appointment. The participants' preferred languages, which included combinations of English, Xhosa, Zulu, Tswana, Sotho, and Pedi, were used. The researcher is sufficiently conversant in all of these languages. The interviews had a duration of about 70 min and were audio-recorded with additional notes on body language and other non-verbal cues made by the interviewer. Each participant selected her own pseudonym. Detailed information on the methodology has been published elsewhere (6).

Data analysis

Translated and transcribed interviews were imported into NVivo software and coded using themes identified by all authors during the pilot phase (6), data collection, and analysis phase (17, 18). Data validation and reliability was ensured through multiple listening of the recordings against transcriptions by the lead author, as well as discussion with all authors on probing strategies, themes, and coding. Data collection methods and thematic analysis for this paper are presented using the COnsolidated criteria for REporting Qualitative research (COREQ) (20).

Results

Description of participants

The 25 participants had a mean age of 30.9 years (range 22–45 years) and mean disease duration of 4.5 years (those living with SLE for at least 1 year were included) (Table 1). The majority were black Africans (n = 18) and the remaining seven were of mixed racial ancestry. Almost 70% of participants were unemployed, and 70% were single (Table 1). The majority (64%) had been pregnant, and at the time of the interview, 44% reported not being sexually active (Table 2).

Thematic analysis

Major themes that arose from the interviews were: pregnancy outcomes; experiences before and after lupus diagnosis; lupus flares in conception and pregnancy; emotional turmoil; family, societal, and cultural pressures; health providers' role and their conflicting information; sexuality; and experiences of contraception and other medications (Table 3).

Pregnancy and SLE

Most participants wished for pregnancy, childbirth, and rearing children, but the unpredictability of SLE gave several participants little or no hope of achieving these goals satisfactorily.

Diagnosis of SLE during pregnancy

For two participants with whom SLE was first diagnosed during pregnancy, anxiety and concern about future pregnancies was expressed. One elaborated:

> Oh! My pregnancy, that is the worst pregnancy ever. I had blood clots on my lungs. Just when one thing stops, another starts. I never want to have a baby again! After the baby was born, I was fine. Then I got really sick … then they only diagnosed me with lupus. They were looking for it the whole time! (Tina, 29 years, mother of one)

Table 1. Summary of the 25 participants' sociodemographic characteristics and clinical features.

	n = 25	%
Age (years)		
> 30	15	60
< 30	10	40
Ethnicity (self-reported)		
Mixed ancestry	7	28
Black African	18	72
Educational level		
Below secondary level	5	20
Secondary level	10	40
At college/university/job training	5	20
Completed college/university/job training	5	20
Job status		
Employed	6	24
Unemployed	17	68
Student	2	8
Disability grant recipient	6	24
Marital status		
Married	4	16
Separated	3	12
Single	18	72
SLE features		
Lupus nephritis	6	24
Skin/discoid lupus	6	24
Arthritis	25	100
Disease activity*		
High disease activity	8	32
Quiescent disease	17	68

SLE, systemic lupus erythematosus; n: number of women.
* The Physicians Global assessment of SLEDAI is a score of 0 to 3 in categories of 0= no activity, 1= mild disease activity, 2= moderate disease activity, 3= severe disease activity.

Table 2. Obstetric history of the 25 systemic lupus erythematosus (SLE) participants.

Obstetric history	n	%
Ever been pregnant		
Yes	16	64
No	9	36
Timing of pregnancy		
Pregnancy before SLE diagnosis (1–5 occurrences per woman)*	6	24
Miscarriage	2	8
Premature birth	2	8
Live, normal pregnancy and birth	4	16
Illnesses associated with SLE flares (speculated)	1	4
Pregnancy after SLE diagnosis (1–2 occurrences per woman)*	7	28
Difficulty conceiving	4	16
Termination of pregnancy	1	4
Miscarriage	2	8
Premature birth	1	4
Caesarean section	4	16
Live, normal pregnancy and birth	1	4
Flares	6	24
Contraception	9	36
Hormonal	7	28
Condom	2	8
Sterilization	1	4
None and sexually active	4	16
None and not sexually active	11	44
On teratogenic drugs and not on contraception	5	20

n, number of women.
*One woman could have been pregnant more than once and such a pregnancy could have had more than one outcome, e.g. premature delivery via caesarean section due to severe flares.

Lupus flares and turbulent pregnancies

Nine out of 10 participants who fell pregnant after their SLE diagnosis described complicated pregnancies, where high blood pressure, pain, and arthritis led to prolonged hospital stays, premature delivery, and disappointment due to caesarean sections. These complications frequently left them traumatized, shocked, or with no desire to have more children.

Narratives described unpredictable, stormy pregnancies, with women facing daily challenges of managing the pregnancy and SLE:

> My pregnancy went well until I got a miscarriage, I was depressed, because I was looking forward to a baby girl. When I was six months pregnant [second attempt], I went for a caesarean. This year I was on a clinical trial, I fell pregnant and wasn't supposed to, and was not ready for another baby. I had an abortion. (Trisha, 29 years, mother of one)
>
> This disease made me suffer a lot when I fell pregnant. That's when it started getting worse. I couldn't walk. I was admitted at the hospital for three weeks. (Letty, 26 years, mother of two)

One participant, a survivor of several suicide attempts, reported feeling sad and having severe pain due to a septic caesarean section wound. She required prolonged hospitalization. Although confused at first, through health education she learnt about the side effects of immunosuppressants.

Emotional experiences during pregnancy

Many participants described emotional turmoil including anxiety, depression, feelings of bitterness, and the weight of the burden of lupus flares during pregnancy. These negative emotions were exacerbated by the loss of intimate relationships and the emotional toll caused

Table 3. Themes arising from narratives during the interviews and number of participants reporting each theme.

Themes expressed	n	%
Pregnancy and SLE	25	100
Diagnosis of SLE during pregnancy	3	12
Lupus flares and turbulent pregnancies	10	40
Emotional experiences during pregnancy	7	28
Deciding not to have children	4	16
Communication with medical personnel	5	20
Family support and conflicts including fertility	5	20
Sexuality and relationships	22	88
Contraception and other medications	14	56

SLE, systemic lupus erythematosus; n, number of participants reporting each theme.

by undesirable pregnancy outcomes such as premature delivery, miscarriages, unexpected caesarean sections, and suspected congenital abnormality.

One participant (Trisha, 29 years, mother of one) spoke of being diagnosed with depression after delivering a stillborn baby. Another participant described the emotional burden of dealing with two conditions at the same time:

> Lupus and at the same time I was pregnant. I even lost my mind during that period. (Letty, 26 years, mother of two)

Another participant's partner worried about the child and himself contracting SLE.

> "What kind of disease is this? Where did you get it? Will the child also have it"? [husband] "Perhaps it's genetic, maybe I got it from my grandparents, I don't know". So, I explain it to him. He asks me, "Won't I catch it?" I said, "No, it's not contagious". (Letty, 26 years, mother of two)

Decisions not to have children

One participant in her twenties disclosed that she had assessed her own condition and came to a realization that her inability to care for herself meant that she could not take care of children, which caused her great sadness.

> The sense [feeling] of not feeling entitled to something; it's painful. It's a bit emotional. If I can't wash my clothes, if I can't clean for myself or can't carry heavy things, how is it going to be possible for me to maintain kids, you know? (Selina, 24 years, nulliparous)

Three childless young participants decided not to have children and relationships at all after learning about SLE and its complications.

Another participant with chronic renal failure dependent on peritoneal dialysis understood the severity of her condition and her advanced age, and described the precautions she took with her husband to prevent any further pregnancies.

Communication with HCWs

Many participants felt that the HCWs communicated poorly with them regarding their illness, which made some of them take a defiant attitude:

> … because I feel like he's [doctor] not God so he can't say that [I can't have a baby]. I'll try and see. I want to experience to be a mother. I tried, and both my children are normal. (Chan, 35 years, mother of two conceived after SLE diagnosis)

One participant who had restricted foetal growth elaborated on her complicated journey of constant discussions with her doctors regarding abortion as an intervention, but luckily underwent induced labour and delivery at 7 months. Another participant described being utterly confused. She was diagnosed with lupus nephritis and had a previous complicated pregnancy which required a caesarean delivery. She had been advised against further pregnancies by her doctors but had religious dilemmas and an uninformed partner:

> I ended up taking him [husband] straight to the doctor for him to understand. It really affected him [emotionally]. I thought about doing sterilization and I said no! I am a believer, I do believe in God's miracles, the Lord will one day answer my prayers. (Sinethemba, 33 years, mother of two)

Family support and conflicts including fertility

Some participants found that family and partner support helped them to cope. However, others felt that their families and partners either misunderstood or were overwhelmed by the complexities of pregnancy and SLE, and thus aggravated their negative feelings of sadness and fear.

One participant was worried about her inability to conceive, and felt that she was being unfairly compared with a new bride in her family who had conceived shortly after marriage. She feared that her uncles would get her husband to replace her with a 'more fertile bride' if she failed to fall pregnant soon. Another participant described how, after discussions with her husband and doctor, she deferred having a child for a 1–2 years to allow the SLE 'to be relaxed first'.

Sexuality and relationship complexities

Most participants, 22 out of 25, reported intimacy problems, and all felt that these issues were related to their underlying diagnosis of SLE. Eleven participants were no longer sexually active. The reasons for not having a sexual partner ranged from aesthetic concerns to pain, fatigue, poor libido, and partner's distrust. This distrust arose from participants' experiences of poor support and infidelity of partners, which resulted in their contracting sexually transmitted infections (STIs). Sadly, most participants had lost hope in finding a partner, were hostile towards men, or could not face starting a new relationship as it appeared to be an added burden to their already existing SLE symptoms:

> I left him! They [men] make me sick. I even wear wedding rings. I say, "Oh I'm sick, please just leave me alone." Sometimes this lupus is a blessing in disguise because I'm going to die. Yes, I'm going to die. Go! (Inn, 40 years, mother of one)

Four participants experienced partner infidelity. A mother of five who was diagnosed with human immunodeficiency virus (HIV) infection disclosed her partner's unprotected sexual affairs with other women.

Another participant feared that discussions with her husband about their sexless marriage might give him permission to have an extramarital affair. Participants explicitly narrated events leading to divorce threats or separation processes:

> I walked with a limp, which didn't make me feel sexy at all, and in bed I couldn't open my legs for him to have sex with me. That was a real turn-off for him – maybe he's using the lupus and my chronic pain for his infidelities. Last year I ended up again with pelvic inflammatory disease; gonorrhoea. He denied it, but I won't stand for it, I've slowly detached myself from being intimate with him. (Debbie, 43 years, mother of two)

Five participants reported loss of libido. One of them had self-doubts in her ability to be a 'good wife' because of her inability to engage sexually owing to pain, vaginal dryness, and swelling. She had constant fears that her husband would leave her. While it was common for partners to become angry when they were refused intimacy, one participant suffered insults and threats that she would be returned to her family as 'she was no longer a good wife'. One participant felt pressure from her partner to give him a baby boy, and described how she endured sex:

> I don't feel anything when having sex. I'm just doing it because I'm there [laughs]. I won't lie! (Kefilwe, 27 years, mother of one)
>
> It becomes painful down there since I'm not turned on and he adds pressure [points at private parts]. Sometimes he gets angry and asks why I allowed my family to accept the dowry whereas I knew that I won't be able to give him what he wants [sobbing]. I do love him; he's the father of my children. (Letty, 26 years, mother of two)

While infidelity and emotional suffering were common, many participants were uneducated, which generally led to unemployment or qualifying only for unsustainable and unsuitable labour-intensive jobs such as domestic work. As a result, they felt forced to maintain their relationships because of financial dependency on their partners.

Contraception and other medications

Ten participants confirmed being on reliable contraception while four were not using any form of contraception despite being sexually active. Most were aware that some medications would need to be changed should they fall pregnant.

One participant had fertility struggles and was trying to conceive with the guidance from her doctor, while the rest of the participants had discontinued their contraception because of undesirable side effects, a decision to conceive, or apathy. None of the latter had discussed this with their doctors. One participant disclosed being pregnant while on contraception while another described receiving conflicting information from her medical team:

> It's confusing – the doctors from haematology told me that chloroquine is not safe for the pregnancy, I must stop it. At rheumatology the doctors said it's OK for the baby. At haematology they told me that I must stop breastfeeding her because I must go back to the medication. (Kefilwe, 27 years, mother of one)

Discussion

In this study, in-depth qualitative methods were used to explore perceptions and experiences of sexual intimacy, fertility, and pregnancy in women with SLE from generally poor socioeconomic backgrounds. Our findings show that many of them felt not only the general burden of living with SLE, but also negative emotions arising from difficult pregnancies, their inability to have children, struggles to maintain intimate relationships, and anxiety related to physical constraints. They also felt that they were often given conflicting and confusing medical advice against conceiving. These women described complicated reproductive health and sexuality experiences resulting from family, social, and cultural constraints, religious beliefs, and lack of knowledge and understanding of SLE.

Studies have shown that pregnant SLE participants have a substantial risk of flares, which increases until 3 months postpartum (12, 21). Most participants who had been pregnant reported severe, frequent flares during pregnancy. This was evident in our cohort, where most participants struggled emotionally because of poor pregnancy outcomes, including premature deliveries, miscarriages, and unexpected caesarean sections.

The compounded effects from family pressure to have children and self-expectations, as a woman, to be a mother, as well as poor partner support and risks of STIs, and religious beliefs, show the complex emotional challenges that these women must deal with, which HCWs are either not aware of or do not show sufficient sensitivity towards. A UK study of 30 women diagnosed with SLE found that they felt that they had either achieved their family goals before SLE diagnosis or were not concerned about pregnancy at the time of the interview. Only two of these 30 participants were unhappy about SLE limiting their plans for having a family. Physical constraints leading to dependency on others, limited career possibilities, and difficulties in concentration were some aspects expressed by women to have affected their HRQoL (22). Although most participants in the UK study reported similar aspects to those in our study, we found that South African participants living with SLE desired to have more children, wished to start a family, and were generally not satisfied with their childbearing or maternal goals.

There is a strong link between social health, emotional health, and sexual health. In this study, most of the women were single, with some expressing feelings of hostility towards men. Many had experienced negative intimacy encounters and were generally unhappy with their sexual health. In an Ecuadorian qualitative study, participants with singlehood status expressed similar fears at the thought of future family prospects (23). Participants from a study in Spain had low scores, indicating impaired sexual functioning, as measured using the Female Sexual Function Index tool (24). Qualitative and interventional studies on sexuality in SLE remain scarce.

A few studies have been published reflecting on the crucial role of a multidisciplinary team in SLE and pregnancy management (25, 26). Better focused patient education around SLE, fertility, and pregnancy is crucial, especially in women from poor socioeconomic backgrounds including poor education, as in our patients. The high unemployment rate seen in our study is a further barrier to optimal care as these women cannot afford additional supportive care since most of them rely solely on government services and disability grants. In our study, most participants had completed schooling with little further training, and were unemployed or did jobs that did not suit their conditions.

A study in the USA found that higher income and possession of medical insurance had a positive influence on the mental health of SLE patients (27). Patients living with SLE have poor socioeconomic status due to work disability, and this worsens outcomes and reduces HRQoL (3, 28). This interaction and the extent of financial dependency on partners are clearly reflected in the narratives of the participants in this study. Many women were left with little choice on how to manage their sexual and reproductive health, and this shows a need for constant counselling for these women.

Our results indicate inadequate and often conflicting information and miscommunication between HCWs and patients. Some women were advised by their clinicians to temporarily cease pregnancy plans or to permanently avoid conception. This advice was strongly rejected by most participants. Spiritual and personal beliefs had a profound influence on decisions not use contraception, which put them at risk of pregnancy with its associated risks of adverse outcomes.

Living with SLE is not a contraindication for pregnancy. Strategies such as risk stratification, preconception counselling, and careful selection of therapies could improve outcomes (29). Multidisciplinary teams, including an experienced rheumatologist and obstetrician, offer the best outcomes for pregnant and postpartum SLE patients (4, 5, 30). We believe that satisfactory reproductive health among SLE patients can be achieved through helping women make decisions to manage their fertility. These include the use of a combination of safe, effective contraception and relevant SLE-related medication targeting remission state. Pregnancy-friendly treatment modalities need to be considered during the conception, pregnancy, and postpartum periods, including breastfeeding. Because of the unknown or unpredictable patterns of the disease, patience and endurance may be a challenge for most women, their partners, and families, hence the need for continuous psychosocial counselling and support.

Limitations

Our results are based on participants' subjective experiences and perceptions and may be biased by participants' mood on the day of the interview and other unknown environmental factors, such as being in a clinical environment or having an interview while waiting for a doctor's appointment. While thematic analysis was discussed, reviewed, and refined by the study team, comprising a rheumatologist, a nurse, and a social scientist, which provided a wide spectrum of perspectives, this might not be enough to negate all biases. However, the discussion and conclusions drawn by this study confirm and modify the data presented by other published studies and therefore affirm the validity of our results.

Conclusion

This study demonstrates the challenges around fertility, pregnancy, childbearing, and sexuality for women with SLE living in poorly resourced areas of South Africa. Better awareness of these challenges among HCWs, together with well-designed healthcare education which considers cultural belief systems, and referrals to psychological support services, is likely to improve communication and promote better decision making. Future interventional studies to assess the cost-effectiveness and impact of multidisciplinary care on pregnancy outcomes are planned.

Acknowledgements

The authors wish to extend their sincere gratitude to all the participants who opened up about their deep intimate and private experiences. We also thank the hospital staff for assistance during the fieldwork. This study was funded by the National Research Fund (NRF), South Africa, Thuthuka grant number 443812, and the Harry Crossley Clinical Research Fellowship 2017 through the University of Cape Town, South Africa.

Disclosure statement

No potential conflict of interest was reported by the authors.

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CHAPTER 6: Fatigue and functioning among women living with systemic lupus erythematosus in South Africa: Validation of narratives using FACIT-Fatigue, FAI and SF-36 tools.

6.1 Overview

This mixed methods study explored the lived experiences of South African women with SLE pertaining to fatigue and general functioning. To give a more in-depth understanding, findings from quantitative component were compared to the participants' narratives.

Author's declarations and contributions: Appendix VII

Fatigue and functioning among women living with systemic lupus erythematosus in South Africa: a mixed methods study.

Introduction: Systematic lupus erythematosus (SLE) is a chronic multi-system disease that negatively affects health-related quality of life (HRQoL). This mixed methods study explored lived experiences of South African (SA) women with SLE.

Methods: 25 consenting SLE patients attending two tertiary hospitals completed the Short Form-36 (SF-36), Functional Assessment Instrument and Functional Assessment of Chronic Illness Therapy (FACIT) for fatigue questionnaires. Individual in-depth interviews using a topic guide were conducted and analysed using NVivo software.

Results: The majority (72.0%) were black Africans, unemployed (76.0%), and had a low level of education (60.0%). The mean (SD) FACIT and FAI scores were 25.2 (±12.5) (quite a bit fatigued) and 1.2 (±0.8) (activities of daily living performed with difficulty). The SF-36 scores were globally low, particularly role physical and role emotional domains. Fatigue and poor functioning were strongly correlated (p=0.01). Majority of participants described fatigue as “taking over their life” and had far-reaching ramifications including loss of employment. Many patients felt misunderstood by clinicians and their families. Suicidal ideations and depressive symptoms due to fatigue symptoms were expressed. The quantitative tools tended to under-report fatigue and poor functioning, while complexities such as difficulties with employment, the impact of poverty, suicidal ideations and disease perceptions were better explored in the interviews.

Conclusion: This study underscores the complex, chronic and challenging life experiences, often exacerbated by and, in turn, exacerbating, poverty amongst women living with SLE in South Africa. Though quantitative tools are essential in determining broad health status, they may be inadequate in capturing important aspects of HRQoL that emerged from the qualitive interviews. Awareness of these limitations, together with psycho-social support and education, might improve HRQoL.

Keywords: Systemic lupus erythematosus, Fatigue, Functioning, FACIT-Fatigue, Functional Assessment Instrument, SF-36, Mixed methods research, Africa.

Background

Systematic lupus Erythematosus (SLE) is a multi-system autoimmune disease with fatigue reported by up to 92.0% of patients [1]. This fatigue is multifactorial and associated with high disease activity and organ damage, but there is limited research on the effects of fatigue on activities of daily living (ADL) [2-4]. The lack of standardised tools or biomarkers to measure fatigue is a major contributor to its underdiagnosis and inadequate management [3, 5].

Amongst SLE patients, high disease activity and pain result in functional disability with an associated reduced health related quality of life (HRQoL) [6]. Functional status can be defined as an individual's ability to carry out their activities of daily living (ADL) or self-care tasks including dressing, bathing, eating, walking, toileting and basic hygiene [7]. In SLE, fatigue is the main contributor to poor self-care [4].

In rheumatology, patient self-reported outcomes measures (PROMs) in addition to clinical and laboratory measures of the disease are becoming increasingly important. PROMs are standardised assessments that set the topics to be addressed, while qualitative research allows the participant to set the topics for discussion on their experiences and perceptions [8].

Mixed methods research (MMR) has been proven to be an effective and efficient model to minimise information gaps and offer deep insights into patient's experiences [9, 10]. In addition, combining qualitative and quantitative research may offer insights into the utility of questionnaires as screening tools in clinical practice and their relation to experiences described by patients. We undertook this study to assess the burden of fatigue and poor functioning amongst SLE patients in a South African setting, using both qualitative and quantitative methods to understand and explore these phenomena.

Participants and Methods

This cross-sectional mixed methods study included female participants aged 18 years and older, diagnosed with SLE for at least one year prior to the study according to the 2010 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE [19]. Recruitment took place between September 2016 and February 2017 in the rheumatology outpatient clinics of two tertiary hospitals: Groote Schuur Hospital, Cape Town as part of a prospective SLE registry, the African Genetics Lupus Network (ALUGEN) [11], and Chris Hani Baragwanath Academic Hospital, Soweto. Ethical clearance was obtained from the Human Research Ethics Committee at the University of Cape Town and the University of Witwatersrand and all participants signed consent before the study. Thirty healthy age-matched females were recruited as controls from outpatient departments.

Socio-demographic characteristics together with clinical details, including the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [12], SLICC-disease Index (SLICC-DI) [13] with a Physician Global Assessment (PGA) score were documented [14].

Quantitative data

All 25 SLE participants were able to read and write, understood and self-completed the Functional Assessment Instrument [15] and the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score and the Short Form 36 (SF-36). Participants completed the questionnaires before the interviews to avoid sensitization. The 30 healthy controls completed the SF-36 questionnaire.

FACIT-Fatigue Scale

The FACIT-fatigue measures fatigue in the past seven days. This 13-question tool has been validated and used across several studies including participants with SLE, and its relevance in patients living in a low and middle income countries has been confirmed [16]. The final scores ranging from 0-52, and are classified into 5 categories with cut-offs between groups of 13, 26, 39, 40 and 52 [17, 18] of which lower scores mean high levels of fatigue.

Functional Assessment Instrument

The FAI was developed to complement the World Health Organisation Disability Schedule (WHODAS 2.0) to assess functional difficulties in relation to everyday activities and tasks particularly relevant to women living in a poorly resourced peri-urban context similar to that of many of the women recruited in this study [19]. The tool consists of 10 questions, and responses range from 0 = “No difficulty” to 4 = “Can never do a task or activity”. A mean score (0-4) is the sum of all the responses and gives the overall level of functioning of a patient. The lower the score, the better the functioning. Not-applicable items with score 5 are excluded from the mean score.

Short Form 36 (SF-36)

The SF-36 measures overall HRQoL and has been validated in various chronic diseases in both high, middle and low income contexts [6, 20, 21]. The 36 questions assess four physical domains: physical functioning (PF), bodily pain, physical functioning (PF), general health (GH), and four mental domains: vitality, role emotional (RE), social functioning (SF) and mental health [22]. A standardised scoring tool with set percentages is used to compile aggregate scores for each domain. The eight domains are scored on a scale from 0%-100% with 100% indicating the best health status [23]. In addition, sub-scores of the physical component score (PCS) and mental component score (MCS) are calculated from the relevant domains.

Qualitative data

Audio-recorded, in-depth individual interviews were conducted using an interview guide with particular focus on fatigue and functioning. The first four participants whose data are included in the analysis were part of a pilot study. Adjustments were made after all the authors discussed and analysed these four transcripts [21]. The audio-recorded interviews lasting an average of 70 minutes per participant were conducted in English, Xhosa, Zulu, Tswana, Sotho, and Pedi languages by AP, a multi-lingual registered nurse and midwife who was not involved in their clinical care. Notes on body language were taken during the interviews and informants each self-selected a pseudonym to protect their identity and ensure anonymity. Data collection took place in a private, neutral and quiet room at each site's outpatient clinic [21]. Interview feedback was discussed with each participant towards the end of the interview and referral for further services was done in cases where participants showed poor coping skills or depression symptoms.

Quantitative data analysis

The FACIT-fatigue, FAI and SF-36 scores were calculated according to each tool's scoring system and descriptive statistics and Spearman coefficients were calculated. IBM-SPSS 25 software was used, and a *p* score of <0.05 was considered significant.

Qualitative data analysis

The qualitative component of this paper is reported according to the Consolidated criteria for Reporting Qualitative research (COREQ) [24]. Themes were identified during the pilot, data collection and data processing phases. NVivo 11 software was used to sort, organize and code the data. Thematic analysis was done with all co-authors on the first four interview transcripts to ensure validity of the coding.

Results

The 25 participants had a mean (SD) age of 30.9 (7.2) years and disease duration of 4.5 (1.2) years, majority were black Africans (72.0%), and the remaining were of mixed racial ancestry (Table 1). Most participants were single and 68.0% were unemployed. Disease activity was generally low at the time of assessment, with a mean (SD) SLEDAI and PGA of 4.4 (6.4) and 0.93 (1.3) respectively.

Quantitative data

The mean (SD) FACIT-fatigue was 25 (12.5) with 56.0% of participants scoring ≥ 14 (severe or extreme fatigue), only 16.0% scoring 40-51 (minimal fatigue) and none reporting no fatigue (Table 2). The FAI mean (SD) score was 1.3 (0.8), suggesting mild impairment. When broken down into areas of activity, the worst affected areas were in exercising, cleaning the house and laundry (Table 3). Only 16 (64%) participants could bathe themselves, the rest either needed assistance or completed the task with some difficulty, and 13 (52.0%) managed house-cleaning with a lot of difficulty, or not at all. Participants struggled less with social interaction and childcare.

For the SF-36, SLE participants had globally reduced scores compared to healthy controls (Figure 1), with particularly low scores in RP, RE and GH.

A strong negative correlation was found between FAI and FACIT-fatigue scores (Table 4). Participants with the lowest fatigue score (more fatigue) had difficulties in completing activities (r= -0.61, *p*=0.001). In addition, FAI scores correlated negatively with the physical domains of RP (r= -550, *p*=0.04) and body pain (r= -500, *p*=0.01). In the mental domains there was a strong correlation with vitality (r= -0.68, *p*<0.001), including with BP and SF, both at a significant correlation of 0.05 level.

The FACIT-fatigue score correlated strongly with vitality (r= 0.58, *p*=0.02), but no other mental domains, and in the physical domains with GH, RP and the FAI. The RE was strikingly low but correlated with PF, vitality (but not with FACIT-fatigue), SF and disease activity, but not with FAI.

SLE disease activity, as measured by the SLEDAI, correlated negatively with vitality and RE, and inexplicably with disease duration, but not with the FACIT-fatigue or FAI. There were no correlations between age and any score.

Qualitative data

Fatigue

Women described fatigue in many aspects of their lives, hindering their optimal daily living. They further disclosed functional limitations when performing ADLs, particularly caring for themselves and others, employment acquisition and maintenance, socializing and exercising.

Seventeen participants expressed severe fatigue during in-depth interviews (Table 5). Deeper questioning revealed that participants felt their fatigue was due to SLE itself, pain, poor adherence to medication, evil spirits, hot weather or as an effect of being overworked. Some participants had been told by health care practitioners that fatigue was normal, while some felt they were perceived as lazy by family members. Only two participants disclosed that they pushed themselves to complete their tasks and did not let fatigue defeat them. Participants related that the main impact of fatigue was on their ability to perform daily activities including domestic and family care responsibilities, and emotional functioning affecting intimate relations. Some common fatigue descriptions from participants were a feeling after doing hard labour or extreme tiredness needing sleep even after doing nothing.

> *It's when I do something small, like making my bed. When done, I must sit for a few minutes, how can I say? When I'm done then I need to sit again, to recover again (Mandy; 28 years, unemployed; FACIT-fatigue: 17; FAI: 1; vitality: 30; PF: 44).*

> *It's not a normal tiredness… Let me just say it feels like a stuck car, you feel like you can't move! Ja? a skorokoronyana car [*Zulu expression for a car damaged beyond repair*] (Selina; 24 years, employed; FACIT-fatigue: 23; FAI: 2; vitality: 45; PF: 40).*

> One participant with severe fatigue described having difficulties with functioning and poor general health, alcohol abuse and several suicidal attempts.

> *I'm always having medication on me, so it's always easy for me to commit suicide… just take the pills. I'm glad today, I'm here. For them [health care practitioners] to understand that this thing is not normal. This fatigue - it's not normal! It's like you are just making it up, it's like, you want attention. "You don't look sick. You look normal." They don't understand (Olivia; 25 years, employed; FACIT-fatigue: 4; FAI: 2.4; vitality: 35; PF: 0).*

Functioning: self-care and care for others

Participants struggled with household duties including self-care and caring for dependents. Pain, due to arthritis or skin lesions was identified as a main contributor to poor functioning by many patients.

> *So, I think that's [pain] what's working on my nerves. And like, not being able to do everyday your wash up, your makeup, your bed, cook or getting back to work-the pain...! (Nino; 27 years old, unemployed; FACIT-fatigue: 23; FAI: 2; vitality: 15; PF: 0; body pain: 0).*

> *It would be difficult for me to wake up on my own. There would have to be someone that would push me up the bed so I can wake up. It's possible for my knees to get dislocated. There must be someone to bath me and dress me up. It's [pain] an on-going occurrence (Thandazile; 45 years old, former domestic worker, mother of four; FACIT-Fatigue: 22;* RP: 69; PF: 0; body pain: 0; vitality: 64).

Functioning: Employment

Employment acquisition and maintenance was a struggle among most SLE women. Two-thirds of patients cited arthritis, pain and/or fatigue as reasons for unemployment. Poor education was also a causative factor of unemployment as hard labour jobs were not an option for many due to physical limitations. Job resignations was a coping strategy for a few women who also felt misunderstood.

> *No, I'm resigning from this [job], I can't take it anymore. Basically, because these chest pains are not going away. It's painful! But still you feel tired after that then basically no one would understand (Phumlani; 28-year-old previous chef; FACIT-fatigue: 22; FAI: 19; vitality: 45; PF: 25; body pain: 22).*

Social functioning

The SF-36 social functioning domain mean (SD) score was 53 (28.3), suggesting marked impairment. Similarly, on the FAI, 68.0% of participants had great difficulty or were unable to spend time doing activities with family and friends. When responding to the question on taking part in community meetings on the FAI tool, 53.0% reported having difficulties. Participants offered reasons for this poor social functioning including fatigue, pain and society's reaction to their illness. This fitted well with the correlations seen between SF, PF, body pain, vitality and RE and negative correlation with the FAI.

> *"The moment you say you have friends, "I have lupus" "I'm sick", they must encourage you, not ask you in tears. I don't need someone who's going to cry when I tell them. Because people will be like, "Lupus will kill you." I have this other friend - on Facebook. There are groups, overseas groups where you chat and make each other understand. She was like "Hi friend, I see that you have lupus" [this online friendship was better for the participant than having local social circles] (Lulu; 23-year-old college student; FACIT-fatigue: 22; FAI: 0; vitality: 62; PF: 63; SF 62).*

> *"I was this lady; I was very outgoing. When I was diagnosed with lupus I was very, like, "No, I don't care anymore, I just want to go away, go in a peaceful place, I know these people are gonna watch me. Oh, my goodness, they're watching at me" (Phumlani; 28-year-old previous chef, with severe discoid rash; FACIT-fatigue: 22; FAI: 1; vitality: 45; PF: 25; SF 25).*

Exercise

Regarding the question of exercise in the FAI, most reported that physical activity was a major challenge reflected by a mean (SD) score of 2.3 (1.5). While only two participants faced no restrictions in doing exercise, 11 (44.0%) participants could not exercise at all. The main reasons for this inactivity was fatigue and pain.

> *…before I eat, before I do anything, I would take two panados for the pain on my hands and feet. I would cry sometimes, it's just very sensitive! (Nino; 27 years old, unemployed; FACIT-fatigue: 23; FAI: 2; vitality: 15; PF: 25).*

> *…the hips and the knees and the feet mostly [pain]. I'm not as flexible as I used to be. I'm unable to sit cross-legs… Fatigue, that's my main [problem] (Debbie; 43 years teacher, FACIT-fatigue: 20; FAI: 0; vitality: 32; PF:73; RP: 25).*

Relation of PROM scores to narratives

Generally, patients expressed greater fatigue, pain and difficulty functioning in the interviews than in the PROMs. During qualitative interviews, 60.0 % of participants disclosed not managing their daily activities while the FAI scores show that 44.0 % reported between *"having difficulties"* through to "*could never do a task".* Six participants who scored *"No difficulties"* on the FAI reported nil or minimal fatigue on the FACIT-fatigue but interestingly reported frequent daily fatigue symptoms during interviews. Their descriptions of fatigue were similar- phrases such as "*shutting off*", "*zoning out*" and "*I would lie in bed with my eyes closed*", possibly indicative of coping strategies to prevent fatigue becoming unmanageable.

One of these participants with fair HRQoL scores described severe fatigue during the interview.

> *It depends on how hard I've pushed myself through the day. I switch off my phone, alarm and carry on sleeping. I feel like there's a weight on my shoulders, that's how tired I am. I can't do anything; I just want to sit there or lie there and do absolutely nothing (Larona; 23-year-old university student* FACIT-fatigue*: 39; FAI: 1; vitality: 70; PF: 85).*

Another participant showed good HRQoL on the SF-36, with an excellent score on the SF-36 physical function and FACIT-fatigue and no initial complaints of fatigue during the interview.

When probed further, she revealed that she had stopped doing a lot of tasks including employment. She described joint pain and aesthetic concerns as reasons for her joblessness and isolation.

> *Gosh! It's difficult pain, it's quite painful, it's hard (shakes head in sadness). When I sit in a chair for a long time, pain develops and when I get up. When I keep touching cold water, I become affected because my hands change color, they become blue or something. I also get swollen in the face (Neelo; 25 years-old former domestic-worker, FACIT-fatigue: 45; FAI: 0; vitality: 65; PF: 100).*

Discussion

This study used a mixed methods approach and investigated fatigue and functioning in SLE patients from two poorly resourced South African contexts. We describe a marked generalized reduction of HRQoL amongst SLE patients compared to their healthy peers, combined with significant fatigue and poor functioning. The FAI, FACIT-fatigue, SF-36 vitality and RP scores all intercorrelated well indicating a link between different HRQoL dimensions.

Most participants verbalized in detail the extent and consequences of fatigue on their lives. Effects of fatigue were reflected in poor functioning in ADL, employment, social functioning and physical exercise. Many participants felt that their fatigue was not appreciated and poorly understood by clinicians, family members and employers. Elsewhere, fatigue has been shown to be the main contributor to poor self-care and poor sexual relationships [4, 25, 26]. Another study found that due to the variability, invisibility and subjectivity of fatigue, most patients suffering from it could be mistakenly viewed as 'normal' meaning their condition was undermanaged [27].

In the present study, fatigue (measured by high FACIT-fatigue or low vitality scores) was associated with physical role limitations, poor functioning in the FAI, and body pain, but not with mental health or emotional impairments. In contrast, most studies in SLE have associated fatigue with psychosocial factors including depression, anxiety, and poor sleep quality [1, 28, 29]. Some researchers purport that the presence of fatigue is an indicator of chronic pain syndrome, mainly as fibromyalgia including psychological factors such as mood disorders [30, 31]. In the present study the scores did not show correlations between role emotional (RE)/ mood and body pain, poor functioning or role physical yet the participants expressed this in the interviews. Pain was reported by many participants in the present study to add to their poor functioning and inability to work. A seven year prospective follow up study highlighted the need for health care workers to monitor and appropriately treat pain in SLE patients. This study which followed sixty-four patients concluded that low SLE related pain intensity is related to low levels of fatigue, psychological disorders such as anxiety and depression resulting in an improved HRQoL [32].

Poor coping mechanisms including frustration, low mood and suicidal ideations were reported by participants in the present study. One coping mechanism used by participants was avoiding a task altogether, or prolonged rest after household chores. Only two participants coped through 'pushing themselves' to start and complete a task. Interventions to manage fatigue and improve functioning need further development [33]. Physical exercise has been shown to improve fatigue symptoms and better physical functioning and in turn, better HRQoL as measured using the fatigue severity score and the PROMIS tool. In particular, light exercise such as swimming, brisk walking or cycling have been documented as the most appropriate and suitable physical activities for SLE patients [34, 35]. One interventional study demonstrated improvement in emotional and physical functioning, role physical, vitality, mental health, social functioning and anxiety and depression scores after psychotherapy [36].

In our study, there was a limited correlation between the quantitative scores and the detailed qualitative reports by the participants. In particular, we note under-reporting of fatigue and poor function in the PROMs, whilst the same patients described considerable problems in the interviews. However, we believe that PROMs on fatigue and function are an important aspect of holistic assessment of the patient. The exclusive use of physical signs and symptoms or laboratory markers to measure disease activity is common amongst clinicians, whereas patients use their self-rated psychological and physical wellbeing to determine their disease state [37, 38].

Several studies have concluded that physicians should regularly assess factors related to fatigue including physical inactivity, obesity, sleep disorders, depression, helplessness, anxiety, vitamin D deficiency, comorbidities and the disease itself, particularly pain [3, 5]. Our study suggests that in addition to administration of PROMs, which offer a broad understanding, clinicians should probe patients' experiences and perceptions of fatigue and poor functioning to better understand and offer appropriate interventions.

Limitations

Both the questionnaires and the interview narratives were subjective and could have been influenced by participants' feelings and the environment at the time of the interview. The thematic analysis was conducted by a team of a nurse, rheumatologist and social scientist, therefore giving different perspectives and input in the process but we acknowledge some themes may have been excluded when refining the coding process. The quantitative sample might also not be large enough to detect some relationships or differences. Despite these limitations, correlations between the study's outcomes and the existing literature substantiates our findings.

Conclusions

This study combines quantitative and qualitative data to highlight the burden of fatigue amongst SLE patients, and explores its effects including poor functioning in the areas of ADL, self-care and exercise, unemployment, and social functioning. Although PROMs may not capture all important aspects of HRQoL, in busy, under-resourced settings these PROMs could be useful in determining broad health status and alerting the clinician on the areas of concern or "red flags". Awareness of the widespread impaired HRQoL amongst SLE patients, in particular poor functioning and high fatigue levels, is key to developing appropriate solutions. Larger longitudinal studies assessing interventional strategies such as physical exercise, career guidance, disease-specific education, psychosocial counselling offering coping skills and, where appropriate, referral to welfare services, and education opportunities are planned.

Take home messages and 'Red flags'

- All HRQoL tools remain useful in determining HRQoL especially in busy, under-resourced settings.
- A low score (poor functioning) in one of the HRQoL tool domains particularly the RE, VITALITY, PF, RF is a marker for further investigation.
- Regular psychosocial counselling as well as probing the patient has potential to uncover health aspects that were misdiagnosed or under-diagnosed clinically especially in those with quiescent disease stage or with better HRQoL scores.

Table 1: Socio-demographic characteristics and clinical features of the 25 SLE participants.

	n=25	%
Age (yrs)		
>30	15	60.0
<30	10	40.0
Ethnicity (self-reported)		
Mixed Ancestry	7	28.0
Black African	18	72.0
Educational level		
Below Secondary level	5	20.0
Completed Secondary level	10	40.0
At college/university/job training	5	20.0
Completed college/university/job training	5	20.0
Job status		
Employed	6	24.0
Unemployed	17	68.0
Student	2	8.0
Disability grant recipient	6	24.0
Marital status		
Married	4	16.0
Separated	3	12.0
Single	18	72.0
SLE features		
Disease duration* (yrs (SD))	4.5 (1.2)	
Nephritis	6	24.0
Skin involvement	6	24.0
Arthritis	25	100.0
SLEDAI mean (SD)	4.4 (6.4)	
Physicians Global assessment of SLEDAI= 0	17	68

*Disease duration was defined as SLE diagnosis to enrolment in the study
n: number of women, SLE: Systemic Lupus Erythematosus, SLEDAI: systemic lupus erythematosus disease assessment index, PGA: physician global assessment.
* The Physicians Global assessment of SLEDAI is a score of 0 to 3 in categories of 0= no activity, 1= mild disease activity, 2= moderate disease activity, 3= severe disease activity.

Table 2: Results of the FAI, **FACIT-fatigue** ***and SF-36 tools***

Quantitative Tools		**SLE patients n=25**	**Healthy controls n=30**
Short-Form-36	Physical functioning - mean (SD)	58 (19.2)	100 (0)
	Role physical mean (SD)	35 (40.8)	100 (0)
	Body pain mean (SD)	53 (31.9)	95 (8)
	General health mean (SD)	48 (23.9)	81 (3.7)
	Vitality mean (SD)	53 (25.6)	90 (9.9)
	Social functioning mean (SD)	53 (28.3)	100 (0)
	Role emotional mean (SD)	45 (38.6)	100 (0)
	Mental health mean (SD)	58 (29.5)	96 (4.1)
	Physical component score mean (SD)	49 (20.6)	93 (3.7)
	Mental component score mean (SD)	51 (22.1)	93 (3.1)
Functioning Assessment Instrument	Mean (SD)	1.3 (0.8)	
	0- “No difficulty”-	24.0%	ND
	1- “A little difficulty”-	32.0%	
	2- “A lot of difficulty (but can still do task)	32.0%	
	3- “Often can't do task or activity at all”-	12.0%	
	4- “Can never do a task or activity”-	0%	
Facit-fatigue Scale	Overall mean (SD)	(25 ± 12.5)	
	No fatigue -n in category	0	ND
	Slight Fatigue – n (%)	n (16.0)	
	Moderate fatigue – n (%)	n (28.0)	
	Severe fatigue – n (%)	n (40.0)	
	Extreme fatigue – n (%)	n (16.0)	

“No fatigue”- score range 52, Slight Fatigue- score range 40-51, “Somewhat fatigued”- score range 27-39, Very fatigued”- score range 14-26, Extreme fatigue”- score range 0-13. “ND” – not done

Table 3: Results of the individual questions of the FAI

Degree of difficulty completing task or activity	0	1	2	3	4	5		
1. Cleaning the house	7	5	8	3	2	-	1.52 (1.3)	"a little-lot of difficulty"
2. Preparing and cooking food for the family	13	6	4	0	2	-	0.88 (1.2)	"a little difficulty"
3. Doing laundry	8	7	3	3	3	1	1.4 (1.4)	"a little difficulty"
4. Bathing yourself	16	5	1	1	1	-	0.64 (1.0)	"a little difficulty"
5. Taking part in community meetings	11	7	4	1	1	-	0.9 (1.1)	"a little difficulty"
6. Taking care of the physical needs of babies and children	7	7	4	2	0	5	1.0 (0.9)	"a little difficulty"
7. Playing with your children & loving them	9	8	1	3	3	4	0.9 (1.0)	"a little difficulty"
8. Spending time and doing activities with family and friends	8	9	6	1	1	-	1.1 (1.0)	"a little difficulty"
9. Exercising	2	8	4	2	9	-	2.3 (1.5)	"a lot of difficulty"
10. Doing volunteer work	7	8	0	0	2	7	1.0 (1.2)	"a little difficulty"

0 = “No difficulty” 1="A little difficulty or some difficulty” 2 =a lot of difficulty 3= "Often can't do task or activity at all" and 4 = “Can never do a task or activity” and 5 = “Not Applicable”.

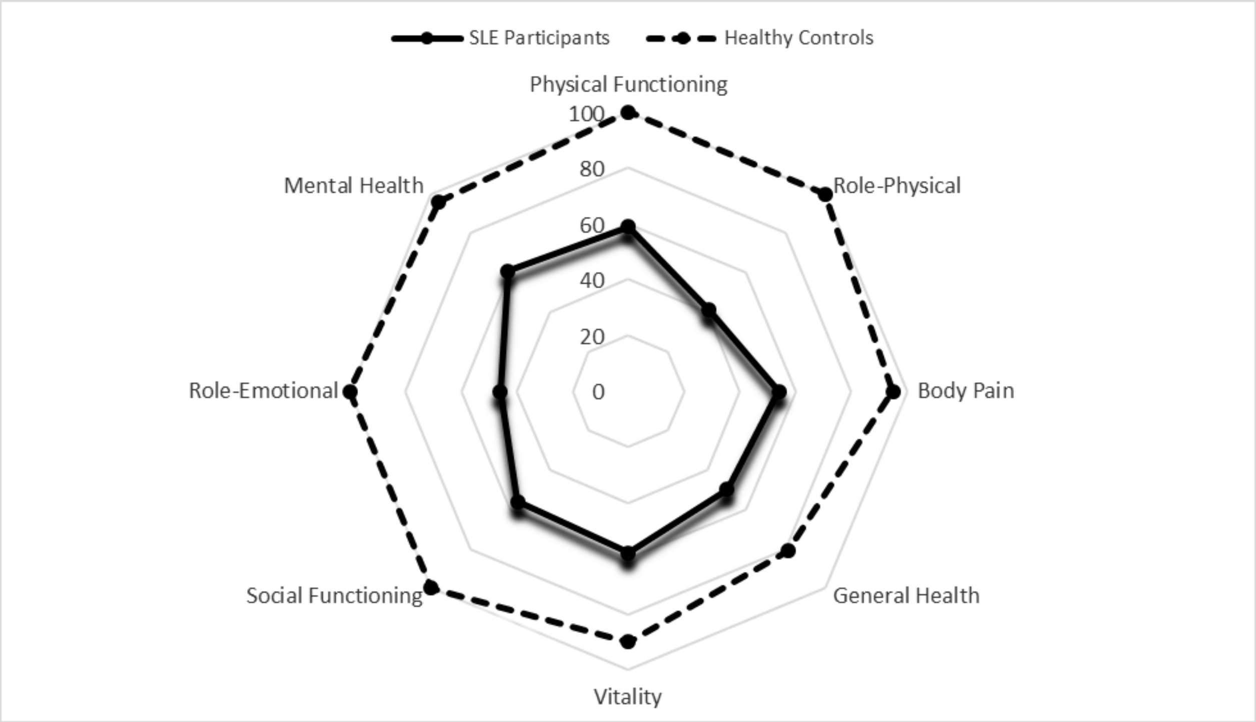

Figure 1: Spidergram the SF-36 domains in the SLE participants versus healthy controls.

Table 4: Spearman’s correlations of SLE patients scores

		PF	RP	BP	GH	VT	SF	RE	MH	Facit_fatigue	FAI	SLEDAI	Disease_duration	Age
SF-36 scores	**PF**	1,000	**.44***	**.65****	0,330	**.49***	**.57****	**.55****	0,210	**.49***	-0,370	-0,130	0,050	-0,040
	RP	**.44***	1,000	**.58****	0,370	**.47***	**.42***	0,209	0,047	**.52****	**-.550****	0,005	-0,005	-0,182
	BP	**.65****	**.58****	1,000	0,315	**.59****	**.53****	0,380	**.44***	**.48***	**-.500***	-0,220	-0,029	-0,063
	GH	0,300	0,369	0,315	1,000	0,236	0,390	0,307	-0,165	**.514****	-0,247	0,015	-0,074	0,010
	VT	**.48***	**.47***	**.59****	0,236	1,000	**.64****	**.68****	**.52****	**.58****	**-.676****	**-.410***	-0,194	-0,150
	SF	**.57****	**.42***	**.53****	0,390	**.64****	1,000	**.70****	**.45***	0,371	**-.422***	-0,354	0,120	-0,213
	RE	**.55****	0,209	0,380	0,307	**.68****	**.70****	1,000	0,388	0,292	-0,301	**-.424***	-0,025	0,059
	MH	0,207	0,047	**.44***	-0,165	**.52****	**.45***	0,388	1,000	0,191	-0,355	-0,396	-0,134	-0,258
Facit_fatig		**.49***	**.52****	**.48***	**.51****	**.58****	0,371	0,292	0,191	1,000	**-.609****	-0,023	-0,103	-0,112
FAI		-0,375	**-.550****	**-.500***	-0,247	**-.676****	**-.422***	-0,301	-0,355	**-.609****	1,000	0,108	0,299	0,020
SLEDAI		-0,132	0,005	-0,216	0,015	**-.410***	-0,354	**-.424***	-0,396	-0,023	0,108	1,000	**.52****	0,284
Disease_duration		0,050	-0,005	-0,029	-0,074	-0,19	0,120	-0,025	-0,134	-0,103	0,299	**.52****	1,000	-0,094
Age		-0,041	-0,182	-0,063	0,010	-0,15	-0,213	0,059	-0,258	-0,112	0,020	0,284	-0,094	1,000

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

BODY PAIN: bodily pain, EF: emotional role functioning, FAI: functional assessment instrument, FACIT-fatigue: Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue, GH: general health, MCS: mental component score, MH: mental health, PCS: physical component score, PF: physical functioning, RP: physical role functioning, SF-36: short form 36, SF: social role functioning, VITALITY: vitality.

Table 5: Themes explored in interviews.

Themes		**n=25**	**%**
Fatigue	Severe fatigue	17	68.0
	Not at all/ a little fatigue	8	32.0
	Defeated by fatigue	15	88.0
	Standing against fatigue	2	12.0
Functioning	Doing daily duties or work without difficulties	1	4.0
	Doing daily duties or work with difficulties	15	60.0
	unable to do daily duties and work at all	9	36.0

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CHAPTER 7: DISCUSSION

This thesis aimed to explore HRQoL among SLE patients attending two tertiary hospitals in SA. We have shown that HRQoL in SLE patients is compromised and this is mostly due to pain, arthritis, discoid skin lesions, psychological distress, lack of support and poor coping mechanisms. The chronic relapsing and unpredictable nature of the disease has been found to significantly affect various spheres of HRQoL for patients. This presents a complex situation to manage for the multi-disciplinary team, family, society and patients.

This research has identified important contributors to the participants' HRQoL which are as follows:

- physical concerns including pain, fatigue and functional disability
- socio-economic status (work function)
- mental health (aesthetic concerns and emotional health)
- social impact
- sexuality and reproduction
- spirituality (coping mechanisms and support including medical care)

7.1 Pain

Almost all the patients in our study identified pain as a major feature of their lives with SLE, with the mean pain score of 45 in the SF-36. The correlations showed that the pain scores were strongly associated with physical functioning and social functioning. As expressed by one study participant, "a day without pain was a marker for happiness". Both discoid skin lesions and arthritis were sources of pain and one or both were experienced by most women limiting their mobility and their ability to do their daily duties. Worsening pain in SLE has been found to be an indicator of high disease activity [35]. Similar to what is reported in this thesis, other studies have found that SLE patients can have unpredictable episodes of pain that frequently becomes chronic, leaving a patient overwhelmed, unable to function and sleep deprived [143]. This is reflected in descriptions from a focus group study in Sweden that concluded that participants found pain very obstructive, making their bodies unreliable which made them fragile [144].

The younger women felt their future goals and dreams were idealistic and improbable considering the pains' chronicity. The participants in our study explained their pain clearly with evocative descriptions of being 'tied in wires around the joints', or having their 'bones chipped away with a nail and a hammer'. These pain pictures can facilitate understanding by clinicians, in the workplace and family and friends. Elsewhere, researchers have highlighted the need to understand pain, evaluate it properly, to give the patient support, and to find relevant interventions for pain in SLE patients [39, 50].

7.2 Fatigue

Our study participants had a low mean score on the FACIT-fatigue tool, indicating high levels of fatigue. While severe fatigue was reported by almost 60% of the participants on the FACIT-fatigue tool, from the narratives about 70% complained about its negative outcomes on their ADL. One study has reported similar findings of more than 90% SLE patients reporting fatigue [52]. As shown in our study and other studies, lack of care for oneself physically remains one of the main negative effects of fatigue [50, 145].

While 17 participants described fatigue, four participants had high scores on the FACIT-fatigue indicating low fatigue. This may reflect the lack of convergence of the PRO measure and the narratives. Alternatively, the participants were having a good day at the data collection time, while narratives may reflect more than one day of experience, and thus capture more fatigue than the PRO.

Similar to pain, understanding fatigue can be challenging for both family, community and employer [31]. For these reasons, we explored the 'fatigue picture', where participants had to give the researcher a visual description of this phenomenon. Our participants described their fatigue as a need to sleep for prolonged periods of time without any relief, and a feeling as if they had completed hard, labor-intensive work. Some participants described being labelled 'lazy' by society, and felt that fatigue was considered normal by the health care professionals and not something to be concerned about. This is noted in other studies [31, 146]. The negative effects of fatigue were also a contributing factor to job loss, poor emotional and social health and had led to depressive symptoms and suicide attempts.

These narrative expressions were generally confirmed by the quantitative tools. Fatigue scores correlated well with functioning; the more fatigued the women were, the poorer the ability to complete their daily activities. Low vitality scores of the SF-36 were associated with high SLEDAI scores, high fatigue, pain and poor functioning. Similarly, another study found fatigue to be associated with pain, tender joints, high disease activity and poor social health [147]. Furthermore, patients with fatigue have been found to have low mental and physical components of the SF-36 [50]. Coping strategies for fatigue remain scarce and are discussed across the literature, such as physical activity, but more research is needed to evaluate this intervention [148-150].

A recent USA cohort study on PROs, fatigue and exercise in SLE patients assigned physical exercise for seven days with intensity measured by an accelerometer [148]. Moderate or vigorous exercise correlated with less fatigue, less pain intensity and better functioning. A Swedish study on physical activity in SLE with matching controls showed that SLE patients engaged in less physical activity compared to their control counterparts [151]. The authors concluded that exercise programmes should be promoted amongst SLE patients. Mild, pain-friendly forms of exercise such as aerobic exercise have been suggested by other researchers [150]. Interestingly, the participants in our study do not affirm the idea that physical exercise could improve energy levels – and many plainly stated that exercise was out of the question.

A review has concluded that early recognition of fatigue, consideration of disease activity, depression, sleep patterns and correct treatment modalities in SLE needs more exploration [152].

Further research focusing specifically on fatigue is needed to find more alternatives to managing fatigue amongst SLE patients.

7.3 Functioning and mobility

Participants in our study generally had poor functioning reflected mostly in the area of completing their daily tasks. The narratives also show poor social and sexual functioning. The locally tested FAI explored different tasks and roles that women discussed in detail during the interviews. The activities reported as most difficult on the FAI were cleaning the house, exercising, caring for dependents and participating in community events – descriptions that were also reflected in the women's narratives. Findings from other studies are not dissimilar to what is presented in our study [31, 153]. When assessed using the SF-36 tool, our patients had poor physical functioning and low physical component scores. In another South African quantitative study SLE, patients scored better on the SF-36 compared to rheumatoid arthritis patients [40] and found strong correlations between disease activity and functioning. In our study, the same correlations were seen between SLEDAI and physical activity, physical functioning and body pain and fatigue. An Ecuadorian qualitative study reported that most women resented their household activities and were seen as 'lazy' when they failed to complete their tasks [31]. Our participants did not resent the tasks, rather longed to do them but had several limitations.

7.4 Self-care and care for others

Similar to our results, studies from LMICs found that participants with SLE were severely compromised especially with self-care [50, 145]. Despite their physical limitations (pain, limited movement and fatigue) and the inability to care for oneself, the women in our study still needed to care for their dependents which included elders in the family and children. Our participants disclosed some feelings of distress and frustration due to these limitations and future family prospects sometimes seemed impossible. A UK qualitative study where most of the patients relied on others for completion of daily activities had similar findings to our study [153].

Physical concerns in SLE are the main driver for poor HRQoL. This thesis' findings corroborate this as participants had, in general, poor physical component scores compared to their healthy counterparts. This was notable in the mean scores of the physical functioning, body pain, role physical and vitality resulting in a poor physical component score of the SF-36. When looking at the participant's narratives, their concerns were pain, fatigue and the difficulties they had in doing their ADLs. Furthermore, though many of women's disease was in a quiescent stage, a substantial proportion still struggled with functional limitations. This limited their ability to reach their goals leading to frustrations and poor coping skills overall. This has been seen in previous studies where pain, fatigue and muscular-skeletal problems were found to be the predominant feature affecting patients' daily lives [48, 50, 144].

To date, coping with poor functioning, lack of mobility, self-care and care for others remains a challenge not only in our study but others as well. For this reason, outcome assessment by health care providers, emotional support with more holistic clinical care are recommended, particularly where poor functioning is a result of fatigue and pain [51, 154, 155]. Important strategies may include cognitive behavioural therapy and coaching sessions with a focus on self-empowerment [156].

7.5 Employment

One of our study's main findings was the multi-faceted consequences of the diagnosis of SLE. Many of our study participants experienced difficulty acquiring and keeping formal employment due to poor physical functioning, with dire SES consequences. Pain, mainly caused by arthritis restricting movement and participants' ability to fulfill their daily job roles, was one of the main drivers of this poor physical function. Discoid skin lesions also led to unemployment, as a result of pain and/or aesthetic concerns. Fatigue was another reason for poor job acquisition and maintenance.

The scoping review findings discussed the association between low educational level, low household income and organ damage. Amongst our participants, low educational status was observed, and this affected participants’ ability to choose a job that would not exacerbate her condition, with a few accepting labor-intensive jobs which they could not later cope with. Some participants suffered from emotional constraints due to lack of financial independence. Other studies have reported on this strong association between SES, poor physical functioning, high disease activity and mental health [42, 112, 157, 158]. Poor educational level has been a predictor of poor HRQoL outcomes in a number of studies [41, 112, 159]. The formally employed women in our study had all obtained tertiary education. For those without tertiary education, employers’ lack of understanding of their diagnosis and the disease’s unpredictable nature seemed an important factor in whether they remained employed or not.

Lack of funds meant some women were not able to access hospital care as they could not pay for transport, or could not access additional private health care services, such as psychotherapy. Similar experiences were reported in an Ecuadorian study where participants’ disease activity was poorly controlled due to poor medical attention as their unemployment status resulted in them not being able to afford medical insurance [31]. Lack of sufficient medical access in developing countries remains a predictor of poor outcomes in contrast to high income countries where, in general, medical costs are low [160]. A Chinese study found a strong association between social assistance grants availability to SLE patients and a better HRQoL as measured by the SF-36 tool [43]. Despite the high unemployment rate in our study, few patients received a state social assistance disability benefit. This may be an area for improvement.

7.6 Poor Mental Health

The SF-36 was used to measure the mental component score of the SLE patients by combining the social functioning, vitality, role emotional and mental health domains. We showed that SLE patients had impaired scores in all these domains. Elsewhere, poor mental health amongst SLE patients has been well described [34, 41, 44, 161]. Factors such as low SES, higher disease activity, lower physical health, organ damage and co-existing medical illnesses are well documented predictors of depression in SLE [42, 48, 162]. A Brazilian study showed strong associations between mental illness, poor education and high disease activity [34]. In the present study, poor mental health was associated with body pain, poor vitality and reduced social functioning. Over two-thirds of our participants had poor mental scores on the SF-36. Of concern, some expressed depressive symptoms, suicidal tendencies and poor adherence to psychiatric medications. A study from India determined that 70% of SLE participants had depressive symptoms and 60% were on antidepressants [45]. These authors highlighted the need to consider the underestimated burden of depressive symptoms in SLE women. In our study, while three women were clinically diagnosed with depression, one was on anti-depressants and had poor coping skills. At the end of the interviews, we referred 5 participants with depressive symptoms to psychosocial services.

Our results confirm the results of a qualitative study conducted in a similar developing context where participants expressed feelings of sadness, worry and fear due to the negative outcomes of living with SLE [31]. The results of our qualitative assessment give an in-depth picture of the association between mental health and other HRQoL domains. The women expressed that their emotional disturbances were due to low energy, constant pain, poor social relations leaving them isolated. Feeling of being a burden to others and poor emotional scores among SLE patients has been determined by other researchers [47, 48].

Most of our participants had poor coping skills and were frequently overwhelmed by feelings of sadness due to the negative disease’s outcomes. A recommendation from Pettersson et al’s qualitative study was that SLE patients could be empowered by feeling that they are in control of their health [54]. A randomized controlled study from Iran found that mindfulness-based cognitive therapy had a positive impact on the psychological state of SLE patients [163]. Based on our findings, we anticipate that similar interventions could contribute significantly to mental health and general HRQoL of our SLE patients.

7.7 The role of sleep, love, acceptance

Our participants reported poor emotional states (mean score 45%) in the SF-36 questionnaire. This low emotional state affected how the women responded to the illness, to everyday living and to future perspectives. Another study has associated poor emotional health with poor sleep [82]. One of the themes in our participants’ narratives was about not getting enough sleep due to pain. Further, many described not feeling fully rested despite prolonged periods of sleep, possibly indicating poor emotional health. Other studies have found associations between depressed mood syndromes with high disease activity, corticosteroid use, older age, high body mass, poor functioning with poor sleep [45, 164, 165].

Female gender, sleep disorder and living in an urban environment have been reported as predisposing factors or triggers for the development of SLE [166]. Researchers suggest that this may show the importance of sleep as a ‘preventative measure’ for SLE. Given our own study’s findings, supported by other studies, we can conclude that poor sleep aggravates SLE’s negative outcomes and therefore should be assessed and managed.

Our narratives showed that some women expressed their low mood as being “out of nothing”, suggesting they felt their feelings were unjustified. When probed further, these women disclosed tendencies of low self-esteem, frequently due to aesthetic concerns, and loss of intimate relationships. Another study from a LMIC found that SLE participants were at risk of depression and anxiety from SLE-related body changes [60]. In our study, many participants struggled with their partners’ poor understanding, lack of affection towards them and infidelity causing additional emotional distress. Similar poor emotional states due to intimate relationship losses were reported in a qualitative study from Ecuador [31]. Frequent SLE flares have been shown to result in high dependency on others and patients who had support from those close to them coped better with these symptoms [167]. Similar to the present study, numerous studies have highlighted the need to appreciate that emotional state in SLE patients is a main contributor to poor HRQoL [168-170]. Empowerment of SLE patients to take control of the disease through psychosocial counseling, and encouraging patients to reach out to their natural support systems are suggested solutions [167, 171].

7.8 Aesthetic concerns

The well-known phrase 'beauty lies on the eyes of the beholder' refers to how other people can grade you as beautiful or not. Most of our study's participants believed others viewed them as not good looking. Disfiguring lesions, alopecia, body changes due to steroid use were some of the main contributing factors to poor social contact and failure to establish sexual relationships. This caused feelings of discomfort, anger and emotional distress. Our participants elaborated on the effects of discoid lupus on the scalp (causing scarring alopecia) as an emotional pain limiting their overall functioning. In a country with high rates of HIV, gaining weight is seen as being healthy while losing weight suggests to others that you have HIV and are stigmatized as such [31, 172]. Similarly, our participants who gained weight as a side effect of glucocorticoid use were viewed by the society as healthy. Our literature review highlights the need for more research on aesthetic concerns, particularly in dark-skinned SLE populations, unlike in developed countries where there is better understanding [173, 174].

7.9 Sexuality and Reproduction

Issues surrounding contraception, fertility, pregnancy, post-partum period and sexuality were under-addressed amongst our participants. Most of the women had undergone various negative experiences during pregnancy including the SLE diagnosis itself, flares of lupus, and unexpected caesarian sections or fetal loss. This has been well documented across the literature although there are conflicting results on whether pregnancy aggravates the illness [175-178]. In the present study, patients revealed the mixed and confusing advice they received during their hospital consultation period regarding whether they should fall pregnant or not, or the best management of their SLE during pregnancy. While almost 40% had turbulent pregnancies, emotional and sexuality problems were an added burden.

Societal pressures to have children and lack of understanding from family and partners were major emotional burdens. Most of our participants wished for a family or more children but the disease limitations, such as functional disability and lack of intimate relationships, became a barrier to achieving this goal. A combination of personal wishes, cultural expectations and spirituality played a significant role in how the women in the present study handled these barriers. Participants in another qualitative study also had negative cultural expectations on reproduction and understanding which were an added emotional burden on them [31]. In contrast, in a UK study only 6% of participants were unhappy about their maternal goals [153].
Although the aspect of sexuality in SLE is not widely researched especially in developing contexts, it is one component that contributes significantly to HRQoL for women living with SLE. The Female Sexual Function Index, the WHOQoL Social sexual activity domain, and interview guides have been used to assess sexual functioning in SLE [31, 179, 180]. Three quantitative studies all highlighted that this domain is difficult to treat or measure [31, 179, 180]. Our qualitative results confirm findings that women with SLE are prone to low libido and sexual dysfunction. Our participants used descriptions such as 'just lying there', 'not feeling anything', 'feeling pain', 'swelling', 'dryness' and 'feeling sad and detached', symptoms suggestive of either Sjögren's syndrome or depressive symptoms, and this is described elsewhere [179]. Many participants felt ''inadequate as a woman'' or emotionally distressed in a relationship as a result of this sexual dysfunction. When probed further, the women reported that their health care provider was unaware of these sexual issues suggesting that during consultations there was no platform to allow for an open, unembarrassed and safe discussion of these intimate details. The same finding was seen in Miles' narrative study where women questioned their sexuality and gender roles in their relationship with men [31].

Our participants have shown that the issue of contraception use among SLE women needs to be addressed. Some women were not on contraception and yet using teratogenic medications to control their SLEs. There is strong evidence that timing pregnancy when the disease is quiescent, prescribing safe medication during pregnancy, and careful antenatal and postpartum care improves pregnancy outcomes [181]. Screening for antiphospholipid antibodies and, in certain cases, use of low dosage aspirin or heparin could improve pregnancy outcomes [182]. It is vital that women plan and discuss their intentions regarding pregnancy and contraception with their health specialists [183, 184]. There have been recommendations that a positive outcome of pregnancy in SLE can be achieved through clear communication and management of both an obstetrician and rheumatologist and other professionals in the multi-disciplinary team [185-187].

7.10 Spirituality as a coping mechanism and support

In the present study, spirituality and personal beliefs played a significant role on how women responded to the diagnosis, medication, care and the environment. A 'belief in God' resulted in participants either having hope for the better or going against the doctor's advice. Participants from two other studies in different settings found that their strong belief system correlated with 'their positive outlook to life' [180, 188]. Considering the disease's unpredictable course, this suggests that participants could cope with the changes having this strong belief system. In our study, participants revealed using traditional and spiritual remedies to ease the symptoms of SLE. This needs more research to determine if these modalities could be useful among SLE patients.

7.11 Coping with medication

In our study, reasons given for poor adherence among 44% of SLE participants were not coping with the overwhelming number of tablets prescribed to be swallowed each day, beliefs on being well especially during remission stage, forgetfulness, undesirable side effects such as weight gain, unpleasant taste, nausea, and the loss of a sense of reality resulting from anti-depressant medications. We chose the title 'Living with SLE in South Africa: A bitter pill to swallow', quoting a participant commenting on about the bitterness of her chloroquine medication and another woman expressing that her life felt bitter after every dosage. According to Kulczycka et al, the use of several medications is a predictor of poor HRQoL and medications that patients use have potential to either negatively or positively affect their HRQoL [174]. Frequently, SLE patients experience polypharmacy, and side-effects from many of these drugs [171]. In our study one patient affirmed this finding by stating that ‘too many medications made her sick as they clashed with one another’. Several studies emphasize the importance of careful review of medication in in SLE patients to achieve optimum results [152]. Simple treatment regimens with instructions including good communication between service providers and SLE patients are proposed as interventions to improve adherence [91]. It has also been suggested that continuous medical treatment is essential for better HRQoL outcomes [188].

7.12 Social impact

Participants in our study had poor social functioning scores on the SF-36 tool. There were strong correlations between this domain and physical functioning, role physical, body pain, vitality, role emotional, mental health and the functional assessment instrument. This reflects the central role that this domain plays in HRQoL. Results from another SA study confirm our findings of low social functioning scores amongst SLE patients [40]. Whilst our study and other studies report poor social functioning, two studies from India and Mexico showed good scores in the social functioning domain of their SLE participants, and the authors from the Indian study concluded that this could be due to the strong family support seen within their community [34, 44]. Another qualitative study on arthritis, found that SLE patients felt excluded socially and lacked their own independence and this was worsened by poverty [116]. The narratives from the women in our study revealed that difficulties explaining the illness and themselves to a society that has a poor understanding of SLE, and aesthetic concerns were the main causes of limited social contact or poor relations. Miles’ qualitative study also disclosed social stigma associated with the aesthetic concerns resulting in some women remaining single [31]. Furthermore, this study and another highlight that personal and social stress were predisposing factors for lupus flares [31, 60]. Better public awareness and understanding of the illness might ameliorate patients’ frustration and withdrawal from social relationships.

CHAPTER 8: CONCLUSION: Breaking the cycle of highs and lows of disease activity, disability and desperation

This study underscores the multifaceted challenges that women living with SLE face in their daily lives. The WHO-ICF model adapted in this study shows the complex interaction between various HRQoL aspects, with a decline in an overall quality of life when one aspect is compromised. Disability is an outcome seen amongst most of the participants in our study as they experience a number of impairments, activity limitations and participation restrictions. The effects of poor physical health, as a direct effect of the disease, has a negative impact on participants' SES, mental health and an overall negative influence on their social interactions with their partners, families and their communities. In addition, the poor mental health also negatively influence the SES and social aspects. The ICF model provides a useful way to address the complexity of these outcomes.

8.1 Holistic consultations

Patients with SLE need comprehensive care and management. To accommodate this, consultation times by the clinician could be made longer. This is not always possible especially in LMIC were there is a limited number of clinicians. Asking relevant key questions at each consultation and using tools such as the SF-36, FACIT-Fatigue and the FAI may assist the health care worker (HCW) to draw a clear conclusion on the patient's response to the diagnosis. We recommend using the WHO-ICF framework to explore which aspects of an SLE patient's life are affected and where interventions, or combinations of interventions, are required (e.g. pain management, family awareness etc.). Some key points using this framework are discussed below.

8.2 Understanding the disability from SLE

Fatigue and pain: the role of patient and service provider

Fatigue and pain need to be acknowledged as main SLE symptoms and therefore should be thoroughly evaluated at every visit. Activity limitations resulting from these and the environmental factors interacting with these need to be properly assessed. The results of this thesis propose a combination of a patient's narratives and specific tools such as the FAI to sufficiently assess how patients function in their daily lives, and at work, home as well as socially.

In clinical practice, the complex and negative dilemmas of living with SLE may not be well captured using quantitative tools. Appreciating that some SLE manifestations are not visual, such as loss of functioning at work, fatigue, pain and emotional distress, could improve holistic assessment of SLE patients during consultations. Asking questions and taking account of patient's descriptions of their daily living experiences during consultations can give more understanding of health status. Some suggested questions are presented below.

How are you feeling physically? How is your pain? How are your energy levels?

Asking patients to describe the physical symptoms they have, exploring their experiences of fatigue and pain including use of examples can give a clear picture and extent of their symptoms. If there are physical symptoms, the patient can be asked to describe the areas of their lives that have been affected as this can give a holistic approach to disease management.

Tell me about the good days you have had? And bad days?

Asking probing questions about their good days, bad days and frequency of fatigue and pain can tell a health care practitioner about an individual's physical ability, how they interact with people and emotional status. If asked at the beginning of the conversation, this question can be a useful ice breaker.

Aesthetic concerns

In Chapter 2, we found that the dermatology life quality index (DLQI) tool was the only questionnaire that has so far been used in assessing aesthetic concerns. We propose further developing tools that measure the impact of DLE or alopecia on patients' lives. Limiting these will reduce the stigma experienced because of visible skin lesions and alopecia.

Interventions such as vigilant sun protection, new therapies to treat skin lesions, together with counselling and emotional support to strengthen coping skills among these patients is essential.

Managing other comorbidities or complications, controlling disease activity and pain with correct therapy to alleviate the symptoms that exacerbate fatigue and poor sleep could improve functioning. Exercise interventions seem to have some potential for providing some benefits as discussed in Chapter 7.

8.3 Barriers and facilitators for functioning – personal factors

Coping mechanisms

Patients need to be empowered to take control of disease symptoms such as fatigue and emotional turmoil through activities such as writing a diary or summary of their daily experiences, how they deal with challenges, questions and concerns, and bring them for discussion during the consultation. Patients who have problems with expressing themselves can have an opportunity to be heard and documenting everything beforehand could prevent critical information being omitted or forgotten.

As enthusiastically expressed in the interviews by our participants, support groups led by a well-trained health care professional for example a social worker or psychologist or disease champions (survivor of the disease) could be very useful for SLE patients, particularly early in their disease.

Family and social circles play a major role in the emotional and social functioning of SLE patients, and these need to be encouraged. Both the literature and our results have shown that patients draw a lot of strength from their families. The loss of intimate relationships which contributed to emotional suffering shows a need to consider the patient's partner, possibly by offering couple's counselling. Involvement of family members and partners during counselling sessions could identify existing or potential problems and allow for collectively agreed upon strategies to help both the family and patient cope better.

What support is available for you?

During consultation, asking patients about the kind of support they have, or think SLE patients need and in addition, probing on patients' own coping mechanisms can give the health care provider an understanding on what helps the patients to cope.

Reproductive and sexual health

Based on our results, all SLE participants of reproductive age, need to discuss reproductive and sexual health and explore family planning options. Open discussions, perhaps including the spouse, will promote clarity on all sides.

Let's talk about your plans for starting or expanding your family.

Our results show a gap in the maternal health aspect of SLE. Women need to be encouraged to disclose their wishes about having children or being pregnant. Using a non-judgemental approach and asking about the information the woman has heard or read about regarding having children when one has lupus, and the issues they anticipate.

Medication and adherence

Patient's understanding of their disease affects how they feel about their disease, and how well they adhere to medication. HCW need to ensure that this understanding is correct, clear and updated. Asking about their medication and how well they are working and any concerns about side effects can elicit some useful information.

Questions like these can give the health care provider a glimpse into patient's adherence, reasons for non-adherence and insight into a patient's confidence in the prescribed medication can address the notion of 'a bitter pill to swallow'. Considering the many reasons for a patient with SLE to use her daily antimalarial medication, patients can be advised on ways to take it that minimizes the bitter taste. Similar discussions about side effects and explanation of the importance of each prescribed medication might be very useful.

Are you using any other medications or remedies for your SLE?

Most patients would give information on the non-prescribed therapies (herbal medication, over-the counter medications, and consultations with alternative practitioners) that they have tried if asked in a non-judgmental way. Discussion and mutual agreement about the place of such treatments can then follow.

Studies that measure adherence should be designed where adherence issues are explored including interventions that facilitate better medication acceptance. Alternative therapies need to be explored and tested to evaluate their effectiveness in disease management.

8.4 Environmental factors

Socio-economic status

Health care professionals need to communicate with patients' employers, schoolteachers (for adolescents) or university lecturers to offer information about SLE, and workplace tasks or job modifications that may be beneficial, possibly with input from an occupational therapist. Assessment of disability and a referral for social grants may be appropriate.

A systematic review [156] including studies that looked at interventions supporting work maintenance and return to work in chronic illnesses proposed that workplace interventions, such as assessment of patients' ability to work and offering work tasks that are not labour intensive, can enable an employee to function optimally and reduce their absence at work.

A South African study actively followed up 35 stroke survivors at their employment site over a period of six months, while control participants had no active workplace follow up [189]. Active follow-up included assessment for work skill, interview sessions where barriers to work were identified, and discussions with employer and patients. At the end of the six months follow up period, 60% of participants on the intervention group had returned to work while only 20% in the control group had resumed their work schedules. Better quality of life was seen in those who returned to work regardless of their assigned group compared to those who did not return to work. The role of an intense programme like this one needs to be explored with SLE patients in our setting.

Training and knowledge

Finally, ongoing training of health care personnel on SLE so that they, in turn can support SLE patients is of vital importance. Better informed primary care workers might reduce late diagnosis and referral, improve understanding of new and novel treatments for SLE, and allow rapid assessment of complications including infections. HCWs can also narratively explore patient's knowledge and source of information through posing this question:

<u>What have you been told about your SLE, and are there things you are uncertain of that you would like to talk about?</u>

Health education plays a major role in patients' care. Lack of information can impede optimal disease management by the patient. Probing the patient on the kind of health education they have received and their interpretation of it, could assist in clarifying misconceptions and updating their current knowledge of the disease, its complication and treatment.

The other important environmental factor that needs improvement is the community's awareness of SLE. Information on television, radio and social media could improve the awareness of SLE for families and the broader community. This can reduce stigma and social isolation of people living with SLE.

In summary we recommend informed and shared decision-making regarding management of SLE patients, counselling and psychotherapy, reinforcement of emotional support, together with devising plans on what works best for the patient and their surrounding while considering the nature of the disease and its outcomes.

Figure 8.1 shows the WHO-ICF framework that would focus on all the elements that need to be considered in finding interventions to improve HRQoL among SLE patients. Using this model with a combination of a mixed methods approach to evaluate and assess the complexity of the illness, understanding the role of all the factors in social functioning and HRQoL could help achieve holistic care and management of the SLE patients.

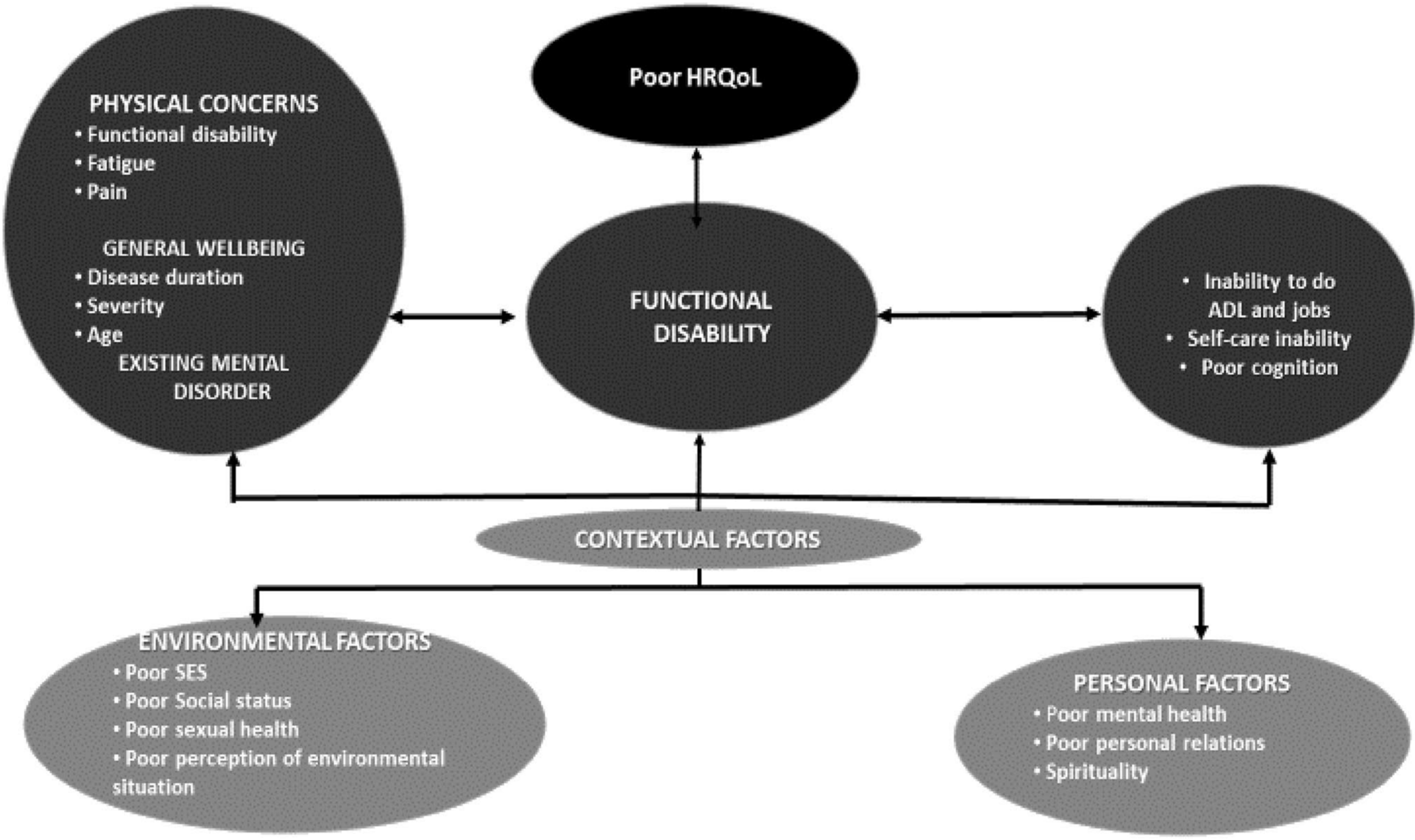

Figure 8.1: A model of an interventional study including care approach for holistic management of an SLE patient as guided by the WHO-ICF framework

8.5 Limitations

The present study has limitations. We included a sample of 25 women for both the quantitative and qualitative study. This sample is not large enough to effectively power the quantitative analysis. However, as the aim of the study was exploratory, 25 participants was seen as an appropriate sample for this qualitative exploration. The inclusion of the quantitative measures allows for an interesting consideration of the relationship between the two sets of information, thus giving a broader understanding of HRQoL.

The results of the narratives and tools are subjective and might have been influenced by participants' mood and the environment. For example, scores indicating less pain, fatigue and functioning on the day of interview coupled with a report of the opposite in the narratives reflect possible differences in perspective – 'today' (which may be a good day) versus 'what happens usually' (a more long-term view). This is a small limitation in the analysis of the quantitative together with the qualitative data. Despite this, the relatively large sample of in-depth interviews that was determined by saturation of data had a possibility of controlling bias.

To increase diversity, we did recruit patients from two hospitals based in different cities, but the demographics of participants were similar. Our study results cannot be generalized to all SLE patients. However, many of the experiences of patients and themes we have noted are described and explored by researchers elsewhere, frequently in high income as well as LMIC settings.

Our study was cross-sectional and therefore we are unable to evaluate if there were any changes in the outcomes that are reported in this thesis nor any direction of causality beyond those reported by the participants. We also narrowed the scope only to women and the FAI tool used particularly explores functioning in women. We aimed at an in-depth exploration of women's experiences without confounding it by gender. Therefore, the study results cannot be generalized to men's experiences of living with SLE. We recommend future longitudinal studies that includes both genders.

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APPENDICES

I: CRF; Patient socio-demographics, screening and Medical data form.

Center No: _________ PID No: ________________
Date: ________________ Visit Type: ________________

Baseline Data

Gender: ____________________ DOB & Age: _____________
Ethnicity: ____________________ Geographic location: _________
Date at SLE diagnosis: _________ Age at diagnosis__________

Eligibility criteria

Circle correct answer. If any of the answer is No, exclude participant from the study.

1. Is the participant female? YES NO
2. SLE/Lupus like according to ACR 1997/SLICC? YES NO
3. Diagnosed with SLE in the last five years? YES NO
4. Adolescent stage (>14 years) from PULSE cohort? YES NO
5. Age <35 ALUGEN study YES NO
6. Has the patient signed informed consent? YES NO

Socio-Demographics

Level of Education: _______________ Occupation: ____________
Loss of work due to SLE: __________ Type of Housing: _______
No in household: _________________ Disability Grant: ________
Total Household Income: __________ Smoking: ___ Alcohol: ___

Obstetric history

Past pregnancies
Year: ______________ Outcome: ____________
Year: ______________ Outcome: ____________
Year: ______________ Outcome: ____________
Any hormonal drugs or contraception used if Yes state: ______________________

Co- Morbidities

WT: _________ HT: ________ BMI: _________
Any Co-Existing Medical conditions if yes state: ____________________________
How many Hospital admissions due to SLE flares since diagnosis? ______________
SLEDAI at present: ______________ SLICC at present: _____
Medications at present: ____

II: Short-Form-36

Center No: _________
PID No: ________________
Date: _______________
Visit Type: ________________

INSTRUCTIONS: Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions. If unsure, please feel free to ask the researcher.	
1. In general, would you say your health is: (Circle One)	1. Excellent 2. Very Good 3. Good 4. Fair 5. Poor

2. Compared to one year ago, how would you rate your health in general at this time? (Circle One)	1. Much better now than one year ago 2. Somewhat better now than one year ago 3. About the same as one year ago 4. Somewhat worse than one year ago 5. Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
(Circle the appropriate number for each question)

Activities	**Yes, limited a lot**	**Yes, limited a little**	**No, not limited**
a. Vigorous activities, such as running, lifting heavy objects, or participation in strenuous sports	1	2	3
b. Moderate activities, such as moving a table, Vacuuming, bowling or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking more than a mile	1	2	3
h. Walking several blocks	1	2	3
i. Walking one block	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of your physical health? (Circle the appropriate number for each question)		
a. Cut down on the amount of time you spent on work or other activities	Yes = 1	No = 2
b. Accomplished less than you would like	Yes = 1	No = 2
c. Were limited in the kind of work or other activities	Yes = 1	No = 2
d. Had difficulty performing the work or other activities (For example – requiring an extra effort)	Yes = 1	No = 2

5. During the past four weeks, have you had any of the following problems with your work or other regular daily activities as result of any emotional problems (such as feeling depressed or anxious)? (Circle the appropriate number for each question)		
a. Cut down on the amount of time you spent on work or other activities	Yes = 1	No = 2
b. Accomplished less than you would like	Yes = 1	No = 2
c. Didn't do work or other activities as carefully as usual	Yes = 1	No = 2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups? (Circle one)	1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely

7. How much bodily pain have you had during the past 4 weeks? (Circle one)	1. None 2. Very mild 3. Mild 4. Moderate 5. Severe 6. Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Circle one)	1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks: (Circle one number on each line)	

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc.)?(Circle one)	1. All of the time 2. Most of the time 3. Some of the time 4. A little of the time 5. None of the time

11. How TRUE or FALSE is each of the following statements to you? (Circle one for each line).					
	Definitely True	Mostly True	Don’t Know	Mostly False	Definitely False
a. I seem to get sick easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

III: Functional assessment instrument

Center No: __________ PID No: __________________
Date: ________________ Visit Type: ________________

1. I am going to ask you about different tasks and activities that you do currently in your everyday life. Thinking about the last 2 weeks, how much difficulty do you have doing the following tasks and activities?

Task or activity	Degree of difficulty completing task or activity					
	No difficulty	a little or some difficulty	a lot of difficulty (but can still do task)	Often can't do task or activity at all	Can never do task or activity	Not appli cable
1. Cleaning the house	0	1	2	3	4	5
2. Preparing and cooking food for the family	0	1	2	3	4	5
3. Doing laundry	0	1	2	3	4	5
4. Bathing yourself	0	1	2	3	4	5
5. Taking part in community meetings	0	1	2	3	4	5
6. Taking care of the physical needs of babies and children (bathing, feeding, preparing for crèche or school, taking to crèche and school, keeping them safe; etc.)	0	1	2	3	4	5
7. Playing with your children and loving them	0	1	2	3	4	5
8. Spending time and doing activities with family and friends	0	1	2	3	4	5
9. Exercising	0	1	2	3	4	5
10. Doing volunteer work (__________________)	0	1	2	3	4	5

IV: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-fatigue) scale

Center No: _________ PID No: ________________
Date: _______________ Visit Type: ________________

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
H17	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
AN1	I feel listless (“washed out”)	0	1	2	3	4
AN2	I feel tired	0	1	2	3	4
AN3	I have trouble starting things because I am tired	0	1	2	3	4
AN4	I have trouble finishing things because I am tired	0	1	2	3	4
AN5	I have energy	0	1	2	3	4
AN7	I am able to do my usual activities	0	1	2	3	4

AN8	I need to sleep during the day	0	1	2	3	4
AN12	I am too tired to eat	0	1	2	3	4
AN14	I need help doing my usual activities	0	1	2	3	4
AN15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
AN16	I have to limit my social activity because I am tired	0	1	2	3	4

V: Interview guide for SLE in Female Study.

	QUESTION	**NOTES/Key Words**
1.	Can you briefly introduce yourself; tell me more about your background?	
• **Now that you agreed to be in the study, I will discuss some areas specific to your everyday life related to having SLE.**		
2.	What do you think is meant by lupus/Systematic Lupus Erythematosus/SLE? Probe: traditional meanings/understanding Other views not medically related	
3.	Tell me about your family, community understanding about lupus Probe: media understanding, traditional meanings/understanding or other views.	
4.	'You have SLE and you have been living with this disease for some time. Describe for me what it means for you to live with SLE.' Probe in detail on good days, bad days, emotions, functioning at work or socially.	
5.	Some women with SLE have described their feelings of hope or depression and helplessness. Tell me how you feel about it Probe: coping mechanisms-patient, family, work	
6.	'You have children/ you have been pregnant, but you lost your baby/you have not had any children or pregnancies as yet.' Describe your experience of having children or being pregnant or what you think may be issues when you decide to fall pregnant or in controlling fertility generally. Probe: What health education did you receive at the hospital?	
7.	Some women have disfiguring lesions/discoid lupus or feel tired al lot. How has this affected the way you view beauty? Probe: What are your experiences of living with disfiguring lesions?	
8.	You have been taking your medication quite well/ you haven't been taking your medication quite well. Prompt: How is the lupus reacting to your medication? Any hopes side effects with chronic treatment? Prompt: Other treatment options?	

9.	There are different support services that SLE patients need. Which ones would you recommend (either from hospital/home/state)?	

VI: Ethics

Information leaflet and Adult Informed Consent

STUDY TITLE: Health related quality of Life, Perceptions and experiences of female patients with Systemic Lupus Erythematosus in South Africa: Exploring Unmet needs using a mixed methods approach.

SPONSOR: National Research Fund

INVESTIGATOR: Dr B Hodkinson (Principal Investigator/ ***PhD supervisor-University of Cape Town***).

Dr M Schneider (Co-Investigator/***PhD co-supervisor-***University of Cape Town) and Ms A Phuti (***PhD Student/co- investigator***-University of Cape Town)

INSTITUTIONS: Groote Schuur Hospital- Rheumatology Department, Dept. of Psychiatry and Mental Health, Alan J Flisher Centre for Public Mental Health), Red Cross War Memorial Children's Hospital, University of Cape Town.

DAYTIME AND AFTER HOURS TELEPHONE NUMBER(S): +27823950503 Dr Hodkinson or +27727645806 Ms Phuti.

To the potential Participant: This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home **an unsigned copy of this consent** form to think about or discuss with family or friends **before making your decision.**

INTRODUCTION

Good day. My name is ………………. and I work for …………… We are inviting you to consider participating in a research study titled: **Health related quality of Life, Perceptions and experiences of female patients with Systemic Lupus Erythematosus in South Africa: Exploring Unmet needs using a mixed methods approach** or short tittle: **Quality of life in females living with lupus.** ***This study is being conducted as part of a PhD or Doctor of philosophy degree studies for Ms Angel Phuti at the University of Cape Town.*** This study is being conducted by researchers in South Africa; Groote Schuur Hospital, Red Cross War Children Memorial Hospital in Cape Town and Chris Hani Baragwanath Hospital in Johannesburg.

Kindly inform the study staff or research if you are involved in any other research study. The study staff are as follows; Dr Bridget Hodkinson- Principal Investigator (University of Cape Town, Groote Schuur Hospital) Dr Marguerite Schneider- Co- Investigator (University of Cape Town) Ms Angel Phuti- Co- Investigator (University of Cape Town). Please ***feel free*** to ask questions. ***You can choose to be in this study or not. Please join when you understand it fully.*** You will be given a signed copy of this consent form for your records.

PURPOSE OF THE STUDY

We understand that you have been diagnosed with a condition called Systematic Lupus Erythematosus or Lupus by your doctor within the last 5 years. Lupus as is commonly known is an autoimmune medical disease ***whereby body is too weak to fight germs***. It affects more women than men. There are many challenges that women or females living with lupus face. Therefore, this study might give us enough information that could be used to help in managing the patients. This study aims to collect this information by asking you some questions related to the things mentioned above. The goal is to measure how women are affected and it seeks to find recommendations to improve care in clinic, home and community settings.

WHO WILL BE MY DOCTOR ON THIS STUDY?

If you choose to take part in this study, you will still follow up at your usual clinic for all your scheduled hospital visits. In addition, you will remain under the care of your current doctor.

WHY IS THIS STUDY BEING DONE?

This research aims to study the quality of life that is related to health in females who were diagnosed with lupus condition. This means we will be studying how much lupus can affect how you feel and your ability to carry daily activities and duties. In addition, we are interested in finding out the experiences and perceptions of living with lupus looking mainly at physical changes, emotional wellbeing, medication adherence, fertility and pregnancy and coping strategies.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

The researchers aim to have approximately 100 participants to measure depression, fatigue/tiredness and ability to carry daily activities and duties. Among these patients about 50 will be interviewed so that we can find detailed, deep information on experiences and perceptions of living with lupus looking mainly at physical changes, emotional wellbeing, medication adherence, fertility and pregnancy and coping strategies.

WHAT IS INVOLVED IN THE STUDY?

The study entails 3 questionnaires, each measuring depression, fatigue and ability to carry daily activities and duties. In addition, there is an audio recorded interview that will last approximately 1 hour of your time in which the researcher finds out detailed, deep information on your experiences and perceptions of living with lupus. Please note that if you consent to participate, then we have to record the interview which assists us on gathering more information. It will be kept strictly confidential and we won't use your real name therefore it cannot be identified. We will collect the following information from you; information about gender, age, social status history, medical history, fertility and pregnancy history, treatment history, family history, current medications to supplement the data collected from the questionnaires and interview.

HOW LONG WILL I BE IN THIS STUDY?

The study will last for 3 years. This is a follow up study where if you are still involved, information will be collected at enrolment then you will be seen by the researcher yearly for two years. The

3 questionnaires and 1 interview will be done at each visit. ***At every follow up visit, you will be required to sign a consent form again before you join.***

WHAT ARE THE RISKS OF THE STUDY?

There are no physical risks involved in the study. However, there is a small chance in loss of confidentiality as your clinical or any referral hospital team may be aware that you are involved in this research, but every attempt will be made to make the procedures extremely confidential and secure. In addition, you might experience some psychosocial distress during the recorded interview since you might have to open up regarding experiences and perceptions in particular your inner feelings which might be emotional for you. Every attempt will be made to make you comfortable and hospital protocols on referral to a trained psychologist or social worker are put in place to handle such situations.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

The benefits to taking part in the study might be that being given a chance to talk about your experiences to someone could feel therapeutic to you. However, the researchers anticipate that through your involvement, the findings will be of benefit in future management and care of females living with lupus.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?

This study is based on ethical principles of the Declaration of Helsinki (1961-2013), the South African Guidelines for Good Clinical Practice (2006) and the Department of Health- South Africa: Ethical Guidelines for Research (2015). These laws and regulations were developed to ensure that as a study participant; your privacy, integrity and security is adhered to at all times.

All information obtained from questionnaires and during interviews is required to be kept strictly confidential. The questionnaires and audio recorded interviews will be carried out in a sensitive and quiet office. ***Though unique participant identifiers or pseudonyms will be used to ensure that no information is linked to you in the end, a separate file consisting of your contact details and name that will be used for follow up visits will be kept in a safe and locked cupboard in a secure office.***

The files and audio recorded materials will be safely locked in secure cupboards at all study sites. After transcriptions of recorded materials is done and verified, the audio records will be deleted in exception of cases where you allow us to retain the audio recordings for usage at scientific conferences.

However, there might be internal auditing done by the Health Research Ethics committee at the University of Cape Town or at University of Witwatersrand to assess if the researchers are conducting the research in an ethical manner. By giving consent to participate in this study, your records are subject to monitoring and evaluation by the ethical boards.

Research findings may be presented at scientific workshop and meetings or published in a scientific journal; your identity will not be revealed.

WHAT ARE THE COSTS?

There will be no payment for taking part in the study and the researchers will not pay for your transport costs.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?

Research studies are voluntary and only include people who choose to take part in. At any stage, you may choose to withdraw without losing your benefits as a patient receiving care at the any hospital. In instances where it is in your best interest or the research output does not add any value, the principal investigator might withdraw you from the study. You will be notified about this procedure prior to being withdrawn.

CONTACT INFORMATION IF I HAVE SUGGESTIONS QUESTIONS OR PROBLEMS?

If you would like to make suggestions or query any information regarding your **rights as a research participant, or complaints regarding this research study**, you may contact Professor Marc Blockman, Chairperson of the University of Cape Town Human Research Ethics Committee or Administrator at University of Witwatersrand Human Research Ethics Committee (HREC) an independent committee established to assist protect the rights of research participants at 021 4066496 or 011 717 1252/2700/1234/2656. For **research information** you can contact the principal Investigator Ms Angel Phuti at 0727645806.

PART II: Certificate of Consent

Certificate of Consent

I have been asked to give consent to participate in this research study which will involve completing one audio recorded interview and three questionnaires. I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this study.

Print Name of Participant ___________________ OR Thumb print of participant

Signature of Participant___________________

Date ____________________________

Day/month/year

Signature of Investigator(s):

_________________________________ Date: ______________

Audio recording of interviews:

I consent to have the interviews audio recorded.

Print Name of Participant___________________ OR Thumb print of participant

Signature of Participant_____________________

Date ____________________________

Day/month/year

Signature of Investigator(s): _________________________________ Date: ______________

Use of Audio Recordings

I hereby allow / do not allow my recordings to be archived for usage in scientific conferences. [Circle the text that applies to you].

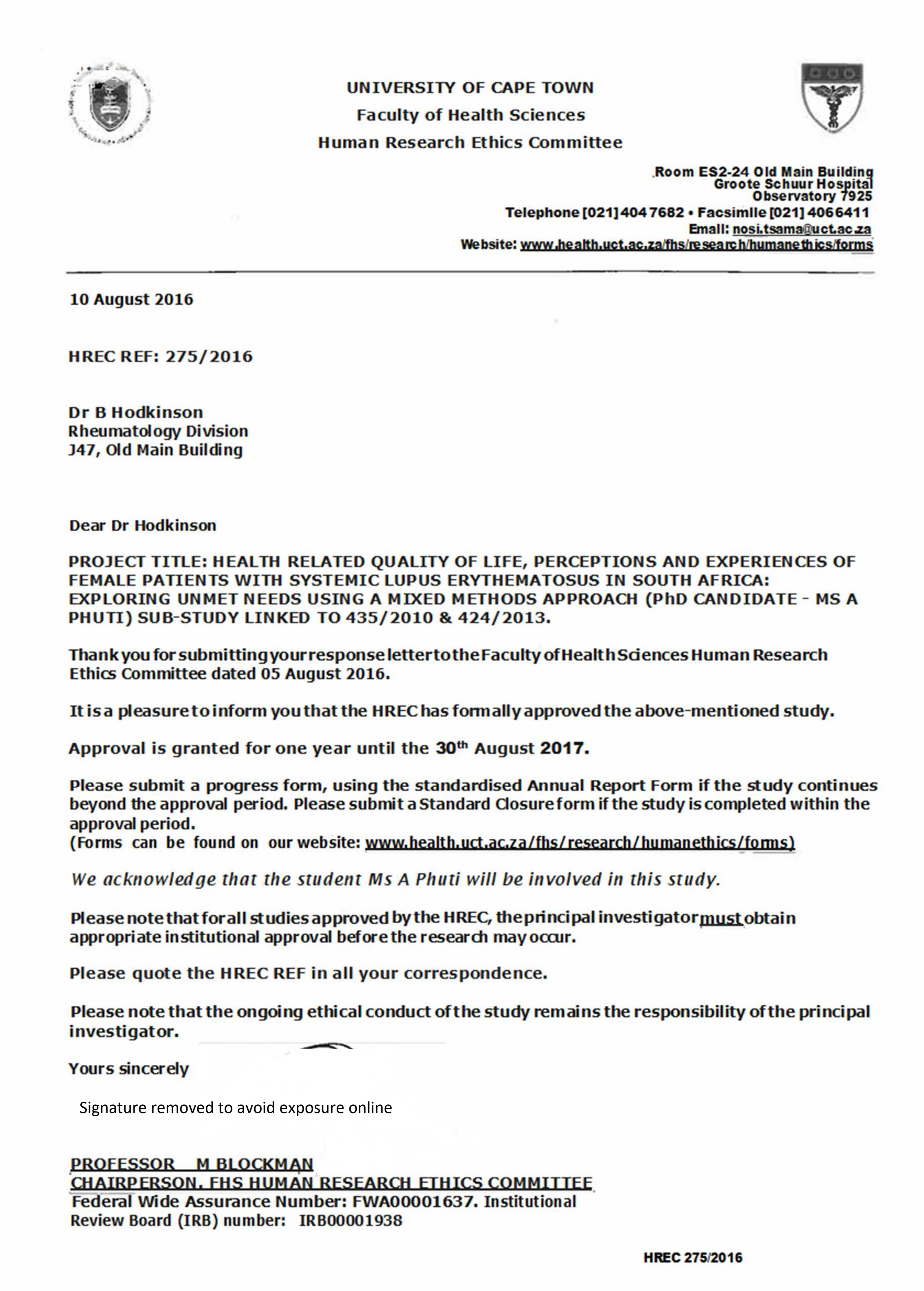
Print Name of Participant__________________ OR Thumb print of participant
Signature of Participant____________________
Date ___________________________
Day/month/year

Signature of Investigator[42]:
_______________________________ Date: _____________

For illiterate participants-Witness needed
I have witnessed the accurate reading of the consent form to the participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____________________ AND Thumb print of participant
Signature of witness ______________________
Date ________________________
Day/month/year

Signature of Investigator(s): _______________________________ Date: _____________



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room ES2-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682 • Facsimile [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

---

10 August 2016

HREC REF: 275/2016

Dr B Hodkinson
Rheumatology Division
J47, Old Main Building

Dear Dr Hodkinson

PROJECT TITLE: HEALTH RELATED QUALITY OF LIFE, PERCEPTIONS AND EXPERIENCES OF FEMALE PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS IN SOUTH AFRICA: EXPLORING UNMET NEEDS USING A MIXED METHODS APPROACH (PhD CANDIDATE - MS A PHUTI) SUB-STUDY LINKED TO 435/2010 & 424/2013.

Thank you for submitting your response letter to the Faculty of Health Sciences Human Research Ethics Committee dated 05 August 2016.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30th August 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student Ms A Phuti will be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval before the research may occur.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

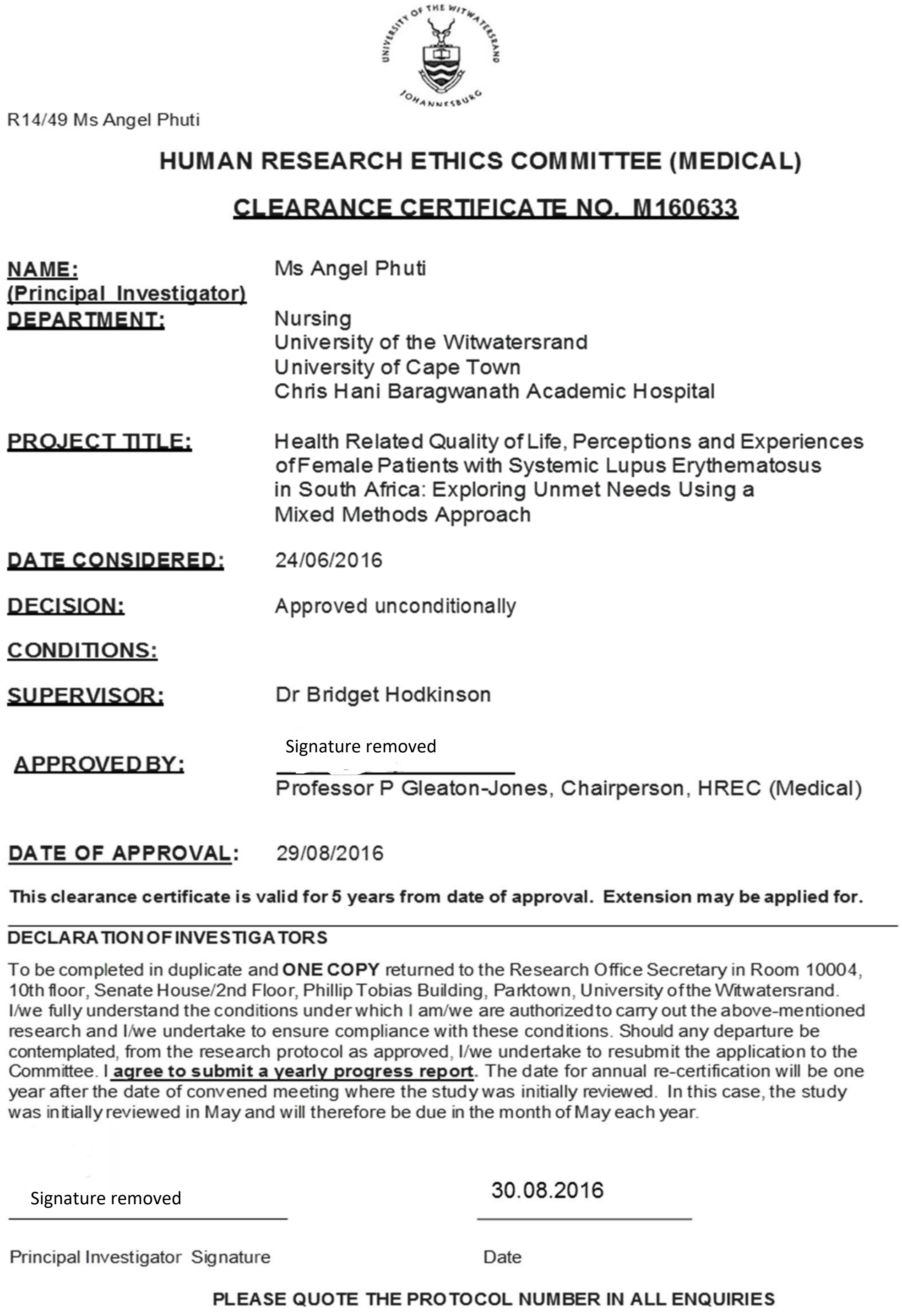
Yours sincerely

Signature removed to avoid exposure online

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938

HREC 275/2016

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.



R14/49 Ms Angel Phuti

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160633

NAME: **(Principal Investigator)** Ms Angel Phuti

DEPARTMENT:
Nursing
University of the Witwatersrand
University of Cape Town
Chris Hani Baragwanath Academic Hospital

PROJECT TITLE: Health Related Quality of Life, Perceptions and Experiences of Female Patients with Systemic Lupus Erythematosus in South Africa: Exploring Unmet Needs Using a Mixed Methods Approach

DATE CONSIDERED: 24/06/2016

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr Bridget Hodkinson

APPROVED BY: Signature removed
Professor P Gleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 29/08/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I **agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in May and will therefore be due in the month of May each year.

Signature removed
Principal Investigator Signature

30.08.2016
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

VII. Statement of Originality, Authors' Contribution and permissions

UNIVERSITY OF CAPE TOWN

Ms Angel Phuti
Department of Medicine
Rheumatology Division
J47 Old Groote Schuur Hospital Observatory 7925 Cape Town South Africa
Tel +27 (0)21 404 2131 Fax +27 (0)21 448 3253
Email:PHTANG001@myuct.ac.za

Faculty of Health Sciences c/o
Doctoral Degrees Board
University of Cape Town
Masingene Building,
Private Bag X3, Rondebosch, 7701

14 05 2019

Dear Sir/Madam

Permission to include published manuscripts or papers under review in a thesis for PhD (Medicine)-Candidate Angel Phuti (PHTANG001).

I am currently completing my PhD at the department of Medicine. The Doctoral Degrees Board Office approved my admission as a candidate for the PhD under the supervision of Prof. B Hodkinson and A/Prof M Schneider on the 23 February 2017. My thesis is titled: Health related quality of Life, Perceptions and experiences of female patients with Systemic Lupus Erythematosus (SLE) in South Africa: Exploring Unmet needs using a mixed methods approach.

This research is a substudy of the African Lupus Genetics Network (ALUGEN) project, an established prospective multi-centred registry of South African SLE patients. Patients were sampled from this registry and enrolled into this sub-study. The following publication gives more information on this registry.

Hodkinson B, Mapiye D, Jayne D, Kalla A, Tiffin N, Okpechi I (2015) The African Lupus Genetics Network (ALUGEN) registry: standardized, prospective follow-up studies in African patients with systemic lupus erythematosus. Lupus. https://doi.org/10.1177/0961203315606984

Throughout the duration of the study, through the guidance of my supervisor, I have published two first-authored papers, a further first-authored one is under review and the fourth one is in preparation. My co-authors include my supervisor (Prof Hodkinson) and co-supervisor (A/Prof Schneider) and two researchers (Prof Tikly and Dr Makan) from Chris Hani Baragwanath Academic Hospital– the second site for data collection.

The published papers include a narrative review pertaining to Health related Quality of Life among SLE patients in a developing context, and a data-based qualitative paper on the experiences of living with SLE for women attending Chris Hani Baragwanath Hospital in Soweto or Groote Schuur Hospital in Cape Town. The paper under review looks specifically at the experiences of the women interviewed on sexual and reproductive health aspects, and the last publication under preparation is on the experiences of fatigue for these women. All these manuscripts are, as stipulated under the DDB, "thematically coherent**,** present a substantive scholarly discourse" and are related to the project and therefore the candidate finds it meaningful to include these manuscripts.

I hereby request permission from the Doctoral Degrees Board to include the two published papers and those under review (2) in the thesis. The thesis will comprise of an introduction, the specific aims and objectives of the overall thesis and a discussion of the thesis which brings together all the papers.

The main aim is to explore the HRQoL, perceptions and experiences of female patients with SLE in South Africa. The PhD objectives are listed below, and the corresponding papers are discussed regarding how they address these objectives:

1. To map the existing literature to collate findings for dissemination, and to identify the gaps for the focus of future research.

The narrative review (below) was conducted to determine any existing information on HRQoL amongst SLE patients living in the developing world or Low and Middle Income Countries, including South Africa. It comprehensively narrates the scope of knowledge on this field which forms the introduction of the thesis. Chapter 1 will give an overview of the literature pertaining to SLE. The current and existing knowledge and conceptions on SLE will be defined. This includes the disease history, pathophysiology, its diagnosis, presentation, a general overview on the management. The narrative review will be reflected on Chapter 2 as a continuation of Chapter 1. Moreover, this publication highlights the knowledge gaps and the main aim of this research. Authors' contributions are described in each certificate of agreement by each co-author. The candidate was involved in conceptualisation, manuscript outline and design, data collection, data analysis and interpretation, 1st draft of the manuscript and simultaneous manuscript review. These were all conducted under the supervision of Professors Hodkinson and Schneider.

Phuti A, Schneider M, Tikly M, Hodkinson B (2018) *Living with systemic lupus erythematosus in the developing world.* Rheum. International:1-13. (narrative review) https://doi.org/ 10.1007/s00296-018-4017-1

2. To explore women living with SLE's experiences using qualitative methods. This will be addressed in Chapter 4 which is based on primary data collected and written up in the paper below. It shows and elaborates all the comprehensive results of the interviews. The results give an overview of the "lived experiences" of SLE experiences by the women included in the study. Themes explored and presented were pain, fatigue, emotional, social and work function, fertility, aesthetic concerns, coping mechanisms and medication

adherence are presented here. Authors' contributions are described in each certificate of agreement by each co-author. The candidate was involved in conceptualisation, manuscript outline and design, Data collection, data analysis and interpretation, 1st draft of the manuscript and simultaneous manuscript review. These were all conducted under the supervision of Professors Hodkinson and Schneider.

Phuti A, Schneider M, Makan K, Tikly M, Hodkinson B (2019) *Living with systemic lupus erythematosus in South Africa; A bitter pill to swallow.* (Qualitative study) https://doi.org/10.1186/s12955-019-1132-y

1. To understand women living with SLE's experiences and perceptions on reproduction.

This is addressed in Chapter 5 which is based on the paper below. This study's objective is specific to sexual and reproductive health and experiences. Findings from the women's narratives show the controversy that surrounds fertility, pregnancy, puerperium, postnatal and sexuality for women living with SLE. A few gaps in practice are identified, discussed and a few recommendations are presented. Authors' contributions are described in each certificate of agreement by each co-author. The candidate was involved in conceptualisation, manuscript outline and design, data collection, data analysis and interpretation, 1st draft of the manuscript and simultaneous manuscript review. These were all conducted under the supervision of Professors Hodkinson and Schneider.

Phuti A, Hodkinson B, Tikly M, Schneider M (2019) *"The feeling of not being entitled to something": Fertility, pregnancy and sexuality among women with systemic lupus erythematosus in South Africa.* (Qualitative study) (under review by Scandinavian Journal of Rheumatology).

2. To explore and investigate fatigue, pain and functioning in SLE female patients.

Chapter 6 (under review by co-authors) use both qualitative and quantitative methods to understand and explore the phenomenon of fatigue and functioning amongst SLE women. The aim is to correlate both sets of findings to give more in-depth understanding of these aspects investigated and explored. We used the Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue tool to measure fatigue, the Short Form (SF36) as a general measure of HRQoL and Functional assessment Instrument (FAI) as a measure of an individual's ability to perform daily activities and responsibilities at home and work. Authors' contributions are described in each certificate of agreement by each co-author. The candidate was involved in conceptualisation, manuscript outline and design, data collection, data analysis and interpretation, 1st draft of the manuscript and simultaneous manuscript review. These were all conducted under the supervision of Professors Hodkinson and Schneider.

Phuti A, Hodkinson B, Tikly M, Schneider M (2019) *Fatigue and functioning among women living with systemic lupus erythematosus in South Africa: Validation of narratives using FACIT-Fatigue, FAI and SF 36 tools.* (Mixed Methods Study) (under review by co-authors).

To seek prognostic factors or "red flags" for poor HRQoL outcomes and indicators for good outcomes. Chapter 7 discusses and links the results of all the papers giving a broader understanding of the findings and demonstrating how the general Health Related Quality of Life (HRQoL) in SLE patients is compromised using the World Health Organisation International (WHO) Classification of Functioning, Disability and Health framework (ICF) identified in our published narrative review. This discussion consists of the results of the FACIT-fatigue tool, SF36, FAI and the following main themes identified during in depth interviews: pain, fatigue, emotional, social and work function, aesthetic concerns, fertility, pregnancy, puerperium, postnatal, sexuality issues, medication adherence and coping mechanisms. Recommendations, novel strategies and implications of care and practice, future research priorities in developing countries are discussed at the end of this chapter. In addition, limitations of this research are identified. (Chapter 3 will discuss the Methodology of the study in detail).

I hereby declare that my co-authors have agreed to the inclusion of these publications and are in consensus for regarding my contribution that qualifies me as a 1st author. For more information, below are the details for my supervisor and co-supervisor:

Professor Bridget Hodkinson: drbridget@gmail.com
A/Prof Marguerite Schneider: marguerite.schneider@uct.ac.za

Enclosed in this application are co-authors agreements for inclusion. I thank you for your consideration.

Kind regards,

Yours sincerely

Signature removed to avoid exposure on the internet

Ms Angel Phuti

University of Cape Town
Department of Psychiatry and Mental Health
Alan J Flisher Center for Public Mental Health

University of Cape Town
Faculty of health sciences
c/o Doctoral Degrees Board

RE: Permission for inclusion of publications in a thesis for PhD Candidate- Phuti, A.

Dear Sir/Madam

I Marguerite Schneider (co-author), hereby give consent for inclusion of the following publication in Ms. Phuti's thesis titled: "Health related quality of Life, Perceptions and experiences of female patients with Systemic Lupus Erythematosus in South Africa: Exploring Unmet needs using a mixed methods approach". In addition, this statement certifies my agreement on the candidate's own contribution including mine as shown below:
Publication 1: Living with systemic lupus erythematosus in the developing world.
Publication 2: Living with systemic lupus erythematosus in South Africa; A bitter pill to swallow.
Publication 3: "The feeling of not being entitled to something": Fertility, pregnancy and sexuality among women with systemic lupus erythematosus in South Africa.
Publication 4: Fatigue and functioning among women living with systemic lupus erythematosus in South Africa: Validation of narratives using FACIT-Fatigue, FAI and SF 36 tools.

Contributions to each paper	**Phuti, A**	**Schneider, M**	**Tikly, M**	**Hodkinson, B**	**Makan, K**
Conceptualization, manuscript outline and design	ALL	ALL		ALL	
Data collection	ALL				
Data analysis and interpretation	ALL	ALL		ALL	
1st draft of the manuscript	ALL				
Simultaneous manuscript review, proof reading and approval for journal submission	ALL	ALL	ALL	ALL	P2

P2: paper 2, ALL: contributed the task to all papers.

Name: Marguerite Schneider (co-author). Signature: Signature removed **Date:** 10.02.2020

Chris Hani Baragwanath Academic Hospital
University of the Witwatersrand
P.O. Bertsham 2013
Johannesburg

University of Cape Town
Faculty of health sciences
c/o Doctoral Degrees Board

RE: Permission for inclusion of publications in a thesis for PhD Candidate- Phuti, A.

Dear Sir/Madam

I Mohammed Tikly (co-author), hereby give consent for inclusion of the following publications in Ms. Phuti's thesis titled: Health related quality of Life, Perceptions and experiences of female patients with Systemic Lupus Erythematosus in South Africa: Exploring Unmet needs using a mixed methods approach. In addition, this statement certifies my agreement on the candidate's own contribution including mine as shown below:

Publication 1: Living with systemic lupus erythematosus in the developing world.
Publication 2: Living with systemic lupus erythematosus in South Africa; A bitter pill to swallow.
Publication 3: "The feeling of not being entitled to something": Fertility, pregnancy and sexuality among women with systemic lupus erythematosus in South Africa.
Publication 4: Fatigue and functioning among women living with systemic lupus erythematosus in South Africa: Validation of narratives using FACIT-Fatigue, FAI and SF 36 tools.

Contributions to each paper	**Phuti, A**	**Schneider, M**	**Tikly, M**	**Hodkinson, B**	**Makan, K**
Conceptualization, manuscript outline and design	ALL	ALL		ALL	
Data collection	ALL				
Data analysis and interpretation	ALL	ALL		ALL	
1st draft of the manuscript	ALL				
Simultaneous manuscript review, proof reading and approval for journal submission	ALL	ALL	ALL	ALL	P2

P2: paper 2, ALL: contributed the task to all papers.

Name: Mohammed Tikly **Signature:** Signature removed to avoid exposure online **Date:** 22 May 2019

Division of Rheumatology, Department of Medicine, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, P.O. Bertsham, 2013, Johannesburg, South Africa; Tel: +27 11 9339377; Fax: +27 11 9334991

University of Cape Town
Faculty of health sciences
c/o Doctoral Degrees Board

RE: Permission for inclusion of publications in a thesis for PhD Candidate- Phuti, A.

Dear Sir/Madam

I Kavita Makan (co-author) hereby give consent for inclusion of the following publication in Ms. Phuti's thesis titled: Health related quality of Life, Perceptions and experiences of female patients with Systemic Lupus Erythematosus in South Africa: Exploring Unmet needs using a mixed methods approach. In addition, this statement certifies my agreement on the candidate's own contribution including mine as shown below:
Publication 2: Living with systemic lupus erythematosus in South Africa; A bitter pill to swallow.

Contributions to each paper	Phuti, A	Schneider, M	Tikly, M	Hodkinson, B	Makan, K
Conceptualization, manuscript outline and design	ALL	ALL		ALL	
Data collection	ALL				
Data analysis and interpretation	ALL	ALL		ALL	
1st draft of the manuscript	ALL				
Simultaneous manuscript review, proof reading and approval for journal submission	ALL	ALL	ALL	ALL	P2

P2: paper 2, ALL: contributed the task to all papers.

Name: Kavita Makan (co-author **Signature:** Signature removed **Date:** 14.05.2019

UNIVERSITY OF CAPE TOWN

RHEUMATOLOGY
IN GOOD HANDS • EZANDLENI EZIKHATHALAYO • IN GOEIE HANDE
UNIVERSITY OF CAPE TOWN

Bridget Hodkinson
MBBCh, PhD, FCP (Sa), Cert Rheum SA

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Cape Town South Africa
Tel +27 (0)21 404 2131
Fax +27 (0)21 448 3253
Mobile +27 (0)82 395 0503
Email: drbridget@gmail.com

22 5 19

The Chairman

Doctoral Degrees Board

Dear Sir/Madam

Letter of support Ms Angel Phuti PHTANG001

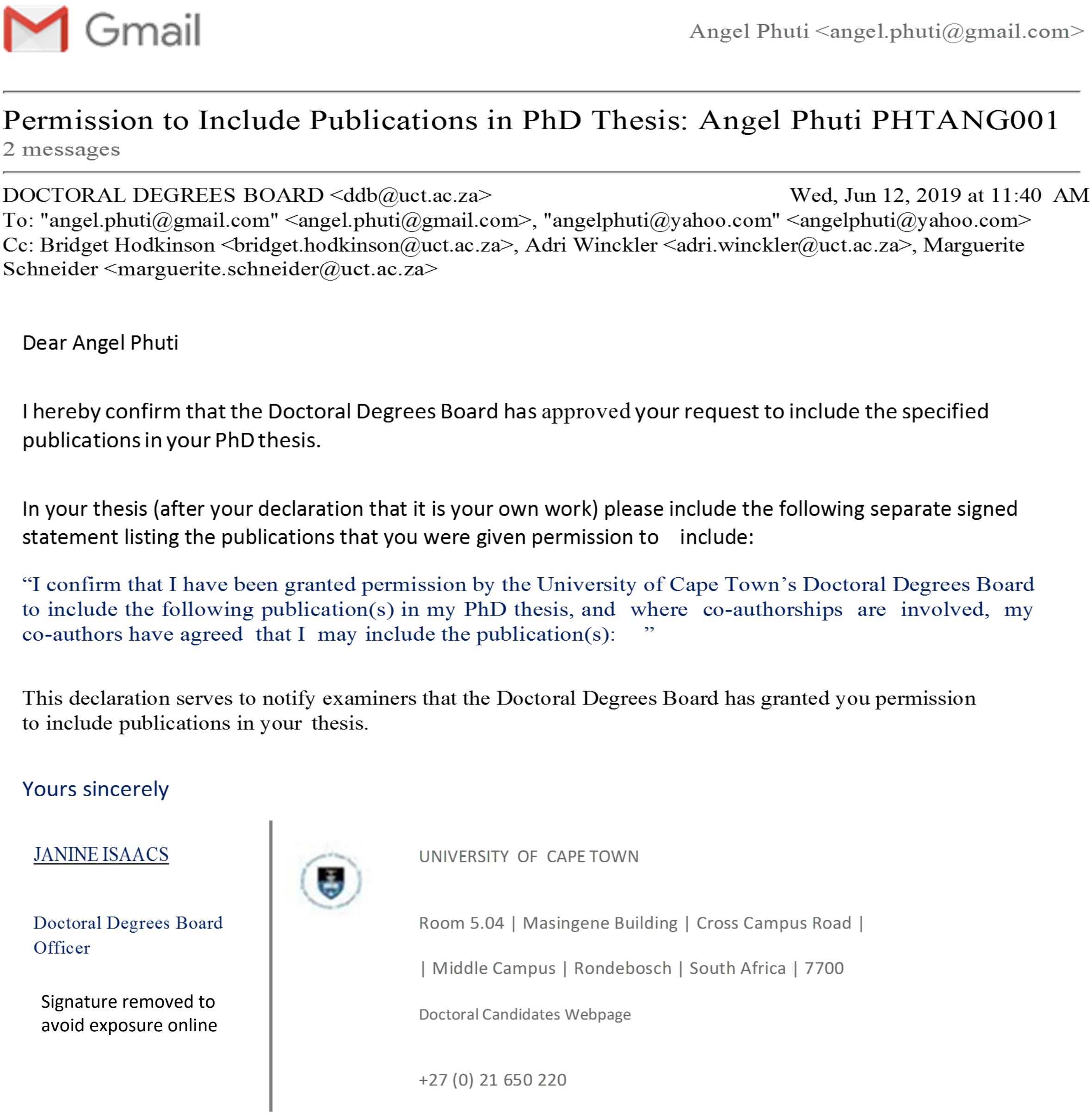
This letter is to confirm my support for Ms Phuti's application to include publications in her thesis and confirms that all the co-authors (including myself) are aware of the proposed thesis structure.
Ms Phuti is first author on all the papers to be submitted as part of the thesis.

Please contact me as necessary

Bridget Hodkinson

PhD supervisor

Professor and Head
Rheumatology
Department of Medicine
Faculty of Health Sciences
University of Cape Town and Groote Schuur Hospital



Gmail Angel Phuti <angel.phuti@gmail.com>

Permission to Include Publications in PhD Thesis: Angel Phuti PHTANG001

2 messages

DOCTORAL DEGREES BOARD <ddb@uct.ac.za> Wed, Jun 12, 2019 at 11:40 AM
To: "angel.phuti@gmail.com" <angel.phuti@gmail.com>, "angelphuti@yahoo.com" <angelphuti@yahoo.com>
Cc: Bridget Hodkinson <bridget.hodkinson@uct.ac.za>, Adri Winckler <adri.winckler@uct.ac.za>, Marguerite Schneider <marguerite.schneider@uct.ac.za>

Dear Angel Phuti

I hereby confirm that the Doctoral Degrees Board has approved your request to include the specified publications in your PhD thesis.

In your thesis (after your declaration that it is your own work) please include the following separate signed statement listing the publications that you were given permission to include:

"I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publication(s) in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publication(s): "

This declaration serves to notify examiners that the Doctoral Degrees Board has granted you permission to include publications in your thesis.

Yours sincerely

JANINE ISAACS

Doctoral Degrees Board Officer

Signature removed to avoid exposure online

UNIVERSITY OF CAPE TOWN

Room 5.04 | Masingene Building | Cross Campus Road |
| Middle Campus | Rondebosch | South Africa | 7700

Doctoral Candidates Webpage

+27 (0) 21 650 220

Declaration - Inclusion of publications.docx
22K

Angel Phuti <angel.phuti@gmail.com> Wed, Jun 12, 2019 at 2:52 PM
To: DOCTORAL DEGREES BOARD <ddb@uct.ac.za>
Cc: angelphuti@yahoo.com, Bridget Hodkinson <bridget.hodkinson@uct.ac.za>, Adri Winckler <adri.winckler@uct.ac.za>, Marguerite Schneider <marguerite.schneider@uct.ac.za>

Dear Janine Isaacs

Thank you very much for this positive feedback. I am indeed delighted!

I shall follow the rest of the guidelines as requested.

Kind regards
Angel Phuti
[Quoted text hidden]

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image003.png
5K