Arthritis Care & Research

Aims and Scope

Arthritis Care & Research is an official journal of the American College of Rheumatology and the Association of Rheumatology Professionals, a division of the College. *Arthritis Care & Research* is a peer-reviewed journal that publishes both original research and review articles that promote excellence in the clinical practice of rheumatology. Relevant to the care of individuals with arthritis and related disorders, major topics are evidence-based practice studies, clinical problems, practice guidelines, health care economics, health care policy, educational, social, and public health issues, and future trends in rheumatology practice.

Volume 77 No. 9 September 2025

Arthritis Care & Research

An Official Journal of the American College of Rheumatology
www.arthritiscareres.org and wileyonlinelibrary.com

Arthritis Care & Research

An Official Journal of the American College of Rheumatology
www.arthritiscareres.org and wileyonlinelibrary.com

VOLUME 77 • SEPTEMBER 2025 • NO. 9

Cover image: The image on the cover (from Patel et al, pages 1069–1077) shows histopathologic findings from right temporal lobe lesion brain biopsy in a patient with acute encephalopathy and painful bilateral cervical lymphadenopathy. Sections show brain parenchyma with patchy perivascular mononuclear, lymphohistiocyte-rich inflammation.

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1045–1065
DOI 10.1002/acr.25528

American College of Rheumatology
Empowering Rheumatology Professionals

2024 American College of Rheumatology (ACR) Guideline for the Screening, Treatment, and Management of Lupus Nephritis

Lisa R. Sammaritano,[1] Anca Askanase,[2] Bonnie L. Bermas,[3] Maria Dall'Era,[4] Alí Duarte-García,[5] Linda T. Hiraki,[6] Brad H. Rovin,[7] Mary Beth F. Son,[8] Anthony Alvarado,[9] Cynthia Aranow,[10] April Barnado,[11] Anna Broder,[12] Hermine I. Brunner,[13] Vaidehi Chowdhary,[14] Gabriel Contreras,[15] Christele Felix,[16] Elizabeth D. Ferucci,[17] Keisha L. Gibson,[18] Aimee O. Hersh,[19] Peter M. Izmirly,[20] Kenneth Kalunian,[21] Diane Kamen,[22] Brandi Rollins,[23] Benjamin J. Smith,[24] Asha Thomas,[25] Homa Timlin,[26] Daniel J. Wallace,[27] Michael Ward,[28] Muayad Azzam,[29] Christie M. Bartels,[30] Joanne S. Cunha,[31] Kimberly DeQuattro,[32] Andrea Fava,[26] Gabriel Figueroa-Parra,[33] Shivani Garg,[30] Jessica Greco,[7] Maria C. Cuéllar-Gutiérrez,[34] Priyanka Iyer,[35] Andrew S. Johannemann,[36] April Jorge,[37] Shanthini Kasturi,[38] Hassan Kawtharany,[29] Jana Khawandi,[29] Kyriakos A. Kirou,[1] Alexandra Legge,[39] Kelly V. Liang,[29] Megan M. Lockwood,[40] Alain Sanchez-Rodriguez,[41] Marat Turgunbaev,[42] Jessica N. Williams,[43] Amy S. Turner,[42] and Reem A. Mustafa[29]

Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the clinician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions, and drug formularies or other third-party analyses that cite ACR guidelines should state this. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

The American College of Rheumatology is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.

Objective. The objective is to provide evidence-based and expert guidance for the screening, treatment, and management of lupus nephritis.

Methods. The Core Team developed clinical questions for screening, treatment, and management of lupus nephritis using the PICO format (population, intervention, comparator, and outcome). Systematic literature reviews were completed for each PICO question, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the quality of evidence and to formulate recommendations. The Voting Panel achieved a consensus ≥70% on the direction (for or against) and strength (strong or conditional) of each recommendation.

Results. We present 28 graded recommendations (7 strong, 21 conditional) and 13 ungraded, consensus-based good practice statements for the screening and management of lupus nephritis. Our recommendations focus on the unifying principle that lupus nephritis therapy is continuous and ongoing, rather than consisting of discrete induction/initial and maintenance/subsequent therapies. Therapy should include pulse glucocorticoids followed by oral glucocorticoid taper and two additional immunosuppressive agents for 3–5 years for those achieving complete renal response.

Conclusion. This guideline provides direction for clinicians regarding screening and treatment decisions for management of lupus nephritis. These recommendations should not be used to limit or deny access to therapies, as treatment decisions may vary due to the unique clinical situation and personal preferences of each individual patient.

SIGNIFICANCE/HIGHLIGHTS:

- Lupus nephritis (LN) therapy should be initiated as soon as possible after diagnosis.
- Conditionally recommended treatment for Class III/IV (with or without Class V) LN includes triple therapy with intravenous glucocorticoids followed by oral glucocorticoid (≤0.5 mg/kg/day prednisone, maximum dose 40 mg/day) taper and:
  a. Mycophenolic acid analog (MPAA) plus belimumab -or-
  b. MPAA plus a calcineurin inhibitor (CNI) -or-
  c. Euro-Lupus Nephritis Trial (ELNT) low-dose cyclophosphamide (CYC) plus belimumab (with substitution of MPAA after completion of CYC).
- Conditionally recommended therapy for pure Class V LN (≥1 g proteinuria) includes combination therapy with intravenous glucocorticoids followed by oral glucocorticoid (≤0.5 mg/kg/day prednisone, maximum dose 40 mg/day) taper and MPAA plus a CNI.
- A glucocorticoid taper goal of ≤5 mg prednisone daily by 6 months is conditionally recommended.
- The conditionally recommended duration of immunosuppressive therapy (beyond hydroxychloroquine) for people with LN who achieve a complete renal response (CRR) is 3-5 years.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease with a prevalence of 72/100,000 persons in the United States.[1] Lupus nephritis (LN) occurs in close to half of SLE patients and carries a mortality rate of up to 30% at 10 years; 10–22% of people with LN will develop end stage kidney disease (ESKD).[2,3] Among those with SLE, male sex, younger age, and African, Hispanic, American Indian/Alaska Native, and Asian ancestry increase the likelihood of LN and ESKD.[4–8] Socially disadvantaged individuals in medically underserved areas have worse kidney outcomes.[9–11]

The American College of Rheumatology (ACR) last published LN clinical practice guidelines in 2012.[12] Recommendations called for induction therapy with high-dose glucocorticoids plus mycophenolate mofetil (MMF) or cyclophosphamide (CYC) and endorsed mycophenolate for maintenance therapy. Since then, belimumab and voclosporin[13,14] have been approved by the US Food and Drug Administration (FDA) for LN treatment, prompting a conceptual shift from induction/initial and maintenance/subsequent therapy to one of combination, ongoing therapy targeting different arms of the immune system.[15–17] Evidence on the relative effectiveness and toxicity of systemic glucocorticoids has also evolved.[18]

Recommendations in this guideline follow certain guiding principles (Table 1) and assume the exclusion of alternative diagnoses. Most are conditional; they are based on systematic literature reviews, values, and preferences elicited from an LN Patient Panel, and the expert opinion of adult and pediatric rheumatologists and nephrologists and a rheumatology physician assistant. The recommendations are intended to promote optimal outcomes for the most encountered LN scenarios; they include therapies available in the United States as of 2024 and apply to LN in adults and children.[19–21] Additional pediatric-specific or older adult concerns are addressed in Good Practice Statements (GPS). We acknowledge that therapeutic decisions vary depending on clinical presentation and patient preferences, and are limited by access to specialists, procedures, and medications. When recommended medications are not available, this guideline should not preclude the use of available traditional therapies. Recommendations are not based on patient-reported race or ethnicity, as evidence

This article is published simultaneously in *Arthritis & Rheumatology*.
Supported by the American College of Rheumatology.

[1]Lisa R. Sammaritano, MD, Kyriakos A. Kirou, MD, DSc: Hospital for Special Surgery - Weill Cornell Medicine, New York, New York; [2]Anca Askanase, MD, MPH: Columbia University, New York, New York; [3]Bonnie L. Bermas, MD: UT Southwestern Medical Center, Dallas, Texas; [4]Maria Dall'Era, MD: University of California, San Francisco; [5]Alí Duarte-García, MD, MSc: Mayo Clinic, Rochester, Minnesota; [6]Linda T. Hiraki, MD, MSc, ScD: The Hospital for Sick Children, Toronto, Ontario, Canada; [7]Brad H. Rovin, MD, Jessica Greco, MD: Ohio State University, Columbus; [8]Mary Beth F. Son, MD: Boston Children's Hospital, Boston, Massachusetts; [9]Anthony Alvarado, MD: Kaiser Permanente, Sacramento, California; [10]Cynthia Aranow, MD: Feinstein Institutes for Medical Research, Manhasset, New York; [11]April Barnado, MD, MSCI: Vanderbilt University Medical Center, Nashville, Tennessee; [12]Anna Broder, MD, MSc: Hackensack University Medical Center, Hackensack, New Jersey; [13]Hermine I. Brunner, MD, MSc, MBA: Cincinnati Children's Hospital, University of Cincinnati, College of Medicine, Cincinnati, Ohio; [14]Vaidehi Chowdhary, MD, MBBS, DM: Yale University School of Medicine, New Haven, Connecticut; [15]Gabriel Contreras, MD, MPH: University of Miami, Miami, Florida; [16]Christele Felix, Rosedale, New York; [17]Elizabeth D. Ferucci, MD, MPH: Alaska Native Tribal Health Consortium, Anchorage; [18]Keisha L. Gibson, MD, MPH: University of North Carolina, Chapel Hill; [19]Aimee O. Hersh, MD: The University of Utah, Salt Lake City; [20]Peter M. Izmirly, MD: NYU Grossman School of Medicine, New York, New York; [21]Kenneth Kalunian, MD: University of California, San Diego; [22]Diane Kamen, MD, MSCR: Medical University of South Carolina, Charleston; [23]Brandi Rollins: Montgomery, Alabama; [24]Benjamin J. Smith, DMSc, PA-C: Florida State University, Tallahassee; [25]Asha Thomas, MD: The Central Texas Veterans Health Care System, Temple; [26]Homa Timlin, MD, MSc, Andrea Fava, MD: Johns Hopkins University, Baltimore, Maryland; [27]Daniel J. Wallace, MD: Cedars-Sinai, Los Angeles, California; [28]Michael Ward, MD, MPH: Verier Outcomes Research LLC Rockville, Maryland; [29]Muayad Azzam, MD, Hassan Kawtharany, MD, Jana Khawandi, MD, Kelly V. Liang, MD, MS, Reem A. Mustafa, MD, PhD, MPH; University of Kansas, Kansas City; [30]Christie M. Bartels, MD, MS, Shivani Garg, MD, PhD: University of Wisconsin, Madison;

Table 1. Guiding Principles*

The goals of LN treatment are to preserve kidney function, reduce morbidity and mortality associated with chronic kidney disease, and minimize medication-related toxicities.
Collaborative care from rheumatology and nephrology should be offered to people with LN whenever possible.
Shared decision-making between clinicians and patients is essential as it respects patient values and preferences, leading to better adherence and outcomes.
Healthcare disparities may impact outcomes in people with LN; equitable implementation of treatment recommendations aims to improve outcomes and alleviate health disparities.
Pediatric and geriatric good practice statements are included when applicable.

* LN, lupus nephritis.

for race- or ethnicity-specific treatment efficacy is limited and confounded by socioeconomic factors. We present 28 Grading of Recommendations Assessment, Development and Evaluation (GRADE)-generated recommendations (7 strong, 21 conditional) and 13 ungraded, consensus-based GPS.

METHODS

This guideline follows the ACR guideline development process and policy directing management of conflicts of interest and disclosures (https://rheumatology.org/clinical-practice-guidelines), which includes GRADE methodology.[22,23] (Supplementary Materials 1). The Core Leadership Team (LRS, RAM, AAskanase, BLB, MD, AD, LTH, BHR, MBFS) drafted clinical population, intervention, comparator, and outcomes (PICO) questions (Supplementary Materials 2). The Literature Review Team performed systematic literature reviews for the PICO questions, graded the quality of evidence (high, moderate, low, very low), and produced an evidence report (Supplementary Materials 3). The evidence was reviewed, recommendations were formulated by the Core Team and voted on by an expert Voting Panel. Additionally, a Patient Panel comprised of 15 people with LN (two of whom also served on the Voting Panel) informed the Voting Panel on patients' perspectives and preferences.

Consensus required ≥70% agreement on direction (for or against) and strength (strong or conditional) of each recommendation. A recommendation is categorized as *strong* if the panel is confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a *conditional* recommendation denotes uncertainty regarding the balance of benefits and harms, low quality of evidence, or that the recommendation is particularly sensitive to individual patient preferences and patient-provider discussion.

The strength of a recommendation determines its clinical implications and should be considered when interpreting and using it for patient care. For patients, a strong recommendation suggests that most people in their situation would want the recommended course of action and only a small proportion would not; for clinicians, it means most patients should receive the recommended course of action. With a conditional recommendation, the implication for patients is that most people in their situation would want the recommended course of action, but many would not; for clinicians, it means they should recognize that different choices will be appropriate for different patients and they must engage in shared decision-making with each patient to arrive at a management decision.

GPS are made when panel members are confident that there is unequivocal benefit or harm despite indirect or inadequate evidence. Some of the original 249 PICO-generated recommendations were combined into broader recommendations, some generated good practice statements, and some were relegated to a future research agenda.

Rosters of the Core Leadership Team, Literature Review Team, Voting Panel, and Patient Panel are included in Supplementary Materials 4. Search strategies and study selection details are provided in Supplementary Materials 5 and 6. Approval from Human Studies Committees was not required.

Scope

This guideline addresses screening and treatment for all people with LN regardless of age, race, ethnicity, and other individual patient variables. It is the first part of a broader ACR SLE guideline project; the second part will include a general approach to SLE therapy as well as organ-specific treatment recommendations.

RESULTS/RECOMMENDATIONS

Terminology, definitions, and abbreviations are summarized in Table 2; recommendations and good practice statements are listed in Table 3.

[31]Joanne S. Cunha, MD: Warren Alpert Medical School of Brown University, East Providence, Rhode Island; [32]Kimberly DeQuattro, MD, MM: University of Pennsylvania, Philadelphia; [33]Gabriel Figueroa-Parra, MD, MSc: Mayo Clinic, Rochester, Minnesota, and University Hospital Dr. José Eleuterio González, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, México; [34]Maria C. Cuéllar-Gutiérrez, MD: Mayo Clinic, Rochester, Minnesota, and Hospital del Salvador, Santiago, Chile; [35]Priyanka Iyer, MD, MPH: University of California Irvine Medical Center, Orange; [36]Andrew S. Johannemann, MD: Carolina Arthritis Center, Greenville, North Carolina; [37]April Jorge, MD: Massachusetts General Hospital, Boston; [38]Shanthini Kasturi, MD, MS: Tufts Medical Center, Boston, Massachusetts; [39]Alexandra Legge, MD, MSc: Dalhousie University, Halifax, Nova Scotia, Canada; [40]Megan M. Lockwood, MD: Georgetown University Hospital, Washington, DC; [41]Alain Sanchez-Rodriguez, MD: Mayo Clinic, Rochester, Minnesota, and Department of Internal Medicine, The American British Cowdray Medical Center, I.A.P., Mexico City, Mexico; [42]Marat Turgunbaev, MD, Amy S. Turner: American College of Rheumatology, Atlanta, Georgia; [43]Jessica N. Williams, MD, MPH: Washington University, St. Louis, Missouri.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25528).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25528.

Address correspondence via email to Lisa R. Sammaritano, MD, at sammaritanol@hss.edu.

Submitted for publication February 27, 2025; accepted in revised form March 3, 2025.

Screening

In people with SLE without known kidney disease, we strongly recommend screening for proteinuria at least every 6–12 months, OR when experiencing extra-renal flares.

The Voting Panel stated that for recent onset, or recently active SLE, LN surveillance every 6 months is most appropriate, consistent with the 2023 ACR SLE quality measures.[24] Conversely, for those with longstanding and mild and inactive SLE, annual testing is adequate. This recommendation is strong, despite a lack of high-certainty evidence, because the risk of missing new onset LN requiring urgent treatment far outweighs the minimal risk of obtaining a urine sample.

Kidney biopsy

GPS: Prompt percutaneous kidney biopsy should be performed in people with SLE when LN is suspected (unless contraindicated or not feasible), as histopathologic biopsy

Table 2. Guideline terminology, definitions, and abbreviations*

Terminology	ACR LN Guideline Definitions[a]
Kidney biopsy	
Diagnostic	Biopsy performed to establish diagnosis and guide treatment
For cause	Biopsy performed in response to clinical indications or change in patient status
Per protocol	Biopsy performed according to a predetermined schedule or study protocol, regardless of clinical response
Therapy	
Initial / induction therapy	Prior terminology: Therapy prescribed immediately after diagnosis of new LN or flare of LN
Subsequent / maintenance therapy	Prior terminology: Therapy prescribed to patients on initial therapy for 6–12 months who have achieved at least a PRR
Lupus nephritis therapy	Preferred terminology: Ongoing therapy (ie, initial plus subsequent therapy) based on current recommendations for combination therapy that starts at diagnosis and continues throughout the treatment course TRIPLE therapy: GC (pulse intravenous: 250–1000 mg methylprednisolone daily × 1–3 days, followed by oral 0.5 mg/kg/day (maximum dose 40 mg/day) taper Plus: two immunosuppressive therapies, usually a) MPAA plus belimumab OR b) MPAA plus CNI OR c) ELNT low-dose CYC plus belimumab (MPAA substituted for CYC after CYC course is completed). DUAL therapy: GC plus one immunosuppressive therapy, usually MPAA or ELNT low-dose CYC
Renal response	
Complete renal response (CRR)	Within 6–12 months of starting therapy (may take >12 months): • Reduction in proteinuria <0.5 g/g (50 mg/mmol) (24-hour collection or urine protein/creatinine ratio); AND • Stabilization or improvement in kidney function (+ 20% baseline i.e. at least 80% of baseline)[b]
Partial renal response (PRR)	Within 6–12 months of starting therapy: • Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) (24-hour collection or urine protein/creatinine ratio); AND • Stabilization of kidney function (+ 20% baseline i.e., at least 80% baseline)[b]
Inadequate renal response/ Nonresponse	Lack of achieving at least a PRR despite adherence to appropriate treatment for active LN of any class by 6–12 months
Refractory disease	Persistently active disease and absence of at least a PRR to at least two different appropriate 6-month courses of therapy for active LN of any class
Proteinuria	Protein as measured by 24-hour collection (g/24hr) or random urine protein-creatinine ratio (g/g)
Glomerular hematuria	Urine sediment positive for acanthocytes, ≥5%, RBC casts
Decreased kidney function	Abnormal eGFR below expected level for age and clinical history, or decreasing eGFR with no attribution other than SLE[c]

* ACR, American College of Rheumatology; CNI, calcineurin inhibitor therapy; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ELNT, Euro-Lupus Nephritis Trial; GC, glucocorticoid; LN, lupus nephritis; MPAA, mycophenolic acid analogs; RBC, red blood cell; SLE, systemic lupus erythematosus.

[a] Terminology and definitions vary across specialties, guidelines, and clinical trials. Those listed here reflect the consensus of the Voting Panel as being both reasonable and relevant; however, no systematic analyses were performed, and others may prefer alternative definitions.

[b] Some experts and clinical trials have included a requirement for low dose of prednisone (eg, ≤5 mg/d equivalent) in addition to proteinuria and renal function requirements for CRR and PRR definitions; however, many do not. This was extensively discussed when definitions were created. Although GC dose is a part of validated SLE remission criteria, and while we recommend a goal of ≤5 mg/d prednisone equivalent by 6 months of therapy in this guideline, we did not consider this to be an appropriate mandatory criterion for the renal response definitions.

[c] Variably defined across studies – both irreversible damage and active disease impact kidney function and proteinuria and may require kidney biopsy to distinguish.

Table 3. Recommendations and good practice statements*

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICOs addressed
SCREENING:			
In people with SLE without known kidney disease, we strongly recommend screening for proteinuria at least every 6–12 months, OR when experiencing extra-renal flares.	Strong	Indirect evidence; Very low	P16(a) (revision)
KIDNEY BIOPSY:			
GPS: Prompt kidney biopsy should be performed in people with SLE when LN is suspected (unless contraindicated or not feasible) as histopathologic biopsy features will confirm the diagnosis, rule out mimicking diseases, and impact therapy decisions.			
In people with SLE who have proteinuria >0.5 g/g and/or impaired kidney function not otherwise explained, we conditionally recommend performing a percutaneous kidney biopsy.	Conditional	Low-Very low	P1(a-e) P3(e-h)
For people with treated LN in remission who present with suspected LN flare (increased proteinuria, hematuria, and/or worsening kidney function), OR for people with ≥6 months of appropriate treatment and ongoing or worsening proteinuria, hematuria, and/or decreased kidney function, we conditionally recommend repeat percutaneous kidney biopsy.	Conditional	Low-Very low	P2(a-e) P4(a-c)
TREATMENT OF ACTIVE LN (CLASS III/IV OR CLASS V)			
GPS: Prompt glucocorticoid treatment should be administered for suspected LN to suppress acute inflammation while awaiting a kidney biopsy and the histopathology results.			
GPS: Dosage of LN medications should be adjusted in people with decreased GFR at initiation of therapy and periodically.			
GPS: Adjunctive treatment with systemic anticoagulation for people with LN and significant risk factors for thrombosis (eg, low serum albumin in context of severe proteinuria) should be discussed with nephrology.			
IN PEOPLE WITH ACTIVE, NEW ONSET OR FLARE OF CLASS III/IV OR CLASS V LN:			
...If not already on HCQ treatment, we strongly recommend initiation and continuation of HCQ to manage and prevent lupus clinical manifestations, unless contraindicated.	Strong	Low-Very low	P15(a)
...With any elevation in level of proteinuria, including <0.5g/g, we conditionally recommend the addition of RAAS-I therapy.	Conditional	Low-Very low	P7(d) P9(a)
...We conditionally recommend pulse intravenous glucocorticoids followed by oral prednisone (≤0.5 mg/kg/d, max of 40 mg/d) with taper to a target dose of ≤5mg/day by 6 months.	Conditional	Moderate-low	P7(a-c) P8(a,b) P9 (a-c)
... Who have achieved and sustained a complete response after treatment with any (triple or dual) immunosuppressive therapy, we conditionally recommend a total duration of therapy of at least 3–5 years.	Conditional	Low	P8(o,p) P10(l,m)
IN PEOPLE WITH ACTIVE, NEW ONSET, OR FLARE OF CLASS III/IV (WITH OR WITHOUT CONCOMITANT CLASS V LN):			
... We conditionally recommend therapy with a triple immunosuppressive regimen consisting of pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, plus:	Conditional	Moderate-Low	P7 (j,k,n-q) P8 (f-h,k-m)
a) MPAA plus belimumab -or-			
b) MPAA plus CNI -or-			
c) Euro-Lupus Nephritis Trial (ELNT) low-dose CYC plus belimumab (MPAA substituted for CYC after CYC course is complete).			
... We conditionally recommend an MPAA-based regimen over a CYC-based regimen.	Conditional	Low-Very low	P7(g,h)
... With proteinuria ≥3g/g, we conditionally recommend a triple immunosuppressive regimen containing pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, plus MPAA plus CNI over a regimen containing belimumab.	Conditional	Low	P7 (l,p)

(Continued)

Table 3. (*Cont'd*)

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICOs addressed
… With extra-renal manifestations, we conditionally recommend a triple immunosuppressive therapy that contains belimumab over a regimen containing a CNI.	Conditional	Low	P7(p2) (revision)
… We conditionally recommend a target MMF dose of 2–3g/d (or equivalent).	Conditional	Very low	P7(l)
… Receiving a CYC-based regimen, we conditionally recommend the ELNT low-dose CYC regimen over a high-dose monthly pulse IV regimen;	Conditional	Very low	P7(e)
We also strongly recommend the ELNT-low dose CYC regimen over a daily oral CYC regimen.	Strong	Very low	P7(f)
… Who have undergone triple immunosuppressive therapy and achieved a complete renal response, we conditionally recommend continuing the same immunosuppressive regime.	Conditional	Moderate-Low	P8.3 (revision) P8 (f-h,k-m)
…Who have undergone triple immunosuppressive therapy and achieved a partial renal response, we conditionally recommend individualizing therapy depending on clinical factors that include the trajectory of response.	Conditional	None	P8.4 (revision)
… Who have undergone dual immunosuppressive therapy (glucocorticoids plus either CYC or MPAA) and achieved a complete renal response, we conditionally recommend continuing therapy with MPAA over AZA.	Conditional	Low	P8.1 (revision) P8(d,e,j)
… who have undergone dual immunosuppressive therapy (glucocorticoids plus either CYC or MPAA) and achieved a partial renal response, we conditionally recommend escalating therapy to a triple immunosuppressive regimen.	Conditional	None	P8.2 (revision) P8 (v-x, aa-cc)
IN PEOPLE WITH ACTIVE, NEW ONSET, OR FLARE OF (PURE) CLASS V LN:			
…With proteinuria ≥1 g/g we conditionally recommend treatment with a triple immunosuppressive regimen consisting of pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily x 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, and MPAA plus CNI (over MPAA plus belimumab, or CYC plus belimumab).	Conditional	Indirect: Very low	P9(p)
…with proteinuria <1 g/g, we conditionally recommend treatment with glucocorticoids and/or immunosuppressant therapy (MPAA, AZA, or CNI) over no glucocorticoid or other immunosuppression.	Conditional	None	P9(b)
NON-RESPONSIVE OR REFRACTORY LN:			
GPS: Medication dose and patient adherence should be assessed as an important first step in evaluating inadequate response or refractory LN, as insufficient treatment is an important cause of non-response.			
In people with any LN class with nonresponse (i.e., have not achieved at least a partial renal response by 6–12 months) we conditionally recommend escalation of treatment:	Conditional	Very low-None	P11.1, P11.2 (revision)
· **For initial dual therapy, escalate to triple therapy (pulse intravenous glucocorticoids, 250–1000 mg methylprednisolone daily for 1–3 days, followed by oral glucocorticoid ≤0.5 mg/kg/day, maximum dose 40 mg/day taper, plus either MPAA plus belimumab, MPAA plus CNI, or ELNT CYC plus belimumab)**.			
· **For initial triple therapy, change to an alternative triple therapy or consider addition of an anti-CD20 agent as a second immunosuppressive**.			
In people with any LN class with refractory disease (i.e., failed two standard therapy courses), we conditionally recommend treatment escalation to a more intensive regimen, including addition of anti-CD20 agents, combination therapy with three non-glucocorticoid immunosuppressives (i.e., MPAA, belimumab and CNI), or referral for investigational therapy.	Conditional	Very low- None	P12.1, P12.2 (revision)
OTHER LUPUS KIDNEY DISEASE:			
GPS: Alternative etiologies of kidney dysfunction in people with SLE should be carefully excluded, including non-inflammatory etiologies such as hypertensive, diabetic, and medication-induced nephropathy.			

(Continued)

Table 3. (*Cont'd*)

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICOs addressed
ADJUNCTIVE / NON-IMMUNOLOGIC TREATMENT:			
*GPS: Adjunctive and non-immunologic therapies and practices should be initiated in addition to appropriate immunosuppressive therapy to improve overall kidney health (*Table 4*).*			
GPS: In children with childhood-onset SLE (cSLE) and LN, glucocorticoid regimens should be reduced to pediatric-appropriate doses for children, as reduction of cumulative glucocorticoid dosing is critically important given the early age of onset of cSLE onset and attendant comorbidities.			
GPS: In children with cSLE and LN, clinicians should monitor for delayed pubertal onset and decreased growth velocity that can result from disease activity and glucocorticoid treatment and consider referral to pediatric endocrinology if indicated.			
GPS: For children with cSLE, a structured, intentional transition from pediatric to adult rheumatology care is indicated to avoid poor outcomes during this vulnerable period.			
GPS: For older people with LN, medication number, type, and dosage should be regularly assessed, given the risks of polypharmacy and age-related decline in GFR in this population.			
MONITORING LN ACTIVITY:			
In people with SLE and LN who have not achieved CRR, we strongly recommend quantifying proteinuria at least every 3 months.	Strong	Indirect evidence; Very low	P16(b,c) (revision)
In people with SLE with known nephritis in sustained clinical renal remission, we strongly recommend quantifying proteinuria every 3–6 months.	Strong	Indirect evidence; Very low	P16(d) (revision)
GPS: In people with LN, serum complement and anti-dsDNA antibody should be measured at every clinic visit (but not more frequently than monthly).			
RENAL REPLACEMENT THERAPIES:			
GPS: Decisions for initiation and type of dialysis and timing for kidney transplant require close collaboration with nephrology.			
In people with LN and ESKD, we strongly recommend kidney transplantation over dialysis.	Strong	High	P18(a)
In people with LN who have progressive loss of kidney function and are nearing ESKD (defined as an eGFR of 15 ml/min/1.73m^2), we conditionally recommend preemptive kidney transplant over dialysis/no preemptive kidney transplant.	Conditional	Very low	P22(a)
In people with LN and ESKD, we conditionally recommend proceeding with kidney transplantation without requiring complete clinical or serologic remission, provided there is no other major organ involvement.	Conditional	Very low	P23(a,b)
In people with LN on current dialysis or after kidney transplantation, we strongly recommend regular follow up with rheumatology.	Strong	Very low	P20(a,b)

* Anti-CD20 therapy: rituximab or obinutuzumab. AZA, azathioprine; CNI, calcineurin inhibitor therapies (cyclosporine, tacrolimus, voclosporin); CRR, complete renal response; CYC, cyclophosphamide; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate (various definitions are used in clinical studies; calculations of eGFR from creatinine in recent research do not include coefficients for race; however, earlier literature does); ESKD, end stage kidney disease; GFR, glomerular filtration rate; GPS, Good Practice Statements; HCQ, hydroxychloroquine; LN, lupus nephritis; MMF, mycophenolate mofetil; MPAA, mycophenolic acid analogs (including mycophenolate mofetil, or MMF, and mycophenolic acid, or MPA); PICO, population, intervention, comparator, outcome; RAAS-I, renin-angiotensin-aldosterone system inhibitors (including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists); SLE, systemic lupus erythematosus.

features will confirm the diagnosis, rule out mimicking diseases, and impact therapy decisions.

Biopsy should be read by a nephropathologist using the International Society of Nephrology (ISN) and Renal Pathology Society (RPS) classification[25] and include LN class and activity/chronicity indices. Risk of major bleeding with kidney biopsy, ie, requiring a blood transfusion or embolization procedure, is very low (~1–2%).[26–31] For people with SLE, risk may be higher (up to 3%) in specific subgroups including those with thrombocytopenia, decreased kidney function, and antiphospholipid syndrome.[26,32–35] Patient representatives shared concerns about the invasive nature of biopsy and emphasized the importance of physicians discussing the procedure's benefits and risks.

While we recommend prompt kidney biopsy with treatment based on histology, biopsy may not always be possible. In the absence of a kidney biopsy, those with nephritic features (eg, hematuria, hypertension, impaired kidney function) are usually best treated according to Class III/IV recommendations, and those with nephrotic features (eg, proteinuria, ≥3.5 g/g, hypoalbuminemia) according to Class V recommendations.

In people with SLE who have proteinuria >0.5 g/g and/or impaired kidney function not otherwise explained, we conditionally recommend performing a percutaneous kidney biopsy.

Kidney biopsy has value in people with SLE with isolated impaired kidney function that is not otherwise explained because histologic disease activity can occur without proteinuria.[36–39]

For people with treated LN previously in remission who later present with suspected LN flare (increased proteinuria, hematuria, and/or worsening kidney function), OR for people with ≥6 months of appropriate treatment and ongoing or worsening proteinuria, hematuria, and/or decreased kidney function, we conditionally recommend repeat percutaneous kidney biopsy.

Clinical judgment and patient preference are essential in deciding when to repeat kidney biopsy. With appropriate medication dosing and adherence, worsening kidney function or proteinuria should prompt consideration of repeat biopsy. Change in kidney histology is found in 40–50% of repeat biopsies.[40–42] While repeat biopsy for isolated significant/increasing hematuria can be considered when other etiologies are excluded, the value of biopsy in the setting of chronic low-level hematuria is uncertain. The Voting Panel did not issue a recommendation on per protocol (ie, scheduled) repeat kidney biopsies but considered this an important research item.

Treatment of LN:

GPS: Prompt glucocorticoid treatment should be administered for suspected LN to suppress acute inflammation while awaiting a kidney biopsy and the histopathology results.

GPS: Dosage of LN medications should be adjusted in people with decreased glomerular filtration rate (GFR) at the initiation of therapy and periodically as indicated during the disease course (Supplementary Materials 7).

GPS: Adjunctive treatment with systemic anticoagulation for people with LN and significant risk factors for thrombosis (e.g., low serum albumin in the context of severe proteinuria) should be discussed with nephrology.

Nephrology guidelines recommend treating patients with a serum albumin concentration below 2.0–2.5 g/dl in the setting of nephrotic range proteinuria with full-dose anticoagulation to prevent clotting unless the risk of bleeding is high.[43]

Class III/IV or Class V LN:

In people with LN who are not already on hydroxychloroquine (HCQ), we strongly recommend initiation and continuation of HCQ to manage and prevent extra-renal manifestations, unless contraindicated.

This is a strong recommendation based on low certainty evidence due to the well-established role for HCQ in overall SLE management. HCQ reduces risk of mortality in people with SLE, including those with lupus nephritis.[44–46] Dose adjustment for low GFR should be considered because kidney disease is a risk factor for retinal toxicity[46] (Supplement Materials 7).

In people with active, new onset or flare of LN with any elevation in proteinuria, including <0.5 g/g, we conditionally recommend the addition of renin-angiotensin-aldosterone system inhibitor (RAAS-I) therapy.

This recommendation applies to any level of persistent proteinuria above the normal range and is based on studies showing the kidney protective effects of RAAS-I in proteinuric LN and advanced chronic kidney disease (CKD).[47] Additionally, a pediatric study demonstrated that addition of RAAS-I led to earlier glucocorticoid discontinuation.[48] Use may be limited by blood pressure or estimated glomerular filtration rate (eGFR).

In people with active, new onset or flare of LN, we conditionally recommend pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) with taper to a target dose of ≤5 mg/day by 6 months.

A recent systematic review and meta-analysis determined that pulse glucocorticoids followed by oral glucocorticoids (up to 40 mg/day) maximized complete renal response while minimizing toxicities.[18,49–51] A range of pulse therapy dosing is presented to accommodate individualized treatment approaches.[52] Lower doses have been utilized in some recent treatment trials,[14] and patients emphasized their preference for minimizing glucocorticoid dose. The tapering regimen in clinical practice should be individualized and based on monitoring of both renal and extra-renal disease activity. Data informing the optimal dosing of glucocorticoids for pure Class V LN are limited.

In people with new onset or flare of LN who have achieved and sustained a complete renal response after treatment with any (triple or dual) immunosuppressive therapy, we conditionally recommend a total duration of immunosuppressive therapy of at least 3–5 years.

The advent of triple therapies blurred the distinction between induction therapy and maintenance therapy. Traditionally, patients were initially treated with one drug plus glucocorticoid followed by a "less toxic" drug for maintenance. Induction implied remission was achieved; however, in the short exposure to induction therapy (usually 3–6 months), most patients did not achieve remission. Maintenance implied maintenance of remission; but for most patients, maintenance served the initial purpose of consolidation.[53]

Current regimens aim to provide initial glucocorticoid and immunosuppressive therapies to rapidly reduce disease activity, with continuation of immunosuppressive therapies until disease is inactive, which often takes at least 12 months. Typically, some immunosuppressive therapy should be continued for at least

3–5 years of total treatment before considering withdrawal.[54,55] Support for a relatively long exposure to immunosuppression comes from repeat biopsy studies showing persistence of immunologic activity and immune complexes for several years after starting therapy; risk of LN flare is increased with withdrawal of immunosuppression while histologic activity remains.[56]

Over time, immunosuppressive therapy dosage may be tapered in stable patients as determined by renal and extra-renal disease activity and medication tolerability. No evidence provides robust guidance regarding optimal tapering practice; these decisions are currently made based on clinical expertise and patient preference. Risk of nephrotoxicity may impact decisions regarding the total duration of therapy with CNIs. HCQ should be continued indefinitely if there are no contraindications.

Class III/IV LN (with or without Class V LN):

Class III/IV LN lesions, characterized by endocapillary hypercellularity, are highly inflammatory and destructive. When occurring concomitantly with Class V, the presence of Class III/IV lesions drives therapy choice. Until complete renal response (CRR) is achieved, patients should be closely monitored and have therapies adjusted accordingly based on individual risk factors including blood pressure, proteinuria, and kidney function (Figure 1).

In people with active, new onset or flare of Class III/IV (±V) LN, we conditionally recommend therapy with a triple immunosuppressive regimen consisting of pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper plus:

a. **MPAA plus belimumab -or-**
b. **MPAA plus CNI -or-**
c. **Euro-Lupus Nephritis Trial (ELNT) low-dose CYC[53] plus belimumab (MPAA substituted for CYC after CYC course complete).**

Recent randomized controlled trials (RCTs) suggesting overall improved outcomes with triple versus dual therapies guided discussion and voting for this recommendation.[13,14] While the trials were randomized and controlled, the certainty of evidence was assessed as low-moderate. The recommendation for triple therapy is conditional, ie, sensitive to individual patient preferences and patient-clinician discussion. A sensitivity analysis excluding Voting Panel members who had relevant conflicts of interest for this recommendation (5 of 21 members) resulted in no change in direction or strength.

Numerous factors will impact a decision regarding type of triple LN therapy. With eGFR ≤45, blood pressure >165/105, or significant chronicity on kidney biopsy, a belimumab regimen is preferred over a CNI regimen because of potential CNI-associated nephrotoxicity and hypertension

Randomized controlled trials demonstrated similar rates of response in people treated with MPAA and CYC-based regimens, however, the Voting Panel favored MPAA because of the better toxicity profile including lower risk of malignancy and lack of impact on fertility.[57] A CYC-based regimen might be favored in certain circumstances, however, including patient preference, medication non-adherence or intolerance, or the presence of rapidly progressive glomerulonephritis with numerous crescents and/or fibrinoid necrosis on biopsy and declining kidney function.

Data in support of ELNT low-dose CYC plus belimumab is more limited because only 26% of Belimumab International Study in Lupus Nephritis (BLISS-LN) trial participants were treated with background ELNT CYC.[58] Subgroup analysis of participants on background ELNT CYC showed a numerically higher but not statistically significant rate of renal response with addition of belimumab versus placebo. In a post-hoc analysis, addition of belimumab to ELNT CYC resulted in fewer LN flares and a reduced rate of eGFR decline compared to placebo[59]; for this reason, this combination was included as a recommended triple therapy.

The combination of ELNT CYC plus CNI has not been studied in RCTs; for this reason, it is not recommended here as triple therapy. However, this combination may be considered despite the lack of supporting data, especially if other therapy options are unavailable, ineffective, or not tolerated. Patient Panel members repeatedly emphasized the challenges of high pill burden, and preference for the route of medication administration (eg, parenteral or oral) may influence the choice of therapy.

In people with active, new onset or flare of Class III/IV (±V) LN with proteinuria ≥3 g/g, we conditionally recommend a triple immunosuppressive regimen containing pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, plus MPAA plus CNI over a regimen containing belimumab.

This recommendation was based on observed rapid reduction of proteinuria with CNIs[14] and the limited efficacy with belimumab in people with baseline proteinuria ≥3 g/g.[59]

In people with active, new onset or flare of Class III/IV (±V) LN with moderate to severe extra-renal manifestations, we conditionally recommend a triple immunosuppressive therapy that contains belimumab over a regimen containing a CNI.

Belimumab is associated with reduction in disease activity and severe flares in nonrenal SLE[54]; in post-hoc analysis it appears especially beneficial for mucocutaneous and musculoskeletal manifestations.[60]

In people with active, new onset or flare of Class III/IV (±V) LN on treatment with MPAA, we conditionally recommend a target MMF dose of 2–3g/d (or equivalent).

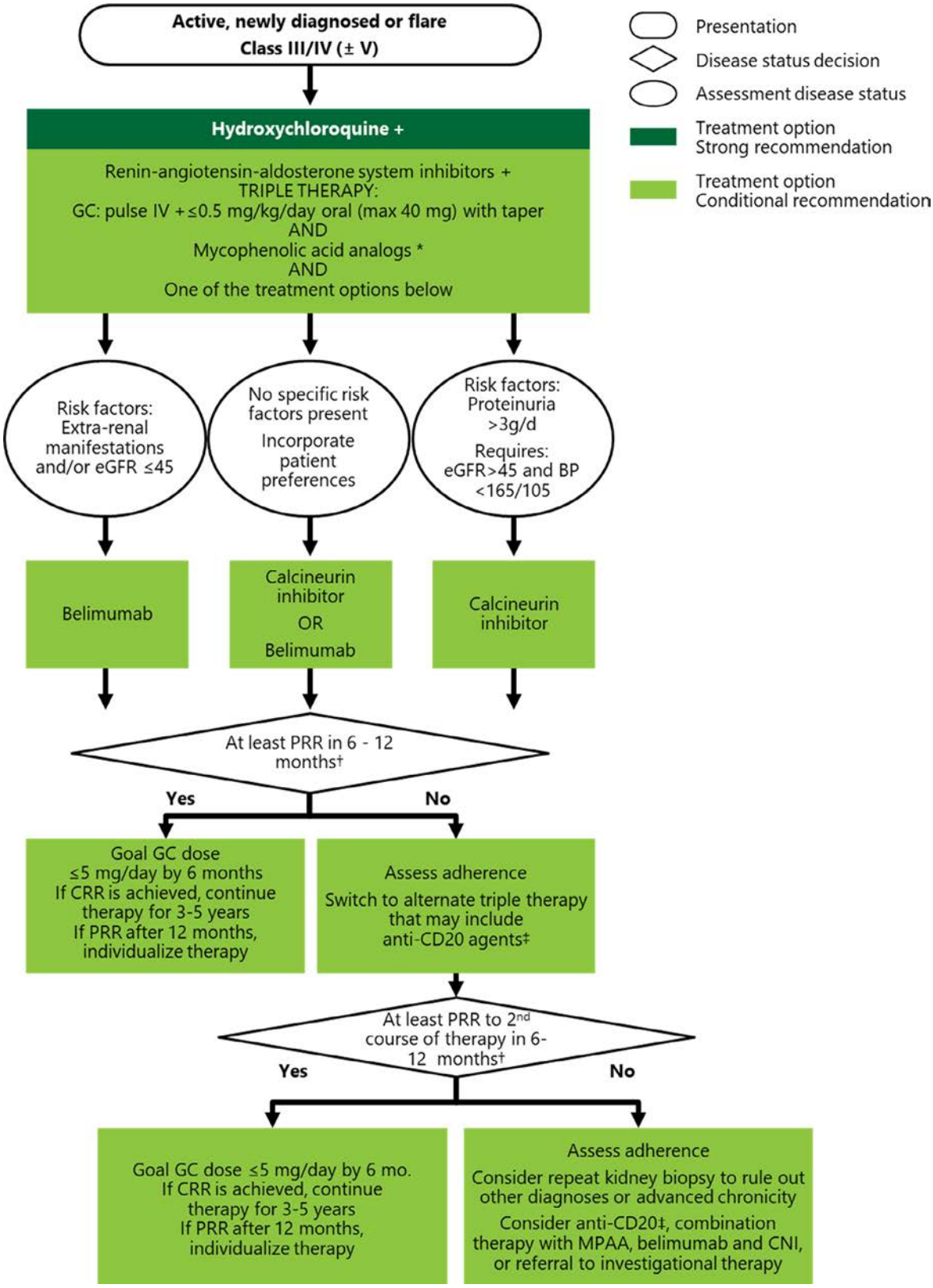

Figure 1. Recommendations for the treatment of class III, IV with or without class V lupus nephritis. * = Alternative triple therapy: glucocorticoids and Euro-Lupus Nephritis Trial low-dose cyclophosphamide and belimumab with mycophenolic acid analogs substituted for cyclophosphamide after the cyclophosphamide course is completed. Mycophenolic acid analogs regimens are preferred over cyclophosphamide regimens. † = Treatment should be escalated or changed earlier, even at ≤3 months, in patients with rapidly declining GFR or increasing proteinuria due to risk for potentially irreversible damage. ‡ = Rituximab, obinutuzumab, or others.

The dose of MPAA should be tailored to the individual patient, balancing the considerations of tolerability, safety, and efficacy. For pediatric patients, the usual starting dose is 1.2–1.4 g/m^2/d; mycophenolic acid levels may aid in tailoring dosage.

In people with active, new onset or flare of Class III/IV (±V) LN receiving a CYC-based regimen, we conditionally recommend the ELNT low-dose CYC regimen over a high-dose monthly pulse IV CYC regimen; we strongly recommend the ELNT low-dose CYC regimen over a daily oral CYC regimen.

An RCT and post-hoc analysis demonstrated that the ELNT regimen of CYC was as effective as intravenous monthly, high-dose CYC in achieving renal response.[61,62] The ELNT regimen is favored because of its better tolerability and toxicity profile, including a lower risk for infertility. Although pediatric data are limited to non-randomized, observational studies, the use of the ELNT regimen is preferred given the potential for multiple CYC courses over time.[63] The Voting Panel unanimously preferred an intravenous regimen over a daily oral CYC regimen because of the cumulative toxicities associated with oral CYC. It is important to provide fertility protective therapies to women and men of reproductive age when using a CYC-based regimen, particularly with high-dose pulse monthly IV CYC or >1 course of the ELNT CYC regimen.

In people with new onset or flare of Class III/IV (±V) LN who have undergone triple immunosuppressive therapy (pulse intravenous glucocorticoids 250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, plus either MPAA plus belimumab, MPAA plus CNI, or CYC plus belimumab) and achieved a complete renal response, we conditionally recommend continuing the same immunosuppressive regimen.

In people with active, new onset or flare of Class III/IV (±V) LN who have undergone triple immunosuppressive therapy with pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, plus either MPAA plus belimumab, MPAA plus CNI, or CYC plus belimumab) and achieved a partial renal response (PRR), we conditionally recommend individualizing therapy depending on clinical factors that include the trajectory of response.

If the patient with PRR is improving with reduction in proteinuria and increasing/stabilization of eGFR, the Voting Panel concurred that continuation of the initial triple immunosuppressive regimen with continued glucocorticoid taper is reasonable. However, if the patient shows indications of worsening disease activity (increasing proteinuria, worsening eGFR), we suggest altering therapy. A repeat kidney biopsy may be helpful to clarify proteinuria etiology (ongoing activity versus fixed damage). A specific duration of therapy is not recommended due to variability in clinical presentations.

In people with new onset or flare of Class III/IV (±V) LN who have undergone dual immunosuppressive therapy (glucocorticoids plus either CYC or MPAA) and achieved a complete renal response, we conditionally recommend continuing therapy with MPAA over switching to azathioprine (AZA).

People planning pregnancy or intolerant of MPAA should be treated with AZA.

In people with new onset or flare of Class III/IV (±V) LN who have undergone dual immunosuppressive therapy (glucocorticoids plus either CYC or MPAA) and achieved a partial renal response, we conditionally recommend escalating therapy to a triple immunosuppressive regimen.

Class V LN:

Class V (membranous) LN accounts for 20% of cases and is characterized by the presence of global or segmental subepithelial immune complex deposits. Class V LN can occur in isolation or in combination with Class III/IV.[64–68] There is limited evidence for management of pure Class V.

In people with active, newly diagnosed or flare of pure Class V lupus nephritis with proteinuria ≥1 g/g, we conditionally recommend treatment with a triple immunosuppressive regimen consisting of glucocorticoids (pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, and MPAA plus CNI (over MPAA plus belimumab or CYC plus belimumab).

Post-hoc analyses from clinical trials support that voclosporin, but not belimumab, added to MPAA and low-dose glucocorticoids achieve earlier reductions in proteinuria in pure class V LN.[69] Alternative regimens include initial therapy with glucocorticoids and MPAA, CNI, CYC, azathioprine, or anti-CD20 therapy[65–68] (Figure 2).

The importance and optimal dosing of glucocorticoid for Class V LN is not certain, as suggested by the conditional nature of this recommendation. The Voting Panel opted to include pulse/oral glucocorticoid therapy with taper plus two immunosuppressive agents here based on improved outcomes in recent pivotal clinical trials of triple therapy[13,14] that included individuals with pure Class V. The certainty of the level of evidence was very low (due to indirectness). Glucocorticoid therapy, sometimes at very high dose, has been used consistently across prior trials that included participants with pure Class V in addition to Class III/IV LN. An RCT of pure Class V (single versus dual) therapies did not support benefit of glucocorticoid monotherapy[64] but showed the combination of prednisone plus CNI or CYC to be more effective than prednisone alone. While we may be able to use lower doses of glucocorticoids for pure Class V than for Class III/IV, we do not have high-level data to inform different dosing levels for Class V vs. III/IV. Clinician-patient discussion should guide

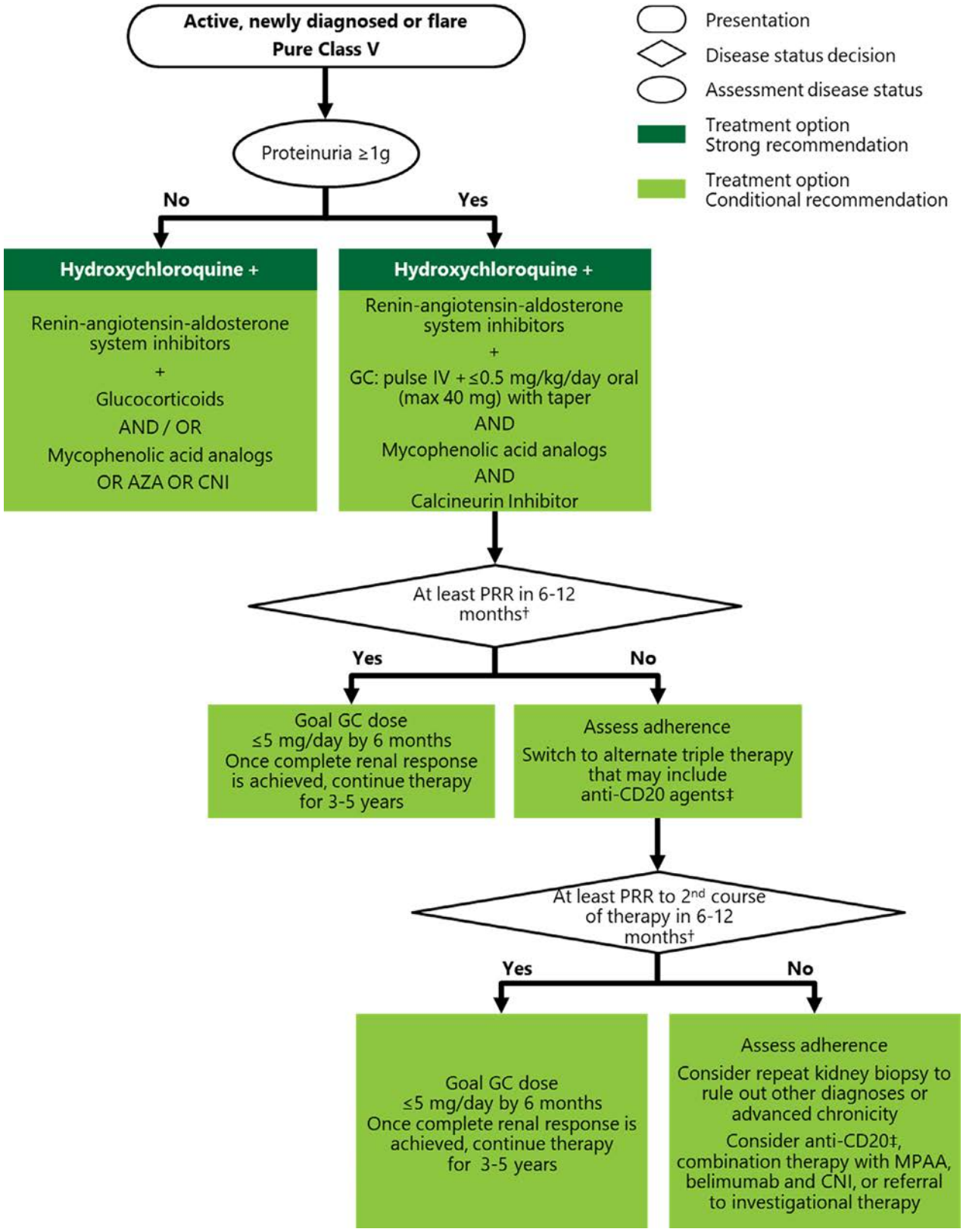

Figure 2. Recommendations for the treatment of pure class V lupus nephritis. † = Treatment should be escalated or changed earlier, even at ≤3 months, in patients with rapidly declining GFR or increasing proteinuria due to risk for potentially irreversible damage. ‡ = Rituximab, obinutuzumab or others. AZA, azathioprine; CNI, calcineurin inhibitors; GC, glucocorticoid; GFR, glomerular filtration rate; kg, kilogram; mg, milligram; MPAA, mycophenolic acid analogs; PRR, partial renal response. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25528/abstract.

therapy decisions, including the lack of high-quality data, the clinal presentation, and the patient's values and preferences.

In people with active, newly diagnosed or flare of pure Class V lupus nephritis with proteinuria <1 g/g, we conditionally recommend treatment with glucocorticoid and/or immunosuppressant therapy (MPAA, AZA, or CNI) over no glucocorticoid or immunosuppressive therapy.

The Voting Panel acknowledged the paucity of high-quality evidence for the treatment of Class V with low-level proteinuria because such patients were not included in clinical trials but expressed concern that low-grade proteinuria might progress to proteinuria >1g/g that could be less responsive to treatment.

Inadequate renal response/refractory LN

GPS: Medication dose and patient adherence should be assessed regularly throughout the course of treatment as an important first step in evaluating inadequate response or refractory LN, as insufficient treatment is a key cause of non-response.

Discussion regarding barriers to adherence (e.g., cost, side effects) is an important first step; strategies to monitor adherence (e.g., medication levels) may also be helpful.[70]

In people with any LN class with inadequate renal response (i.e., have not achieved at least a partial renal response by 6–12 months), we conditionally recommend escalation of treatment:

- **For initial dual therapy: escalate to triple therapy (glucocorticoids plus either MPAA plus belimumab, MPAA plus CNI, or ELNT CYC plus belimumab)**.
- **For initial triple therapy: change to an alternative (listed) triple therapy or consider addition of an anti-CD20 agent to MPAA or ELNT CYC**.

There are limited uncontrolled data[71–75] to guide therapy – including optimal timing – for inadequate renal response. Choice of therapy in the setting of inadequate response varies depending on several factors including the medication used initially, patient and clinician preference, and tolerability. Close monitoring is essential: treatment should be escalated or changed earlier, even at ≤3 months, in patients with rapidly declining GFR or increasing proteinuria due to risk of potentially irreversible damage.

In people with any LN class with refractory disease (ie, failed two standard therapy courses), we conditionally recommend treatment escalation to a more intensive regimen, including the addition of anti-CD20 agents, combination therapy with three non-glucocorticoid immunosuppressive agents (ie, MPAA, belimumab and CNI), or referral for investigational therapy.

When refractory LN is diagnosed, one may consider a kidney biopsy to assess the extent of chronic damage and determine whether escalating therapy is warranted. In cases of true refractory LN, meta-analyses suggest that 50–80% of patients convert to partial or complete responders with rituximab.[76,77] Other B cell targeted approaches,[78–80] as well as combination B cell therapies,[81–83] show utility in refractory LN and may offer future therapy options. (See Figure 3 for a Treatment Overview.)

Other lupus kidney disease

GPS: Alternative etiologies of kidney dysfunction in people with SLE should be carefully excluded, including non-inflammatory etiologies such as hypertensive, diabetic, and medication-induced nephropathy.

Less common manifestations of lupus kidney disease include thrombotic microangiopathy (TMA), Class II LN, and lupus podocytopathy. These were discussed by the Voting Panel but not formally voted upon given their lower incidence relative to Classes III/IV and V LN. The 2024 KDIGO clinical practice guideline for the treatment of lupus nephritis[84] provides details regarding clinical presentation and suggested management for these less common lupus kidney issues.

TMA

TMA is a histopathologic finding indicative of endothelial injury. Underlying causes include acute antiphospholipid antibody (aPL) nephropathy,[85] thrombotic thrombocytopenic purpura, complement-mediated TMA, and others. Because these conditions require different treatments, accurate diagnosis is important and often requires hematology consultation. While there was insufficient consensus to form a recommendation regarding aPL nephropathy or other TMAs in the context of LN, there have been reports of treatment with anticoagulation, plasma exchange, or C5 inhibitor therapy in this situation.[86,87]

Class II LN

Class II (mesangial) LN is characterized by expanded matrix with immune complexes confined primarily to the mesangium. Extensive podocyte effacement suggests lupus podocytopathy.[88]

The Voting Panel did not reach a consensus to formulate a recommendation for treatment although RAAS-I therapy is usual; however, repeat biopsy to assess for class switch or lupus podocytopathy may be considered in the setting of increasing proteinuria noted on follow-up.

Lupus podocytopathy

Podocytopathy usually presents with nephrotic range proteinuria; electron microscopy shows diffuse podocyte foot process effacement without subepithelial or subendothelial deposition.[89] Glucocorticoid and other immunosuppressive

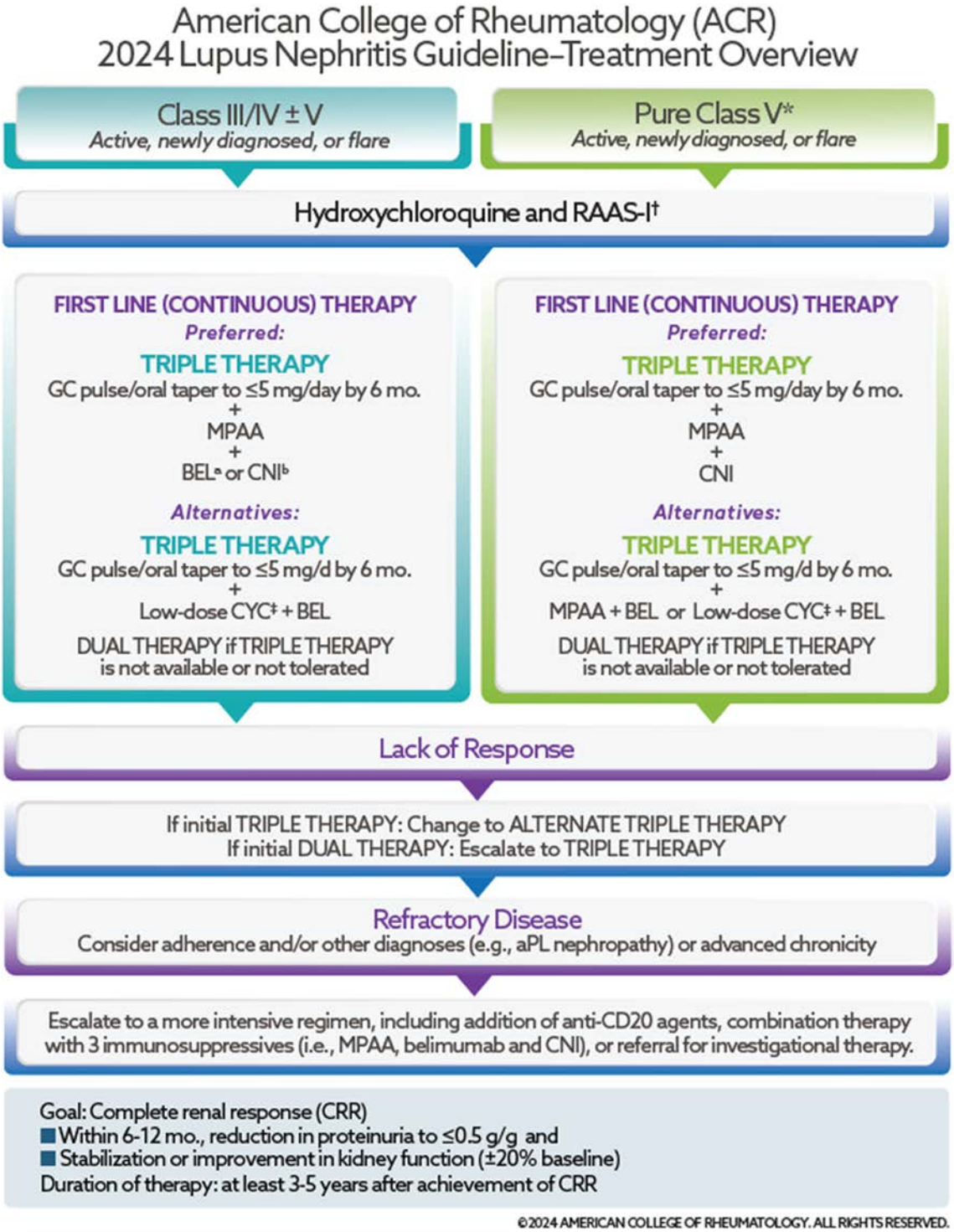

Figure 3. American College of Rheumatology 2024 Lupus Nephritis Guideline treatment overview. * For ≥1 gm protein; for <1 gm, treat with GC and/or immunosuppression. † Discuss adjunctive treatment with systemic anticoagulation with nephrology for patients with LN and significant factors for thrombosis (eg, low serum albumin in context of severe proteinuria). ‡ Substitute MPAA once low-dose CYC cycle is completed. a: Recommended preferentially when significant extrarenal manifestations are present. b: Recommended preferentially when proteinuria is ≥3.0 gm. GC pulse/oral taper: pulse intravenous GCs (250–1,000 mg methylprednisolone daily for 1–3 days) followed by oral GC ≤0.5 mg/kg/day (maximum dose 40 mg/day) and taper. Low-dose CYC: as per Euro-Lupus Nephritis Trial protocol,[61] 500 mg IV CYC every 2 weeks for 6 doses. Dual therapy: GC plus/oral taper plus one immunosuppressive agent, usually MPAA or low-dose CYC. RAAS-I, renin-angiotensin-aldosterone system inhibitors; GC, glucocorticoid; MPAA, mycophenolic acid analogs (including mycophenolate mofetil [MMF]; BEL, belimumab; CNI, calcineurin inhibitor; CYC, cyclophosphamide. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25528/abstract.

treatments are common[90]; therapy is best managed in collaboration with nephrology colleagues.

Adjunctive / non-immunologic treatments and good practice guidance

GPS: Adjunctive and non-immunologic therapies and practices should be added to appropriate immunosuppressive therapy to improve overall kidney health.

In addition to non-immunosuppressive kidney therapies such as RAAS-I, management of cardiovascular health, bone health, infection risk, and reproductive concerns should be addressed as summarized in Table 4.

GPS: In children with childhood-onset SLE (cSLE) nephritis, glucocorticoid regimens should use pediatric-appropriate doses for children, as reduction of cumulative glucocorticoid dosing is critically important given the early age of cSLE onset and attendant comorbidities.

GPS: In children with cSLE nephritis, clinicians should monitor for delayed pubertal onset and decreased growth velocity that can result from disease activity and glucocorticoid treatment and consider referral to pediatric endocrinology if indicated.

GPS: For children with cSLE nephritis, a structured, intentional transition[91–94] from pediatric to adult rheumatology care is indicated to avoid poor outcomes during this vulnerable period.

GPS: For older people with LN, medication number, type, and dosage should be regularly assessed, given the risks of polypharmacy and age-related decline in GFR in this population.

Monitoring LN activity

Treatment trials in SLE measure proteinuria rather than albuminuria. The gold standard for assessing proteinuria, the 24-hour urine collection, is challenging to implement in clinical practice; random urine protein-to-creatinine ratios are usually adequate. The first void of the day sample[95,96] is the most accurate for the spot urine collection but may not be feasible. Unexpected results on random testing should be followed by a 24-hour collection, especially before any change in therapy.

In people with LN who have not achieved CRR, we strongly recommend quantifying proteinuria at least every 3 months.

In people with LN in sustained clinical renal remission, we strongly recommend quantifying proteinuria every 3–6 months.

These recommendations are strong despite a lack of high-certainty evidence because in people undergoing treatment for LN who have not achieved complete renal response, quantifying

Table 4. Good practice guidance: adjunctive therapies for patients with lupus nephritis*

General considerations		Guidance
Kidney health: Non-pharmacologic	Diet	Limit sodium intake (suggest ≤2g sodium/day) Avoid high protein intake if eGFR <60 (suggest <1g/kg/day)
Kidney health: Pharmacologic	RAAS-I	Recommended for all LN patients, if tolerated
	SGLT2-I	Consider for stable LN patients with DM, CKD, moderate-high proteinuria, or heart failure (use with caution in patients on high-dose immunosuppression due to increased risk of urinary tract infection)
Cardiovascular health	Lifestyle	Avoid smoking, exercise, optimize BMI
	Blood pressure	Systolic BP <120 if tolerated
	Lipid management	Dyslipidemia management per CVD risk reduction guidelines
	CVD risk assessment	Estimate 10-year cardiovascular risk using a validated risk tool
Bone health	Screening and treatment	See ACR Glucocorticoid-induced Osteoporosis Guideline[125]
Infection	Screening	Screening for hepatitis B, hepatitis C, and tuberculosis
	Vaccination	See ACR Vaccine Guideline[126]
	Prophylactic therapies	Consider prophylaxis for PJP and hepatitis B when indicated
Reproductive health	Contraception	See ACR Reproductive Health Guideline[127] Use highly effective method (eg, IUD) If on MPAA, use IUD or two other forms
	Pregnancy	See ACR Reproductive Health Guideline[127] Contraindicated with active LN Azathioprine and tacrolimus are pregnancy-compatible: use when LN is in remission but ongoing treatment is required
	Fertility	See ACR Reproductive Health Guideline[127] Gonadotropin releasing hormone agonist co-therapy recommended in females treated with CYC. Consider IVF for oocyte/embryo cryopreservation if stable disease still requiring ongoing teratogenic therapies and concern for age-related infertility

* ACR, American College of Rheumatology; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; CYC, cyclophosphamide; DM, diabetes mellitis; eGFR, estimated glomerular filtration rate; IVF, in vitro fertilization; IUD, intrauterine device; LN, lupus nephritis; MPAA, mycophenolic acid analogs; PJP, pneumocystis jirovecii pneumonia; RAAS-I, renin-angiotensin-aldosterone system inhibitors; SGLT2-I, sodium-glucose cotransporter-2 inhibitors.

proteinuria every three months may prompt adjustment of treatment regimen. In people with LN who have sustained complete renal response, quantifying proteinuria every 3–6 months will minimize the risk of missing an LN flare that would require more aggressive treatment. While we are certain about the beneficial effects of monitoring and screening for proteinuria in both diagnosis and prognosis, there is a lack of evidence regarding the optimal screening interval, and the overall certainty of the evidence is very low. The benefit of potentially preserving long-term kidney function far outweighs the minimal risk of obtaining a urine sample.

GPS: For people with LN, serum complement and anti–double-stranded DNA (dsDNAAU: Expanded version of dsDNA was added before acronym at first mention in manuscript.) antibody should be measured at every clinic visit (but not more frequently than monthly).

While hypocomplementemia and elevated anti-dsDNA antibodies have only modest sensitivity and specificity for LN activity, several studies[97–99] suggest they may herald new onset LN or LN flare. Changes in these levels should prompt careful clinical and laboratory assessment but should not necessarily trigger preemptive treatment in the absence of clinical manifestations, unless previous individual clinical experience suggests otherwise. Anti-C1q antibodies[100] correlate better with LN flares[101,102]; however, this antibody testing may not be universally available. Emerging biomarkers' utility will be reviewed for future guideline updates as these become validated.

Renal replacement therapies (dialysis and transplant)

GPS: Decisions for initiation and type of dialysis and timing of kidney transplant require close collaboration with nephrology.

Ten to twenty-two percent of people with LN will develop ESKD.[2,3] Treatment options include hemodialysis or peritoneal dialysis, or a kidney transplant. Individual patient characteristics and preferences should impact dialysis modality choice. People undergoing peritoneal dialysis have a higher risk of infections, especially peritonitis. Hemodialysis has inherent complications – bloodstream infections and thrombosis – related to vascular access. People with antiphospholipid antibodies are at higher risk of vascular access complications and allograft thrombosis.[103,104]

In people with LN and ESKD, we strongly recommend kidney transplantation over dialysis without kidney transplantation.

Transplantation significantly reduces mortality, cardiovascular disease events, infections, and risk of flares compared to dialysis.[105] The Patient Panel highlighted both the poor quality of life associated with dialysis and the challenges of accessing transplantation. People with ESKD due to LN are less likely to receive a kidney transplant compared to people with other glomerulonephritides.[106]

In people with LN who have progressive loss of kidney function and are nearing ESKD (defined as an eGFR of 15 ml/min/1.73m^2), we conditionally recommend preemptive kidney transplant over dialysis/no preemptive kidney transplant.[107]

Preemptive kidney transplantation improves survival compared to non-preemptive approaches in people with CKD,[108,109] and an observational study suggested that preemptive kidney transplantation improves survival in people with LN compared to non-preemptive approaches.[110] The Voting Panel emphasized the benefits of avoiding dialysis morbidity but recognized transplant access limitations.

In people with LN and ESKD, we conditionally recommend proceeding with kidney transplantation without requiring complete clinical or serologic remission of SLE, provided there is no other major organ involvement.

Limited data indicate that lupus activity does not significantly affect allograft function.[111] The Voting Panel emphasized that transplant eligibility should not be based on serologic activity as it does not appear to have an impact on transplant outcome.[112] The recurrence of LN in the allograft is rare (10%) and often mild, with predominantly mesangial lesions.[113]

In people with LN on current dialysis or after kidney transplantation, we strongly recommend regular follow up with rheumatology.

Despite a low recurrence rate of LN in transplanted kidneys, regular rheumatology follow up is recommended even for people with SLE who have ESKD or are post kidney transplant. The recommendation is strong despite low certainty of evidence supporting the benefit of regular rheumatology follow up, due to the essential role of rheumatologists in managing the broader health issues associated with lupus. At least 50% of people with ESKD due to LN in the US remain on immunosuppression[114]; those who are co-managed with a rheumatologist (≥2 rheumatology visits per year) have higher survival rates.[107]

DISCUSSION

Lupus nephritis is among the most common severe manifestation of SLE. In this guideline, we propose treatment with triple therapy (glucocorticoids plus two immunosuppressive medications) as the most desirable therapy for LN, preferring MPAA regimens over CYC regimens. We also propose a lower dose glucocorticoid regimen (after initial intravenous pulse) to minimize toxicity, with a prednisone goal of ≤5 mg/day by 6 months of therapy. These recommendations are conditional and require discussion between clinicians and patients because multiple factors impact therapy choice.

We do not specify a particular CNI because comparative effectiveness and safety studies are not available, and accessibility may dictate the choice of CNI. Ongoing monitoring is essential as long-term nephrotoxicity is an important concern with any CNI.

These recommendations apply to adults and children with LN. The Guideline Team analyzed pediatric-specific LN data when available, as LN affects up to half of individuals with cSLE.[115,116] Since cSLE LN treatment includes higher cumulative doses of glucocorticoids and CYC,[117] these recommendations propose corticosteroid regimens that differ from other pediatric-specific options.[118] While efficacy evidence for this change is indirect, it acknowledges pediatric-specific concerns regarding glucocorticoid effects on growth and pubertal development. We also emphasize the necessity of structured transition to adult rheumatology and nephrology care.[118–121] Despite recent improvements in LN outcomes, youth of historically marginalized groups remain at higher risk for ESKD and dialysis.[122,123]

Two major themes emerged from the Patient Panel discussion. First, shared decision-making is a dynamic, ongoing process influenced by the patient's values, individual disease course, stage of life, medication tolerance, efficacy, and side effects; as such, an individual patient's decisions regarding management evolve over time. Second, patients emphasized the importance for clinicians to recognize pill burden, discuss all medication options, and provide close monitoring with the shared goals of preservation of kidney function, overall health, and optimal quality of life.

Current gaps in the LN literature identified through our systemic literature review and evidence analysis helped to identify important areas of study for a future research agenda (Supplementary Materials 8), including new agents and strategies to improve outcomes for people with LN. During this guideline's manuscript preparation, a positive phase 3 trial reported that addition of the humanized anti-CD20 therapy obinutuzumab to standard therapy (glucocorticoid and mycophenolate mofetil) led to a significantly greater likelihood of complete renal response at 76 weeks than did standard therapy alone, although infectious risk (particularly COVID-19) was higher.[124] Further studies on this and other agents may lead to more targeted and effective LN strategies and will be reflected in updated revisions of this guideline.

With the development of this guideline, the ACR recognizes the key role of clinical rheumatologists in managing LN. Important goals of this guideline are to provide substance and direction for therapy decisions after clinician-patient discussions, and to encourage close working relationships between rheumatologists and nephrologists to enhance collaborative care.

ACKNOWLEDGMENTS

We thank the patients who (along with authors Christele Felix and Brandi Rollins) participated in the Patient Panel meeting: Hiya Bhavsar, Seneka Epasinghe, Monique C. Gore-Massy, Natacha Guerrero, Jolanda Jackson, Ksisha Johnson, Marimee Jules, Wambui Machua, Michael Okechuku, Nahirannette Pulido, Bené Williams, and Brian L. Ung. We thank the Lupus Foundation of America and its Research Accelerated by You (RAY) patient and caregiver registry for assistance with recruitment for the Patient Panel. We thank Ashira D. Blazer, MD, MSC, Titilola Falasinnu, PhD, and Julie Bolvig for their assistance with the literature review. We thank the ACR staff, including Regina Parker for assistance in coordinating the administrative aspects of the project and Cindy Force for assistance with manuscript preparation. We thank Kathryn Vela for her assistance in developing the literature search strategy, performing the initial literature search, and performing the update searches. We also thank Larry J. Prokop, MLIS, for his peer review of the literature search strategy. This article is simultaneously published in *Arthritis & Rheumatology* and *Arthritis Care & Research* by The American College of Rheumatology. The articles are identical, and either citation can be used when referencing one of the articles.

REFERENCES

1. Izmirly PM, Parton H, Wang L, et al. Prevalence of systemic lupus erythematosus in the United States: Estimates from a meta-analysis of the Centers for Disease Control and Prevention National Lupus Registries. Arthritis Rheumatol 2021;73:991–996.
2. Hocaoğlu M, Valenzuela-Almada MO, Dabit JY, et al. Incidence, prevalence, and mortality of lupus nephritis: a population-based study over four decades using the Lupus Midwest Network. Arthritis Rheumatol 2023;75:567–573.
3. Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971–2015: a systematic review and Bayesian meta-analysis. Arthritis Rheumatol 2016;68:1432–1441.
4. Dall'Era M, Cisternas MG, Snipes K, et al. The incidence and prevalence of systemic lupus erythematosus in San Francisco County, California: The California Lupus Surveillance Project. Arthritis Rheumatol 2017;69:1996–2005.
5. Drenkard C, Lim SS. Update on lupus epidemiology: advancing health disparities research through the study of minority populations. Curr Opin Rheumatol 2019;31:689–696.
6. Izmirly PM, Wan I, Sahl S, et al. The incidence and prevalence of systemic lupus erythematosus in New York County (Manhattan), New York: The Manhattan Lupus Surveillance Program. Arthritis Rheumatol 2017;69:2006–2017.
7. Lim SS, Bayakly AR, Helmick CG, et al. The incidence and prevalence of systemic lupus erythematosus, 2002–2004: The Georgia Lupus Registry. Arthritis Rheumatol 2014;66:357–368.
8. Somers EC, Marder W, Cagnoli P, et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. Arthritis Rheumatol 2014;66:369–378.
9. Feldman CH, Hiraki LT, Liu J, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000–2004. Arthritis Rheum 2013;65:753–763.
10. Mahmood SB, Aziz M, Malepati D, et al. Evaluating sex differences in the characteristics and outcomes of lupus nephritis: a systematic review and meta-analysis. Glomerular Dis 2024;4:19–32.
11. Yelin E, Trupin L, Yazdany J. A prospective study of the impact of current poverty, history of poverty, and exiting poverty on accumulation of disease damage in systemic lupus erythematosus. Arthritis Rheumatol 2017;69:1612–1622.
12. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2012;64:797–808.
13. Furie R, Rovin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med 2020;383:1117–1128.
14. Rovin BH, Teng YKO, Ginzler EM, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind,

randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2021;397:2070–2080.

15. Anders HJ, Lei Y, Rovin BH. Induction and maintenance therapy of lupus nephritis: an obituary. Kidney Int 2021;99:288–291.
16. Alamilla-Sanchez ME, Alcala-Salgado MA, Alonso-Bello CD, et al. Mechanism of action and efficacy of immunosupressors in lupus nephritis. Int J Nephrol Renovasc Dis 2021;14:441–458.
17. Crow MK. Pathogenesis of systemic lupus erythematosus: risks, mechanisms and therapeutic targets. Ann Rheum Dis 2023;82: 999–1014.
18. Figueroa-Parra G, Cuéllar-Gutiérrez MC, González-Treviño M, et al. Impact of glucocorticoid dose on complete response, serious infections, and mortality during the initial therapy of lupus nephritis: a systematic review and meta-analysis of the control arms of randomized controlled trials. Arthritis Rheumatol 2024;76:1408–1418.
19. Balevic SJ, Niu J, Chen J, et al. Extrapolation of adult efficacy data to pediatric systemic lupus erythematosus: evaluating similarities in exposure-response. J Clin Pharmacol 2023;63:105–118.
20. Brunner HI, Martini A, Lovell DJ, et al. Clinical trials in children and adolescents with systemic lupus erythematosus: methodological aspects, regulatory landscape and future opportunities. Ann Rheum Dis 2019;78:162–170.
21. Pottackal G, Travis J, Neuner R, et al. Application of Bayesian Statistics to Support Approval of Intravenous Belimumab in Children with Systemic Lupus Erythematosus in the United States. 2019;71(suppl 10). https://acrabstracts.org/abstract/application-of-bayesian-statistics-to-support-approval-of-intravenous-belimumab-in-children-with-systemic-lupus-erythematosus-in-the-united-states/.
22. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66: 726–735.
23. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–926.
24. Bartels CM, Jorge A, Feldman CH, et al. Development of American College of Rheumatology quality measures for systemic lupus erythematosus: a modified Delphi process with Rheumatology Informatics System for Effectiveness (RISE) registry data review. Arthritis Care Res (Hoboken) 2023;75:2295–2305.
25. Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney Int 2018; 93:789–796.
26. Corapi KM, Chen JL, Balk EM, et al. Bleeding complications of native kidney biopsy: a systematic review and meta-analysis. Am J Kidney Dis 2012;60:62–73.
27. Deonaraine KK, Carlucci PM, Fava A, et al. Safety of procuring research tissue during a clinically indicated kidney biopsy from patients with lupus: data from the Accelerating Medicines Partnership RA/SLE Network. Lupus Sci Med 2021;8:e000522.
28. Halimi JM, Gatault P, Longuet H, et al. Major bleeding and risk of death after percutaneous native kidney biopsies: a French nationwide cohort study. Clin J Am Soc Nephrol 2020;15:1587–1594.
29. Palsson R, Short SAP, Kibbelaar ZA, et al. Bleeding complications after percutaneous native kidney biopsy: results from the Boston Kidney Biopsy Cohort. Kidney Int Rep 2020;5:511–518.
30. Poggio ED, McClelland RL, Blank KN, et al. Systematic review and meta-analysis of native kidney biopsy complications. Clin J Am Soc Nephrol 2020;15:1595–1602.
31. Schorr M, Roshanov PS, Weir MA, et al. Frequency, timing, and prediction of major bleeding complications from percutaneous renal biopsy. Can J Kidney Health Dis 2020;7:2054358120923527.
32. Chen TK, Estrella MM, Fine DM. Predictors of kidney biopsy complication among patients with systemic lupus erythematosus. Lupus 2012;21:848–854.
33. Jordan N, Chaib A, Sangle S, et al. Association of thrombotic microangiopathy and intimal hyperplasia with bleeding post-renal biopsy in antiphospholipid antibody-positive patients. Arthritis Care Res (Hoboken) 2014;66:725–731.
34. Kang ES, Ahn SM, Oh JS, et al. Risk of bleeding-related complications after kidney biopsy in patients with systemic lupus erythematosus. Clin Rheumatol 2023;42:751–759.
35. Sun YS, Sun IT, Wang HK, et al. Risk of complications of ultrasound-guided renal biopsy for adult and pediatric patients with systemic lupus erythematosus. Lupus 2018;27:828–836.
36. Carlucci PM, Li J, Fava A, et al. High incidence of proliferative and membranous nephritis in SLE patients with low proteinuria in the Accelerating Medicines Partnership. Rheumatology (Oxford) 2022; 61:4335–4343.
37. De Rosa M, Rocha AS, De Rosa G, et al. Low-grade proteinuria does not exclude significant kidney injury in lupus nephritis. Kidney Int Rep 2020;5:1066–1068.
38. Stamenkovic I, Favre H, Donath A, et al. Renal biopsy in SLE irrespective of clinical findings: long-term follow-up. Clin Nephrol 1986; 26:109–115.
39. Wakasugi D, Gono T, Kawaguchi Y, et al. Frequency of class III and IV nephritis in systemic lupus erythematosus without clinical renal involvement: an analysis of predictive measures. J Rheumatol 2012;39:79–85.
40. Fava A, Fenaroli P, Rosenberg A, et al. History of proliferative glomerulonephritis predicts end stage kidney disease in pure membranous lupus nephritis. Rheumatology (Oxford) 2022;61:2483–2493.
41. Gao JJ, Cai GY, Liu SW, et al. Characteristics and influence factors of pathologic transformation in the subclasses of class IV lupus nephritis. Rheumatol Int 2012;32:1751–1759.
42. Moroni G, Porata G, Raffiotta F, et al. Predictors of increase in chronicity index and of kidney function impairment at repeat biopsy in lupus nephritis. Lupus Sci Med 2022;9:e000721.
43. KDIGO 2021 Clinical practice guideline for the management of glomerular diseases. Kidney Int 2021;100:S1–S276.
44. Pons-Estel GJ, Alarcón GS, McGwin G, Jr., et al. Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort. Arthritis Rheum 2009;61: 830–839.
45. Cai T, Zhao J, Yang Y, et al. Hydroxychloroquine use reduces mortality risk in systemic lupus erythematosus: a systematic review and meta-analysis of cohort studies. Lupus 2022;31:1714–1725.
46. Rosenbaum JT, Costenbader KH, Desmarais J, et al. American College of Rheumatology, American Academy of Dermatology, Rheumatologic Dermatology Society, and American Academy of Ophthalmology 2020 Joint Statement on hydroxychloroquine use with respect to retinal toxicity. Arthritis Rheumatol 2021;73: 908–911.
47. Ku E, Inker LA, Tighiouart H, et al. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers for advanced chronic kidney disease: a systematic review and retrospective individual participant-level meta-analysis of clinical trials. Ann Intern Med 2024;177:953–963.
48. Chang JC, Weiss PF, Xiao R, et al. Use of renin angiotensin aldosterone system inhibitors in children with lupus and time to glucocorticoid discontinuation. Kidney Int 2022;102:395–404.

49. Bandhan IH, Islam MN, Ahmad HI, et al. Outcome of low-dose prednisolone use for the induction of remission in lupus nephritis patients. Int J Rheum Dis 2022;25:121–130.
50. Bharati J, Rathi M, Ramachandran R, et al. Comparison of two steroid regimens in induction therapy of proliferative lupus nephritis: a randomized controlled trial. Indian J Nephrol 2019;29:373–375.
51. Zeher M, Doria A, Lan J, et al. Efficacy and safety of enteric-coated mycophenolate sodium in combination with two glucocorticoid regimens for the treatment of active lupus nephritis. Lupus 2011;20: 1484–1493.
52. Webel ML, Ritts RE, Jr., Taswell HF, et al. Cellular immunity after intravenous administration of methylprednisolone. J Lab Clin Med 1974;83:383–392.
53. Malvar A, Alberton V, Lococo B, et al. Remission of lupus nephritis: the trajectory of histological response in successfully treated patients. Lupus Sci Med 2023;10:e000932.
54. Chakravarty EF, Utset T, Kamen DL, et al. Mycophenolate mofetil withdrawal in patients with systemic lupus erythematosus: a multicentre, open-label, randomised controlled trial. Lancet Rheumatol 2024;6:e168–e177.
55. Jourde-Chiche N, Costedoat-Chalumeau N, Baumstarck K, et al. Weaning of maintenance immunosuppressive therapy in lupus nephritis (WIN-Lupus): results of a multicentre randomised controlled trial. Ann Rheum Dis 2022;81:1420–1427.
56. Malvar A, Alberton V, Lococo B, et al. Kidney biopsy-based management of maintenance immunosuppression is safe and may ameliorate flare rate in lupus nephritis. Kidney Int 2020;97:156–162.
57. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009;20:1103–1112.
58. Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum 2011;63:3918–3930.
59. Rovin BH, Furie R, Teng YKO, et al. A secondary analysis of the Belimumab International Study in Lupus Nephritis trial examined effects of belimumab on kidney outcomes and preservation of kidney function in patients with lupus nephritis. Kidney Int 2022;101:403–413.
60. Manzi S, Sánchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis 2012;71:1833–1838.
61. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121–2131.
62. Wofsy D, Diamond B, Houssiau FA. Crossing the Atlantic: the Euro-Lupus nephritis regimen in North America. Arthritis Rheumatol 2015;67:1144–1146.
63. Wang CS, Sadun RE, Zhou W, et al. Renal response outcomes of the EuroLupus and National Institutes of Health cyclophosphamide dosing regimens in childhood-onset proliferative lupus nephritis. Arthritis Rheumatol 2024;76:469–478.
64. Austin HA, 3rd, Illei GG, Braun MJ, et al. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. J Am Soc Nephrol 2009;20:901–911.
65. Chavarot N, Verhelst D, Pardon A, et al. Rituximab alone as induction therapy for membranous lupus nephritis: a multicenter retrospective study. Medicine (Baltimore) 2017;96:e7429.
66. Liu Z, Zhang H, Liu Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med 2015; 162:18–26.
67. Mok CC, Ying KY, Yim CW, et al. Very long-term outcome of pure lupus membranous nephropathy treated with glucocorticoid and azathioprine. Lupus 2009;18:1091–1095.
68. Radhakrishnan J, Moutzouris DA, Ginzler EM, et al. Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. Kidney Int 2010;77:152–160.
69. Arriens C, Teng YKO, Ginzler EM, et al. Update on the efficacy and safety profile of voclosporin: an integrated analysis of clinical trials in lupus nephritis. Arthritis Care Res (Hoboken) 2023;75:1399–1408.
70. Garg S, Plantinga LC. A bitter pill to swallow: the challenge of medication nonadherence in systemic lupus erythematosus. J Rheumatol 2024;51:841–844.
71. Cortés-Hernández J, Torres-Salido MT, Medrano AS, et al. Long-term outcomes--mycophenolate mofetil treatment for lupus nephritis with addition of tacrolimus for resistant cases. Nephrol Dial Transplant 2010;25:3939–3948.
72. Dall'Era M, Stone D, Levesque V, et al. Identification of biomarkers that predict response to treatment of lupus nephritis with mycophenolate mofetil or pulse cyclophosphamide. Arthritis Care Res (Hoboken) 2011;63:351–357.
73. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. Arthritis Rheum 2004;50:3934–3940.
74. Kapitsinou PP, Boletis JN, Skopouli FN, et al. Lupus nephritis: treatment with mycophenolate mofetil. Rheumatology (Oxford) 2004;43: 377–380.
75. Mackay M, Dall'Era M, Fishbein J, et al. Establishing surrogate kidney end points for lupus nephritis clinical trials: development and validation of a novel approach to predict future kidney outcomes. Arthritis Rheumatol 2019;71:411–419.
76. Alshaiki F, Obaid E, Almuallim A, et al. Outcomes of rituximab therapy in refractory lupus: a meta-analysis. Eur J Rheumatol 2018;5: 118–126.
77. Arora S, Rovin BH. Expert perspective: an approach to refractory lupus nephritis. Arthritis Rheumatol 2022;74:915–926.
78. Roccatello D, Fenoglio R, Caniggia I, et al. Daratumumab monotherapy for refractory lupus nephritis. Nat Med 2023;29:2041–2047.
79. Segarra A, Arredondo KV, Jaramillo J, et al. Efficacy and safety of bortezomib in refractory lupus nephritis: a single-center experience. Lupus 2020;29:118–125.
80. Zhang H, Liu Z, Huang L, et al. The short-term efficacy of bortezomib combined with glucocorticoids for the treatment of refractory lupus nephritis. Lupus 2017;26:952–958.
81. Aranow C, Allaart CF, Amoura Z, et al. Efficacy and safety of sequential therapy with subcutaneous belimumab and one cycle of rituximab in patients with systemic lupus erythematosus: the phase 3, randomised, placebo-controlled BLISS-BELIEVE study. Ann Rheum Dis 2024;83:1502–1512.
82. Atisha-Fregoso Y, Malkiel S, Harris KM, et al. Phase II randomized trial of rituximab plus cyclophosphamide followed by belimumab for the treatment of lupus nephritis. Arthritis Rheumatol 2021;73: 121–131.
83. Shipa M, Embleton-Thirsk A, Parvaz M, et al. Effectiveness of belimumab after rituximab in systemic lupus erythematosus: a randomized controlled trial. Ann Intern Med 2021;174:1647–1657.
84. KDIGO 2024 Clinical practice guideline for the management of lupus nephritis. Kidney Int 2024;105:S1–S69.
85. Barbhaiya M, Zuily S, Naden R, et al. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol 2023;75:1687–1702.

86. Sciascia S, Yazdany J, Dall'Era M, et al. Anticoagulation in patients with concomitant lupus nephritis and thrombotic microangiopathy: a multicentre cohort study. Ann Rheum Dis 2019;78:1004–1006.
87. Wright RD, Bannerman F, Beresford MW, et al. A systematic review of the role of eculizumab in systemic lupus erythematosus-associated thrombotic microangiopathy. BMC Nephrol 2020; 21:245.
88. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 2004;65:521–530.
89. Chen D, Hu W. Lupus podocytopathy: a distinct entity of lupus nephritis. J Nephrol 2018;31:629–634.
90. Xia W, Deng J, Zhuang L, et al. Risk factors for acute kidney injury and kidney relapse in patients with lupus podocytopathy. Clin Kidney J 2024;17:sfae148.
91. Pediatric to Adult Rheumatology Care Transition. Accessed April 14, 2025. https://rheumatology.org/pediatric-to-adult-rheumatology-care-transition
92. Cintron D, Chang JC, Sadun RE. Transition to adult rheumatology care: a disease-specific guide. J Clin Rheumatol 2024;30:159–167.
93. Ciosek AL, Makris UE, Kramer J, et al. Health literacy and patient activation in the pediatric to adult transition in systemic lupus erythematosus: patient and health care team perspectives. ACR Open Rheumatol 2022;4:782–793.
94. Dushnicky MJ, Fine C, Cellucci T, et al. Mind the gap: a longitudinal analysis of the experiences of adolescents and parents in a rheumatology transition clinic. J Clin Rheumatol 2023;29:235–239.
95. Kamińska J, Dymicka-Piekarska V, Tomaszewska J, et al. Diagnostic utility of protein to creatinine ratio (P/C ratio) in spot urine sample within routine clinical practice. Crit Rev Clin Lab Sci 2020;57: 345–364.
96. Rahman MM, Azad K, Ahmed N, et al. Spot morning urine protein creatinine ratio and 24 hour urinary total protein excretion rate. Mymensingh Med J 2006;15:146–149.
97. Barnado A, Carroll RJ, Casey C, et al. Phenome-wide association study identifies dsDNA as a driver of major organ involvement in systemic lupus erythematosus. Lupus 2019;28:66–76.
98. Birmingham DJ, Irshaid F, Nagaraja HN, et al. The complex nature of serum C3 and C4 as biomarkers of lupus renal flare. Lupus 2010;19: 1272–1280.
99. Fasano S, Pierro L, Borgia A, et al. Biomarker panels may be superior over single molecules in prediction of renal flares in systemic lupus erythematosus: an exploratory study. Rheumatology (Oxford) 2020;59:3193–3200.
100. Akhter E, Burlingame RW, Seaman AL, et al. Anti-C1q antibodies have higher correlation with flares of lupus nephritis than other serum markers. Lupus 2011;20:1267–1274.
101. Fava A, Wagner CA, Guthridge CJ, et al. Association of autoantibody concentrations and trajectories with lupus nephritis histologic features and treatment response. Arthritis Rheumatol 2024;76:1611–1622.
102. Izmirly PM, Kim MY, Carlucci PM, et al. Longitudinal patterns and predictors of response to standard-of-care therapy in lupus nephritis: data from the Accelerating Medicines Partnership Lupus Network. Arthritis Res Ther 2024;26:54.
103. Taghavi M, Jabrane A, Jacobs L, et al. Antiphospholipid antibodies associated with native arteriovenous fistula complications in hemodialysis patients: a comprehensive review of the literature. Antibodies (Basel) 2024;13:1.
104. Wagenknecht DR, Becker DG, LeFor WM, et al. Antiphospholipid antibodies are a risk factor for early renal allograft failure. Transplantation 1999;68:241–246.
105. Jorge A, Wallace ZS, Lu N, et al. Renal transplantation and survival among patients with lupus nephritis: a cohort study. Ann Intern Med 2019;170:240–247.
106. O'Shaughnessy MM, Montez-Rath ME, Lafayette RA, et al. Differences in initial treatment modality for end-stage renal disease among glomerulonephritis subtypes in the USA. Nephrol Dial Transplant 2016;31:290–298.
107. Broder A, Khattri S, Patel R, et al. Undertreatment of disease activity in systemic lupus erythematosus patients with endstage renal failure is associated with increased all-cause mortality. J Rheumatol 2011; 38:2382–2389.
108. Azegami T, Kounoue N, Sofue T, et al. Efficacy of pre-emptive kidney transplantation for adults with end-stage kidney disease: a systematic review and meta-analysis. Ren Fail 2023;45:2169618.
109. Rana Magar R, Knight SR, Maggiore U, et al. What are the benefits of preemptive versus non-preemptive kidney transplantation? A systematic review and meta-analysis. Transplant Rev (Orlando) 2023; 37:100798.
110. Naveed A, Nilubol C, Melancon JK, et al. Preemptive kidney transplantation in systemic lupus erythematosus. Transplant Proc 2011; 43:3713–3714.
111. Chung MC, Yu TM, Shu KH, et al. Influence of pretransplantation dialysis time and lupus activity on outcome of kidney transplantation in systemic lupus erythematosus. Transplant Proc 2014;46: 336–338.
112. Yap KS, Urowitz MB, Mahood Q, et al. The utility of lupus serology in predicting outcomes of renal transplantation in lupus patients: systematic literature review and analysis of the Toronto lupus cohort. Semin Arthritis Rheum 2017;46:791–797.
113. Burgos PI, Alarcón GS, McGwin G, Jr., et al. Disease activity and damage are not associated with increased levels of fatigue in systemic lupus erythematosus patients from a multiethnic cohort: LXVII. Arthritis Rheum 2009;61:1179–1186.
114. Broder A, Mowrey WB, Valle A, et al. Prescribing patterns of hydroxychloroquine and glucocorticoids among lupus patients after new-onset end-stage renal disease. Arthritis Care Res (Hoboken) 2022; 74:2024–2032.
115. Hiraki LT, Feldman CH, Liu J, et al. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. Arthritis Rheum 2012;64:2669–2676.
116. Vazzana KM, Daga A, Goilav B, et al. Principles of pediatric lupus nephritis in a prospective contemporary multi-center cohort. Lupus 2021;30:1660–1670.
117. Hiraki LT, Hamilton J, Silverman ED. Measuring permanent damage in pediatric systemic lupus erythematosus. Lupus 2007;16: 657–662.
118. Chalhoub NE, Wenderfer SE, Levy DM, et al. International consensus for the dosing of corticosteroids in childhood-onset systemic lupus erythematosus with proliferative lupus nephritis. Arthritis Rheumatol 2022;74:263–273.
119. de Gruijter NM, Naja M, Peckham H, et al. A systematic review exploring the bidirectional relationship between puberty and autoimmune rheumatic diseases. Pediatr Rheumatol Online J 2021;19:47.
120. Rygg M, Pistorio A, Ravelli A, et al. A longitudinal PRINTO study on growth and puberty in juvenile systemic lupus erythematosus. Ann Rheum Dis 2012;71:511–517.
121. Sontichai W, Liao F, Dominguez D, et al. Timing of childhood-onset systemic lupus erythematosus diagnosis relative to menarche and the impact on final adult height. Arthritis Care Res (Hoboken) 2022; 74:199–207.

122. Chang JC, Sears C, Torres V, et al. Racial disparities in renal outcomes over time among hospitalized children with systemic lupus erythematosus. Arthritis Rheumatol 2022;74:1430–1439.
123. Hiraki LT, Lu B, Alexander SR, et al. End-stage renal disease due to lupus nephritis among children in the US, 1995–2006. Arthritis Rheum 2011;63:1988–1997.
124. Furie RA, Rovin BH, Garg JP, et al. Efficacy and safety of obinutuzumab in active lupus nephritis. N Engl J Med Preprint posted online February 7, 2025. https://doi.org/10.1056/NEJMoa2410965.
125. Humphrey MB, Russell L, Danila MI, et al. 2022 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheumatol 2023;75(12):2088–102.
126. Bass AR, Chakravarty E, Akl EA, et al. 2022 American College of Rheumatology guideline for vaccinations in patients with rheumatic and musculoskeletal diseases. Arthritis Care Res 2023;75(3):449–64.
127. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Rheumatol 2020;72(4):529–56.

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1066–1068
DOI 10.1002/acr.25573

EDITORIAL

The Importance of Thinking Outside the (Medical) Box: The Impact of Lifestyle on the Outcomes of Rheumatic and Musculoskeletal Conditions and the Promise of Lifestyle Medicine

Patricia Katz,[1] Brian J. Andonian,[2] and Sarah L. Patterson[1]

The last two decades have seen tremendous changes in treatments available for rheumatic diseases that have dramatically improved disease trajectories for many people with these conditions. Yet a substantial number of them continue to experience significant levels of pain, fatigue, and other symptoms despite first- and even second-line pharmacologic treatment, leading to significant interest among both patients and providers in other ways to address these symptoms. Lifestyle medicine (LM), a medical subspecialty that integrates lifestyle evaluation and interventions as a primary modality for the care of patients with chronic diseases, may offer a solution.[1] The foundation of LM includes six interdependent pillars: exercise, stress management, restorative sleep, nutrition, avoiding risky substances, and positive social connection.

Evidence has accrued on the positive effects of physical activity and exercise on outcomes for people with a range of rheumatic and musculoskeletal diseases (RMDs), including osteoarthritis (OA), rheumatoid arthritis (RA), fibromyalgia, spondyloarthritis, systemic lupus erythematosus (SLE), and psoriatic arthritis.[2–6] However, despite the strong body of evidence in support of physical activity interventions, they are rarely prescribed in clinical practice. Evidence is also accruing on the negative effects of stress on health outcomes among people with RMDs,[7–9] but few resources are readily available to bolster stress resilience among affected individuals. Two studies in this issue of *Arthritis Care & Research* (Hudson et al; Aydemir et al) as well as one in the January 2025 issue (Huber et al) focused on the third pillar of LM: the complex issue of sleep and how sleep is associated with the health and symptoms of people with rheumatic diseases.[10–12]

In the first study, Hudson and colleagues, recognizing the high frequency of sleep problems among people with fibromyalgia, reviewed the evidence for pharmacologic and nonpharmacologic interventions to improve sleep among this group.[10] Their findings revealed that although some pharmacologic treatments were moderately effective, interventions that increased physical activity seemed to have the greatest positive effects. In addition, although pharmacologic treatments often came with concurrent negative side effects, the exercise interventions showed exclusively positive off-target effects, including improvements in overall quality of life.

The other two studies focused on the relationship between sleep and pain in two different types of arthritis: OA and RA. Even though different disease entities were studied, both studies found that poor sleep was generally associated with worse pain. These two studies had unique and important strengths. In the study by Huber and colleagues, sleep was measured objectively using actigraphy.[11] Both incident and worsening pain among individuals with knee OA (KOA) were studied. The authors' hypothesis that sleep would mediate the relationship between neighborhood disadvantage and KOA-related pain was confirmed. They found that neighborhood disadvantage led to worse sleep, which, in turn, led to greater pain. Similarly, in a longitudinal study in which time ordering of sleep disturbance and pain could be observed, Aydemir and colleagues found a relationship between impaired sleep and greater pain among participants in their early RA cohort.[12] Instead of testing the common assumption that pain leads to sleep disturbance, this study leveraged longitudinal data to examine the effect of sleep disturbance on subsequent pain. The results showed that sleep problems were significantly associated with pain six months later, even after adjusting for covariates such as depression.

Aydemir and colleagues[12] proposed inflammation as a link between sleep disturbance and subsequent pain, highlighting

[1]Patricia Katz, PhD, Sarah L. Patterson, MD: University of California San Francisco, San Francisco; [2]Brian J. Andonian, MD, MHSc: Duke University School of Medicine, Durham, North Carolina.

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25573.

Address correspondence via email to Patricia Katz, PhD, at Patti.katz@ucsf.edu.

Submitted for publication March 7, 2025; accepted in revised form March 10, 2025.

that the relationship between sleep and symptom severity in RA is mediated by both psychological and biologic mechanisms. Given that systemic inflammation is a biologic cornerstone of RMDs, the impact of sleep on immune function is highly relevant to this patient population and is well supported by prior studies demonstrating that sleep disorders adversely alter immune function.[13] Insufficient restorative sleep may also impact the risk of developing autoimmunity, a hypothesis supported by studies in which nonapnea sleep disorders conferred increased risk of developing RA, ankylosing spondylitis, SLE, and systemic sclerosis.[14] Sleep is not the only lifestyle factor with evidence for important effects on immune functioning; physical inactivity,[15] high-calorie and low-nutrient dietary patterns (eg, the standard American diet and diets containing an abundance of highly processed foods),[16] and poorly managed psychosocial stress[17] have also been associated with pathologic systemic inflammation. Conversely, healthy dietary patterns, such as the Mediterranean diet and whole-food plant-based diets, have been shown to improve disease activity and markers of systemic inflammation among people living with RMDs such as RA.[18]

Findings from both Hudson and Huber illustrate the complex interplay among different lifestyle behaviors and environmental factors in the context of RMDs. Hudson and colleagues[10] noted an important relationship between physical activity and sleep in people living with fibromyalgia. Huber and colleagues[11] found evidence for a model in which neighborhood disadvantage affects multiple aspects of lifestyle—greater psychological stress (feeling less safe), worse sleep (more noise), and less physical activity (less walkability and safe spaces for outdoor recreation)—which in turn leads to greater osteoarthritic pain. These observations underscore the need for research and clinical programs that target improvements in multiple lifestyle factors (eg, stress, sleep, and physical activity) to comprehensively address predictors of disease outcomes among patients living with RMDs.

The US-based Lifestyle Rheumatology Research Group, led by co-chairs and academic rheumatologists Drs Brian Andonian and Sarah Patterson, has taken on the challenge of improving the evidence on effective strategies for applying LM in rheumatology practice. The goal of the group is to build community and connect academic rheumatologists and researchers with specific interest in LM for rheumatic diseases. The group's vision is to facilitate collaboration, share ideas, and help grow the field of lifestyle rheumatology.

Lifestyle medical care for patients with chronic diseases, including rheumatic diseases, requires a multidisciplinary approach. This lifestyle approach involves breaking down silos of care between, but not limited to, physical therapy, occupational therapy, dieticians, mental health specialists, and behavioral counseling and health coaching and the primary clinician. At a minimum, it is important for rheumatology providers to be knowledgeable about the evidence for lifestyle interventions to impact disease- and symptom-specific outcomes.[19] Perhaps most importantly for rheumatology providers, patients with rheumatic diseases are increasingly requesting lifestyle guidance specifically from their rheumatology clinics.[20]

The publication of the "2022 American College of Rheumatology Guideline for Exercise, Rehabilitation, Diet, and Additional Integrative Interventions for Rheumatoid Arthritis" marked an important step forward for increasing awareness and detailing current evidence in lifestyle rheumatology.[21] The American College of Rheumatology (ACR) guideline included primarily conditional recommendations but one "strong" integrative intervention recommendation for patients with RA to consistently engage in exercise versus no exercise. The ACR guideline does not build on this recommendation to give guidance on specific exercise types, amounts, or methods of delivery in clinical practice because of the overall lack of evidence available. To "inspire much-needed future research in this area to generate higher-certainty evidence," the ACR guideline outlined a research agenda that included a call for more data to guide personalized exercise and lifestyle prescriptions and monitoring for patients with RA.

Though we agree that evidence for lifestyle rheumatology interventions needs to grow to improve the field, it is also important to acknowledge the unique differences in studying lifestyle factors compared to pharmacologic interventions. First, there are unique methodologic and logistic challenges involved in studying lifestyle factors, such as the difficulty of blinding study participants to lifestyle interventions (people know when they are exercising and eating vegetables!), which ultimately leads to more complicated study designs. Second, with less opportunities for private sector organizations to profit from effective nonpharmacologic therapies compared to drugs and devices, there is a critical gap in funding to support rigorous trials at the intersection of LM and rheumatology. Most lifestyle interventions have a favorable safety profile compared to novel medications (especially immunosuppressive agents), and thus it may be reasonable to incorporate certain lifestyle prescriptions in routine rheumatology care at a lower grade of evidence compared to riskier treatments.

Ultimately, more research is still needed to continue to build evidence and novel programs and disseminate key lifestyle findings via top rheumatology journals, such as the three articles mentioned in this editorial. These three studies highlight the impact of sleep disturbances on outcomes in a range of conditions. In conjunction with other research on lifestyle issues such as physical activity, stress, and nutrition, they contribute to a growing body of literature on how factors outside pharmacologic treatment affect the lives and health outcomes of individuals with RMDs. We advocate for more similar research to elucidate the effects of lifestyle factors on the health and disease activity of people with RMDs and, perhaps even more critically, to identify effective and efficient ways for this information to be communicated to physicians and for physicians to communicate it to their patients. A general recommendation to "exercise more" or "get more

sleep" is unlikely to have much impact on a patient's behavior. Specific prescriptions and accountable treatment plans are needed to guide patient behaviors and expectations.

Improved collaborative efforts promise to better define effective lifestyle approaches that improve outcomes and the well-being of patients with rheumatic diseases. With support from patients, the rheumatology community, and multidisciplinary allied health providers, the Lifestyle Rheumatology Research Group hopes to build and broadly disseminate resources for applying LM in rheumatology and to provide concrete resources for clinicians to guide patients toward healthier behaviors and outcomes.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Katz confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Lippman D, Stump M, Veazey E, et al. Foundations of lifestyle medicine and its evolution. Mayo Clin Proc Innov Qual Outcomes 2024; 8(1):97–111.
2. Kraus VB, Sprow K, Powell KE, et al; 2018 Physical Activity Guidelines Advisory Committee. Effects of physical activity in knee and hip osteoarthritis: a systematic umbrella review. Med Sci Sports Exerc 2019; 51(6):1324–1339.
3. Metsios GS, Kitas GD. Physical activity, exercise and rheumatoid arthritis: effectiveness, mechanisms and implementation. Best Pract Res Clin Rheumatol 2018;32(5):669–682.
4. Andrade A, Dominski FH, Sieczkowska SM. What we already know about the effects of exercise in patients with fibromyalgia: an umbrella review. Semin Arthritis Rheum 2020;50(6):1465–1480.
5. Boudjani R, Challal S, Semerano L, et al. Impact of different types of exercise programs on ankylosing spondylitis: a systematic review and meta-analysis. Disabil Rehabil 2023;45(24):3989–4000.
6. Blaess J, Goepfert T, Geneton S, et al. Benefits & risks of physical activity in patients with systemic lupus erythematosus: a systematic review of the literature. Semin Arthritis Rheum 2023;58:152128.
7. Patterson S, Trupin L, Hartogensis W, et al. Perceived stress and prediction of worse disease activity and symptoms in a multiracial, multiethnic systemic lupus erythematosus cohort. Arthritis Care Res (Hoboken) 2023;75(8):1681–1689.
8. Evers AW, Verhoeven EW, van Middendorp H, et al. Does stress affect the joints? Daily stressors, stress vulnerability, immune and HPA axis activity, and short-term disease and symptom fluctuations in rheumatoid arthritis. Ann Rheum Dis 2014;73(9):1683–1688.
9. Luo G, Boelle PY, Turbelin C, et al. Abrupt and unexpected stressful life events are followed with increased disease activity in spondyloarthritis: a two years web-based cohort study. Joint Bone Spine 2019; 86(2):203–209.
10. Hudson J, Imamura M, Robertson C, et al. Effects of pharmacologic and nonpharmacologic interventions for the management of sleep problems in people with fibromyalgia: systematic review and network meta-analysis of randomized controlled trials. Arthritis Care Res (Hoboken) 2025;77(9):1095–1105.
11. Huber FA, Gonzalez C, Kusko DA, et al. Neighborhood disadvantage and knee osteoarthritis pain: do sleep and catastrophizing play a role? Arthritis Care Res (Hoboken) 2025;77(1):95–103.
12. Aydemir B, Schieir O, Valois MF, et al. Association between sleep disturbance and subsequent pain interference in patients with early rheumatoid arthritis. Arthritis Care Res (Hoboken) 2025;77(9):1078–1084.
13. Irwin MR. Sleep and inflammation: partners in sickness and in health. Nat Rev Immunol 2019;19(11):702–715.
14. Hsiao YH, Chen YT, Tseng CM, et al. Sleep disorders and increased risk of autoimmune diseases in individuals without sleep apnea. Sleep 2015;38(4):581–586.
15. Abramson JL, Vaccarino V. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. Arch Intern Med 2002;162(11):1286–1292.
16. Wang YB, Page AJ, Gill TK, et al. The association between diet quality, plant-based diets, systemic inflammation, and mortality risk: findings from NHANES. Eur J Nutr 2023;62(7):2723–2737.
17. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol 2005;5(3):243–251.
18. Walrabenstein W, Wagenaar CA, van der Leeden M, et al. A multidisciplinary lifestyle program for rheumatoid arthritis: the 'Plants for Joints' randomized controlled trial. Rheumatology (Oxford) 2023; 62(8):2683–2691.
19. Thomas R, Berry A, Swales C, et al. Strategies to enhance physical activity in people with rheumatoid arthritis: a Delphi survey. Musculoskeletal Care 2023;21(3):723–732.
20. Thomsen T, Aadahl M, Hetland ML, et al. Physical activity guidance in the rheumatology clinic—what matters for patients with rheumatoid arthritis? A qualitative study. Rheumatol Int 2024;44(1):181–189.
21. England BR, Smith BJ, Baker NA, et al. 2022 American College of Rheumatology guideline for exercise, rehabilitation, diet, and additional integrative interventions for rheumatoid arthritis. Arthritis Care Res (Hoboken) 2023;75(8):1603–1615.

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1069–1077
DOI 10.1002/acr.25563

American College of Rheumatology
Empowering Rheumatology Professionals

CLINICOPATHOLOGIC CONFERENCE

A 27-Year-Old Woman With Acute Encephalopathy and Painful Bilateral Cervical Lymphadenopathy

Aakash V. Patel, Eli Miloslavsky, Haatem Reda, James R. Stone, and Marcy B. Bolster

CASE PRESENTATION

Chief symptoms

The patient, a 27-year-old woman, was admitted for altered mental status and painful bilateral cervical lymphadenopathy.

History of the present illness

The patient, with a history of Kikuchi–Fujimoto (Kikuchi) disease no longer requiring treatment, was in her usual state of health before developing constitutional symptoms, including night sweats, malaise, anorexia, and nightly fevers up to 103°F, approximately four weeks before admission. At that time, she also noticed painful bilateral cervical lymphadenopathy, diffuse arthralgia and myalgia, and marked lower-extremity predominant pruritus. She completed a course of prednisone, tapered over 10 days from 40 mg daily, without improvement in her pruritus or other symptoms. She had traveled to Aruba two weeks before admission for a one-week vacation. The patient stated she felt unwell the entire duration of her vacation due to fevers; she denied consuming raw foods or being bitten by an animal. During the week before admission, the patient began to experience generalized weakness and fatigue; she required assistance from her mother to shower, brush her teeth, and comb her hair. In the 24 hours before admission, the patient became confused and made nonsensical statements. She was subsequently found to be less responsive and stopped following commands, prompting her mother to bring her to the emergency department.

Medical history

The patient had prior diagnoses of asthma, anxiety, and migraine headaches. She had a history of relapsing Kikuchi disease, which had been diagnosed eight years before the current admission. At that time, she experienced new painful bilateral cervical lymphadenopathy in the setting of fevers. Magnetic resonance imaging (MRI) of the neck showed cervical and supraclavicular lymphadenopathy up to 2.4 cm in size. A right posterior cervical lymph node excisional biopsy revealed necrotizing histiocytic lymphadenitis, consistent with Kikuchi disease. She was treated with moderate doses of systemic glucocorticoids, which were tapered over six weeks, leading to a marked reduction in her cervical lymphadenopathy and associated pain. The patient was lost to follow-up but re-established care with rheumatology five years later (three years before admission) due to recurrence of painful cervical and axillary lymphadenopathy associated with fever and diffuse arthralgia. She had only a modest response to prednisone at 60 mg daily, prompting a left posterior cervical lymph node excisional biopsy, again demonstrating necrotizing histiocytic lymphadenitis. She ultimately experienced complete resolution of lymphadenopathy and associated symptoms following an extended course of systemic glucocorticoids tapered over six months in addition to treatment with hydroxychloroquine (HCQ) and mycophenolate mofetil (MMF) at 1 g twice daily. The patient did not demonstrate clinical or serologic features of systemic lupus erythematosus (SLE). The patient was again lost to follow-up with rheumatology until the current admission. As such, she had not continued taking HCQ or MMF.

Social and family history

The patient worked as a middle school Spanish teacher. There was no history of tobacco or illicit drug use; the patient reported consuming one or two drinks of alcohol every week. The patient had a boyfriend with whom she was sexually active. There was no family history of autoimmune disease.

Aakash V. Patel, MD, Eli Miloslavsky, MD, Haatem Reda, MD, James R. Stone, MD, PhD, Marcy B. Bolster, MD: Massachusetts General Hospital, Boston.
Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25563.

Address correspondence via email to Aakash V. Patel, MD, at apatel112@mgh.harvard.edu.
Submitted for publication November 1, 2024; accepted in revised form April 17, 2025.

Review of systems

Additional symptoms included red, watery, pruritic eyes; nausea; nonbilious, nonbloody emesis; and right lower quadrant abdominal pain. The review of systems was negative for hair loss, sicca symptoms, oral or genitourinary ulcers, pleuritic chest pain, dyspnea, diarrhea, dysuria, hematuria, photosensitivity, rash, or prior blood clots. The patient was gravida 0.

Physical examination

Vital signs revealed a temperature of 102.8°F and a heart rate of 137 beats per minute. She was normotensive with normal oxygen saturation. The patient was somnolent but arousable. She was unable to answer orientation questions and was only intermittently able to follow simple commands. At times, she made nonsensical statements. She moved freely in bed, including all extremities, and withdrew from pain. Reflexes were graded 2+ in upper and lower extremities. Pupils were equal, round, and reactive to light with intact extraocular movements. There was no facial droop. The patient was unable to cooperate with cranial nerve, sensory, full motor, and cerebellar testing.

Her examination was otherwise notable for enlarged and exquisitely tender bilateral cervical lymph nodes. She had a pustular rash consistent with acne vulgaris on her back and neck. The patient had full range of motion of all joints without joint swelling or deformities. She did not have oral ulcers. Results of cardiopulmonary and abdominal examinations were normal.

Laboratory and imaging evaluation

Laboratory evaluation revealed mild transaminitis and acute kidney injury in the absence of proteinuria or hematuria (Table 1). There were no cytopenias. She had elevated levels of serum markers of inflammation and low-titer antinuclear antibodies (ANAs) of 1:160 in a speckled pattern; extractable nuclear antibodies were negative, and complement levels were normal. Serum protein electrophoresis did not reveal paraproteinemia. A lumbar puncture was performed on admission. A cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis with an elevated total protein level of 91 mg/dL (Table 2). A thorough evaluation for infection, including serum and CSF serologic tests and cultures, was unrevealing. Results of paraneoplastic and autoimmune encephalitis serologic tests from serum samples and CSF were negative.

A head computed tomography (CT) scan did not reveal an acute process, but neck CT imaging was notable for numerous enlarged bilateral cervical lymph nodes up to 2 cm in size. CT of the chest, abdomen, and pelvis did not reveal significant lymphadenopathy or other abnormalities. A brain MRI study without contrast demonstrated small foci of T2 fluid-attenuated inversion recovery (FLAIR)–hyperintense signal and restricted diffusion involving the splenium of the corpus callosum, left periatrial white matter, and left periventricular white matter (Figure 1A). Brain magnetic resonance angiography was notable for preserved flow with no vascular abnormalities. An echocardiogram showed normal biventricular function without valvular abnormalities or visualized vegetations.

THE PATIENT'S COURSE

On hospital day two, the patient's mentation continued to worsen. A repeat brain MRI with and without contrast showed multiple new as well as progressed sites of FLAIR hyperintensity involving the supratentorial brain, many of which also demonstrated restricted diffusion and/or abnormal enhancement (Figure 1B). Given the unrevealing infectious evaluation along with the patient's rapidly progressive neurologic features, the patient was started on intravenous (IV) pulse-dose methylprednisolone at 1,000 mg daily. Unfortunately, even after receiving five days of IV pulse-dose methylprednisolone, there was no meaningful improvement in the patient's mentation. Another lumbar puncture was performed, which was again notable for CSF lymphocyte-predominant pleocytosis (66 white blood cells per microliter; 76% lymphocytes) with an elevated CSF protein level (143 mg/dL). The patient remained on high-dose systemic glucocorticoids.

On hospital day eight, another brain MRI scan demonstrated increased FLAIR hyperintensity in the right temporal lobe, the left hippocampus, and the left parahippocampal gyrus but with some decrease in the conspicuity of the other supratentorial lesions (Figure 1C). The patient's mentation was unimproved, and infectious evaluation results remained negative.

CASE SUMMARY

The patient, a 27-year-old woman with a history of relapsing Kikuchi disease, presented with altered mental status in the setting of one month of painful bilateral cervical lymphadenopathy and fever. On arrival to the emergency department, she had a fever and signs of encephalopathy with moderately enlarged tender bilateral cervical lymphadenopathy. She had elevated levels of serum markers of inflammation, along with CSF findings of lymphocytic pleocytosis and elevated protein levels. Brain MRI revealed multiple cortical, subcortical, and callosal enhancing T2-FLAIR hyperintensities with associated restricted diffusion. A thorough infectious evaluation was unrevealing. During the first week following admission, the patient had rapid clinical and radiologic progression of meningoencephalitis despite IV pulse-dose glucocorticoids.

DIFFERENTIAL DIAGNOSIS

We considered infectious, neoplastic, and inflammatory etiologies, as outlined in this section.

Table 1. Laboratory test results in a 27-year-old woman with acute encephalopathy and painful bilateral cervical lymphadenopathy*

Laboratory test	Result	Normal range
Hematology		
White blood cell count, 10^3/μL	7.90 (74% PMNs, 1.7% myelocytes)	4.5–11.0
Hemoglobin, g/dL	12.9 (MCV 88.3)	12.0–16.0
Platelet count, 10^3/μL	371	150–400
Chemistry studies		
Sodium, mmoles/L	136	135–145
Potassium, mmoles/L	4.5	3.4–5.0
Chloride, mmoles/L	100	98–108
CO_2, mmoles/L	23	23–32
Blood urea nitrogen, mg/dL	23	8–25
Creatinine, mg/dL	1.3	0.6–1.50
Estimated glomerular filtration rate, mL/min/1.73 m^2	57	>59
Glucose mg/dL	128	70–110
Calcium mg/dL	9.1	8.5–10.5
Total protein, g/dL	7.4	6.0–8.3
Albumin g/dL	4	3.5–5.0
Total bilirubin, mg/dL	0.4	0.0–1.0
Aspartate aminotransferase, IU/L	46	9–32
Alanine aminotransferase, IU/L	46	7–33
Alkaline phosphatase, IU/L	91	30–100
Lactic acid, mmoles/L	2.1	0.5–2.0
Urine		
Blood	Negative	Negative
Protein	Negative	Negative
Protein/creatinine ratio	230	<300
Immunology		
Erythrocyte sedimentation rate, mm/h	54	0–19
C-reactive protein level, mg/L	53	<8
ANA titer	1:160 (speckled)	<1:40
dsDNA antibody titer	Negative	Negative
Ro/La antibodies	Negative	Negative
Smith/RNP antibodies	Negative	Negative
ANCA	Negative	Negative
C3, mg/dL	92	81–157
C4, mg/dL	17	12–39
Serum protein electrophoresis	No M-spike	No M-spike
Free kappa/lambda ratio	0.84	0.30–1.70
Cryoglobulins	Negative	Negative
Antiphospholipid antibodies	Negative	Negative
AGNA-1 antibody	Negative	Negative
AMPA receptor antibody	Negative	Negative
Amphiphysin antibody titer	Negative	Negative
Antineuronal nuclear antibody	Negative	Negative
ANNA types 2 and 3	Negative	Negative
CASPR2-IgG antibody	Negative	Negative
CRMP-5 IgG antibody	Negative	Negative
GAD65 antibody	Negative	Negative
$GABA_B$ receptor antibody	Negative	Negative
PCA-TR antibody	Negative	Negative
NMDA NR1 antibody	Negative	Negative
NMO-aquaporin-4 antibody	Negative	Negative
Yo (Purkinje) 1 and 2 antibody titer	Negative	Negative
Infectious disease		
Hepatitis A IgM antibody	Negative	Negative
Hepatitis B core antibody	Negative	Negative
Hepatitis B surface antigen	Negative	Negative
Hepatitis C antibody	Negative	Negative
HIV-1/2 antibody/antigen	Negative	Negative
T-spot tuberculosis test	Negative	Negative
Treponemal antibodies	Negative	Negative
Lyme antibodies	Negative	Negative
Viral respiratory PCR panel	Not detected	Not detected
Influenza A and B PCR	Not detected	Not detected
RSV PCR	Not detected	Not detected
SARS-CoV-2 PCR	Not detected	Not detected
Blood cultures	No growth	No growth
CMV DNA, IU/mL	Not detected	Not detected
Anaplasmosis and ehrlichiosis DNA	Not detected	Not detected
Toxoplasmosis and West Nile IgM antibodies	Negative	Negative
Zika and chikungunya IgM antibodies	Negative	Negative

* AGNA-1, antiglial/neuronal nuclear antibody-type 1; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ANNA, antineuronal nuclear antibody; CASPR2, contactin-associated protein-like 2; CMV, cytomegalovirus; CRMP-5, collapsin response mediator protein-5; dsDNA, double-stranded DNA; $GABA_B$, γ-aminobutyric acid type B; GAD65, glutamic acid decarboxylase 65-kilodalton isoform; MCV, mean corpuscular volume; NMDA, *N*-methyl-D-aspartate; PCA-TR, Purkinje cell cytoplasmic antibody-Tr; PCR, polymerase chain reaction; PMN, polymorphonuclear cell; RSV, respiratory syncytial virus.

Neuropsychiatric SLE. Kikuchi disease can be associated with autoimmune conditions, especially SLE,[1,2] and interestingly, in some cases, it precedes the onset of SLE. Neuropsychiatric SLE generally occurs within the first year after SLE diagnosis and can affect the central and peripheral nervous systems.[3] Common imaging findings in neuropsychiatric SLE include cortical atrophy, cerebral infarctions, and periventricular and subcortical white matter lesions.[3] Although this patient's brain imaging findings are supportive of an acute demyelinating process, she lacked clinical features of SLE, and her relatively low-titer ANA with negative extractable nuclear antibodies, normal complement levels, negative antiphospholipid antibodies, lack of cytopenias, and normal urine sediment are not suggestive of a diagnosis of SLE and/or neuropsychiatric SLE.

Primary angiitis of the central nervous system. Primary angiitis of the central nervous system (CNS) generally presents with progressive headache and cognitive impairment[4]; however, in a minority of patients, it can cause acute encephalopathy and ischemic stroke. CSF analysis generally reveals

Table 2. Cerebrospinal fluid analysis in a 27-year-old woman with acute encephalopathy and painful bilateral cervical lymphadenopathy*

Laboratory test	Result	Normal range
General		
Appearance	Clear, colorless	Clear, colorless
Total protein, mg/dL	91	5–55
Glucose, mg/dL	53	50–75
White blood cell count, /μL	75 (75% lymphocytes, 5% PMNs)	<5
Infectious		
Culture/smear	Negative	Negative
Fungal culture with wet preparation	Negative	Negative
Varicella DNA	Not detected	Not detected
HSV types 1 and 2 DNA	Not detected	Not detected
Cryptococcus antigen	Negative	Negative
West Nile virus RNA	Not detected	Not detected
Immunology		
Amphiphysin antibody	Negative	Negative
ANNA types 1, 2, and 3	Negative	Negative
CRMP-5 IgG antibody	Negative	Negative
$GABA_B$ receptor antibody	Negative	Negative
GAD65 antibody	Negative	Negative
Glial nuclear type 1 antibody	Negative	Negative
NMDA R1 antibody	Negative	Negative
PCA types 1 and 2	Negative	Negative
Ribosomal P protein antibody	Negative	Negative
Yo (Purkinje) antibody titer	Negative	Negative

* ANNA, antineuronal nuclear antibody; CRMP-5, collapsin response mediator protein-5; $GABA_B$, γ-aminobutyric acid type B; GAD65, glutamic acid decarboxylase 65-kilodalton isoform; HSV, herpes simplex virus; NMDA, *N*-methyl-D-aspartate; PCA, Purkinje cell cytoplasmic antibody; PMN, polymorphonuclear cell.

increased levels of protein and nucleated cells. Supportive features on brain or blood vessel imaging include ischemia with segmental stenosis of the vasculature in multiple distributions. It can be challenging to establish a definitive diagnosis of primary angiitis of the CNS, especially in the absence of diagnostic biomarkers, though conventional angiography and histopathologic examination have utility. A prior study demonstrated an 81% response rate with glucocorticoid monotherapy.[5] The lack of vessel wall thickening or enhancement on this patient's imaging suggests against primary angiitis of the CNS; however, given the aforementioned diagnostic challenges, we believed this condition remained a strong consideration.

Intravascular lymphoma. Intravascular lymphoma is characterized by infiltration of small and medium-sized blood vessels by non-Hodgkin lymphoma cells.[6] Rarely, the CNS vasculature can be involved, leading to various neurologic deficits and cognitive dysfunction resulting from cerebral ischemia. Patients with intravascular lymphoma involving the CNS often experience rapid clinical deterioration and increased mortality due to diagnostic challenges and subsequent lack of timely treatment, which includes chemotherapeutic agents. Although this patient presented with enlarged bilateral cervical lymph nodes, she had a normal serum protein electrophoresis pattern; additionally, no malignant cells were identified in the CSF. Nonetheless, these findings do not exclude the possibility of intravascular lymphoma, a difficult-to-confirm diagnosis, and we therefore considered this in our differential diagnosis.

Primary CNS infection. We considered numerous infectious etiologies, such as herpes simplex virus (HSV) encephalitis, toxoplasma encephalitis, West Nile virus encephalitis, cryptococcal meningitis, and tuberculosis, given the patient's clinical deterioration following initiation of systemic glucocorticoids. Each of these conditions can potentially cause fever and acute encephalopathy.[7] Examination of the CSF often reveals pleocytosis with an elevated protein level, though the CSF can also be normal (though rarely in HSV encephalitis). Brain MRI can demonstrate abnormal signal involving the basal ganglia, thalami, and/or temporal lobes. In this patient, HSV types 1 and 2 DNA and West Nile virus RNA were not detected in the CSF; the result of cryptococcus antigen testing in the CSF was negative.

Furthermore, results of West Nile and cryptococcus peripheral serologic tests were negative. The result of tuberculosis testing with interferon-γ release assay was negative. Lastly, this patient notably had recently traveled to Aruba, albeit after she had already started to develop symptoms. Chikungunya and Zika viruses can rarely cause encephalitis and are prevalent in tropical areas such as the Caribbean. Serologic testing results for these were also negative.

Neurologic manifestation of Kikuchi disease. Kikuchi disease often presents with self-limited painful cervical lymphadenopathy and other symptoms, such as fever and arthralgia.[2] Most cases resolve spontaneously within a few months; nonsteroidal anti-inflammatory drugs or short courses of systemic glucocorticoids can be used for patients with prolonged courses or debilitating symptoms. Cervical lymph node biopsy, demonstrating necrotizing histiocytic lymphadenitis, is usually diagnostic of Kikuchi disease. Neurologic involvement with Kikuchi disease is rare but has been described[8,9]; manifestations have been reported to include aseptic meningitis and encephalitis.[1,8] We were particularly intrigued by this patient's history of relapsing Kikuchi disease, as she had histopathologic features on cervical lymph node biopsy consistent with Kikuchi disease at two prior time points with interval remission. The patient's most recent episode, three years before this admission, interestingly required a lengthy course of systemic glucocorticoids as well as the use of other immunomodulatory agents, including HCQ and MMF, to resolve her symptoms. The presence of recurrent episodes and the need for treatment with prolonged immunomodulatory therapies are

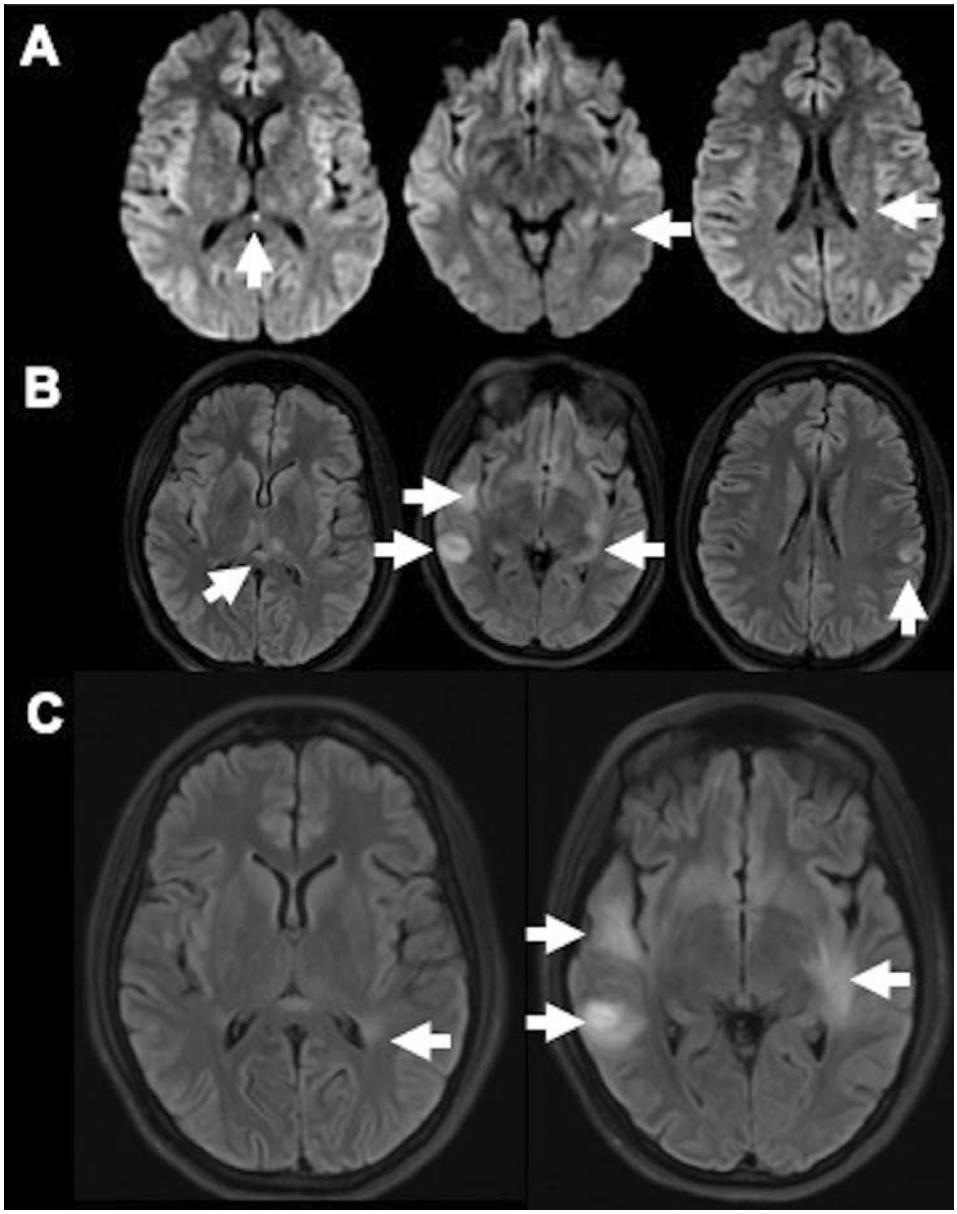

Figure 1. Evolution of brain MRI findings in a 27-year-old woman with acute encephalopathy and painful bilateral cervical lymphadenopathy. (A) Initial MRI of the brain showed multiple foci of restricted diffusion (arrows) present and involving the splenium of the corpus callosum, left periatrial white matter, and left periventricular white matter. (B) Repeat MRI of the brain on hospital day two revealed multiple new and progressed sites of FLAIR hyperintensity (arrows) involving the supratentorial brain, including the thalami, right basal ganglia, bilateral temporal lobes, left insula, right frontal lobe, left parietal lobe, and splenium of the corpus callosum. (C) MRI of the brain on hospital day eight demonstrated an increased extent of FLAIR hyperintensity (arrows) in the left hippocampus, left parahippocampal gyrus, and right temporal lobe but with some decrease in the conspicuity of the FLAIR hyperintensity involving the thalami, right basal ganglia, and left frontoparietal lesions. FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

features atypical of Kikuchi disease.[2] Her presenting features during this hospital admission elicited further concern for another recurrence of Kikuchi disease given the tender bilateral cervical lymphadenopathy appreciated on examination and on imaging. The limited number of reported cases describing neurologic manifestations of Kikuchi disease makes it challenging to identify risk factors for this severe phenotype. Although typically a refractory response to systemic glucocorticoids would be unusual for Kikuchi disease, this patient had demonstrated a refractory nature to immunosuppression with glucocorticoids alone, previously requiring additional immunomodulatory agents, thus keeping Kikuchi disease in our differential diagnosis.

Other diagnostic considerations. There are other inflammatory and autoimmune processes, such as sarcoidosis, antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis,

and Behçet disease, that can involve the CNS and manifest as encephalopathy and brain parenchymal masses or lesions[10–12]; patients with these conditions can experience profound morbidity despite receiving standard-of-care treatment, which includes systemic glucocorticoids. Although all three of these diagnoses can very rarely manifest with isolated neurologic involvement, the lack of systemic features, such as mediastinal or hilar lymphadenopathy, pulmonary-renal disease, and oral or genital ulcerations, respectively, makes these diagnoses highly unlikely.[13–15] Additionally, ANCA serologic test results were negative, and although this does not rule out ANCA-associated vasculitis, it does suggest against it.

SUBSEQUENT PATIENT'S COURSE

Given the diagnostic uncertainty and lack of clinical improvement, an interdisciplinary decision was made to proceed with biopsy of a right temporal lobe lesion, which was performed on hospital day 11. Histopathologic examination revealed brain parenchyma with patchy perivascular mononuclear, lymphohistiocyte-rich inflammation (Figure 2A–D). Immunohistochemical staining highlighted $CD68^+$ macrophages (Figure 2C) and $CD3^+$ T lymphocytes (including a mix of $CD4^+$ and $CD8^+$ populations, Figure 2D) in prominent perivascular distributions. There was no evidence of lymphoma, vasculitis, or infection. These histopathologic findings were similar to those from a cervical lymph node biopsy performed during the patient's previous episode of Kikuchi disease three years before the current admission (Figure 3A–C). Given these findings, the patient's presentation was believed to be best explained by neurologic involvement of Kikuchi disease.

The patient continued to take prednisone at 100 mg daily following the initial five-day IV pulse-dose glucocorticoids. Two weeks after her hospital admission, the patient's mentation began to improve. She was alert and oriented, was able to respond to all commands, and answered all questions; she was not, however, able to engage in prolonged conversation, and she had pronounced short-term memory deficits. With this substantial improvement, the patient was discharged from the hospital, at which time prednisone was tapered to 60 mg daily and the patient was started on HCQ at 300 mg daily as well as MMF, which was up-titrated to 1,500 mg twice daily. The patient's cognition continued to improve following hospital discharge. She underwent repeat brain MRI 25 days after her initial presentation, which remarkably demonstrated resolution of all supratentorial lesions, with only postsurgical changes involving the right temporal lobe (Figure 4). Four months following her hospital admission, while tapering systemic glucocorticoids, the patient had a recurrence of neck pain and headache, though without encephalopathy or lymphadenopathy; a repeat lumbar puncture reassuringly did not reveal CSF pleocytosis or an elevated protein level. Brain

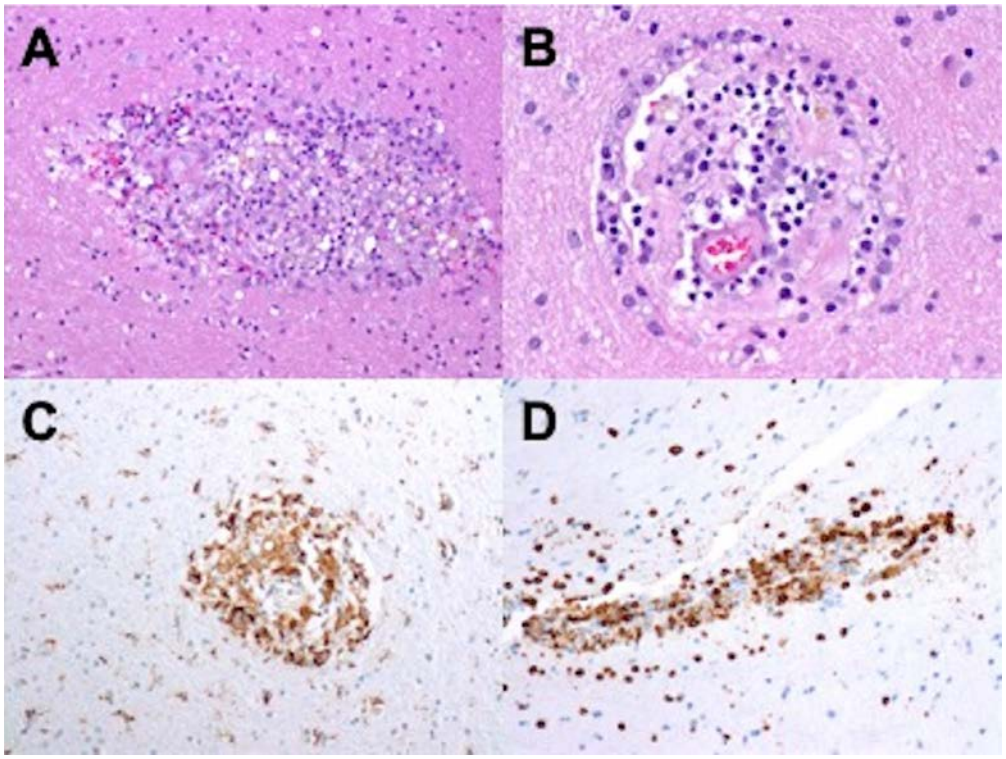

Figure 2. Histopathologic findings from a right temporal lobe lesion brain biopsy in a 27-year-old woman with acute encephalopathy and painful bilateral cervical lymphadenopathy. (A and B) Sections show brain parenchyma with patchy perivascular mononuclear, lymphohistiocyte-rich inflammation. Immunohistochemical staining highlighted (C) $CD68^+$ macrophages and (D) $CD3^+$ T lymphocytes, including a mix of $CD4^+$ and $CD8^+$ populations, in prominent perivascular distributions.

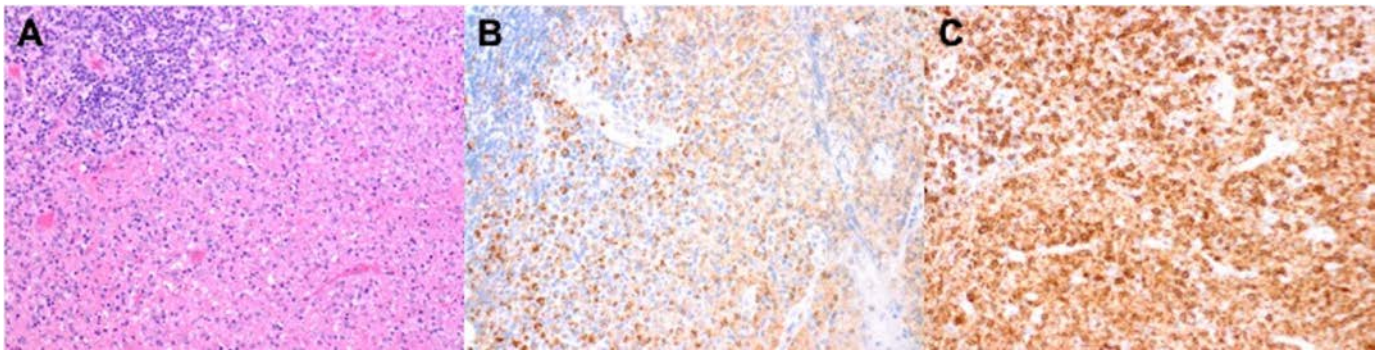

Figure 3. Histopathologic findings from a cervical lymph node biopsy performed during the Kikuchi disease episode three years before the current admission in a 27-year-old woman with acute encephalopathy and painful bilateral cervical lymphadenopathy. (A) Sections show cervical lymph node tissue with mononuclear, lymphohistiocyte-rich inflammation. Immunohistochemical staining highlighted (B) $CD68^+$ macrophages and (C) $CD3^+$ T lymphocytes, including a mix of $CD4^+$ and $CD8^+$ populations, with extensive geographic necrosis throughout the cervical lymph node tissue. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25563/abstract.

MRI did not demonstrate recurrent lesions. Her systemic glucocorticoids were increased to allow more time for the MMF and HCQ to reach full efficacy. The patient was successfully tapered off systemic glucocorticoids 11 months after her initial presentation, without disease recurrence. She continued to experience significant improvement in cognitive, emotional, and physical functioning following aggressive physical, occupational, and speech therapy while remaining on MMF at 1,500 mg twice daily and HCQ at 300 mg daily; after approximately one year, she was able to return to work in her full capacity. Testing for SLE and other systemic autoimmune rheumatic diseases remained unrevealing.

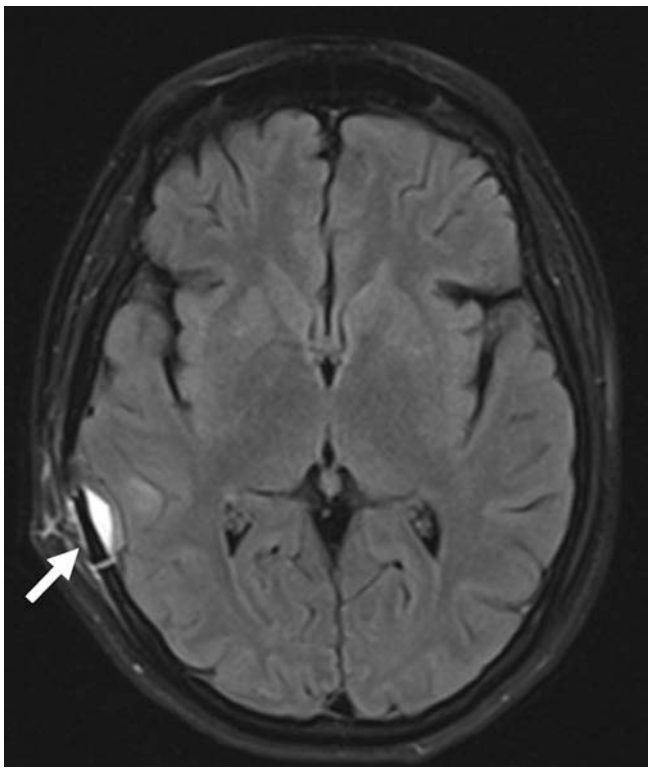

Figure 4. Magnetic resonance imaging of the brain 25 days after a 27-year-old woman initially presented with acute encephalopathy and painful bilateral cervical lymphadenopathy. There is resolution of all supratentorial lesions, with only postsurgical changes involving the right temporal lobe (arrow).

DISCUSSION

Kikuchi disease, characterized by the presence of painful cervical lymphadenopathy with associated constitutional symptoms such as fever and arthralgia, is more prevalent in young Asian women.[2] It is generally a transient, self-limited disease, with spontaneous resolution occurring within a few months in a majority of cases. Kikuchi disease can be triggered by infections, including viruses such as Epstein-Barr virus, HSV, human herpesvirus, and varicella-zoster virus, though many cases are idiopathic. Although most cases are self-limited, treatment can include nonsteroidal anti-inflammatory drugs or systemic glucocorticoids for those patients experiencing significant discomfort from painful cervical lymphadenopathy. An excisional cervical lymph node biopsy can identify characteristic histopathologic findings, including necrotizing histiocytic lymphadenitis. Kikuchi disease is generally monophasic; recurrence is atypical and occurs in less than 5% of cases.

Kikuchi disease is associated with many autoimmune diseases, most notably SLE, which can occur before, during, or after the onset of Kikuchi disease.[16] Patients with Kikuchi disease and SLE share many similar clinical features, such as fever and lymphadenopathy, and both primarily affect young women; histopathologic features of Kikuchi disease have been noted in up to 20% of patients with SLE with lymphadenopathy.[17] Patients with Kikuchi disease therefore require close monitoring for evolution to SLE or other systemic autoimmune rheumatic diseases.

Extranodal involvement of Kikuchi disease is uncommon,[2] and specifically, involvement of the CNS is rare,[8,9] with fewer than 100 cases reported per our review of the literature. Neurologic manifestations can include aseptic meningitis and, much less frequently, encephalitis[1,8]; we identified only a few cases of encephalitis associated with Kikuchi disease in the literature.[18–27] A review of 41 cases of aseptic meningitis attributed to Kikuchi disease revealed more common involvement among male and female patients in their second, third, or fourth decade of life.[28] Symptoms primarily included headache and neck stiffness and, less frequently, confusion, which occurred in only eight (20%) patients. A CSF examination generally showed lymphocytic or monocytic pleocytosis with increased protein levels and sterile cultures. Approximately one-quarter of patients had abnormalities identified on cross-sectional imaging of the brain. Twenty-three patients were treated with systemic glucocorticoids, and of these, 18 (78%) experienced complete recovery. Some patients experienced neurologic symptoms for up to four months, with six patients experiencing relapse of aseptic meningitis. Notably, to our knowledge, there has only been one published report outlining a case in which a brain biopsy was performed in a patient with CNS involvement of Kikuchi disease,[18] and a histopathologic examination revealed an abundance of $CD68^+$ macrophages and histiocytes, as were similarly observed in our patient's brain biopsy. These findings are also strikingly consistent with cervical lymph node histopathology in Kikuchi disease. However, in contrast to previously reported cases of neurologic involvement of Kikuchi disease,[28] our patient required multiple immunomodulatory therapies, including MMF and HCQ, to induce remission and permit tapering of systemic glucocorticoids.

This case highlights the importance of considering neurologic involvement of Kikuchi disease in patients with bilateral cervical lymphadenopathy and rapidly progressive meningoencephalitis, a feature that is not observed in most systemic autoimmune rheumatic diseases. In a patient with known Kikuchi disease, given the lack of specific biomarkers or assays for the rare complication of CNS involvement as well as the need to rule out CNS infection, a biopsy of amenable lesions identified on brain imaging should be considered when noninvasive evaluation is unrevealing or when patients do not respond to empiric therapies. Our case also elucidates concordance of histopathologic features between affected brain tissue and enlarged cervical lymph nodes in this patient with neurologic involvement of Kikuchi disease. Among affected patients who are slow to respond or refractory to systemic glucocorticoids, the addition of other immunomodulatory agents should be considered.

FINAL DIAGNOSIS

Neurologic involvement of Kikuchi–Fujimoto disease

REFERENCES

1. Mahajan VK, Sharma V, Sharma N, et al. Kikuchi-Fujimoto disease: a comprehensive review. World J Clin Cases 2023;11(16):3664–3679.
2. Perry AM, Choi SM. Kikuchi-Fujimoto disease: a review. Arch Pathol Lab Med 2018;142(11):1341–1346.
3. Popescu A, Kao AH. Neuropsychiatric systemic lupus erythematosus. Curr Neuropharmacol 2011;9(3):449–457.
4. Birnbaum J, Hellmann DB. Primary angiitis of the central nervous system. Arch Neurol 2009;66(6):704–709.
5. Salvarani C, Brown RD Jr, Calamia KT, et al. Primary central nervous system vasculitis: analysis of 101 patients. Ann Neurol 2007;62(5):442–451.
6. Bhagat R, Shahab A, Karki Y, et al. Intravascular lymphoma-associated stroke: a systematic review of case studies. Cureus 2023;15(12):e50896.
7. Archibald LK, Quisling RG. Central nervous system infections. In: Layon AJ, Gabrielli A, Friedman WA, eds. Textbook of Neurointensive Care. 2nd ed. Springer; 2013:427–517.
8. Dumas G, Prendki V, Haroche J, et al. Kikuchi-Fujimoto disease: retrospective study of 91 cases and review of the literature. Medicine (Baltimore) 2014;93(24):372–382.
9. Huang Y, Wang X, Wang L, et al. Kikuchi–Fujimoto disease associated with the central nervous system in children. Pediatr Discov 2023;1(2):e23.
10. Wludarczyk A, Szczeklik W. Neurological manifestations in ANCA-associated vasculitis - assessment and treatment. Expert Rev Neurother 2016;16(8):861–863.
11. Caruso P, Moretti R. Focus on neuro-Behçet's disease: a review. Neurol India 2018;66(6):1619–1628.
12. Lacomis D. Neurosarcoidosis. Curr Neuropharmacol 2011;9(3):429–436.
13. Weng J, Du Z, Zhang Y. CNS limited ANCA-associated vasculitis presenting as an isolated intraparenchymal mass. J Neuroimmunol 2022;364:577791.
14. Ascaso FJ, Rodriguez A, Cristóbal JA. Cranial hypertension as first manifestation of Behçet's disease: a case report. Doc Ophthalmol 2002;105(3):291–299.
15. Sedeta E, Ilerhunmwuwa NP, Hindu Pahlani R, et al. A diagnostic dilemma: a case of neurosarcoidosis without systemic sarcoidosis. Cureus 2023;15(8):e42844.
16. Sopeña B, Rivera A, Vázquez-Triñanes C, et al. Autoimmune manifestations of Kikuchi disease. Semin Arthritis Rheum 2012;41(6):900–906.
17. Sopeña B, Rivera A, Chamorro A, et al. Clinical association between Kikuchi's disease and systemic lupus erythematosus: a systematic literature review. Semin Arthritis Rheum 2017;47(1):46–52.
18. Kido H, Kano O, Hamai A, et al. Kikuchi-Fujimoto disease (histiocytic necrotizing lymphadenitis) with atypical encephalitis and painful testitis: a case report. BMC Neurol 2017;17(1):22.
19. Jasti DB, Naveen Prasad SV, Naveen T, et al. Kikuchi-Fujimoto disease presenting as brainstem encephalitis with secondary blepharospasm. J Neurosci Rural Pract 2016;7(1):157–160.
20. Shafqat S, Memon SB, Hyder S, et al. Brainstem encephalitis with Kikuchi-Fujimoto disease. J Coll Physicians Surg Pak 2003;13(11):663–664.
21. Guéguen A, Sené T, Maillart E, et al. Encephalitis and CSF increased level of interferon-α in Kikuchi–Fujimoto disease. BMJ Case Rep 2012;2012:bcr0120125579.
22. Byun JH, Park SE, Nam SO, et al. Three children of meningoencephalitis with Kikuchi necrotizing lymphadenitis. Brain Dev 2018;40(3):251–255.
23. Iwamoto N, Funahashi M, Shinohara K, et al. Two cases of Kikuchi disease presenting with aseptic meningitis and encephalitis. Intern Med 2022;61(17):2687–2689.

24. Chen S, Liang XL, He S, et al. Encephalitis in Kikuchi-Fujimoto disease being immune-mediated. Neurol Sci. 2022;43(6):3983–3987.
25. Lay-Son L, Espinoza-Martínez L. Encephalitis associated to Kikuchi-Fujimoto's disease in a young woman: a case report. Neurol Asia 2011;16(1):81–83.
26. Gonçalves LF, Debelenko LV, Bhambhani KJ, et al. Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease) with CNS involvement in a child. Pediatr Radiol 2014;44(2):234–238.
27. Tan YJ, Chuah TY. Brainstem encephalitis: an unusual neurologic complication of Kikuchi-Fujimoto disease. Research Square Preprint posted online April 22, 2024. doi:10.21203/rs.3.rs-4254649/v1
28. Song Y, Liu S, Song L, et al. Case report: histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease) concurrent with aseptic meningitis. Front Neurol 2021;12:565387.

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1078–1084
DOI 10.1002/acr.25568

American College of Rheumatology
Empowering Rheumatology Professionals

Association Between Sleep Disturbance and Subsequent Pain Interference in Patients With Early Rheumatoid Arthritis

Burcu Aydemir,[1] Orit Schieir,[2] Marie-France Valois,[2] Lutfiyya N. Muhammad,[1] Jing Song,[1] Dorothy Dunlop,[1] Rowland W. Chang,[1] Susan J. Bartlett,[2] Louis Bessette,[3] Gilles Boire,[4] Glen Hazlewood,[5] Carol Hitchon,[6] Janet Pope,[7] Carter Thorne,[8] Diane Tin,[8] Vivian P. Bykerk,[9] and Yvonne C. Lee[1]

Objective. This study investigated whether sleep disturbance can predict the extent to which pain interferes with daily functioning in patients with early rheumatoid arthritis (RA).

Methods. Data were from adults with early RA (joint symptoms ≤12 months) enrolled in the Canadian Early Arthritis Cohort between 2016 and 2023. Participants underwent standardized clinical assessments and completed Patient-Reported Outcomes Measurement Information System measures at 0, 6, 12, 18, and 24 months to assess sleep disturbance (primary predictor) and pain interference (primary outcome). Linear mixed-effects models were used to estimate crude and adjusted (age, sex, body mass index, education, income, smoking status, comorbidities, disease activity, treatment, and depression) effects of sleep disturbance on pain interference over the 24-month study period. The analysis was lagged so that repeat measures of sleep disturbance at 0, 6, 12, and 18 months were evaluated as predictors of pain interference 6 months later at 6, 12, 18, and 24 months' follow-up.

Results. The analysis included 502 patients with early RA. At baseline, the sample was 68% female and 81% White; the mean age was 56 (SD 14) years, and the mean disease duration was 5.4 (SD 2.9) months. The unadjusted and adjusted linear mixed-effects models revealed a significant association between sleep disturbance and subsequent pain interference scores, indicating that worse sleep six months prior was associated with greater pain interference at the following six-month evaluation.

Conclusion. These findings underscore the importance of addressing sleep disturbances as part of pain management strategies soon after RA diagnosis. Identifying and targeting problematic sleep disturbances early on may help improve long-term pain outcomes.

INTRODUCTION

Pain and sleep disturbances have many debilitating effects on physical and mental functioning. In patients with rheumatoid arthritis (RA), pain is a common symptom and primary reason for seeking care.[1] In addition to pain, more than half of individuals with RA suffer from sleep disturbances.[1–5] These disturbances encompass challenges such as difficulty initiating sleep and recurrent nocturnal awakenings. The prevailing notion is that pain causes sleep disturbances,[4,6–9] but the interplay between sleep and pain is complex.

A growing consensus posits a reciprocal relationship between sleep disturbances and pain in the general population, and a few studies suggest that sleep disturbances can lead to

The Canadian Early Arthritis Cohort study was independently designed and implemented by the investigators. It has been financially supported through unrestricted research grants from Pfizer Canada, AbbVie Corporation, Hoffman La Roche Limited, Sandoz Biopharmaceuticals Canada, Fresenius Kabi Canada, Viatris Canada, Jamp Pharma (BIOJAMP), Celltrion Healthcare Canada, Amgen Canada, Janssen Canada, UCB Canada, Bristol-Myers Squibb Canada, Medexus Pharmaceuticals, Sanofi Genzyme, Eli Lilly Canada, Merck Canada, Gilead Sciences Canada, and Organon Canada. Dr Aydemir's work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH (grant T32-AR-007611) and National Center for Advancing Translational Sciences, NIH (grant K12-TR-005104). Dr Muhammad, Ms. Song, and Drs Dunlop and Chang's work was supported by NIAMS, NIH (grant P30-AR-072579). Dr Lee's work was supported by NIAMS, NIH (grants R01-AR-064850 and K24-AR-080840).

[1]Burcu Aydemir, PhD, Lutfiyya N. Muhammad, PhD, MPH, Jing Song, MS, Dorothy Dunlop, PhD, Rowland W. Chang, MD, MPH, Yvonne C. Lee, MD, MMSc: Northwestern University Feinberg School of Medicine, Chicago, Illinois; [2]Orit Schieir, PhD, Marie-France Valois, MSc, Susan J. Bartlett, PhD: McGill University, Montreal, Quebec, Canada; [3]Louis Bessette, MD, MSc: Universite Laval, Quebec City, Quebec, Canada; [4]Gilles Boire, MD, MSc: Universite de Sherbrooke, Sherbrooke, Quebec, Canada; [5]Glen Hazlewood, MD, PhD: University of Calgary, Calgary, Alberta, Canada; [6]Carol Hitchon, MD, MSc: University of Manitoba, Winnipeg, Manitoba, Canada; [7]Janet Pope, MD, MPH: Western University Schulich School of Dentistry and Medicine, London,

SIGNIFICANCE & INNOVATIONS

- The focus on early rheumatoid arthritis (RA) is significant because the first few years after symptom onset may represent a critical window of opportunity to alter the long-term consequences of disease (eg, chronic pain and disability).
- The choice of pain interference as the primary outcome is significant because previous studies demonstrated that among patients with RA, the effect of pain on daily function is likely higher than would be expected based on assessments of pain intensity alone.
- Study results support addressing problematic sleep patterns following RA symptom onset to enhance long-term pain management in patients with RA.

heightened pain severity in established RA cohorts.[10–12] One experimental study demonstrated that one night of restricted sleep led to increases in pain severity and the number of painful joints the next day.[12] Our research group also reported cross-sectional associations between sleep disturbances and pain sensitivity,[10] as well as longitudinal associations between sleep disturbances and pain intensity.[12] To date, no studies have investigated the longitudinal association between sleep disturbances and subsequent long-term consequences of pain (eg, pain interference) in patients with early RA.

Pain interference is an important construct that describes the consequences of pain and how it interferes with important aspects of life (eg, social, mental, and physical functioning). Patients have identified it as pivotal to their quality of life.[13] Pain interference is distinct from pain intensity, which describes the magnitude of perceived pain experienced. Among patients with RA, median pain interference scores on a standardized common metric (Patient-Reported Outcomes Measurement Information System [PROMIS]) were 10 points higher than median pain intensity scores.[14] These results indicate that pain has a greater impact on daily function than would be expected from assessments of pain intensity scores alone. Because pain interference incorporates both pain and function, it may be an important outcome to assess longitudinally. It is possible that sleep disturbances may drive changes in pain interference; however, this directional impact is yet to be explored.

The aim of this study was to estimate to what extent self-reported sleep disturbance may be associated with pain interference six months later in patients with early RA. We hypothesized that greater self-reported sleep disturbance would be associated with greater subsequent pain interference. Understanding the relationship between sleep disturbances early in the disease process and long-term consequences of pain may provide us with better opportunities for prevention and treatment (eg, cognitive behavioral therapy, light therapy).

PATIENTS AND METHODS

This study analyzed data collected at 0 (baseline), 6, 12, 18, and 24 months from adults with early RA enrolled in the Canadian Early Arthritis Cohort (CATCH) between January 2016 and March 2023. Briefly, CATCH is a multicenter observational prospective cohort study of adults diagnosed with early RA (joint symptoms ≤12 months) by a rheumatologist from academic and community clinics across Canada. Participants are eligible for enrollment if they are >18 years old, have joint symptoms for ≥6 weeks and ≤12 months, and have two or more swollen joints or one swollen metacarpophalangeal or proximal interphalangeal joint, with one of the following features: rheumatoid factor (RF) ≥20 IU, positive test for anti–citrullinated protein antibodies (ACPAs), morning stiffness ≥45 minutes, response to nonsteroidal anti-inflammatory drug treatment, or a painful metatarsophalangeal joint squeeze test. Participants included in the present analysis had to have PROMIS sleep disturbance and pain interference scores at baseline, and they also had to contribute at least one pair of sleep disturbance and pain interference measures six months apart (ie, baseline sleep disturbance and six-month pain interference; Figure 1). Participants were excluded or withdrawn (if identified after inclusion) for the following diagnoses: psoriatic arthritis or infectious, crystal-induced, or connective tissue diseases. Further details of the CATCH study and protocols have been reported previously.[15] Approval from each participating site's institutional review board was obtained. All participants enrolled in the study provided written informed consent.

Patient-reported outcomes measures. Participants completed the PROMIS-29 v2.0 profile measure to assess sleep disturbance (primary exposure) and pain interference (primary outcome) over the past seven days.[16] The sleep disturbance domain includes questions about perceptions of sleep quality, depth, and restoration. The pain interference domain measures the extent to which pain interferes with physical, mental, and social functioning. All PROMIS raw scores are converted to a mean T-score of 50 with a SD of 10 based on the general US population.[17] Higher scores for sleep disturbance and pain

Ontario, Canada; [8]Carter Thorne, MD, Diane Tin, BScPhm: Southlake Regional Health Centre, Newmarket, Ontario, Canada; [9]Vivian P. Bykerk, MD: Hospital for Special Surgery, New York, New York.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25568).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25568.

Address correspondence via email to Burcu Aydemir, PhD, burcu.aydemir@northwestern.edu.

Submitted for publication June 6, 2024; accepted in revised form April 29, 2025.

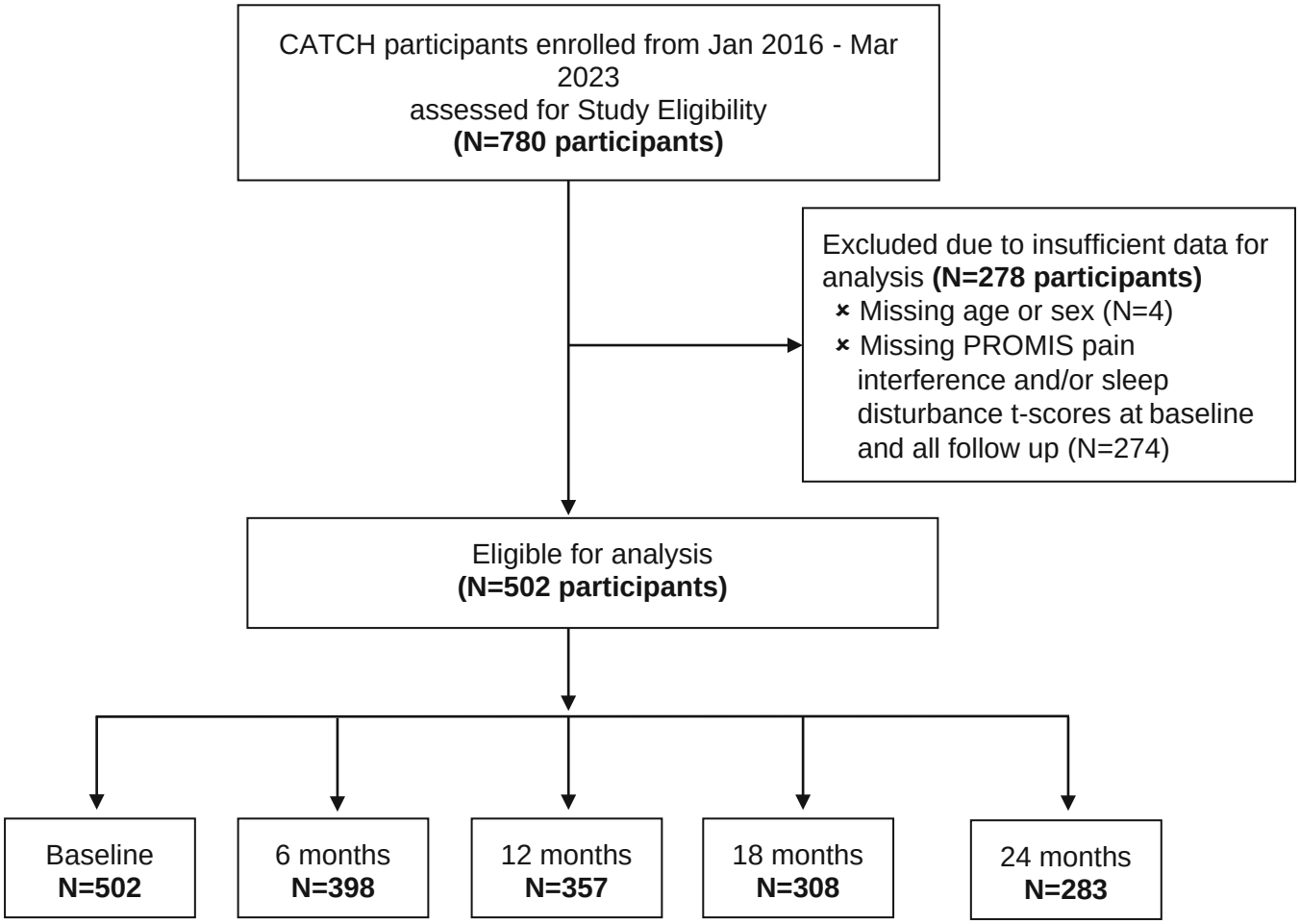

Figure 1. Flowchart of participants fulfilling eligibility criteria with PROMIS data available at each time point. CATCH, Canadian Early Arthritis Cohort; PROMIS, Patient-Reported Outcomes Measurement Information System.

interference represent more of the concept being measured (eg, greater disturbance and interference).

Demographic and clinical characteristics. Participants completed baseline study case report forms, which included self-reported age, sex, income, smoking status, height and weight (used to calculate body mass index [BMI]), education, and self-reported physician-diagnosed health conditions (used to calculate the Rheumatic Disease Comorbidity Index [RDCI]).[18] Tender and swollen 28-joint counts and medication use were ascertained by the rheumatology health care team. Standard laboratory tests were performed to assess ACPA, RF, and C-reactive protein (CRP) levels and/or the erythrocyte sedimentation rate.

Statistical analysis. Descriptive statistics were used to summarize baseline sample characteristics. To examine the temporal relationship between sleep disturbance and pain interference in our longitudinal analysis, we used linear mixed-effects models with random intercepts for participants and a compound symmetry covariance structure. Specifically, we estimated the effects of lagged measures of sleep disturbance at 0, 6, 12, and 18 months on pain interference 6 months later at 6, 12, 18, and 24 months. This modeling approach was chosen to account for the hierarchical structure of the data, repeated measurements, and covariance structure among participants. Model fit was assessed using diagnostic metrics, and assumptions of normality and homoscedasticity of residuals were checked visually using diagnostic plots. Mixed-effects models leverage all available data, averaging across time points without requiring complete data for each participant. As a result, no participant was dropped from the analysis, and only observed data from available study visits were included in the model.

Multivariable linear mixed models were adjusted for baseline measures of age, sex, BMI, education, income, smoking status, RDCI, and time-varying (updated) measures of swollen joint count, CRP level, steroid use, and disease-modifying antirheumatic drug (DMARD) treatment (methotrexate and advanced therapy). We adjusted for both CRP level and swollen joint count as opposed to a composite measure of disease

activity because composite measures include tender joint count and patient global assessment, which can be heavily influenced by pain. These covariates were treated as fixed effects in the models. The strength of associations was described using regression coefficients (β) with 95% confidence intervals (CIs).

A supplemental model of the adjusted analysis was performed with the PROMIS sleep disturbance score treated as a categorical term (none < 55, mild = 55–59, moderate = 60–69, or severe disturbance ≥ 70). To address the possible influence of depression, we conducted a sensitivity analysis to examine whether the association between sleep disturbances and subsequent pain interference remained robust after accounting for symptoms of depression as a lagged covariate. Symptoms of depression over the past seven days were assessed as part of the depression domain included in the PROMIS-29. To account for potential temporal confounding, we also performed a sensitivity analysis adjusting for time-varying concurrent baseline pain interference, defined as pain interference assessed at the same time as the time-varying exposure (sleep disturbance). All data analyses were performed using SAS (version 9.4; SAS Institute, Inc).

RESULTS

Characteristics of the study sample. The analysis included 502 participants who contributed a total of 1,153 study visits/time points to the unadjusted modeling and 844 study visits/time points to the adjusted modeling (Table 1). At baseline, the mean ± SD age was 56 ± 14 years, the mean ± SD disease duration was 5.4 ± 2.9 months, and the mean ± SD Clinical Disease Activity Index score was 25.8 ± 13.7; 68% were female, 81% identified as White, 73% were seropositive (RF/ACPA), and 76% were treated with methotrexate. The mean ± SD T-score for PROMIS pain interference was 60.4 ± 8.6, and the mean ± SD T-score for PROMIS sleep disturbance was 53.5 ± 8.8 at baseline. At baseline, 80% of the sample had T-scores ≥55 (mild to severe) for pain interference. Forty-four percent had T-scores ≥55 (mild to severe) for sleep disturbance.

Unadjusted effects of sleep disturbance on pain interference. Participants who reported higher sleep disturbance subsequently reported greater pain interference at the following six-month evaluation (β 0.76, 95% CI 0.49–1.02). Specifically, for every 5-unit increase in sleep disturbance T-score, there was a corresponding 0.76-unit increase in pain disturbance T-score six months later.

Adjusted effects of sleep disturbance on pain interference. Higher sleep disturbance was associated with greater pain interference at the subsequent six-month evaluation, even after adjusting for age, sex, BMI, education, income, smoking status, RDCI, swollen joint count, CRP level, steroid use, and DMARD therapy (adjusted β 0.76, 95% CI 0.44–1.09; Table 2). Specifically, for every 5-unit increase in sleep disturbance T-score, there was a 0.76-unit increase in pain disturbance T-score six months later. In the supplemental model using categorical sleep disturbance, the results remained consistent, indicating that higher levels of sleep disturbance (moderate to severe) were associated with greater pain interference (Supplementary Table 1). In the sensitivity analysis adjusting the multivariable model by time-varying symptoms of depression, the direction and significance of the effect of sleep disturbance on subsequent pain interference remained unchanged (Supplementary Table 2). Similarly, in the sensitivity analysis adjusting for time-varying concurrent

Table 1. Baseline demographic and clinical characteristics of early RA sample (N = 502)*

Characteristic	Value
Demographic	
Age, mean (SD), y	56 (14)
Female, %	68
White, %	81
BMI ever ≥30, %[a]	32
Postsecondary education, %	61
Income ≤$50,000, %[a]	37
Current smoker, %	15
RDCI, mean (SD)	1.4 (1.4)
RA disease characteristics	
Disease duration, mean (SD), mo	5.4 (2.9)
Meet 1987 ARA classification criteria[b] for RA or 2010 ACR/EULAR RA classification criteria,[c] %	77
Clinical Disease Activity Index, mean (SD)	25.8 (13.7)
Seropositivity (RF/ACPA), %[a]	73
CRP, median (IQR), mg/L	6.9 (2.9–18.5)
TJC-28, median (IQR)	7 (3–12)
SJC-28, median (IQR)	6 (3–10)
Patient global assessment score, mean (SD)	4.8 (2.8)
Assessor global assessment score, mean (SD)	5.2 (2.5)
Treatment, frequency, n (%)	
Oral steroids	156 (31)
MTX	384 (76)
Non-MTX DMARDs	281 (56)
Advanced therapy	2 (0)
TNFi	2 (0)
JAKi	0 (0)
Other MOA (all other biologics/biosimilars)	0 (0)
PROMIS T-score, mean (SD)	
Sleep disturbance	53.5 (8.8)
Pain interference	60.4 (8.6)

* ACPA, anti–citrullinated protein antibody; ACR, American College of Rheumatology; ARA, American Rheumatism Association; BMI, body mass index; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; EULAR, European League of Rheumatologists; IQR, interquartile range; JAKi, JAK inhibitors; MOA, mechanism of action; MTX, methotrexate; PROMIS, Patient-Reported Outcomes Measurement Information System; RA, rheumatoid arthritis; RDCI, Rheumatic Disease Comorbidity Index; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; TNFi, tumor necrosis factor inhibitors.
[a] Percentage of nonmissing.
[b] Arnett et al.[21]
[c] Aletaha et al.[22]

Table 2. Linear mixed-effects regression models estimating association of PROMIS sleep disturbance with pain interference over 2 y of follow-up in patients with early RA (N = 502)*

Variables	Unadjusted model[a]		Adjusted multivariable model[b,c]	
	Regression coefficient	95% CI	Regression coefficient	95% CI
Intercept	45.32	42.20 to 48.43	39.26	34.83 to 43.69
Time (mo)	−0.03	−0.09 to 0.02	−0.004	−0.09 to 0.08
Baseline time invariant variables				
Age (y)[d]	–	–	−0.01	−0.07 to 0.05
Female sex	–	–	**3.27**	**1.64 to 4.90**
Obese BMI (≥30)	–	–	**2.00**	**0.11 to 3.89**
Postsecondary education	–	–	−0.45	−2.11 to 1.20
Income >$50,000	–	–	0.74	−1.14 to 2.61
Smoking, current vs past or never	–	–	**3.25**	**1.13 to 5.38**
Comorbidity score (0–9)	–	–	**1.24**	**0.69 to 1.78**
Time-varying variables (lagged by 6 mo)				
Sleep disturbance T score[e]	**0.76**	**0.49 to 1.02**	**0.76**	**0.44 to 1.09**
SJC-28	–	–	0.00	−0.12 to 0.12
CRP (mg/L)	–	–	0.04	0.00 to 0.08
RA treatment				
Oral steroids	–	–	1.25	−0.28 to 2.77
MTX	–	–	−0.71	−2.15 to 0.72
Advanced therapy	–	–	−0.73	−2.85 to 1.38

* Bold values indicate significant associations. BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; MTX, methotrexate; PROMIS, Patient-Reported Outcomes Measurement Information System; RA, rheumatoid arthritis; SJC, swollen joint count.
[a] 1,153 visits included in unadjusted model.
[b] Model adjusted for age (centered at the mean), sex, BMI, education, income, current smoking status, comorbidity index, as well as SJC-28, CRP, MTX use, oral steroids use, and advanced therapy use, which were lagged from the previous visit.
[c] 844 visits included in adjusted model.
[d] Per 10-y increase.
[e] Per 5-unit increase in PROMIS sleep disturbance T-score.

baseline pain interference, results remained consistent in direction and statistically significant (Supplementary Table 3).

DISCUSSION

This study estimated adjusted associations between sleep disturbance and subsequent pain interference six months later among a large sample of patients with early RA receiving routine care in rheumatology practices across Canada. We found modest longitudinal associations between sleep disturbance and subsequent pain interference in both unadjusted and adjusted analyses. Our findings indicated that in patients with early RA, more disturbed sleep was associated with greater pain interference six months later. This association persisted even after accounting for potential confounders, such as steroid use, DMARD therapy, and other demographic and clinical factors.

To our knowledge, this is the first study to examine the association of sleep disturbances on subsequent pain interference in patients with newly diagnosed (early) RA over 24 months. Although the overall effects observed were modest, the relationship between sleep disturbances and subsequent pain interference remained significant. Our findings align with prior reports in established RA cohorts, highlighting a significant association between sleep disturbances and various pain measures.[4,6,11,12] Collectively, these results suggest that sleep disturbances could play a role in both the onset and persistence of pain in RA. In addition, there is also prior evidence supporting the inverse relationship between sleep and pain in patients with early RA. A large population-based study investigated predictors of self-reported sleep measures among Swedish patients with RA with a disease duration of 1 to 12 years[9] and showed that problems with sleep increased with disease duration. Pain attributed to RA, assessed by a numeric rating scale, and functional impairment were the strongest predictors of reduced sleep quality. Although our study differs in terms of analysis, assessments, and follow-up periods, a reciprocal relationship likely exists between sleep problems and pain outcomes, whereby each influences the other in addition to influences from other factors over time.

A particularly noteworthy contribution of our study is the unique focus on the directional impact of sleep disturbances on pain interference, providing a novel and clinically meaningful perspective. Using a lagged repeated-measures design in an early RA cohort, we were able to capture within-person changes over time, offering a more robust understanding of how sleep disturbances may influence pain interference. This approach advances the understanding of the sleep-to-pain pathway and highlights the importance of considering temporal relationships in this context.

Importantly, our outcome of interest (pain interference) is distinct from pain intensity, which has been the most used pain assessment among previous studies. Pain interference encompasses the extent to which pain disrupts daily activities and quality of life, reflecting a broader and more functional dimension of the pain experience. Although the pathways linking sleep disturbances and pain interference likely involve pain intensity, other factors may also contribute, warranting further exploration in future research.

One potential factor linking these constructs is depression. In cross-sectional investigations, depression has been significantly associated with sleep disturbances in RA cohorts.[3,6,7] Our sensitivity analysis accounting for time-varying symptoms of depression demonstrated similar findings as the main model, though there was a slight decrease in the β coefficient for sleep disturbance. This observation suggests that depressive symptoms may partially explain the relationship between sleep disturbances and subsequent pain interference. In other words, depressive symptoms may contribute to, but do not fully account for, the impact of sleep disturbances on pain interference.

Dysregulated central pain processing may be another mechanism linking sleep disturbance with pain interference. In a cross-sectional analysis of 58 women with RA and 54 matched controls, sleep disturbances partially mediated the relationship between RA and abnormalities in descending pain inhibition.[10] In other words, patients with RA may have abnormalities in descending pain inhibition, at least in part, because they are not sleeping well. In a longitudinal analysis in a different cohort, sleep disturbance predicted higher pain intensity. This relationship was mediated by enhanced pain sensitivity and ascending pain facilitation.[11] Together, these findings suggest that underlying abnormalities in pain processing may be another potential link between sleep disturbances and pain interference.

Inflammation may also play an important role in the association between sleep disturbance and pain. Studies have demonstrated that poor sleep could lead to elevated levels of proinflammatory cytokines, which may exacerbate pain.[19,20] This inflammatory response could serve as a biologic mediator between sleep disturbance and heightened pain interference. This potential pathway warrants further exploration of inflammatory biomarkers in future research. More longitudinal studies in patients with early RA not only investigating the underlying causes of sleep disturbances but also examining how confounding processes may mediate the relationship between sleep disturbance and pain outcomes are needed to provide a more comprehensive understanding of the sleep–pain connection.

Several noteworthy implications emerge from our study. First, our findings support the importance of monitoring and addressing sleep disturbances in the comprehensive management of RA. Early intervention might be particularly crucial to mitigate the development of persistent sleep problems and adverse pain outcomes. Additionally, various self-report instruments are available for assessing pain in RA, and our choice to focus on pain interference is motivated by its reflection of pain consequences on daily functioning, encapsulating both pain and overall function. Given the variable responses to pain among patients, with some adapting to limitations and others avoiding activities exacerbating pain, measures such as PROMIS pain interference may offer a valuable supplement in research and clinical care. Future studies should consider incorporating patient-reported sleep disturbances and pain interference because these measures may provide essential insights into tracking improvements in RA management.

It is important to acknowledge that although the effect size for the relationship between sleep disturbance and pain interference was statistically significant, the magnitude of effect was modest. However, our results were consistent across several sensitivity analyses, suggesting that these relationships are real. Although this effect may not have a direct clinical impact, we still believe it is a valuable contribution to understanding the nuanced relationship between sleep disturbance and pain interference. These findings provide support for designing and implementing additional studies to further probe these relationships. There may be subgroups of patients in whom these relationships are stronger. It is also possible that our patient-reported measure of sleep disturbance was not nuanced enough to capture specific types of sleep disturbance that may have a greater impact on pain interference (eg, sleep duration or fragmentation, sleep efficiency, circadian rhythm disorders). Further research is needed to identify (1) specific subgroups for whom a sleep-targeted intervention may be particularly beneficial and (2) specific types of intervention (eg, sleep restriction, cognitive behavioral therapy, light therapy) that may be particularly effective for minimizing pain interference.

A major strength of our study includes the real-world sample of patients with early RA. Additionally, the longitudinal design with lagged repeated measurements allowed us to explore the relationship between sleep disturbance and pain interference in the early stages of the disease over the first 24 months following diagnosis. There are a few limitations to our findings. First, we used patient-reported assessments for sleep and pain interference to address our hypothesis. Reliance on patient-reported data introduces potential bias, as certain participants may consistently report more symptoms or experiences, which could influence observed associations. Results may vary across different forms of assessments, such as objectively measured sleep parameters (eg, actigraphy, polysomnography). However, there are strengths to using patient-reported measurements. These measures reflect the patient experience and are feasible to implement, requiring minimal effort to administer and score. Additionally, this study was not set up to examine impact closer in time. Examining the relationship between sleep disturbances and pain interference from day to day or over shorter time frames (eg, three months) may yield different findings. Similarly, we were unable to assess

the impact of duration of sleep disturbances, such that persistent or temporary sleep problems may impact pain outcomes differently. Lastly, although we accounted for several important confounders, it is unlikely we were able to eliminate all potential sources of biases from unmeasured confounding. Further investigations are warranted to examine how other factors may contribute to or potentially mediate the relationship between sleep disturbances and pain interference.

In conclusion, our study reveals a consistent and significant association between heightened sleep disturbance and the subsequent escalation of pain interference over time. These results highlight the critical role of addressing sleep disruptions as an integral component of pain management strategies, particularly in the early stages following RA diagnosis. Identification and early intervention in problematic sleep patterns may contribute to enhanced long-term pain outcomes.

ACKNOWLEDGMENT

The authors would like to thank Dr Edward Keystone for his contributions to the CATCH study.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Aydemir confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ROLE OF THE STUDY SPONSOR

Pfizer Canada, AbbVie, Hoffman-La Roche, Sandoz Biopharmaceuticals Canada, Fresenius Kabi Canada, Viatris Canada, Jamp Pharma, Celltrion Healthcare Canada, Amgen Canada, Janssen Canada, UCB Canada, Bristol-Myers Squibb Canada, Medexus Pharmaceuticals, Sanofi Genzyme, Eli Lilly Canada, Merck Canada, Gilead Sciences Canada, and Organon Canada played no part in planning or conducting the study. Publication of this article was not contingent upon the approval of these funding sources.

REFERENCES

1. Heiberg T, Finset A, Uhlig T, et al. Seven year changes in health status and priorities for improvement of health in patients with rheumatoid arthritis. Ann Rheum Dis 2005;64(2):191–195.
2. Katz P, Pedro S, Michaud K. Sleep disorders among individuals with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2023;75(6):1250–1260.
3. Hughes M, Chalk A, Sharma P, et al. A cross-sectional study of sleep and depression in a rheumatoid arthritis population. Clin Rheumatol 2021;40(4):1299–1305.
4. Grabovac I, Haider S, Berner C, et al. Sleep quality in patients with rheumatoid arthritis and associations with pain, disability, disease duration, and activity. J Clin Med 2018;7(10):336.
5. Drewes AM, Jennum P, Andreasen A, et al. Self-reported sleep disturbances and daytime complaints in women with fibromyalgia and rheumatoid arthritis. J Musculoskeletal Pain 1994;2(4):15–31.
6. Nicassio PM, Ormseth SR, Kay M, et al. The contribution of pain and depression to self-reported sleep disturbance in patients with rheumatoid arthritis. Pain 2012;153(1):107–112.
7. Taylor-Gjevre RM, Gjevre JA, Nair B, et al. Components of sleep quality and sleep fragmentation in rheumatoid arthritis and osteoarthritis. Musculoskeletal Care 2011;9(3):152–159.
8. Westhovens R, Van der Elst K, Matthys A, et al. Sleep problems in patients with rheumatoid arthritis. J Rheumatol 2014;41(1):31–40.
9. Lyne L, Åkerstedt T, Alfredsson L, et al. Sleep problems in rheumatoid arthritis over 12 years from diagnosis: results from the Swedish EIRA study. RMD Open 2022;8(1):e001800.
10. Lee YC, Lu B, Edwards RR, et al. The role of sleep problems in central pain processing in rheumatoid arthritis. Arthritis Rheum 2013;65(1):59–68.
11. Song J, Muhammad LN, Neogi T, et al. Pain sensitization as a potential mediator of the relationship between sleep disturbance and subsequent pain in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2023;75(4):778–784.
12. Irwin MR, Olmstead R, Carrillo C, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. Sleep 2012;35(4):537–543.
13. Bacalao EJ, Greene GJ, Beaumont JL, et al. Standardizing and personalizing the treat to target (T2T) approach for rheumatoid arthritis using the Patient-Reported Outcomes Measurement Information System (PROMIS): baseline findings on patient-centered treatment priorities. Clin Rheumatol 2017;36(8):1729–1736.
14. Bartlett SJ, Orbai AM, Duncan T, et al. Reliability and validity of selected PROMIS measures in people with rheumatoid arthritis. PLoS One 2015;10(9):e0138543.
15. Bykerk VP, Jamal S, Boire G, et al. The Canadian Early Arthritis Cohort (CATCH): patients with new-onset synovitis meeting the 2010 ACR/EULAR classification criteria but not the 1987 ACR classification criteria present with less severe disease activity. J Rheumatol 2012;39(11):2071–2080.
16. Katz P, Pedro S, Michaud K. Performance of the Patient-Reported Outcomes Measurement Information System 29-item profile in rheumatoid arthritis, osteoarthritis, fibromyalgia, and systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2017;69(9):1312–1321.
17. PROMIS reference populations. Accessed January 7, 2024. https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/reference-populations
18. England BR, Sayles H, Mikuls TR, et al. Validation of the Rheumatic Disease Comorbidity Index. Arthritis Care Res (Hoboken) 2015;67(6):865–872.
19. Irwin MR, Straub RH, Smith MT. Heat of the night: sleep disturbance activates inflammatory mechanisms and induces pain in rheumatoid arthritis. Nat Rev Rheumatol 2023;19(9):545–559.
20. Irwin MR, Olmstead R, Bjurstrom MF, et al. Sleep disruption and activation of cellular inflammation mediate heightened pain sensitivity: a randomized clinical trial. Pain 2023;164(5):1128–1137.
21. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315–324.
22. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis and Rheum 2010;62(9):2569–2581.

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1085–1094
DOI 10.1002/acr.25543

American College of Rheumatology
Empowering Rheumatology Professionals

Perceived Stress and Prediction of Worse Patient-Reported Outcomes in a Rheumatoid Arthritis Cohort

Sarah L. Patterson, Joonsuk Park, Wendy Hartogensis, and Patricia Katz

Objective. Studies have suggested a potential link among traumatic experiences, psychologic stress, and autoimmunity, but the impact of stress on disease activity and symptom severity in rheumatoid arthritis (RA) remains unclear. We examined whether perceived stress independently associates with worse RA disease outcomes at subsequent visits over 18 months of follow-up.

Methods. Participants were enrolled in a longitudinal RA cohort with study assessments every six months. We measured stress via the four-item Perceived Stress Scale and the following disease outcomes: patient-reported disease activity (Rheumatoid Arthritis Disease Activity Index), pain (Patient-Reported Outcome Measurement Information System [PROMIS] Pain Interference), fatigue (PROMIS Fatigue), and physical function (PROMIS Physical Function). Time-lagged linear mixed effects models evaluated longitudinal associations of stress with all four outcomes at the subsequent time point while controlling for potential confounders.

Results. The sample (N = 133) was 88% female, 45% White, 35% Hispanic, 9% African American, and 6% Asian American; the mean ± SD age was 58 ± 13 years. In adjusted time-lagged longitudinal analyses, stress independently associated with greater self-reported disease activity (β = 0.11, 95% confidence interval [CI] 0.03–0.19), more pain (β = 0.61, 95% CI 0.29–0.94), more fatigue (β = 0.71, 95% CI 0.32–1.11), and lower physical function (β = –0.33, 95% CI –0.59 to –0.06). The effect size represented clinically significant differences for pain, fatigue, and physical function, but not disease activity.

Conclusion. Among a longitudinal RA cohort, those with greater perceived stress had worse pain, greater fatigue, and lower physical function at follow-up. Findings underscore the need to integrate stress resilience interventions and programs that augment psychosocial support in health care systems that serve people living with RA.

INTRODUCTION

Rheumatoid arthritis (RA) is characterized by joint and systemic inflammation and is frequently complicated by chronic pain, functional limitations, and premature cardiovascular disease.[1] It is also characterized by periods of disease exacerbation (ie, flares), but factors responsible for these fluctuations in disease activity remain poorly understood.[2] For example, there are known triggers for RA flares, such as infections and tapering immunosuppressive treatments, but affected individuals commonly experience disease flares without a clear preceding trigger. Furthermore, even among those who achieve low disease activity by physician assessment, many continue to experience negative disease impacts such as persistent pain, fatigue, and functional disability.[3,4] Therefore, there is a critical need to understand risk factors and predictors of changes in disease activity, symptom severity, and physical function among people living with RA.

Previous studies have found independent associations among perceived stress, stress-related disorders such as posttraumatic stress disorder (PTSD), and increased risk of incident inflammatory arthritis,[5–7] suggesting a potential role for psychologic stress in the etiopathogenesis of RA. In a study of 80 individuals with a confirmed diagnosis of RA followed for up to six months, Evers et al[8] found that worrying associated with higher patient-reported disease activity, swollen joint count, and pain

Supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant R01-AR-072040). Dr Patterson's work was supported by the National Center for Complementary and Integrative Health (grant K23-AT-011768-01).

Sarah L. Patterson, MD, Joonsuk Park, MSc, Wendy Hartogensis, PhD, Patricia Katz, PhD: University of California, San Francisco.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25543).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25543.

Address correspondence via email to Patricia Katz, PhD, at patti.katz@ucsf.edu.

Submitted for publication May 31, 2024; accepted in revised form March 21, 2025.

SIGNIFICANCE & INNOVATIONS

- This is the largest study to examine the longitudinal association between psychologic stress and disease outcomes in rheumatoid arthritis (RA).
- After adjusting for potential confounding factors, patients with RA with greater perceived stress had significantly worse pain, greater fatigue, and lower physical function at subsequent visits compared to those with lower stress.
- Interventions to increase stress resilience and accessible psychosocial support services for people living with RA may improve both psychologic distress and disease outcomes in this high-risk group.

one month later, whereas exposure to daily stressors associated with worse subsequent fatigue. That study was limited by a relatively short follow-up period and the omission of assessments to understand participants' appraisals of stressful experiences. More work is needed to determine whether negative perceptions of stressful experiences confer an increased risk for worse RA outcomes over an extended period, as well as identify resources that may improve the ability to manage stress,[9] both of which will directly inform whether stress reduction is an appropriate target for improving outcomes in people living with this disease.

In this study, we investigated the relationship between perceived stress and subsequent patient-reported outcomes among people with RA. Specifically, we conducted a longitudinal time-lagged observational cohort study of individuals with RA over 18 months of follow-up to determine the independent association of perceived stress with patient-reported disease activity, pain, fatigue, and physical function. In a secondary exploratory analysis, we examined associations of exposure to stressful life events and stress resilience with each of the aforementioned disease outcomes.

PATIENTS AND METHODS

Study design and participants. Participants were involved in a prospective longitudinal cohort study of sleep disorders in RA (RAZZ). Briefly, during 2017 through 2022, participants were recruited from rheumatology clinics in the San Francisco Bay Area and from a database of individuals with RA who had participated in previous research and had consented to being contacted about subsequent studies. Inclusion criteria were a diagnosis of RA by a board-certified rheumatologist, fluent in English or Spanish, not currently pregnant, and not currently being treated for obstructive sleep apnea.

Participants completed assessments every 6 months for up to 18 months. Initially, the study visits were conducted in person, however, the study transitioned to remote data collection in 2020 during the COVID-19 pandemic. During each study assessment period, participants completed an interview with a trained research coordinator—either in person before March 2020 or via telephone after March 2020—that included medical history, current medication use, smoking, perceived psychologic stress, RA disease activity, and RA symptoms. The study was approved by the University of California, San Francisco Institute Review Board, and all participants provided informed consent.

Outcome measures. The first outcome variable we evaluated was patient-reported disease activity, measured using the Rheumatoid Arthritis Disease Activity Index (RADAI). The RADAI has been validated and shown to correlate with other measures of RA disease activity, including the Disease Activity Score in 28 joints (DAS28).[10,11] It includes five items that address current and past global disease activity, pain, morning stiffness, and a joint count for which respondents rate the pain severity in 16 different joints or groups of joints. The composite score has a score range of 0 to 10, and cutoffs for low, moderate, and high disease activity are <2.2, ≥2.2 to ≤4.9, and >4.9, respectively. The estimated minimally important difference (MID) for the RADAI is 1 to 1.4 points.[12]

Other outcome variables were areas of unmet need commonly reported by individuals with RA, specifically pain, fatigue, and physical function, measured via the Patient-Reported Outcome Measurement Information System (PROMIS) version 1.1 Pain Interference 4a scale, PROMIS version 1.0 Fatigue 4a scale, and PROMIS version 2.0 10-item Physical Function 10a scale, respectively.[13] Higher Pain Interference and Fatigue scores indicate greater pain and fatigue, respectively; higher Physical Function scores reflect better functional status. PROMIS scales were converted to T scores with a population mean ± SD of 50 ± 10, using PROMIS scoring tables. Previous research to characterize the MIDs for these three PROMIS instruments among people with rheumatic diseases have estimated the MIDs for each scale to be approximately two points.[14–17]

Independent variables. The primary predictor variable was perceived stress, whereas secondary predictor variables included exposure to stressful life events and resilience to stress. Perceived stress was assessed using Cohen's abbreviated four-item Perceived Stress Scale (PSS), which yields scores ranging from 0 (low stress) to 16 (high stress). The PSS is a validated and widely used measure of the degree to which an individual perceives their life as uncontrollable, unpredictable, and overwhelming.[18] Although the PSS was developed in the 1980s, it continues to be the gold standard instrument for assessing perceived stress and has been correlated with biologic markers of stress and disease.[19–21] Because there is no standardized cutoff for PSS, the top quartile (PSS >10) and bottom quartile (PSS <7) of scores for the PSS at baseline were used to define high stress and low stress, respectively, whereas the two middle quartiles defined moderate stress.

Resilience to psychologic stress is commonly defined as the capacity of individuals to cope successfully with change, adversity, or risk.[22] We measured resilience at the baseline study visit using the Brief Resilient Coping Scale (BRCS), a four-item instrument that measures an individual's ability to cope with stress in ways that are flexible and effective.[23,24] Total scores range from 4 to 20, with low scores indicating low resilient coping and high scores indicating high resilient coping. We defined the high stress–resilience group by those with scores in the top quartile of BRCS scores (BRCS >14) and low or moderate resilience by the lower three quartiles of scores (BRCS ≤14).

Exposure to stressful life events was measured using the Stressful Life Events Screening Questionnaire (SLESQ), a validated 13-item self-reported measure that assesses lifetime exposure to 11 specific and 2 general categories of traumatic events.[25,26] Examples of such traumatic events include a life-threatening accident and physical or sexual abuse. The score is a summation of the number of stressful events the participant has experienced or witnessed. The SLESQ was added as a measure to the RAZZ study after enrollment had started and thus was collected on a subset of participants in the overall cohort (n = 63 with SLESQ data vs N = 133 for total cohort).

Other measures. Participants were asked about sociodemographic characteristics, including sex, age, race, educational attainment (categorized as ≥ or < a bachelor's degree), and income (categorized as household income ≤ or > 125% of the federal poverty level). The presence of autoantibodies to rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) was measured via enzyme-linked immunosorbent assay performed by Quest Diagnostics commercial laboratory or by chart review of medical records. Height and weight were assessed at the baseline visit by direct measurement during in-person visits and by patient report during remote study visits to calculate body mass index. Participants were also queried regarding smoking status; age of RA diagnosis; major comorbidities such as cardiovascular disease, diabetes mellitus, asthma, and cancer; and RA medication use, including glucocorticoids (GCs) and other immunomodulatory medications.

Statistical analysis. Differences in characteristics of participants in the high-stress (n = 33) versus low or moderate stress (n = 100) groups at baseline were assessed using *t*-tests or the Wilcoxon rank-sum test for continuous variables and the chi-square test or Fischer's exact test for categorical variables. SLESQ data were available on only a subset (47.3%) of patients in the overall cohort. Because missing SLESQ data were due to a protocol change unrelated to observed or (likely) unobserved data, missingness was considered at least missing at random and plausibly missing completely at random, and multiple imputation was not used.[27] To support this assumption, we also evaluated differences between patients with SLESQ data (n = 63) compared to the overall cohort (N = 133) using the same tests of association used to compare baseline characteristics by stress group.

Using data collected at baseline, we first analyzed cross-sectional associations of PSS to BRCS and SLESQ via Spearman correlation coefficients. Next, we used multivariable linear regression to compare disease outcomes among participants in the high-PSS group to the rest of the cohort adjusted for age, sex, race and ethnicity, educational attainment, body mass index, and disease duration. Covariates were selected a priori and parsimoniously based on factors likely to influence both the predictor variables (stress) and RA outcome variables, with the goal of adjusting for potential confounders without overfitting the models. We considered including income as a covariate in the regression models; however, we ultimately excluded it because it was collinear with educational attainment. We then conducted two additional cross-sectional multivariable regression models to investigate associations between (1) stress resilience (BRCS) and each of the disease outcomes at baseline and (2) stressful life events (SLESQ) and each of the disease outcomes at baseline. For the SLESQ analysis, we compared RA outcomes among patients with 0 to 3 stressful events to those with ≥4 events based on the distribution of SLESQ scores (above and below the mean score).

To test the robustness of cross-sectional findings, we conducted sensitivity analyses that represented derivations of the primary cross-sectional analyses. First, we repeated the PSS cross-sectional analyses using data from the subset of individuals who completed the SLESQ to compare the independent associations of perceived stress to RA outcomes versus stressful events to RA outcomes. Next, we reran each primary cross-sectional analysis while treating the stress variables (PSS, SLESQ, and BRCS) as continuous rather than categorical in case categorizing them had changed our findings.

For the longitudinal analysis, we first used linear mixed effects modeling to investigate the time-lagged association between perceived stress as a continuous variable and each of the four disease outcomes at the subsequent assessment period over 18 months of follow-up, adjusting for covariates (same used in cross-sectional models above). Next, to facilitate data interpretation and presentation, we generated adjusted means for each outcome variable across three levels of perceived stress: low stress (bottom quartile of PSS), moderate stress (two middle quartiles of PSS), and high stress (top quartile of PSS). We then conducted a longitudinal sensitivity analysis in which we included history of cardiovascular disease—defined as a diagnosis of coronary artery disease, myocardial infarction, and/or stroke—as a covariate along with the other covariates in the main regression model. Please see the supplementary materials (Supplementary Methods) for additional detail regarding longitudinal analysis methods.

Several procedures were used to ensure the integrity of each model. The normality of residuals was evaluated visually with boxplots, normal probability plots, and normal quantile plots; collinearity was assessed by calculating a variance inflation factor; and homoscedasticity was confirmed by plots of fitted values versus residuals, White's test, and Breusch-Pagan test. All analyses were performed using Stata 17 (StataCorp).

RESULTS

Sample characteristics. Sample characteristics (N = 133) are shown in Table 1. Mean RA disease duration was 16 years, and 73% of participants had seropositive RA based on positive testing for antibodies to either RF or CCP. At the time of the baseline assessment, 44% of participants reported current RA treatment with methotrexate and 55% were taking a biologic disease-modifying antirheumatic drug. Approximately one-third of the study sample was taking oral prednisone; however, only 8% were taking a daily prednisone dosage of ≥7.5 mg/day. The most common comorbidities were obesity and asthma (33% and 16% of the overall cohort, respectively).

Compared to the rest of the cohort, the patients in the high-stress group (n = 33) were similar in age, sex, race, ethnicity, educational attainment, income, RA disease duration, CCP positivity, immunomodulatory medication use, and comorbidities. The only statistically significant difference in sociodemographic and health factors between stress groups was that a greater proportion of the high-stress group was RF positive compared to those in the low or moderate stress group (78% vs 57%, respectively). The mean ± SD perceived stress scores among the entire cohort, high-stress group, and moderate or low stress group were 8.4 ± 3.3, 12.8 ± 2.5, and 7.0 ± 2.1, respectively. We noted a few statistically significant differences in the baseline characteristics of RAZZ participants who completed the SLESQ versus those who did not: those who completed the SLESQ were more likely to identify as non-Hispanic White (57% vs 45%) and have a college degree and less likely to have below poverty-level income, obesity, or history of smoking compared to those without SLESQ data (Supplementary Table 1).

Baseline-adjusted associations of high perceived stress with stress resilience, exposure to stressful events, and RA outcomes. As expected, perceived stress positively correlated with SLESQ (ρ = 0.28, P = 0.03) and negatively correlated with BRCS (ρ = –0.31, P = 0.0004). In cross-sectional multivariable regression analysis, high stress was associated with significantly greater pain interference, worse fatigue, and lower physical function, but not with patient-reported disease activity after adjustment (Table 2). The high-stress group had a mean adjusted Pain Interference score of 59.6 (95% confidence interval [CI] 56.8–62.4) compared to 54.5 (95% CI 52.9–56.0) among the rest of the cohort, and mean adjusted Fatigue score of 58.7 (95% CI 55.4–62.0) compared to 52.5 (95% CI 50.7–54.3) in the comparator group. The mean adjusted physical function scores were 40.2 (95% CI 37.6–42.9) in the high-stress group versus 43.4 (95% CI 41.9–45.0) in the low or moderate stress group. The independent relationships of perceived stress to RA outcomes were similar in the sensitivity analyses using data from the subset of participants who completed the SLESQ (Supplementary Table 2) and using the continuous form of the PSS (Supplementary Table 3).

Baseline-adjusted associations of exposure to stressful events with RA outcomes. We next examined the cross-sectional relationship of exposure to stressful life events (SLESQ) and RA outcomes adjusted for potential confounders, among the subset who completed the SLESQ. Comparing participants with ≥4 stressful events (n = 28) to those with ≤3 (n = 35), we found that those who had experienced more stressful life events had higher adjusted Pain Interference scores (mean 58.2 [95% CI 54.8–61.7] vs 50.6 [95% CI 47.5–53.6]) than those with less exposure (Table 3). There was also weak evidence of an association between greater stressful event exposure and higher fatigue (54.0 vs 48.1, P = 0.092) with a clinically meaningful difference in fatigue based on stress exposure, although that relationship did not meet the cutoff for statistical significance. There were no statistically significant associations between exposure to stressful events and RA disease activity or physical function. The independent relationships of stressful life events to RA outcomes were similar in the sensitivity analyses using the continuous SLESQ score (Supplementary Table 4).

Baseline-adjusted associations of stress resilience with RA outcomes. The final cross-sectional analysis examined the relationship of resilience to stress with each of the four outcomes after adjusting for the same covariates included in the other regression models. We found a statistically significant independent association between higher resilience and lower fatigue (Table 4). The adjusted mean PROMIS Fatigue score was 49.6 (95% CI 45.4–53.8) among participants with the highest resilience scores (top quartile) versus 55.0 (95% CI 53.2–56.9) among the rest of the cohort. There were no statistically significant differences in RA disease activity, pain interference, or physical function between the high-resilience and low- or moderate-resilience groups. The independent relationships of resilience to RA outcomes were similar in the sensitivity analysis that used the continuous form of BRCS (Supplementary Table 5).

Longitudinal associations of perceived stress with subsequent RA outcomes. In the final analysis, we used time-lagged mixed effects models to examine the relationship between perceived stress at the previous time point with RA outcomes at the subsequent time point after adjusting for the same baseline confounders. We found that higher perceived

Table 1. Baseline characteristics of patients with RA by perceived stress*

Characteristics	Overall (N = 133)	Perceived stress group[a]	
		Low or moderate stress (n = 100)	High stress (n = 33)
Socioeconomic factors			
Age, mean ± SD	58.0 ± 13.4	58.9 ± 13.4	55.2 ± 13.3
Female, n (%)	117 (88.0)	87 (87.0)	30 (90.9)
Race and ethnicity, n (%)			
Non-Hispanic White	60 (45.1)	48 (48.0)	12 (36.4)
Hispanic	46 (34.6)	31 (31.0)	15 (45.5)
African American	12 (9.0)	10 (10.0)	2 (6.1)
Asian American	8 (6.0)	5 (5.0)	3 (9.1)
Other or more than one race	7 (5.3)	6 (6.0)	1 (3.0)
Education less than college degree, n (%)	47 (35.3)	31 (31.0)	16 (48.5)
Below poverty-income, n (%)	19 (14.3)	14 (14.0)	5 (15.2)
RA-specific characteristics			
RA disease duration, mean ± SD	15.9 ± 12.7	16.4 ± 13.2	14.3 ± 11.0
RF positive, n (%)[b]	77 (61.6)	55 (56.7)	22 (78.6)
Anti-CCP antibody positive, n (%)[c]	79 (65.3)	60 (62.5)	19 (76.0)
Seropositive by RF and/or CCP, n (%)[d]	91 (73.4)	68 (70.8)	23 (82.1)
Treated with methotrexate, n (%)	58 (43.6)	45 (45.0)	13 (39.4)
Treated with TNFi, n (%)	54 (40.6)	44 (44.0)	10 (30.3)
Treated with any csDMARD, n (%)	86 (64.7)	66 (66.0)	20 (60.6)
Treated with any biologic DMARD, n (%)	73 (54.9)	57 (57.0)	16 (48.5)
No DMARD treatment, n (%)	21 (15.8)	13 (13.0)	8 (24.2)
No RA treatment (DMARD or steroid), n (%)	16 (12.0)	10 (10.0)	6 (18.2)
Current systemic glucocorticoid use, n (%)	44 (33.1)	35 (35.0)	9 (27.3)
Prednisone dose ≥7.5 mg/d, n (%)	11 (8.3)	10 (10.0)	1 (3.0)
Patient-reported outcomes, mean ± SD			
Disease activity by RADAI[e]	3.3 ± 2.0	3.2 ± 2.1	3.6 ± 1.6
Pain interference (PROMIS)	55.7 ± 8.8	54.3 ± 9.1	60.2 ± 5.9
Fatigue (PROMIS)	54.0 ± 9.9	52.5 ± 9.9	58.6 ± 8.1
Physical function (PROMIS)	42.7 ± 8.2	43.6 ± 8.4	39.8 ± 7.1
Comorbidities and health behaviors			
Cardiovascular disease, n (%)[f]	11 (8.3)	9 (9.0)	2 (6.1)
Diabetes mellitus, n (%)	14 (10.5)	11 (11.0)	3 (9.1)
Asthma, n (%)	21 (15.8)	15 (15.0)	6 (18.2)
History of malignancy, n (%)	11 (8.3)	10 (10.0)	1 (3.0)
Body mass index, mean ± SD	27.7 ± 5.8	27.9 ± 6.0	26.9 ± 5.1
Obesity, n (%)	43 (32.3)	35 (35.0)	8 (24.2)
Smoked ever, n (%)	52 (39.1)	41 (41.0)	11 (33.3)

* CCP, cyclic citrullinated peptide; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; PROMIS, Patient-Reported Outcome Measurement Information System; RA, rheumatoid arthritis; RADAI, Rheumatoid Arthritis Disease Activity Index; RF, rheumatoid factor; TNFi, tumor necrosis factor inhibitor.
[a] High stress defined by scores in the top quartile of the 4-item Perceived Stress Scale (Perceived Stress Scale >10); low or moderate stress defined by scores in the three lower quartiles of the Perceived Stress Scale (Perceived Stress Scale 0–10).
[b] RF, n = 125 (missing data, n = 8).
[c] CCP, n = 121 (missing data, n = 12).
[d] RF positive and/or anti-CCP positive, n = 124 (missing data, n = 9).
[e] RADAI, range 0–10.
[f] Cardiovascular disease: history of stroke, coronary artery disease, and/or myocardial infarction.

stress independently associated with worse RA outcomes at the subsequent time point for all four outcomes: worse RA disease activity, higher pain, higher fatigue, and lower physical function (Table 5). Using the longitudinal time-lagged mixed effects models to estimate adjusted means for outcome across three levels of perceived stress—low, moderate, and high—we found a dose-response effect between stress level at the previous time point and worse RA outcomes at the subsequent time point (Table 5).

Patients with previously high versus low stress levels had adjusted mean pain interference scores of 56.6 (95% CI 54.7–58.6) versus 52.2 (95% CI 50.4–53.9), adjusted mean fatigue scores of 54.9 (95% CI 52.5–57.2) versus 49.2 (95% CI 47.2–51.3), and higher patient-reported disease activity (adjusted mean RADAI 3 [95% CI 2.6–3.4] vs 3.6 [95% CI 3.2–4.1]). There was an inverse relationship between previous stress and physical function; patients with previously high perceived stress had lower mean adjusted

Table 2. Adjusted means for RA outcomes at baseline by perceived stress*

RA outcomes	Adjusted mean[a]		Difference in adjusted means (95% CI)	*P* value
	Low or moderate stress[b] (n = 100)	High stress[b] (n = 33)		
RA disease activity[c]	3.3	3.5	0.19 (−0.61 to 0.98)	0.639
Pain interference[d]	54.4	59.7	5.32 (2.10 to 8.55)	**0.001**
Fatigue[e]	52.5	58.6	6.04 (2.21 to 9.86)	**0.002**
Physical function[f]	43.5	40.1	−3.37 (−6.49 to −0.26)	**0.034**

* *P* values that met the threshold for statistical significance ($P < 0.05$) are indicated in bold. CI, confidence interval; RA, rheumatoid arthritis.
[a] Adjusted means calculated from multivariable regression analysis adjusted for age, sex, race and ethnicity, educational attainment, body mass index, and disease duration. The n for the multivariable regression was 133.
[b] High stress defined by participants with scores in the top quartile for the 4-item Perceived Stress Scale (Perceived Stress Scale >10). Low or moderate stress defined by Perceived Stress Scale scores in lower three quartiles (Perceived Stress Scale 0–10).
[c] Assessed via the Rheumatoid Arthritis Disease Activity Index, score range 0–10. Cut points for low, moderate, and high disease activity: <2.2, ≥2.2 to ≤4.9, and >4.9, respectively.
[d] Assessed via the Patient-Reported Outcomes Measurement Information System Pain Interference 4a scale, score range 41.6–75.6.
[e] Assessed via the Patient-Reported Outcomes Measurement Information System Fatigue 4a scale, score range 33.7–75.8.
[f] Assessed via the Patient-Reported Outcomes Measurement Information System Physical Function 10a scale, score range 20.9–61.9.

physical function scores (41.8 [95% CI 39.9–43.6] vs 44.4 [95% CI 42.7–46.0]). These findings were unchanged in sensitivity analyses adjusting for comorbid cardiovascular disease in addition to other covariates (Supplementary Table 6).

DISCUSSION

This is the largest longitudinal study to investigate a potentially causal relationship between perceived stress and worse patient-reported outcomes in RA. We found that previously high perceived stress associated with worse patient-reported outcomes at follow-up visits, including clinically meaningful differences in pain, fatigue, and physical function based on previous estimates of the MIDs for each relevant measure.[14–17] Similarly, there was a statistically significant association between perceived stress at previous time points and worse patient-reported disease activity; however, the effect size for that relationship was small and may not be clinically meaningful when compared to the estimated MID for the RADAI.[12] Additionally, in cross-sectional analyses, we found a significant independent association between greater stress resilience and less severe fatigue, as well as a link between exposure to more stressful life events and a higher burden of pain.

Our findings contribute to a growing body of literature implicating psychologic distress as a risk factor for worse disease outcomes in RA. A previous study by Mikuls et al[28] found that, among US veterans with RA, the presence of comorbid PTSD independently associated with greater pain, more tender joints, worse patient global scores, and greater physical impairment compared to patients without PTSD. In another study evaluating the relationship between mental health and RA outcomes, Matcham et al[29] found that baseline depressive or anxiety symptoms significantly associated with worse disease activity (via DAS28) during follow-up, and that persistent mood symptoms associated with reduced treatment response to prednisolone. Perhaps most similar to our study, Evers et al[8] observed patients with RA for six months at one-month intervals and found that higher worry scores associated with greater patient-reported disease activity (via RADAI), more swollen joints, and greater pain one month later,

Table 3. Adjusted means for RA outcomes at baseline by exposure to stressful life events*

RA outcomes	Adjusted mean[a]		Difference in adjusted means (95% CI)	*P* value
	Stressful events 0–3 (n = 35)	Stressful events 4–12 (n = 28)		
RA disease activity[b]	2.7	3.4	0.74 (−0.44 to 1.92)	0.216
Pain interference[c]	50.4	58.5	8.17 (3.29 to 13.05)	**0.001**
Fatigue[d]	49.1	53.9	4.72 (−0.85 to 10.29)	0.095
Physical function[e]	43.7	41.2	−2.51 (−6.77 to 1.75)	0.243

* *P* values that met the threshold for statistical significance ($P < 0.05$) are indicated in bold. Assessed via the Stressful Life Events Screening Questionnaire, score range 0–13. Patients with <4 stressful events were compared to those with ≥4 events. CI, confidence interval; RA, rheumatoid arthritis.
[a] Adjusted means calculated from multivariable regression analysis adjusted for age, sex, race and ethnicity, educational attainment, body mass index, and disease duration. The n for the multivariable regression was 63.
[b] Assessed via the Rheumatoid Arthritis Disease Activity Index, score range 0–10. Cut points for low, moderate, and high disease activity: <2.2, ≥2.2 to ≤4.9, and >4.9, respectively.
[c] Assessed via the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference 4a scale, score range 41.6–75.6.
[d] Assessed via the Patient-Reported Outcomes Measurement Information System Fatigue 4a scale, score range 33.7–75.8.
[e] Assessed via the Patient-Reported Outcomes Measurement Information System Physical Function 10a scale, score range 20.9–61.9.

Table 4. Adjusted means for RA outcomes at baseline by resilience group*

RA outcomes	Adjusted mean[a]		Difference in adjusted means (95% CI)	*P* value
	Low or moderate resilience (n = 107)	High resilience[b] (n = 22)		
RA disease activity[c]	3.4	3.0	−0.35 (−1.30 to 0.59)	0.456
Pain interference[d]	56.2	53.2	−3.00 (−6.95 to 0.96)	0.136
Fatigue[e]	55.1	49.4	−5.66 (−10.29 to −1.02)	**0.017**
Physical function[f]	42.4	44.7	2.33 (−1.41 to 6.06)	0.220

Note: *P*-values that met the threshold for statistical significance ($p < 0.05$) are indicated in bold.
* CI, confidence interval; RA, rheumatoid arthritis.
[a] Adjusted means calculated from multivariable regression analysis adjusted for age, sex, race and ethnicity, educational attainment, body mass index, and disease duration. The n for the multivariable regression was 129.
[b] High resilience defined by scores in the top quartile of scores for the four-item Brief Resilience Coping Scale. Low or moderate resilience represented by scores in the lower three quartiles for the Brief Resilience Coping Scale.
[c] Assessed via the Rheumatoid Arthritis Disease Activity Index, score range 0–10. Cut points for low, moderate, and high disease activity: <2.2, ≥2.2 to ≤4.9, and >4.9, respectively.
[d] Assessed via the Patient-Reported Outcomes Measurement Information System Pain Interference 4a scale, score range 41.6–75.6.
[e] Assessed via the Patient-Reported Outcomes Measurement Information System Fatigue 4a scale, score range 33.7–75.8.
[f] Assessed via the Patient-Reported Outcomes Measurement Information System Physical Function 10a scale, score range 20.9–61.9.

whereas more daily stressors associated with worse subsequent fatigue. Our study builds on the work by Evers et al,[8] with different psychologic predictor variables, longer follow-up (18 months instead of 6 months), and longer intervals between assessments, demonstrating that high perceived stress independently predicts significant detriments in RA outcomes six months later.

Our study also builds on previous studies demonstrating a differential relationship of stressful events versus an individuals' appraisal of those events to health outcomes. Using data collected at baseline from the subset of participants who completed the SLESQ, we found that exposure to more stressful life events significantly and independently associated with greater pain interference but not patient-reported disease activity, fatigue, or physical function, whereas perceived stress significantly associated with three of our four outcomes at the same time point. Similarly, in the study by Evers et al,[8] they found that worrying, but not exposure, to daily stressors associated with worse disease activity, swollen joint count, and pain at the subsequent visit. Furthermore, Geenen et al,[30] in a review of 56 publications on the impact of stressors on health status in RA, concluded that "most studies suggested no association between major [stressful] life events and health status." The difference in the relationship we and others have observed between stressful exposures versus perceived stress or worrying and risk of worse patient-reported outcomes suggests that an individual's appraisal of stressful events, more than whether the event occurs, holds the greatest relevance for health outcomes in RA. This is a favorable finding given that one's response to stressful life events may be amenable to change, whereas many stressful life events (eg, death of a loved one, natural disaster, job loss, etc) are unavoidable.

Interestingly, we found that stress associated with disease activity in the time-lagged longitudinal analysis, but not in the baseline cross-sectional analysis. Our group observed a similar relationship between stress and disease activity in a previously published study of individuals with systemic lupus erythematosus; in that study, perceived stress did not associate with physician-assessed disease activity at baseline but it independently associated with worse disease activity at the follow-up

Table 5. Time-lagged longitudinal associations of perceived stress with RA outcomes*

RA outcomes at follow-up	Adjusted mean[a] (95% CI)			β (95% CI)[b]
	Low stress (n = 45)	Moderate stress (n = 55)	High stress (n = 33)	
RA disease activity[c]	3.0 (2.6 to 3.4)	3.2 (2.8 to 3.5)	3.6 (3.2 to 4.1)	0.11 (0.03 to 0.19)
Pain interference[d]	52.2 (50.4 to 53.9)	53.7 (52.3 to 55.1)	56.6 (54.7 to 58.6)	0.61 (0.29 to 0.94)
Fatigue[e]	49.2 (47.2 to 51.3)	51.3 (49.7 to 52.9)	54.9 (52.5 to 57.2)	0.71 (0.32 to 1.11)
Physical function[f]	44.4 (42.7 to 46.0)	43.4 (42.0 to 44.7)	41.8 (39.9 to 43.6)	−0.33 (−0.59 to −0.06)

* Perceived stress assessed via the four-item Perceived Stress Scale. CI, confidence interval; RA, rheumatoid arthritis.
[a] Adjusted means were calculated based on time-lagged longitudinal mixed effects models of RA outcomes as a function of Perceived Stress Scale (continuous variable) at previous time points, adjusted for age, sex, race and ethnicity, educational attainment, body mass index, and disease duration. Model postestimation was then used to estimate adjusted means for each outcome over three levels of stress: low (bottom quartile of Perceived Stress Scale), moderate (two middle quartiles of Perceived Stress Scale), and high (top quartile of Perceived Stress Scale).
[b] Beta, or model coefficients on the continuous Perceived Stress Scale variable, represent the unit change in the outcome for each 1-unit change in Perceived Stress Scale. Beta point estimates (and 95% CIs) are shown.
[c] Assessed via the Rheumatoid Arthritis Disease Activity Index, score range 0–10.
[d] Assessed via the Patient-Reported Outcomes Measurement Information System Pain Interference 4a scale, score range 41.6–75.6.
[e] Assessed via the Patient-Reported Outcomes Measurement Information System Fatigue 4a scale, score range 33.7–75.8.
[f] Assessed via the Patient-Reported Outcomes Measurement Information System Physical Function 10a scale, score range 20.9–61.9.

visit.[31] This difference in the relationship of stress to disease activity cross-sectionally versus longitudinally suggests there is a lag between experiencing high stress and developing worse disease activity in both RA and systemic lupus erythematosus, and the lagged association supports the possibility of a causal relationship. Because the effects size for the association between perceived stress and subsequent disease activity was small, our results suggest that perceived stress is one of many factors that contribute to fluctuations in RA disease activity over time.

There are several potential mechanisms by which perceived stress may contribute to worse outcomes in RA. Exposure to stressful experiences can lead to activation of the two physiologic stress response systems, the sympathetic autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, both of which play an important role in regulating immune function.[32] For example, the HPA axis regulates secretion of GCs, endogenous hormones with potent anti-inflammatory properties that inhibit expression of inflammatory genes. Stress may cause worse outcomes in RA via "GC resistance": chronic stress reduces GC sensitivity in immune cells, thereby impairing the ability of the HPA axis to regulate the immune system.[33] Stress may also inhibit parasympathetic cholinergic anti-inflammatory pathways, resulting in a dysregulated autonomic profile associated with the etiopathogenesis of RA.[34] In addition to impacting biologic pathways, stress may indirectly contribute to worse disease activity by prompting unhealthy behaviors such as smoking, medication nonadherence, and irregular sleep.[35–37] Finally, chronically elevated stress in the absence of sufficient social support may lead to mood disorders such as major depressive disorder and generalized anxiety disorder, both of which are associated with impaired pain tolerance, fatigue, and worse perceptions of overall health.[38] Further studies are required to elucidate mechanisms of stress-illness effects in RA to inform targeted interventions that improve both stress resilience and disease outcomes.

Although previous studies in RA have found an inverse correlation between stress resilience and psychologic variables such as depression and anxiety,[39–41] this is the first study to our knowledge to examine the independent relationship of resilience to RA disease outcomes. We found that greater resilience via the BRCS independently associated with lower fatigue but did not significantly associate with disease activity, pain, or physical function. This finding suggests that, among individuals with RA, a healthy coping strategy in the face of adversity may mitigate the severity of fatigue without directly influencing other physical symptoms. Another potential explanation is that the BRCS does not adequately capture the most relevant behaviors and attitudes that confer stress resilience in our study population. A third possibility is that resilience acts indirectly on health outcomes by modifying perceptions of stressful events and circumstances as opposed to directly influencing clinical outcomes. Future work in this area should employ multiple measures of resilience collected at multiple time points to examine whether different types of resilience influence subsequent RA outcomes.

The primary limitation of this study is the observational design, which comes with the risk of unmeasured confounding and precludes the ability to make strong statements about causation. We hypothesize that stress adversely impacts disease activity and symptoms via both physiologic and psychosocial mechanisms, but we acknowledge that the relationship between stress and RA activity is likely to be bidirectional, given that living with RA is itself a stressor. However, we believe we were able to estimate the proximal effect of stress on downstream variables by evaluating the time ordering of predictor and outcome variables and by using a time-lagged analytic approach to examine the relationship of stress with outcomes at subsequent time points. We also used conservative regression models to adjust for potential confounders with the goal of isolating the independent relationship of stress to each of our outcome variables. Another limitation of this study is that less than half of the participants were administered the SLESQ, and thus we may have been inadequately powered to detect significant associations between exposure to stressful events and RA outcomes. Finally, although we used a well-validated instrument to assess RA disease activity, we did not have physician joint examinations or laboratory data and therefore could not analyze the relationship between stress and more objective assessments of disease activity such as swollen joint count, C-reactive protein levels, or DAS28.

In conclusion, among a socioeconomically diverse RA cohort, we found that greater perceived stress independently associated with worse disease activity, greater symptom burden, and lower physical function at subsequent visits over 18 months of follow-up. We also found that exposure to a greater number of stressful life events associated with worse pain interference and that stress resilience associated with less fatigue, even after adjusting for potential confounders. These findings have important clinical implications and underscore the need to integrate effective interventions to bolster stress resilience and programs that augment psychosocial support in health care systems that serve people living with RA. In addition to reducing psychologic distress, such interventions may attenuate disease activity and ameliorate the most difficult symptoms, namely pain and fatigue, reported by people living with RA.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Katz confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Hunter TM, Boytsov NN, Zhang X, et al. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004-2014. Rheumatol Int 2017;37(9):1551–1557.
2. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365(23):2205–2219.
3. Ishida M, Kuroiwa Y, Yoshida E, et al. Residual symptoms and disease burden among patients with rheumatoid arthritis in remission or low disease activity: a systematic literature review. Mod Rheumatol 2018;28(5):789–799.
4. Santos EJF, Duarte C, Marques A, et al. Effectiveness of non-pharmacological and non-surgical interventions for rheumatoid arthritis: an umbrella review. JBI Database Syst Rev Implement Reports 2019;17(7):1494–1531.
5. Lee YC, Agnew-Blais J, Malspeis S, et al. Post-traumatic stress disorder and risk for incident rheumatoid arthritis. Arthritis Care Res (Hoboken) 2016;68(3):292–298.
6. O'Donovan A, Cohen BE, Seal KH, et al. Elevated risk for autoimmune disorders in Iraq and Afghanistan veterans with posttraumatic stress disorder. Biol Psychiatry 2015;77(4):365–374.
7. Polinski KJ, Bemis EA, Feser M, et al. Perceived stress and inflammatory arthritis: a prospective investigation in the studies of the etiologies of rheumatoid arthritis cohort. Arthritis Care Res (Hoboken) 2020; 72(12):1766–1771.
8. Evers AW, Verhoeven EW, van Middendorp H, et al. Does stress affect the joints? Daily stressors, stress vulnerability, immune and HPA axis activity, and short-term disease and symptom fluctuations in rheumatoid arthritis. Ann Rheum Dis 2014;73(9):1683–1688.
9. Schneider RH, Grim CE, Rainforth MV, et al. Stress reduction in the secondary prevention of cardiovascular disease: randomized, controlled trial of transcendental meditation and health education in Blacks. Circ Cardiovasc Qual Outcomes 2012;5(6):750–758.
10. Fransen J, Langenegger T, Michel BA, et al. Feasibility and validity of the RADAI, a self-administered Rheumatoid Arthritis Disease Activity Index. Rheumatology (Oxford) 2000;39(3):321–327.
11. Stucki G, Liang MH, Stucki S, et al. A self-administered Rheumatoid Arthritis Disease Activity Index (RADAI) for epidemiologic research. Psychometric properties and correlation with parameters of disease activity. Arthritis Rheum 1995;38(6):795–798.
12. England BR, Tiong BK, Bergman MJ, et al. 2019 Update of the American College of Rheumatology Recommended Rheumatoid Arthritis Disease Activity Measures. Arthritis Care Res (Hoboken) 2019; 71(12):1540–1555.
13. Khanna D, Krishnan E, Dewitt EM, et al. The future of measuring patient-reported outcomes in rheumatology: Patient-Reported Outcomes Measurement Information System (PROMIS). Arthritis Care Res (Hoboken) 2011;63(Suppl 11):S486–S490.
14. Hays RD, Spritzer KL, Fries JF, et al. Responsiveness and minimally important difference for the patient-reported outcomes measurement information system (PROMIS) 20-item physical functioning short form in a prospective observational study of rheumatoid arthritis. Ann Rheum Dis 2015;74(1):104–107.
15. Katz P, Kannowski CL, Sun L, et al. Estimation of minimally important differences and patient acceptable symptom state scores for the Patient-Reported Outcomes Measurement Information System Pain Interference short form in rheumatoid arthritis. ACR Open Rheumatol 2020;2(6):320–329.
16. Katz P, Pedro S, Alemao E, et al. Estimates of responsiveness, minimally important differences, and patient acceptable symptom state in five patient-reported outcomes measurement information system short forms in systemic lupus erythematosus. ACR Open Rheumatol 2020;2(1):53–60.
17. Beaumont JL, Fries JF, Curtis JR, et al. Minimally Important Differences for Patient-Reported Outcomes Measurement Information System (Promis) fatigue and pain interference scores. Value Health 2015;18(3):A165–A166.
18. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24(4):385–396.
19. Cohen S, Janicki-Deverts D. Who's stressed? Distributions of psychological stress in the United States in probability samples from 1983, 2006, and 2009. J Appl Soc Psychol 2012;42(6):1320–1334.
20. Patterson SL, Sagui-Henson S, Prather AA. Measures of psychosocial stress and stressful exposures. Arthritis Care Res (Hoboken) 2020;72 Suppl 10(Suppl 10):676–685.
21. Stress Measurement Network. Accessed January 14, 2024. https://www.stressmeasurement.org/
22. Jackson D, Firtko A, Edenborough M. Personal resilience as a strategy for surviving and thriving in the face of workplace adversity: a literature review. J Adv Nurs 2007;60(1):1–9.
23. Ruiz-Robledillo N, De Andrés-García S, Pérez-Blasco J, et al. Highly resilient coping entails better perceived health, high social support and low morning cortisol levels in parents of children with autism spectrum disorder. Res Dev Disabil 2014;35(3):686–695.
24. Sinclair VG, Wallston KA. The development and psychometric evaluation of the Brief Resilient Coping Scale. Assessment 2004;11(1): 94–101.
25. Goodman LA, Corcoran C, Turner K, et al. Assessing traumatic event exposure: general issues and preliminary findings for the Stressful Life Events Screening Questionnaire. J Trauma Stress 1998;11(3): 521–542.
26. Green BL, Chung JY, Daroowalla A, et al. Evaluating the cultural validity of the Stressful Life Events Screening Questionnaire. Violence Against Women 2006;12(12):1191–1213.
27. Laird NM. Missing data in longitudinal studies. Stat Med 1988;7(1-2): 305–315.
28. Mikuls TR, Padala PR, Sayles HR, et al. Prospective study of posttraumatic stress disorder and disease activity outcomes in US veterans with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2013;65(2): 227–234.
29. Matcham F, Norton S, Scott DL, et al. Symptoms of depression and anxiety predict treatment response and long-term physical health outcomes in rheumatoid arthritis: secondary analysis of a randomized controlled trial. Rheumatology (Oxford) 2016;55(2):268–278.
30. Geenen R, Van Middendorp H, Bijlsma JW. The impact of stressors on health status and hypothalamic-pituitary-adrenal axis and autonomic nervous system responsiveness in rheumatoid arthritis. Ann N Y Acad Sci 2006;1069(1):77–97.
31. Patterson S, Trupin L, Hartogensis W, et al. Perceived stress and prediction of worse disease activity and symptoms in a multiracial, multiethnic systemic lupus erythematosus cohort. Arthritis Care Res (Hoboken) 2023;75(8):1681–1689.
32. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol 2005;5(3):243–251.
33. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 2000;21(1):55–89.
34. Koopman FA, Tang MW, Vermeij J, et al. Autonomic dysfunction precedes development of rheumatoid arthritis: a prospective cohort study. EBioMedicine 2016;6:231–237.
35. Gianfrancesco MA, Trupin L, Shiboski S, et al. Smoking is associated with higher disease activity in rheumatoid arthritis: a longitudinal study controlling for time-varying covariates. J Rheumatol 2019;46(4): 370–375.
36. Lee YC, Chibnik LB, Lu B, et al. The relationship between disease activity, sleep, psychiatric distress and pain sensitivity in

rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther 2009;11(5):R160.

37. Pasma A, Schenk CV, Timman R, et al. Non-adherence to disease-modifying antirheumatic drugs is associated with higher disease activity in early arthritis patients in the first year of the disease. Arthritis Res Ther 2015;17(1):281.
38. IsHak WW, Wen RY, Naghdechi L, et al. Pain and depression: a systematic review. Harv Rev Psychiatry 2018;26(6):352–363.
39. Liu L, Xu X, Xu N, et al. Disease activity, resilience and health-related quality of life in Chinese patients with rheumatoid arthritis: a multi-center, cross-sectional study. Health Qual Life Outcomes 2017; 15(1):149.
40. Xu S, Zhang Q, Zhou J. The mediating role of psychological resilience on the negative effect of pain in patients with rheumatoid arthritis: a cross-sectional study. PLoS One 2023;18(12):e0295255.
41. Strand EB, Zautra AJ, Thoresen M, et al. Positive affect as a factor of resilience in the pain-negative affect relationship in patients with rheumatoid arthritis. J Psychosom Res 2006;60(5):477–484.

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1095–1105
DOI 10.1002/acr.25505

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

REVIEW ARTICLE

Effects of Pharmacologic and Nonpharmacologic Interventions for the Management of Sleep Problems in People With Fibromyalgia: Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Jemma Hudson,[1] Mari Imamura,[1] Clare Robertson,[1] Daniel Whibley,[2] Lorna Aucott,[1] Katie Gillies,[1] Paul Manson,[1] Debra Dulake,[1] Abhishek Abhishek,[3] Nicole K. Y. Tang,[4] Gary J. Macfarlane,[1] and Miriam Brazzelli[1]

Objective. Fibromyalgia is a chronic condition characterized by widespread musculoskeletal pain and fatigue. Almost everyone with fibromyalgia has sleep problems. We aimed to evaluate the effectiveness and safety of current interventions for the management of fibromyalgia-related sleep problems.

Methods. Major electronic databases were searched in November 2021. We focused on randomized controlled trials assessing pharmacologic and/or nonpharmacologic interventions in adults and children and identified 168 studies for inclusion. We assessed the methodologic quality of included studies using the Cochrane Risk-of-Bias tool. Our primary outcome of interest was sleep quality assessed using validated patient-reported outcome measures.

Results. Results from primary studies were analyzed using network meta-analyses (NMA). The NMA for sleep quality included 65 studies evaluating 35 treatment categories (8,247 participants). Most studies were at high overall risk of bias. Compared with placebo or sham treatments, there was some evidence that exercise (specifically land-based aerobic exercise training in combination with flexibility training [standardized mean difference (SMD) −4.69, 95% credible interval (CrI) −8.14 to −1.28] and aquatic-based aerobic exercise training [SMD −2.63, 95% CrI −4.74 to −0.58]) may improve sleep. There was also a suggestion that land-based strengthening exercise, psychological and behavioral therapy with a focus on sleep, electrotherapy, weight loss, dental splints, antipsychotics, and tricyclics may have a modest effect on sleep.

Conclusion. There is a low level of certainty surrounding the effectiveness of interventions for the management of sleep problems in people with fibromyalgia, but some forms of exercise training appear more likely to provide an improvement in sleep quality.

INTRODUCTION

Fibromyalgia is a complex, heterogeneous condition[1] that affects 2% to 3% of the global population.[2] In the absence of a cure, a range of treatments are offered to alleviate symptoms. Most people with fibromyalgia complain about sleep problems.[3,4] Fibromyalgia-related sleep problems are poorly managed, and after an initial diagnosis, people continue to seek help to improve their sleep for many years.[5]

The 2015 European guidelines for the management of fibromyalgia considered sleep as a key outcome of interest.[1] Although general recommendations were made for interventions to

The views and opinions expressed in this publication are those of the authors and do not necessarily reflect those of the NHS, the National Institute for Health and Care Research (NIHR), the Health and Social Care Delivery Research Program, or the Department of Health and Social Care.

Supported by the NIHR Health Technology Assessment Program (project 132999).

[1]Jemma Hudson, PhD, Mari Imamura, PhD, Clare Robertson, MSc, Lorna Aucott, PhD, Katie Gillies, PhD, Paul Manson, BA, Debra Dulake, Gary J. Macfarlane, PhD, Miriam Brazzelli, PhD: University of Aberdeen, Aberdeen, United Kingdom; [2]Daniel Whibley, PhD: University of Aberdeen, Aberdeen, United Kingdom, and University of Michigan, Ann Arbor; [3]Abhishek Abhishek, PhD: University of Nottingham, Nottingham, United Kingdom; [4]Nicole K. Y. Tang, PhD: University of Warwick, Coventry, United Kingdom.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25505).

Author disclosures and graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25505.

Address correspondence via email to Miriam Brazzelli, PhD, at m.brazzelli@abdn.ac.uk.

Submitted for publication June 19, 2024; accepted in revised form January 21, 2025.

SIGNIFICANCE & INNOVATIONS

- This systematic review and network meta-analysis provides a comprehensive and up-to-date synthesis of randomized clinical trials investigating pharmacologic and nonpharmacologic interventions for fibromyalgia-related sleep problems.
- A wide range of interventions, especially nonpharmacologic interventions, have been tested in fibromyalgia trials with very low-to-moderate certainty regarding effectiveness.
- Our results indicate that engaging in some forms of exercise—such as land-based aerobic exercise training in combination with flexibility training and aquatic-based aerobic exercise training—may improve sleep quality in people with fibromyalgia.
- Certain pharmacologic interventions may also be effective in improving sleep but not without side effects.

manage sleep, these were graded as "weak" due to a paucity of published evidence at that time. Additionally, sleep was not the primary focus of the guidelines. Previously published evidence reviews informed the National Institute of Health and Care Excellence (NICE) draft guidelines for the management of chronic pain; however, these cluster a wide range of conditions (including osteoarthritis, mechanical back pain, and fibromyalgia) and do not have a specific focus on sleep.[6] Given the number of published randomized controlled trials (RCTs) in this field since 2015, the objective of this study was to undertake a comprehensive evidence synthesis and network meta-analysis (NMA) to assess the clinical effectiveness and adverse events of pharmacologic and nonpharmacologic treatments for the management of fibromyalgia-related sleep problems.

PATIENTS AND METHODS

This systematic review and NMA was conducted in line with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[7] and in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8] The study protocol was registered in the PROSPERO database (CRD42021296922).

Search strategy. Comprehensive search strategies were developed by an information scientist with input from our expert advisers to identify RCTs in patients with fibromyalgia with sleep as an outcome. The searches were not restricted by publication date or language, and we used the Cochrane Highly Sensitive Search Strategy filter for identifying RCTs. The following databases were searched in November 2021: Ovid MEDLINE, Embase, PyscINFO, Allied and Complementary Medicine Database, EBSCO CINAHL, Clarivate Science Citation Index, and the Cochrane Central Register of Controlled Trials. Reference lists of systematic reviews and included studies were checked to identify additional potentially relevant reports. Details of the search strategies are reported in Supplementary Material S2.

Study selection. Studies were eligible for inclusion if they were RCTs with a parallel-group, cross-over, or cluster design comparing pharmacologic and nonpharmacologic interventions to treat sleep problems in adults and children with fibromyalgia versus usual care, placebo, no treatment (including waiting list), or another active intervention. Studies that compared two or more regimens of the same treatment (eg, varying doses of the same drug) were excluded if a placebo or another intervention group was not considered. Two reviewers (MI and CR) independently screened a sample of 100 titles and abstracts at the beginning of the study selection process and compared results to ensure consistency. The remaining citations were divided into two sets and allocated to the same two reviewers. All potentially relevant articles were retrieved in full and assessed by one reviewer for inclusion with a second reviewer checking all articles that were labeled unclear and 10% of the excluded articles. Disagreements were resolved by discussion between reviewers.

Data extraction. The primary outcomes of interest were sleep quality (patient's experience of sleep and perceived sleep quality) and adverse events. Secondary outcomes were sleep efficiency (calculated as total sleep time/total time in bed × 100%), duration of sleep and/or total sleep time, and disease-specific quality of life (QoL). For sleep quality, we identified through an update of a previously published systematic review[9] five patient-reported outcome measures (PROMs) validated in people with fibromyalgia. These outcome measures were the Pittsburgh Sleep Quality Index (PSQI),[10] the Medical Outcomes Study Sleep Scale (MOS-SS),[11] the Jenkins Sleep Scale (JSS),[12] the Fibromyalgia Sleep Diary (FMSD),[13] and the Sleep Quality Numeric Rating Scale (SQ-NRS).[14] Single-item numerical rating scales (NRS) or visual analog scales (VAS) broadly measuring a similar sleep quality construct to that of the SQ-NRS were also considered proxy measures. In the absence of an accepted fibromyalgia-specific QoL tool, we used the Fibromyalgia Impact Questionnaire (FIQ)[15] and the Short Form 36 Health Survey (SF-36) physical component summary (PCS) and mental component summary (MCS) as a proxy for disease-specific measures.[16] Information on how sleep duration and efficiency were assessed (eg, self-reported or objectively measured) was not consistently reported across included studies. We recorded adverse events that occurred in ≥10% of participants in included studies and serious adverse events. Outcomes were collected at the end of the intervention period or the first assessment point thereafter.

For each study, we extracted information on study design, participants, interventions, and outcome measures. The risk of bias (RoB) in included studies was assessed using the revised Cochrane RoB tool and associated full guidance document.[17] Two reviewers (CR and MI) conducted dual independent data extraction and RoB assessment from 10% of the included studies using a bespoke pro forma. Single data extraction and RoB assessment were undertaken by the two reviewers for the remaining studies, with one reviewer checking the information extracted by the other reviewer for consistency. Any discrepancy was resolved by discussion between reviewers or consultation with a third reviewer (MB). Two reviewers working together evaluated the certainty of the evidence included in the NMA, using the Confidence in NMA (CINeMA) approach,[18] which is broadly based on the Grading of Recommendations Assessment, Development and Evaluation framework.[19]

Data analysis. We pooled all sleep quality PROMs together to form an overarching sleep quality outcome. We also analyzed each individual outcome through sensitivity analyses (results not presented).

For studies reporting more than one sleep quality outcome, we specified a hierarchy based on the most frequently reported outcome across included studies. The adopted hierarchical order was as follows: PSQI, MOS-SS, JSS, FMSD, and SQ-NRS. Because a mixture of "change from baseline" and "final score" were available from the included studies, we converted the final score to "change from baseline" when baseline values were available. For the imputation of the change from baseline SD, we used a correlation coefficient as per the recommendation of the Cochrane Handbook for Systematic Reviews of Intervention.[7] Because we had no available data to calculate the correlation coefficient, we chose a 0.5 value and performed a sensitivity analysis assuming a correlation coefficient of 0.8 to assess whether the results changed. The effect size calculated was the standardized mean difference (SMD), which divides the difference in mean between interventions by the estimated pooled between-person SD for that trial. Because some studies had small sample sizes, we used the Hedges (adjusted) G method.[20] Effect sizes reported were either SMD for the sleep quality outcome and mean differences (MD) for the remaining outcomes, with 95% confidence intervals or credible intervals (CrI).

Whenever possible, we performed pairwise and NMAs of all relevant outcome variables. For each pairwise meta-analysis, a random-effects model was used to compare the direct evidence, with the percentage of variation across studies due to heterogeneity being assessed by I^2 statistic.

For each outcome, an NMA was performed to combine both direct and indirect evidence using a Bayesian framework, according to guidance from the NICE Decision Support Unit in the United Kingdom and reported in adherence with the PRISMA for NMAs.[8] Random-effects models with a normal likelihood were used because all our outcomes were continuous. Convergence was assessed using history, autocorrelation, and Brooks-Gelman Rubin plots. A sensitivity analysis, which removed pharmacologic interventions from the main analysis, showed only minimal differences (results not presented). Consistency was evaluated by examining the agreement between direct and indirect evidence in all closed loops. To explore the presence of inconsistency for any treatment contrast in the network, we performed a node-splitting analysis. We also estimated the ranking probabilities of the different interventions using the surface under the cumulative ranking (SUCRA) curve, which is a numeric presentation of the likelihood that an intervention is successful, as well as rankograms. The network diagrams and the node-splitting analysis were performed in Stata 17[21] whereas all remaining analysis was completed using the WinBUGS (Medical Research Council Biostatistics Unit).[22]

Data availability. The main technical data of this evidence synthesis are presented in the text or contained within tables, figures, and supplemental material. Additional results not presented in this manuscript, data used to analyze secondary outcomes, and additional raw data extracted from the included studies can be obtained from the corresponding author on request.

RESULTS

The literature searches identified 4,113 citations, and 378 full-text records were assessed for eligibility. Of these, 90 (total n = 12,082 participants) assessed sleep quality using one of the PROMs validated in people with fibromyalgia (ie, PSQI, MOS-SS, JSS, FMSD, and SQ-NRS) and were included in the NMA (Figure 1).

Of the 90 studies, all participants were adults, 94% were women, with an average age ranging from 35.1 to 57.7 years. According to the information from 30 studies that reported ethnicity, most participants were "White" or "Caucasian." Further details of study characteristics are presented in Supplementary Material S3. Across studies, a total of 97 active treatments, alone or in combination, were assessed. Most (78%) were nonpharmacologic treatments. These treatments were grouped into 45 categories (34 nonpharmacologic and 11 pharmacologic) according to their characteristics and mode of action.

RoB of included studies. The summary of the RoB assessment for studies included in the NMA is shown in Figure 2. Eighty-two (91.1%) were judged as high RoB in at least one domain; therefore, the overall RoB was judged as high. Seven studies (7.8%) were given an overall judgment of "some concerns"[23–29], and one study (1.1%) had an overall judgment of low risk.

Sleep quality outcome. Sixty-five studies (72%) assessed sleep quality and were included in the NMA (n = 8,247

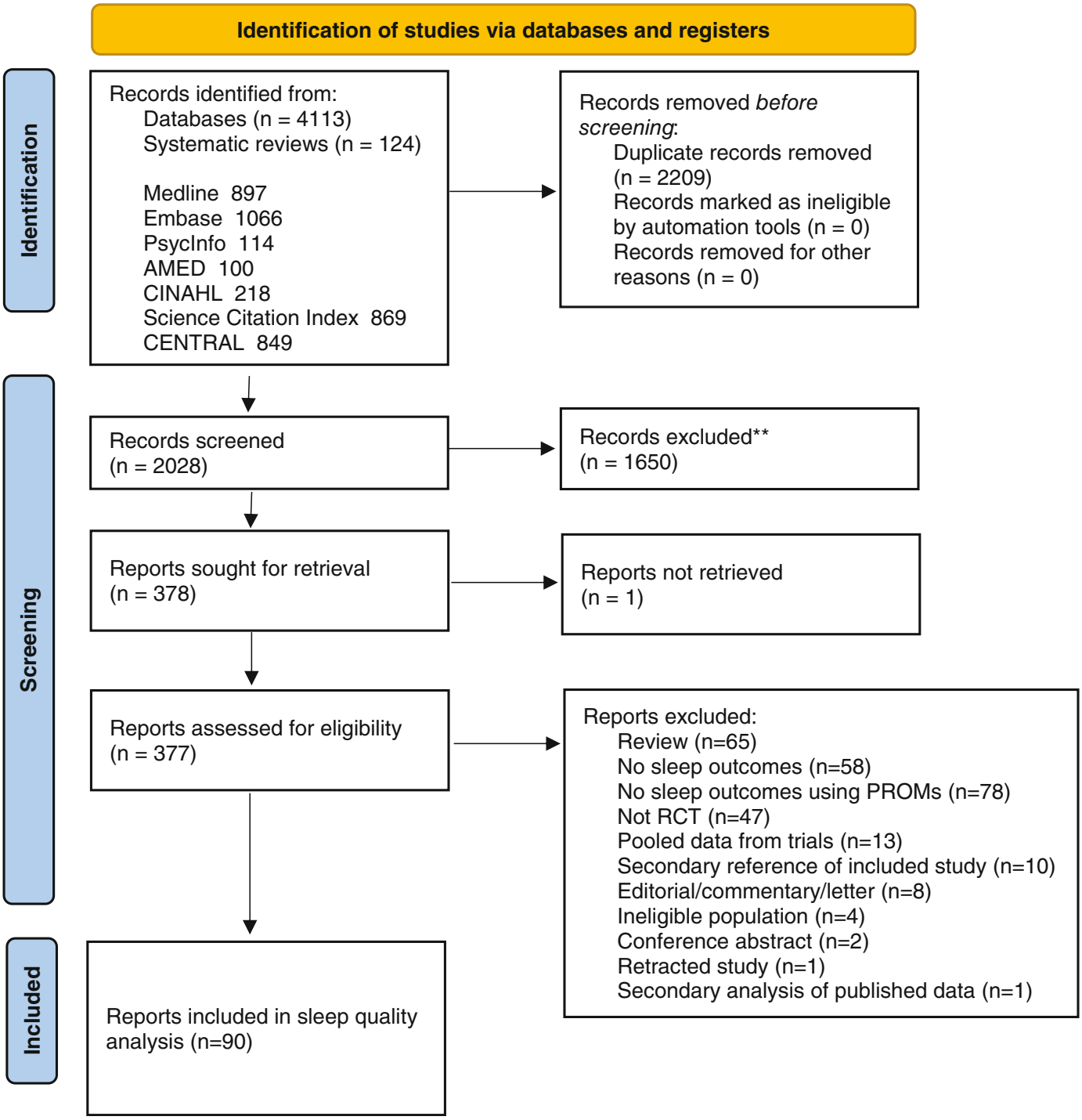

Figure 1. PRISMA flow diagram for identification of the quantitative studies. For more information, visit: http://www.prisma-statement.org/. *Source*: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. AMED, Allied and Complementary Medicine Database; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROM, patient-reported outcome measure; RCT, randomized controlled trial.

participants, 35 treatments). Studies were excluded from the network if they did not provide all required data (13 studies),[27,30–41] were disconnected from the main network (4 studies),[23,25,26,42] evaluated an intervention and a comparator that belonged to the same category (5 studies),[43–47] or did not clarify whether the outcome was an index or subscale of a validated scale (2 studies);[28,48] 1 study[49] was removed because of data outliers (mean and SD were considerably different). The network comprises

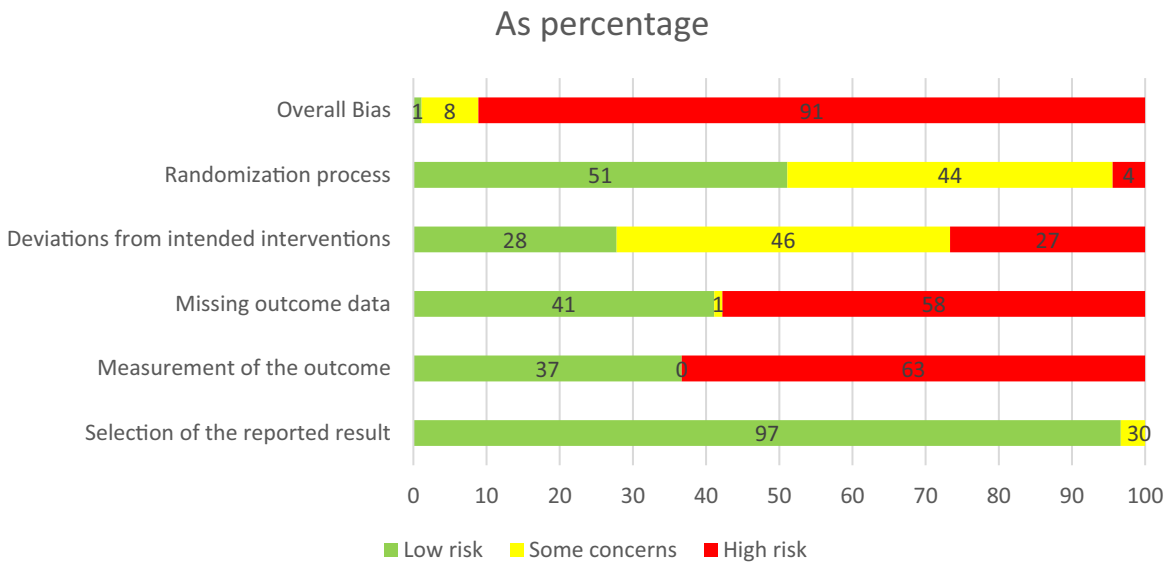

Figure 2. Summary of RoB assessment of the included studies. RoB, risk of bias.

39 studies providing PSQI outcome data, 13 providing MOS-SS data, 6 JSS data, 3 VAS data, 2 SQ-NRS, and 1 study each providing FMSD and NRS data. Figure 3 shows the network plot for eligible comparisons for sleep quality. Most interventions were compared with either placebo or sham or usual care. Of the 35 interventions, most were nonpharmacologic (n = 26). For cross-over trials, we only used data from the first phase before the cross-over.

Table 1 shows the NMA results for the interventions versus placebo or sham (see Supplementary Material S4 for all other comparisons). The sensitivity analysis, in which we assumed a higher correlation for calculating SD for those studies that did not provide a change from baseline score, showed similar results.

Compared with placebo or sham treatment (n = 2,087), there was evidence of a beneficial effect on sleep quality for aquatic-based aerobic exercise training (n = 59; SMD −2.63, 95% CrI −4.74 to −0.58) and land-based aerobic exercise training in combination with flexibility exercise training (n = 32; SMD −4.69, 95% CrI −8.14 to −1.28). There was also a suggestion of a modest effect on sleep for land-based strengthening exercise training (n = 56; SMD −0.95, 95% CrI −3.89 to 2.04), psychological or behavioral therapy (PT/BT) with a focus on sleep (PT/BT sleep; n = 94; SMD −0.89, 95% CrI −2.39 to 0.61), weight loss (n = 41; SMD −1.15, 95% CrI −3.55 to 1.27), electrotherapy (n = 20; SMD −0.98, 95% CrI −3.28 to 1.34), dental splint (n = 29; SMD −1.62, 95% CrI −4.862 to 1.65), tricyclics (n = 43; SMD −1.26, CrI −4.47 to 1.93), and antipsychotics (n = 53; SMD −1.28, CrI −3.56 to 0.97); however, this could not be confirmed with certainty because of the width of the CrI, and our certainty in the current evidence was generally low. We found a positive effect for hyperbaric oxygen therapy (n = 9; SMD −4.51, 95% CrI −7.44 to −1.56) compared with placebo or sham, but this estimate was derived from indirect evidence and based on the assessment of only nine participants in the intervention group. For most other pharmacologic and nonpharmacologic interventions, there was no clear evidence of an improvement in sleep quality, and the certainty of evidence is low to very low.

QoL outcome: FIQ. Fifty-two (n = 7,127 participants, 35 interventions) of the 56 studies that reported FIQ were included in the NMA (four studies were excluded because they did not form part of the main network). Results are presented in Table 2 and Supplementary Material 4. Improvements in FIQ were observed for land-based aerobic exercise in combination with mixed flexibility exercise training (n = 32; MD −19.91, 95% CrI −34.89 to −4.94), multidisciplinary training (n = 81; MD −17.31, 95% CrI −28.38 to −6.29), land-based mind-body exercise training (n = 420; MD −16.18, 95% CrI −22.72 to −9.73), generic psychological or behavioral therapy (PT/BT generic) with relaxation (n = 29; MD −12.07, 95% CrI −20.75 to −3.35), PT/BT sleep (n = 77; MD −11.68, 95% CrI −20.34 to −3.11), and generic PT/BT (n = 145; MD −6.23, 95% CrI −12.02 to −0.62) compared with placebo or sham. Positive effects were observed for participants receiving antioxidants (n = 12; MD −17.75, 95% CrI −34.91 to −0.61), iron replacement (n = 38; MD −15.10, 95% CrI −30.41 to −0.06), serotonin reuptake inhibitors (SRI) (n = 573; MD −9.85, 95% CrI −15.80 to −3.80), and central nervous system (CNS) depressants (n= 881; MD −8.83, 95% CrI −14.77 to −2.74). In general, the magnitude of effects varied across interventions. A large positive effect was also observed after hyperbaric oxygen therapy (n = 9; MD −26.29, 95% CrI −37.56 to −15.15); however, as before, we question the reliability of this estimate due to the very small sample (nine patients in

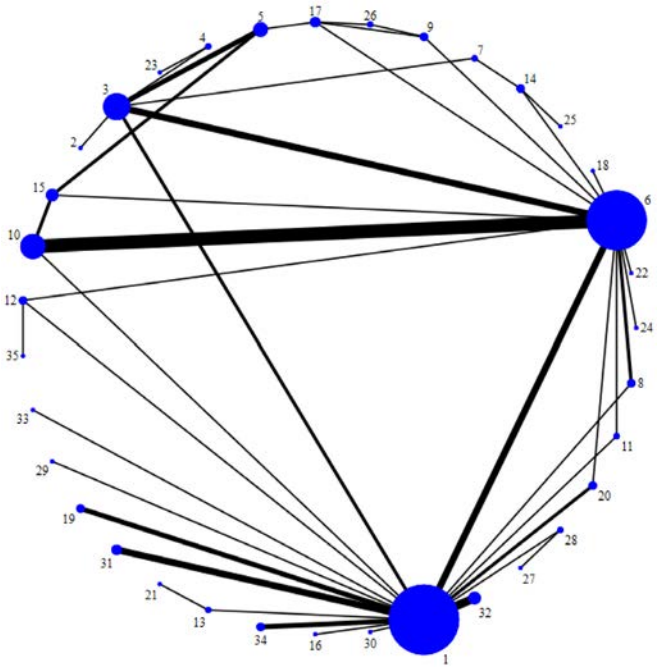

Figure 3. Network diagram for sleep outcome. 1, placebo or sham; 2, education and LD flexibility exercise; 3, LD mind-body exercise; 4, LD aerobic exercise; 5, education; 6, usual care; 7, AQ aerobic exercise; 8, nutrition; 9, balneotherapy; 10, generic PT/BT; 11, manual therapy; 12, relaxation; 13, electrotherapy; 14, LD flexibility exercise; 15, PT/BT targeted to sleep; 16, AQ mind-body exercise; 17, AQ mixed exercise; 18, weight loss; 19, neuromodulation; 20, nonmainstream practice; 21, dental splint; 22, hyperbaric oxygen therapy; 23, LD aerobic exercise and LD flexibility exercise; 24, multidisciplinary; 25, LD flexibility exercise and manual therapy; 26, balneotherapy and AQ mixed exercise; 27, tricyclics; 28, antipsychotics; 29, endogenous hormones; 30, antioxidant; 31, SRIs; 32, gabapentinoid; 33, analgesic; 34, CNS depressants; and 35, LD strengthening exercise. Circle size represents the number of randomized participants; line width represents the number of direct comparisons. AQ, aquatic; CNS, central nervous system; LD, land-based; PT/BT, psychological or behavioral therapy; SRI, serotonin reuptake inhibitor. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25505/abstract.

the intervention group) and lack of a proper comparator intervention.

QoL outcome: SF-36 MCS score. Of the studies that reported SF-36 MCS, 15 of 17 (n = 359, 13 interventions) were included in the NMA (two were excluded as they were not linked in the network). Land-based mind-body exercise (n = 281; MD 7.27, 95% CrI 1.11–13.94) and education (n = 22; MD 10.31, 95% CrI 2.06–19.35) were associated with an improvement in SF-36 MCS score compared with placebo or sham (Table 2, Supplementary Material 4). In contrast, there was evidence that SF-36 MCS scores were worse after nutrition (n = 36) than after placebo or sham (n = 1,167; MD −7.96, 95% CrI −14.83 to −1.11), but there was no clear evidence that SF-36 MCS scores were worse after usual care and electrotherapy than after placebo or sham. The remaining interventions showed no clear evidence of a positive effect when compared with placebo or sham.

Table 1. Primary outcome (sleep quality): NMA evidence plus GRADE*

Interventions	SMD (95% CrI)	GRADE
Education + LD flexibility exercise	0.61 (−1.90 to 3.15)	Very low[a,b,e]
LD mind-body exercise	−0.20 (−1.27 to 0.89)	Low[a,d]
LD aerobic exercise	−0.14 (−2.63 to 2.30)	Very low[a,b,e]
Education	0.08 (−1.32 to 1.47)	Very low[a,b,e]
Usual care	−0.17 (−1.07 to 0.72)	Low[a,c]
AQ aerobic exercise	−2.63 (−4.74 to −0.58)	Low[a,e]
Nutrition	−0.16 (−1.81 to 1.49)	Low[a,b]
Balneotherapy	−0.60 (−2.55 to 1.35)	Very low[a,d,e]
Generic PT/BT	−0.44 (−1.57 to 0.66)	Low[a,d]
Manual therapy	−0.52 (−2.18 to 1.15)	Low[a,d]
Relaxation	−0.62 (−2.57 to 1.34)	Low[a,d]
Electrotherapy	−0.98 (−3.28 to 1.34)	Very low[a,d,e]
LD Flexibility exercise	0.49 (−1.56 to 2.56)	Very low[a,b,e]
PT/BT sleep	−0.89 (−2.39 to 0.61)	Very low[a,c,e]
AQ mind-body exercise	4.26 (1.76–6.76)	Low[a,e]
AQ Mixed exercise	−0.19 (−1.91 to 1.52)	Very low[a,b,e]
Weight loss	−1.15 (−3.55 to 1.27)	Very low[a,d,e]
Neuromodulation	−0.25 (−1.55 to 1.05)	Very low[a,d,e]
Nonmainstream practice	−1.15 (−2.66 to 0.33)	Moderate[a]
Dental splint	−1.62 (−4.86 to 1.65)	Low[a,e]
HBOT	−4.51 (−7.44 to −1.56)	Low[a,e]
LD aerobic exercise + LD flexibility exercise	−4.69 (−8.14 to −1.28)	Low[a,e]
Multidisciplinary	1.79 (−0.61 to 4.20)	Low[a,e]
LD Flexibility exercise + manual therapy	0.78 (−2.30 to 3.83)	Very low[a,b,e]
Balneotherapy + AQ mixed exercise	0.38 (−2.19 to 2.89)	Very low[a,b,e]
Tricyclics	−1.26 (−4.47 to 1.93)	Very low[a,b,e]
Antipsychotics	−1.28 (−3.56 to 0.97)	Very low[a,d,e]
Endogenous hormones	0.24 (−2.06 to 2.53)	Low[a,e]
Antioxidant	−0.29 (−2.61 to 2.06)	Low[b,e]
SRI	−0.02 (−1.13 to 1.10)	Very low[a,b,e]
Gabapentinoid	−0.42 (−1.41 to 0.56)	Very low[a,b,e]
Analgesic	−0.24 (−2.46 to 1.94)	Very low[a,d,e]
CNS depressants	−0.19 (−1.50 to 1.13)	Very low[a,b,e]
LD strengthening exercise	−0.95 (−3.89 to 2.04)	Very low[a,d,e]

* Negative values indicate a better outcome, whereas positive values indicate a worse outcome. AQ, aquatic; CrI, credible interval; CNS, central nervous system; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HBOT, hyperbaric oxygen therapy; LD, land-based; NMA, network meta-analysis; PT/BT, psychological or behavioral therapy; PT/BT sleep, PT/BT targeted to sleep; SMD, standardized mean difference; SRI, serotonin reuptake inhibitor.
[a] Downgraded by one level due to major concerns on the within-study bias.
[b] Downgraded by one level due to major concerns on imprecision.
[c] Downgraded by one level due to major concerns on heterogeneity.
[d] Downgraded by one level due to some concerns on both imprecision and heterogeneity.
[e] Downgraded by one level due to major concerns on incoherence.

QoL outcome: SF-36 PCS score. Of the studies that reported SF-36 PCS scores, 16 of 17 (n = 401 participants, 13 interventions) were included in the analysis (one was excluded as it did not link with other studies). Compared with placebo or

Table 2. Secondary outcomes (quality of life)*

Interventions	FIQ[a] MD (95% CrI)	SF-36 MCS[b] MD (95% CrI)	SF-36 PCS[b] MD (95% CrI)
Education + LD flexibility exercise	2.14 (−11.61 to 15.64)	1.27 (−7.30 to 10.30)	0.59 (−5.42 to 7.95)
LD mind-body exercise	−16.18 (−22.72 to −9.73)	7.27 (1.11–13.94)	7.61 (3.56–13.06)
LD aerobic exercise	−9.23 (−21.46 to 3.07)	4.23 (−3.49 to 12.33)	6.17 (1.05–12.81)
Education	−4.79 (−12.87 to 3.21)	10.32 (2.06–19.35)	3.29 (−3.10 to 11.04)
AQ flexibility exercise	5.58 (−8.00 to 19.30)	NA	NA
Usual care	0.79 (−3.72 to 5.15)	−0.46 (−5.22 to 4.36)	0.68 (−2.48 to 3.87)
AQ aerobic exercise	−8.92 (−23.46 to 5.59)	NA	NA
Nutrition	−5.06 (−12.99 to 2.86)	−7.96 (−14.83 to −1.11)	0.82 (−4.02 to 5.43)
Balneotherapy	−5.58 (−18.68 to 7.68)	NA	NA
Generic PT/BT	−6.23 (−12.02 to −0.62)	NA	NA
Manual therapy	−9.22 (−20.18 to 1.81)	NA	NA
Relaxation	1.80 (−7.29 to 10.91)	NA	NA
Electrotherapy	−9.16 (−21.59 to 2.98)	−0.78 (−5.26 to 3.62)	−0.08 (−4.13 to 3.97)
LD flexibility exercise	5.07 (−12.93 to 23.41)	NA	NA
PT/BT sleep	−11.68 (−20.34 to −3.11)	NA	NA
AQ mind-body exercise	2.02 (−6.29 to 10.45)	NA	NA
AQ Mixed exercise	1.51 (−7.50 to 10.66)	NA	NA
Weight loss	−3.75 (−13.74 to 6.21)	NA	NA
Neuromodulation	0.37 (−8.82 to 9.53)	NA	NA
Nonmainstream practice	−6.20 (−15.49 to 3.18)	3.84 (−1.68 to 9.22)	1.73 (−2.45 to 5.75)
HBOT	−26.29 (−37.56 to −15.15)	NA	NA
LD aerobic exercise + LD flexibility exercise	−19.91 (−34.89 to −4.94)	NA	NA
Generic PT/BT + relaxation	−12.07 (−20.75 to −3.35)	NA	NA
Multidisciplinary	−17.31 (−28.38 to −6.29)	NA	NA
LD flexibility exercise + manual therapy	−0.32 (−26.12 to 25.78)	NA	NA
Balneotherapy + AQ mixed exercise	−5.75 (−18.97 to 7.71)	NA	NA
Tricyclics	−10.63 (−27.49 to 6.09)	NA	NA
Antipsychotics	−6.63 (−19.43 to 6.12)	NA	NA
Antioxidant	−17.75 (−34.91 to −0.61)	7.27 (−1.68 to 15.62)	5.00 (−0.43 to 10.80)
SRI	−9.85 (−15.80 to −3.80)	1.79 (−0.84 to 4.62)	1.50 (−0.45 to 3.79)
Iron replacement	−15.10 (−30.41 to −0.06)	NA	NA
Gabapentinoid	−3.86 (−8.18 to 0.40)	0.87 (−2.22 to 4.11)	0.10 (−2.32 to 2.51)
Analgesic	−3.29 (−11.68 to 5.19)	NA	NA
CNS depressants	−8.83 (−14.77 to −2.74)	1.09 (−1.80 to 4.22)	2.93 (1.10–4.79)

* AQ, aquatic; CNS, central nervous system; CrI, credible interval; FIQ, Fibromyalgia Impact Questionnaire; HBOT, hyperbaric oxygen therapy; LD, land-based; MCS, mental component summary; MD, mean difference; NA, not applicable; PCS, physical component summary; PT/BT, psychological or behavioral therapy; PT/BT sleep, PT/BT targeted to sleep; SF-36, Short Form 36 Health Survey; SRI, serotonin reuptake inhibitor.
[a] Higher scores indicate a worse outcome.
[b] Negative values indicate a worse outcome, whereas positive values indicate a better outcome.

sham (n = 1,355), a better SF-36 PCS score was recorded after land-based mind-body exercise training (n = 281; MD 7.61, 95% CrI 3.56–13.06), land-based aerobic exercise training (n = 75; MD 6.17, 95% CrI 1.05–12.81), and use of CNS depressants (n = 874; MD 2.93, CrI 1.10–4.79) (Table 2, Supplementary Material 4). There was insufficient evidence that electrotherapy (n = 20) had a positive effect on the SF-36 PCS score compared with placebo or sham (MD –0.82, 95% CrI –4.13 to 3.97), and there was no clear evidence that the effects of the remaining interventions were different from those of placebo or sham.

Sleep duration. Sleep duration was reported in two studies (n = 363 participants, three interventions). There was insufficient evidence that gabapentinoid (n = 169) increased sleep duration compared with placebo or sham (n = 179; MD 7.40, 95% CrI –9.84 to 24.74), whereas SRI (n = 15) appeared to be detrimental to sleep duration compared with placebo or sham (n = 179; MD –24.40, 95% CrI –59.81 to 21.96) (see Supplementary Material S5).

Consistency between direct and indirect evidence. For sleep quality, there was evidence of inconsistency between direct and indirect evidence for usual care and aquatic-based aerobic exercise compared with land-based mind-body exercise, land-based flexibility exercise compared with usual care, and land-based flexibility exercise compared with aquatic-based aerobic exercise (Supplementary Material S4). For FIQ, for some intervention comparisons (generic psychological or behavioral therapy compared with placebo or sham, and sleep-focused psychological or behavioral therapy compared

with education or usual care), the node-splitting analysis showed significant disagreement (inconsistency) between direct and indirect estimates (Supplementary Material S5). For SF-36 MCS and PCS, there was no need to check for the presence of inconsistency between direct and indirect estimates as the only two closed loops in the network were from a single three-arm trial (Supplementary Material S5).

Ranking of interventions. For sleep quality and FIQ, hyperbaric oxygen therapy and land-based aerobic with flexibility exercise training were ranked as the top two interventions (these were not evaluated for SF-36). However, it is important to note that SUCRA does not consider the magnitude of differences in effects between interventions, as well as the body and quality of evidence that contributes to each treatment comparison. Moreover, between the five considered outcomes, we observed some inconsistencies. For example, antioxidant therapy and land-based mind-body exercise were ranked low for the sleep quality outcome but not for FIQ. For these reasons, we have little confidence in the SUCRA findings alone.

Adverse events. Data on adverse events were available from 18 of 90 studies (20%) that assessed pharmacologic interventions and 2 of 90 studies (2.2%) that assessed nonpharmacologic interventions. Due to the heterogeneity across included studies, we have summarized adverse events narratively.

In general, nonpharmacologic treatments under investigation were generally well tolerated, with most reported adverse events being mild or moderate in severity such as stiffness and fatigue. In contrast, pharmacologic treatments were commonly associated with adverse events like dizziness, somnolence, headache, and dry mouth.

DISCUSSION

This evidence synthesis included 90 RCTs assessing sleep quality in patients with fibromyalgia. To our knowledge, our study is the most comprehensive approach to assess the current evidence on pharmacologic and nonpharmacologic interventions for fibromyalgia-related sleep problems.

The findings of our NMA on sleep quality using validated PROMs show that, compared with placebo or sham treatment, some forms of exercise such as land-based aerobic exercise training combined with flexibility exercise training and aquatic aerobic exercise training, may improve sleep quality, although our certainty in the current evidence is generally low. For all other pharmacologic and nonpharmacologic interventions, there was a modest effect on sleep quality compared with placebo or sham treatment (CrI indicated uncertainty, and the certainty of evidence is low to very low). Notably, we did not observe a significant, beneficial effect of pharmacologic interventions on sleep quality.

Compared with placebo or sham treatment, some interventions positively affected participants' QoL. Using the FIQ, an improvement in QoL was observed among participants who undertook land-based aerobic and flexibility exercise training, multidisciplinary training, land-based mind-body exercise training, either generic PT/BT or PT/BT sleep, generic PT/BT alongside relaxation, and pharmacologic treatments including antioxidant, iron replacement, SRIs, and CNS depressants, although the magnitude of the effect varied. An improvement in the SF-36 MCS score was observed after land-based mind-body exercise and education interventions, whereas an improvement in the SF-36 PCS score was observed after land-based mind-body exercise training, land-based aerobic exercise training, and use of CNS depressants.

Overall, our analyses were hampered by the lack of head-to-head comparisons for active treatments. Most interventions were compared with either placebo, sham, or usual care. Some of the nonpharmacologic studies failed to compare their active interventions with sham procedures that involved appropriate control strategies in terms of exposure time (frequency and duration) and "attention" received from the therapist and/or instructor. Appropriate sham controls have been used in similar clinical areas and are considered particularly useful for studies with subjective or self-reported endpoints (eg, improvement of symptoms) and when the risk of the sham procedures is low (eg, less intensive or generic physical activity or procedure).[50,51] Furthermore, the recent Control Interventions in Physical, Psychological, and Self-Management Therapy Trials (CoPPS) statement recommends designing control interventions that are as similar as possible to the interventions under investigation, apart from the components the trial aims to assess.[52] Appropriate sham-control could potentially reduce bias by allowing for blinding of participants.[53] Blinding in nonpharmacologic RCTs can be challenging. When patients are unblinded and aware they are receiving the treatment under investigation, their self-reported outcomes may be biased by higher expectations of improvement. Conversely, those who know they are not receiving the intervention may have much lower expectations or even experience a nocebo response.[54,55]

Most of the studies that contributed to the network were small (<100 participants), with short-term follow up (around 3 months) and assessed a diverse range of interventions. To make the NMA feasible, we grouped the 97 different active interventions into 45 categories according to their characteristics and mode of action; however, inevitably, the individual interventions varied within the category groups. The limited number of studies available for each intervention comparison also precluded a meaningful assessment of publication bias. We were also only able to analyze average treatment effects and not relevant clinical and demographic modifiers at the patient level (eg, severity of disease, duration of illness, extent and nature of sleep disturbances, and level of physical activity before and during treatment). Sleeplessness may also be exacerbated by mood disorders such as

depression, which are common among people with fibromyalgia; however, due to inconsistent reporting across studies, we could not explore this further.[56]

Unfortunately, our primary outcome, sleep quality, was not consistently and objectively measured across studies; several different PROMs were used. Because there is no consensus on which is the best outcome measure to use in the field of fibromyalgia, we decided to combine studies irrespective of the way sleep quality was measured, provided that a validated instrument was used. This might have contributed to heterogeneity and inconsistency in the network, thus limiting the reliability of our findings. Furthermore, the interpretation of results was complicated by the lack of information on their minimally important clinical difference. Our original plan was to conduct a component NMA to disentangle the effect of each component of the interventions assessed by the included studies, but this proved impossible due to the lack of suitable data.

According to CINeMA, for many comparisons included in our NMA, our certainty of the evidence was rated as low to very low (sleep quality outcome). The level of certainty was downgraded for within-study bias, primarily due to an inadequate reporting of randomization and allocation concealment methods as well as issues related to missing outcome data. The certainty level was also downgraded for imprecision because of the low number of studies available for each comparison and their small sample size, as well as heterogeneity and incoherence across comparisons. Given our CINeMA findings, we were unable to conduct sensitivity analyses restricted to high-quality studies.

There are several published systematic reviews assessing different forms of exercise training and other nonpharmacologic interventions for the management of fibromyalgia symptoms.[57–60] 60 Although not primarily focused on sleep problems, they all identify similar limitations to those we observed here, including heterogeneity across studies in terms of study protocols, insufficient evidence to establish the effectiveness of one intervention compared with another, lack of appropriate comparator treatments, insufficient statistical power in most studies and low-to-moderate quality of the evidence. One systematic review that aimed to evaluate the effectiveness of nonpharmacologic treatments for fibromyalgia revealed that all types of exercise, except for flexibility exercises, helped reduce pain intensity, whereas aerobic and strengthening exercises helped improve sleep quality.[61] However, the authors identified only a limited number of studies, usually of small sample sizes, for each form of exercise (10 for aerobic exercise, 9 for strengthening, and 2 for flexibility) and found considerable heterogeneity in outcome measures, intervention programs, and control interventions, in line with our findings.

Overall, there is a suggestion that some forms of exercise training, psychological and behavioral therapy, and some pharmacologic treatments may play a role in improving fibromyalgia-related sleep problems and/or patients' QoL. However, the limitations of the current evidence do not allow reliable conclusions about optimal interventions for treating sleep problems in people with fibromyalgia. There is a clear need to improve the quality of existing evidence. It is worth noting that most participants were middle-aged women from high-income countries. Information on ethnicity and level of education was often not reported. Future studies should be properly designed and include an adequate number of diverse patients to reduce bias and to ensure results are generalizable.[62] Interventions should be compared with established therapies or adequate sham treatments to demonstrate their comparative efficacy and safety. Descriptions of placebo and sham treatments should be guided by the Template for Intervention Description and Replication-Placebo checklist.[63] There should also be consensus on the best way to capture fibromyalgia symptoms. Currently, having different tools to measure symptoms not only impacts the ability to synthesize research evidence but also confuses health professionals and patients when trying to document and tackle fibromyalgia-related symptoms. The development of a core outcome set for measuring sleep outcomes in both adults and children with fibromyalgia would be beneficial for informing new standardized PROMs in this field. It would also be crucial to involve people with fibromyalgia in the conception and content validation of any tool measuring sleep, ensuring that PROMs cover what matters most to patients.

ACKNOWLEDGMENTS

We are grateful to the researchers, health professionals, and patient partners who were involved in the Advisory Group and specifically to Pamela Andrews, Scottish Medicines Consortium and National Cancer Medicines Advisory Group, Healthcare Improvement Scotland; Filip Bellon, Faculty of Nursing and Physiotherapy, Universitat de Lleida, Catalonia, Spain; Carolina Climent Sanz, Universitat de Lleida, Catalonia, Spain; Daniel Clauw, Professor of Anesthesiology Medicine (Rheumatology) and Psychiatry at the University of Michigan; Anna Durrans, Research Programme Manager, Versus Arthritis; Michael Prior, patient partner from Nottingham; Des Quinn, chair of Fibromyalgia Action UK; Neil W. Scott, Medical Statistics Team, Institute of Applied Health Sciences, University of Aberdeen; and David Walsh, Professor of Rheumatology at the University of Nottingham and Consultant Rheumatologist at Sherwood Forest Hospitals NHS Foundation Trust. We also thank Catriona Young, postgraduate student, University of Aberdeen, for her help in assessing a sample of full-text papers that were initially excluded because they did not report sleep outcomes in their title or abstract and Beverley Smith and Anne Buckle for their secretarial and administrative support.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Brazzelli confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 2017;76(2):318–328.
2. Jones GT, Atzeni F, Beasley M, et al. The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. Arthritis Rheumatol 2015;67(2):568–575.
3. Boomershine CS. A comprehensive evaluation of standardized assessment tools in the diagnosis of fibromyalgia and in the assessment of fibromyalgia severity. Pain Res Treat 2012;2012:653714.
4. Mease PJ, Arnold LM, Crofford LJ, et al. Identifying the clinical domains of fibromyalgia: contributions from clinician and patient Delphi exercises. Arthritis Rheum 2008;59(7):952–960.
5. Hughes G, Martinez C, Myon E, et al. The impact of a diagnosis of fibromyalgia on health care resource use by primary care patients in the UK: an observational study based on clinical practice. Arthritis Rheum 2006;54(1):177–183.
6. National Institute for Health and Care Excellence. Chronic pain in over 16s: assessment and management: draft for consultation, August 2020. National Institute for Health and Care Excellence; 2020. Accessed October 14, 2022. https://www.nice.org.uk/guidance/ng193/documents/draft-guideline
7. Higgins J, Green S, Thomas J, et al, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 2021*. Accessed June 2021. https://training.cochrane.org/handbook
8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372(71):n71.
9. Climent-Sanz C, Marco-Mitjavila A, Pastells-Peiró R, et al. Patient reported outcome measures of sleep quality in fibromyalgia: a COSMIN systematic review. Int J Environ Res Public Health 2020;17(9):2992.
10. Buysse DJ, Reynolds CF III, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193–213.
11. Hays R, Stewart A. Sleep measures. In: Stewart A, Ware J, eds. Measuring Functioning and Well-Being: the Medical Outcomes Study Approach. Duke University Press; 1992:235–259.
12. Jenkins CD, Stanton BA, Niemcryk SJ, et al. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol 1988;41(4):313–321.
13. Kleinman L, Mannix S, Arnold LM, et al. Assessment of sleep in patients with fibromyalgia: qualitative development of the Fibromyalgia Sleep Diary. Health Qual Life Outcomes 2014;12(1):111.
14. Cappelleri JC, Bushmakin AG, McDermott AM, et al. Psychometric properties of a single-item scale to assess sleep quality among individuals with fibromyalgia. Health Qual Life Outcomes 2009;7(1):54.
15. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991;18(5):728–733.
16. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30(6):473–483.
17. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
18. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. PLoS One 2014;9(7):e99682.
19. Brignardello-Petersen R, Bonner A, Alexander PE, et al; GRADE Working Group. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol 2018;93:36–44.
20. Morton SC, Murad MH, O'Connor E, et al. Quantitative synthesis—An Update. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality (US); 2018.
21. *Stata 17*. Version 17. StataCorp; 2021. https://www.stata.com/
22. Lunn DJ, Thomas A, Best N, et al. WinBUGS - A Bayesian modelling framework: Concepts, structure, and extensibility. Stat Comput 2000;10(4):325–337.
23. Guinot M, Maindet C, Hodaj H, et al. Effects of repetitive transcranial magnetic stimulation and multicomponent therapy in patients with fibromyalgia: a randomized controlled trial. Arthritis Care Res (Hoboken) 2021;73(3):449–458.
24. Samartin-Veiga N, Pidal-Miranda M, Gonzalez-Villar AJ, et al. Transcranial direct current stimulation of three cortical targets is no more effective than placebo as treatment for fibromyalgia: a double-blind sham-controlled clinical trial. Pain 2021;163(7):e850–e861.
25. Mirzaei A, Zabihiyeganeh M, Jahed SA, et al. Effects of vitamin D optimization on quality of life of patients with fibromyalgia: a randomized controlled trial. Med J Islam Repub Iran 2018;32(1):29.
26. de Zanette SA, Vercelino R, Laste G, et al. Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: a phase II, randomized, double-dummy, controlled trial. BMC Pharmacol Toxicol 2014;15(1):40.
27. Gilron I, Chaparro LE, Tu D, et al. Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial. Pain 2016;157(7):1532–1540.
28. Boomershine CS, Koch TA, Morris D. A blinded, randomized, placebo-controlled study to investigate the efficacy and safety of ferric carboxymaltose in iron-deficient patients with fibromyalgia. Rheumatol Ther 2018;5(1):271–281.
29. Mameli S, Pisanu GM, Sardo S, et al. Oxytocin nasal spray in fibromyalgic patients. Rheumatol Int 2014;34(8):1047–1052.
30. Arcos-Carmona IM, Castro-Sánchez AM, Matarán-Peñarrocha GA, et al. [Effects of aerobic exercise program and relaxation techniques on anxiety, quality of sleep, depression, and quality of life in patients with fibromyalgia: a randomized controlled trial]. Med Clin (Barc) 2011;137(9):398–401.
31. Calandre EP, Rodriguez-Claro ML, Rico-Villademoros F, et al. Effects of pool-based exercise in fibromyalgia symptomatology and sleep quality: a prospective randomised comparison between stretching and Ai Chi. Clin Exp Rheumatol 2009;27(5 Suppl 56):S21–S28.
32. Castro-Sanchez AM, Mataran-Pearrocha GA, Granero-Molina J, et al. Benefits of massage-myofascial release therapy on pain, anxiety, quality of sleep, depression, and quality of life in patients with fibromyalgia. Evid Based Complement Alternat Med 2011;2011:561753.
33. Castro Sánchez AM, García López H, Fernández Sánchez M, et al. Improvement in clinical outcomes after dry needling versus myofascial release on pain pressure thresholds, quality of life, fatigue, pain intensity, quality of sleep, anxiety, and depression in patients with fibromyalgia syndrome. Disabil Rehabil 2019;41(19):2235–2246.
34. Goldway N, Ablin J, Lubin O, et al. Volitional limbic neuromodulation exerts a beneficial clinical effect on fibromyalgia. Neuroimage 2019;186:758–770.
35. Crofford LJ, Rowbotham MC, Mease PJ, et al; Pregabalin 1008-105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52(4):1264–1273.
36. Mataran-Penarrocha GA, Castro-Sanchez AM, Garcia GC, et al. Influence of craniosacral therapy on anxiety, depression and quality of life in patients with fibromyalgia. Evid Based Complement Alternat Med 2011;2011:178769.

37. Mease PJ, Russell IJ, Arnold LM, et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. J Rheumatol 2008;35(3):502–514.
38. Merchant RE, Andre CA, Wise CM. Nutritional supplementation with Chlorella pyrenoidosa for fibromyalgia syndrome: a double-blind, placebo-controlled, crossover study. J Musculoskeletal Pain 2001; 9(4):37–54.
39. Onieva-Zafra MD, Parra-Fernández ML, Fernandez-Martinez E. Benefits of a home treatment program using guided imagery relaxation based on audio recordings for people with fibromyalgia. Holist Nurs Pract 2019;33(2):111–120.
40. Spaeth M, Bennett RM, Benson BA, et al. Sodium oxybate therapy provides multidimensional improvement in fibromyalgia: results of an international phase 3 trial. Ann Rheum Dis 2012;71(6):935–942.
41. Yeephu S, Suthisisang C, Suttiruksa S, et al. Efficacy and safety of mirtazapine in fibromyalgia syndrome patients: a randomized placebo-controlled pilot study. Ann Pharmacother 2013;47(7–8): 921–932.
42. Moustafa IM, Diab AA. The addition of upper cervical manipulative therapy in the treatment of patients with fibromyalgia: a randomized controlled trial. Rheumatol Int 2015;35(7):1163–1174.
43. Maddali Bongi S, Del Rosso A, Di Felice C, et al. Rességuier method and Qi Gong sequentially integrated in patients with fibromyalgia syndrome. Clin Exp Rheumatol 2012;30(6 Suppl 74):51–58.
44. Martínez-Rodríguez A, Rubio-Arias JÁ, Ramos-Campo DJ, et al. Psychological and sleep effects of tryptophan and magnesium-enriched Mediterranean diet in women with fibromyalgia. Int J Environ Res Public Health 2020;17(7):2227.
45. Picard P, Jusseaume C, Boutet M, et al. Hypnosis for management of fibromyalgia. Int J Clin Exp Hypn 2013;61(1):111–123.
46. Slim M, Calandre EP, Garcia-Leiva JM, et al. The effects of a gluten-free diet versus a hypocaloric diet among patients with fibromyalgia experiencing gluten sensitivity-like symptoms. J Clin Gastroenterol 2017;51(6):500–507.
47. Van Gordon W, Shonin E, Dunn TJ, et al. Meditation awareness training for the treatment of fibromyalgia syndrome: a randomized controlled trial. Br J Health Psychol 2017;22(1):186–206.
48. González-Viejo MA, Avellanet M, Hernández-Morcuende MI. [A comparative study of fibromyalgia treatment: ultrasonography and physiotherapy versus sertraline treatment]. Ann Readapt Med Phys 2005; 48(8):610–615.
49. Castel A, Cascón R, Padrol A, et al. Multicomponent cognitive-behavioral group therapy with hypnosis for the treatment of fibromyalgia: long-term outcome. J Pain 2012;13(3):255–265.
50. McCaskey MA, Wirth B, Schuster-Amft C, et al. Postural sensorimotor training versus sham exercise in physiotherapy of patients with chronic non-specific low back pain: an exploratory randomised controlled trial. PLoS One 2018;13(3):e0193358.
51. Naranjo-Cinto F, Cerón-Cordero AI, Figueroa-Padilla C, et al. Real versus sham manual therapy in addition to therapeutic exercise in the treatment of non-specific shoulder pain: a randomized controlled trial. J Clin Med 2022;11(15):4395.
52. Hohenschurz-Schmidt D, Vase L, Scott W, et al. Recommendations for the development, implementation, and reporting of control interventions in efficacy and mechanistic trials of physical, psychological, and self-management therapies: the CoPPS Statement. BMJ 2023; 381:e072108.
53. Hohenschurz-Schmidt D, Draper-Rodi J, Vase L, et al. Blinding and sham control methods in trials of physical, psychological, and self-management interventions for pain (article I): a systematic review and description of methods. Pain 2023;164(3):469–484.
54. Wartolowska KA, Hohenschurz-Schmidt D, Vase L, et al. The importance of using placebo controls in nonpharmacological randomised trials. Pain 2023;164(5):921–925.
55. Webster RK, Howick J, Hoffmann T, et al. Inadequate description of placebo and sham controls in a systematic review of recent trials. Eur J Clin Invest 2019;49(11):e13169.
56. Arnold LM, Bennett RM, Crofford LJ, et al. AAPT diagnostic criteria for fibromyalgia. J Pain 2019;20(6):611–628.
57. Busch AJ, Barber KA, Overend TJ, et al. Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev 2007;(4):CD003786.
58. Bidonde J, Busch AJ, Schachter CL, et al. Aerobic exercise training for adults with fibromyalgia. Cochrane Database Syst Rev 2017;6(6): CD012700.
59. Bidonde J, Busch AJ, Webber SC, et al. Aquatic exercise training for fibromyalgia. Cochrane Database Syst Rev 2014;2014(10): CD011336.
60. Langhorst J, Klose P, Dobos GJ, et al. Efficacy and safety of meditative movement therapies in fibromyalgia syndrome: a systematic review and meta-analysis of randomized controlled trials. Rheumatol Int 2013;33(1):193–207.
61. Kundakci B, Kaur J, Goh SL, et al. Efficacy of nonpharmacological interventions for individual features of fibromyalgia: a systematic review and meta-analysis of randomised controlled trials. Pain 2022; 163(8):1432–1445.
62. National Institute for Health and Care Research. Improving inclusion of under-served groups in clinical research: Guidance from INCLUDE project. August 7, 2020. www.nihr.ac.uk/documents/improving-inclusion-of-under-served-groups-in-clinical-research-guidance-from-include-project/25435
63. Howick J, Webster RK, Rees JL, et al. TIDieR-Placebo: a guide and checklist for reporting placebo and sham controls. PLoS Med 2020; 17(9):e1003294.

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1106–1111
DOI 10.1002/acr.25542

Monitoring of Juvenile Idiopathic Arthritis–Associated Uveitis in Long-Term Disease Remission: Consensus-Based Recommendations From the Multinational Interdisciplinary Working Group for Uveitis in Childhood

Ivan Foeldvari,[1] Ameenat Solebo,[2] Harry Petrushkin,[3] Sheila T. Angeles-Han,[4] Regitze Bangsgaard,[5] Joan Calzada-Hernández,[6] Tamas Constantin,[7] Joke de Boer,[8] Jesus Díaz-Cascajosa,[9] Mia Glerup,[10] Helene Ingels,[11] Sebastian Kramer,[12] Elisabetta Miserocchi,[13] Ellen Nordal,[14] Rotraud K. Saurenmann,[15] Gabriele Simonini,[16] Joost F. Swart,[17] Jan Titz,[12] and Jordi Antón[18]

Objective. We aimed to develop consensus-based recommendations for the monitoring of children with juvenile idiopathic arthritis–associated uveitis (JIAU) in long-term remission, addressing the absence of international guidance on monitoring schedules for these children and young people.

Methods. The Multinational Interdisciplinary Working Group for Uveitis in Childhood convened experts from 10 countries, including pediatric rheumatologists and ophthalmologists, alongside parents of affected children. A review of key longitudinal cohort studies informed a structured consensus process comprising discussion, recommendation development, and voting for adoption, with a consensus threshold of ≥80% needed for adoption. Recommendation development focused on three principal questions: stratification of the risk of poor outcomes, the natural history of JIAU postremission, and the impact of delayed examination.

Results. The group established several key recommendations, including a standard monitoring frequency of every 4 months for the first four years following medication cessation, ongoing assessments for patients with structural complications, and low-frequency monitoring every 6 months for those in stable, drug-free remission for over four years. There was unanimous agreement on these recommendations.

Conclusion. These consensus-based recommendations provide a framework for monitoring children with JIAU in remission, enhancing the quality of care and optimizing resource use in eye health services. Ongoing research is essential to refine these guidelines as new evidence emerges regarding biomarkers and imaging techniques for disease recurrence.

INTRODUCTION

Childhood onset uveitis is an intraocular inflammatory disorder that affects between 8% and 30% of children with juvenile idiopathic arthritis (JIA).[1–4] The frequent absence of self-reported ocular symptoms increases the risk of late detection.[5] The irreversibility of the blinding structural complications that follow delayed detection have necessitated disease population

[1]Ivan Foeldvari, MD: Hamburger Zentrum für Kinder- und Jugendrheumatologie, am Schön Klinik Hamburg Eilbek, Hamburg, Germany; [2]Ameenat Solebo, PhD: Great Ormond Street Hospital NHS Foundation Trust, University College London Great Ormond Street Institute of Child Health, and National Institute for Health and Care Research Great Ormond Street Biomedical Research Centre, London, United Kingdom; [3]Harry Petrushkin, PhD: Great Ormond Street Hospital NHS Foundation Trust and Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom; [4]Sheila T. Angeles-Han, MD: Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio; [5]Regitze Bangsgaard, MD: Copenhagen University Hospital, Glostrup, Rigshospitalet, Copenhagen, Denmark; [6]Joan Calzada-Hernández, MD: Hospital Sant Joan de Déu, Barcelona, Spain; [7]Tamas Constantin, MD: Semmelweis University, Budapest, Hungary; [8]Joke de Boer, MD: University Medical Center Utrecht, Utrecht, The Netherlands; [9]Jesus Díaz-Cascajosa, MD: Hospital Sant Joan de Déu, Barcelona, Spain; [10]Mia Glerup, MD: Aarhus University Hospital, Aarhus, Denmark; [11]Helene Ingels, MD: Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [12]Sebastian Kramer, Jan Titz, Patients Representative, Hamburg, Germany; [13]Elisabetta Miserocchi, MD: San Raffaele Scientific Institute, University Vita-Salute, Milan, Italy; [14]Ellen Nordal, MD: University Hospital of North Norway, University of Tromsø The Arctic University of Norway, Tromsø, Norway; [15]Rotraud K. Saurenmann, MD: Kantonsspital, Winterthur, University Children's Hospital, Zurich, Switzerland; [16]Gabriele Simonini, MD: ERN-ReCONNET Center, Meyer Children's Hospital IRCCS, Firenze, Italy; [17]Joost F. Swart, MD: Wilhelmina Children's Hospital and University Medical Center Utrecht, Utrecht, The Netherlands; [18]Jordi Antón, MD: Hospital Sant Joan de Déu and Medicine and Health Sciences School, Universitat de Barcelona, Barcelona, Spain.

Drs Foeldvari and Solebo are co-first authors and contributed equally to this work.

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25542.

Address correspondence via email to Ivan Foeldvari, MD, at sperchstunde@kinderrheumatologie.de.

Submitted for publication November 13, 2024; accepted in revised form March 19, 2025.

SIGNIFICANCE & INNOVATIONS

- This is the first consensus guidance for disease monitoring in children with juvenile idiopathic arthritis–associated uveitis who have reached long-term remission.
- Discussion across this multinational group identified two groups with different monitoring needs: those with drug-controlled disease and those with drug-free remission (without the use of systemic or topical medication).
- The age of 18 years was agreed as a exit threshold for formal monitoring in juvenile idiopathic arthritis–associated uveitis remission. This was not in response to an absence of ongoing disease risk, but rather a reflection of the lack of evidence on risk profiles in adult disease.

interventions, specifically regular eye examination, aimed at timely diagnosis.[6–10] Following diagnosis, children typically continue to require regular monitoring of disease to ensure maintenance of disease control.

Clinical care has benefited from the development of recommendations around the frequency of screening ophthalmic examination for children who are at risk of a first episode of JIA-associated uveitis (JIAU).[6,10] There is also guidance on disease monitoring for those with JIAU in which the severity of inflammation drives the frequency of eye examinations.[8,9,11] To the best of our knowledge, there has not yet been an international, multidisciplinary effort to develop guidance for disease monitoring for the 1 in 3 children with JIAU who enter long-term uveitis remission.[4] This absence acts as a barrier to timely examination of children who remain at risk or may result in unnecessary use of eye health care services. To address this gap, the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC), an international collaboration of specialists aiming to tackle the challenges related to the assessment and management of pediatric noninfectious uveitis, developed consensus-based recommendations to guide health professionals managing children and young people with JIAU in remission.

MATERIALS AND METHODS

Recommendation development was driven by the evidence base and expert opinion, in line with earlier MIWGUC consensus activities,[12–14] and as recommended by the EULAR updated standardized operating procedures[15] and the Accurate Consensus Reporting Document guidance on consensus activities.[16] The expert MIWGUC consensus group for this consensus activity comprised eight pediatric rheumatologists and five ophthalmologists with expertise in JIAU, and three parents of children with uveitis, representing 10 countries (Denmark, Germany, Hungary, Italy, The Netherlands, Norway, Spain, Switzerland, United Kingdom, and the United States).

To develop a summary of the current relevant evidence base for an ophthalmic monitoring pathway of children with uveitis in remission, MIWGUC used a review of key longitudinal cohort studies undertaken before the consensus meeting.[17] This summation focused on three key questions, chosen to address the three overarching principles that were identified and agreed by the group before the meeting: (1) what are the determinants of poor outcome for children with established JIAU, questioned to build an evidence base around the principle of stratification of ongoing need for ophthalmic care following established disease remission; (2) what is the long-term natural history of JIAU during childhood following remission, questioned to address the principle around the duration of the monitoring program; and (3) what is the impact of delayed clinical examination on outcomes, questioned to address the principle of the "degree" of need, with need being the driver for determining the frequency of ocular examination. The evidence summation was then presented at an in-person group meeting held over two days in January 2024 in Barcelona, Spain.

On day 1, following presentation of the data, a roundtable discussion took place where all attendees were asked to sequentially provide monitoring recommendations; further to-and-fro discussion followed this round. At the end of the day, the group created a list of draft recommendations for voting. On day 2, there was first a consensus vote on each recommendation, following a nominal group technique successfully used for other activities.[13] A majority threshold of ≥80% was needed for acceptance as a recommendation. If that threshold was not reached, a discussion on rewording of the recommendation followed, and if the majority agreed on retention of the reworded recommendation, a second vote was taken. For each recommendation, every member of the group was required to vote to allow progression to the next recommendation. A draft of the seven recommendations was then sent to all group members following the face-to-face meeting for final approval and comments.

For this process, the group agreed to use the previously accepted definition of uveitis remission[12]: inactive disease for at least 6 months on medication or for >3 months after discontinuation of all antiinflammatory treatments for uveitis. Inactive uveitis was defined as both eyes fulfilling the following criteria: (1) slit lamp total number of anterior chamber (AC) cells: inflammatory cell grade of zero using the Standardization of Uveitis Nomenclature scale,[18] in patients with aphakia, and some AC cells may be present in the anterior vitreous; (2) ophthalmologist global assessment of uveitis activity on visual analog scale (VAS) score of 0 (VAS scoring ranges from 0 to 100 mm); and (3) absence of optic disc edema, macular edema, or vitreous haze. There was agreement during the meeting that these definitions may be revised in the future based on updates to international consensus definitions of inactive disease.[18] Revision may also be needed if the definition

of remission changes to accept a few AC "cells" in the eyes of healthy adolescents.[19,20] Institutional Research Board ethics approval was not necessary for this continuation of activities of the long-established MIWGUC group.[7,12–14]

RESULTS

Development of the monitoring in disease remission pathway was focused on the three overarching principles

Overarching principle: stratification of risk. Although the evidence base on stratification of the risk of poor outcomes for children diagnosed with JIAU is strong, suggesting that younger age, presence of antinuclear antibodies, and presence of complications at uveitis onset all predict poor outcomes,[5,6,21–24] the evidence base on the determinants of disease recurrence for those who achieve remission are weak. There is, however, strong evidence on predictors of poorer outcomes for the wider population of children with visual disorders. Childhood visual impairment from any cause has a significant negative impact on quality of life in adulthood,[25,26] there is a lifelong risk of ongoing sight loss in those with a history of ocular hypertension or glaucoma,[27] and visually impactful structural complications (eg, ocular hypertension and glaucoma, cataract, and epiretinal membranes) typically progressively worsen in the presence of uncontrolled inflammation.[5] There was also recognition that the disorders grouped within "structural complications" would differ with regards to severity, risk of progression, impact on sight, and reversibility of sight loss. Children with complications that could progress without treatment and result in painless sight loss—with the exemplar complication being secondary glaucoma—require ongoing careful monitoring. Conversely, children with nonprogressive and visually insignificant cataract may be considered to have a stable structural complication.

Group discussion identified two groups within the population of children with JIAU in remission with different monitoring needs: those with drug-controlled disease and those who maintain drug-free remission (without the use of systemic or topical medication). For children with drug-controlled disease, the aim of monitoring would not be limited to eliciting evidence of loss of effectiveness of treatment. Monitoring would also be necessary to identify a safe time for drug tapering or cessation.[28,29]

An additional determination for monitoring need is the duration of time during which a disease recurrence is likely for a child with JIAU in remission. The evidence base suggests that disease recurrence typically occurs during the first year and is uncommon after 4 years following treatment cessation.[30–33] Other key considerations included reports of JIAU disease flares following established remission with onset of the peripubertal phase[34,35] and following infectious disease events,[36] although causal relationships between these events and disease flares could not be definitively determined. It was agreed that parents and patients should be counseled on the possibility of JIAU recurrence in some children in the event of the above but also on the unpredictability of these events.

Overarching principle: exit from monitoring. Transition from child to adult health services is a vulnerable time for children with chronic disease, with challenges exacerbated for those with rare, complex multisystem disorders. Clarity of guidance on the management of "exit" from a formal monitoring regimen was a necessary focus for MIWGUC.[37,38] The group had earlier reached a consensus that ongoing ophthalmic surveillance to detect the first episode of JIAU should continue until adulthood (18 years of age).[13] It was therefore considered reasonable to use this age threshold for monitoring in children and young people in JIAU remission. This was not in response to an absence of ongoing disease risk but rather a reflection of the lack of evidence on risk profiles for adult patients.[4] Again, on exit from monitoring, young people should be made aware of the ongoing possibility of disease recurrence.

Overarching principle: frequency of monitoring visits. Findings from the review of the evidence base were inconsistent or lacking on the "safe" duration of intraocular inflammation. This duration would be the time window after which irreversible complications would be expected to develop, should a hypothetical child develop recurrence of ocular inflammation the day after a monitoring visit at which they were declared inactive. Robust evidence on the duration of this window is unlikely to emerge due to the ethical challenges of undertaking interventional research that would involve allowing children to continue with active uveitis. Additionally, this time window is likely to be dependent on multiple interrelated factors, such as the level of inflammation.

MIWGUC earlier reached a consensus that a 3- to 4-month window was most likely to be needed to ensure prompt detection of new episodes of asymptomatic ocular inflammation in children with JIA and that children at lower risk due to years reached without uveitis should be monitored using a 6-month interval.[13] These recommendations are consistent with guidance from other groups, including the American College of Rheumatology (ACR) and the United Kingdom's Paediatric Ocular Inflammation Group.[8,9,11,13] These groups recommended ophthalmic monitoring at least every 3 months for children with established JIAU and/or chronic anterior uveitis on stable therapy but did not report guidance on monitoring frequency for those children in long-term disease remission.

Group discussion identified a consensus that those children who have been judged to have successfully attained drug-free remission for >3 months would be a more stable population with regards to the risk of new episodes of asymptomatic ocular inflammation. This would not, however, obviate the need for more frequent surveillance in the first months following treatment

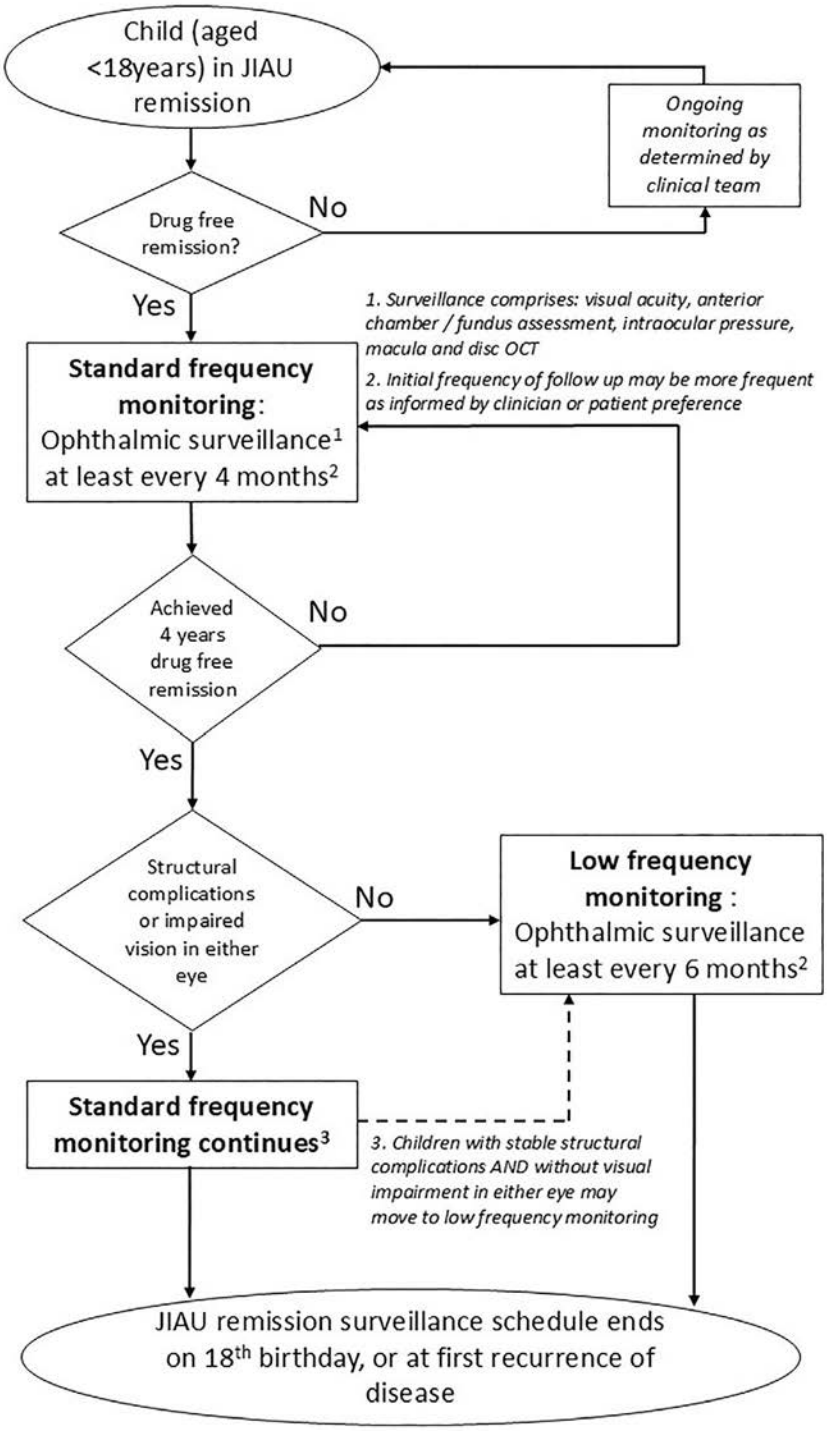

Figure 1. Algorithm for long-term ophthalmic monitoring for children with JIAU in disease remission. JIAU, juvenile idiopathic arthritis–associated uveitis; OCT, optical coherence tomography.

cessation for children in remission, as strongly recommended by the ACR.

The considerations above were used to create a list of statements presented to MIWGUC to determine agreement. The statements, and results of the vote (16 MIWGUC members involved), are presented below. Because these are consensus-based rather than evidence-based statements, MIWGUC also recommends that they are reviewed as new evidence emerges and accumulates.

The following are MIWGUC consensus statements on ophthalmic monitoring of children with uveitis in remission:

1. Standard frequency monitoring comprises ophthalmic examination at least every 4 months. Agreement: 16/16.

2. Monitoring comprises visual acuity, AC and assessment or fundus assessment, intraocular pressure measurement (IOP), and macular and disc optical coherence tomography. Agreement: 16/16.
3. Standard monitoring should be undertaken for the first four years following cessation of medication. Agreement: 16/16.
4. Patients with established structural complications (including a history of elevation of IOP) generally require ongoing standard frequency examination even after 4 years of treatment cessation. Agreement 16/16.
5. Low-frequency monitoring comprises ophthalmic examinations at least every 6 months. Agreement: 16/16.
6. Children who are without structural complication and have maintained drug-free remission for 4 years or more should undergo low-frequency monitoring. Agreement: 16/16.
7. Patients with stable structural complications and without visual impairment in either eye may move to low-frequency examination after 4 years drug-free remission. Agreement: 16/16.

The statements above resulted in the pathway in Figure 1.

DISCUSSION

Following a consensus approach developed by a multinational expert group and underpinned by frameworks successfully applied by other consensus development groups, we present recommendations on disease monitoring pathways in children whose JIAU has reached long-term remission. These recommendations include the frequency, mode, and duration of ongoing monitoring.

It was recognized that some patients and families would desire more frequent monitoring examinations, particularly if disease was previously severe or refractory to initial treatment or in the event of other drivers of patient and/or family need, such as psychosocial comorbidities.[39,40] In that event, these consensus guidelines could provide reassurance for families. Nevertheless, there should be scope for flexibility of implementation of the guidelines, as per clinician judgment, to personalize monitoring with more frequent examinations in response to patient and/or family need.

Strengths and limitations. The high levels of agreement indicate the strong support across a multinational group for the recommendations, which should support their adoption. However, although our multinational group covers a wide geographic area, it does not include clinicians from middle- or lower-income countries, where health care services may not allow for the monitoring pathway described by our recommendations. Another limitation is that the evidence based on this topic is scarce. Until the emergence of a more robust evidence base, these recommendations form a "best practice" model that supports care development across different settings.

Our consensus-based recommendations can help guide physicians' approach to ongoing examination of patients with JIAU in long-term drug-controlled and drug-free remission. This may also support more effective use of eye care services. Refinement of the protocol in view of emerging evidence on biomarkers for disease recurrence and imaging-based ocular examinations will be needed in the near future.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Foeldvari confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Yu HH, Chen PC, Wang LC, et al. Juvenile idiopathic arthritis-associated uveitis: a nationwide population-based study in Taiwan. PLoS One 2013;8(8):e70625.
2. Angeles-Han ST, Pelajo CF, Vogler LB, et al; CARRA Registry Investigators. Risk markers of juvenile idiopathic arthritis-associated uveitis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. J Rheumatol 2013;40(12):2088–2096.
3. Saurenmann RK, Levin AV, Feldman BM, et al. Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term followup study. Arthritis Rheum 2007;56(2):647–657.
4. Rypdal V, Glerup M, Songstad NT, et al; Nordic Study Group of Pediatric Rheumatology. Uveitis in juvenile idiopathic arthritis: 18-year outcome in the population-based Nordic cohort study. Ophthalmology 2021;128(4):598–608.
5. Hettinga YM, Verhagen FH, van Genderen M, et al. Characteristics of childhood uveitis leading to visual impairment and blindness in the Netherlands. Acta Ophthalmol 2014;92(8):798–804.
6. Angeles-Han ST, Srivastava SK. Screening, monitoring, and treating children with juvenile idiopathic arthritis-associated uveitis: visualizing better outcomes. J Rheumatol 2022;50(3):300–303.
7. Foeldvari I, Maccora I, Petrushkin H, et al. New and updated recommendations for the treatment of juvenile idiopathic arthritis–associated uveitis and idiopathic chronic anterior uveitis. Arthritis Care Res (Hoboken) 2023;75(5):975–982.
8. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis-associated uveitis. Arthritis Care Res (Hoboken) 2019;71(6):703–716.
9. Constantin T, Foeldvari I, Anton J, et al. Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. Ann Rheum Dis 2018;77(8):1107–1117.
10. Foster H, Ramanan AV. 'The eyes have it!' The need to improve awareness and access to early ophthalmological screening for

juvenile idiopathic arthritis associated uveitis. Rheumatology (Oxford) 2009;48(4):330–331.
11. Solebo AL, Rahi JS, Dick AD, et al; Members of the POIG Uveitis Delphi Group. Areas of agreement in the management of childhood non-infectious chronic anterior uveitis in the UK. Br J Ophthalmol 2020; 104(1):11–16.
12. Foeldvari I, Klotsche J, Simonini G, et al. Proposal for a definition for response to treatment, inactive disease and damage for JIA associated uveitis based on the validation of a uveitis related JIA outcome measures from the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC). Pediatr Rheumatol Online J 2019; 17(1):66.
13. Foeldvari I, Bohn M, Petrushkin H, et al. A practical approach to uveitis screening in children with juvenile idiopathic arthritis. Br J Ophthalmol 2025;109(3):372–376.
14. Heiligenhaus A, Foeldvari I, Edelsten C, et al; Multinational Interdisciplinary Working Group for Uveitis in Childhood. Proposed outcome measures for prospective clinical trials in juvenile idiopathic arthritis-associated uveitis: a consensus effort from the multinational interdisciplinary working group for uveitis in childhood. Arthritis Care Res (Hoboken) 2012;64(9):1365–1372.
15. van der Heijde D, Aletaha D, Carmona L, et al. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. Ann Rheum Dis 2015;74(1):8–13.
16. Gattrell WT, Logullo P, van Zuuren EJ, et al. ACCORD (ACcurate COnsensus Reporting Document): a reporting guideline for consensus methods in biomedicine developed via a modified Delphi. PLoS Med 2024;21(1):e1004326.
17. Solebo AL, Kellett S, Rahi J, et al; Pediatric Ocular Inflammation UNICORN Study Group. Development of a nationally agreed core clinical dataset for childhood onset uveitis. Front Pediatr 2022;10: 881398.
18. Jabs DA, Nussenblatt RB, Rosenbaum JT, et al. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol 2005;140(3):509–516.
19. Solebo AL. Why do we treat? Defining disease control in juvenile idiopathic arthritis–associated uveitis. J Rheumatol Published online July 1, 2023. https://doi.org/10.3899/jrheum.2022-1336.
20. Solebo AL, Bellchambers A, Kellett S, et al. Establishing the normative data set necessary for imaging-based childhood uveitis surveillance: a cross-sectional study. Invest Ophthalmol Vis Sci 2024;65(1):9.
21. Edelsten C, Lee V, Bentley CR, et al. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. Br J Ophthalmol 2002;86(1):51–56.
22. de Boer J, Wulffraat N, Rothova A. Visual loss in uveitis of childhood. Br J Ophthalmol 2003;87(7):879–884.
23. de Boer J, Steijaert A, van den Bor R, et al. Development of macular edema and impact on visual acuity in uveitis associated with juvenile idiopathic arthritis. Ocul Immunol Inflamm 2015;23(1):67–73.
24. Gregory AC II, Kempen JH, Daniel E, et al; Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study Research Group. Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: the Systemic Immunosuppressive Therapy for Eye Diseases Study. Ophthalmology 2013;120(1): 186–192.
25. Cumberland PM, Rahi JS; UK Biobank Eye and Vision Consortium. Visual function, social position, and health and life chances: the UK Biobank Study. JAMA Ophthalmol 2016;134(9):959–966.
26. Rahi JS, Cumberland PM, Peckham CS. Visual impairment and vision-related quality of life in working-age adults: findings in the 1958 British birth cohort. Ophthalmology 2009;116(2):270–274.
27. Tan SZ, Yau K, Steeples LR, et al. Incidence, management and outcome of raised intraocular pressure in childhood-onset uveitis at a tertiary referral centre. Br J Ophthalmol 2019;103(6):748–752.
28. Marelli L, Romano M, Pontikaki I, et al. Long term experience in patients with JIA-associated uveitis in a large referral center. Front Pediatr 2021;9:682327.
29. Simonini G, Taddio A, Cattalini M, et al. Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. Arthritis Care Res (Hoboken) 2011;63(4):612–618.
30. Simonini G, Bracaglia C, Cattalini M, et al. Predictors of relapse after discontinuing systemic treatment in childhood autoimmune chronic uveitis. J Rheumatol 2017;44(6):822–826.
31. Kalinina Ayuso V, van de Winkel EL, Rothova A, et al. Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. Am J Ophthalmol 2011;151(2):217–222.
32. McCracken C, Shantha JG, Yeh S, et al. Relapse and remission in children with chronic noninfectious uveitis treated with methotrexate. J Rheumatol 2022;49(11):1289–1291.
33. Saboo US, Metzinger JL, Radwan A, et al. Risk factors associated with the relapse of uveitis in patients with juvenile idiopathic arthritis: a preliminary report. J AAPOS 2013;17(5):460–464.
34. de Gruijter NM, Naja M, Peckham H, et al. A systematic review exploring the bidirectional relationship between puberty and autoimmune rheumatic diseases. Pediatr Rheumatol Online J 2021;19(1):47.
35. Hoeve M, Kalinina Ayuso V, Schalij-Delfos NE, et al. The clinical course of juvenile idiopathic arthritis-associated uveitis in childhood and puberty. Br J Ophthalmol 2012;96(6):852–856.
36. Hügle B, Krumrey-Langkammerer M, Haas JP. Infection with SARS-CoV-2 causes flares in patients with juvenile idiopathic arthritis in remission or inactive disease on medication. Pediatr Rheumatol Online J 2021;19(1):163.
37. Parker DM, Angeles-Han ST, Stanton AL, et al. Chronic anterior uveitis in children: psychosocial challenges for patients and their families. Am J Ophthalmol 2018;191:xvi–xxiv.
38. Mikola K, Rebane K, Arnstad ED, et al. Transitioning patients with juvenile idiopathic arthritis to adult care: the Nordic experience. Pediatr Rheumatol Online J 2022;20(1):84.
39. McDonald J, Cassedy A, Altaye M, et al. Comprehensive assessment of quality of life, functioning, and mental health in children with juvenile idiopathic arthritis and noninfectious uveitis. Arthritis Care Res (Hoboken) 2022;74(8):1311–1320.
40. Miserocchi E, Modorati G, Mosconi P, et al. Quality of life in patients with uveitis on chronic systemic immunosuppressive treatment. Ocul Immunol Inflamm 2010;18(4):297–304.

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1112–1124
DOI 10.1002/acr.25550

Understanding Contributors of Resilience in Youth With Childhood-Onset Systemic Lupus Erythematosus Through a Socioecological Lens: A Mixed-Methods Study

Isabella Zaffino,[1] Louise Boulard,[1] Joanna Law,[1] Asha Jeyanathan,[1] Lawrence Ng,[1] Sandra Williams-Reid,[2] Kiah Reid,[2] Angela Cortes,[2] Eugene Cortes,[2] Ashley Danguecan,[2] Deborah M. Levy,[3] Linda T. Hiraki,[3] and Andrea M. Knight[4]

Objective. This study aimed to identify themes contributing to resilience in childhood-onset systemic lupus erythematosus (cSLE), distinguish between profiles of resilience, and examine how they relate to underlying themes and patient characteristics.

Methods. We conducted a mixed-methods study of 21 patients with cSLE aged 11 to 19 years at a Canadian tertiary care center from October 2022 to July 2024. We purposively sampled patients belonging to ethnically and culturally diverse backgrounds to complete semistructured interviews. We qualitatively defined features of resilience and distinguished profiles of low versus high socioecological resilience according to patient median on the Child and Youth Resilience Measure-Revised (CYRM-R). Profiles were then related to sociodemographic (eg, adverse childhood experiences, health literacy), disease features (eg, age at diagnosis, disease duration), and patient-reported outcomes (eg, anxiety and depressive symptoms).

Results. Factors contributing to resilience were grouped into five themes: familial environment, social support beyond family, health services and information, life with SLE, and sense of self. Cultural influences were reported to impact several themes. Patients with high resilience (scores above 73 on CYRM-R) reported more facilitators in each thematic area, whereas patients with low resilience experienced more challenges in these areas, in addition to greater number of adverse childhood experiences, lower health literacy, earlier age at diagnosis, longer disease duration and poorer mental health.

Conclusion. Findings support a dynamic model of resilience, shaped by a combination of sociodemographic, disease, personal, cultural and social factors. This improved understanding of resilience may help direct comprehensive care for youth with cSLE and guide targeted interventions for youth at risk of poor outcomes.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with heterogeneous clinical manifestations.[1] Childhood-onset SLE (cSLE), affecting 10% to 20% of all patients with SLE, is characterized by increased disease damage and multiorgan disease activity.[1]

Resilience measures an individual's ability to effectively overcome adversity. Although increased resilience is associated with improved clinical and mental health outcomes in populations with chronic disease,[2] literature about patients with cSLE is scarce. Only a single study has examined individual psychological resilience,[3] that is, an individual's innate mental capacity to overcome adversity.[3,4] However, it is important to

Supported by the Lupus Research Alliance, the US Department of Defense, SickKids Garry Hurvitz Centre for Brain and Mental Health Outcomes, and a Canadian Institutes for Health Research - Canada Research Chair Tier 2 in Mental Health and Chronic Disease of Childhood (to Dr Knight).

[1]Isabella Zaffino, HBSc, Louise Boulard, HBA, Joanna Law, HBSc, MHSc, Asha Jeyanathan, HBSc, Lawrence Ng, BSc: SickKids Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada; [2]Sandra Williams-Reid, OCD, Kiah Reid, BA, Angela Cortes, BA, Eugene Cortes, MMSc, Ashley Danguecan, PhD, CPsych: The Hospital for Sick Children, Toronto, Ontario, Canada; [3]Deborah M. Levy, MD, MS, Linda T. Hiraki, MD, ScD: SickKids Research Institute, The Hospital for Sick Children, and University of Toronto, Toronto, Ontario, Canada; [4]Andrea M. Knight, MD, MSCE: The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada.

Authors Zaffino and Boulard are co-first authors and contributed equally to this work.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25550).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25550.

Address correspondence via email to Andrea M. Knight, MD, MSCE, at andrea.knight@sickkids.ca.

Submitted for publication December 21, 2024; accepted in revised form April 3, 2025.

SIGNIFICANCE & INNOVATIONS

- This study provides a comprehensive exploration of resilience in youth with childhood-onset systemic lupus erythematosus (cSLE), emphasizing how both socioecological and individual psychological factors interact to influence resilience profiles, disease outcomes, and mental health.
- We provide insight into the unique strengths and challenges of diverse youth with cSLE, which is limited in the current literature.
- Our approach addresses a gap in understanding the complex interplay between individual, family, and cultural dynamics in this population.
- Findings underscore the need for family-centered approaches, culturally sensitive mental health supports, and self-management strategies to enhance resilience in youth with cSLE to improve long-term clinical and psychosocial outcomes.

also examine resilience within an individual's environment, defined as socioecological resilience.[5] Addressing this is crucial because SLE disproportionately affects marginalized populations.[6] Further, socioecological factors (eg, discrimination, income) play a significant role in patient outcomes, such as disease activity and physical functioning.[6]

The Disability-Stress-Coping Model conceptualizes resilience in terms of risk and protective factors contributing to biopsychosocial disease adjustment in pediatric populations.[7] Although the model encompasses individual and social factors, better characterization pertaining to cSLE is needed. In addition to the racial and economic disparities observed in patients with cSLE,[6] this population is also characterized by a high proportion of adolescents who face unique changes in psychosocial development such as achieving greater autonomy, complexities in maintaining peer relationships, and changes within the family unit. Although the current model strictly characterizes resilience factors as either barriers or facilitators, resilience is a dynamic process rather than a stable trait.[8] Thus, better characterization of resilience within youth with cSLE is needed.

Because cSLE primarily affects racially and ethnically marginalized pediatric populations who often face barriers such as limited financial resources, geographic limitations, and language barriers when obtaining health care, a disproportionate impact on biopsychosocial well-being exists. Because these patient perspectives are scarce in the literature, we purposively sampled from this population to explore the socioecological resilience factors specific to these patients. This study aimed to (1) identify themes contributing to resilience in patients with cSLE, (2) distinguish profiles of low versus high socioecological resilience, (3) relate the profiles to themes of resilience, and (4) relate the profiles to patient characteristics and outcomes.

PATIENTS AND METHODS

Setting and participants. This mixed-methods study was conducted between October 2022 to July 2024 at The Hospital for Sick Children (SickKids) in Toronto, Canada. Participants were recruited from a larger study examining mental health care disparities in patients with cSLE who met the following inclusion criteria: (1) diagnosis of cSLE according to American College of Rheumatology or Systemic Lupus International Collaborating Clinics classification criteria,[9,10] (2) under 19 years old, and (3) ongoing care at the SickKids Lupus Clinic or the SickKids Lupus Neuropsychology service. For this study, additional eligibility criteria were: (1) age of at least 12 years old, and (2) willingness to discuss their mental health experiences. We used purposive sampling, a technique allowing for intentional selection of participants with specific characteristics, to ensure an enriched representation of youth from ethnically diverse backgrounds, reflecting the population with cSLE. This study was approved by the Research Ethics Board at the Hospital for Sick Children (REB #1000078857).

Data collection. *Patient characteristics.* Resilience levels were collected using self-report questionnaires during the original study visit. Socioecological resilience was measured using the 17-Item Child and Youth Resilience Measure-Revised (CYRM-R) questionnaire,[5] assessing family, peer, and community support factors, with scores ranging from 17 to 85 points. Individual psychological resilience was measured using the 10-item Connor-Davidson Resilience Scale (CD-RISC 10) questionnaire with scores ranging 0 to 40 points.[3] On both measures, higher scores indicate greater resilience.

Sociodemographic characteristics collected via patient self-report included: age, gender, ethnicity, poverty status, adverse childhood experiences (ACEs), and health literacy. Parental assistance was provided when needed. Patients were asked to report their gender as male, female, or other (option to specify). Ethnicity was based on the census categories for country of family origin used by Statistics Canada,[11] categorized as European (British, French, Northern, Southern, Eastern, and Western European), Asian (East Asian, South Asian, Southeast Asian, West Asian, and Pacific Islander), Arabic, African and Caribbean, American (Indigenous and Latin American), multiethnic (indicating more than one ethnic origin), and other (self-identified other ethnic origin). Poverty status was determined using the low-income cut-offs by Statistics Canada, considering self-reports of household income level and number of individuals residing in a household.[12]

ACEs, defined as traumatic or stressful events occurring before 18 years old, were measured using the validated 19-item Pediatric ACEs and Related Life Events Screener (PEARLs).[13] Scores range 0 to 19 points and indicate the number of ACEs exposed to.[13] The Health Literacy Assessment Scale for Adolescents (HAS-A) was used to assess health literacy across three domains; communication (comfort or ability to ask health provider

questions), confusion (challenges in understanding health information), and functional (reading and numeracy skills).[14] On the communication subscale, scores 0 to 14 indicate high communication health literacy, and scores 15 to 20 indicate low communication health literacy. On the confusion subscale, scores 0 to 7 indicate low confusion, and scores 8 to 16 indicate high confusion. On the functional subscale, scores 0 to 11 indicate high functional health literacy, and scores 12 to 24 indicate lower functional health literacy.[14]

Neighborhood-level marginalization was measured using the 2021 Ontario Marginalization (ON-Marg) Index. Patient postal codes that were extracted from medical charts were mapped to dissemination areas via the Postal Code Conversion File[15] in which corresponding marginalization scores were assigned.[15] Patients were categorized into quintiles from 1 (least marginalized) to 5 (most marginalized) according to the distribution of z-scores in Ontario. Dimensions evaluated included material resources (assesses community poverty; captures economic opportunities, education, and housing) and racialized and newcomer populations (assesses proportion of recent immigrants and visible minorities; reflects structural racialization and xenophobia).[16]

Disease characteristics collected via medical chart review included: age at diagnosis, disease duration, disease activity, disease damage, and history of major organ involvement. Disease duration was calculated from the diagnosis to the study visit date. Disease activity was measured using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K).[17] Scores range from 0 to 105 points, with higher scores indicating greater disease activity and those greater than or equal to 4 indicating active disease. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) was used to measure irreversible damage across 12 organ systems.[17] We defined scores greater than 0 at the last study visit indicative of damage. History of major organ involvement was established based on the presence of neuropsychiatric lupus and/or lupus nephritis, diagnosed by the patient's rheumatologist.

Patient-reported outcomes included depressive and anxiety symptoms, executive functioning, pain interference, and fatigue and were assessed using self-report questionnaires. The 21-item Beck Depression Inventory - Second Edition (BDI-II) evaluates depressive symptoms in individuals aged 13 years and older.[18] Raw scores were converted to T-scores (mean = 50 and SD = 10); higher T-scores indicate more severe depressive symptoms.[18] Data from one participant under 13 years old who completed the Child Depressive Inventory-2, were excluded from this analysis. The 41-item Screen for Child Anxiety Related Emotional Disorders (SCARED) assesses anxiety symptoms in children aged 8 to 18 years.[19] Scores range from 0 to 82 points, with scores greater than or equal to 25 indicating clinical anxiety. Higher scores indicate more severe symptoms.[19] Executive functioning was evaluated using the 55-item Behavior Rating Inventory of Executive Functioning (BRIEF-2) in children aged 5 to 18 years.[20] Raw scores were converted to T-scores (mean = 50 and SD = 10); higher scores indicate more frequent executive functioning difficulties. Pain interference and fatigue were measured with the 37-Item Patient-Reported Outcomes Measurement Information Systems (PROMIS SF 37).[21] Raw scores were transformed into T-scores (mean = 50 and SD = 10); higher scores indicate greater levels of pain interference and fatigue.

Interviews. Interviews were conducted by a research assistant trained in qualitative interview techniques, using a constructed interview guide (Supplementary File 1) based on Kilbourne's determinants of health disparities model.[22] Before data collection, the interview guide was pilot-tested to ensure clarity and relevance.

Participants were selected, with an estimated sample size of n = 25 to reach thematic saturation. Saturation was determined to have been reached after 21 interviews, at which point recruitment was stopped. Participants received a gift card for their participation. Interviews occurred virtually (translation services were provided for non-English speaking participants) and were digitally recorded, transcribed, de-identified, and entered into NVivo software.[23]

Data analysis. Interview coding for qualitative analysis was completed using a mixed deductive-inductive approach. An a priori coding system adapted from Wallander and Varni's resilience framework and Kilbourne's determinants of health disparities model was used to identify themes of resilience.[7,22] During line-by-line reading, new codes were generated, evaluated and revised as appropriate. Coding involved at least two coders (among AD, IZ, JL, and LB), and review sessions were conducted to discuss code revisions and discrepancies. Any discrepancies were resolved by consensus with a third reviewer. Themes were derived, and illustrative quotes were extracted from coded text.

Mixed-methods analysis integrating qualitative and quantitative data was completed using previously published methodology in cSLE qualitative research.[24] Focusing on socioecological resilience, patients were assigned a low or high resilience profile based on the median socioecological resilience (CYRM-R) score of our sample. We then compared patients in the low versus high resilience profiles by the number of barriers and facilitators for resilience reported in the interview data in each of the identified thematic areas. We also described sociodemographic characteristics, disease characteristics, and patient-reported outcome measures among both resilience profiles.

RESULTS

Baseline cSLE cohort characteristics. Of 73 eligible patients approached between October 2022-July 2024 at the SickKids Lupus Clinic, 35 provided informed consent, and 21 participated in the study. Patient characteristics of the cohort with cSLE are presented in Table 1.

Table 1. Characteristics of the cohort with cSLE*

Cohort Characteristics	Total Cohort (n = 21)[a]
Sociodemographic characteristics	
Age at study visit, mean ± SD, y	15.2 ± 1.9
Gender, n (%)	
Female	17 (81.0)
Male	3 (14.3)
Other, nonbinary	1 (4.8)
Ethnicity, n (%)	
African or Caribbean	3 (14.3)
East Asian	5 (23.8)
European	1 (4.8)
Latin American	1 (4.8)
Multiethnic	1 (4.8)
South Asian	5 (23.8)
Southeast Asian	4 (19.0)
Household income below poverty line, n (%)	6 (28.6)
Ontario Marginalization	
Material resources score, mean ± SD	0.66 ± 1.2
Highest quintile, n (%)	9 (45.0)
Racialized and newcomer population score, mean ± SD	1.54 ± 0.8
Highest quintile, n (%)	14 (66.7)
ACEs and Related Life Events (PEARLs), mean ± SD	2.4 ± 2.3
Health Literacy (HAS-A)[b]	
Communication, mean ± SD	15.1 ± 4.4
Low (worse), n (%)	7 (33.3)
High (better), n (%)	14 (66.7)
Confusion, mean ± SD	4.7 ± 3.4
High (worse), n (%)	4 (19.0)
Low (better), n (%)	17 (81.0)
Functional, mean ± SD	7.2 ± 4.3
High (worse), n (%)	4 (19.0)
Low (better), n (%)	17 (81.0)
Disease characteristics	
Age at diagnosis in years, mean ± SD	12.5 ± 4.4
Disease duration in years, mean ± SD	2.36 ± 1.9
Disease activity (SLEDAI), mean ± SD	3.9 ± 3.3
Active disease (≥4), n (%)	12 (57.1)
Disease damage (SDI, score >0), n (%)	0 (0.0)
Presence of major organ disease, n (%)	11 (52.4)
Lupus nephritis	9 (42.9)
Neuropsychiatric lupus	1 (4.8)
Both lupus nephritis and neuropsychiatric lupus	1 (4.8)
Resilience levels	
Socioecological (CYRM-R), median (IQR)	73.0 (69.0–78.0)
Individual psychological (CD-RISC 10), median (IQR)	23.0 (20.0–29.0)
Patient-reported measures	
Depressive symptom (BDI-II) total T score, mean ± SD	62.5 ± 15.2
Anxiety symptom (SCARED) total score, mean ± SD	26.2 ± 14.5
Clinically elevated anxiety symptoms (scores ≥ 25), n (%)	10 (47.6)
Executive functioning (BRIEF-2) total score, mean ± SD	57.8 ± 14.1
Pain Interference (PROMIS) total score, mean ± SD	46.2 ± 11.5
Fatigue (PROMIS) total score, mean ± SD	52.1 ± 12.1

* ACEs, adverse childhood experiences; BDI-II, Beck Depression Inventory - Second Edition; BRIEF-2, Behavior Rating Inventory of Executive Functioning; CD-RISC 10, 10-item Connor-Davidson Resilience Scale; cSLE, childhood-onset systemic lupus erythematosus; CYRM-R, Child and Youth Resilience Measure-Revised; HAS-A, Health Literacy Assessment Scale for Adolescents; IQR, interquartile range; ON-Marg, Ontario Marginalization index; PEARLs, Pediatric adverse childhood experiences and Related Life Events Screener; PROMIS, Patient-Reported Outcomes Measurement Information Systems; SCARED, Screen for Child Anxiety Related Emotional Disorders; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

[a] Missing data: ethnicity (n = 1), income (n = 1), ON-Marg (n = 1), depression (n = 2), anxiety (n = 1), executive function (n = 3), pain interference (n = 4), and fatigue (n = 4).

[b] In the HAS-A communication subscale, higher scores indicate better health literacy and lower scores indicate worse health literacy. On the confusion and functional subscales, higher scores indicate worse health literacy, whereas lower scores indicate better health literacy.

The cohort consisted of 17 (81%) females with an average age of 15.2 ± 1.9 years. The most frequently reported ethnic groups were 23.8% East Asian and 23.8% South Asian. Twenty-nine percent of the cohort had a household income below the poverty line. For neighborhood-level marginalization, 45% belonged to the most marginalized quintile for the material resources dimension of the marginalization measure (ON-Marg), and 67% for the racialized and newcomer dimension. Patients experienced an average of 2.4 ± 2.3 ACEs. Low health literacy was most frequently reported on the communication subscale (33%).

The mean age at diagnosis was 12.5 ± 4.4 years and disease duration was 2.4 ± 1.9 years. Average disease activity was 3.9 ± 3.3 on the SLEDAI-2K with 57% having active disease. Eleven participants (52%) had a history of major organ disease. No patient had disease damage.

The median socioecological resilience (CYRM-R) score was 73 (interquartile range [IQR] 69–78). Patients with scores less than 73 were designated as a low resilience profile, whereas scores greater than 73 were designated as a high resilience profile. The median individual psychological resilience (CD-RISC 10) score was 23 (IQR 20–29).

Average BDI-II depressive symptoms were 62.5 ± 15.2. Average SCARED anxiety symptoms were 26.2 ± 14.5, with 47.6% of patients exhibiting clinically elevated anxiety symptoms. Mean PROMIS pain interference and fatigue scores were 46.2 ± 11.5) and 52.1 ± 12.1, respectively.

Table 2. Representative quotes of themes of resilience for youth with cSLE*

Themes	Barriers to resilience	Facilitators of resilience
Family environment		
Family dynamics	"My family, they wouldn't really understand, so I just don't really tell them."	"Ways I will calm myself down would be like, I'll either talk to my brother, talk to my mom, or my friends."
	"It's just that they don't like to show their emotions. So when I see my mom cry like what? Is there something wrong happening? Like something very bad?"	"My parents are the ones that keeping track of [my medication], mostly my mom. I'll say my relationship is very, very strong with my parents."
Cultural influence	"I feel like a lot of Chinese culture [is] like, 'oh you're not feeling depressed. It's just all in your head.' I mean, like it is in your head, but it's not like in your head the way that they say it is."	"If I'm feeling really stressed or overwhelmed, that's when I'll pray [...] I think there's something about saying the prayers and chanting it that does feel grounding and safe."
	"I think sometimes, if I don't agree with what they're saying that's because sometimes I feel that there is a disconnect, and that might be a generational thing, or it might be because they're immigrants."	"If I'm at the temple, it feels really calm, and it's really a nice safe space."
Social support beyond the family		
Peers	"I also have been bullied multiple times. A student once said at elementary school that that my stretch marks, he called them fish gills and called me a fish and made fun of me."	"They've been very caring and stuff, like together they made like gift baskets for me. It was very cute."
	"I have lupus, and when I told like a few classmates about this, one kid coughed in my face because I said, like, oh, I get sick easily because I'm being compromised."	"Yeah, I think I was actually really lucky because my best friend from high school, she ended up in the same program as me. So, we're in a lot of the same classes together. So, I always have someone by my side for them."
School	"On the first day of school, I always tell the teachers that there's a chart that they have to know about me because I don't wanna talk to them face to face. But then they never go through the chart."	"My teachers and my guidance counselor also told me that I have access to more support if I needed it and I just needed to tell them."
		"I can take frequent breaks if I need extra support with my studies."
Health service and information		
Clinical encounters	"At first, I was upset at my family doctor for almost not diagnosing me because she said that everything was fine, even though I showed her my symptoms and they were really lupus. It was almost obvious I had lupus, but my doctor just didn't acknowledge that."	"Oh they're really nice people, they explained it really well too... like, what the problem is, what you need to do and stuff."
	"It's just as a kid I would have liked the reassurance of 'OK, this is what it is. Here is what's gonna happen.' Instead of just being like, 'OK, here's the diagnosis. Here's some medications. Good luck, kiddo.'"	"They're all really nice. And welcoming. So I feel good around them."
		"I think what they've already told us, when you get older, there will be a bunch of kids the same age as you to tell you about how everything works, and when you become an adult what to do. So, I think that's what reassured me."
Patient knowledge and preference	"I might explain it to them [the doctors], but they probably won't understand how I'm explaining it [the pain] to them."	"I just googled common lupus symptoms. I read a book about some of the symptoms to make sure because sometimes you might have it and you don't know you have it."
	"I haven't told them [how not being able to exercise makes me feel] yet. Because I don't know where to start."	"And because I've watched them [the doctors] for a year now, I've done a lot of research and I know a lot about lupus and a lot about how rheumatologists see their patients."
Life with lupus		
Current experience	"It was a combination of sadness and anger because I wasn't able to move, get out of bed. I needed both my parents' support just to go to the bathroom and that, well, at that point I was feeling really, really angry and sad."	"And I've gotten used to [lupus]. So it doesn't even come to mind most of the time."

(Continued)

Table 2. (*Cont'd*)

Themes	Barriers to resilience	Facilitators of resilience
	"It was really hard to do anything because my legs always hurt. And so then I would miss a lot of school. And that would cause me to be stressed because of the amount of work that I miss."	"As much as it is bad, it's something that, mostly grown-ups handle. So, as a kid who can handle it, I've learned to take all the benefits out of it. And then that's like all learning."
		"So, in middle school, I think I just started taking that on as like, I needed to advocate that I have lupus. I'm not gonna be away on these days because of that, and it's not like I'm skipping class or I just don't want to be in class. It's actually for a reasonable reason."
Anticipation of future	"I just don't want to die. I don't want my kidneys to fail."	"I do think about that, but I know things will pan out and there will be solutions because I know 10 years ago there weren't as many solutions as now."
	"Sometimes I think about when I'm older, how often would flare-ups happen and if they do, how much will I be limited to? What will I be able to do? What won't I be able to do?"	"I'd say for me the reason why I think [lupus] has a more positive effect on my life is because I know I can get through this if I keep doing what I do. You know, taking medication, eating healthy, getting a lot of sleep."
	"And I'm kind of also scared about when I'm too old for [the pediatric hospital]. I'm scared of my lupus flares up as an adult. I don't know how that would work."	
Sense of self		
Personal abilities	"And I really like structure, like I *really* like. I thrive on routine, so having to reorient myself for university was hard."	"And I want to continue to do that in the future. I'm in high school, right? I want to do electrical engineering in university as my major. Yeah it's mostly fun—it's not really learning, like it seems more fun."
		"Yeah. I think like for me, like I really like school. Like, I'm actually very engaged with the stuff I learn with."
Belonging	"For some teachers, I don't think it's important to vocalize that I have lupus because I don't want to see them to see me as any different."	"I think with having lupus and the different mental health aspects to it, I've related to kids that are from [Hospital]. I definitely think I relate to them more or I have more of a connection with them because I understand what they went through."
	"And I have a sore body sometimes or I get exhausted easily compared to others. And seeing that other students around me are not feeling the same way—they can run fine or they're not yawning all the time like I am. That is bothersome to me."	"I know they can relate, my friends have problems too. My best friend, she has Type 1 diabetes, so she knows what it's like to have a noncommunicable disease like that."
	"Honestly, I don't know their full-on life like they have normal lives, not any medical issues that they have, so I still feel different. As well as like parents are worried, like, 'are you OK? Do you need to rest?' I'm like, 'yeah, I'm fine.'"	"My uncle also had to use cortisone for a while, but for something different. And that was actually very helpful. He was literally telling me whatever I was experiencing like he was experiencing exact same thing. That was a shared experience."
Perception of self	"I don't want to cry in front of them. I don't want them to think I'm weird. Maybe I just care about what other people think. A lot."	"I don't like that some kids don't have an autoimmune disease like me, but they have some other problems that they suffer with, and they get pretty down from that. So when I hear their experiences with that and how they feel and how they feel down when I compare my mental health and theirs, I'm doing better."
	"I don't really like talking about my emotions because I've developed some sort of sense that it might be a little bit of a burden."	"When I'm crying, it's what I go to because, what do I do, just sit there and wallow in self-pity? No."

* cSLE, childhood-onset systemic lupus erythematosus.

Themes shaping resilience. Five central themes shaping resilience in youth with cSLE emerged. Illustrative quotes are presented in Table 2.

Familial environment. Eleven (52%) patients identified actions by family members that supported their physical well-being such as parental assistance with treatment adherence. Parents demonstrated initiative in understanding their child's diagnosis by independently seeking information about the disease. Notably, two (10%) patients received guidance from other family members diagnosed with SLE. Ten (48%) patients turned to parents or siblings for emotional support. However, nine (43%) patients reported actions that hindered their well-being, including seven

(33%) who mentioned an inability to discuss their emotional state because of a lack of mental health openness.

Patients were also asked about their family dynamics and home environments. Sixteen (76%) patients highlighted positive aspects including 11 (52%) who reported closeness to parents. Four (19%) patients reported having a good relationship with their siblings. Conversely, 13 (61%) patients mentioned poor familial dynamics including negative relationships, caregiver conflicts, financial burden, and lack of communication. Of these patients, five (23%) reported ACEs such as caregiver mental illness, divorced caregivers, death of a parent, and physical abuse.

Regarding cultural influences, 10 (48%) patients noted benefits from their familial background such as strong cultural values, community belonging, religious coping, and personal growth from their immigration experience. Despite this, 14 (67%) patients reported a lack of mental health awareness, community and religious pressures, and language barriers within the family.

Social support beyond family. Patients were asked about additional social support received. Thirteen (62%) patients reported strong peer relationships, often turning to friends when feeling down. Despite this, ten (48%) participants identified negative aspects of peer relationships. Of these patients, four (19%) experienced a lack of close friendships due to changing schools, the COVID-19 pandemic, and an inability to discuss their disease. Additionally, two (10%) patients were bullied, with one targeted for SLE symptoms specifically.

Support from educational institutions varied. Twelve (57%) patients reported active implementation of accommodations such as individualized education plans (IEPs), extra breaks, and assignment extensions. Three (14%) patients benefited from caring teachers. However, one patient reported a negative encounter with a teacher who refused to read their IEP.

Health services and information. Fifteen patients (71%) reported positive patient-clinician relationships, describing interactions as comfortable. Patients endorsed open communication particularly with providers who gave thorough explanations of diagnoses, treatment plans, and transitional care information. These relationships were strengthened by continuous care, with one patient stating: "some of the doctors I've had have gone through major events in my life." Six (29%) patients valued the mental health referrals and resources provided during clinic visits. Conversely, three (14%) mentioned difficulties in obtaining their diagnosis, citing long wait-times and feelings of dismissal by providers upon initial symptom presentation. Four (19%) patients reported communication difficulties due to an inability to articulate needs and fears of misunderstandings.

Although patients initially had a limited understanding of their diagnosis, four (19%) reported seeking information from external sources to gain further information on disease management, which served to manage expectations. However, one patient reported that searching for SLE information caused fear of disease complications rather than reassurance.

Life with SLE. Seventeen (81%) patients reported physical symptoms of SLE, including pain, swelling, and medication side effects. Patients reported limitations on functioning such as fatigue, distractibility, inability to participate in sports, and difficulties walking and writing. One participant noted that managing their symptoms "feels like a nuisance." Despite this, nine (43%) patients exhibited personal growth from their experience. Among them, six (29%) patients described benefiting from self-management strategies regarding medication adherence, anti-inflammatory diets, and sun sensitivity. Patients also mentioned developing increased self-competence and knowledge from their experience with SLE, with one inspired to pursue a career in rheumatology.

Eleven (52%) patients anticipated negative outcomes related to their future including increased symptoms, limitations on educational and professional development, apprehension about transition to adult care and fears of death. However, six patients (29%) expressed a positive outlook, expecting minimal impacts through consistent disease management, and remaining hopeful of medical advancements.

Sense of self. Thirteen patients (62%) reported possessing positive personal attributes and qualities associated with their sense of confidence. Among these patients, eight (38%) discussed career aspirations and goal-setting behaviors, and three (14%) emphasized dedication to academic studies.

Seven (33%) youth described feelings of nonbelonging, such as feeling different than healthy peers. Four (19%) described feelings of resentment toward their friends, with one patient stating, "people my age don't have to worry about their body as much." Patients also described feeling left out from activities, reinforcing their perception of not being normal. Many voiced not disclosing their condition to friends and teachers, with one stating "I don't want them to see me as different." This contrasts the ten (48%) youth who stated feeling they could relate to others, such as peers with chronic illness and classmates also requiring accommodations. Ten patients (48%) reported feeling burdensome, concerned about putting strain on others. Two patients (10%) feared judgment from others stating, "I think it might make me an attention-seeker." Nine patients (43%) had a positive self-perception, describing enjoying feelings of achievement and helping others.

Resilience profiles: relationship of themes and patient characteristics. Participants with both high and low resilience differed in the number of barriers and facilitators experienced per thematic area, shown in Figure 1 and Table 3. Although youth with high resilience also experienced barriers, they consistently reported a greater number of facilitators in each theme, with the exception of *familial environment*. In both groups, barriers were most frequently reported in *life with SLE*. Youth with low resilience next frequently reported challenges in

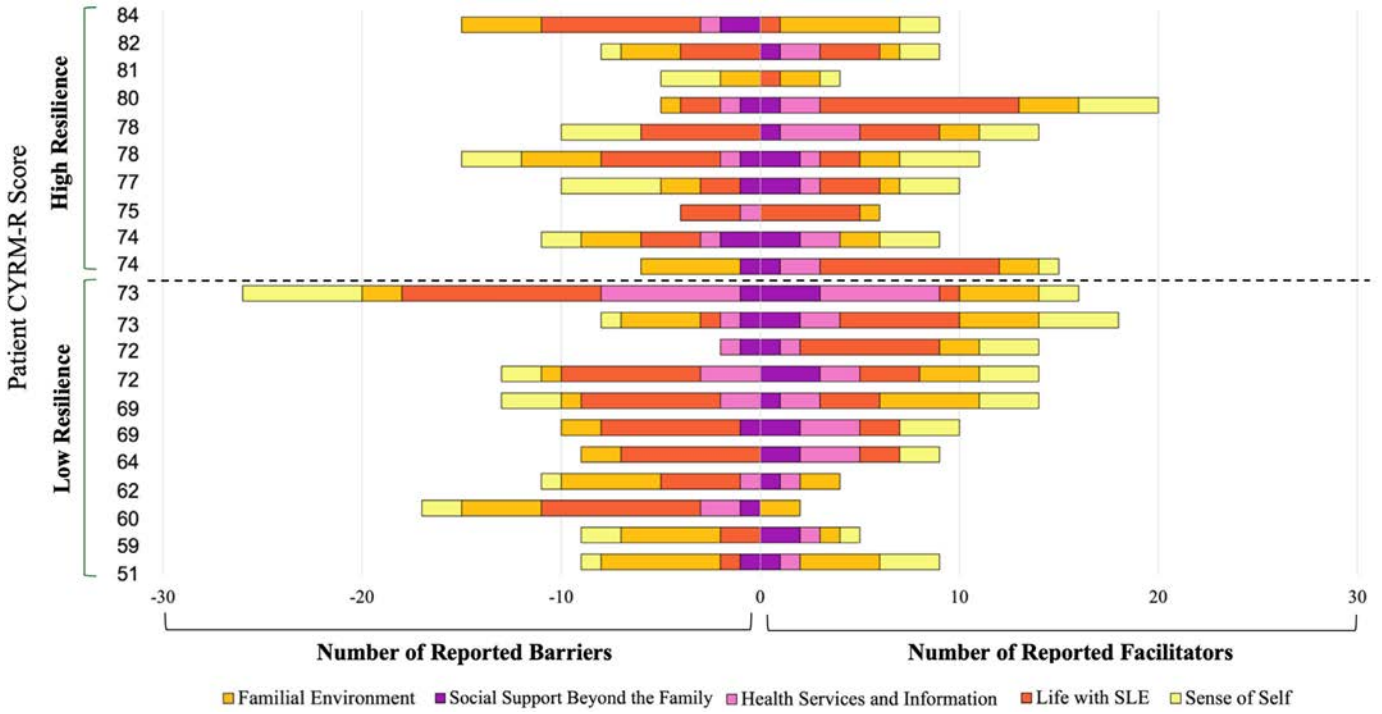

Figure 1. Individual patient profiles of socioecological resilience: distribution of qualitative themes for barriers and facilitators across the spectrum of resilience scores. Individual patient profiles (each represented by a horizontal bar, n = 21) are plotted according to their socioecological resilience scores as measured by the CYRM-R scale. Each patient profile shows the number of barriers (negative numbers) and facilitators (positive numbers) of resilience as reported in qualitative interviews, color-coded by theme. The cohort is grouped according to low versus high socioecological resilience on the CYRM-R measure. Patients with resilience scores at or below the median score of 73 (indicated by dotted line) were attributed a low resilience profile, and patients with scores higher than 73 were attributed a high resilience profile. CYRM-R, Child and Youth Resilience Measure-Revised; SLE, systemic lupus erythematosus.

familial environment, and *sense of self*. Youth with high resilience most frequently reported facilitators in *life with SLE*, *familial environment*, and *sense of self*.

Different patterns of patient characteristics emerged between resilience profiles, as demonstrated in Table 4. Poverty levels were similar across groups. Compared with their high resilience counterparts, patients with low resilience had a greater number of ACEs, lower health literacy communication, younger age at diagnosis, longer disease duration, and higher depressive and anxiety symptoms.

Integrating both our quantitative findings and qualitative themes and subthemes, we propose a model in which various socioecological and individual psychological factors contribute to resilience in youth with cSLE, ultimately shaping disease and mental health outcomes (Figure 2).

DISCUSSION

This mixed-methods study explored resilience across individual and socioecological domains in patients with cSLE, identifying five themes: *familial environment*, *social support beyond family*, *health services and information*, *life with SLE*, and *sense of self*. Patients with higher resilience reported more facilitators in areas such as *life with SLE*, *sense of self*, and *social support beyond the family*, despite also encountering barriers. They had fewer ACEs, better health literacy, and lower levels of depressive

Table 3. Barriers and facilitators per theme across resilience profiles*

Themes	Number of reported barriers (n = 216)		Number of reported facilitators (n = 222)	
	High resilience, n (%)	Low resilience, n (%)	High resilience, n (%)	Low resilience, n (%)
Life with SLE	34 (17)	54 (25)	38 (17)	24 (11)
Familial environment	24 (11)	32 (15)	22 (10)	27 (12)
Sense of self	18 (8)	18 (8)	23 (10)	24 (11)
Health services and information	5 (2)	17 (8)	14 (6)	22 (10)
Social support beyond family	8 (4)	6 (3)	10 (5)	18 (8)

* Shown are the number of barriers and facilitators to resilience per theme and resilience profile in order of most reported. SLE, systemic lupus erythematosus.

Table 4. Differences in characteristics between youth with cSLE with low versus high resilience*

Characteristics	Low resilience (n = 11)[a]	High resilience (n = 10)[b]
Sociodemographic characteristics		
Age at study visit, mean ± SD y	15.2 ± 1.9	15.2 ± 2.0
Gender, n (%)		
Female	7 (63.6)	10 (100.0)
Male	3 (27.3)	0 (0.0)
Other, nonbinary	1 (9.1)	0 (0.0)
Ethnicity, n (%)		
African or Caribbean	0 (0.0)	3 (30.0)
East Asian	4 (36.4)	1 (10.0)
European	1 (9.1)	0 (0.0)
Latin American	1 (9.1)	0 (0.0)
Multiethnic	0 (0.0)	1 (10.0)
South Asian	2 (18.2)	3 (30.0)
Southeast Asian	3 (27.4)	1 (10.0)
Household income below poverty line, n (%)	3 (27.3)	3 (30.0)
Ontario Marginalization		
Material resources score, mean ± SD	0.57 ± 1.1	0.8 ± 1.4
Highest quintile, n (%)	4 (40.0)	5 (50.0)
Racialized and newcomer population score, mean ± SD	1.5 ± 0.8	1.57 ± 0.9
Highest quintile, n (%)	7 (70.0)	7 (70.0)
ACEs and related life experiences (PEARLs), mean ± SD	3.2 ± 2.6	1.6 ± 1.8
With ACEs (score >0), n (%)	10 (91.0)	6 (60.0)
HAS-A scores[c]		
Communication, mean ± SD	13.3 ± 5.0	17.1 ± 2.7
Low (worse), n (%)	5 (45.5)	2 (20.0)
High (better), n (%)	6 (54.5)	8 (80.0)
Confusion, mean ± SD	5.2 ± 1.9	4.1 ± 4.6
High (worse), n (%)	2 (18.2)	2 (20.0)
Low (better), n (%)	9 (81.8)	8 (80.0)
Functional, mean ± SD	8.6 ± 2.9	5.7 ± 5.1
High (worse), n (%)	2 (18.2)	2 (20.0)
Low (better), n (%)	9 (81.8)	8 (80.0)
Disease characteristics		
Age at diagnosis, mean ± SD y	11.7 ± 4.7	13.4 ± 4.0
Disease duration, mean ± SD y	2.9 ± 2.0	1.8 ± 1.6
Disease activity (SLEDAI), mean ± SD	3.8 ± 3.4	3.9 ± 3.3
Active disease (≥4), n (%)	6 (54.5)	6 (60.0)
Disease damage (SDI) (Score >0), n (%)	0 (0.0)	0 (0.0)
Presence of major organ disease, n (%)	5 (45.5)	6 (60.0)
Lupus nephritis	4 (36.4)	5 (50.0)
Neuropsychiatric lupus	0 (0.0)	1 (10.0)
Both lupus nephritis and neuropsychiatric lupus	1 (9.1)	0 (0.0)
Resilience levels		
Individual psychological (CD-RISC 10), median (IQR)	20.0 (15.0–25.0)	29.0 (23.0–33.0)
Patient-reported measures		
Depressive symptom (BDI-II) total T score, mean ± SD	68 ± 16.7	55 ± 9.3
Anxiety symptom (SCARED) total score, mean ± SD	25.5 ± 15.0	26.9 ± 14.6
Clinically elevated anxiety symptoms (scores ≥ 25), n (%)	7 (63.6)	3 (30.0)
Executive functioning (BRIEF-2) total score, mean ± SD	60.0 ± 17.3	55.1 ± 9.5
Pain Interference (PROMIS) total score, mean ± SD	45.3 ± 10.1	47.2 ± 13.5
Fatigue (PROMIS) total score, mean ± SD	54.3 ± 11.0	49.8 ± 13.7

* ACEs, adverse childhood experiences; BDI-II, Beck Depression Inventory - Second Edition; BRIEF-2, Behavior Rating Inventory of Executive Functioning; CD-RISC 10, 10-item Connor-Davidson Resilience Scale; cSLE, childhood-onset systemic lupus erythematosus; CYRM-R, Child and Youth Resilience Measure-Revised; HAS-A, Health Literacy Assessment Scale for Adolescents; IQR, interquartile range; ON-Marg, Ontario Marginalization Index; PEARLs, Pediatric adverse childhood experiences and Related Life Events Screener; PROMIS, Patient-Reported Outcomes Measurement Information Systems; SCARED, Screen for Child Anxiety Related Emotional Disorders; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

[a] Missing low: ON-Marg (n = 1), executive function (n = 1), pain interference (n = 2), and fatigue (n = 2).

[b] Missing high: ethnicity (n = 1), income (n = 1), depression (n = 2), anxiety (n = 1), executive function (n = 2), pain interference (n =2), fatigue (n = 2).

[c] In the HAS-A communication subscale, higher scores indicate better health literacy, and lower scores indicate worse health literacy. On the confusion and functional subscales, higher scores indicate worse health literacy, whereas lower scores indicate better health literacy.

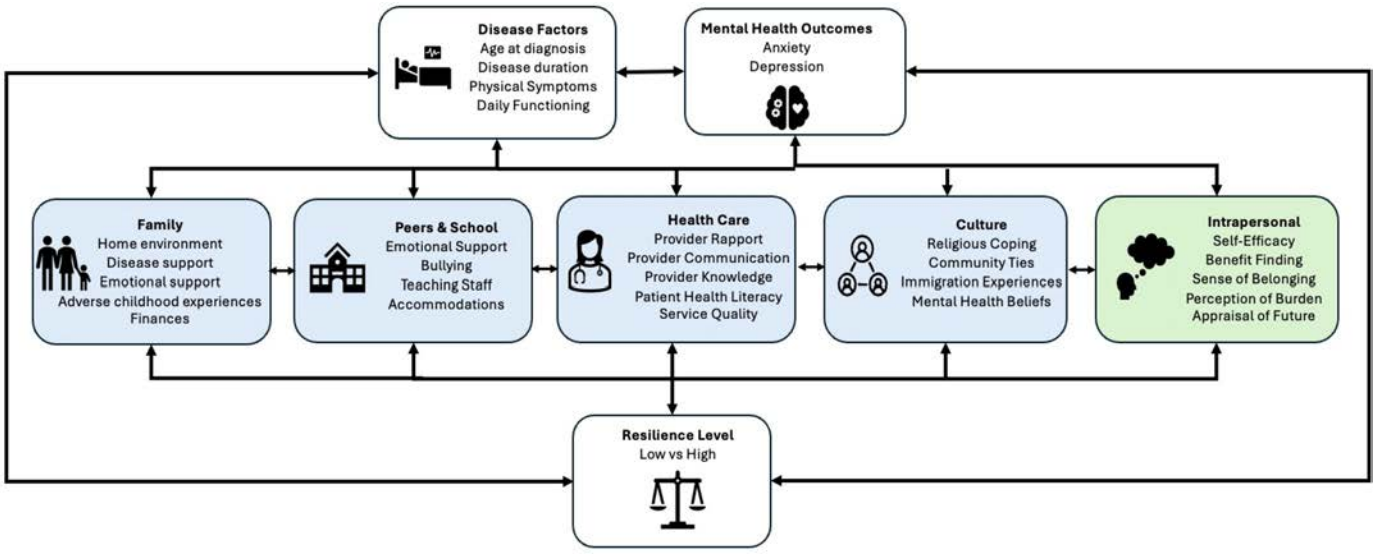

Figure 2. A dynamic model of resilience in youth with childhood-onset systemic lupus erythematosus (cSLE). The model proposes factors influencing resilience in patients with cSLE. Socioecological factors are represented in blue (family, peers and school, health care, culture) and individual psychological factors are represented in green (intrapersonal attributes). Each factor plays the role of either a barrier or facilitator depending on the circumstance (whether the factor is positive or negative). These factors are associated with the development of a low or high resilience profile. The bidirectional nature of the model proposes that although resilience may vary as changes in socioecological and individual psychological resilience factors occur, thereby altering disease and mental health outcomes, these factors may also play a role in mediating resilience. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25550/abstract.

and anxiety symptoms compared with their low resilience counterparts. In contrast, those with low resilience most frequently reported barriers in life with SLE, familial environment, and sense of self. They experienced more ACEs, lower health literacy, earlier diagnosis, longer disease duration, and poorer mental health. These findings underscore the influence of biopsychosocial factors influencing resilience in youth with cSLE and their subsequent impact on patient outcomes.

Resilience levels in our cohort were similar to those of adolescents with chronic musculoskeletal pain, with both groups exhibiting lower resilience than adolescents with Type 1 diabetes, inflammatory bowel disease, and cancer. These findings may be explained by socioecological challenges experienced by both groups.[25] Additionally, the mental health of our cohort is comparable with that of most cohorts with cSLE and other pediatric rheumatology patients, with 20% to 40% experiencing depression and anxiety symptoms.[26]

Half of our cohort reported receiving assistance from family members for both disease-related and emotional challenges. Children with cSLE often experience feelings of isolation due to their illness. However, such feelings tend to be lower among patients whose caregivers demonstrate an understanding of their child's disease.[27] Given the lack of cSLE awareness, a better understanding of parental health literacy is warranted. Further, strategies to improve caregiver health literacy are crucial because of the potential influence on patient clinical outcomes, as well as psychosocial well-being.

The influence of general family dynamics as a mediator of resilience was explored. Although some patients in our cohort reported having caring family members, others described financial strain, a lack of communication and conflict. These factors are quantitatively reflected in our cohort, with 42% of patients in the highest quintile of the marginalization measure (ON-Marg) material resource dimensions. Such environments heighten the risk of poor parent-adolescent relationships and low emotional support.[28] Further, ACEs reported in our cohort frequently involved the family unit. Considering the buffering role positive familial relationships play in mediating resilience, interventions aiming to strengthen familial relationships could enhance patient resilience.

Because we purposively selected patients from racially-marginalized populations, we explored cultural contributors to resilience. Although few patients described distressing immigration experiences, they subsequently reported personal growth and strengthened family ties. Additionally, half our cohort endorsed strong cultural values and community connections-factors associated with increased resilience in immigrant populations.[29] Further, patients reported using religion as a coping strategy, mirroring findings in which spiritual practices were associated with improved mental health in racialized adolescents and adult chronic illness populations.[30,31]

However, some patients linked their cultural background to a lack of mental health discussion. Open communication about emotional health is essential for fostering supportive environments. However, in communities where mental health is stigmatized, patients may not receive adequate support. Because poor mental health negatively impacts treatment adherence and

disease management,[32] access to culturally sensitive supports and self-care practices remains crucial in enhancing quality of life for patients with cSLE.

Many youths emphasized the importance of peers as a facilitator of resilience, echoing findings from a juvenile idiopathic cohort linking strong peer relationships with high resilience.[4] As adolescents shift focus from family to peers, strong peer relationships are vital for fostering resilience and mitigating familial strain.[33]

Patients reported mixed experiences with receiving school supports. Cognitive difficulties and physical limitations were reported to impact academic and extracurricular involvement. In a previous qualitative study, caregivers endorsed the need for increased cSLE awareness at school, to reduce related challenges.[34] School advocacy may improve educational environments by ensuring proper accommodation implementation and enhancing communication, consequently reducing stigma.

When encountering health care providers, many patients reported strong clinician relationships, emphasizing the role of good rapport in fostering resilience. Motivational interviewing techniques, such as empathetic listening and open-ended questioning may help establish trust and communication.[35] This is especially important for patients with cSLE because manifestations can mimic those of nonchronic conditions, leading patients to misinterpret or ignore symptoms. Our study underscores the need for better provider education to improve diagnosis and identification, ultimately reducing health care usage and disease flares.[36]

Disease manifestations may also be a contributor to varied resilience. Research indicates patients with SLE experience low health-related quality of life in physical, social, and psychological domains.[37] Although most patients reported physical challenges and functional limitations, others did not. Because SLE is heterogenous, such findings may be attributed to variations in disease manifestation, progression and management.

Many patients expect SLE to negatively impact their future. Although disease progression is unpredictable, this appraisal may foster learned helplessness and anxiety. In contrast, some patients perceived positive changes from adversity, viewing SLE as an opportunity to learn, pursue medical careers, and help others in need. In patients with adult SLE, benefit-finding is associated with better physical and emotional well-being, fostering optimism and improving psychosocial adjustment.[38,39]

Patients reported actively engaging in disease self-management, aligning with the concept of self-efficacy. In health contexts, self-efficacy reflects a patient's confidence in managing health behaviors and ability to make positive health changes.[40] In adult SLE, low self-efficacy is linked to organ damage, poor medication adherence, and lower self-care motivation.[41,42] Thus, enhancing self-efficacy may improve disease management. Contrasting adult populations, evidenced both in past literature and our findings, pediatric disease self-management is often shared between youth and caregivers.[43] Therefore, it is important for clinicians to foster a family-centered approach to care, with the goal of promoting competence and autonomy to youth when approaching transition to adult health care.

Many youths still reported feeling different compared with their healthy peers. Adolescence is a critical period of personal development, and cSLE may add further challenges in maintaining acceptance by peers.[44] Interventions such as camps bringing together youth with cSLE have been found to improve patient resilience by fostering belonging.[27] In contrast, some patients expressed confidence in their abilities, showing ambition in their goals and satisfaction in their achievements. Strengthening self-esteem may enhance resilience in youth with SLE.[45]

Our findings link low resilience profiles with patient characteristics such as higher number of ACEs, lower health literacy, and younger age at diagnosis. Poverty levels did not significantly differ across resilience groups, an unexpected finding given the well-established link between socioeconomic adversity and poorer health outcomes.[6] However, this may highlight the importance of our newly identified protective effects, such as self-efficacy and social support, in buffering the effects of poverty. These results highlight the need for targeted screening and efficacious resource allocation to support youth at risk for low resilience, aiding their biopsychosocial adjustment to illness.

Findings support fostering resilience to better mental health, which is associated with improved medication adherence, and more successful transition to adult care.[46–48] Therefore, resilience-based interventions may be crucial for improving mental health outcomes and managing cSLE. Such interventions, proven feasible and acceptable, reducing depression and anxiety in patients with cancer, cystic fibrosis, and diabetes,[49] may similarly enhance the well-being of patients with cSLE. Given the dynamic nature of resilience, an individualized approach is needed. Beyond current intervention components like stress management, goal-setting, and meaning making,[49] our findings suggest strengthening familial support, school advocacy, and improving patient-provider interactions can help overcome the barriers faced by youth with cSLE to improve patient well-being.

Our study has limitations. The small sample size may limit the generalizability of our findings. Although our cohort reflects a typical lupus population, the predominance of female participants and exclusive use of English interviews may limit generalizability to male patients and those with language barriers. Additionally, the cross-sectional design prevented us from evaluating resilience over time or comparing resilience factors with healthy peers.

Our study has several strengths. It advances the limited research on resilience in patients with cSLE. By purposively sampling racially-marginalized patients, we highlight important socioecological factors specific to these groups, offering unique insights into their experiences. Additionally, interviews provided an in-depth understanding of patient experiences that may not be captured by other data collection methods.

In conclusion, this study adds valuable insights to the limited research conducted on resilience in patients with cSLE, investigating barriers and facilitators specific to underrepresented populations. Our findings highlight the importance of considering socioecological factors to better characterize resilience in patients with cSLE. Future studies should aim to explore such factors on a longitudinal scale to better understand how factors may affect resilience over time.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Knight confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol 2010;6(9):538–546.
2. van der Laan SEI, Berkelbach van der Sprenkel EE, Lenters VC, et al. Defining and measuring resilience in children with a chronic disease: a scoping review. Advers Resil Sci 2023;4(2):105–123.
3. Campbell-Sills L, Stein MB. Psychometric analysis and refinement of the Connor-Davidson Resilience Scale (CD-RISC): validation of a 10-item measure of resilience. J Trauma Stress 2007;20(6):1019–1028.
4. Trachtman R, Samuels J, Wojtal E, et al. Resilience and its associations in children with systemic lupus erythematosus and juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2023;21(1):67.
5. Jefferies P, McGarrigle L, Ungar M. The CYRM-R: a Rasch-validated revision of the child and youth resilience measure. J Evid Based Soc Work (2019) 2019;16(1):70–92.
6. Williams JN, Drenkard C, Lim SS. The impact of social determinants of health on the presentation, management and outcomes of systemic lupus erythematosus. Rheumatology (Oxford) 2023;62(Suppl 1): i10–i14.
7. Wallander JL, Varni JW, Babani L, et al. Family resources as resistance factors for psychological maladjustment in chronically ill and handicapped children. J Pediatr Psychol 1989;14(2):157–173.
8. Leys C, Arnal C, Wollast R, et al. Perspectives on resilience: personality trait or skill? Eur J Trauma Dissociation 2020;4(2):100074.
9. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64(8): 2677–2686.
10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40(9):1725.
11. Census of population. Statistics Canada website. Updated May 7, 2025. Accessed May 21, 2025. https://www12.statcan.gc.ca/census-recensement/index-eng.cfm
12. Low income cut-offs (LICOs) before and after tax by community size and family size, in current dollars. Statistics Canada website. Updated May 1, 2025. Accessed May 21, 2025. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1110024101
13. Thakur N, Hessler D, Koita K, et al. Pediatrics adverse childhood experiences and related life events screener (PEARLS) and health in a safety-net practice. Child Abuse Negl 2020;108:104685.
14. Manganello JA. Health literacy and adolescents: a framework and agenda for future research. Health Educ Res 2008;23(5):840–847.
15. Postal Code OM Conversion File. Statistics Canada website. Published December 13, 2017. Accessed August 6, 2024. https://www150.statcan.gc.ca/n1/en/catalogue/92-154-X
16. Ontario Marginalization Index (ON-Marg). Public Health Ontario website. Accessed July 22, 2024. https://www.publichealthontario.ca/en/Data-and-Analysis/Health-Equity/Ontario-Marginalization-Index
17. Lattanzi B, Consolaro A, Solari N, et al. Measures of disease activity and damage in pediatric systemic lupus erythematosus: British Isles Lupus Assessment Group (BILAG), European Consensus Lupus Activity Measurement (ECLAM), Systemic Lupus Activity Measure (SLAM), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Physician's Global Assessment of Disease Activity (MD Global), and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI; SDI). Arthritis Care Res (Hoboken) 2011;63(Suppl 11):S112–S117.
18. Richter P, Werner J, Heerlein A, et al. On the validity of the Beck Depression Inventory. A review. Psychopathology 1998;31(3): 160–168.
19. Birmaher B, Khetarpal S, Brent D, et al. The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric characteristics. J Am Acad Child Adolesc Psychiatry 1997;36(4):545–553.
20. Gioia GA, Isquith PK, Guy SC, et al. BRIEF2: Behavior rating inventory of executive function professional manual. Psychological Assessment Resources; 2015.
21. Selewski DT, Troost JP, Cummings D, et al. Responsiveness of the PROMIS® measures to changes in disease status among pediatric nephrotic syndrome patients: a Midwest pediatric nephrology consortium study. Health Qual Life Outcomes 2017;15(1):166.
22. Kilbourne AM, Switzer G, Hyman K, et al. Advancing health disparities research within the health care system: a conceptual framework. Am J Public Health 2006;96(12):2113–2121.
23. NVivo. Version 14. Lumivero; 2023. Accessed June 2, 2025. www.lumivero.com.
24. Knight A, Vickery M, Fiks AG, et al. The illness experience of youth with lupus/mixed connective tissue disease: a mixed methods analysis of patient and parent perspectives. Lupus 2016;25(9):1028–1039.
25. Gmuca S, Xiao R, Urquhart A, et al. The role of patient and parental resilience in adolescents with chronic musculoskeletal pain. J Pediatr 2019;210:118–126.e2.
26. Treemarcki EB, Danguecan AN, Cunningham NR, et al. Mental health in pediatric rheumatology: an opportunity to improve outcomes. Rheum Dis Clin North Am 2022;48(1):67–90.
27. Blamires J, Foster M, Napier S, et al. Experiences and perspectives of children and young people living with childhood-onset systemic lupus erythematosus-an integrative review. Children (Basel) 2023;10(6):1006.
28. Adjei NK, Jonsson KR, Straatmann VS, et al; ORACLE consortium. Impact of poverty and adversity on perceived family support in adolescence: findings from the UK Millennium Cohort Study. Eur Child Adolesc Psychiatry 2024;33(9):3123–3132.
29. Lee J, Hong J, Zhou Y, Robles G. The Relationships between loneliness, social support, and resilience among Latinx immigrants in the United States. Clin Soc Work J 2020;48(1):99–109.
30. Ibrahim N, Che Din N, Ahmad M, et al. The role of social support and spiritual wellbeing in predicting suicidal ideation among marginalized adolescents in Malaysia. BMC Public Health 2019;19(Suppl 4):553.

31. Kütmeç Yilmaz C, Kara FŞ. The effect of spiritual well-being on adaptation to chronic illness among people with chronic illnesses. Perspect Psychiatr Care 2021;57(1):318–325.
32. Davis AM, Graham TB, Zhu Y, et al. Depression and medication nonadherence in childhood-onset systemic lupus erythematosus. Lupus 2018;27(9):1532–1541.
33. Herzer M, Umfress K, Aljadeff G, et al. Interactions with parents and friends among chronically ill children: examining social networks. J Dev Behav Pediatr 2009;30(6):499–508.
34. Harry O, Crosby LE, Smith AW, et al. Self-management and adherence in childhood-onset systemic lupus erythematosus: what are we missing? Lupus 2019;28(5):642–650.
35. Erickson SJ, Gerstle M, Feldstein SW. Brief interventions and motivational interviewing with children, adolescents, and their parents in pediatric health care settings: a review. Arch Pediatr Adolesc Med 2005;159(12):1173–1180.
36. Oglesby A, Korves C, Laliberté F, et al. Impact of early versus late systemic lupus erythematosus diagnosis on clinical and economic outcomes. Appl Health Econ Health Policy 2014;12(2): 179–190.
37. Elera-Fitzcarrald C, Fuentes A, González LA, et al. Factors affecting quality of life in patients with systemic lupus erythematosus: important considerations and potential interventions. Expert Rev Clin Immunol 2018;14(11):915–931.
38. Katz P, Dall'Era M, Trupin L, et al. Impact of limited health literacy on patient-reported outcomes in systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2021;73(1):110–119.
39. Kritikos TK, Stiles-Shields C, Winning AM, et al. A systematic review of benefit-finding and growth in pediatric medical populations. J Pediatr Psychol 2021;46(9):1076–1090.
40. Sood P, Romero S, Velozo C, et al. Defining self-efficacy for managing chronic conditions and identifying priority sub-domains: a web-based DELPHI technique. Arch Phys Med Rehabil 2015;96(10):e43.
41. Sun K, Eudy AM, Criscione-Schreiber LG, et al. Racial differences in patient-provider communication, patient self-efficacy, and their associations with systemic lupus erythematosus-related damage: a cross-sectional survey. J Rheumatol 2021;48(7):1022–1028.
42. Barr AC, Clowse M, Maheswaranathan M, et al. Association of hurried communication and low patient self-efficacy with persistent nonadherence to lupus medications. Arthritis Care Res (Hoboken) 2023; 75(1):69–75.
43. Lozano P, Houtrow A. Supporting self-management in children and adolescents with complex chronic conditions. Pediatrics 2018; 141(Suppl 3):S233–S241.
44. Birkeland MS, Breivik K, Wold B. Peer acceptance protects global self-esteem from negative effects of low closeness to parents during adolescence and early adulthood. J Youth Adolesc 2014;43(1):70–80.
45. Liu Q, Jiang M, Li S, et al. Social support, resilience, and self-esteem protect against common mental health problems in early adolescence: a nonrecursive analysis from a two-year longitudinal study. Medicine (Baltimore) 2021;100(4):e24334.
46. Knight A, Weiss P, Morales K, et al. Depression and anxiety and their association with healthcare utilization in pediatric lupus and mixed connective tissue disease patients: a cross-sectional study. Pediatr Rheumatol Online J 2014;12(1):42.
47. Julian LJ, Yelin E, Yazdany J, et al. Depression, medication adherence, and service utilization in systemic lupus erythematosus. Arthritis Rheum 2009;61(2):240–246.
48. Lau CS, Mak A. The socioeconomic burden of SLE. Nat Rev Rheumatol 2009;5(7):400–404.
49. Rosenberg AR, Bradford MC, McCauley E, et al. Promoting resilience in adolescents and young adults with cancer: results from the PRISM randomized controlled trial. Cancer 2018;124(19): 3909–3917.

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1125–1134
DOI 10.1002/acr.25536

Analysis of the Longitudinal Behavior of Serum Levels of Soluble Flt1 and Placental Growth Factor in Pregnant Patients With Systemic Lupus Erythematosus

Nilson R. de Jesús, Guilherme R. de Jesús, Marcela I. Lacerda, Flávia C. dos Santos, Jeane de S Nogueira, Luiz Cristóvão Porto, Evandro S. F. Coutinho, and Evandro M. Klumb

Objective. This study analyzed longitudinal trajectories of soluble Flt1 (sFlt1) levels, placenta growth factor (PlGF) levels, and sFlt1:PlGF ratios in a cohort of pregnant patients with systemic lupus erythematosus (SLE).

Methods. Blood samples were collected (14–18, 24–26, 30–32, 34–36, and 38–40 weeks), stored at –80°C, and evaluated for serum levels of sFlt1, PlGF, and sFlt1:PlGF ratios. Patients were classified as inactive SLE (Systemic Lupus Erythematosus Pregnancy Disease Activity Index [SLEPDAI] <4), active disease (SLEPDAI ≥4), or preeclampsia (PE). Medians and interquartile ranges were calculated for each group, and linear models with random effects were used.

Results. A total of 527 samples were obtained from 163 patients, and all patients were subsequently classified as having inactive disease (109 patients [66.9%]), active disease (33 patients [20.2%]), and inactive disease with PE (21 patients [12.9%]). In exploratory analysis, patients with PE had higher mean serum levels of sFlt1 and sFlt1:PlGF ratios and lower PlGF levels than patients with inactive and active SLE ($P = 0.01$ to $P < 0.001$). Using linear models with random effects, there was no significant differences in mean serum levels of these angiogenic markers comparing inactive and active disease. Patients with PE showed a marked increase in sFlt1 levels from the 24th week, constantly low PlGF levels from the 14th week, and progressive increase of sFlt1:PlGF ratio during pregnancy. All these differences were statistically significant compared to the groups without PE.

Conclusion. Pregnant patients with SLE who developed PE had higher sFlt1 levels and sFlt1:PlGF ratios and lower PlGF levels, and these last two changes were detected at the beginning of second trimester, before clinical manifestation. SLE activity did not interfere with longitudinal behavior of these angiogenic markers.

INTRODUCTION

Pregnancy in patients with systemic lupus erythematosus (SLE) has an increased risk of adverse events including miscarriages, infections, premature delivery, intrauterine growth restriction, and preeclampsia (PE) compared to the general population.[1] There is also an increased risk of lupus flares that contribute to the increased frequency of some of these events and require specific immunosuppressive treatments.[2]

The first studies reporting the involvement of angiogenic and antiangiogenic angiogenic markers in the pathogenesis of PE were published in the late 1990s. Torry et al[3] analyzed the serum levels of placenta growth factor (PlGF) in healthy pregnant people without SLE and found statistically significant lower levels in those who developed PE. Additionally, the study by Maynard et al[4] showed that this reduction in circulating levels of PlGF, and vascular endothelial growth factor (VEGF) was associated with an increase in serum soluble Flt1 (sFlt1) levels. The authors also demonstrated that the excess of sFlt1 in vitro resulted in endothelial

Supported in part by GSK Investigator Sponsored Studies (grants 9329 and 213105).

Nilson R. de Jesús, MD, PhD; Guilherme R. de Jesús, MD, PhD; Marcela I. Lacerda, MD, PhD; Flávia C. dos Santos, MD, PhD; Jeane de S. Nogueira, BSc, PhD; Luiz Cristóvão Porto, MD, PhD; Evandro S. F. Coutinho, MD, PhD; Evandro M. Klumb, MD, PhD: Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25536).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25536.

Address correspondence via email to Guilherme R. de Jesús, MD, PhD, at guilhermedejesus@gmail.com.

Submitted for publication June 12, 2024; accepted in revised form March 20, 2025.

SIGNIFICANCE & INNOVATIONS

- Pregnant patients with systemic lupus erythematosus (SLE) who developed preeclampsia (PE) had higher soluble Flt1 (sFlt1) levels and sFlt1:placenta growth factor (PlGF) ratios and lower PlGF levels compared to patients with inactive and active SLE.
- These changes could be detected as early as the second trimester, several weeks before clinical manifestation of PE.
- SLE activity did not interfere with longitudinal behavior of these angiogenic markers, presenting a pattern similar to that observed in pregnant patients with inactive SLE and significantly different from that found in patients with inactive SLE prone to developing PE.
- Analysis of sFlt1 levels, PlGF levels, and sFlt1:PlGF ratio may help establish an early and accurate differential diagnosis between active disease and PE and also predict adverse events in pregnancy.

dysfunction, and that this imbalance could be reversed by exogenous VEGF and PlGF.[4] Based on these initial observations, over the last three decades, there has been great interest in studying the behavior of these angiogenic markers in normal pregnancies, in those that develop PE, and those with associated comorbidities.[5–9]

The classic clinical manifestations of PE, including hypertension and proteinuria, are very similar to those of active lupus nephritis (LN). Therefore, differentiating between these two conditions is always a challenge and virtually impossible with traditional laboratory assessments. A cross-sectional study of patients with SLE demonstrated that the analysis of serum levels of angiogenic (PlGF) and antiangiogenic (sFlt1) angiogenic markers may allow accurate differentiation between these two conditions.[10] Moreover, there is also evidence that the pathologic changes observed in PlGF and sFlt1 serum levels occur early in pregnancy.[11]

However, the longitudinal trajectory of these two angiogenic markers levels throughout pregnancy in patients with SLE, and whether disease activity, including LN, influences these levels in the long term have not yet been well elucidated. This study aimed to analyze the longitudinal behavior of sFlt1 levels, PlGF levels, and sFlt1:PlGF ratio in a cohort of pregnant patients with SLE and to correlate these changes with adverse pregnancy outcomes.

PATIENTS AND METHODS

Patients. This prospective study included patients with SLE who had single pregnancies between May 2015 and May 2023. All enrolled patients met the revised diagnostic criteria for SLE stated by the American College of Rheumatology[12] and were followed up at a single center, the high-risk prenatal clinic of a tertiary health unit (Prenatal Care of Autoimmune Diseases and Thrombophilia, Universidade do Estado do Rio de Janeiro, Brazil). All patients with SLE attending the high-risk prenatal clinic were invited to participate in the present study and all agreed. Inclusion was performed sequentially according to routine prenatal appointment scheduling. Clarifications regarding the research protocol were provided and the informed consent form was signed before the research interview. Participants' race was self-reported according to the classification of the Brazilian Institute of Geography and Statistics. Disease activity was assessed for all patients in the study group using a semistructured questionnaire, a complete physical examination, and laboratory tests. Patients with malformed fetuses, twin pregnancies, and no data on delivery and those who did not sign the informed consent form were excluded from the study. All patients who developed PE superimposed on SLE activity were excluded from the main groups to prevent this association from acting as a confounding factor. This study was approved by the Hospital Universitario Pedro Ernesto Research Ethics Committee (registration number: 2866/2011-CEP/HUPE/CAAE: 0017.0.228.000-11). All clinical manifestations, laboratory changes specific to SLE, and permanent damage accrual as defined by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index[13] were obtained through a review of medical records and direct interviews with each patient, at which point a specific clinical form was filled out for this study.

Screening and follow-up visits. At the initial prenatal visit, in addition to medical and obstetric history and a complete physical examination, blood samples were obtained for a complete blood counts and measurement of serum aspartate aminotransferase, alanine aminotransferase, and creatinine, research of anti-Ro, anti-La, anti-RNP, anti-DNA, anticardiolipin, and anti-beta2glycoprotein I antibodies, and lupus anticoagulant. Urinalysis, 24-hour proteinuria, and/or urinary protein:creatinine ratio were also requested. Monthly clinical care was provided by a multidisciplinary team of obstetricians and rheumatologists. Consultations and complementary examinations were performed according to the clinical needs. Gestational outcomes were assessed by reviewing the medical records and analyzing the following parameters: route of delivery, gestational age at delivery, birth weight, Apgar score, and presence of adverse events (premature delivery, premature rupture of membranes, PE, gestational hypertension, gestational diabetes, placental abruption, fetal death, and neonatal death).

SLE activity and diagnosis of PE. Clinical assessment of disease activity was performed at each prenatal visit, and laboratory tests for this assessment were routinely requested every trimester or earlier whenever a flare was suspected. SLE activity was classified according to the Systemic Lupus Erythematosus Disease Activity Index score adapted to pregnancy (Systemic Lupus Erythematosus Pregnancy Disease Activity Index [SLEPDAI])[14] at the moment of blood collection. Analysis of serum

parameters for the SLEPDAI score (complement, anti-DNA, thrombocytopenia, and leukopenia) was based on data available in the patient's medical records at the time of consultation. Urinalysis was performed using phase microscopy and included detection of cellular casts, dysmorphic hematuria, and pyuria to calculate the SLEPDAI score. Proteinuria was measured in a 24-hour urine sample or estimated using the urinary protein:creatinine ratio in an isolated urine sample when the former was not available. A SLEPDAI score greater than or equal to 4 was assumed to indicate moderately active disease, whereas patients with a SLEPDAI score less than 4 were classified as having mild activity or remission. This cutoff to define activity during pregnancy has been previously used by our group[10] and other authors.[14]

PE was diagnosed according to the criteria provided by the American College of Obstetricians and Gynecologists.[15] For patients who already had proteinuria at the start of prenatal care, the worsening of this condition was considered in the context of differential diagnosis between PE and SLE renal activity.

Maternal angiogenic factor assay. Peripheral venous blood samples were collected at the following gestational age intervals after enrollment: 14 to 18, 24 to 26, 30 to 32, 34 to 36, and 38 to 40 weeks (when possible, ie, when labor had not yet occurred). The samples were centrifuged for 15 minutes at 2,500 revolutions per minute, and the serum was stored at –80°C until cytokine level measurement, according to the manufacturer's recommendations. The serum levels of PlGF and sFlt1 (picograms per milliliter) were assessed after delivery, with the researchers being anonymized to the pregnancy outcomes, using the Elecsys PlGF and Elecsys sFlt1 automated electrochemiluminescence immunoassay system (Cobas 8000 e701 module, Roche Diagnostics).

Analysis. To obtain homogeneous groups in relation to disease activity and PE, all patients were classified into the three groups only after delivery. Those who remained quiescent throughout pregnancy were classified as "inactive" (group 1). Those who developed disease activity (with SLEPDAI ≥ 4) at any time during pregnancy were all classified as active SLE (group 2), and the patients who developed PE (all with quiescent SLE) constituted group 3. Definitive outcome groups were assigned after a careful review of each case by a rheumatologist and an obstetrician specialized in high-risk pregnancies. Descriptive analysis included measures of central tendency and dispersion (mean, SD, median, and interquartile range [IQR]) for numerical data and frequency and percentage for categorical data. The comparison of delivery and newborn characteristics among the groups (inactive, active disease, and PE) was made using Student's *t*-test for independent samples and the chi-square test or Fisher's exact test for categorical data.

Over different gestational periods, the medians and IQRs of serum sFlt1 levels, PlGF levels, and sFLt1:PlGF ratios were calculated for each group. The Kruskal-Wallis test was used to compare the distribution of these cytokine levels in each group. If the hypothesis of equality between the groups was rejected, a post hoc two-by-two comparison was performed using the Wilcoxon rank sum test. We opted for nonparametric tests because the distribution of the outcome variables did not meet the assumption of data normality.

Linear models with random effects (or mixed-effects models) were used, with serum sFlt1 levels, PlGF levels, and the sFLt1:PlGF ratio as dependent variables. This choice considered the inherent correlation between measurements collected from the same patient at different points in time. Moreover, mixed-effects models allow for the inclusion of individuals in the analysis even if they miss some measurements or have a different number of repeated measurements than the remaining individuals. Logarithmic transformation was applied to each of the three variables to better fit the assumption of data normality. Thus, the exponential of the adjusted coefficients indicated an average multiplicative increase in the levels of these angiogenic markers between the groups. Group 1 (pregnant patients with inactive SLE and no PE) was used as a reference for these comparisons.

The intercept variance (between groups) indicates how much the mean values of groups vary around the overall intercept. It reflects the differences between groups (inactive disease, active SLE, and PE) in the variables (sFlt1 levels, PlGF levels, and sFlt1:PlGF ratio). A high intercept variance suggests significant differences across groups. The residual variance (within groups) represents the unexplained noise in the data after accounting for the main factors under investigation. It indicates the variation among individuals within the same group that the model cannot explain. Essentially, it captures the individual differences that persist within the group. Finally, the intraclass correlation (ICC) measures how much individuals within the same group resemble each other compared to those in different groups. It is used to assess the reliability of measurements or the degree of similarity within groups. The ICC ranges from 0 to 1, in which a value closer to 1 indicates that individuals in the same group are very similar (indicating significant within-group correlation), whereas a value closer to 0 suggests little similarity within groups.

Moreover, during the analysis, we implemented models adjusted for gestational period, exposure, and the interaction between these variables. No adjustment was made by the SLEPDAI as a nominal variable because this variable was used in the construction of the three groups to be compared. Its introduction into the multivariate model would be a source of collinearity, leading to problems in model fitting. We tested the statistical significance of the interaction terms. In addition, we evaluated the graphical representation of these effects by displaying the predicted values of each outcome variable on the original scale at different gestational ages. A significance level of 5% was considered

in all analyses, which were conducted using R software (version 4.1.2).

RESULTS

Among all pregnant patients followed up at the high-risk prenatal clinic, 185 patients met the eligibility criteria and were included in this study. Of these, three patients (1.6 %) did not complete the study due to miscarriage (pregnancy interrupted before the 20th week), and nine patients did not complete the study (4.8 %) due to loss of follow-up. Five patients were excluded because of twin pregnancies, two patients with malformed fetuses were excluded, and three patients with both active disease and PE were excluded to avoid defining a new disease category with a small sample size. Thus, the study group comprised 163 patients: 109 patients (66.9%) in the inactive SLE group (group 1), 33 patients (20.2%) in the active SLE group (group 2), and 21 patients (12.9%) in the PE group (group 3) (Supplementary Figure S1). Among all patients classified as having active disease, 20 of 33 patients (60.6%) were diagnosed with active nephritis due to at least one renal variable in SLEPDAI. A total of 527 blood samples were obtained, with the following distribution: 12 patients (7.4%) had five samples collected, 51 patients (31.3%) had four samples collected, 67 patients (41.1%) had three samples collected, 29 patients (17.8%) had two samples collected, and 4 patients (2.4%) had one sample collected.

The clinical and demographic characteristics of the patients are shown in Table 1. The average duration (in years) between SLE diagnosis and pregnancy was shorter in the active disease group (5.2 years) than in the other two groups ($P = 0.001$). The frequency of associated antiphospholipid syndrome (APS), history of nephritis, and chronic hypertension were similar among the three groups.

The incidence of prematurity, intrauterine growth restriction, and small for gestational age newborn was very high in the PE group (76.2%, 61.9%, and 76.2%, respectively) and differed significantly from the other two groups ($P < 0.0001$ for all variables). These results were probably related to the higher occurrence of early PE cases (57.1% were born earlier than 34 weeks) and the need based on clinical indications to deliver the newborn sooner. The average gestational age at birth in this group was 32.6 weeks, and the mean birthweight was 1,579.1 g, resulting in a greater need for admission to the neonatal intensive care unit (73.6%). The analysis of these results also revealed statistically significant differences when compared with those of the other groups.

The medians and IQRs of serum sFlt1 levels, PlGF levels, and sFlt-1:PlGF ratios estimated in the samples collected throughout pregnancy are shown in Tables 2, 3, and 4. In preliminary analysis, each sample was evaluated independently. All patients showed rising sFlt1 levels during pregnancy, but those who

Table 1. Clinic and demographic variables and gestational outcomes of patients with inactive SLE, active SLE, and SLE and preeclampsia*

	Inactive SLE (n = 109)	Active SLE (n = 33)	SLE and Preeclampsia (n = 21)	*P* value[a]
Clinical and demographic variables				
Age mean ± SD, y	28.6 ± 5.6	27.2 ± 6.2	28.2 ± 6.5	0.48
Race, n (%)				
Black person and Brazilian Mestizo	72 (66)	27 (81.8)	17 (80.9)	
White person	37 (34)	6 (18.2)	4 (19.1)	0.12
Primigravida	42 (38.5)	13 (39.4)	7 (33.3)	0.88
Duration of SLE, mean ± SD, y	9.45 ± 6.2	5.2 ± 4.6	8.3 ± 6.0	**0.001**
Antiphospholipid syndrome, n (%)	4 (3.7)	2 (6.0)	3 (14.3)	0.14
SLICC/ACR-DI ≥ 1, n (%)	18 (16.5)	7 (21.2)	6 (26.6)	0.40
History of nephritis	43 (39.4)	19 (57.6)	11 (52.4)	0.14
Classes III or IV	17 (39.5)	7 (36.8)	6 (54.5)	0.60
Chronic hypertension, n (%)	23 (21.1)	9 (27.3)	7 (33.3)	0.42
Obesity	32 (29.3)	10 (30.3)	7 (33.3)	0.93
Gestational results				
Prematurity, n (%)	7 (6.4)	12 (36.4)	16 (76.2)	**<0.0001**
Intrauterine growth restriction, n (%)	11 (10)	8 (24.2)	13 (61.9)	**<0.0001**
Stillbirth / neonatal death, n (%)	1 (0.9)	2 (6.0)	3 (14.2)	0.05
Gestational age at delivery,[b] mean ± SD, wk	38.0 ± 2.2	36.9 ± 2.2	32.6 ± 4.6	**<0.0001**
Birth weight,[b] mean ± SD, g	2,964.1 ± 542.6	2,640.7 ± 587.9	1,579.1 ± 853.9	**<0.0001**
Small for gestational age newborn, n (%)	6 (5.5)	6 (18.2)	16 (76.2)	**<0.0001**
5th min Apgar score[b] mean ± SD	8.9 ± 0.8	8.9 ± 0.6	8.2 ± 1.2	**0.002**
Admission to NICU,[b] n (%)	3 (2.7)	8 (25.8)	14 (73.6)	**<0.0001**

* Bolded values are statistically significant differences between the three groups ($P < 0.05$). ACR-DI, American College of Rheumatology Damage Index; NICU, neonatal intensive care unit; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus Erythematosus Collaborating Clinics.
[a] The chi-square test was used for categorical variables and analysis of variance (ANOVA) for continuous variables.
[b] Stillbirths were excluded from this analysis.

Table 2. Comparison of median serum soluble Flt1 (sFlt1) levels (pg/mL) according to the outcome group (inactive SLE, active SLE or SLE and preeclampsia) during different periods of pregnancy*

Sample period	Inactive SLE, median (IQR)	Active SLE, median (IQR)	SLE and preeclampsia, median (IQR)	*P* value (Kruskal-Wallis)	*P* value (Wilcoxon comparisons 2 × 2)
14–18 wk	1,636.0 (1,010.0–2,268.0) (n = 65)	1,782.0 (1,428.0–2,817.0) (n = 18)	2,043.0 (1,849.0–3,177.5) (n = 11)	0.06	Inactive SLE × active SLE: 0.660; inactive SLE × SLE and preeclampsia: 0.083; active SLE × SLE and preeclampsia: $p > 0.99$[a]
24–26 wk	1,541.0 (1,011.6–2,125.5) (n = 91)	2,018.1 (1,419.2–3,363.8) (n = 24)	6,909.0 (2,990.8–8,844.2) (n = 16)	**<0.001**	Inactive SLE × active SLE: **0.04**; inactive SLE × SLE and preeclampsia: **<0.001**; active SLE × SLE and preeclampsia: **0.01**
30–32 wk	1,766.0 (1,208.9–2,504.0) (n = 98)	1,749.0 (1,396.4–2,926.0) (n = 26)	6,875.0 (4,585.0, 13,221.0) (n = 13)	**<0.001**	Inactive SLE × active SLE: >0.9; inactive SLE × SLE and preeclampsia: **<0.001**; active SLE × SLE and preeclampsia: **<0.001**
34–36 wk	2,694.0 (1,851.0–3,867.5) (n = 90)	2,569.5 (2,060.8–3,393.2) (n = 24)	5,442.0 (4,759.0–8,406.0) (n = 9)	**<0.001**	Inactive SLE × active SLE: >0.9; inactive SLE × SLE and preeclampsia: **0.001**; active SLE × SLE and preeclampsia: **<0.001**
38–40 wk	2,839.0 (2,022.0–4,209.5) (n = 35)	3,570.0 (3,543.0–3,790.0) (n = 5)	7,343.5 (6,946.2, 7,740.8) (n = 2)	0.06	Inactive SLE × active SLE: 0.549; inactive SLE × SLE and preeclampsia: 0.144; active SLE × SLE and preeclampsia: 0.286[a]

* Bolded values are statistically significant differences between the three groups ($P < 0.05$). IQR, interquartile range; SLE, systemic lupus erythematosus.
[a] Some results in the Kruskal-Wallis test had borderline *P* values in relation to the 5% significance level. Therefore, these comparisons 2 × 2 were maintained.

progressed to PE presented more pronounced elevations, with statistically significant differences ($P = 0.01$ to $P < 0.001$) in the samples obtained between 24 and 36 weeks, compared with the other two groups (Table 2). The medians PlGF levels in patients with and without active SLE were not significantly different. These levels presented an initial increase after 14 weeks,

Table 3. Comparison of median serum placenta growth factor (PlGF) levels (pg/mL) according to the outcome group (inactive SLE, active SLE or SLE and preeclampsia) during different periods of pregnancy*

Sample period	Inactive SLE, median (IQR)	Active SLE, median (IQR)	SLE and Preeclampsia, median (IQR)	*P* value (Kruskal-Wallis)	*P* value (Wilcoxon comparisons 2 × 2)
14–18 wk	174.0 (128.5–267.0) (n = 65)	162.6 (119.0–208.8) (n = 18)	63.0 (39.5–101.0) (n = 11)	**<0.001**	Inactive SLE × active SLE: >0.9; inactive SLE × SLE and preeclampsia: **<0.001**; active SLE × SLE and preeclampsia: **0.001**
24–26 wk	551.2 (384.1–819.4) (n = 91)	389.0 (300.9–534.1) (n = 24)	73.2 (23.6–237.6) (n = 16)	**<0.001**	Inactive SLE × active SLE: **0.03**; inactive SLE × SLE and preeclampsia: **<0.001**; active SLE × SLE and preeclampsia: **<0.001**
30–32 wk	745.5 (397.5–1,085.7) (n = 98)	433.9 (199.3–783.5) (n = 26)	80.0 (58.0–153.5) (n = 13)	**<0.001**	Inactive SLE × active SLE: **0.03**; inactive SLE × SLE and preeclampsia: **<0.001**; active SLE × SLE and preeclampsia: **<0.001**
34–36 wk	489.8 (304.0–918.5) (n = 90)	285.8 (206.5–485.2) (n = 24)	87.0 (67.0–116.0) (n = 9)	**<0.001**	Inactive SLE × active SLE: **0.04**; inactive SLE × SLE and preeclampsia: **0.001**; active SLE × SLE and preeclampsia: **<0.001**
38–40 wk	304.9 (177.5–603.1) (n = 35)	284.0 (251.9–307.9) (n = 5)	87.8 (82.7–92.9) (n = 2)	0.14	Inactive SLE × active SLE: 0.55; inactive SLE × SLE and preeclampsia: 0.18; active SLE × SLE and preeclampsia: 0.29[a]

* Bolded values are statistically significant differences between the three groups ($P < 0.05$). IQR, interquartile range; SLE, systemic lupus erythematosus.
[a] Some results in the Kruskal-Wallis test had borderline *P* values in relation to the 5% significance level. Therefore, these comparisons 2 × 2 were maintained.

Table 4. Comparison of median serum soluble Flt1:placenta growth factor (sFlt1:PlGF) ratio levels according to the outcome group (inactive SLE, active SLE or SLE and preeclampsia) during different periods of pregnancy*

Sample period	Inactive SLE, median (IQR)	Active SLE, median (IQR)	SLE and preeclampsia, median (IQR)	*P* value (Kruskal-Wallis)	*P* value (Wilcoxon comparisons 2 × 2)
14–18 wk	9.2 (5.1–11.6) (n = 65)	10.0 (7.3–14.1) (n = 18)	28.0 (22.2–81.5) (n = 11)	**<0.001**	Inactive SLE × active SLE: 0.81; inactive SLE × SLE and preeclampsia: **<0.001**; active SLE × SLE and preeclampsia: **0.007**
24–26 wk	2.7 (1.7–3.6) (n = 91)	5.5 (3.2–7.2) (n = 24)	97.2 (13.4–481.9) (n = 16)	**<0.001**	Inactive SLE × active SLE: **<0.001**; inactive SLE × SLE and preeclampsia: **<0.001**; active SLE × SLE and preeclampsia: **0.001**
30–32 wk	2.1 (1.6–4.5) (n = 98)	4.2 (2.4–12.1) (n = 26)	118.5 (33.7–174.0) (n = 13)	**<0.001**	Inactive SLE × active SLE: **0.01**; inactive SLE × SLE and preeclampsia: **<0.001**; active SLE × SLE and preeclampsia: **<0.001**
34–36 wk	4.4 (2.6–12.7) (n = 90)	11.1 (5.1–16.4) (n = 24)	86.5 (47.8–125.5) (n = 9)	**<0.001**	Inactive SLE × active SLE: 0.11; inactive SLE × SLE and preeclampsia: **0.001**; active SLE × SLE and preeclampsia: **<0.001**
38–40 wk	9.3 (3.9–24.2) (n = 35)	12.6 (10.9–14.0) (n = 5)	85.8 (76.3–95.3) (n = 2)	0.07	Inactive SLE × active SLE: >0.9; inactive SLE × SLE and preeclampsia: 0.036; active SLE × SLE and preeclampsia: 0.286[a]

* Bolded values are statistically significant differences between the three groups ($P < 0.05$). IQR, interquartile range; SLE, systemic lupus erythematosus.
[a] Some results in the Kruskal-Wallis test had borderline *P* values in relation to the 5% significance level. Therefore, these comparisons 2 × 2 were maintained.

and a subsequent decrease after 30 weeks. Patients predisposed to developing PE had significantly lower medians values ($P = 0.001$ to <0.001) than those in the other two groups (Table 3). The median sFlt1:PlGF ratios in patients with and without SLE activity showed an initial drop after 14 weeks, followed by an increase after 30 weeks. The difference between the two groups was not statistically significant. The median sFlt1:PlGF ratios throughout pregnancy were significantly higher in patients with PE than in those with inactive or active SLE ($P = 0.007$ to < 0.001) (Table 4). A subanalysis of sFlt1:PlGF ratio including only patients with active nephritis compared to patients who developed PE provided similar results (Supplementary Table S1). The analysis using linear models with random effects (mixed-effects models), showed that patients in the PE group had average sFlt1 levels and sFlt1:PlGF ratio values that were 2.96 times (95% confidence interval [CI] 2.30–3.80; $P < 0.001$) and 18.3 times (95% CI 12.2–27.4; $P < 0.001$) higher than those in the inactive SLE group, respectively (Table 5).

The estimated values and CIs for sFlt1, PlGF, and sFlt1:PlGF ratio calculated using linear models with random effects, considering the interaction between each of the samples and the outcome groups, are presented in Figure 1A–C and Supplementary

Table 5. Estimates of the parameters of the adjusted linear models with random effects for the logarithm of sFlt1, PlGF, and sFlt1:PlGF ratio according to the outcome group (inactive SLE, active SLE or SLE and preeclampsia)*

Variable	sFlt1		PlGF		sFlt1:PlGF	
	Exp (beta) (95% CI)	*P* value	Exp (beta) (95% CI)	*P* value	Exp (beta) (95% CI)	*P* value
Outcome group						
Inactive SLE	–		–		–	
Active SLE	1.21 (0.99–1.48)	0.07	0.72 (0.55–0.94)	**0.02**	1.68 (1.21–2.32)	**0.002**
SLE and preeclampsia	2.96 (2.30–3.80)	**<0.001**	0.16 (0.11–0.22)	**<0.001**	18.3 (12.2–27.4)	**<0.001**
Intercept variance (between groups)	0.22		0.36		0.47	
Residual variance (within groups)	0.13		0.28		0.62	
Intraclass correlation	0.63		0.56		0.43	

* CI, confidence interval; Exp, exponential of adjusted coefficients; PlGF, placenta growth factor; sFlt1, soluble Flt1; SLE, systemic lupus erythematosus.

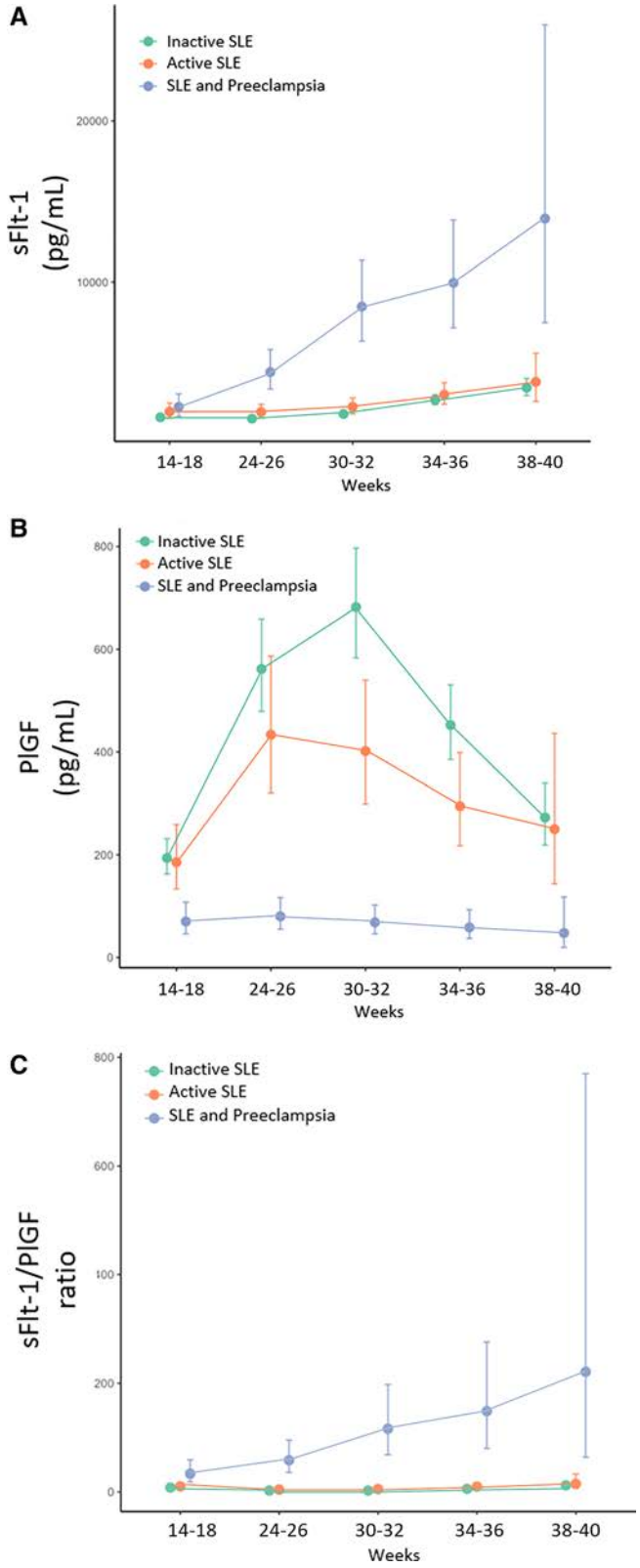

Figure 1. Predicted values with respective 95% confidence intervals of (A) sFlt1, (B) PlGF, and (C) sFlt1/PlGF ratio using linear models with random effects, considering the interaction between each of the samples and the outcome group. PlGF, placenta growth factor; sFlt1, soluble Flt1; SLE, systemic lupus erythematosus.

Tables S2, S3, and S4. The predicted mean concentrations of sFlt1 levels in patients with inactive and active SLE remained stable up to 30 weeks, whereas after this gestational age, there were mean increases of 205 pg/mL per week in group 1 and 193.5 pg/mL in group 2 until the end of pregnancy. However, the differences were not statistically significant between the groups. In contrast, patients who developed PE showed an increase in sFlt1 levels from the 24th week, with an average increase of 680 pg/mL until the end of pregnancy, whereas differences were statistically significant between this group and groups 1 and 2 (Figure 1A).

Concerning the estimated mean levels of PlGF, patients in the two groups without PE had increasing estimated mean levels of PlGF for up to 30 weeks (from 194 pg/mL to 681 pg/mL in group 1 and from 185 pg/mL to 401 pg/mL in group 2), followed by a decline in these concentrations, with no statistically significant differences between them. In contrast, patients who later developed PE showed nearly stable average PlGF concentrations (70, 80, 68, 58, and 47 pg/mL) throughout pregnancy. These values were significantly lower than those observed in patients with inactive or active SLE. This significant difference was observed in the first samples analyzed (14–18 weeks) and persisted until delivery. The curves of the estimated mean values of the sFlt1:PlGF ratio in patients with inactive and active SLE showed an initial decline for up to 30 weeks and then raised. However, the curve of these values in patients who later developed PE showed a different pattern, with a steady increase from the beginning of the second trimester (14–18 weeks). The difference between the mean values of the estimated sFlt1:PlGF ratio in the PE group was statistically significant compared to that in the other two groups.

DISCUSSION

Few studies have evaluated whether SLE activity, especially active LN, could compromise the ability of angiogenic and antiangiogenic factors to differentiate the clinical manifestations of SLE from those of PE. Comparison of the three groups (inactive SLE with no PE, active SLE with no PE, and SLE complicated by PE) revealed that SLE activity did not interfere with the longitudinal behavior of angiogenic and antiangiogenic markers. Analysis of the trajectories of these angiogenic markers during pregnancy showed no differences between the first two groups; however, levels of angiogenic markers in both groups were significantly different from those in patients who developed PE.

Some studies have investigated sFlt1 and PlGF levels in normal pregnancies and pregnancies complicated by PE.[3–5,16] In a case-control study, Levine et al[5] observed that in normal pregnancies, sFlt1 levels remained stable during the early and middle stages of pregnancy, followed by a steady increase from 33 to 36 weeks. This increase in sFlt1 levels was accompanied by a downward trend in serum PlGF levels. The authors speculated

that, at the end of an uncomplicated pregnancy, the control of placental vascular growth is probably slowed down by the reversal of angiogenic to antiangiogenic state. However, in pregnancies predisposed to develop PE, this change occurs earlier and more abruptly, exaggerating the normal processes of managing placental growth and function. Several studies have shown that the serum concentration of sFlt1 is elevated in patients with PE, even before the clinical diagnosis of the disease, and this elevation can precede the onset of clinical manifestations by 6 to 11 weeks.[5,17] Another important characteristic related to the imbalance of these angiogenic markers in patients with PE is the association between sFlt1 serum levels and disease severity; that is, serum levels of sFlt1 are higher in early-onset PE (<34 weeks) than in late-onset PE (>34 weeks).[16] Unfortunately, none of these studies included patients with SLE.

Elucidating the role of angiogenic and antiangiogenic cytokine serum levels behavior between nonpregnant and pregnant patients with SLE is warranted because pregnant patients with SLE, mainly those with LN, are at an increased risk of PE. Moreover, its clinical manifestations (hypertension and proteinuria) are similar to those of active LN, and the differential diagnosis between these two conditions remains a major challenge. In a cross-sectional study, our group previously analyzed the serum levels of VEGF, PlGF, and sFlt1 in nonpregnant patients with inactive and active SLE and compared the results with those of healthy patients in the control group. We found that patients with active SLE had higher serum levels of both angiogenic and antiangiogenic angiogenic markers than patients with inactive SLE or healthy patients.[6] To evaluate whether serum levels of VEGF, PlGF, and sFlt1 are useful in differentiating PE from active LN during pregnancy in patients with SLE, we conducted a second cross-sectional study comparing the mean serum levels of these angiogenic markers in patients with inactive disease, active nephritis, and SLE with superimposed PE. Comparison of the three groups revealed that patients with PE had significantly lower serum PlGF levels, whereas sFlt1 and sFlt1:PlGF ratios were significantly higher. In addition, we observed an increase in the serum levels of VEGF in patients with active LN, which was unexpected in patients with PE. In this study, we concluded that these angiogenic markers may be useful in the differential diagnosis of PE and active LN.[10]

Few studies have evaluated the longitudinal behavior of serum angiogenic factors in pregnant patients with SLE.[7,18] Leaños-Miranda et al[18] investigated whether these angiogenic markers were associated with the risk of developing PE in patients with SLE. They conducted a case-control study of 42 patients who developed PE and 75 patients with normal pregnancies. As observed in our study, lower levels of PlGF, higher levels of sFlt1 and soluble endoglin (sEng), and a higher sFlt1:PlGF ratio were found in patients prone to developing PE than in those with uncomplicated pregnancies. Another important observation was that in patients who developed early-onset or late-onset PE, abnormal cytokine fluctuations became significant from 12 weeks of pregnancy onward.[18] Mayer-Pickel et al[7] longitudinally (12–36 weeks) measured the serum levels of PlGF, sFlt1, and sEng in patients with SLE and APS to identify, early on, the imbalance in the serum levels of these angiogenic factors in patients who later developed PE. The authors observed that in both patients with SLE and APS, the imbalance of these angiogenic markers occurred early in pregnancy and suggested their potential utility as early predicting factors for the development of PE in these patients.[7]

Using data and samples from the predictors of pregnancy outcome: biomarkers in antiphospholipid antibody syndrome and systemic lupus erythematosus study, Kim et al[11] selected 492 pregnant patients with SLE and/or APS to assess, early in pregnancy, the potential of angiogenic factors (PlGF, sFlt1, and sEng) to identify patients who were more likely to present adverse pregnancy outcomes (APOs). Circulating levels of sFlt1, PlGF, and sEng were measured monthly, and the patients were classified as having severe APO (PE < 34 weeks, fetal or neonatal death, indicated preterm delivery at <30 weeks) and as having moderate APO (PE ≥ 34 weeks, indicated preterm delivery at 30–36 weeks, growth restriction without PE). The authors observed that between 12 and 15 weeks, serum sFlt1 levels were the strongest predictor of severe APO, and at 16 to 19 weeks, the combination of sFlt1 and PlGF was even more predictive. In addition, they found that in patients who developed moderate APOs, antiangiogenic factors increased later in pregnancy, suggesting that the time of onset and duration of dysregulation of angiogenic factors are related to the severity of APOs.

In studies that longitudinally assessed the serum levels of these angiogenic markers in pregnant patients with SLE, patients with active disease were either excluded or analyzed together with patients with inactive disease, which may have impeded adequate interpretation of the fluctuations in these cytokine levels due to different clinical scenarios during pregnancy. Our study is the first to compare the longitudinal behavior of PlGF and sFlt1 in pregnant patients with SLE who developed PE with those in pregnant patients with active and inactive SLE.

Most studies that have analyzed the serum levels of angiogenic factors during different gestational periods[5,7,18] calculated the medians and IQRs of the variables. Comparative tests were performed to evaluate the statistical significance of the differences between groups. Nevertheless, it is important to note that repeated measurements violate the independence assumption as they are correlated (not independent) observations. In our case, these angiogenic markers were observed in the same individual because our investigation was focused on their trajectories. We considered the autocorrelation between repeated measures in the same individual, because a value obtained for an individual at a certain time point is influenced by previous measurements and influences subsequent ones. Therefore, these values were not independent of each other.[19]

In their pivotal study, Levine et al[5] showed that the behavior of PlGF in pregnant patients without SLE who later developed PE followed a pattern similar to that of patients who had a normal course of pregnancy, that is, an increase in mean concentrations until the beginning of the third trimester and a subsequent decline, but with statistically significant lower levels. The PE "pattern" could be identified early in pregnancy, even in the beginning of the second trimester.[5,20] In contrast, in the present study, the concentration of PlGF showed a nearly linear pattern with consistently low mean levels (70, 80, 68, 58, and 47 pg/mL). We speculate that this difference is probably due to a greater number of patients developing early and more severe PE. In a cohort of pregnant patients without SLE, Chappell et al[21] found that in patients at <35 weeks with suspected PE, a PlGF concentration <100 pg/mL predicted severe PE requiring delivery within 14 days. In another study, Parchem et al[22] found that PlGF levels <100 pg/mL could predict adverse maternal gestational outcomes. Moreover, in patients with severe or early-onset PE, PlGF concentrations may be so low that they are undetectable using available PlGF assays.[23] The results of this study reinforce the use of these angiogenic markers, which are commercially available, in predicting PE in patients with lupus, as well.

The main limitation of this study is that the patients were recruited from a single center, which can limit the generalization of the results, and the relatively low number of patients with PE. However, the differences in the analyzed cytokine levels between the groups were statistically significant. Nevertheless, this study has some positive aspects: (1) to the best of our knowledge, this is the largest cohort to analyze angiogenic and antiangiogenic factors in patients with SLE, which also included active disease as a variable, a factor to be considered in clinical practice; (2) all cases were reviewed by obstetricians and rheumatologists experienced in pregnancies with SLE, which ensures the appropriate group allocation; and (3) this is the first study to use a linear model with random effects to analyze these biomarkers longitudinally in a cohort of pregnant patients with SLE.

We have shown that throughout pregnancy in patients with SLE predisposed to develop PE, sFlt1 levels, and the sFlt1:PlGF ratio are elevated, whereas PlGF levels are reduced. The last two changes were detected before the clinical manifestation of the disease and at the beginning of the second trimester. We also demonstrated that SLE activity did not interfere with the behavior of these cytokine levels during pregnancy, presenting a pattern similar to that observed in pregnant patients with inactive SLE and significantly different from that found in patients prone to developing PE. Indeed, even patients with active SLE and superimposed PE, presented cytokines trajectories similar to those with PE and inactive SLE (data shown in Supplementary Table S5 and Supplementary Figure S2). These results support our proposal to measure serum levels of these angiogenic markers in pregnant patients with SLE to establish an early and accurate differential diagnosis between active disease and PE[10] and to predict adverse events in pregnancy.[11]

ACKNOWLEDGMENTS

The Article Processing Charge for the publication of this research was funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) (ROR identifier: 00x0ma614).

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr de Jesús confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ROLE OF THE STUDY SPONSOR

GSK had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by GSK.

REFERENCES

1. de Jesús GR, Mendoza-Pinto C, de Jesús NR, et al. Understanding and managing pregnancy in patients with lupus. Autoimmune Dis 2015;2015:943490.
2. Rodrigues BC, Lacerda MI, Ramires de Jesús GR, et al. The impact of different classes of lupus nephritis on maternal and fetal outcomes: a cohort study of 147 pregnancies. Lupus 2019;28(4):492–500.
3. Torry DS, Wang HS, Wang TH, et al. Preeclampsia is associated with reduced serum levels of placenta growth factor. Am J Obstet Gynecol 1998;179(6 Pt 1):1539–1544.
4. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003; 111(5):649–658.
5. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004;350(7):672–683.
6. de Jesús GR, de Jesús NR, Levy RA, et al. The use of angiogenic and antiangiogenic factors in the differential diagnosis of pre-eclampsia, antiphospholipid syndrome nephropathy and lupus nephritis. Lupus 2014;23(12):1299–1301.
7. Mayer-Pickel K, Stern C, Eberhard K, et al. Angiogenic factors in pregnancies of women with antiphospholipid syndrome and systemic lupus erythematosus. J Reprod Immunol 2018;127:19–23.
8. Lee SM, Lee EM, Park JK, et al. Metabolic biomarkers in midtrimester maternal plasma can accurately predict adverse pregnancy outcome in patients with SLE. Sci Rep 2019;9(1):15169.
9. Tamil Barathi P, Mohanapriya A. Pre-eclampsia: re-visiting pathophysiology, role of immune cells, biomarker identification and recent advances in its management. J Reprod Immunol 2024:163:104236.
10. de Jesús GR, Lacerda MI, Rodrigues BC, et al. Soluble Flt-1, placental growth factor, and vascular endothelial growth factor serum levels to differentiate between active lupus nephritis during pregnancy and preeclampsia. Arthritis Care Res (Hoboken) 2021;73(5):717–721.
11. Kim MY, Buyon JP, Guerra MM, et al. Angiogenic factor imbalance early in pregnancy predicts adverse outcomes in patients with lupus

and antiphospholipid antibodies: results of the PROMISSE study. Am J Obstet Gynecol 2016;214(1):108.e1–108.e14.

12. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40(9):1725.
13. Gladman DD, Goldsmith CH, Urowitz MB, et al. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index for systemic lupus erythematosus international comparison. J Rheumatol 2000;27(2):373–376.
14. Andreoli L, Gerardi MC, Fernandes M, et al. Disease activity assessment of rheumatic diseases during pregnancy: a comprehensive review of indices used in clinical studies. Autoimmun Rev 2019; 18(2):164–176.
15. ACOG Practice Bulletin No. 202: gestational hypertension and preeclampsia. Obstet Gynecol 2019;133(1):1.
16. Chaiworapongsa T, Romero R, Espinoza J, et al. Evidence supporting a role for blockade of the vascular endothelial growth factor system in the pathophysiology of preeclampsia. Young Investigator Award. Am J Obstet Gynecol 2004;190(6):1541–1547; discussion 7–50.
17. Chaiworapongsa T, Romero R, Kim YM, et al. Plasma soluble vascular endothelial growth factor receptor-1 concentration is elevated prior to the clinical diagnosis of pre-eclampsia. J Matern Fetal Neonatal Med 2005;17(1):3–18.
18. Leaños-Miranda A, Campos-Galicia I, Berumen-Lechuga MG, et al. Circulating angiogenic factors and the risk of preeclampsia in systemic lupus erythematosus pregnancies. J Rheumatol 2015;42(7): 1141–1149.
19. Muhammad LN. Guidelines for repeated measures statistical analysis approaches with basic science research considerations. J Clin Invest 2023;133(11):e171058.
20. Chaemsaithong P, Gil MM, Chaiyasit N, et al. Accuracy of placental growth factor alone or in combination with soluble fms-like tyrosine kinase-1 or maternal factors in detecting preeclampsia in asymptomatic women in the second and third trimesters: a systematic review and meta-analysis. Am J Obstet Gynecol 2023;229(3):222–247.
21. Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. Circulation 2013;128(19):2121–2131.
22. Parchem JG, Brock CO, Chen HY, et al; Preeclampsia Triage by Rapid Assay Trial (PETRA) Investigators. Placental growth factor and the risk of adverse neonatal and maternal outcomes. Obstet Gynecol 2020;135(3):665–673.
23. Stepan H, Galindo A, Hund M, et al. Clinical utility of sFlt-1 and PlGF in screening, prediction, diagnosis and monitoring of pre-eclampsia and fetal growth restriction. Ultrasound Obstet Gynecol 2023;61(2): 168–180.

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1135–1140
DOI 10.1002/acr.25544

American College of Rheumatology
Empowering Rheumatology Professionals

BRIEF REPORT

Systemic Lupus International Collaborating Clinics Frailty Index Predicts Worsening Health-Related Quality of Life, Data From the Almenara Lupus Cohort

Anubhav Singh,[1] Rocío V. Gamboa-Cárdenas,[2] Victor Pimentel-Quiroz,[2] Zoila Rodriguez-Bellido,[3] Cesar Pastor-Asurza,[3] Risto Perich-Campos,[3] Graciela S. Alarcón,[4] and Manuel Francisco Ugarte-Gil[2]

Objective. The Systemic Lupus International Collaborating Clinics Frailty Index (SLICC-FI) as a predictor of quality of life (QoL) in patients with systemic lupus erythematosus (SLE) has not been evaluated longitudinally. We estimated the association of SLICC-FI scores with future QoL in our prevalent Latin American Mestizo cohort.

Methods. Patients from a single-center SLE cohort were included. Health-related QoL was ascertained with the LupusQoL tool, and frailty was ascertained with the SLICC-FI. Generalized estimating equations were performed, using each domain of the LupusQoL as an outcome in the subsequent visit, and the SLICC-FI (as a continuous variable) in the previous visit. Alternative analyses were also conducted including the SLICC-FI as a categorical variable. In both approaches, the multivariable models were adjusted for possible confounders (age at diagnosis, sex, socioeconomic status, ethnicity, Systemic Lupus Erythematosus Disease Activity Index 2000, SLICC/American College of Rheumatology damage index [SDI], disease duration at baseline, prednisone daily dose, antimalarial and immunosuppressive drug treatment, and the same domain of the LupusQoL in the previous visit).

Results. A total of 428 patients and 2,645 visits were included in this study, and they were observed for 4.71 ± 3.52 years. At baseline, the mean ± SD of disease duration, SDI scores, and SLICC-FI scores were 7.2 ± 6.6 years, 1.0 ± 1.3, and 0.17 ± 0.05, respectively.

In the main analysis, after adjusting for possible confounders, higher SLICC-FI scores predicted a higher LupusQoL score in the domains of pain, planning, emotional health, and fatigue. In the alternative analyses, after adjustment, the frail and least fit categories were predictive of higher LupusQoL scores in the domain of fatigue, and frailty (SLICC-FI score of >0.21) predicted worse body image compared with least fit (SLICC-FI score 0.03–0.10).

Conclusion. Higher SLICC-FI scores predicted worse health-related QoL as measured by higher LupusQoL scores from patients from the Almenara lupus cohort. Our findings reinforce the prognostic value of this tool in patients with SLE.

INTRODUCTION

Frailty as a construct in geriatric medicine was operationalized by Fried et al in 2001[1] by establishing it as an independent clinical syndrome with well-defined criteria. Given its usefulness in health services research in geriatric populations, attempts to adopt frailty in terms of deficit accumulation[2] as a prognostic tool in various disease processes has been successfully tried.

The Almenara Lupus Cohort has been partially supported by institutional grants from EsSalud (grants 1483-GCGP-ESSALUD-2013, 1733-GCGP-ESSALUD-2014, and the 2015 Kaelin Prize 04-IETSI-ESALUD-2016), from the Pan American League of Associations for Rheumatology (PANLAR) (2015 PANLAR Prize and the 2018 H. Ralph Schumacher, MD Journal of Clinical Rheumatology/PANLAR Prize), from the Fundación Instituto Hipólito Unanue, Lima, Perú, and from Janssen Pharmaceuticals.

[1]Anubhav Singh, MD: Baptist Hospitals, Sam Houston State University, Houston, Texas; [2]Rocío V. Gamboa-Cárdenas, MD, MSc, Victor Pimentel-Quiroz, MD, Manuel Francisco Ugarte-Gil MD, MSc, PhD: Universidad Científica del Sur and Hospital Guillermo Almenara Irigoyen, Lima, Perú; [3]Zoila Rodriguez-Bellido, MD, Cesar Pastor-Asurza, MD, Risto Perich-Campos, MD, MSc: Universidad Nacional Mayor de San Marcos and Hospital Guillermo Almenara Irigoyen, Lima, Perú; [4]Graciela S. Alarcón, MD, MPH: University of Alabama at Birmingham, and Universidad Peruana Cayetano Heredia, Lima, Perú.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25544).

Author disclosures and graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25544.

Address correspondence via email to Manuel Francisco Ugarte-Gil, MD, MSc, PhD, at mugarte@cientifica.edu.pe.

Submitted for publication November 21, 2024; accepted in revised form March 20, 2025.

SIGNIFICANCE & INNOVATIONS

- The Systemic Lupus International Collaborating Clinics Frailty Index (SLICC-FI) is a valuable tool that has been shown to predict damage accrual and other adverse outcomes like hospitalization and mortality in patients with systemic lupus erythematosus (SLE).
- Our study demonstrates that the SLICC-FI tool independently predicted worsening quality of life in patients with SLE.
- The correlations observed between the pain, emotional health, and fatigue domains of the Lupus Quality of Life (LupusQoL) and the SLICC-FI tools emphasize the fact that frailty is multidimensional in its scope and affects patients globally.
- Patients categorized as frail had higher LupusQoL domain scores compared with the less fit categories, highlighting the significance of the SLICC-FI as an important prognostic tool.

Assessing frailty in patients with systemic lupus erythematosus (SLE) according to that approach was first proposed by the Systemic Lupus International Collaborating Clinics (SLICC) group with the introduction of the SLICC Frailty Index (SLICC-FI).[3] This novel tool incorporates some disease activity (Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K])[4] features, damage accrued (SLICC/American College of Rheumatology damage index [SDI]),[5] health-related quality of life (HRQoL) ascertained with the Medical Outcomes Survey Short Form-36 (SF-36),[6] plus some comorbidities into one comprehensive instrument.[3] Since then, the SLICC-FI has shown discriminant ability in predicting adverse health outcomes like hospitalizations[7], mortality,[8] and damage accrual[9] in different cohorts with SLE.

Patient reported outcomes (PROs) in patients with SLE have shown mixed concordance with commonly used physician reported tools like the SLEDAI-2K and the SLE Disease Activity Score (SLE-DAS).[10,11] Both generic and SLE-specific PROs have demonstrated reliability in independent reviews.[11] The performance of these two types of PROs have been similar in multiple studies,[6,12] although a recent meta-analysis indicated that disease-specific instruments offer greater sensitivity to change in disease activity and organ damage.[13]

The SLICC-FI has been evaluated in two cross-sectional studies, both demonstrating its association with impaired quality of life (QoL) measured by the LupusQoL[14] and the Patient Reported Outcomes Measurement Information System (PROMIS),[15] respectively. However, longitudinal data to illustrate its predictive value has been lacking. Thus, we aimed at evaluating the SLICC-FI as a potential predictor of QoL as measured by an SLE-specific HRQoL instrument, the LupusQoL, in patients from the Almenara lupus cohort.

PATIENTS AND METHODS

Starting in 2012, all patients with SLE older than 18 years of age presenting to the rheumatology department of the Guillermo Almenara Irigoyen Hospital in Lima, Perú, have been invited to participate in this cohort. Recruitment is currently ongoing. Patients with other autoimmune diseases, with the exceptions of Sjogren syndrome and antiphospholipid syndrome, are excluded. The study has been approved by this hospital's institutional review board (3474-OCID-G-RAA-ESSALUD-11, 271-CEI-CIDG-RAA-ESSALUD-13, 302-CEI-ICD-G-RAA-14, 3027-OCID-G-RAA-ESSALUD-15 and 4072-OCID-G-HNGAI-ESSALUD-2017). Patients who sign the informed consent forms are evaluated using a prespecified protocol, which includes an interview, medical records review, physical examination, and laboratory tests.

All patients in this cohort met the 1997 Revised and Updated American College of Rheumatology classification criteria for SLE at entry.[16] Demographic data included were sex, age at diagnosis, socioeconomic status according to the Graffar method[17] and educational level, defined as years of formal education. Clinical variables included were the SLEDAI-2K, the SDI, and disease duration at baseline; therapeutic variables included were the use of prednisone (dose at each visit) and of immunosuppressive and antimalarial drugs. These data were recorded at baseline and at each visit.

HRQoL was assessed with the LupusQoL[11] (eight domains including physical function, pain, planning, intimate relationship, burden to others, emotional health, body image, and fatigue); these eight domains are scored from 0 (worst) to 100 (best). The minimal clinically important difference values for the LupusQoL domains are for deterioration from –2.4 to –8.7, and for improvement from 3.5 to 7.3.[18]

Frailty was ascertained with the SLICC-FI; this instrument uses the concept of deficit accumulation across multiple systems.[3] These deficits could be either a symptom, a disease process, a functional impairment, or a laboratory abnormality for a total of 48 items; these items have been selected after a thorough review. The SLICC-FI scores are calculated by combining individual health deficit scores to arrive at numerical values ranging from 0 to 1. Based on the ranges of these deficits, the following categories have been established: robust (SLICC-FI score ≤0.03), relatively less fit (SLICC-FI score of >0.03 to ≤0.10), least fit (SLICC-FI score of >0.10 to ≤0.21), and frail (SLICC-FI score >0.21). There were two items that could not be included in the calculation of the SLICC-FI score: the first, endocarditis or myocarditis, because it was not recorded in our database; and the second, anxiety and mood disorders, because both manifestations had been included as a single item in our cohort. Thus, the total number of items used to calculate the SLICC-FI score was 46 instead of 48. The sum of the scores

for these items was then divided by 46; this provided a final score ranging between 0 and 1.

The SLICC-FI was computed at each visit. Patients were classified in one of the following categories: robust (SLICC-FI score ≤0.03), relatively less fit (SLICC-FI score >0.03 to ≤0.10), least fit (SLICC-FI score >0.10 to ≤0.21), and frail (SLICC-FI score >0.21). The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Statistical analyses. Categorical variables are reported as numbers and percentages, whereas numerical variables are reported as means and standard deviations. Generalized estimating equations were performed for each domain of the LupusQoL (as a continuous variable) as an outcome in a given visit and for the SLICC-FI (as a continuous variable) in the previous visit. Alternative analyses were also conducted including the SLICC-FI as a categorical variable (robust, less fit, least fit, and frail). Univariable and multivariable analyses were conducted. In both approaches, the multivariable model was adjusted for possible confounders (age at diagnosis, sex, socioeconomic status, ethnicity, SLEDAI-2K, SDI, disease duration at baseline, prednisone daily dose, antimalarial and immunosuppressive drug use, and the same domain of the LupusQoL in the previous visit). The model employed a gamma distribution with link identity function. To account for correlations within participants, linear exponent autoregressive first order correlation matrixes and robust SEs were used for all the models. The models employed a gamma distribution with a goodness of fit quasi likelihood under independence model criterion (QIC) value, which are shown in Supplementary Table 1. When the value reported by the patient was zero, a value of one was assigned, so it could be included in the gamma distribution. Lower QIC values indicate a better predictive value for the model. Collinearity has been evaluated using the variance inflation factor (VIF). Collinearity was defined as a VIF greater than 5; in our case all VIFs were less than 5. Statistical significance was set at $P < 0.05$. All analyses were performed using the SPSS 28.0 statistical package (IBM).

RESULTS

Baseline characteristics. Included in the study were 428 patients and 2645 visits, with a mean ± SD age at baseline of 42.4 ± 12.8 years; 392 (91%) patients were women, and the mean ± SD age of diagnosis was 35.2 ± 13.4 years, with mean ± SD follow up of 4.71 ± 3.52 years. At baseline, the mean ± SD for disease duration was 7.2 ± 6.6 years, mean ± SD for SDI score was 1.0 ± 1.3, and mean ± SD for SLICC- FI score was 0.17 ± 0.05; 62 (14.7%) patients were classified as frail, 325 (77.0%) were classified as least fit, 35 (8.3%) were classified as less fit; no patient was classified as robust. The mean ± SD of the LupusQoL domain scores were 66.5 ± 23.8 for physical function, 67.9 ± 26.6 for pain, 69.3 ± 28.9 for planning, 58.6 ± 35.4 for intimate relationship, 50.4 ± 31.2 for burden to others, 64.9 ± 24.7 for emotional health, 61.5 ± 25.8 for body image, and 60.6 ± 26.5 for fatigue. Baseline demographic and clinical information of the studied patients are provided in Supplementary Table 2. Mean LupusQoL domain scores (in the subsequent visit) of SLICC-FI (in the previous visit) categories of frail, least fit, and less fit are shown in Figure 1.

Relationship between SLICC-FI and LupusQoL. As shown in Table 1, the SLICC-FI tool predicted higher LupusQoL scores in all domains in the univariable analysis. After adjusting for possible confounders in the multivariable analysis, the SLICC-FI scores continued to predict LupusQoL scores in the domains of pain, planning, emotional health, and fatigue. These data are depicted in Table 1. In the alternative analysis, frail and least fit categories predicted higher LupusQoL scores in the domains of pain, planning, emotional health, and fatigue in unadjusted analysis and the domain of fatigue after adjustment for confounders. The frail category also predicted a higher LupusQoL score in the domain of body image in adjusted analysis. These data are shown in Table 2.

DISCUSSION

The SLICC-FI predicted a higher HRQoL, mainly in the domains of pain, planning, emotional health, and fatigue, even after adjustment for possible confounders. The assessment of HRQoL in patients with SLE has been challenging because of the relative lack of consensus about which is the optimal tool to assess it; in addition, there is significant heterogeneity of the tools used in the different published studies, limiting the ability to compare them.[11,12] These challenges are further compounded because of their uncertain association with the more commonly used physician reported measures like disease activity (SLEDAI-2K)[10] and organ damage (SDI).[12] The Definition of Remission in SLE task force and, more recently, the Outcome Measures in Rheumatology group have highlighted the significance of PROs in SLE research.[19] Recently, more studies have evaluated SLE-specific QoL measures and established their concordance with SLE disease activity[13] and the SDI.[12] Given the clinical significance of HRQoL assessments in patients with SLE as highlighted by these groups, it is important to identify its predictors.

Novel comprehensive measures like the SLICC-FI, which assess physical deficit accumulation, have shown positive associations with the SDI,[9] hospitalizations,[7] and mortality[8] in different cohorts. Fourteen out of the 48 deficits considered during the construction of this index[3] are related to function, mobility, health attitude, and mental health, primarily derived from the SF-36.

Baseline frailty assessed with the self-reported Fatigue, Resistance, Aerobic Capacity, Illnesses and Loss of Weight scale

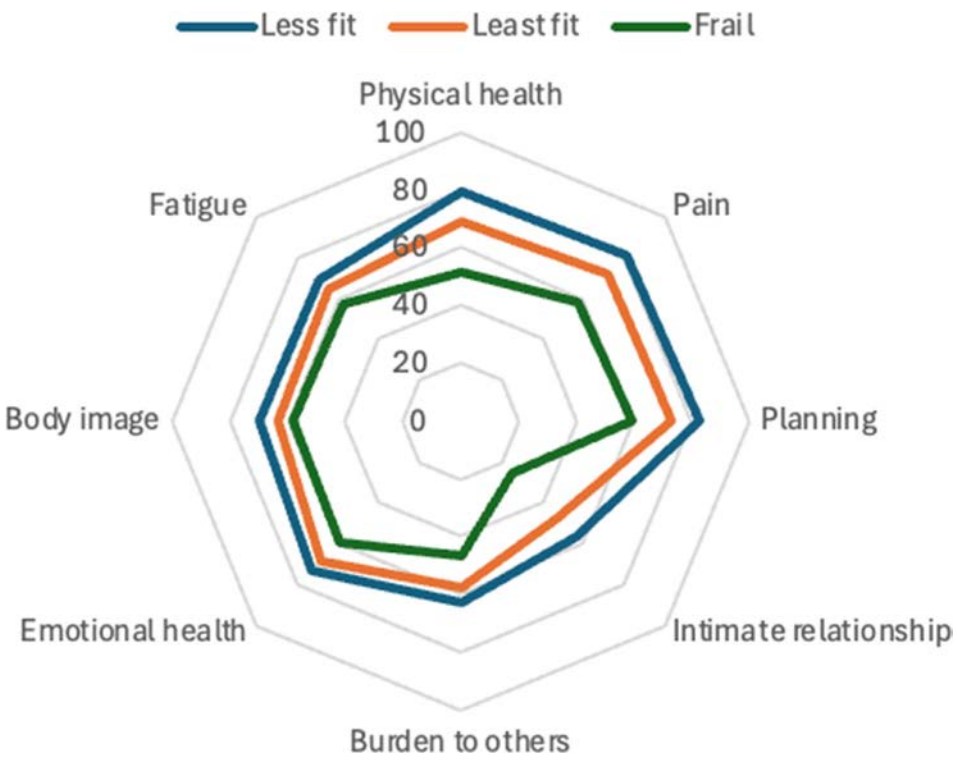

Figure 1. LupusQoL domain scores (0–100) (in the subsequent visit) and SLICC-FI categories of less fit, least fit, and frail (in the previous visit). LupusQoL, Lupus quality of life; SLICC-FI, Systemic Lupus International Collaborating Clinics Frailty Index.

has been shown to be a predictor of self-reported disability on the Valued Life Activities scale, and other aspects of HRQoL on the PROMIS scale.[16] A recent cross-sectional study in a Greek patient cohort showed the association of the SLICC-FI with the LupusQoL,[14] albeit the population studied had a lower mean SLICC-FI score (0.09) compared with that of our cohort (0.17). Additionally, frailty had a negative impact on activities of daily living in the same study.

Our study, to our knowledge, is the first longitudinal study that showed that increases on the SLICC-FI score predict increasing LupusQoL scores independent of other clinical or demographic characteristics. In our study, the strongest association between the SLICC-FI score and the LupusQoL score was seen in the domains of pain, planning, emotional health, and fatigue when compared with the domains of body image, burden to others, intimate relationship, and physical function. Given that the impact of frailty is multidimensional, this is an expected result. The domains of physical function, intimate relationship, burden to others, and body image showed a trend toward an association in the unadjusted model without reaching statistical significance in the adjusted model (Table 1). The overall trend seen highlights the global impact of frailty on an individual.

Another important finding is the trend of higher LupusQoL domain scores in the population categorized as frail compared with the population categorized as least fit on the SLICC-FI (Table 2). These findings point toward a poor HRQoL experienced by the population with the most severe deficits (indicated by higher scores) in the SLICC-FI domains, suggesting that SLICC-FI is a useful tool to identify and categorize those at higher risk of poor HRQoL among patients living with SLE. Notably, none of our patients were deemed as robust (SLICC-FI score ≤0.03), and only

Table 1. The predictive value of the SLICC-FI (per 0.05 increase, as a continuous variable) for HRQoL in patients with SLE*

	Unadjusted model		Adjusted model[a]	
Domain, mean ± SD	B ± SE	*P* value	B ± SE	*P* value
Physical function	**−2.63 ± 0.69**	**<0.001**	−1.00 ± 0.91	0.274
Pain	**−3.53 ± 0.79**	**<0.001**	**−2.67 ± 1.16**	**0.022**
Planning	**−2.65 ± 0.77**	**<0.001**	**−2.64 ± 1.13**	**0.019**
Intimate relationship	**−4.58 ± 1.11**	**<0.001**	−3.19 ± 1.70	0.061
Burden to others	**−2.85 ± 0.81**	**<0.001**	−0.55 ± 1.13	0.624
Emotional health	**−1.55 ± 0.72**	**0.031**	**−2.26 ± 1.00**	**0.024**
Body image	**−2.19 ± 0.85**	**0.010**	−1.79 ± 1.19	0.133
Fatigue	**−1.30 ± 0.53**	**0.016**	**−3.25 ± 1.09**	**0.003**

* The B coefficient corresponds to an increase of 0.05 on the Systemic Lupus International Collaborating Clinics Frailty Index (SLICC-FI). Bold text signifies statistically significant data. HRQoL, health-related quality of life; QoL, quality of life; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

[a] Adjusted for age at diagnosis, sex, socioeconomic status, ethnicity, SLEDAI-2K, SDI, disease duration at baseline, prednisone daily dose, antimalarial and immunosuppressive drug use, and the same domain of the LupusQoL in the previous visit.

Table 2. The predictive value of the SLICC-FI (per 0.05 increase, as a categorical variable) on HRQoL in patients with SLE*

	Unadjusted model				Adjusted model[a]			
	Frail[b]		Least fit[b]		Frail[b]		Least fit[b]	
Domain, mean ± SD	B ± SE	*P* value	B ± SE	*P* value	B ± SE	*P* value	B ± SE	*P* value
Physical function	−2.93 ± 1.73	0.091	**−2.38 ± 0.90**	**0.008**	−0.74 ± 3.18	0.816	−0.18 ± 2.05	0.931
Pain	**−6.55 ± 2.08**	**0.002**	**−3.01 ± 1.18**	**0.011**	−1.63 ± 4.05	0.688	−1.97 ± 2.63	0.454
Planning	**−4.00 ± 2.07**	**0.054**	**−2.99 ± 1.22**	**0.014**	−2.73 ± 3.65	0.454	−0.96 ± 2.13	0.651
Intimate relationship	**−6.87 ± 3.46**	**0.047**	−0.37 ± 2.43	0.878	−4.95 ± 2.98	0.096	−2.82 ± 2.04	0.168
Burden to others	**−5.35 ± 2.44**	**0.028**	−1.85 ± 1.62	0.255	−1.49 ± 3.52	0.672	−0.36 ± 2.70	0.895
Emotional health	**−5.82 ± 2.1**	**0.005**	**−2.86 ± 1.26**	**0.024**	−4.34 ± 3.15	0.169	−2.65 ± 2.17	0.223
Body image	−4.53 ± 2.73	0.097	**−4.32 ± 1.93**	**0.026**	**−5.83 ± 2.53**	**0.021**	−2.24 ± 1.91	0.241
Fatigue	**−3.82 ± 1.67**	**0.022**	**−2.89 ± 1.11**	**0.009**	**−9.29 ± 4.15**	**0.025**	**−7.46 ± 3.37**	**0.027**

* The B coefficient corresponds to the increase on the specific domain when a patient is frail or least fit, compared to less fit. Bold text signifies statistically significant data. HRQoL, health-related quality of life; QoL, quality of life; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC-FI, Systemic Lupus International Collaborating Clinics Frailty Index.
[a] Adjusted for age at diagnosis, sex, socioeconomic status, ethnicity, SLEDAI-2K, SDI, disease duration at baseline, prednisone daily dose, antimalarial and immunosuppressive drug use, and the same domain of the LupusQoL in the previous visit.
[b] In this model, the category of less frail was included as the reference group.

8.3% were categorized as less fit (SLICC-FI score of 0.03–0.10). These results add to the growing literature demonstrating that SLICC-FI scores are a predictor of clinically meaningful outcomes. The use of this metric to determine which patients may require more rigorous support to prevent poor outcomes is the ultimate goal of such studies, including the one presented.

Our study has some limitations; notably, this study was conducted in a single center with a primarily Mestizo population (European and Amerindian ancestry); this can limit its generalizability to other populations. Moreover, we cannot exclude the impact of socioeconomic factors and the patients' education level on the application of the studied instruments. The patients in this cohort have a variable disease duration, and thus, our findings may not be generalizable to all patients. An important strength of our study, however, is the relatively high proportion of patients with significant organ damage and higher levels of SLICC-FI scores than those reported by others, thus reflecting the challenges our patients face because of their high disease burden and frailty. Additional longitudinal studies in diverse large patient cohorts are ultimately needed to substantiate our findings. In conclusion, the SLICC-FI has shown to be a valuable instrument to predict HRQoL in patients with SLE in a prevalent Latin American Mestizo cohort.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Ugarte-Gil confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ROLE OF THE STUDY SPONSOR

Janssen Pharmaceuticals had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Janssen Pharmaceuticals.

REFERENCES

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146–M157.
2. Motta F, Sica A, Selmi C. Frailty in rheumatic diseases. Front Immunol 2020;11:576134.
3. Legge A, Kirkland S, Rockwood K, et al. Construction of a frailty index as a novel health measure in systemic lupus erythematosus. J Rheumatol 2020;47(1):72–81.
4. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29(2):288–291.
5. Gladman DD, Urowitz MB. The SLICC/ACR damage index: progress report and experience in the field. Lupus 1999;8(8):632–637.
6. Devilliers H, Amoura Z, Besancenot JF, et.al. Responsiveness of the 36-item short form health survey and the lupus quality of life questionnaire in SLE. Rheumatology (Oxford) 2015;54(5):940–949.
7. Legge A, Kirkland S, Rockwood K, et al. Prediction of hospitalizations in systemic lupus erythematosus using the systemic lupus international collaborating clinics frailty index. Arthritis Care Res (Hoboken) 2022;74(4):638–647.
8. Legge A, Kirkland S, Rockwood K, et al. Evaluating the properties of a frailty index and its association with mortality risk among patients with systemic lupus erythematosus. Arthritis Rheumatol 2019;71(8):1297–1307.
9. Elera-Fitzcarrald C, Gamboa-Cárdenas RV, Reatégui-Sokolova C, et al. The SLICC-FI predicts damage accrual in SLE patients. Data from the Almenara lupus cohort. Lupus 2022;31(13):1666–1670.
10. Lai NS, Lu MC, Chang HH, et al. A comparison of the correlation of Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and systemic lupus erythematosus disease activity

score (SLE-DAS) with health-related quality of life. J Clin Med 2021; 10(10):2137.

11. Strand V, Simon LS, Meara AS, et al. Measurement properties of selected patient-reported outcome measures for use in randomised controlled trials in patients with systemic lupus erythematosus: a systematic review. Lupus Sci Med 2020;7(1):e000373.
12. Louthrenoo W, Kasitanon N, Morand E, et.al. Comparison of performance of specific (SLEQOL) and generic (SF36) health-related quality of life questionnaires and their associations with disease status of systemic lupus erythematosus: a longitudinal study. Arthritis Res Ther 2020;22(1):8.
13. Shi Y, Li M, Liu L, et al. Relationship between disease activity, organ damage and health-related quality of life in patients with systemic lupus erythematosus: a systemic review and meta-analysis. Autoimmun Rev 2021;20(1):102691.
14. Keramiotou K, Anagnostou C, Konstantonis G, et.al. SLICC-Frailty Index is independently associated with impaired physical function, activities of daily living and quality of life measures. Rheumatology (Oxford) 2022;61(9):3808–3813.
15. Lieber SB, Nahid M, Legge A, et al. Comparison of two frailty definitions in women with systemic lupus erythematosus. Rheumatology (Oxford) 2024;63(5):1384–1390.
16. Hochberg MC. Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40(9): 1725
17. Méndez Castellano H, de Méndez MC. Sociedad y estratificación: método graffar-m Mendez castellano. Fundacredesa; 1994.
18. McElhone K, Abbott J, Sutton C, et al. Sensitivity to change and minimal important differences of the LupusQoL in patients with systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2016;68(10): 1505–1513.
19. Nielsen W, Strand V, Simon L, et al. OMERACT systemic lupus erythematosus domain survey. Semin Arthritis Rheum. 2024;68:152520.
20. Lieber SB, Nahid M, Rajan M, et al. Association of baseline frailty with patient-reported outcomes in systemic lupus erythematosus at 1 year. J Frailty Aging 2023;12(3):247–251.

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1141–1148
DOI 10.1002/acr.25553

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

BRIEF REPORT

Two-Year Follow-Up of a Multidisciplinary Lifestyle Intervention for Rheumatoid Arthritis and Osteoarthritis

Carlijn A. Wagenaar,[1] Wendy Walrabenstein,[1] Marike van der Leeden,[2] Franktien Turkstra,[3] Martijn Gerritsen,[3] Jos W. R. Twisk,[4] Maarten Boers,[4] Martin van der Esch,[5] Henriët van Middendorp,[6] Peter J. M. Weijs,[7] and Dirkjan van Schaardenburg[1]

Objective. The Plants for Joints (PFJ) intervention, including a whole-food plant-based diet, exercise, and stress reduction, reduced signs and symptoms of rheumatoid arthritis (RA) or metabolic syndrome–associated hip or knee osteoarthritis (MSOA) compared to usual care. This study aimed to examine outcomes two years after the PFJ intervention.

Methods. After two 16-week randomized controlled trials in people with (1) RA or (2) MSOA, control groups received the active PFJ intervention. All participants were then observed in a two-year observational extension study. Primary outcomes were Disease Activity Score in 28 joints (DAS28) (RA) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (MSOA). Secondary outcomes included body composition, metabolic outcomes, medication changes, and adherence to intervention recommendations. Within-group differences were assessed using linear mixed models, comparing the start and end of the intervention to two years after intervention.

Results. A total of 48 of 77 participants with RA (62%) and 44 of 64 participants with MSOA (69%) completed the extension study. Two years after the intervention, the DAS28 in participants with RA (–0.9 points, 95% confidence interval [CI] –1.2 to –0.6 points) and WOMAC score in participants with MSOA (–8.8 points, 95% CI –12.6 to –5.1 points) were significantly lower than start intervention. In addition, C-reactive protein in the RA group and weight, body mass index, waist circumference, and diastolic blood pressure in the MSOA group were significantly lower compared to start intervention. Primary end points remained similar from the end of the intervention to the end of the extension study. During the extension study, medication use decreased slightly, and participants continued to follow the intervention recommendations.

Conclusion. Two years after the PFJ intervention, improvements in RA disease activity, MSOA symptoms and functioning, and intervention adherence were sustained.

INTRODUCTION

The Plants for Joints (PFJ) randomized controlled trial investigated the effect of a multidisciplinary lifestyle intervention based on a whole-food plant-based diet, physical activity, and stress management in people with low to moderately active rheumatoid arthritis (RA) or metabolic syndrome–associated hip or knee osteoarthritis (MSOA).[1] After four-month intervention, participants

EudraCT: NL 66649.048.18.
ICTRP: NL7800 and NL7801.
The randomized controlled trial was funded by Reade (Amsterdam, The Netherlands), Reade Foundation (Amsterdam, The Netherlands), Stichting Vermeer 14 (private foundation, Amsterdam, The Netherlands), and W. M. de Hoop Stichting (private foundation, Bussum, The Netherlands). The extension study was funded by The Netherlands Organisation for Health Research and Development (ZonMw; 555003210). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

[1]Carlijn A. Wagenaar, MD, Wendy Walrabenstein, PhD, Dirkjan van Schaardenburg, MD, PhD: Reade Center for Rheumatology and Rehabilitation, Amsterdam University Medical Centers, Universiteit van Amsterdam, and Amsterdam Rheumatology and Immunology Center, Amsterdam, The Netherlands; [2]Marike van der Leeden, PhD: Reade Center for Rheumatology and Rehabilitation, Amsterdam University Medical Centers, Vrije Universiteit, and Amsterdam Movement Sciences Research Institute, Amsterdam, The Netherlands; [3]Franktien Turkstra, MD, PhD, Martijn Gerritsen, MD, PhD: Reade Center for Rheumatology and Rehabilitation, Amsterdam, The Netherlands; [4]Jos W. R. Twisk, PhD, Maarten Boers, MD, PhD: Amsterdam University Medical Centers, Vrije Universiteit, Amsterdam, The Netherlands; [5]Martin van der Esch, PhD: Reade Center for Rheumatology and Rehabilitation and Amsterdam University of Applied Sciences, Amsterdam, The Netherlands; [6]Henriët van Middendorp, PhD: Leiden University, Leiden, The Netherlands; [7]Peter J. M. Weijs, PhD: Amsterdam University Medical Centers, Vrije Universiteit and Amsterdam University of Applied Sciences, Amsterdam, The Netherlands.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25553).

Author disclosures and graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25553.

Address correspondence via email to Carlijn A. Wagenaar, MD, at c.a.wagenaar@amsterdamumc.nl.

Submitted for publication December 10, 2024; accepted in revised form April 8, 2025.

SIGNIFICANCE & INNOVATIONS

- In two randomized controlled trials the 16-week Plants for Joints (PFJ) multidisciplinary lifestyle intervention significantly improved disease activity or symptoms and metabolic health in people with rheumatoid arthritis (RA) or metabolic syndrome–associated hip or knee osteoarthritis (MSOA).
- After two years, improvements in disease activity (RA), symptoms, and functioning (MSOA) and metabolic outcomes, as well as adherence to intervention recommendations, were largely sustained.
- These long-term findings support the PFJ intervention as add-on treatment in people with RA or MSOA.

with RA showed significant disease activity reduction (mean Disease Activity Score in 28 joints [DAS28] –0.9 points),[2] and participants with MSOA had less pain and stiffness, and improved physical function (mean Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] score –11 points) compared to a usual care control group.[3] Both RA and MSOA groups had improved metabolic outcomes, including weight, fat mass, hemoglobin A1c (HbA1c), and low-density lipoprotein (LDL) cholesterol.[2,3] After completing the randomized controlled trials, the control groups received the same intervention, and all participants took part in an observational extension study. A year after the PFJ lifestyle intervention, improvements of disease activity and metabolic outcomes within RA and MSOA groups were sustained and related to intervention adherence, with a net decrease of medication.[4] Because improvements in health behavior and status are not always maintained after a successful lifestyle intervention, all participants were followed up for an additional year. This study aimed to determine disease activity, metabolic health, medication use, and adherence to intervention recommendations two years after intervention in participants with RA and participants with MSOA. Results are presented separately for RA and MSOA but combined in one report, as the same intervention was used.

MATERIALS AND METHODS

Design, study sample, and intervention. This study reports the second year of the PFJ extension study; first-year outcomes were previously published.[4] The design, study sample, and intervention were previously described.[1–4] Briefly, two assessor-masked open-label randomized controlled trials compared the effect of a multidisciplinary lifestyle intervention to routine care in people with (1) RA or (2) MSOA between May 2019 and December 2021 at the Reade rehabilitation and rheumatology clinic in Amsterdam, The Netherlands.[1–3] People aged ≥18 years were included if they had (1) RA according to the American College of Rheumatology (ACR)/EULAR 2010 criteria, with 2.6 ≤ DAS28 ≤ 5.1, and stable treatment with or without disease-modifying antirheumatic drugs for ≥3 months[5,6] or (2) hip and/or knee osteoarthritis (OA) according to the ACR clinical criteria and metabolic syndrome according to the National Cholesterol Education Program criteria.[7–9] At the start of the intervention, participants received individual intakes with a dietitian and a physical therapist. During the four-month intervention, mixed groups of participants with RA and participants with MSOA received theoretical and practical education about a calorie-unrestricted whole-food plant-based diet, physical activity, and sleep and stress management during 10 group meetings of 6 to 12 participants.[1]

After completing the randomized controlled trial, control group participants began the lifestyle intervention. Following the active intervention period, all participants were invited to join an extension study with measurements at 6, 12, 18, and 24 months. Participants were encouraged to adhere to the intervention's recommendations and received monthly newsletters and optional bimonthly webinars.[4] The original trial protocol included a one-year extension study, but extra resources allowed for a second follow-up year, requiring additional written informed consent.

The Medical Ethical Committee of the Amsterdam University Medical Centers approved the study protocol (EudraCT number NL66649.048.18), and all participants provided written informed consent. Study protocols were prospectively registered (International Clinical Trial Registry Platform numbers NL7800 and NL7801) and published.[1] Data will be shared on reasonable request.

Primary and secondary outcomes. The primary outcome for RA was the mean change in DAS28 from the start and end of the intervention compared to the end of the extension study. DAS28 was assessed by an independent research nurse. The primary outcome for MSOA was the WOMAC total score (range 0–96, best to worst) measured over the same time with digital questionnaires.[10] Secondary outcomes included components of the primary outcomes, anthropometric, and metabolic outcomes. Adverse events and joint-replacement surgeries were recorded.

Medication changes. Medication use was recorded at each measurement, and changes in medication from the start of the intervention to the end of the extension study were classified as "increase," "stable," or "decrease."[4] Therapeutic injections in MSOA were also recorded. During the extension study, participants with RA and a DAS28 <2.6 received a protocol as a suggested approach to taper antirheumatic medication with their rheumatologist (Supplementary Material S1). Changes in antirheumatic medication intensity were classified by an independent committee according to prespecified criteria.

Adherence to intervention recommendations. Adherence was assessed at each measurement using an adapted version of the Lifestyle Index Adherence Score, in which

a score of 1.0 indicates 100% adherence to program recommendations: attending all 10 meetings during the intervention, doing stress-reducing activities 6 days/wk for 10 min/day, doing physical activity 5 days/wk for 30 min/day, and having a mean intake of ≥14 g fiber/1,000 kilocalories (kcal) and <10% saturated fatty acids of total kcal/day (energy%).[1] A score greater than 1.0 reflects higher minutes of stress-relieving or physical activity, greater fiber intake, and/or lower saturated fat intake. Dietary intake was measured for four days with a validated digital food diary (Mijn Eetmeter).[11] A two-day dietary recall was conducted for participants who had difficulty or had not filled in the food diary themselves. Minutes of physical and stress-reducing activities in the past week were assessed with a digital questionnaire. The intensity and mode of physical activity, as well as webinar attendance during the extension study, were not recorded.

Statistical analysis. Participants with RA and participants with MSOA were analyzed separately. To estimate the within-group change over time (start intervention to end extension and end intervention to end extension) in primary and secondary outcomes, linear mixed models were used. In these models, time was treated as a categorical variable using dummy variables, and the intervention and control groups were combined into one cohort, all starting at month 0 (month 0 for the intervention group and month 4 for the control group). To assess the assumptions of the linear mixed models, we examined the normality of residuals using histograms. If assumptions were violated, such as non-normality, outcomes were log-transformed before rerunning the models, and within-group differences were reported as median difference of complete paired values determined with a Wilcoxon test. The linear mixed models, with the ability to handle data missing at random, incorporated all available participant data until the point they were lost to follow-up, when applicable. Within-group changes in primary and secondary outcomes for subgroups of extension study completers and dropouts were assessed using linear mixed models. The Wilcoxon test was used to evaluate whether changes in DAS28 or WOMAC differed significantly between completers and dropouts. Medication changes are described with descriptive statistics. Tertiles of the Lifestyle Index Adherence Score were created, and changes in DAS28 or WOMAC per group were summarized descriptively. All analyses were performed with R version 4.3.1 (2023-06-16) and *P* values <0.05 were considered statistically significant.

RESULTS

RA. A total of 48 of the 77 trial completers (62%) also completed the two-year follow-up. A total of 92% of all trial participants were female, with a mean age of 55 (SD 12) years and a mean baseline body mass index (BMI) of 26 (SD 4) (Supplementary Table 1). Twenty-nine participants withdrew from the extension study (17 participants in year 2), primarily due to busy schedules, the numerous study measurements, or not providing additional permission for the second follow-up year (Supplementary Figure 1A).

Two years after the intervention, DAS28 was significantly lower than at the start: mean –0.9 (95% confidence interval [CI] –1.2 to –0.6, Figure 1A; Supplementary Figure 2A). During the

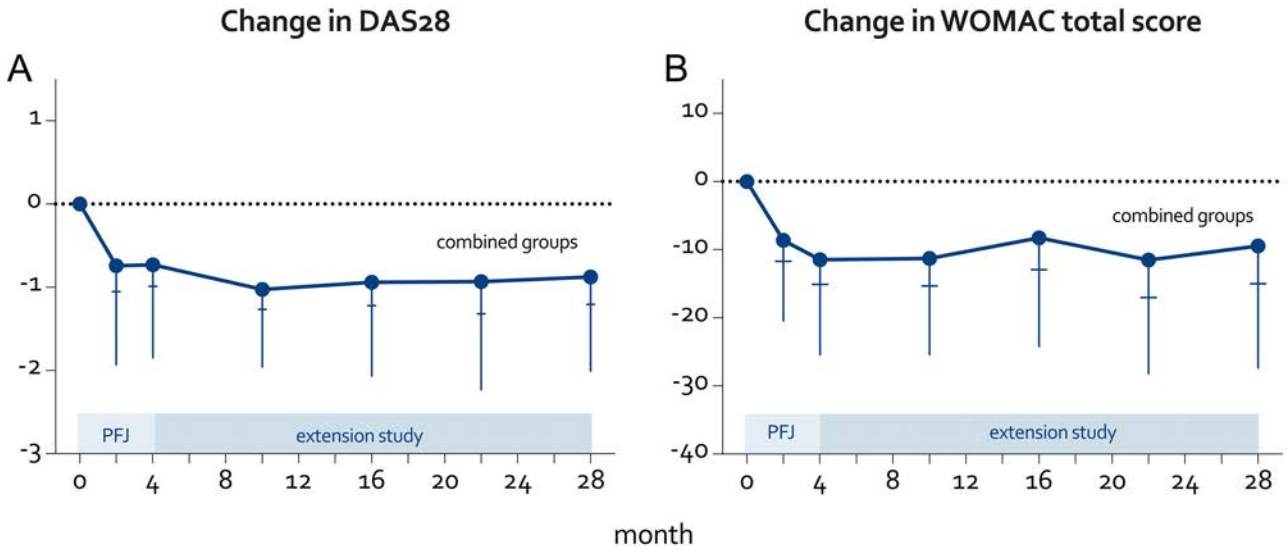

Figure 1. Mean change in DAS28 for (A) participants with rheumatoid arthritis and (B) WOMAC total score for participants with metabolic syndrome–associated hip or knee osteoarthritis for the whole cohort (all participants, data combined at start of active PFJ intervention). Error bars represent 95% confidence intervals (horizontal) and SDs (vertical). *P* values from linear mixed models assessing within-group differences between the start of the intervention and the end of the extension study are shown. DAS28, Disease Activity Score in 28 joints; PFJ, Plants for Joints; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

extension study, DAS28 showed a further small, nonsignificant reduction (mean −0.1 [95% CI −0.4 to 0.2]) compared to the end of the intervention (Table 1). Tender joint count and general health components of the DAS28 remained improved two years after the intervention, and there was no longer a significant difference in the erythrocyte sedimentation rate and swollen joint count

Table 1. Primary and secondary outcomes for participants with rheumatoid arthritis of the Plants for Joints two-year extension study*

	Intervention		Extension study		Start intervention to end extension (95% CI)	End intervention to end extension (95% CI)
	Start (n = 77)	End (n = 77)	12 mo (n = 65)	24 mo (n = 48)		
DAS28 and components						
DAS28 ESR, mean (SD)	3.85 (0.86)	3.09 (1.22)	2.84 (1.08)	2.84 (1.14)	−0.9 (−1.2 to −0.6)	−0.1 (−0.4 to 0.2)
DAS28 ESR (seropositive),[a] mean (SD)	3.88 (0.92)	3.26 (1.29)	2.93 (1.11)	2.90 (1.08)	−0.8 (−1.2 to −0.5)	−0.1 (−0.5 to 0.2)
DAS28 ESR (seronegative),[a] mean (SD)	3.76 (0.67)	2.62 (0.87)	2.60 (0.98)	2.67 (1.32)	−1.1 (−1.6 to −0.6)	0.0 (−0.5 to 0.6)
Swollen joint count, median (IQR)	1 (0 to 3)	0 (0 to 2)	0 (0 to 1)	1 (0 to 2)	0 (−2 to 1)[b]	1 (0 to 0)[b]
Tender joint count, median (IQR)	3 (1 to 6)	1 (0 to 3)	1 (0 to 3)	0 (0 to 2)	−2 (−2 to −1)	0 (−1 to 0)
General health (VAS), median (IQR)	52 (36 to 64)	26 (10 to 44)	22 (4 to 36)	22 (5 to 46)	−23 (−29 to −16)	−1 (−7 to 6)
ESR, median (IQR), mm/hr	15 (7 to 26)	14 (7 to 27)	12 (5 to 24)	12 (5 to 28)	−2 (−5 to 2)[b]	0 (−4 to 4)[b]
DAS28 ESR <2.6 (%)	–	29 (39)	25 (39)	18 (38)	–	–
DAS28 CRP	2.64 (1.07)	1.84 (1.38)	1.55 (1.25)	1.43 (1.21)	−1.1 (−1.4 to −0.7)	−0.2 (−0.5 to 0.1)
CRP, median (IQR), mg/L	2.4 (1.1 to 5.4)	2.1 (0.7 to 5.2)	1.6 (0.7 to 2.9)	1.3 (0.7 to 3.5)	−1.2 (−2.1 to −0.3)[b]	−0.6 (−1.9 to 0.3)[b]
Serology, median (IQR)						
Rheumatoid factor, kU/L	21.0 (1.2 to 69.0)	14.0 (1.5 to 59.5)	13.5 (1.3 to 39.5)	16.0 (3.1 to 36.0)	−2.0 (−9.6 to −0.9)[b]	−0.3 (−5.3 to 1.6)[b]
ACPA, kU/L	48 (2 to 470)	47 (2 to 605)	73 (2 to 585)	83 (3 to 600)	2 (−18 to 60)[b]	1 (−9 to 23)[b]
Body composition, mean (SD)						
Weight, kg	74.5 (12.9)	71.5 (12.9)	74.6 (13.0)	73.7 (12.6)	0.8 (−0.2 to 1.8)	3.8 (2.9 to 4.8)
BMI, kgm^{-2}	26.3 (4.3)	25.2 (4.4)	26.1 (4.3)	25.8 (3.9)	0.3 (−1.0 to 0.6)	1.3 (1.0 to 1.7)
Waist circumference, cm	91.0 (11.2)	87.6 (11.2)	89.8 (11.4)	89.4 (10.7)	−0.4 (−1.8 to 1.0)	3.0 (1.6 to 4.5)
Waist circumference (female participants)[c]	90.2 (11.1)	86.9 (11.1)	89.0 (11.4)	88.3 (10.5)	0.0 (−1.6 to 1.5)	3.3 (1.8 to 4.9)
Waist circumference (male participants)[c]	100.3 (8.4)	96.2 (9.7)	97.3 (8.5)	96.8 (9.4)	−3.5 (−6.0 to −1.0)	0.5 (−1.4 to 2.5)
Metabolic markers						
HbA1c, mean (SD), mmol/mol	36.9 (6.4)	36.0 (6.0)	36.5 (7.0)	37.7 (7.2)	0.6 (−0.1 to 1.2)	1.3 (0.7 to 2.0)
Fasting blood glucose, median (IQR), mmol/L	5.1 (4.8 to 5.4)	4.9 (4.6 to 5.1)	4.9 (4.7 to 5.2)	5.0 (4.7 to 5.3)	−0.1 (−0.3 to 0.1)	0.0 (−0.2 to 0.2)
LDL cholesterol, mean (SD), mmol/L	3.1 (0.9)	2.7 (0.8)	2.9 (0.9)	3.0 (0.9)	0.0 (−0.2 to 0.1)	0.3 (0.2 to 0.5)
HDL cholesterol, mean (SD), mmol/L	1.6 (0.4)	1.6 (0.4)	1.7 (0.4)	1.8 (0.4)	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.3)
Triglycerides, mean (SD), mmol/L	1.1 (0.5)	1.0 (0.4)	1.0 (0.4)	1.0 (0.4)	0.0 (−0.1 to 0.1)[b]	0.0 (−0.1 to 0.1)[b]
Systolic blood pressure, mean (SD), mm Hg	134 (19)	128 (18)	134 (22)	134 (20)	−1 (−5 to 3)	6 (1 to 10)
Diastolic blood pressure, mean (SD), mm Hg	86 (11)	84 (11)	86 (12)	85 (12)	−1 (−4 to 2)	1 (−2 to 5)

* Outcomes from the Plants for Joints cohort at the start and end of the 16-week intervention period as well as during the two-year extension study (12 and 24 months after completing the intervention). Within-group differences are shown between the start and end of the lifestyle intervention and end of the 24-month follow-up determined using the linear mixed model when model assumptions were met. ACPA, anti–citrullinated protein antibody; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; VAS, visual analog scale.
[a] Seropositive, n = 57; seronegative, n = 20.
[b] Within-group differences were reported as median difference of complete paired values determined with a Wilcoxon test for outcomes that did not meet model assumptions.
[c] Female participants, n = 71; male participants, n = 6.

compared to the start of the intervention (Table 1). Results were similar in participants who completed the two-year extension study versus those who discontinued prematurely (mean DAS28 change during intervention: completer –0.9, dropout –0.6, P = 0.4; mean change up to first-year extension study: completer –1.0, dropout –0.9, P = 0.9; Supplementary Table 2).

Of the 39 participants who completed the follow-up and used antirheumatic medication, 17 participants (44%) decreased or stopped medication use (n = 12 decreased and n = 5 stopped, with an average dosage reduction of 58%). Ten participants (26%) maintained stable use, and 12 participants (31%) increased medication (n = 9 added medication, n = 2 switched due to disease activity, and n = 1 had a glucocorticoid injection) (Supplementary Tables 3 and 4). Thirty participants (65%) had improved DAS28 scores (11 with DAS28 <2.6) with stable or less medication compared to baseline. Two years after the intervention, high-density lipoprotein (HDL) cholesterol was increased, and C-reactive protein (CRP) levels remained significantly lower compared to the start of the intervention (Table 1). However, weight, BMI, waist circumference, HbA1c, LDL cholesterol, and systolic blood pressure increased during the extension study, although all (except HbA1c) stayed below starting values (Table 1).

OA. A total of 44 of the 64 trial completers (69%) also completed the two-year follow-up. A total of 84% of all trial participants were female, with a mean age of 63 (SD 6) years and a mean baseline BMI of 33 (SD 5) (Supplementary Table 5). Eighteen participants withdrew from the extension study (five in year 2), primarily due to busy schedules, the numerous study measurements, or not providing additional permission for the second follow-up year (Supplementary Figure 1B).

Two years after the intervention, WOMAC total was significantly lower than at the start: mean –8.8 (95% CI –12.6 to –5.1, Figure 1B; Supplementary Figure 2B). No significant change in WOMAC score was observed between the end of the intervention and the end of the extension study (mean 2.6 [95% CI –0.9 to 6.2]) (Table 2). Furthermore, all components of the WOMAC were significantly improved two years after intervention compared to the start of the intervention (Table 2). Results were similar in participants who completed the two-year extension study versus those who discontinued prematurely (mean WOMAC total change during intervention: completer –12.0, dropout –10.0, P = 0.6; mean change up to first-year extension study: completer –8.5, dropout –4.3, P = 0.7; Supplementary Table 2).

Two years after the intervention, weight, waist circumference, and diastolic blood pressure remained significantly lower than at the start (Table 2). However, BMI, waist circumference, HbA1c, and fasting blood glucose levels increased during the extension study but stayed below starting values (Table 2). Of the 19 participants who completed the extension study and used pain medication, 10 participants (53%) decreased or stopped, whereas 9 patients (47%) had increased pain medication (Supplementary Table 3). Furthermore, of those who completed the follow-up and used lipid-lowering medication, seven participants (44%) decreased, six participants (38%) remained stable, and three participants (19%) increased their medication. During the second year of the extension study, one participant received a hyaluronic acid injection in the knee, and another had knee replacement surgery; both remained in the study. Adverse events for the second year of the extension study for RA and MSOA are described in Supplementary Table 6. Adverse events in the second year were uncommon and mostly mild, with a few moderate events (flu) and two severe events (colon carcinoma and pyelonephritis).

Adherence to intervention recommendations. Adherence was largely sustained during the extension study: RA Lifestyle Index Adherence Score declined slightly from 1.05 (53% of participants had a score ≥1; end intervention) to 0.99 (45% of participants; end extension study), and MSOA score 1.02 (53%) to 0.99 (45%), respectively (Supplementary Tables 7 and 8). Participants with an adherence score ≥1 at the end of the two-year extension study showed a trend toward greater changes in DAS28 or WOMAC total scores from the start of intervention to the end of the extension study compared to those with scores <1 (Supplementary Table 9). Two years after the intervention, the median intake of saturated fat (9 energy%, recommendation <10%), fiber (19 g/1,000 kcal, recommendation ≥14 g/1,000 kcal), and time spent on physical activity (193 min/wk, recommendation ≥150 min/wk) were compliant with recommendations in both groups. Time spent per week on stress-relieving activities remained relatively stable throughout the extension study (36–31 min/wk, recommendation ≥60 min/wk) (Supplementary Tables 7 and 8).

DISCUSSION

Two years after the intervention, DAS28 in participants with RA and WOMAC in participants with MSOA remained significantly lower than at the start, surpassing the minimal clinically important difference of 0.8 (based on the inclusion criteria) for RA and 20% for pain and physical function for MSOA.[12,13] The (already low) erythrocyte sedimentation rate and swollen joint count in participants with RA did not remain significantly lower, possibly due to the reduced sample size. Primary outcomes in both groups remained stable during the extension period. These results were achieved despite 44% of participants with RA and 53% of participants with MSOA reducing or stopping antirheumatic or pain medication, respectively.

At the end of the two-year extension study, participants with RA showed significant improvements in CRP and HDL cholesterol, whereas participants with MSOA had significant reductions in weight, BMI, waist circumference, and diastolic blood pressure compared to the start of intervention. Sustained weight loss and improved waist circumference are notable, as maintaining weight

Table 2. Primary and secondary outcomes for participants with osteoarthritis of the Plants for Joints two-year extension study*

	Intervention		Extension study		Start intervention to end extension (95% CI)	End intervention to end extension (95% CI)
	Start (n = 64)	End (n = 62)	12 mo (n = 49)	24 mo (n = 44)		
WOMAC score, mean (SD)						
WOMAC total (0–96)	38.2 (16.2)	26.9 (18.9)	30.4 (18.6)	27.0 (18.8)	−8.8 (−12.6 to −5.1)	2.6 (−0.9 to 6.2)
WOMAC pain (0–20)	7.4 (3.0)	5.1 (3.7)	5.9 (3.7)	4.9 (3.8)	−2.2 (−3.1 to −1.4)	0.1 (−0.7 to 0.9)
WOMAC stiffness (0–8)	4.0 (1.8)	3.0 (2.0)	3.5 (2.2)	3.3 (1.8)	−0.6 (−1.0 to −0.1)	0.5 (0.0 to 1.0)
WOMAC function (0–68)	26.8 (12.8)	18.9 (14.0)	21.1 (13.7)	18.9 (14.0)	−6.3 (−8.9 to −3.3)	1.9 (−0.8 to 4.6)
Inflammation, median (IQR)						
C-reactive protein, mg/L	1.9 (1.0 to 4.5)	1.3 (0.8 to 3.0)	1.4 (0.9 to 3.3)	1.4 (0.9 to 3.1)	−0.3 (−1.0 to 0.6)[a]	0.3 (0.0 to 0.0)[a]
Body composition, mean (SD)						
Weight, kg	94.9 (15.9)	90.2 (14.9)	90.7 (13.2)	92.1 (12.8)	−3.8 (−5.5 to −2.1)	1.5 (−0.2 to 3.2)
BMI, kgm^{-2}	33.3 (5.3)	31.7 (5.0)	31.5 (3.9)	32.3 (4.7)	−1.3 (−1.8 to −0.7)	0.6 (0.0 to 1.1)
Waist circumference, cm	110.0 (12.9)	104.6 (12.3)	105.7 (11.5)	106.7 (9.0)	−3.8 (−5.8 to −1.7)	2.2 (0.4 to 4.1)
Waist circumference (female participants)[b]	108.9 (13.3)	103.3 (12.5)	107.2 (11.8)	105.8 (8.7)	−3.3 (−5.5 to −1.1)	2.7 (0.6 to 4.8)
Waist circumference (male participants)[b]	116.0 (8.9)	112.6 (7.7)	108.8 (10.2)	112.2 (9.4)	−6.3 (−11.8 to −0.8)	−0.5 (−5.0 to 4.1)
Metabolic markers						
HbA1c, mean (SD), mmol/mol	42.6 (8.4)	40.3 (7.2)	40.2 (7.5)	41.0 (6.7)	−0.7 (−1.5 to 0.2)	1.6 (0.6 to 2.5)
Fasting blood glucose, median (IQR), mmol/L	5.8 (5.3 to 6.5)	5.5 (5.1 to 6.2)	5.4 (5.1 to 5.9)	5.7 (5.0 to 6.3)	−0.2 (−0.4 to 0.0)	0.3 (0.0 to 0.5)
LDL cholesterol, mean (SD), mmol/L	3.6 (1.3)	3.3 (1.2)	3.3 (1.4)	3.5 (1.0)	−0.1 (−0.3 to 0.1)	0.2 (−0.1 to 0.4)
HDL cholesterol, mean (SD), mmol/L	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)
Triglycerides, median (IQR), mmol/L	1.6 (1.2 to 2.2)	1.6 (1.0 to 2.1)	1.5 (1.1 to 2.1)	1.5 (1.0 to 1.9)	−0.1 (−0.4 to 0.0)[a]	0.4 (−0.2 to 0.2)[a]
Systolic blood pressure, mean (SD), mm Hg	145 (18)	144 (19)	142 (16)	140 (15)	−5 (−10 to 1)	−4 (−10 to 1)
Diastolic blood pressure, mean (SD), mm Hg	91 (11)	89 (11)	86 (8)	85 (9)	−5 (−8 to −3)	−4 (−6 to −1)

* Outcomes from the Plants for Joints cohort at start and end of the 16-week intervention period as well as during the two-year extension study (12 and 24 months after completing the intervention). Within-group difference shown between the start and end of the lifestyle intervention and end of the 24-month follow-up determined using the linear mixed model when model assumptions were met. BMI, body mass index; CI, confidence interval; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Within-group differences were reported as median difference of complete paired values determined with a Wilcoxon test for outcomes that did not meet model assumptions.

[b] Female participants, n = 54; male participants, n = 10.

loss over time is typically difficult, and most individuals tend to regain more than half of the lost weight after two years.[14] During the extension study, weight, BMI, waist circumference, HbA1c, and LDL cholesterol in participants with RA and BMI, waist circumference, HbA1c, and fasting blood glucose levels in participants with MSOA increased, but remained below starting values. This could be due to lower adherence; although our adherence data do not support this, potential underreporting cannot be dismissed.

Lifestyle interventions for RA and OA are clinically relevant as adjunct therapies, helping to reduce disease activity, manage symptoms, and prevent comorbidities. However, their implementation is challenging because of limited access, motivation, and time and cost constraints. The group-based approach of our intervention, focused on lifestyle education rather than intensive, individualized care, is a key strength and shows strong potential for real-world clinical implementation. Although few studies report long-term follow-up, this study demonstrates sustained benefits, with key factors including social support, an enthusiastic and knowledgeable team, increased health awareness, and motivation from positive effects.[15] The intervention's emphasis on consistency over perfection enables participants to integrate sustainable habits and recover from setbacks.

Strengths of the study include the long-term assessment of effectiveness, medication changes, and adherence and the inclusion of only participants with (low to moderately) active RA. Limitations include the lack of a control group, >30% loss to follow-up, and unmonitored cointerventions such as physical activity or other lifestyle programs. Self-reported adherence data are a limitation due to potential recall bias or underreporting, although 24-hour dietary recalls by dietitians helped mitigate underreporting when food diaries were incomplete or unrealistic. The long-term effect of the intervention on DAS28, WOMAC, and metabolic outcomes may be overestimated due to data lost from participants who dropped out. Although linear mixed models account for missing data assumed to be missing at random, nonrandom missing data cannot be ruled out, particularly as changes in primary and secondary outcomes were slightly larger in participants who completed the extension study compared to those who dropped out. Conversely, reductions in antirheumatic medication may (partially) offset the intervention effect on DAS28. Lastly, because of the multidisciplinary nature, it is impossible to single out the effect of specific components of the lifestyle intervention. Significant improvements in disease activity in RA and pain, stiffness, and physical function in MSOA observed during the PFJ intervention were observed up to two years after program completion, confirming the durability of lifestyle modifications and their positive effects.

ACKNOWLEDGMENTS

We thank the Reade Biobank technicians Toni de Jong-de Boer and Corrie Verdoold, radiologist Mies Korteweg; registered dietitians Pauline Kortbeek, Anna Kretova, Melissa Dijkshoorn, Marieke van de Put, Michelle Bisschops, Alie Tooonstra, and Sanne Kodde; and Martijn Gerritsen, Sjoerd Heslinga, and Bas Dijkshoorn (Medication Committee). During the preparation of this work, the authors used ChatGPT to improve readability and language by checking grammar and making suggestions for improving sentence structure. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Wagenaar confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Walrabenstein W, van der Leeden M, Weijs P, van Middendorp H, et al. The effect of a multidisciplinary lifestyle program for patients with rheumatoid arthritis, an increased risk for rheumatoid arthritis or with metabolic syndrome-associated osteoarthritis: the "Plants for Joints" randomized controlled trial protocol. Trials 2021;22(1):715.
2. Walrabenstein W, Wagenaar CA, van der Leeden M, et al. A multidisciplinary lifestyle program for rheumatoid arthritis: the 'Plants for Joints' randomized controlled trial. Rheumatology (Oxford) 2023; 62(8):2683–2691.
3. Walrabenstein W, Wagenaar CA, van de Put M, et al. A multidisciplinary lifestyle program for metabolic syndrome-associated osteoarthritis: the "Plants for Joints" randomized controlled trial. Osteoarthritis Cartilage 2023;31(11):1491–1500.
4. Wagenaar CA, Walrabenstein W, van der Leeden M, et al. Long-term effectiveness of a lifestyle intervention for rheumatoid arthritis and osteoarthritis: 1-year follow-up of the 'Plants for Joints' randomised clinical trial. RMD Open 2024;10(1):e004025.
5. Fransen J, van Riel PLCM. DAS remission cut points. Clin Exp Rheumatol 2006;24(6)(suppl 43):S-29-32.
6. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62(9):2569–2581.
7. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106(25):3143–3421.
8. Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34(5):505–514.
9. Altman R, Asch E, Bloch D, et al; Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29(8): 1039–1049.
10. Roorda LD, Jones CA, Waltz M, et al. Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis 2004;63(1):36–42.

11. Ocké M, Dinnissen C, Stafleu A, et al. Relative validity of MijnEetmeter: a food diary app for self-monitoring of dietary intake. Nutrients 2021; 13(4):1135.
12. Aletaha D, Funovits J, Ward MM, et al. Perception of improvement in patients with rheumatoid arthritis varies with disease activity levels at baseline. Arthritis Rheum 2009;61(3):313–320.
13. Tubach F, Ravaud P, Martin-Mola E, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: results from a prospective multinational study. Arthritis Care Res (Hoboken) 2012; 64(11):1699–1707.
14. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. Med Clin North Am 2018;102(1):183–197.
15. Wagenaar CA, Toonstra A, Walrabenstein W, et al. How the Plants for Joints multidisciplinary lifestyle intervention achieved its effects: a mixed methods process evaluation. BMC Public Health 2024;24(1): 1034–1032.

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1149–1156
DOI 10.1002/acr.25547

American College of Rheumatology
Empowering Rheumatology Professionals

Risk of Hepatotoxicity in Patients With Gout Treated With Febuxostat or Benzbromarone: A Propensity Score–Matched Cohort Study

Wenyan Sun,[1] Lingling Cui,[1] Robert Terkeltaub,[2] Ying Chen,[1] Xinde Li,[3] Xiaoyu Cheng,[1] Tian Liu,[1] Nicola Dalbeth,[4] and Changgui Li[3]

Objective. The objective of this study was to evaluate and compare the risk of hepatotoxicity associated with the use of febuxostat and benzbromarone in patients with gout.

Methods. New users of febuxostat or benzbromarone with monitoring of liver function at least three times in a year after initiation of the study drugs were identified from an electronic medical record database. Propensity score matching (PSM) was performed between the two groups 1:1 matched for age, sex, and pretreatment alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Kaplan-Meier analysis was used to estimate the probability of hepatotoxicity (defined as ALT or AST > 3× upper limit of normal). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox regression. Subgroup analysis was performed based on age, body mass index, and comorbidities.

Results. A total of 2,338 patients with gout were eligible. A total of 37% of patients experienced Common Terminology Criteria for Adverse Events version 5 grades 1 to 3 for AST or ALT abnormality. After PSM, 488 febuxostat users were matched, with 488 participants receiving benzbromarone with a mean follow-up of 1.20 years. The incidence of hepatotoxicity was 39.6 and 16.8 per 1,000 person-years for febuxostat users and benzbromarone users, respectively. Febuxostat use was associated with a significantly greater risk of hepatotoxicity than benzbromarone (adjusted HR 2.75, 95% CI 1.28–5.91), especially in patients with elevated transaminases at baseline. Findings did not differ according to prespecified subgroups.

Conclusion. Febuxostat use is associated with a significantly greater risk of mild-to-moderate perturbation of liver function compared to benzbromarone in patients with gout.

INTRODUCTION

Although urate-lowering therapy (ULT) is widely available and effective, gout remains poorly treated, partly because of concerns about drug side effects. Allopurinol is recommended as the preferred first-line agent, although this can cause a rare hypersensitivity syndrome that is more common in people of Southeast Asian descent (eg, Chinese, Korean, Thai).[1] Febuxostat has comparable ULT efficacy to allopurinol.[2] Benzbromarone is a potent and effective uricosuric agent primarily used in Asia and was withdrawn from some European markets due to the risk of rare, severe, and potentially lethal liver injury.[3] That limited its expanded global approval. However, the benzbromarone drug withdrawal decision has been questioned based on the estimated risk of hepatotoxicity estimated[4,5] to be <1:17,000. Moreover, benzbromarone has high efficacy and safety even for patients with chronic kidney disease,[6] as well as a superior efficacy of urate-lowering in the urate underexcretion subtype that comprises at least ~60% of gout.[7]

Supported by the National Key R&D Program of China (2022YFC2503300 and 2022YFE0107600), Shandong Provincial key research and development program for major scientific and technological innovation (2021CXGC011103 and 2021ZDSYS06), Shandong Provincial Natural Science Foundation (ZR2023MH213), and Shandong Provincial Science Foundation for Youth Scholars (ZR2023QH147).

[1]Wenyan Sun, PhD, Lingling Cui, PhD, Ying Chen, MD, Xiaoyu Cheng, MD, Tian Liu, MD: The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China; [2]Robert Terkeltaub, MD: University of California, San Diego; [3]Xinde Li, MD, Changgui Li, MD: The Affiliated Hospital of Qingdao University and Institute of Metabolic Diseases, Qingdao University, Qingdao, Shandong, China; [4]Nicola Dalbeth, MD: University of Auckland, Auckland, New Zealand.

Sun and Cui are co-first authors and contributed equally to this work. Dr Dalbeth and Li are co-senior authors and contributed equally to this work.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25547).

Author disclosures and graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25547.

Address correspondence via email to Changgui Li, MD, at changguili@vip.163.com or to Nicola Dalbeth, MD, at n.dalbeth@auckland.ac.nz.

Submitted for publication December 10, 2024; accepted in revised form March 28, 2025.

SIGNIFICANCE & INNOVATIONS

- The incidence of aspartate aminotransferase or alanine aminotransferase abnormality and hepatotoxicity in patients with gout taking benzbromarone or febuxostat was investigated using a propensity score–matched cohort study design.
- In patients with gout, treatment with febuxostat is associated with a significantly greater risk of hepatotoxicity compared to benzbromarone.
- This study indicates that severe hepatotoxicity with benzbromarone is rare and occurs less frequently than with febuxostat.

Approximately one-quarter of people with gout have metabolic dysfunction–associated steatohepatitis (MASH), which in turn may increase the risk of drug-induced liver injury.[8] Thus, monitoring of serum liver function tests (LFTs) has been recommended during ULT.[9,10] Although rare severe hepatotoxicity cases were reported for both febuxostat and benzbromarone,[3,11] the incidence of abnormal liver function tests for febuxostat has been reported to be 2% to 13% (average ~3.5%), in which most adverse events are mild to moderate in severity and reversible after discontinuation of the medication,[12] and for benzbromarone is 0.1% in clinical trials.[13]

A meta-analysis included both two randomized control trials and one cohort study identified that benzbromarone had relatively lower alanine aminotransferase (AST) or aspartate aminotransferase (ALT) value than febuxostat at 10 weeks to 12 months, whereas the included studies were relatively short term and often had a small sample size.[14] In contrast, other cohort studies reported that no significant difference in transferase levels between the two groups.[15,16] There is currently a lack of comparative data on hepatic safety of relatively long-term febuxostat or benzbromarone use. Understanding the risk of hepatotoxicity and ULT use may help guide decisions about specific ULT agents. The aim of this real-world cohort study was to evaluate and compare the risk of hepatotoxicity associated with the use of febuxostat and benzbromarone in patients with gout.

MATERIALS AND METHODS

Study cohort and design. The study cohort was from an electronic medical record database Biobank Information Management System (BIMS) (Haier) at the Affiliated Hospital of Qingdao University. The database included people seen at the Shandong Gout Clinical Medical Center with a diagnosis of gout and demographic characteristics, serum biochemical test value, and treatment regimens recorded at each clinic visit since 2016. Race and ethnicity were assessed through self-reported methods using a fixed set of standardized categories. Patients who started febuxostat or benzbromarone and had at least three tests of ALT or AST in a year after initiation of the study drugs were included in the analysis. Patients were excluded for the following reasons: age <18 years old, no follow-up data, allopurinol starters, and baseline ALT or AST above 120 U/L. Febuxostat-starters were matched 1:1 to benzbromarone-starters according to age, sex, ALT, and AST value at the baseline time. The flowchart is shown in Figure 1.

Every patient provided written informed consent to import their electronic health records into the BIMS. Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research. The study was approved by the ethics committee of the Affiliated Hospital of Qingdao University. The data used in this study are available upon agreement from the scientific committee.

Exposure and outcome. Baseline was the index date that febuxostat or benzbromarone was first prescribed. Covariates were age, sex, body mass index (BMI), alcohol drinking status, smoking status, duration of gout, serum biochemical variables (serum urate, AST, ALT, fasting blood glucose, triglyceride, cholesterol, and serum creatinine levels), and comorbidities (self-reported hypertension, diabetes, hepatosteatosis, cardiovascular disease, nephrolith, renal cyst, or renal insufficiency). Follow-up commenced and continued until December 2023, unless patients were censored for the following reasons: episode of hepatotoxicity, loss to follow-up, or discontinued the study drug.

The primary outcome was hepatotoxicity, which was defined in this analysis as the first event of either ALT or AST above three times the upper limit of normal (ULN).[17] Severity of LFT abnormality was also assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version[18] 5.0. CTCAE grades AST increase and ALT increase as grade 1: above the ULN to 3.0 × ULN if baseline was normal, 1.5 to 3.0 × baseline if baseline was abnormal; grade 2: >3.0 to 5.0 × ULN if baseline was normal, >3.0 to 5.0 × baseline if baseline was abnormal; grade 3: >5.0 to 20.0 × ULN if baseline was normal, >5.0 to 20.0 × baseline if baseline was abnormal; and grade 4: >20.0 × ULN if baseline was normal, >20.0 × baseline if baseline was abnormal. The CTCAE grade was determined based on either the highest AST or ALT value during the follow-up period.

Statistical analysis. To reduce the effect of potential confounders, we performed 1:1 matching with a caliper of 0.1 pooled SDs using nearest neighbor matching of the two groups for age, sex, ALT, and AST. Comparisons between the two groups before and after propensity score matching (PSM) were explored with a standardized mean difference (SMD). Crude rates of hepatotoxicity were calculated per 1,000 person-years for all patients. Kaplan-Meier analysis and robust Cox regression (univariately or multivariately adjusted) were used to estimate the risk of hepatotoxicity episode using the Survival package, with hazard ratios (HRs) and 95% confidence intervals (CIs) calculated. Subgroup analyses including prespecified subgroups of age, BMI, duration,

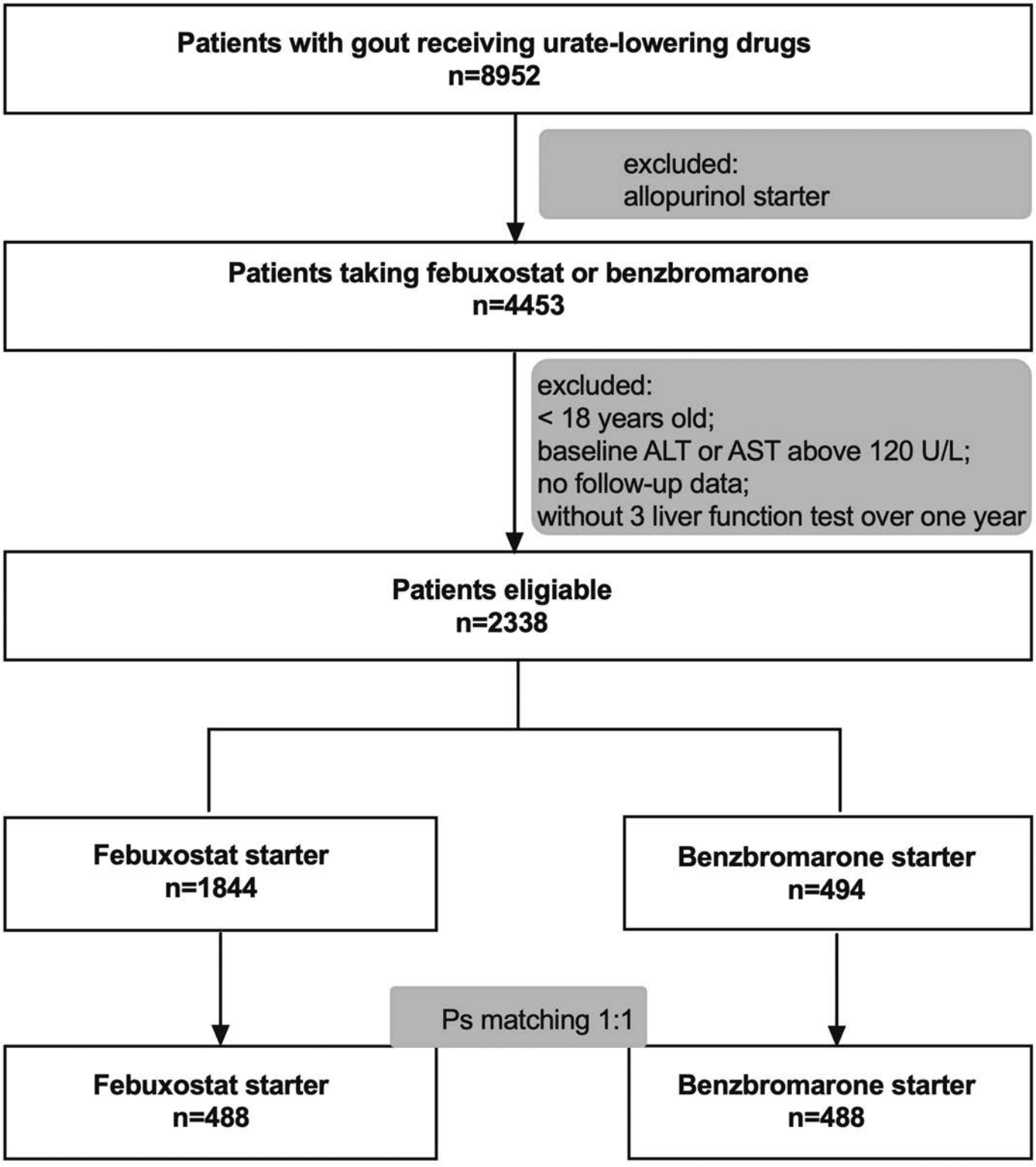

Figure 1. Flow of patients in the analysis. ALT, alanine aminotransferase; AST, aspartate aminotransferase; Ps, propensity score.

and comorbidities were used to examine how the risks of hepatotoxicity differed. Sensitivity analyses were performed in those with different follow-up periods and selection criteria. The inverse probability of treatment weighting (IPTW) using propensity score (based on age, sex, BMI, serum urate, AST, ALT, fasting blood glucose, triglyceride, and estimated glomerular filtration rate) was

Table 1. Baseline characteristics of study participants (before and after PSM)*

Characteristic	Before matching			After PSM		
	Febuxostat	Benzbromarone	SMD	Febuxostat	Benzbromarone	SMD
Participants, n	1,844	494		488	488	
Sex, n (%)			0.055			0.071
Female	44 (2.4)	8 (1.6)		13 (2.7)	8 (1.6)	
Male	1,800 (97.6)	486 (98.4)		475 (97.3)	480 (98.4)	
Age, mean (SD), yr	46.03 (14.74)	43.20 (15.05)	0.19	44.80 (14.70)	43.52 (14.85)	0.087
BMI, mean (SD), kg/m^2	27.49 (3.65)	26.70 (3.34)	0.224	27.45 (3.72)	26.75 (3.31)	0.197
Duration of gout, mean (SD), yr	7.46 (6.31)	5.94 (5.98)	0.247	7.57 (6.93)	6.01 (5.99)	0.241
Smoker, n (%)	636 (47.3)	135 (38.1)	0.185	156 (41.5)	134 (38.2)	0.068
Drinker, n (%)	753 (82.7)	189 (78.1)	0.115	207 (83.5)	188 (78.3)	0.131
ALT, mean (SD), U/L	34.62 (20.70)	34.67 (21.55)	0.002	34.83 (20.90)	34.95 (21.53)	0.006
AST, mean (SD), U/L	23.61 (9.08)	23.52 (8.81)	0.01	23.64 (8.97)	23.55 (8.84)	0.009
FBG, mean (SD), mmol/L	5.73 (0.92)	5.57 (0.68)	0.199	5.70 (0.96)	5.58 (0.68)	0.15
TG, mean (SD), mmol/L	2.30 (1.87)	2.01 (1.23)	0.187	2.29 (1.69)	2.02 (1.23)	0.183
Serum urate, mean (SD), μmol/L	503.06 (129.19)	480.66 (107.31)	0.189	501.51 (130.14)	480.46 (107.14)	0.177
Total cholesterol, mean (SD), mmol/L	4.98 (1.00)	4.91 (0.96)	0.064	5.01 (0.97)	4.93 (0.95)	0.079
eGFR, mean (SD), mL/min/1.73m^2	89.71 (21.71)	94.94 (18.48)	0.26	89.75 (21.12)	94.65 (18.35)	0.248
Hypertension, n (%)	810 (44.0)	148 (30.1)	0.292	197 (40.4)	148 (30.5)	0.208
Diabetes, n (%)	109 (5.9)	21 (4.3)	0.075	29 (5.9)	21 (4.3)	0.073
Cardiovascular disease, n (%)	71 (3.9)	27 (5.5)	0.078	13 (2.7)	27 (5.6)	0.147
Dyslipidemia, n (%)	1,092 (59.3)	266 (54.2)	0.104	277 (56.8)	265 (54.6)	0.043
Renal disease, n (%)	500 (27.2)	31 (6.3)	0.582	119 (24.4)	31 (6.4)	0.514
Liver disease, n (%)	579 (31.5)	156 (31.8)	0.008	153 (31.4)	156 (32.2)	0.019

* Dyslipidemia was hypertriglyceridemia or hypercholesteremia. Renal disease was defined as those with nephrolith, renal cyst, or renal insufficiency. Liver disease was defined as those with hepatosteatosis or abnormal liver function tests (AST or ALT is greater than the upper limit of normal) at baseline. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; PSM, propensity score matching; SMD, standardized mean difference; TG, triglyceride.

performed to balance observable characteristics between groups. A P value <0.05 was considered statistically significant. All statistical analyses were conducted using R (version 4.2.1).

RESULTS

Of the 8,952 patients with gout who had data available (all were Chinese patients), 1,844 patients and 494 patients started febuxostat or benzbromarone, respectively, with at least three AST or ALT measurements per year in the cohort. Comparison between included patients and those excluded due to lack of three tests of ALT or AST were shown in Supplementary Table S1, showing balanced baseline ALT or AST. Among them, 488 patients were matched based on age, sex, and baseline AST and ALT. Baseline characteristics of these two groups were compared (Table 1). The patients were, on average, 44 to 45 years of age and were predominantly male participants. The two groups were similar in many respects including serum urate, cholesterol, and fasting blood glucose levels. However, some variables were not balanced with the SMD above the threshold of 0.1 even after PSM. To make more variables balanced (SMD < 0.1), further IPTW was performed in the sensitivity analysis. Febuxostat and benzbromarone usage patterns are summarized in Supplementary Table S2.

Table 2. Proportion of LFTs abnormalities and hepatotoxicity events*

	Events of LFT abnormalities, n (%)	Events of hepatotoxicity, n (%)
Febuxostat	751 (39.7)	76 (4.0)[a]
Grade 1	720 (38.0)	31 (1.6)
Grade 2	24 (1.3)	24 (1.3)
Grade 3	7 (0.4)	7 (0.4)
Benzbromarone	113 (22.9)	9 (1.8)[b]
Grade 1	109 (22.1)	4 (0.8)
Grade 2	3 (0.6)	3 (0.6)
Grade 3	1 (0.2)	1 (0.2)

* ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; LFT, liver function test.
[a] There were 14 individuals who met the criteria for hepatotoxicity but not the CTCAE grade 1 to 4 for ALT or AST elevation due to elevated baseline ALT or AST levels.
[b] There was one individual who met the criteria for hepatotoxicity but not the CTCAE grade 1 to 4 for ALT or AST elevation due to elevated baseline ALT or AST levels.

The mean follow-up was longer in febuxostat users (1.34 years) compared with benzbromarone users (1.09 years). There were no fatal hepatic adverse events during treatment. The reasons for discontinuing the study drug were mainly low medication adherence, with other reasons including elevated transaminases, COVID-19, skin allergies, chest pain, diarrhea, dizziness, and muscle soreness in the febuxostat group; and elevated transaminases, dizziness, COVID-19, rash, heartburn, and asthenia in the benzbromarone group. Overall, 864 people experienced a CTCAE ALT or AST increase, with CTCAE grade

Table 3. Propensity score–matched association of febuxostat or benzbromarone with the hazard of incident hepatotoxicity*

	Events, n	Person- years	IR	Unadjusted HR (95% CI)	Adjusted for age and sex HR (95% CI)
Before matching	–	–	–	2.11 (1.06–4.21)	2.28 (1.14–4.56)
Febuxostat	77	2,474	31.1	–	–
Benzbromarone	9	539	16.7	–	–
After PSM	–	–	–	2.59 (1.21–5.56)	2.75 (1.28–5.91)
Febuxostat	25	632	39.6	–	–
Benzbromarone	9	535	16.8	–	–
With IPTW	–	–	–	2.11 (1.03–4.33)	2.12 (1.03–4.35)

* CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IR, incidence rate per 1,000 person-years; PSM, propensity score matching.

1 (38.0% of patients), grade 2 (1.3% of patients), and grade 3 (0.4% of patients) in the febuxostat group, and CTCAE grade 1 (22.1% of patients), grade 2 (0.6% of patients), and grade 3 (0.2% of patients) in the benzbromarone group (Table 2). No CTCAE grade 4 elevations were observed. For the primary analysis of hepatotoxicity, defined as >3 × ULN, a total of 86 events occurred. Of note, all grade-2 to –3 individuals were those experiencing hepatotoxicity, whereas most grade-1 events represented mild liver abnormalities. In the matched cohort, the incidence of hepatotoxicity was lower among benzbromarone users (16.8 of 1,000 person-years) versus febuxostat users (39.6 of 1,000 person-years) (Table 3). The reverse Kaplan-Meier survival plots are shown in Figure 2 and demonstrated that the hepatotoxicity risk remained different throughout the follow-up period. After adjustment for age and sex, febuxostat use was associated with a greater risk of hepatotoxicity (adjusted HR 2.75, 95% CI 1.28–5.91) compared to benzbromarone.

In subgroup analysis, the greater risk of hepatotoxicity associated with febuxostat in comparison with benzbromarone was similar among each of these stratified subgroups including baseline liver disease, with all *P* for interaction >0.05 (Figure 3). Risk factors were explored in patients taking febuxostat or benzbromarone separately (Supplementary Table S3). Individuals with previous liver disease (hepatosteatosis or abnormal LFTs) were more likely to develop hepatotoxicity.

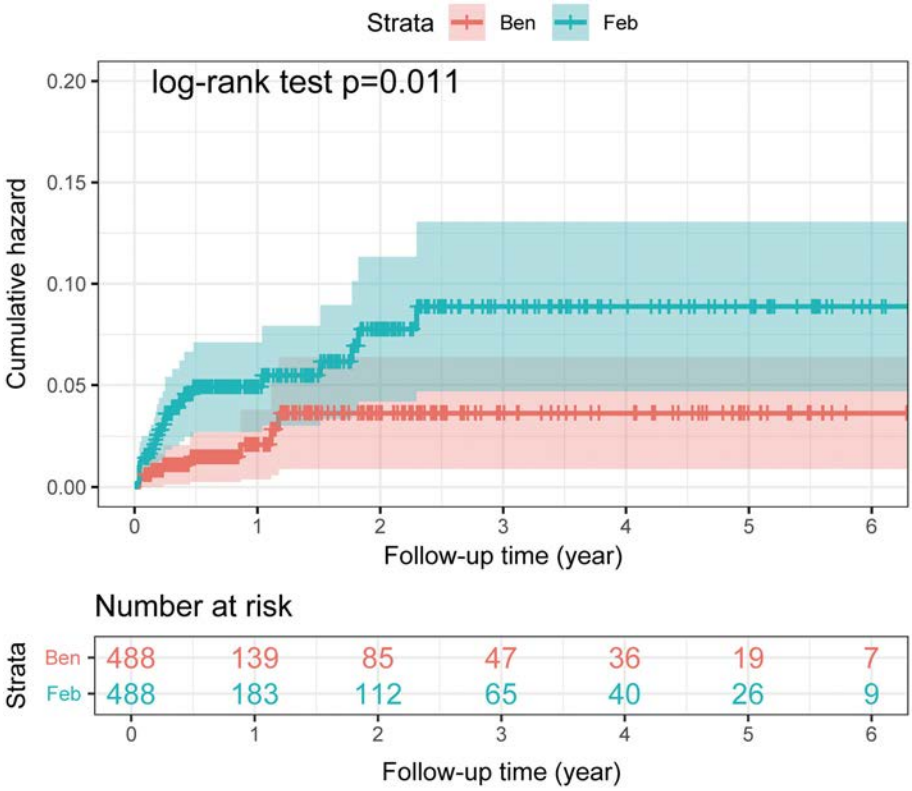

Figure 2. Risk of hepatotoxicity between Ben and Feb groups in the matched cohort. Ben, benzbromarone; Feb, febuxostat.

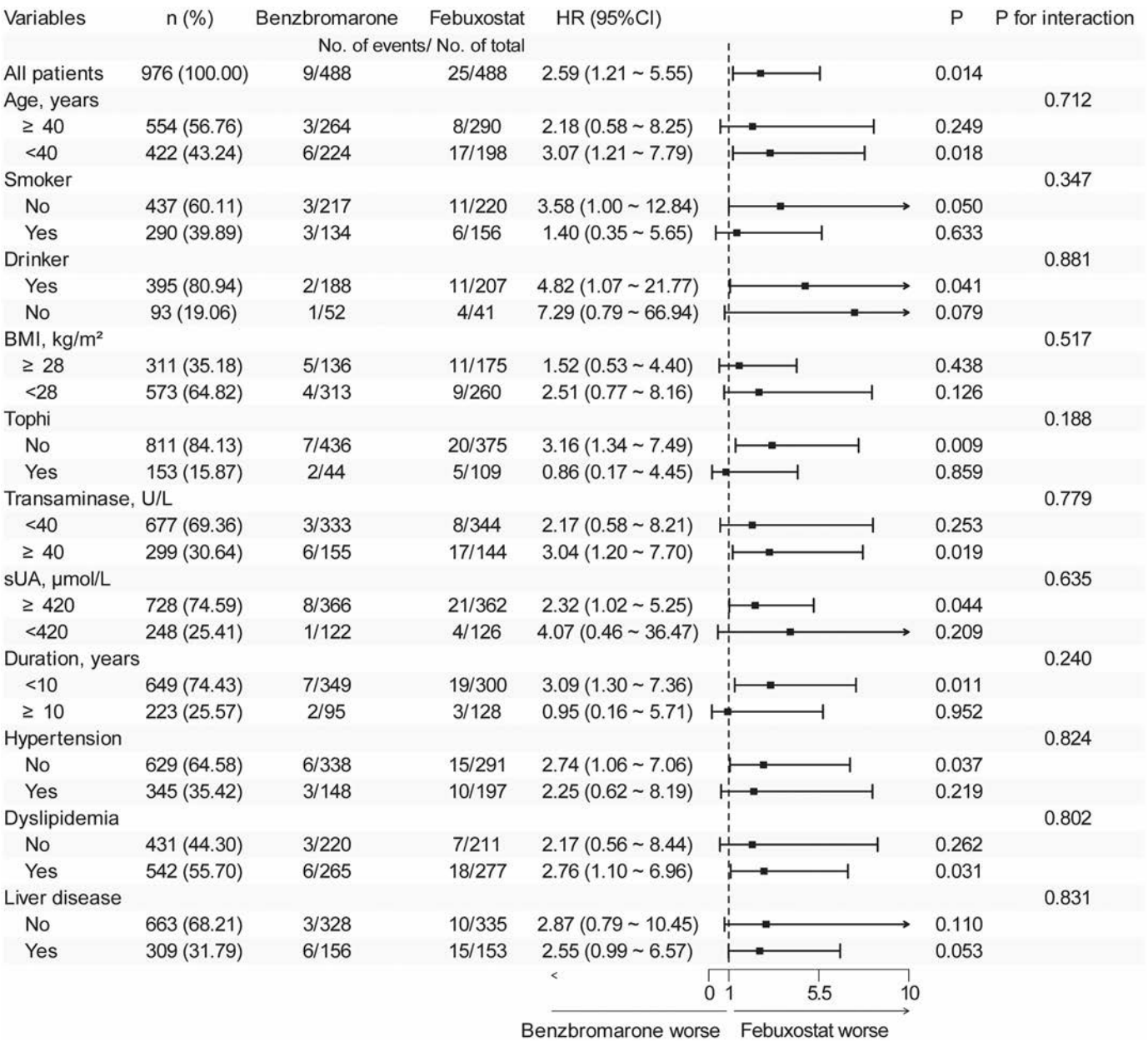

Figure 3. Subgroup analysis according to baseline variables of hepatotoxicity risk associated with febuxostat or benzbromarone in the matched cohort. Liver disease included hepatosteatosis or abnormal liver function tests. BMI, body mass index; CI, confidence interval; HR, hazard ratio; sUA, serum uric acid.

Further, we performed a subgroup analysis for those stratified ALT or AST, showing that hepatotoxicity appeared to occur with increasing levels of transaminases, especially above 40 U/L (Supplementary Table S4).

We performed several sensitivity analyses. To include as many patients as possible, the IPTW was performed, and the conclusions were stable (Table 3, Supplementary Table S5). When limiting the follow-up period from baseline to 180 or 365 days in the matched cohort, febuxostat use was associated with more hepatotoxicity episodes compared to benzbromarone (HR 3.75, 95% CI 1.50–9.30, P = 0.005 for 180 days of follow-up; 3.34, 95% CI 1.41–7.90, P = 0.006 for 365 days of follow-up). Furthermore, only the patients in the overall cohort having at least five liver tests in a year were included, and the result stayed significant (HR 2.11, 95% CI 1.06–4.21, P = 0.034).

DISCUSSION

This study has shown that episodes of hepatotoxicity (defined as ALT or AST >3 × ULN) are significantly more common for patients with gout starting febuxostat compared with benzbromarone. These

episodes are mostly mild-to-moderate elevations in transaminases, with very few episodes of grade 3 or 4 ALT or AST elevation.

Regular monitoring of liver function during ULT is recommended to identify abnormal liver tests. The results of this analysis align with short-term clinical trials have shown that febuxostat has a more significant effect on increasing transaminases than benzbromarone.[7,19] Previous studies have been limited by short-term observation period of change of AST or ALT, and not as the main outcome. In this study that focused on long-term hepatic safety, mild LFT abnormalities were common in both groups, with a higher proportion of any grade 1 to 3 elevations in the setting of febuxostat use. It remains unclear if hepatocyte damage would persist or progress with long-term administration of ULT.

Febuxostat is metabolized via liver, the hepatotoxicity primarily resulting from glucuronidation and to a lesser extent via cytochrome (CYP) 450 system.[12] Although preclinical studies indicated beneficial effects including attenuation of insulin resistance and lipid peroxidation of febuxostat in an animal model of MASH,[20] in the original phase 2 trials of febuxostat, more AST or ALT elevations were observed compared with placebo.[21,22] Subsequently, diabetes, colchicine use, and pre-existing liver disease were significantly associated with increased risk of hepatotoxicity while taking febuxostat.[23,24] In this study, we found those with baseline LFT abnormality were more likely to have abnormal LFTs during treatment, independent of other confounders, similarly when taking febuxostat or benzbromarone.

Benzbromarone remains markedly restricted due to concerns about rare episodes of severe hepatotoxicity.[25] Identifiable susceptibility factors include CYP2C9 polymorphisms, metabolic epoxidation, and inactivation of cytochrome P450 3A4 for hepatotoxicity.[26–28] However, our study indicates liver toxicity with benzbromarone is very rare, supporting it as a useful agent that has less hepatoxicity than febuxostat. At present, there is a deep pipeline of benzbromarone analogs in clinical development, with several currently in clinical trials.[29] These benzbromarone analogs have been designed to further limit hepatotoxicity while preserving and, in some cases, enhancing urate lowering. In the future, the case for choosing a benzbromarone analog over febuxostat as a urate-lowering drug option may only be strengthened.

There are limitations in this study. First, this finding applies to a specific cohort from a single center in China. It may not be applicable to other countries or populations. In the cohort, the drug use was retrieved from patient records, so medication adherence was not verified, and a drug dose-dependent risk was not assessed. Additionally, selection bias may be existing while we validate it in another cohort with more LFTs. Although PSM and IPTW was performed to control for potential confounders, residual confounding remained including concomitant drugs and consumption degree due to incomplete records. In addition, very few participants with age 60+ years or diabetes developed an event in this cohort, which deserves further study in these specified groups. The analysis also did not include other measures of liver function (such as bilirubin, serum albumin, and prothrombin ratio), so a full assessment of liver function was not undertaken.

Hepatic safety, particularly in those with pre-existing liver disease, is an important consideration in prescribing either febuxostat or benzbromarone. Despite the widespread limitation of benzbromarone due to concerns about severe hepatotoxicity, these events are rare, and benzbromarone has a lower risk of hepatotoxicity than febuxostat.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Li confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. González-Galarza FF, Takeshita LY, Santos EJ, et al. Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. Nucleic Acids Res 2015;43 (Database issue):D784–D788.
2. O'Dell JR, Brophy MT, Pillinger MH, et al. Comparative effectiveness of allopurinol and febuxostat in gout management. NEJM Evid 2022; 1(3):10.1056/evidoa2100028.
3. Zhang MY, Niu JQ, Wen XY, et al. Liver failure associated with benzbromarone: a case report and review of the literature. World J Clin Cases 2019;7(13):1717–1725.
4. Lee MH, Graham GG, Williams KM, et al. A benefit-risk assessment of benzbromarone in the treatment of gout. Was its withdrawal from the market in the best interest of patients? Drug Saf 2008;31(8):643–665.
5. Azevedo VF, Kos IA, Vargas-Santos AB, et al. Benzbromarone in the treatment of gout. Adv Rheumatol 2019;59(1):37.
6. Fujimori S, Ooyama K, Ooyama H, et al. Efficacy of benzbromarone in hyperuricemic patients associated with chronic kidney disease. Nucleosides Nucleotides Nucleic Acids 2011;30(12):1035–1038.
7. Yan F, Xue X, Lu J, et al. Superiority of low-dose benzbromarone to low-dose febuxostat in a prospective, randomized comparative effectiveness trial in gout patients with renal uric acid underexcretion. Arthritis Rheumatol 2022;74(12):2015–2023.
8. Kuo CF, Yu KH, Luo SF, et al. Gout and risk of non-alcoholic fatty liver disease. Scand J Rheumatol 2010;39(6):466–471.
9. Yu KH, Chen DY, Chen JH, et al. Management of gout and hyperuricemia: multidisciplinary consensus in Taiwan. Int J Rheum Dis 2018; 21(4):772–787.
10. El Miedany Y, Gadallah NA, Mansour M, et al. Egyptian consensus on treat-to-target approach of gout: evidence-based clinical practice guidelines for the management of gout. Egypt Rheumatol Rehabil 2022;49(28).
11. Bohm M, Vuppalanchi R, Chalasani N; Drug-Induced Liver Injury N; Drug-Induced Liver Injury Network (DILIN). Febuxostat-induced acute liver injury. Hepatology 2016;63(3):1047–1049.

12. National Institutes of Health and LiverTox. Drug record: Febuxostat. Accessed October 29, 2018. https://www.ncbi.nlm.nih.gov/books/NBK548645/.
13. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Benzbromarone. Accessed September 5, 2017. https://www.ncbi.nlm.nih.gov/books/NBK548732/.
14. Yan CQ, Liang C, Lan ZR, et al. Comparison of the efficacy of febuxostat vs. benzbromarone in the treatment of gout: a meta-analysis in Chinese gout patients. Eur Rev Med Pharmacol Sci 2023;27(24):11988–12003.
15. Liu D, Zhou B, Li Z, et al. Effectiveness of benzbromarone versus febuxostat in gouty patients: a retrospective study. Clin Rheumatol 2022;41(7):2121–2128.
16. Yu H, Liu X, Song Y, et al. Safety and efficacy of benzbromarone and febuxostat in hyperuricemia patients with chronic kidney disease: a prospective pilot study. Clin Exp Nephrol 2018;22(6):1324–1330.
17. Humphreys JH, Warner A, Costello R, et al. Quantifying the hepatotoxic risk of alcohol consumption in patients with rheumatoid arthritis taking methotrexate. Ann Rheum Dis 2017;76(9):1509–1514.
18. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2017. Accessed November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
19. Liang N, Sun M, Sun R, et al. Baseline urate level and renal function predict outcomes of urate-lowering therapy using low doses of febuxostat and benzbromarone: a prospective, randomized controlled study in a Chinese primary gout cohort. Arthritis Res Ther 2019;21(1):200.
20. Nishikawa T, Nagata N, Shimakami T, et al. Xanthine oxidase inhibition attenuates insulin resistance and diet-induced steatohepatitis in mice. Sci Rep 2020;10(1):815.
21. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. Arthritis Rheum 2005;52(3):916–923.
22. Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008;59(11):1540–1548.
23. Lee JS, Won J, Kwon OC, et al. Hepatic safety of febuxostat compared with allopurinol in gout patients with fatty liver disease. J Rheumatol 2019;46(5):527–531.
24. Oh YJ, Moon KW. Combined use of febuxostat and colchicine does not increase acute hepatotoxicity in patients with gout: a retrospective study. J Clin Med 2020;9(5):1488.
25. Stamp LK, Haslett J, Frampton C, et al. The safety and efficacy of benzbromarone in gout in Aotearoa New Zealand. Intern Med J 2016;46(9):1075–1080.
26. Roberts RL, Wallace MC, Wright DF, et al. Frequency of CYP2C9 polymorphisms in Polynesian people and potential relevance to management of gout with benzbromarone. Joint Bone Spine 2014;81(2):160–163.
27. Wang H, Peng Y, Zhang T, et al. Metabolic epoxidation is a critical step for the development of benzbromarone-induced hepatotoxicity. Drug Metab Dispos 2017;45(12):1354–1363.
28. Tang LWT, Verma RK, Fan H, et al. Mechanism-based inactivation of cytochrome P450 3A4 by benzbromarone. Mol Pharmacol 2021;99(4):266–276.
29. Terkeltaub R. Emerging urate-lowering drugs and pharmacologic treatment strategies for gout: a narrative review. Drugs 2023;83(16):1501–1521.

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1157–1164
DOI 10.1002/acr.25548

Colchicine Concentrations and Relationship With Colchicine Efficacy and Adverse Events: Post Hoc Analysis of a Randomized Clinical Trial of Colchicine for Gout Flare Prophylaxis

Lisa K. Stamp,[1] Anne Horne,[2] Borislav Mihov,[2] Jill Drake,[3] Janine Haslett,[3] Peter Chapman,[4] Daniel F. B. Wright,[5] Christopher Frampton,[3] and Nicola Dalbeth[6]

Objective. Our objective was to examine the relationship between colchicine plasma concentrations and clinical and demographic factors and to determine the relationship between colchicine concentrations and colchicine efficacy and colchicine-specific adverse events.

Methods. Post hoc analyses were undertaken using data from a 12-month randomized controlled trial involving 200 people with gout that compared low-dose colchicine to placebo for the first six months while starting allopurinol, with a further six-month follow-up. Steady-state colchicine plasma concentrations were measured 30 to 80 minutes post dose (assumed peak) and just before the dose (trough) at month three, and creatine kinase (CK) levels were measured at months zero, three, and six. Self-reported gout flares, adverse events, and serious adverse events were collected monthly.

Results. Peak and trough colchicine concentrations were available for 79 participants in the colchicine arm. Multivariable analysis showed that those taking a statin and non-Māori and non-Pacific ethnicity were independently associated with higher trough concentrations, and age older than 60 years was independently associated with higher peak concentrations. Trough and peak colchicine concentrations were significantly higher in those who had any adverse event between months four and six. However, there was no association between colchicine concentrations and colchicine-specific adverse events (gastrointestinal and muscle) or with CK changes in the colchicine-treated patients.

Conclusion. Trough or peak colchicine concentrations are not associated with gout flare prophylaxis efficacy. There is no consistent relationship between colchicine concentrations and colchicine-specific adverse events. Although colchicine concentrations increase with concomitant statin use, this does not result in muscle-related adverse events. These findings indicate that colchicine therapeutic drug monitoring is of limited value in clinical practice.

INTRODUCTION

Low-dose oral colchicine (0.5 mg once or twice daily) is one of the first-line recommended therapies for prevention of gout flares when commencing urate-lowering therapy.[1] Although colchicine may be effective, it has a number of potential adverse events, of which the most common are gastrointestinal, including nausea and diarrhea. In people with gout, gastrointestinal adverse events are dose dependent, with more gastrointestinal adverse events observed in those who received a higher dose

ACTRN Trial identifier: 12618001179224.
Supported by the Health Research Council of New Zealand and Arthritis New Zealand.
[1]Lisa K. Stamp, FRACP: University of Otago, Christchurch, Christchurch, and Health New Zealand Te Whatu Ora, New Zealand; [2]Anne Horne, MBChB, Borislav Mihov, BPhty: University of Auckland, Auckland, New Zealand; [3]Jill Drake, RN, Janine Haslett, RN, Christopher Frampton, PhD: University of Otago, Christchurch, Christchurch, New Zealand; [4]Peter Chapman, FRACP: Health New Zealand, Te Whatu Ora, New Zealand; [5]Daniel F. B. Wright, PhD: University of Sydney, St Vincent's Hospital, and St Vincent's Clinical Campus, University of New South Wales Medicine, Sydney, New South Wales, Australia; [6]Nicola Dalbeth, FRACP: Health New Zealand, Te Whatu Ora, and University of Auckland, Auckland, New Zealand.
Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25548).
Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25548.
Address correspondence via email to Lisa K. Stamp, FRACP, at lisa.stamp@cdhb.health.nz.
Submitted for publication December 15, 2024; accepted in revised form April 2, 2025.

SIGNIFICANCE & INNOVATIONS

- Colchicine concentrations increase with concomitant statin use; this does not result in muscle-related adverse events.
- Regular monitoring of creatine kinase (CK) may not be required; rather, targeted measurement of CK in individuals with muscle symptoms may be more appropriate.
- Colchicine therapeutic drug monitoring is of limited value in clinical practice.

(4.8 mg over four hours) versus a low dose (1.8 mg over one hour) in a study of gout flares, albeit with no difference in circulating maximum concentration (C_{max}) between the two colchicine doses in healthy volunteers.[2] Other less common adverse events include bone marrow suppression and neuromyotoxicity, which may occur with more prolonged use.[3]

Impaired kidney function, which is common in people with gout, is reported to be a predictor of colchicine adverse events.[4] Because of the risk, it has been suggested that a complete blood count and a creatine kinase (CK) measurement should be performed every six months in patients who are receiving long-term prophylactic colchicine, defined as 0.5 mg daily for six or more months.[5] The prolonged period suggested for anti-inflammatory prophylaxis and the risk of adverse events have led to a general reluctance to use prophylaxis by many clinicians and people with gout. A study of a nurse-led educational intervention for people with gout with recurrent flares reported that only 4% of participants opted for anti-inflammatory prophylaxis when urate-lowering therapy was increased.[6] Thus, the ability to accurately predict who may obtain the most clinical benefit with the least adverse events based on clinical factors would be of clinical use.

Colchicine is rapidly absorbed from the gastrointestinal tract, with an oral bioavailability of around 50% on average. Colchicine is primarily eliminated through biliary excretion and feces. Colchicine is mainly transported into the gastrointestinal tract by the multidrug resistance transporter molecule P-glycoprotein.[7] Enteric and hepatic cytochrome P450 3A4 (CYP3A4), which catalyzes demethylation of colchicine to inactive metabolites, also contributes to colchicine metabolism, along with a minor (10%–20%) contribution to elimination via the kidneys.[8] Importantly, CYP3A4 and P-glycoprotein are very frequently colocalized, such that many drugs mutually and robustly inhibit CYP3A4 and P-glycoprotein.[9] Colchicine is also subject to a range of drug interactions, particularly with CYP3A4 inhibitors, which can result in a doubling of colchicine plasma concentrations, and with P-glycoprotein inhibitors, which may quadruple colchicine concentrations.[10]

Therapeutic drug monitoring (TDM) is the use of drug concentrations to guide therapy to improve drug efficacy and/or reduce toxicity. It has particular benefits for drugs with a narrow therapeutic range, in which the difference between clinically effective concentrations and concentrations associated with adverse events is small. Colchicine has a narrow therapeutic range, with many patients experiencing dose-dependent gastrointestinal toxicity. Plasma colchicine concentrations have been measured in some cases of fatal colchicine overdose, with levels ranging from 10 to 250 ng/mL (10–250 μg/L).[11] Effective steady-state plasma concentrations have been reported to range from 0.5 to 3 μg/L, with toxic effects occurring[12] at approximately 3 μg/L. Colchicine doses of 0.5 mg twice daily and 0.6 mg daily have been reported to maintain serum levels within the steady-state range in healthy individuals and those with mild to moderate renal impairment or concomitant use of most interacting medications.[13]

To date no studies have specifically examined the relationship of colchicine concentrations with clinical efficacy and/or colchicine-specific adverse events in people with gout. Thus, the aim of this study was to examine the relationship between colchicine concentrations and clinical and demographic factors, including age, body weight, renal function, sex, ethnicity, and concomitant medications, and to determine the relationship between colchicine concentrations and colchicine efficacy (defined as occurrence of gout flares) and colchicine-specific adverse events, with a particular focus on gastrointestinal and muscle-related adverse events.

MATERIALS AND METHODS

Study design. Post hoc analyses of the 12-month "Is colchicine prophylaxis required with start-low go-slow allopurinol dose escalation in gout?" noninferiority randomized controlled trial were undertaken (ACTRN 12618001179224). The methods and results of the full trial have been reported.[14] Briefly, this was a one-year double-blind placebo-controlled noninferiority trial with participants randomized 1:1 to colchicine at 0.5 mg daily or placebo for the first six months. All participants commenced allopurinol, increasing monthly to achieve a target urate level of <0.36 mmol/L. Starting doses of allopurinol were 50 mg daily in those with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and 100 mg daily in those with eGFR ≥60 mL/min/1.73 m^2. The allopurinol doses were increased monthly by 50 mg daily in those with eGFR <60 mL/min/1.73 m^2 and by 100 mg daily in those with eGFR ≥60 mL/min/1.73 m^2 until the serum urate level was <0.36 mmol/L (6 mg/dL) for three consecutive visits. Ethical approval was obtained from the Health and Disability Ethics Committee, New Zealand (18/STH/156), and all participants provided written informed consent.

Participants were seen in person every three months by study coordinators, with intervening monthly telephone assessments. Gout flares, defined as self-reported gout flares requiring treatment, were recorded at each monthly assessment. Adverse events and serious adverse events were collected monthly and coded according to Common Terminology Criteria for Adverse

Events (CTCAE v5.0). Participants were asked about the occurrence of any adverse events as well as colchicine-specific adverse events (abdominal pain, nausea, vomiting, diarrhea, muscle weakness, and myalgia). Blood samples were obtained monthly for serum urate and creatinine; every three months for complete bloodcount, alanine transaminase, alkaline phophatase, and gamma glutamyl transferase; and at baseline, month three, and month six for CK. Nonfasting plasma samples were collected for trough colchicine plasma concentrations (just before the next colchicine dose) and the assumed peak (30–60 minutes post dose) colchicine concentrations at month three.

Colchicine assay. Colchicine concentrations in plasma were performed using a liquid chromatography tandem mass spectrometry (LC-MS/MS) assay developed and validated by Clinical Pharmacology, University of Otago, Christchurch and Toxicology, Canterbury Health Laboratories. Briefly, 50 mL of the internal standard (IS) colchicine-d6 (5.0 ng/mL colchicine-d6 in water) was added to 50 mL of the plasma sample, followed by 200 mL of acetonitrile to precipitate the proteins for plasma sample cleanup. After centrifugation, the clear supernatant was diluted 1:1 with the mobile phase, and then a 10-mL aliquot was injected into the AB Sciex API 4000 LC-MS/MS system. The AB Sciex API 4000 LC-MS/MS system consisted of a Shimadzu LC-20AD HPLC system (Shimadzu Corporation) interfaced with an AB Sciex API 4000 triple quadrupole mass spectrometer (Applied Biosystems) equipped with a TurboIonSpray source. Chromatographic separation of colchicine and colchicine-d6 was achieved under gradient elution of 10 m*M* ammonium acetate and acetonitrile using an Agilent Poroshell 120 EC-C18 50 × 3.0 mm, 2.7-µm column (Agilent Technologies). Colchicine and the IS colchicine-d6 were monitored by performing multiple-reaction monitoring scans in positive electrospray ionization mode. The optimized precursor-to-product ion transitions monitored for colchicine $[M + H]^+$ and colchicine-d6 $[M + H]^+$ were mass/charge (m/z) 400.2 > 358 and m/z 406.2 > 362, respectively. Analyst software (Applied Biosystems) was used to control the equipment, to coordinate data acquisition, and to analyze data. Under the chromatographic conditions employed, the total analysis time was six minutes for each sample, and colchicine and colchicine-d6 peaks were free of interference from any other peaks present in the plasma blanks. The colchicine standard curve was adequately fitted by 1/x weighted quadratic regressions over the concentration range of 0.1 to 10 ng/mL ($r > 0.999$), and the lower limits of the quantification was 0.1 ng/mL. The accuracy and precision were assessed at the low-, medium-, and high-level quality controls (QCs). There was no constant direction to the bias (ie, plus or minus) for QCs, and the mean values were within ±4.0% of the spiked values. The intraday and interday coefficients of variation over the analyzed concentration ranges were <7.0%. The recoveries of colchicine from plasma at concentrations of QC were similar and consistent, with mean values >90%. No significant matrix effects were observed.

Statistics. Peak and trough colchicine concentrations at month three were compared between the demographic and clinical features using one-way analysis of variance (ANOVA). Similarly, these concentrations were compared between disease states, the occurrence of gout flares, and the presence of treatment-emergent adverse events using one-way ANOVA. A multivariable regression analysis was also undertaken to explore the potentially independent associations of the demographic and clinical features with the peak and trough colchicine concentrations at month three. These regression models included all the demographic and clinical features and used forward and backward stepwise procedures. Gout flare states at the month six visit were defined as previously described[15]: (1) patient acceptable state (PASS), no gout flares in the preceding six months; (2) low disease activity (LDA) state, one flare in the preceding six months; and (3) non-LDA/PASS, more than one gout flare in each of the preceding six months. CK levels and changes at months three and six were compared between the demographic and clinical features using one-way ANOVA. The associations between colchicine and CK concentrations were tested using Pearson's correlation coefficients. The colchicine and CK concentrations were log transformed before analysis to normalize distributions and are summarized as geometric means or geometric mean ratios (GMRs) with 95% confidence intervals (CIs). All analyses were undertaken using SPSS v29.0. Analyzed data may be made available to external collaborators upon reasonable request following review by the trial steering committee with appropriate acknowledgments.

RESULTS

Baseline characteristics of participants included in this analysis. Peak and trough colchicine concentrations were available for 79 participants in the colchicine arm. Demographics of the 79 participants at month three are outlined in Supplementary Table 1. The median time between the dose of colchicine and peak samples was 30 (interquartile range 30–70) minutes.

Relationship between colchicine concentrations and participant variables. As expected, mean trough colchicine concentrations were lower than mean peak concentrations (0.30 ng/mL vs 0.61 ng/mL; $P < 0.001$). Trough colchicine concentrations were significantly higher in participants who were >60 years of age, were of non-Māori or non-Pacific ethnicity, had eGFR <60 mL/min/1.73 m^2, had a body mass index of <30, and were taking a statin (Table 1). Peak colchicine concentrations were also significantly higher in those >60 years of age and those taking a statin (Table 1).

Table 1. Relationship between mean trough and peak colchicine concentrations and clinical and demographic factors*

	Trough colchicine concentration, ng/mL		Peak colchicine concentration, ng/mL	
	Mean (95% CI)	*P*	Mean (95% CI)	*P*
Age		0.002		0.01
<60 y (n = 44)	0.24 (0.20–0.29)		0.51 (0.41–0.64)	
≥60 y (n = 35)	0.39 (0.31–0.48)		0.77 (0.61–0.98)	
Sex		0.55		0.62
Female (n = 6)	0.26 (0.10–0.69)		0.71 (0.34–1.47)	
Male (n = 73)	0.30 (0.26–0.35)		0.61 (0.51–0.72)	
Ethnicity		0.005		0.09
Māori (n = 12)	0.20 (0.12–0.33)		0.57 (0.34–0.98)	
Pacific peoples (n = 11)	0.21 (0.13–0.34)		0.40 (0.26–0.62)	
Non-Māori/non-Pacific peoples (n = 56)	0.35 (0.30–0.41)		0.68 (0.56–0.82)	
eGFR		0.002		0.14
≤60 mL/min/1.73 m^2 (n = 12)	0.49 (0.33–0.74)		0.76 (0.50–1.18)	
>60 mL/min/1.73 m^2 (n = 67)	0.27 (0.34–0.32)		0.59 (0.49–0.71)	
BMI		0.02		0.22
<30 (n = 32)	0.37 (0.31–0.45)		0.69 (0.56–0.87)	
≥30 (n = 47)	0.26 (0.21–0.32)		0.57 (0.45–0.71)	
Statin		<0.001		0.02
Yes (n = 19)	0.49 (0.38–0.64)		0.87 (0.61–1.25)	
No (n = 60)	0.26 (0.22–0.30)		0.55 (0.46–0.66)	
Calcium channel blocker		0.72		0.18
Yes (n = 8)	0.32 (0.16–0.64)		0.86 (0.51–1.44)	
No (n = 71)	0.30 (0.25–0.35)		0.59 (0.50–0.71)	

* BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtrtation rate.

Multivariable analysis showed that those taking a statin (0.39 ng/mL vs 0.22 ng/mL, GMR 1.76, 95% CI 1.30–2.40) and those of non-Māori or non-Pacific ethnicity (0.39 ng/mL vs 0.26 ng/mL, GMR 1.54, 95% CI 1.15–2.05) were independently associated with higher trough colchicine concentrations. Only age >60 years (0.77 ng/mL vs 0.51 ng/mL, GMR 1.51, 95% CI 1.10–2.07) was independently associated with higher peak colchicine concentrations.

Relationship between colchicine concentrations, gout flares, and gout disease activity states. There was no significant difference in mean trough or peak colchicine concentrations at month three between the three gout flare states in months one to six (Table 2). Likewise, there was no association between colchicine concentrations at month three and experience of at least one gout flare between months zero and three or months four and six (Table 2). There was no association between colchicine concentration at month three and experience of at least one gout flare between months seven and nine, the period immediately after colchicine had been stopped (Table 2).

Relationship between colchicine concentrations and colchicine-specific adverse events. Trough and peak colchicine concentrations were significantly higher in those who had any adverse event between months four and six (Table 3). However, there was no significant association between colchicine concentrations and colchicine-specific gastrointestinal or muscle-related adverse events. The small number of participants with myalgia or muscle cramps (n = 1–2) precluded further analysis of differences in colchicine concentrations.

Relationship between participant demographics and CK and colchicine concentrations. In all trial participants (N = 200), baseline CK levels were significantly higher in men, those >60 years of age, Pacific peoples, those with eGFR >60 mL/min/1.73 m^2, and those whose occupation involved physical or manual labor (Supplementary Table 2). There was a significant increase in CK levels from baseline to month three in Māori and from baseline to month six in Pacific peoples (Table 4). No other variables were associated with a change in CK levels (Table 4). In the 79 participants with colchicine concentrations, there was no significant correlation between trough or peak colchicine concentrations and CK levels at month three ($r = -0.17$, $P = 0.13$; and $r = -0.12$, $P = 0.30$, respectively).

DISCUSSION

In this analysis of a randomized clinical trial of colchicine for gout flare prophylaxis, there was no significant association between trough or peak colchicine concentrations and occurrence of gout flares. There was also no consistent relationship between trough or peak colchicine concentrations and colchicine-specific adverse events. However, both trough peak colchicine concentrations were higher in those with any adverse

Table 2. Peak and trough colchicine concentrations and gout flare outcomes*

	Trough colchicine concentration, ng/mL		Peak colchicine concentration, ng/mL	
	Mean (95% CI)	*P*	Mean (95% CI)	*P*
Months 1–6		0.52		0.52
PASS (n = 28)	0.33 (0.25–0.42)		0.70 (0.53–0.92)	
LDA (n = 16)	0.32 (0.23–0.44)		0.59 (0.41–0.85)	
Non-LDA/PASS (n = 35)	0.27 (0.22–0.34)		0.57 (0.44–0.72)	
Months 0–3		0.42		0.37
No flare (n = 39)	0.32 (0.26–0.4)		0.67 (0.53–0.84)	
Flare (n = 39)	0.29 (0.23–0.35)		0.57 (0.45–0.72)	
Months 3–6		0.21		0.13
No flare (n = 3)	0.36 (0.25–0.53)		0.79 (0.54–1.15)	
Flare (n = 52)	0.28 (0.23–0.34)		0.56 (0.46–0.69)	
Months 7–9		0.28		0.11
No flare (n = 19)	0.35 (0.26–0.48)		0.83 (0.59–1.15)	
Flare (n = 43)	0.29 (0.23–0.35)		0.60 (0.48–0.75)	

* PASS: no gout flares in the preceding six months; LDA: one flare in the preceding six months; non-LDA/PASS: more than one gout flare in each of the preceding six months. CI, confidence interval; LDA, low disease activity state; PASS, patient acceptable state.

Table 3. Relationship between trough and peak colchicine concentrations and AEs*

	Trough colchicine concentration, ng/mL		Peak colchicine concentration, ng/mL	
	Mean (95% CI)	*P*	Mean (95% CI)	*P*
Any AE months 0–6		0.27		0.26
Yes (n = 70)	0.31 (0.26–0.36)		0.64 (0.53–0.76)	
No (n = 9)	0.24 (0.14–0.40)		0.47 (0.27–0.82)	
Any AE months 0–3		0.46		0.45
Yes (n = 60)	0.31 (0.26–0.37)		0.64 (0.52–0.78)	
No (n = 19)	0.27 (0.19–0.38)		0.55 (0.40–0.75)	
Any AE months 4–6		0.01		0.04
Yes (n = 55)	0.34 (0.29–0.40)		0.69 (0.57–0.83)	
No (n = 24)	0.22 (0.17–0.29)		0.47 (0.35–0.65)	
Any gastrointestinal AE months 0–6		0.87		0.38
Yes (n = 26)	0.29 (0.22–0.40)		0.56 (0.41–0.75)	
No (n = 53)	0.30 (0.25–0.36)		0.65 (0.53–0.79)	
Any gastrointestinal AE months 0–3		0.46		0.29
Yes (n = 23)	0.27 (0.20–0.38)		0.54 (0.38–0.75)	
No (n = 56)	0.31 (0.26–0.37)		0.65 (0.54–0.79)	
Any gastrointestinal AE months 4–6		0.50		0.28
Yes (n = 7)	0.35 (0.14–0.92)		0.82 (0.47–1.43)	
No (n = 72)	0.30 (0.25–0.34)		0.60 (0.50–0.71)	
Any muscle AE months 0–6		0.36		0.18
Yes (n = 13)	0.35 (0.23–0.54)		0.52 (0.31–0.88)	
No (n = 66)	0.29 (0.25–0.34)		0.64 (0.53–0.76)	
Any muscle AE months 1–3		0.96		0.44
Yes (n = 7)	0.30 (0.14–0.62)		0.50 (0.20–1.27)	
No (n = 72)	0.30 (0.26–0.35)		0.63 (0.53–0.74)	
Any muscle AE months 4–6		0.20		0.83
Yes (n = 8)	0.40 (0.26–0.62)		0.58 (0.28–1.21)	
No (n = 71)	0.29 (0.25–0.34)		0.62 (0.41–0.75)	
Any muscle weakness months 0–6		0.62		0.25
Yes (n = 11)	0.33 (0.20–0.53)		0.49 (0.26–0.91)	
No (n = 68)	0.30 (0.25–0.35)		0.64 (0.54–0.76)	
Any muscle weakness months 0–3		0.46		0.24
Yes (n = 5)	0.24 (0.09–0.65)		0.42 (0.10–1.82)	
No (n = 74)	0.30 (0.26–0.35)		0.63 (0.54–0.74)	
Any muscle weakness months 4–6		0.20		0.83
Yes (n = 8)	0.40 (0.26–0.62)		0.58 (0.28–1.21)	
No (n = 71)	0.29 (0.25–0.34)		0.62 (0.52–0.73)	

* AE, adverse event; CI, confidence interval.

Table 4. Change in CK from month 0 to month 3, and month 0 to month 6, in all trial participants*

	Colchicine		Placebo	
	n	Mean (95% CI)	n	Mean (95% CI)
Change in CK from month 0 to month 3				
Age				
<60 y	53	0.90 (0.76–1.06)	47	0.93 (0.80–1.08)
≥60 y	37	1.2 (1.0–1.43)	43	0.96 (0.84–1.09)
Sex				
Female	6	1.0 (0.74–1.31)	6	0.92 (0.73–1.16)
Male	84	1.01 (0.89–1.15)	84	0.94 (0.85–1.05)
Ethnicity				
Māori	12	1.27 (1.10–1.47)	11	1.11 (0.74–1.67)
Pacific peoples	12	1.16 (0.71–1.90)	7	0.92 (0.89–1.28)
Non-Māori/non-Pacific peoples	66	0.94 (0.82–1.09)	72	0.92 (0.83–1.02)
eGFR				
<60 mL/min/1.73 m^2	12	1.17 (0.87–1.17)	13	1.13 (0.841.51)
≥60 mL/min/1.73 m^2	78	0.99 (0.86–1.13)	77	0.91 (0.83–1.01)
BMI				
<30	37	1.01 (0.84–1.21)	46	0.96 (0.84–1.11)
≥30	49	1.03 (0.86–1.24)	40	0.88 (0.78–0.98)
Statin				
Yes	22	1.12 (0.86–1.46)	27	1.01 (0.83–1.22)
No	68	0.97 (0.84–1.13)	63	0.92 (0.82–1.03)
Calcium channel blocker				
Yes	9	1.07 (0.81–1.41)	16	1.00 (0.78–1.27)
No	81	1.00 (0.88–1.15)	74	0.93 (0.84–1.04)
Physical or manual occupation				
Yes	26	0.98 (0.78–1.24)	29	0.85 (0.70–1.04)
No	64	1.02 (0.88–1.19)	61	0.99 (0.89–1.10)
Change in CK from month 0 to month 6				
Age				
<60 y	53	1.02 (0.82–1.28)	45	1.02 (0.84–1.23)
≥60 y	38	1.15 (0.98–1.35)	44	1.03 (0.89–1.19)
Sex				
Female	7	1.2 (0.96–1.41)	6	0.85 (0.56–1.30)
Male	84	1.07 (0.91–1.25)	83	1.03 (0.91–1.17)
Ethnicity				
Māori	12	1.49 (1.15–1.94)	10	1.18 (0.89–1.56)
Pacific peoples	12	1.36 (1.00–1.85)	8	0.87 (0.51–1.48)
Non-Māori/non-Pacific peoples	67	0.97 (0.81–1.16)	71	1.02 (0.89–1.17)
GFR				
<60 mL/min/1.73 m^2	12	1.23 (0.94–1.63)	16	0.85 (0.61–1.20)
≥60 mL/min/1.73 m^2	79	1.05 (0.89–1.24)	73	1.06 (0.94–1.21)
BMI				
<30	34	1.08 (0.92–1.28)	44	0.90 (0.75–1.11)
≥30	51	1.09 (0.87–1.36)	39	1.07 (0.95–1.21)
Statin				
Yes	23	1.09 (0.89–1.34)	28	1.01 (0.83–1.22)
No	68	1.07 (0.89–1.28)	61	1.03 (0.88–1.20)
Calcium channel blocker				
Yes	10	1.12 (0.75–1.67)	15	1.14 (0.81–1.58)
No	81	1.07 (0.91–1.25)	74	1.00 (0.88–1.14)
Physical or manual occupation				
Yes	26	1.21 (0.94–1.55)	28	1.00 (0.81–1.24)
No	65	1.03 (0.86–1.23)	61	1.03 (0.89–1.19)

* Data presented are the geometric mean ratios of CK between month 0 and month 3 or 6. BMI, body mass index; CI, confidence interval; CK, creatine kinase; eGFR, estimated glomerular filtration rate.

event in months four to six. Although trough and peak colchicine concentrations were higher in those taking a statin, there was no association with an increase in CK levels or muscle-related adverse events.

From a clinical perspective TDM is likely to be more useful when colchicine is being used in the long term for prophylaxis while starting urate-lowering therapy rather than in the short term for gout flares. However, we have shown that there is no reliable

association between trough or peak colchicine concentrations and either efficacy, defined as gout flares, or colchicine-specific adverse events. The lack of a relationship with efficacy is not necessarily unexpected because the majority of colchicine accumulates in neutrophils, and its therapeutic effects are mediated through its ability to bind within cells to tubulin monomers, thus preventing the formation of microtubule heterodimers, which are involved in cell division, signal transduction, regulation of gene expression, and migration.[16] It is possible that the higher dose of colchicine for prophylaxis of 0.5 mg twice daily may be more effective at preventing gout flares when starting allopurinol. Interestingly, both trough and peak colchicine concentrations were higher in those with any adverse event in months four to six. However, these results may be confounded by older age and worse renal function as markers of more comorbidities and higher risk of adverse events generally. In this prophylaxis study, colchicine was used at a lower dose and for a much longer duration (0.5 mg daily for six months) compared to the dose and duration for gout flare (1.2 mg stat followed by 0.6 mg after one hour). This likely, at least in part, explains the lower peak concentrations observed in our study as compared to a previous study of the higher dose in healthy volunteers, as the longer duration of therapy could allow more penetration of colchicine into cells and tissues.[2]

Of interest we have shown that both trough and peak colchicine concentrations are higher in those individuals receiving a statin. The interaction between colchicine and statins is well recognized, as both are substrates and inhibitors of CYP3A4 and P-glycoprotein. Approximately 5% of colchicine is metabolized by CYP3A4 into inactive metabolites, with the majority of colchicine excreted via the liver and kidneys mediated by P-glycoprotein. Simvastatin and atorvastatin are substrates of the CYP3A4 enzyme and P-glycoprotein and are thus subject to interactions with colchicine, resulting in increased colchicine concentrations.[17] In comparison, pravastatin and rosuvastatin are not substrates of CYP enzymes, and hence the concomitant use of CYP inhibitors or inducers, such as colchicine, does not affect them. Our finding that colchicine concentrations are higher in those receiving a statin is therefore not unexpected. Of more importance to patients and health care providers is whether there are clinically meaningful adverse events associated with the combination of colchicine and a statin. Both colchicine and statins can cause myopathy. There are four statin-associated myopathy clinical phenotypes: rhabdomyolysis, myalgia or mild hyper-CKemia (defined as less than five times the upper limit normal), self-limited toxic statin myopathy, and myositis, which is typically an immune-mediated necrotizing myopathy with anti–3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies. The number of participants in our study was too small to undertake reliable analysis of those taking a statin and colchicine; however, there was no increase in muscle-related adverse events, including myalgia, in the whole group receiving colchicine compared to those receiving placebo. More recent larger studies have shown no increased risk of colchicine-related adverse events in those also receiving a statin.[18,19] For example, in a study of 674 people with gout, 486 received colchicine alone and 188 received colchicine and a statin. The incidence of myopathy was 2.7% in those taking both drugs, compared to 1.4% in those taking colchicine alone (P = 0.33).[18] Multivariable analysis revealed an increased risk of myopathy in those with chronic kidney disease (hazard ratio [HR] 29.06), liver cirrhosis (HR 10.68), higher colchicine doses (HR 20.96), and concomitant CYP3A4 inhibitor use (HR 12.02). However, concomitant use of statins was not associated with increased risk of myopathy, even after adjustment for confounders (HR 1.12).[18] In keeping with our findings of no increased risk of myopathy or muscle-related adverse events, we observed no significant increase in CK levels over six months in those taking colchicine. It is important to recognize that there is variation in CK levels depending on age, renal function, physical activity, and ethnicity. Given the findings of our study and other recent studies, regular monitoring of CK may not be required; rather, targeted measurement of CK levels in individuals with muscle symptoms may be more appropriate.

Strengths of this study include analysis of a randomized clinical trial with consistent measurement of adverse events and blood tests, together with comprehensive concomitant medication data collection. Limitations are that the study was not powered to detect rare adverse events due to colchicine and that the study design did not allow analysis of the safety of higher doses of colchicine or longer durations. The study was not designed as a formal pharmacokinetics study. It is important to note that there is substantial variation in colchicine bioavailability in healthy individuals, with additional variation possible in people with gout, because of polypharmacy and genetic variants in transporters, among other factors. In addition, there is widespread distribution of colchicine into cells and tissues, where its anti-inflammatory effects are exerted, compared to the much lower levels observed in plasma. The inability to assess drug concentration in tissues where colchicine exerts its anti-inflammatory effects, such as leucocytes, as well as calculate the volume of distribution is a limitation. The samples collected did not allow us to accurately calculate volume of distribution or area under the curve, and there is wide variation in these parameters, as shown in a small study in healthy volunteers in which total body colchicine clearance was approximately doubled and the area under the curve was approximately four times less for healthy individuals compared with older individuals.[20] Finally, the sampling may have missed the true peak concentrations in some individuals.

In conclusion, colchicine concentrations are not associated with gout flare prophylaxis efficacy, and there is no consistent relationship between colchicine concentrations and colchicine-specific adverse events. Although colchicine concentrations increase with concomitant statin use, this does not result in muscle-related adverse events. These findings indicate that colchicine TDM is of limited value in routine clinical practice.

ACKNOWLEDGMENTS

Open access publishing facilitated by University of Otago, as part of the Wiley - University of Otago agreement via the Council of Australian University Librarians.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Stamp confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res (Hoboken) 2020;72(6):744–760.
2. Terkeltaub RA, Furst DE, Bennett K, et al. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. Arthritis Rheum 2010;62(4):1060–1068.
3. Kuncl RW, Duncan G, Watson D, et al. Colchicine myopathy and neuropathy. N Engl J Med 1987;316(25):1562–1568.
4. Wallace SL, Singer JZ, Duncan GJ, et al. Renal function predicts colchicine toxicity: guidelines for the prophylactic use of colchicine in gout. J Rheumatol 1991;18(2):264–269.
5. Mikuls TR, MacLean CH, Olivieri J, et al. Quality of care indicators for gout management. Arthritis Rheum 2004;50(3):937–943.
6. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. Ann Rheum Dis 2013;72(6):826–830.
7. Gómez-Lumbreras A, Boyce RD, Villa-Zapata L, et al. Drugs that interact with colchicine via inhibition of cytochrome P450 3A4 and P-glycoprotein: a signal detection analysis using a database of spontaneously reported adverse events (FAERS). Ann Pharmacother 2023;57(10):1137–1146.
8. US Food and Drug Administration. FDA Colcrys label 2020. Accessed August 28, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022352s026lbl.pdf
9. Wacher VJ, Wu CY, Benet LZ. Overlapping substrate specificities and tissue distribution of cytochrome P450 3A and P-glycoprotein: implications for drug delivery and activity in cancer chemotherapy. Mol Carcinog 1995;13(3):129–134.
10. Vrachatis DA, Papathanasiou KA, Giotaki SG, et al. Repurposing colchicine's journey in view of drug-to-drug interactions. A review. Toxicol Rep 2021;8:1389–1393.
11. Kintz P, Jamey C, Tracqui A, et al. Colchicine poisoning: report of a fatal case and presentation of an HPLC procedure for body fluid and tissue analyses. J Anal Toxicol 1997;21(1):70–72.
12. Molad Y. Update on colchicine and its mechanism of action. Curr Rheumatol Rep 2002;4(3):252–256.
13. Karatza E, Ismailos G, Karalis V. Colchicine for the treatment of COVID-19 patients: efficacy, safety, and model informed dosage regimens. Xenobiotica 2021;51(6):643–656.
14. Stamp L, Horne A, Mihov B, et al. Is colchicine prophylaxis required with start-low go-slow allopurinol dose escalation in gout? A non-inferiority randomised double-blind placebo-controlled trial. Ann Rheum Dis 2023;82(12):1626–1634.
15. Taylor W, Dalbeth N, Saag KG, et al. Flare rate thresholds for patient assessment of disease activity states in gout. J Rheumatol 2021;48(2):293–298.
16. Terkeltaub RA. Colchicine update: 2008. Semin Arthritis Rheum 2009;38(6):411–419.
17. Davis MW, Wason S. Effect of steady-state atorvastatin on the pharmacokinetics of a single dose of colchicine in healthy adults under fasted conditions. Clin Drug Investig 2014;34(4):259–267.
18. Kwon OC, Hong S, Ghang B, et al. Risk of colchicine-associated myopathy in gout: influence of concomitant use of statin. Am J Med 2017;130(5):583–587.
19. Alfehaid LS, Farah S, Omer A, et al. Drug-drug interactions and the clinical tolerability of colchicine among patients with COVID-19: a secondary analysis of the COLCORONA Randomized Clinical Trial. JAMA Netw Open 2024;7(9):e2431309.
20. Rochdi M, Sabouraud A, Girre C, et al. Pharmacokinetics and absolute bioavailability of colchicine after i.v. and oral administration in healthy human volunteers and elderly subjects. Eur J Clin Pharmacol 1994;46(4):351–354.

Arthritis Care & Research
Vol. 77, No. 9, September 2025, pp 1165–1166

American College of Rheumatology
Empowering Rheumatology Professionals

LETTER

DOI 10.1002/acr.25529

Lower environmental temperature and higher relative humidity had significant associations with worsened Raynaud phenomenon in systemic sclerosis: comment on the article by Taylor et al

To the Editor:

We read with interest the recent publication by Taylor and colleagues on the impact of season, environmental temperature, and humidity on Raynaud phenomenon (RP) in an Australian systemic sclerosis cohort.[1] The authors concluded that lower environmental temperature and higher relative humidity had significant associations with worsened RP in this systemic sclerosis cohort, which suggests an important role for dry warmth in managing this condition.[1] We support and appreciate the authors' work and agree with their conclusions, but we have some concerns about some of the details in the article.

First, the relative humidity is a measure of the ratio of the amount of moisture in the air to the maximum amount of moisture the air could hold at the same temperature.[1] However, this measurement method may not fully and accurately reflect the humidity conditions in the actual environment where the patients are located. For instance, in some coastal areas, although the relative humidity is high, the actual perceived humidity may differ from the measured value because of factors such as sea breezes. Moreover, humidity measurements are usually taken at fixed heights and locations, whereas patients may move around and be exposed to different humidity conditions at different times and places throughout the day, which may differ from the humidity measured by meteorological stations. Additionally, the evaporation is measured by the millimeters of water evaporating from a Class A evaporation pan, and this measurement method may not accurately reflect the evaporation conditions in the environment where the patients are.[1] For example, in some mountainous or forested areas, the actual evaporation rate may differ from the measured value because of factors such as vegetation cover and terrain. Furthermore, the measurement of evaporation is typically conducted in open areas, whereas the environment where the patients are may have obstructions such as buildings or trees. These obstructions can affect air circulation and solar radiation, thus impacting the evaporation rate.

Second, this study did not analyze the interactions between season, temperature, and humidity.[1] In reality, there may be complex interactions among these factors that collectively affect the deterioration of RP. For example, the combination of low temperature and high humidity may have a greater impact on the deterioration of RP, and this interaction was not reflected in the study.[1] If these interactions could be analyzed, it might provide a more comprehensive understanding of how season, temperature, and humidity affect RP.

Third, this study primarily focused on the impact of season, temperature, and humidity on RP but did not consider other climatic factors, such as wind speed and daylight hours.[1] These climatic factors also affect RP. For instance, when wind speed is higher, it might accelerate the heat loss from the skin surface, thus exacerbating RP symptoms; when daylight hours are longer, it might increase skin temperature and alleviate RP symptoms. If these climatic factors could be incorporated into the research scope, it might provide a more comprehensive assessment of how climate affects RP.

Fourth, this study primarily focused on the impact of climatic factors on RP, but did not consider other nonclimatic factors such as exercise and psychological stress.[1] These nonclimatic factors may also affect RP. For instance, moderate exercise can promote blood circulation and reduce RP symptoms; high psychological stress may lead to vasoconstriction and exacerbate RP symptoms.[2,3] If these nonclimatic factors could be included in the research scope, it might provide a more comprehensive assessment of the pathogenesis and influencing factors of RP.

Finally, although the results of this study indicate a correlation between season, temperature, and humidity with the deterioration of RP, there may be other unmeasured factors that simultaneously affect both RP deterioration and environmental factors that lead to this correlation. For example, the amount of time patients spend indoors, as well as their clothing habits, may influence their exposure to environmental temperature and humidity, as well as the severity of RP symptoms. In conclusion, before these issues are clarified, this study's findings should be interpreted cautiously.

We would like to thank the members and staff of the Department of Rheumatology and Immunology of The Second Affiliated Hospital of Soochow University who contributed to this manuscript.

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25529.

Gang Wang, MD
Zhichun Liu, MD
zcliurheu@suda.edu.cn
The Second Affiliated Hospital of Soochow University
Suzhou, China

1. Taylor L, Hansen D, Morrisroe K, et al. Impact of season, environmental temperature, and humidity on Raynaud phenomenon in an Australian systemic sclerosis cohort. Arthritis Care Res (Hoboken) 2025;77(1):61–68.
2. Herrick AL. The pathogenesis, diagnosis and treatment of Raynaud phenomenon. Nat Rev Rheumatol 2012;8(8):469–479.
3. Reilly A, Snyder B. Raynaud phenomenon: whether it's primary or secondary, there is no cure, but treatment can alleviate symptoms. Am J Nurs 2005;105(8):56–65.

DOI 10.1002/acr.25530

Reply

To the Editor:

We write to thank doctors Wang and Liu for their comments on our article, "The Impact of Season, Environmental Temperature and Humidity on Raynaud Phenomenon in an Australian Systemic Sclerosis Cohort."[1] We agree that there are many climatic factors to consider, but perhaps the most important factor is the ambient temperature where people spend most of their time. Indeed, migratory patterns suggest that people with systemic sclerosis cohort (SSc) have a tendency to relocate to warmer climates to improve their Raynaud phenomenon (RP)[2,3] because anecdotally RP is exacerbated by cooler climates. We applied a novel approach to estimating the impact of climate conditions on patients with SSc by interrogating freely available meteorological data at the patients' residential addresses within the month of a clinical assessment.[1]

The novelty of this study lies in its Australian context, wherein climate ranges from temperate (with seasonal variation in temperature) to tropical (predominantly warm throughout the year). Although we are limited by the type of data we have access to, the strength of this study is that it uses data from a large cohort spread across the diverse climate conditions that Australia has to offer. Previous research on this topic has been of small sample size and short duration follow-up.[4] Our sample size was close to 2,000 participants with over 9,000 clinical assessments over a median follow-up of 4.3 years.[1]

Our first-of-a-kind, retrospective evaluation of the relationship between self-reported RP worsening among patients with SSc and local mean meteorological patterns by no means captures skin temperature or humidity exposure of individual patients on a daily basis. Behavioral factors that alter individuals' exposure to their natural environment, for example, spending significant time away from their residential address, type of clothing worn, or use of air conditioning, are outside the scope of the Australian Scleroderma Cohort Study data. However, we were able to demonstrate a significant seasonal association with self-reported worsening RP symptoms, across spring, autumn, and winter, compared with summer.[1] Furthermore, our multivariable models suggest that environmental factors beyond temperature may play a role in the pathogenesis of RP.[1]

Although further research may help delineate the impact of environmental factors other than temperature and humidity, the findings of our study highlight the importance of dry warmth in the management of RP, which is a ubiquitous feature of SSc with significant impact on patient quality of life.

The Australian Scleroderma Cohort Study is supported by Janssen, Boehringer Ingelheim, Scleroderma Australia, Scleroderma Victoria, Arthritis Australia, Musculoskeletal Australia (muscle, bone and joint health), Australian Rheumatology Association, and St. Vincent's Hospital Melbourne Information Technology Department and Research Endowment Fund. Dr. Nikpour's work was supported by a National Health & Medical Research Council of Australia Investigator Grant (GNT1176538).

Alicia Calderone, MPH
Dylan Hansen, MBioStat
Laura Taylor, MBBS
St. Vincent's Hospital Melbourne
Melbourne, Victoria, Australia
Mandana Nikpour, MBBS, PhD
mandana.nikpour@sydney.edu.au
The University of Sydney, Sydney, New South Wales, Australia and Royal Prince Alfred Hospital Camperdown
Camperdown, New South Wales, Australia

1. Taylor L, Hansen D, Morrisroe K, et al. Impact of season, environmental temperature, and humidity on Raynaud phenomenon in an Australian systemic sclerosis cohort. Arthritis Care Res (Hoboken) 2025;77(1):61–68.
2. Maricq HR, Carpentier PH, Weinrich MC, et al. Geographic variation in the prevalence of Raynaud's phenomenon: a 5 region comparison. J Rheumatol 1997;24(5):879–889.
3. Abbot S, McWilliams L, Spargo L, et al. Scleroderma in Cairns: an epidemiological study. Intern Med J 2020;50(4):445–452.
4. Watson HR, Robb R, Belcher G, et al. Seasonal variation of Raynaud's phenomenon secondary to systemic sclerosis. J Rheumatol 1999;26(8):1734–1737.

1. Taylor L, Hansen D, Morrisroe K, et al. Impact of season, environmental temperature, and humidity on Raynaud phenomenon in an Australian systemic sclerosis cohort. Arthritis Care Res (Hoboken) 2025;77(1):61–68.
2. Herrick AL. The pathogenesis, diagnosis and treatment of Raynaud phenomenon. Nat Rev Rheumatol 2012;8(8):469–479.
3. Reilly A, Snyder B. Raynaud phenomenon: whether it's primary or secondary, there is no cure, but treatment can alleviate symptoms. Am J Nurs 2005;105(8):56–65.

DOI 10.1002/acr.25530

Reply

To the Editor:

We write to thank doctors Wang and Liu for their comments on our article, "The Impact of Season, Environmental Temperature and Humidity on Raynaud Phenomenon in an Australian Systemic Sclerosis Cohort."[1] We agree that there are many climatic factors to consider, but perhaps the most important factor is the ambient temperature where people spend most of their time. Indeed, migratory patterns suggest that people with systemic sclerosis cohort (SSc) have a tendency to relocate to warmer climates to improve their Raynaud phenomenon (RP)[2,3] because anecdotally RP is exacerbated by cooler climates. We applied a novel approach to estimating the impact of climate conditions on patients with SSc by interrogating freely available meteorological data at the patients' residential addresses within the month of a clinical assessment.[1]

The novelty of this study lies in its Australian context, wherein climate ranges from temperate (with seasonal variation in temperature) to tropical (predominantly warm throughout the year). Although we are limited by the type of data we have access to, the strength of this study is that it uses data from a large cohort spread across the diverse climate conditions that Australia has to offer. Previous research on this topic has been of small sample size and short duration follow-up.[4] Our sample size was close to 2,000 participants with over 9,000 clinical assessments over a median follow-up of 4.3 years.[1]

Our first-of-a-kind, retrospective evaluation of the relationship between self-reported RP worsening among patients with SSc and local mean meteorological patterns by no means captures skin temperature or humidity exposure of individual patients on a daily basis. Behavioral factors that alter individuals' exposure to their natural environment, for example, spending significant time away from their residential address, type of clothing worn, or use of air conditioning, are outside the scope of the Australian Scleroderma Cohort Study data. However, we were able to demonstrate a significant seasonal association with self-reported worsening RP symptoms, across spring, autumn, and winter, compared with summer.[1] Furthermore, our multivariable models suggest that environmental factors beyond temperature may play a role in the pathogenesis of RP.[1]

Although further research may help delineate the impact of environmental factors other than temperature and humidity, the findings of our study highlight the importance of dry warmth in the management of RP, which is a ubiquitous feature of SSc with significant impact on patient quality of life.

The Australian Scleroderma Cohort Study is supported by Janssen, Boehringer Ingelheim, Scleroderma Australia, Scleroderma Victoria, Arthritis Australia, Musculoskeletal Australia (muscle, bone and joint health), Australian Rheumatology Association, and St. Vincent's Hospital Melbourne Information Technology Department and Research Endowment Fund. Dr. Nikpour's work was supported by a National Health & Medical Research Council of Australia Investigator Grant (GNT1176538).

Alicia Calderone, MPH
Dylan Hansen, MBioStat
Laura Taylor, MBBS
St. Vincent's Hospital Melbourne
Melbourne, Victoria, Australia
Mandana Nikpour, MBBS, PhD
mandana.nikpour@sydney.edu.au
The University of Sydney, Sydney, New South Wales, Australia and Royal Prince Alfred Hospital Camperdown
Camperdown, New South Wales, Australia

1. Taylor L, Hansen D, Morrisroe K, et al. Impact of season, environmental temperature, and humidity on Raynaud phenomenon in an Australian systemic sclerosis cohort. Arthritis Care Res (Hoboken) 2025;77(1):61–68.
2. Maricq HR, Carpentier PH, Weinrich MC, et al. Geographic variation in the prevalence of Raynaud's phenomenon: a 5 region comparison. J Rheumatol 1997;24(5):879–889.
3. Abbot S, McWilliams L, Spargo L, et al. Scleroderma in Cairns: an epidemiological study. Intern Med J 2020;50(4):445–452.
4. Watson HR, Robb R, Belcher G, et al. Seasonal variation of Raynaud's phenomenon secondary to systemic sclerosis. J Rheumatol 1999;26(8):1734–1737.