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.

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Cover image: The image on the cover (from Eloseily et al; pages 513–521) is a heatmap showing z scores of genes that were down-regulated after 18 weeks (right; baseline shown at left) of tofacitinib treatment in patients with juvenile idiopathic arthritis (false discovery rate <0.05 and logFC less than −0.7). Annotated genes are from ontologies related to type I and type II interferon activity (brown) as well as IL-7 signaling (yellow).

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American College of Rheumatology
Empowering Rheumatology Professionals

EDITORIAL

State of the Advanced Practice Provider in Rheumatology

Lisa Carnago[1] and Allison Dimsdale[2]

The rheumatology field faces a shortage of clinicians, with estimates suggesting a deficit of 4,000 full-time providers by 2030.[1] Rheumatology cases are unique in their medical complexity, so the introduction of advanced practice providers (APPs) such as nurse practitioners and physician assistants into team-based care models has been welcomed as a strategy to increase timely patient access to rheumatology care. Between 2008 and 2016, the prevalence of APPs employed in specialty clinical practice settings increased by 22%,[2] yet within nearly the same timeframe (2009–2020), the prevalence of APPs working specifically in rheumatology rose by 141%, whereas the prevalence of rheumatologists rose by only 20%.[3] This modest increase in rheumatologists cannot counterbalance retirements or meet the increasing demand for care[1] and provider services including evaluation, diagnosis, and ongoing medical management.[4,5]

Rheumatology is a growing specialty that requires in-depth knowledge of multiple diverse and chronic conditions, and prior studies in clinical practices that incorporate APPs have shown decreased disease activity in patients with rheumatoid arthritis, thus confirming their professional capabilities and value.[6] Rheumatology patients often present with complex medical conditions, including autoimmune diseases and chronic pain syndromes; therefore, the ramp-up time for APPs to train in rheumatology may be longer than in many other specialties, often extending beyond one year. Additional challenges include difficulties in establishing role clarity and a need for specialized academic programs or certifications tailored to rheumatology. This editorial describes critical considerations for rheumatology practices seeking to successfully integrate and retain APPs to optimize access to needed services.

Integrating APPs: building highly effective interprofessional teams

The US health care system currently faces a significant shortage of physicians (MDs), with a projected shortfall of more than 100,000 by 2030.[7] This worrisome gap can be addressed by integrating APPs, who are trained and board-certified, into teams whose goals include decreasing the complexity of physician work, increasing the number of clinicians for complex patients, and achieving a return on investment. This return can be measured individually by relative value units or in aggregate by evaluating patient access to the team. It should be recognized that about one year of investment (eg, money, effort, time) is usually required to ramp up a new clinician in a new specialty. Effective team building requires a thorough assessment of available resources and patient needs, carefully designing team roles and responsibilities, and developing robust communication strategies to ensure seamless collaboration. A patient-centered approach is paramount for ensuring that care provision aligns with unique patient needs and preferences.

The integration of APPs into clinical practice requires a shift in practice from solo practitioners caring for patients to a team-based model of care, described as "the provision of health services to individuals, families, and communities by at least two health providers who work collaboratively with patients and their caregivers—according to the patient's preferences—to achieve shared goals…[and] coordinated, high-quality care."[8] Team-based models have been shown to improve efficiency, quality of care, and patient outcomes,[9] but there is limited evidence regarding strategies to integrate APPs into rheumatology practice optimally; related challenges include few clearly defined training recommendations, role ambiguity, and increasing patient complexity. Despite these obstacles, practices can take steps to foster a culture and organizational structures that support APP integration by incorporating five key elements of highly effective teams: effective communication, clear role definition, shared goals, mutual trust, and leadership support.[8]

Effective communication is essential for high-functioning teams. Collegial and team-based communication between patients and physicians, as well as between physicians and APPs, is imperative to successful APP integration into team-

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based models of care.[10] The language used when communicating with APPs, other team members, and patients is an important consideration. For example, when discussing patient cases among team members, consider referring to patients as "our patients" to foster a collegial atmosphere in which team members are regarded as equals, each of whom brings a unique lens and set of skills to the care of patients. This sense of equality will foster improved responsibility sharing among team members.[10]

Establishing and communicating expectations, both to patients and among clinicians, is an integral part of clear role delineation. At the organizational level, the creation and operationalization of the team-based model of care should be transparent and incorporate scripting from the front desk staff, scheduling, and nursing, thus allowing clinicians to share, reinforce, and frame the team-based structure, essentially setting patient and clinician expectations for care delivery. For instance, rather than stating to a patient, "You will need to see my APP colleague in three months because my appointments are booked out for the next nine months," a physician might explain, "In our practice, we use a team-based model to provide you with the highest quality of care promptly, so you may see an APP in addition to me. I would like you to meet [insert provider name] at your next visit in 3 months. Our team collaborates fully on your care, so you will hear from one of us if there is anything that we need to discuss with you." This clear communication showcases the practice's team-based structure, sets expectations for the patient, and reassures the patient of their physician's continued involvement in their care. Note, too, that the physician referred to "an APP" rather than "my APP" to convey the equality of the team and the physician's trust in and respect for their APP colleague. Although it can be challenging to define team member roles within rheumatology clearly, role delineation is a worthwhile undertaking that can help to determine the needed model of care while assuring patients that their care is a fully shared goal.

The creation of shared goals is a crucial priority of highly effective teams, and it must be considered when integrating APPs into rheumatology practice. This component of successful integration is accomplished by developing a common and delineated purpose based upon "collective interests" that demonstrate "shared ownership."[10] These goals must be team-oriented group goals and should not be separated as physician-, nurse-, and APP-specific goals. It is essential to remember that, for group goals to be practical, the role of the team must be clearly defined.

Mutual trust is essential to effective team-based models of care and an important consideration for APP integration. Mutual trust must be earned[8,10] through ongoing interactions over time; fostering supportive and respectful relationships within a structured team-based model of care is imperative for building and maintaining trust. When integrating an APP into practice, teams should consider having them begin working with the members with whom they will partner when their training is complete to engender trust. It is important to remember that trust can be lost; therefore, all team members must work to maintain trust by modeling essential values such as honesty in communication, a disciplined work ethic, openness to creative potential solutions to problems, humility when working with colleagues with different levels of training, and curiosity about possible improvements to the quality of care delivered.[8]

Leadership support is the lynchpin to a successful team-based model of care and highly effective teams. All team members must communicate and feel leadership support through the leader's actions.[8] Without a palpable sense of leadership and organizational support, many other considerations pertaining to a team-based model of care will become obsolete or unattainable.

Benefits of incorporating APPs into rheumatology practice

Incorporating an APP into rheumatology practice has multiple benefits. First, the rheumatology APP performs patient care functions similar to their physician colleagues. They are licensed and prepared to perform physical assessments and medical diagnoses, order and interpret testing, and prescribe medication and treatments.[11] Second, studies have shown that APPs have similar patient satisfaction scores to their physician counterparts and can improve the care of patients with rheumatoid arthritis.[6,11] Third, use of an APP in clin ical practice has been shown to generate an acceptable return on investment in models ranging from autonomous practice to shared visits as part of a care team.[12] In summary, APPs bring numerous advantages to patients and practices, including high-quality patient-centered care, improved outcomes for complex conditions such as rheumatoid arthritis, and enhanced patient satisfaction and access to care.

Barriers to integrating an APP into rheumatology practice

Despite the benefits of including APPs in rheumatology practice, barriers at multiple levels may create suboptimal conditions for integration. Many organizations have defined roles or responsibilities for the APP,[12] yet there are multiple challenges to operationalizing these roles within rheumatology practice. Additional barriers pertain to the need for a defined scope of practice or role. APPs' competence and comfort with typically high and increasing patient complexity may be affected by their training, experience, and support, suggesting a need to consider and augment these areas when integrating an APP into clinical practice. Moreover, the current barriers affecting access to rheumatology and primary care clinicians (eg, physician turnover and lack of rheumatology physicians to see patients in follow-up) present challenges to defining the role of the APP in this specialty. There is a general lack of guidance about whether it is more appropriate for the APP to see new or return patients. For instance, an APP working within

a large academic medical center might be expected to assess, manage, and treat patients with complex diagnoses (eg, positive autoantibodies such as antinuclear antibody or rheumatoid factor, inflammatory arthritis, vasculitis, sarcoidosis, scleroderma, associated chronic pain conditions) as well as address primary care concerns such as blood pressure and cholesterol management, immunization, and cancer screening.

The role of the rheumatology APP is evolving, but lack of clarity regarding the models of care in which they operate makes it difficult to optimize their integration into clinical practice. These models of care are largely undefined and understudied, and feasibility and acceptability concerns have yet to be considered within rheumatology. Additionally, the model of care may vary depending on the population served (adult vs pediatric), practice setting (rural vs urban, academic vs community),[11,13] or specific needs of the practice, suggesting that a tailored approach may be necessary. To improve access to rheumatology care, provide a more complete understanding of how to incorporate APPs within rheumatology practices, and clarify needed training models, further descriptions and evaluations of current APP utilization within various models of care are warranted. Table 1 shows potential models adapted from Chaney et al[12] and Dimsdale[14] for integrating APPs into rheumatology, based upon models seen in practice.

Preparing APPs for rheumatology

Several solutions exist to address the increasing demands on a shrinking rheumatology physician workforce, such as "on-the-job training" and postgraduate fellowships for APPs. On-the-job training takes time and requires existing clinicians to be willing to train others. It involves paying a full-time salary for learning time without an immediate increase in patient access. On-the-job training allows APPs to learn in a real-world setting, but it can be resource-intensive and may take time to alleviate the burden on existing providers. Still, potential pitfalls must also be considered and addressed, including the financial costs associated with training programs, the need for ongoing mentorship and support, and the potential for role confusion among team members.

Table 1. Models of care: integrating an APP*

Model of care	Description
Autonomous/ independent	APP manages all aspects of patient care and collaborates with an MD when needed. May include independent panel or shared panel.
Parallel	APP and MD are in the same clinic location. May use a shared model (but not shared billing) and collaborate as needed.
Specialty-specific follow-up	MD sees patient for initial visit; then APP and MD alternate visits based on patient preference and acuity.
Tandem	APP sees patient, completes documentation, and presents the patient to the MD. MD then repeats specific elements of the visit, and APP coordinates care after the visit. Similar to resident or fellow model.
Leverage	APP performs work, allowing the MD to increase clinical volume.

* APP, advanced practice provider; MD, physician.

A second potential solution includes the use of postgraduate fellowships. Like the medical model, APPs can be trained alongside other fellows using the same curricula, learning pathways, and tools. This usually involves one year of intensive training at less than a full-time salary. At the end of the fellowship, the APP is fully trained and ready to begin practice without an extensive ramp-up, and the initial provider salary may reflect the year of intensive training, rendering the fellow financially "whole" at the two- or three-year time point. Benefits to fellowships include trust-building among medical staff, APPs, and patients during the training period and increased resources and high-quality, high-value care obtained through adding an APP to the team. Postgraduate fellowships provide a structured and comprehensive training experience, ensuring that APPs are well-prepared to handle the complexities of rheumatology care. For example, Duke University Health System offers an intentionally structured fellowship program to incorporate and train APPs.[13]

Several questions remain about the implementation of APP fellowship programs. For instance, should APPs be trained by the clinicians that they will be working with? In light of the aforementioned high clinical demands in rheumatology, preparing APPs to work in practices external to the training site presents challenges related to funding the effort, determining who will provide the training, and associated compensation. Pertinent considerations include whether it is more effective for future collaborating clinicians to train the APPs directly or for an external entity to take on this role and train APPs for other practices. This decision is complicated by significant differences in normative practice patterns among rheumatologists and the need to build mutual trust among providers.[8,15]

Conclusions

In conclusion, integrating APPs into rheumatology practice is essential to meet increasing patient care demands and complexity with high-quality, coordinated care. However, the need for clearly defined roles, training standards, and evidence on optimal models of care for APPs continues to hinder their full integration into clinical practice. To address these challenges, health care organizations should (a) invest in developing standardized training programs, (b) clearly define the role of APPs in care delivery, and (c) promote interdisciplinary collaboration by adopting principles of highly effective teams within their models of care. Further research is needed to evaluate the effectiveness of various team-based care models, identify best practices for APP integration in different clinical settings, and enhance quality patient care and resource availability. Such efforts can address unique challenges

in rheumatology and implement effective training and team-building strategies.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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Profile and Attributes of Physician Assistants/Associates in Rheumatology: An In-Depth Analysis

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Objective. This work describes the demographics and practice characteristics of physician assistants/associates (PAs) practicing in rheumatology.

Methods. We examined 2022 cross-sectional data from the National Commission on Certification of PAs. The investigation included demographics and practice characteristics of PAs working in rheumatology compared to those working in all other specialties. We analyzed data using descriptive and bivariate statistics comparing the two groups.

Results. In 2022, 430 PAs self-reported practicing in rheumatology. The median age of these PAs was 39 years, and 84.7% self-identified as female. They primarily (78.8%) worked in office-based private practices and were more likely to engage in telemedicine services (62.5%) than their colleagues in all other specialties. PAs in rheumatology typically worked similar hours as their peers in other medical disciplines but saw a higher proportion of patients in the 61 to 80 range. At the same time, PAs in rheumatology reported slightly higher job satisfaction and lower burnout symptom rates compared to PAs practicing in other disciplines.

Conclusion. Understanding the characteristics and employment settings of PAs in rheumatology is crucial to estimating the health workforce supply and demand in this discipline. Further research should explore the economics of PAs in rheumatology, including aspects of teamwork, scope of practice, patient outcomes, and satisfaction.

INTRODUCTION

Extensive research has firmly established that the United States could face a substantial shortage of 124,000 physicians and surgeons by[1] 2034. This includes shortfalls in primary and specialty care and rheumatologists' service delivery.[1] Affirming this, the 2015 American College of Rheumatology Work Study estimates a shortfall of 4,882 rheumatology providers, which includes rheumatologists, physician assistants/associates (PAs), and nurse practitioners (NPs), by[2] 2030. Furthermore, this workforce study anticipated a 30.9% decrease in rheumatologists' supply from 2015 to 2030. In contrast, there is an expected increase in the supply of NPs and PAs by 40.4% and 45.3%, respectively, during the same period.[2] However, the total supply of the rheumatology workforce was still projected to decline by 25.2% from 2015 to[2] 2030. A similar scenario is found in the pediatric rheumatology workforce.[3] Driven by the shortage of rheumatologists,[2] raised demand for more rheumatic disease services,[4,5] and the aging population,[6] more workforce research is needed in this specialized medical discipline.

PAs have worked in rheumatology since the 1970s, and their role has been previously described in the literature.[5,7] The medical literature has demonstrated that patients with rheumatic disease accept PAs well and that PAs provide quality patient care.[6,8] Using PAs and NPs in rheumatology practice has been suggested to address the supply and demand gap of needed rheumatology clinicians on more than one occasion.[1,9] Until now, insufficient data have been published on the demographic and practice characteristics of PAs in clinical rheumatology.

We seek to evaluate the characteristics of clinically active PAs working in rheumatology. The intent is to enhance the workforce research on this specialty and inform policymakers, hospital system administrators, practice administrators, physicians, and other health care providers about this cadre of health professionals. The following research question guides our study: What are the characteristics of PAs in rheumatology,

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SIGNIFICANCE & INNOVATIONS

- Physician assistants/associates (PAs) are one solution to the growing supply and demand gap in the rheumatology provider workforce.
- The number of PAs who work in rheumatology has steadily increased in recent years.
- Knowing the characteristics of PAs who work in rheumatology will aid in recruiting and retaining PAs in this specialty.
- PAs who work in rheumatology are more satisfied and report fewer burnout symptoms when compared to their PA colleagues in other disciplines.

and how do these characteristics compare to PAs practicing in all other specialties?

MATERIALS AND METHOD

We used the administrative and 2022 PA Professional Profile workforce data set from the National Commission on Certification of PAs (NCCPA). The PA Professional Profile contains specific self-reported information from board-certified US PAs.[10] The NCCPA invites all PAs to answer questions about their role and practice setting, and participation is voluntary. The variables in the profile include key questions such as demographics, education, and practice attributes, which were initially established in 2012 and guided by the health workforce minimum data set recommendations.[11,12] The variables in the profile mostly remain constant (to allow for assessing trends over time) with periodic updates and additions. For instance, telemedicine and burnout questions were added to the profile in 2017 and 2020, respectively, and the practice specialty selections ("Which of the following [medical specialties] best describes your principal area of clinical practice?") were included in[10,11,13] 2012. However, a few new specialties have been added over time (eg, interventional radiology, most recently) as PAs reported in the other open-ended responses to work in disciplines not available in the closed-ended response options. PAs have the option to update their profile at any time; however, most do so every two years when they log in to report continuing medical education credits.

From the total 168,318 board-certified PAs at the end of 2022, 140,815 PAs (87.3%) responded to the PA Professional Profile, and 27,503 (12.7%) did not. Among PAs who completed the PA profile, 117,748 responded to the specialty question ("Which of the following best describes your principal area of clinical practice?"). We excluded from the analysis PAs who did not update their NCCPA profile in the last three years, were inactive clinically, or did not respond to the practice specialty question. To determine whether there were differences between respondents and nonrespondents in the PA profile data, we used administrative data, which is nearly complete and contains age, sex, rural or urban setting, and US region. We found no statistical difference by sex (70.6% vs 71.1%, female) and US region (34.4% vs 34.8%, South); however, slight differences were observed in age for nonresponders versus responders (median age 36 vs 38 years) and urban or rural setting (92.8% vs 94.5%, urban).

The variables of interest included demographics (eg, age, sex, race, ethnicity, US region), income range, clinical practice attributes (eg, practice setting, years certified as a PA, weekly patient load, weekly work hours, use of telemedicine services), job satisfaction, burnout symptoms assessed via a validated scale,[14,15] and retirement plans. Burnout was measured using a single-item question.[14] The self-reported single-item burnout question used in the PA profile was compared with the gold standard Maslach Burnout Inventory (MBI)[16] in a large sample of practicing physicians and determined that the single-item measure is comparable to the MBI and elicited similar results[14]; thus, the single-item burnout question was incorporated into the PA Professional Profile in 2020.

The variables described previously were used to determine potential differences between PAs working in rheumatology and PAs in other medical disciplines. PAs in all other medical disciplines include the 70 medical fields that PAs practice in. A complete list of all medical specialties in which PAs practice is found in the 2022 NCCPA Statistical Profile of Board Certified PAs by Specialty Annual Report.[10] The analysis consisted of descriptive and bivariate assessments comparing the two groups, with a P value <0.05 deemed statistically significant. Nonparametric tests such as Pearson chi-Square or Mann-Whitney U-test (as appropriate) were used to analyze the two groups (PAs practicing in rheumatology vs PAs in all other specialties). SPSS (Version 29.0; IBM Corp) was used to conduct the analyses. This study was determined to be exempt by the Sterling Institutional Review Board (institutional review board no. 9942).

RESULTS

We found that 430 of PAs (0.4%) self-identified as providing patient care in rheumatology as their primary specialty versus 117,318 PAs (99.6%) in all other clinical specialties. Notably, the proportion of PAs working in rheumatology has experienced a growth rate of 93.7% since 2015 (Figure 1). In terms of demographic characteristics, a higher percentage of PAs in rheumatology, when compared to PAs in all other disciplines, identify as female (84.7% vs 69.6%; $P < 0.001$) and Asian (10.0% vs 6.3%; $P = 0.009$) and dwell in urban settings (96.7% vs 92.5%; $P = 0.007$). The median age for PAs in rheumatology is the same as that of all other specialties (39 years) and with a similar age distribution (Table 1).

The principal practice setting of PAs in rheumatology is shown in Figure 2. More than three-quarters of PAs (78.8%) in rheumatology provide care in office-based private practices

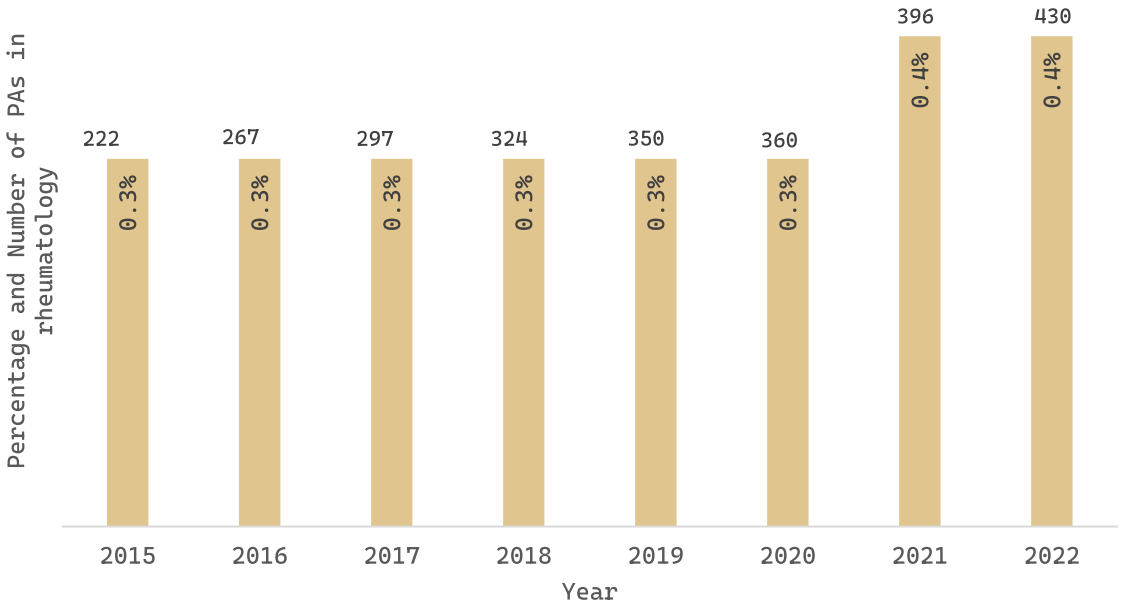

Figure 1. Trends of PAs in rheumatology (2015–2022). PA, physician assistant/associate.

versus 37.0% of PAs in all other disciplines ($P < 0.001$). Fewer PAs in rheumatology practice in hospital-based settings (15.8%) and "other" employment settings (5.3%).

Conversely, two-thirds of PAs (66.4%) in rheumatology see between 41 to 60 and 61 to 80 patients each week compared to the percentage of all other PAs who see between 41 to

Table 1. Demographic characteristics of PAs in rheumatology compared to PAs in other medical disciplines

	PAs in rheumatology (n = 430)	PAs in all other specialties (n = 117,318)	*P* value
Age group, n (%), yr			0.481
Less than 30	52 (12.1)	13,743 (11.7)	
30–39	175 (40.7)	47,172 (40.2)	
40–49	119 (27.7)	30,118 (25.7)	
50–59	59 (13.7)	16,878 (14.4)	
60 and over	25 (5.8)	9,407 (8.0)	
Age, yr			0.458
Mean (SD)	40.8 (10.5)	41.3 (10.9)	
Median (IQR)	39 (32–47)	39 (33–48)	
Sex, n (%)			<0.001
Female	364 (84.7)	81,646 (69.6)	
Male	66 (15.3)	35,658 (30.4)	
Race, n (%)			0.009
White	350 (83.7)	94,847 (84.5)	
Asian	42 (10.0)	7,079 (6.3)	
Black/African American	9 (2.2)	3,870 (3.4)	
Multirace	7 (1.7)	2,544 (2.3)	
Other[a]	10 (2.4)	3,955 (3.5)	
Ethnicity, n (%)			0.792
Non-Hispanic/non-Latino or non-Spanish origin	393 (92.9)	105,205 (93.2)	
Hispanic/Latino or Spanish origin	30 (7.1)	7,638 (6.8)	
US region, n (%)			0.613
South	154 (35.8)	40,316 (34.5)	
Midwest	92 (21.4)	23,084 (19.7)	
Northeast	96 (22.3)	28,758 (24.6)	
West	88 (20.5)	24,737 (21.2)	
Urban–rural setting, n (%)			0.007
Urban	415 (96.7)	107,953 (92.5)	
Rural or isolated	14 (3.3)	8,707 (7.5)	

* IQR, interquartile range; PA, physician assistant/associate.
[a] Other includes those who selected "other," Native Hawaiian/Pacific Islander, and American Indian or Alaska Native.

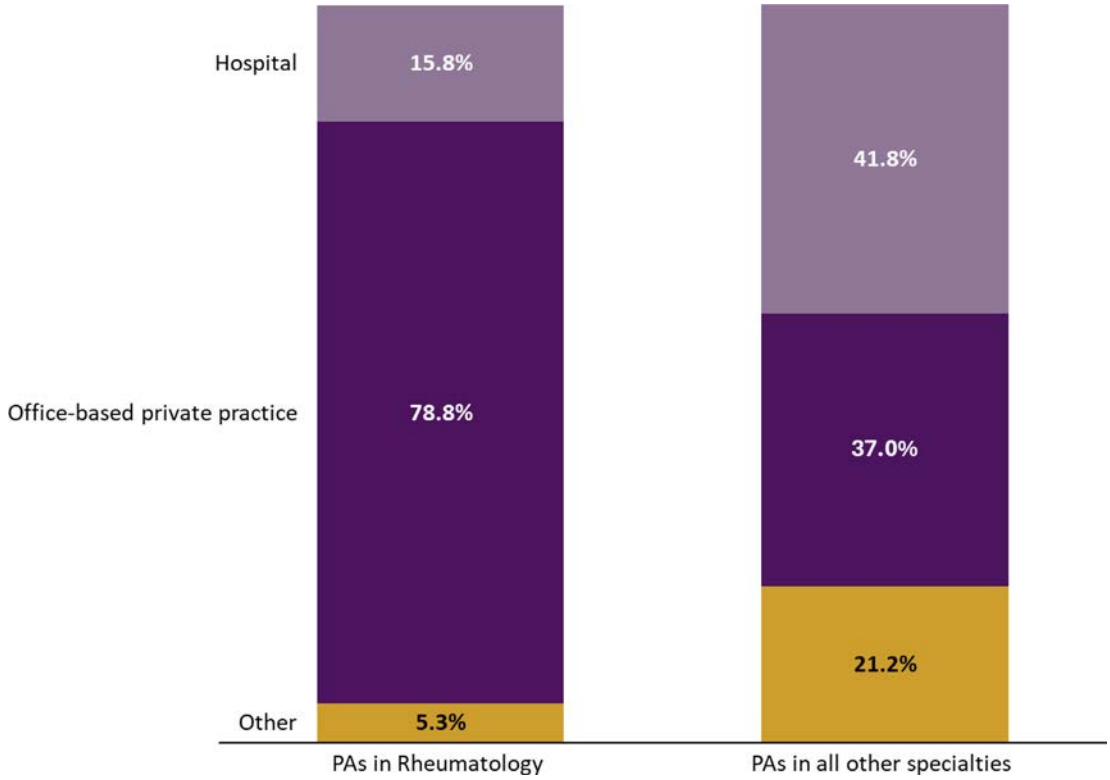

Figure 2. Employment setting of PAs in rheumatology compared to PAs in all other specialties. PA, physician assistant/associate. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25462/abstract.

60 and 61 to 80 patients each week (44.2%). Notably, all other PAs demonstrate a more distributed number of patients seen each week (Figure 3). Rheumatology PAs seeing numbers of patients in these midrange groupings is likely to be due, in part, to the level of complexity of patients with rheumatic disease. The number of hours worked weekly is comparable for PAs in rheumatology and PAs in all other specialties, equaling a median of 40 hours for both cohorts (P = 0.806). Additionally, 62.5% of PAs in rheumatology reported using telemedicine in their practice compared to 40.2% of those in other medical disciplines (P < 0.001).

When comparing self-reported income, PAs practicing in rheumatology reported a median income lower than that of PAs in all other specialties ($105,000 vs $115,000; P < 0.001; Figure 4). This finding of lower salary parallels salaries for rheumatologists compared to their physician colleagues who work in other medical specialties.[17] However, compared to PAs in all other medical and surgical disciplines, a higher percentage of

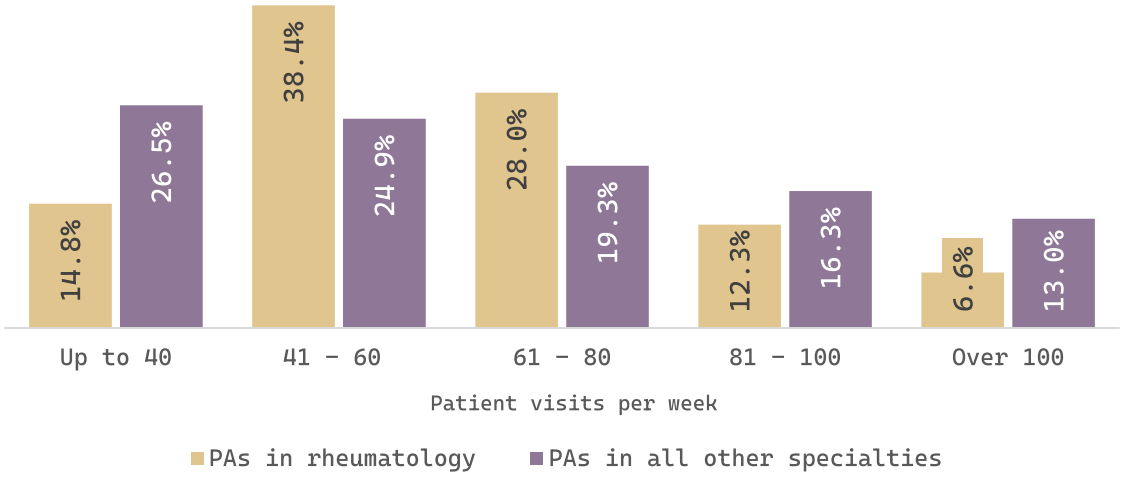

Figure 3. Number of patient visits seen weekly by PAs in rheumatology compared to PAs in all other specialties (P < 0.001). PA, physician assistant/associate. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25462/abstract.

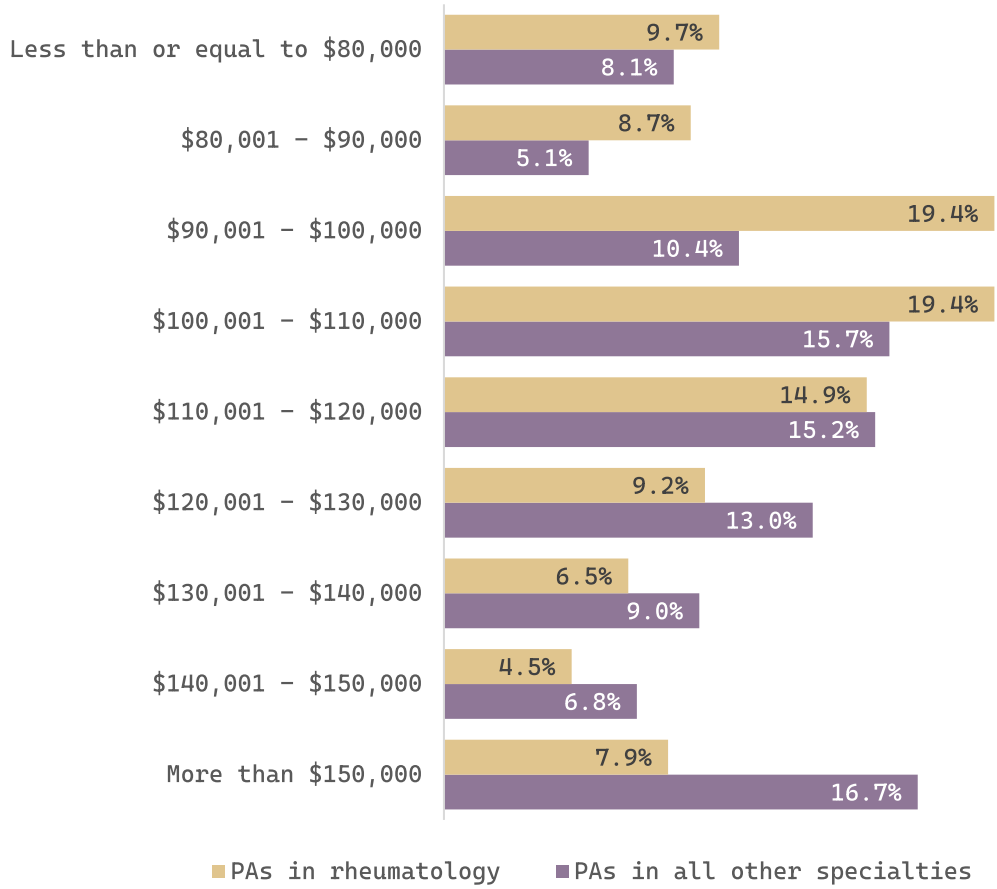

Figure 4. Salary of PAs in rheumatology and PAs in all other specialties ($P < 0.001$). PA, physician assistant/associate. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25462/abstract.

those practicing in rheumatology indicate slightly higher levels of job satisfaction (87.6% vs 83.6%; $P = 0.026$) and no symptoms of burnout (72.2% vs 67.8%; $P = 0.050$). Moreover, PAs in rheumatology were less likely to plan on leaving their position in the next year compared to those in other specialties (5.1% vs 8.7%; $P = 0.008$) (Figure 5).

DISCUSSION

Innovation is essential to bridge the supply and demand gap in the rheumatology health provider workforce needed to serve individuals with rheumatic conditions. PAs are part of a solution to fill this workforce supply and demand gap.[18] As the shortage of rheumatologists persists and the demand for rheumatic disease services increases,[19] the number of PAs specializing in rheumatology is increasing. A more recent study by Mannion and colleagues[20] found that from 2009 to 2020, the growth rate of PAs and NPs entering the rheumatology field increased by 141%.

Several notable observations are made from this study. As of 2022, 430 board-certified PAs work in rheumatology, indicating a 93.7% growth rate since 2015. PAs in rheumatology reside in urban regions, primarily provide care in office-based private practice settings, and actively participate in telemedicine. The majority distribution of PAs in urban locations mirrors previous reports of the distribution of rheumatologists.[21] Rheumatologists tend to practice in areas with higher population densities, thus leading to higher incomes when compared to all other rheumatologists and near rheumatology training programs.[21] With the need to provide rheumatology care in rural settings, innovative ideas should be considered to recruit PAs to more remote locations. One strategy emerged during the COVID-19 pandemic: to increase the use of virtual visits.[22] PAs in rheumatology have telemedicine experience; technology can be employed to increase access to more persons with rheumatic disease. A PA communicating with their collaborating physician as required by state statute, when needed, with technology provides an opportunity.

Rheumatology care delivery services occur primarily in ambulatory care and outpatient settings. Although some PAs in rheumatology have a role in hospital settings, the office-based private practice setting may appeal more to those seeking normative working hours. Moreover, PAs in rheumatology appear to be satisfied with their careers, which may be supported by reporting less burnout than their peers across all roles. Similar to their rheumatologist physician colleagues, initiatives should be considered and implemented to maintain low burnout and high job satisfaction levels for PAs who work in rheumatology.[23]

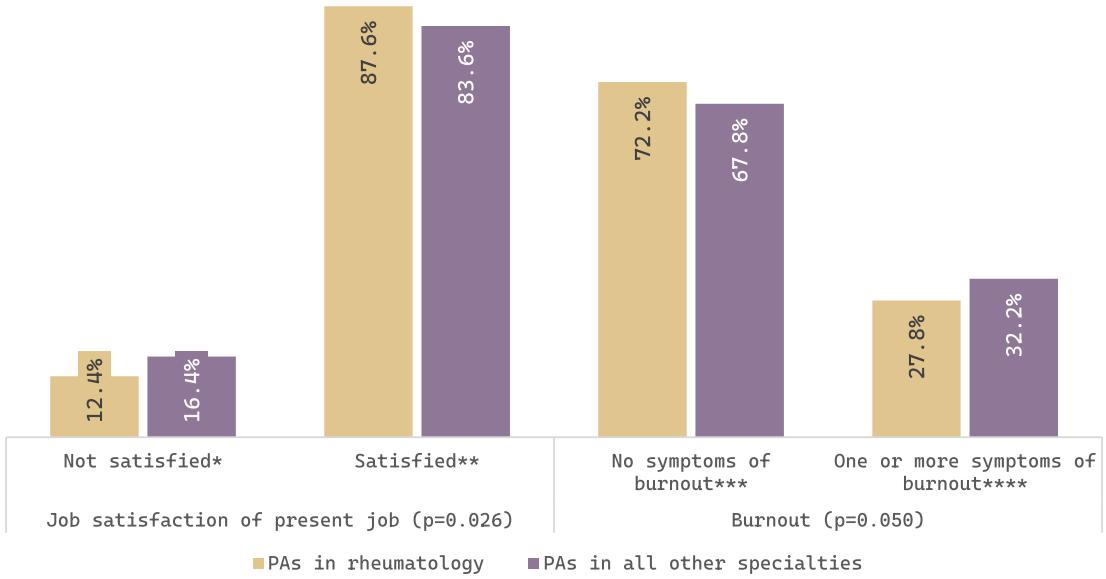

Figure 5. Job satisfaction and burnout of PAs in rheumatology compared to PAs in all other specialties. *Not satisfied includes "neither satisfied nor dissatisfied," "somewhat dissatisfied," "mostly dissatisfied," and "completely dissatisfied." **Satisfied includes "completely satisfied," "mostly satisfied," and "somewhat satisfied." ***No symptoms of burnout include "I enjoy my work, I have no symptoms of burnout," and "Occasionally, I am under stress, and I don't always have as much energy as I once did, but I don't feel burned out." ****One or more burnout symptoms include "I am definitely burning out and have one or more symptoms of burnout, such as physical and emotional exhaustion," "The symptoms of burnout that I'm experiencing won't go away. I think about frustration at work a lot," and "I feel completely burned out and often wonder if I can go on. I am at the point where I may need some changes or may need to seek some sort of help." PA, physician assistant/associate. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25462/abstract.

Rheumatology is recognized as a cognitive specialty that requires experience to understand the nuances of the conditions treated in this field. Tools exist to aid PAs who are new to rheumatology to get up to date as quickly as possible.[21] Recruiting, retaining, training, and supporting PAs throughout their careers in rheumatology must be a paramount priority, in parallel to similar activities for other rheumatology health care providers, to ensure the rheumatology workforce functions most efficiently and to the highest level of their training and licensure. Through their foundational medical education, PAs are prepared to contribute to the rheumatology team.[7] The Rheumatology Core Curriculum for NPs and PAs has been provided to guide those new to rheumatology.[24] The American College of Rheumatology also created the Advanced Rheumatology Course. This online, modular-based educational tool includes core, adult, and pediatric content for PAs and other health professionals that could be valuable to those beginning their rheumatology careers.

This study draws on the PA Professional Profile, a comprehensive national health professional data collection administered by the NCCPA. However, we acknowledge certain inherent limitations. This included the reliance on mostly self-reported data, which may introduce social desirability and recall biases. The PA Professional Profile is also voluntary, thus increasing the risk of incomplete responses. Despite these limitations, the response rate for the PA Professional Profile in 2022 was reported[10] at 83.7%. Moreover, comparisons of PA profile respondents with nonrespondents with available administrative data revealed no major differences in age, sex, and rural-urban setting.

Furthermore, a previous study using the PA Professional Profile validated the data by comparing the results with federal data.[25] There was overlap and similarity of the results in that study,[25] suggesting that the NCCPA data are reliable. At the same time, future research could expand the usefulness of the data by adjusting for covariates and comparing it with other federal- and state-based data.

Examining the demographic characteristics and employment settings of PAs in rheumatology is crucial to estimating the health workforce supply and demand in this discipline. Our analysis indicates that the supply of PAs in rheumatology is modest yet expanding. PAs in rheumatology predominantly identify as female, reside in urban locations, practice in office-based private settings, are more inclined to provide telemedicine services for their patients, and express high levels of employment satisfaction. PAs in rheumatology are increasing at a modest rate, thus suggesting a notable potential for PAs, although currently underused, to have a significant role and potential to positively affect the rheumatology workforce. Efforts to eliminate barriers for PAs to work in rheumatology practices are worthy and should be pursued. With this foundation, further research should explore the economics of PAs in clinical rheumatology, including aspects of teamwork, scope of practice, patient outcomes, and satisfaction.

AUTHOR CONTRIBUTIONS

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

Study conception and design. Smith, Hooker, Bruza-Augatis, Puckett, Kozikowski.

Acquisition of data. Bruza-Augatis, Puckett, Kozikowski.

Analysis and interpretation of data. Bruza-Augatis, Puckett, Kozikowski.

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Association Between 25-hydroxyvitamin D Levels and Adverse Pregnancy Outcomes in Systemic Lupus Erythematosus

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Objective. We evaluated the association of 25-hydroxyvitamin D (25(OH)D) levels with adverse pregnancy outcomes in systemic lupus erythematosus (SLE).

Methods. The Hopkins Lupus Cohort includes visits of pregnant patients, including assessment of 25(OH)D levels at each visit. We examined the relationship between 25(OH)D levels and adverse pregnancy outcomes (miscarriage, preterm delivery, and small for gestational age). We also used a time-to-event analysis to assess whether time-varying of 25(OH)D levels were associated with time to miscarriage or preterm delivery.

Results. In subgroups of patients defined by the average of 25(OH)D levels, we observed significantly different risks of miscarriage (P = 0.0045), preterm delivery (P = 0.0007), and the composite measure of all three adverse pregnancy outcomes (P = 0.011). The highest risks were observed among those with the lowest or highest levels of vitamin D. Nine of 10 pregnant patients with low vitamin D levels during the second trimester resulted in having a premature delivery. The time-to-event model confirmed the same U-shaped association after adjustment for SLE disease activity; however, the increased risk among those with highest levels of vitamin D was not statistically significant. Body mass index did not appear to be a confounding factor.

Conclusion. Our study is not able to prove causation, but the results strongly suggest an association of 25(OH)D at both lower and higher levels with adverse pregnancy outcomes. We recommend the monitoring of maternal serum 25(OH)D levels during SLE pregnancies, aiming for the ideal range of 40 to 59 ng/mL.

INTRODUCTION

Systemic lupus erythematosus (SLE) is associated with an increased risk of adverse pregnancy outcomes, including preterm delivery, preeclampsia, intrauterine growth restriction, and fetal loss.[1–12] Active disease, hypocomplementemia, anti–double-stranded DNA, previous nephritis or proteinuria occurring in the first 20 gestational weeks, gestational hypertension, low platelet count, and presence of lupus anticoagulant are potential risk factors.[4–6,13–23]

Vitamin D deficiency has been associated with adverse pregnancy outcomes in the general female population. The general population studies, however, vary in terms of the study population, the definition of preterm delivery, low birth weight, and the cutoff level and timing of the vitamin D measurements. Table 1 shows summarized results from some of the key studies, including meta-analyses, US case-control studies, and recent large East and South Asian studies in the general female population. One meta-analysis found an association with small for gestational age,[24] but the other meta-analysis[25] found an association with preterm delivery. The US case-control studies were negative, but one South Asian study found an association with preterm delivery.[26]

Vitamin D has important immunomodulatory properties. In vitro, vitamin D exerts an anti-inflammatory and antiproliferative effect by promoting a T helper 1 (tumor necrosis factor α [TNF-α], interleukin-2 [IL-2], and interferon-γ) to T helper 2 (IL-4, IL-5, IL-10, and GATA binding protein 3) polarization as well as T helper 17 (IL-12, IL-23, IL-6, and IL-17) to regulatory T cell (IL-10, transforming growth factor β, FoxP3, and CTLA-4) state.[27] It affects the

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SIGNIFICANCE & INNOVATIONS

- This is the first study on the role of 25-hydroxyvitamin D (25(OH)D) levels on outcomes in pregnant patients with lupus.
- We found that both low and high maternal 25(OH)D levels were associated with adverse pregnancy outcomes.
- Adverse pregnancy outcomes were lowest in patients with 25(OH)D levels of 40 to 59 ng/mL.

development and function of natural killer cells.[28] Vitamin D deficiency is associated with increased cellular and autoimmune abnormalities, including higher prevalence of antiphospholipid antibodies, antinuclear antibody, and anti–single-stranded DNA antibody, as well as a higher percentage of B cells, natural killer cells, and TNF-α–expressing T helper cells.[29,30]

There is an inverse relationship between body mass index and 25-hydroxyvitamin D (25(OH)D).[31] The response to vitamin D supplementation can be reduced with obesity.[32] Maternal obesity is known to be associated with obstetrical complications for the birthing parent and the child, as well as adverse pregnancy outcomes.[33,34]

Although the association between vitamin D deficiency and adverse pregnancy outcomes in the general female population has been extensively studied, the role of vitamin D in SLE pregnancy has not been previously studied, to our knowledge. Therefore, in this study, we evaluated 25(OH)D levels and adverse pregnancy outcomes in pregnant patients with SLE.

PATIENTS AND METHODS

Study design. The Hopkins Lupus Cohort includes patients with confirmed SLE classification based on the Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification criteria[35] living in the Baltimore (Maryland, United States) area and seen about every six weeks during pregnancy by protocol. The cohort was approved by the Johns Hopkins University School of Medicine Institutional Review Boards (PRN number NA_00039294). Patients' rights, safety, and well-being were protected based on the principles of the Declaration of Helsinki. All patients gave written informed consent. The participants' health and private data were kept confidential. The study protocol includes pregnancy outcomes and 25(OH)D levels since 2009.

All pregnant patients were prescribed prenatal multivitamins, which typically contain 400 IU (range 100–800) of vitamin D. Those with low vitamin D were supplemented with weekly vitamin D at 50,000 IU or daily at 1,000 to 5,000 IU as needed to achieve a 25(OH)D level of 40 ng/mL or higher, based on the longitudinal analysis of the Hopkins Lupus Cohort, which reported that a level of 40 ng/mL improved proteinuria and global lupus activity.[36]

Inclusion and exclusion criteria. Pregnancies occurring during cohort participation were excluded if there were no 25(OH)D level measures made during pregnancy, if the outcomes of pregnancies were missing (data on due date, birth date, gestational age, and/or complications of pregnancies), if the pregnancy was terminated, or if the pregnancy was not singleton.

Patients with SLE. The mean age at conception was 32 years (range 16–45 years). A total of 46% of the patients were White, 37% were Black, and 17% were other races. Mean SLE duration at conception was 8.6 years (range 0–24 years). Mean age at SLE diagnosis was 23.5 years (range 7–45 years). A total of 93% of patients had at least 12 years of education. A total of 2% of patients had diabetes, 32% had hypertension, 21% had ever smoked, 5% were current smokers, 28% were obese, 34% were taking immunosuppressive medications, 97% were taking hydroxychloroquine, 27% were taking prednisone with a mean daily prednisone dose of 3.5 mg/day, and 83% were taking vitamin D supplementation (in addition to prenatal vitamins) during pregnancy.

In terms of the prevalence of the SLICC classification criteria, 45% of patients had acute cutaneous lupus, 17% had chronic cutaneous lupus, 53% had lupus alopecia, 51% had oral or nasal ulcers, 64% had arthritis, 40% had serositis, 51% had lupus nephritis, 5% had neurologic involvement, 8% had hemolytic anemia, 61% had leukopenia or lymphopenia, 22% had thrombocytopenia, 97% had ANA, 68% had anti–double-stranded DNA, 33% had anti-Smith antibodies, 65% had low complement, and 57% had antiphospholipid antibodies. SLE disease activity was measured at each cohort visit using the Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI).[37] The mean SELENA-SLEDAI score before pregnancy was 2.5 (range 0–23), and the mean SELENA-SLEDAI score during pregnancy was 1.7 (range 0–18).

Pregnancies. There were a total of 298 pregnancies documented in the cohort database with a date of conception from January 2009 to June 2022. Of these, 7 were voluntarily terminated, 8 had missing information on gestational age, 10 were not singleton, and 13 had no measure of 25(OH)D levels in the cohort database. The analysis was based on the remaining 260 pregnancies.

Adverse pregnancy outcomes. Preterm delivery was defined as delivery earlier than gestational week 37. Miscarriage was defined as spontaneous loss of pregnancy before gestational week 20. Small for gestational age (SGA) was defined as less than or equal to 10% fetal growth percentile given sex, gestational age, and weight of the baby. Fetal growth percentiles were calculated using an online calculator (https://www.peditools.org/fenton2013/) based on the Fenton growth charts.[38] The composite adverse

Table 1. Summary of some previous studies on vitamin D and adverse pregnancy outcomes in the general population*

Study design	Reference study	Patient population	25(OH)D measure	Trimester of 25(OH)D measures	Outcome studied	Results
Meta-analysis of observational studies	Aghajafari et al[24] (2013)	–	Vit D of <15 or <32	Before or after week 16	SGA (six studies)	SGA pooled OR 1.85 (95% CI 1.52–2.26)
			Vit D <15		Birth weight (four studies)	Low birth weight random weighted mean difference −130.92 g (95% CI 186.69−75.14)
Meta-analysis of longitudinal studies	Amegah et al[25] (2017)		Vit D <30		Preterm birth at <32–34 weeks (two studies)	Summary RR 1.83 (95% CI 1.23–2.74)
					Preterm birth at <35–37 weeks (seven studies)	Summary RR 1.13 (95% CI 0.94–1.36)
			Vit D <20		Preterm birth at <32–34 weeks (two studies)	Summary RR 1.86 (95% CI 1.28–2.68)
					Preterm birth at <35–37 weeks (four studies)	Summary RR 1.36 (95% CI 1.04–1.78)
			Vit D <30	First trimester	Miscarriage at <20 weeks (three studies)	Summary RR 1.04 (95% CI 0.95–1.13)
			Vit D <30	First or second trimester	Stillbirth at >20 weeks (two studies)	Summary RR 1.02 (95% CI 0.96–1.09)
Nested case-control, United States	Thorp et al[40] (2012)	131 pregnancies with a history of preterm delivery vs 134 controls	Vit D	At weeks 16–22	Preterm birth at <37 weeks or <32 weeks	OR 1.33 (95% CI 0.48–3.70) for lowest vs highest quartile
			Vit D in a subset of 80 cases and 88 controls	At weeks 25–28		Full data not presented in the article
Nested case-control, United States	Baker et al[41] (2011)	40 cases of preterm delivery between weeks 23 and 34 vs 120 controls delivering at >37 weeks	Vit D <20	First trimester	Preterm birth	7.5% vs 6.7%
Nested case-control, Bangladesh	Tahsin et al[26] (2023)	262 cases of preterm birth vs 668 controls	Vit D <12	At weeks 24–28	Preterm birth at week <37	Adjusted OR 1.53 (95% CI 1.10–2.12)
Mendelian randomization, China	Cheng et al[42] (2023)	187 cases of preterm birth vs 3,219 controls	Vit D <20	First trimester Second trimester Third trimester	Preterm birth at week <37	OR 1.00 (95% CI 0.96–1.05) OR 1.01 (95% CI 0.97–1.06) OR 1.01 (95% CI 0.99–1.03)

* 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; OR, odds ratio; RR, relative risk; SGA, small for gestational age; Vit D, vitamin D.

pregnancy outcome was defined as the occurrence of miscarriage, premature delivery, or SGA.

Measurements. The 25(OH)D levels were measured by chemiluminescence immunoassay at each cohort visit during each pregnancy. We evaluated lupus anticoagulant[39] and anticardiolipin during the first trimester of pregnancies. A positive lupus anticoagulant test was defined by the Russell viper venom time ≥45 seconds with mixing and confirmatory testing. A positive anticardiolipin was defined by either IgG, IgM, or IgA level ≥20 standard units. The body mass index was calculated based on the weight observed in the cohort visit within one year preceding the date of conception when available (n = 193), or alternatively if not available, within the first trimester (n = 27). A total of 220 patients with body mass index measurements were included in the analysis. Race was self-reported by choosing from a fixed set of categories.

Statistical analysis (tests used and adjustment). We examined the risks of adverse pregnancy outcomes in subgroups defined by average vitamin D levels during each pregnancy. To assess the statistical significance of observed differences, we used generalized estimating equations to account for the correlation between repeated pregnancies from the same patients. In some analyses, because of the small number of outcomes, we used Fisher's exact test to assess statistical significance. In addition, we fit a Cox proportional hazards model in which the event was time until either miscarriage or preterm delivery, full-term pregnancies were censored, and the independent variables were the most recent past vitamin D level and potential confounders (SLE disease activity, race, and renal disease activity).

RESULTS

Among the 260 pregnancies, 128 women had one pregnancy, 41 had two pregnancies, 10 had three pregnancies, and 5 had four pregnancies. Overall, 118 (45.3%) had an adverse pregnancy outcome.

Table 2 shows the adverse pregnancy outcomes in pregnancies with different mean 25(OH)D levels during pregnancy. In general, the risk of adverse pregnancy outcomes was highest among those with relatively low or relatively high 25(OH)D levels. All 11 (100%) of those with mean 25(OH)D less than 20 ng/mL resulted in either a miscarriage or a preterm delivery. Figure 1 shows the U-shaped curve association between vitamin D level and all adverse pregnancy outcomes.

In additional analyses, we examined the relationship between pregnancy outcomes and 25(OH)D measured in either the first trimester (Supplement Table 1) or second trimester (Supplement Table 2). Although we did not observe a strong relationship between first trimester 25(OH)D and pregnancy outcomes, 25(OH)D levels during the second trimester were strongly related to premature delivery. Specifically, 9 of 10 pregnancies with low 25(OH)D levels measured during the second trimester resulted in a premature delivery.

To address whether the observed relationship between adverse outcomes and 25(OH)D might have been due to confounding by race (because Black race is associated with lower 25(OH)D levels), we examined the relationship by self-identified race. The results are in Table 3. Although there is some variability, possibly because of small numbers in some subgroups, within each stratum we observed similar patterns of increased risk among those in the lowest and highest vitamin D groups.

Similarly, we examined the association between vitamin D and pregnancy outcomes in strata defined by a history of antiphospholipid antibodies (Table 4). Again, similar patterns were observed in each stratum.

Table 5 shows the results of the proportional hazard model showing the hazard ratios of miscarriage or preterm delivery in subgroups defined by the most recent past 25(OH)D measured during pregnancy, SELENA-SLEDAI, lupus nephritis, and race adjusting for the other variables in the table. We observed elevated risk of miscarriage or preterm delivery by 1.34 to 3.35–fold among those with low and high 25(OH)D, relative to those with

Table 2. Adverse pregnancy outcomes by mean 25(OH)D during pregnancy*

Mean 25(OH)D during pregnancy, ng/mL	Miscarriage, n (%)[a]	Preterm delivery, n (%)[b]	SGA, n (%)[c]	Miscarriage, preterm delivery, or SGA, n (%)[d]
<20 (n = 11)	4 (36)	7 (100)	4 (57)	11 (100)
20–29 (n = 45)	9 (20)	14 (39)	6 (17)	26 (58)
30–39 (n = 72)	9 (13)	21 (33)	8 (13)	33 (45)
40–49 (n = 80)	4 (5)	15 (20)	9 (12)	24 (29)
50–59 (n = 26)	2 (8)	6 (25)	4 (17)	8 (31)
60+ (n = 17)	5 (29)	4 (33)	2 (17)	11 (61)

* 25(OH)D, 25-hydroxyvitamin D; SGA, small for gestational age.
[a] $P = 0.0045$ based on a Fisher's exact test.
[b] $P = 0.0007$ based on a Fisher's exact test (among those without a miscarriage).
[c] $P = 0.11$ based on a Fisher's exact test (among those without a miscarriage).
[d] $P = 0.011$ based on a generalized estimating equation model, pooling the groups with vitamin D levels below 30 ng/mL.

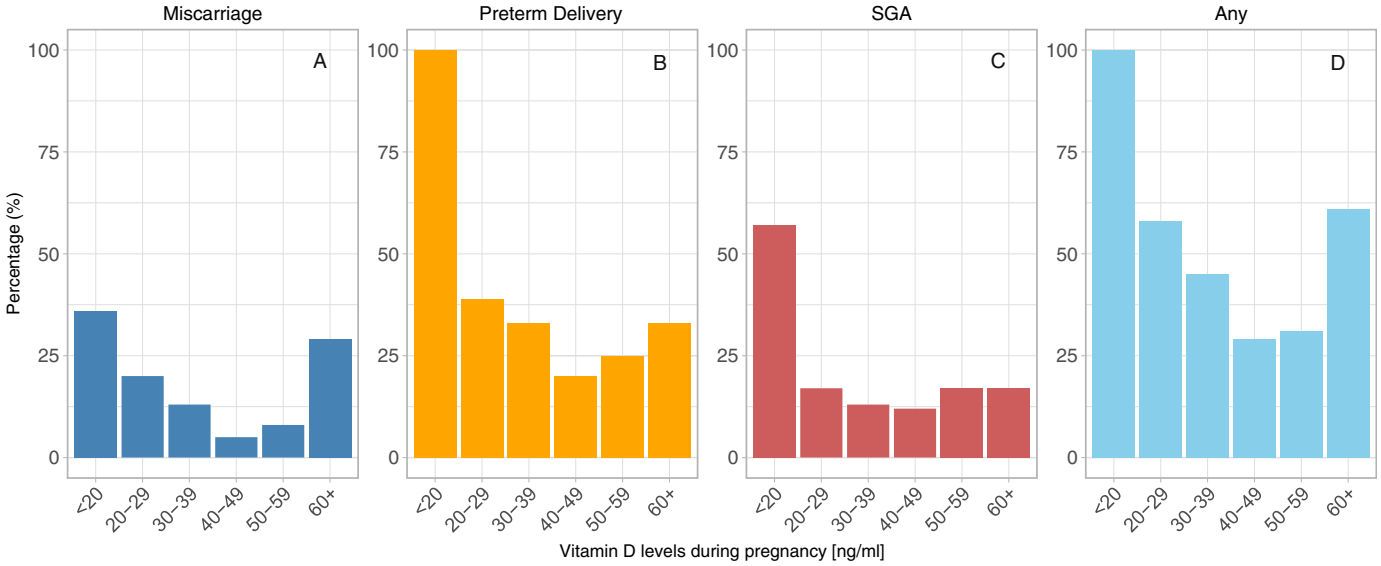

Figure 1. Adverse pregnancy outcomes occurrence (%) by 25-hydroxyvitamin D levels during pregnancy. (A) Miscarriage; (B) preterm delivery; (C) SGA; (D) miscarriage, preterm delivery, or SGA. SGA, small for gestational age.

25(OH)D in the range of 40 to 59 ng/mL. SELENA-SLEDAI score >4 was associated with a 3.32-fold higher risk of miscarriage or preterm delivery compared to those with SELENA-SLEDAI score <1. Patients with races other than White were at a 1.93-fold higher risk of miscarriage or preterm delivery.

We looked at body mass index as a potential cofounder (Supplement Table 3). Prepregnancy body mass index was unknown in 26% of the patients because their first cohort visit occurred during pregnancy. We examined the relationship between 25(OH)D levels and body mass index in the available sample and found no association. Using the available data, the U-shaped association between the 25(OH)D level and adverse pregnancy outcomes was still apparent (but weaker) after adjusting for the body mass index.

DISCUSSION

We found a U-shaped association between maternal 25(OH)D and the risk of miscarriage, preterm delivery, and combined adverse pregnancy outcomes in SLE. The risk of adverse pregnancy outcomes was lowest with a 25(OH)D level in the range of 40 to 59 ng/mL and highest with both lower and higher 25(OH)D levels. The strongest association that we observed was between second trimester vitamin D levels and premature delivery.

The association of low 25(OH)D levels with adverse pregnancy outcomes has been suggested in some meta-analyses and case-control studies,[24–26] but not confirmed in others[40–42] in the general female population. To the best of our knowledge, 25(OH)D levels have not been previously studied serially in lupus

Table 3. Adverse pregnancy outcomes by 25(OH)D levels in strata defined by race*

Mean 25(OH)D during pregnancy, ng/mL	Miscarriage, preterm delivery, or SGA		
	White patients, proportion (%)[a]	Black patients, proportion (%)[b]	Other patients, proportion (%)[c]
<20	0/0	8/8 (100)	3/3 (100)
20–29	8/18 (44)	14/20 (70)	4/7 (57)
30–39	11/35 (31)	14/27 (52)	7/10 (70)
40–49	9/43 (21)	10/23 (43)	7/14 (50)
50–59	3/16 (19)	5/6 (83)	3/4 (75)
60+	4/7 (57)	3/5 (67)	4/5 (80)

* 25(OH)D, 25-hydroxyvitamin D; SGA, small for gestational age.
[a] $P = 0.34$ based on a generalized estimating equation model.
[b] $P = 0.059$ based on a generalized estimating equation model pooling those with vitamin D less than 30 ng/mL.
[c] $P = 0.81$ based on a generalized estimating equation model pooling those with vitamin D less than 30 ng/mL.

Table 4. Adverse pregnancy outcomes by 25(OH)D levels in strata defined by history of antiphospholipid antibodies*

Mean 25(OH)D during pregnancy, ng/mL	Miscarriage, premature delivery, or SGA	
	No history of anticardiolipin or lupus anticoagulant, proportion (%)[a]	History of anticardiolipin or lupus anticoagulant, proportion (%)[b]
<20	6/6 (100)	5/5 (100)
20–29	14/21 (67)	12/24 (50)
30–39	14/30 (47)	18/42 (43)
40–49	15/37 (41)	11/43 (46)
50–59	2/5 (40)	9/21 (43)
60+	4/6 (67)	7/11 (64)

* 25(OH)D, 25-hydroxyvitamin D; SGA, small for gestational age.
[a] $P = 0.12$ based on a generalized estimating equation model pooling those with vitamin D less than 30 ng/mL.
[b] $P = 0.14$ based on a generalized estimating equation model pooling those with vitamin D less than 30 ng/mL.

Table 5. Variables associated with miscarriage or preterm delivery based on a proportional hazard model*

Variable	Comparison	Unadjusted hazard ratio (95% CI)	*P* value	Adjusted hazard ratio[a] (95% CI)	*P* value
Most recent past 25(OH)D levels (ng/mL)	<20 vs 40–60	5.25 (2.63–10.50)	<0.0001	3.35 (1.64–6.80)	0.0009
	20–30 vs 40–60	2.02 (1.11–3.67)	0.022	1.53 (0.84–2.80)	0.17
	30–40 vs 40–60	1.64 (0.99–2.73)	0.055	1.51 (0.91–2.51)	0.11
	60+ vs 40–60	1.60 (0.82–3.12)	0.17	1.34 (0.69–2.62)	0.39
SELENA-SLEDAI	2–3 vs 0–1	1.75 (1.03–2.95)	0.037	1.68 (0.96–3.00)	0.070
	4+ vs 0–1	3.89 (2.52–6.00)	<0.0001	3.32 (1.94–5.68)	<0.0001
Renal activity	Yes vs no	3.18 (1.83–5.52)	<0.0001	1.27 (0.67–2.41)	0.46
Race	Non-White patients vs White patients	2.80 (1.82–4.29)	<0.0001	1.93 (1.21–3.09)	0.0060

* 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index.
[a] Adjusted for the other variables on this table.

pregnancies, and the effect of high 25(OH)D levels have not been previously studied in the general female population. We are not able to explain the U-shaped curve. We hypothesize that at higher levels, vitamin D can recruit different immunologic networks leading to the increased risk of adverse pregnancy outcomes or a negative impact on calcium-related placental pathways. A similar U-shaped curve has been observed for vitamin D and cardiovascular events in chronic kidney disease.[43]

This was not a strict study of natural 25(OH)D levels because most patients received supplementation (at a minimum prenatal vitamins). Most patients with SLE are vitamin D deficient or insufficient. The role of vitamin D supplementation in general female pregnancy has been studied. The results of these studies are contradictory. The studies have significant variability in the timing and the dose of intervention, the goal of the 25(OH)D level, and different outcomes studied. A meta-analysis of 13 randomized clinical trials (n = 2,299) in 2015 found vitamin D supplementation was associated with higher birth weight and birth length, but not with improvement in other outcomes.[44] Initially, the World Health Organization in 2016 recommended against vitamin D supplementation for pregnant patients to improve maternal and perinatal outcomes.[45]

A meta-analysis of 43 trials (n = 8,406) in 2017 did report a benefit of vitamin D supplementation on birth weight and risk of SGA (but not preterm birth). The findings, however, were not robust in sensitivity, and subgroup analyses were based on mostly small, low-quality studies. The authors therefore concluded that the evidence was insufficient to guide clinical or policy recommendations.[46]

A 2019 Cochrane systematic review that included 30 trials (n = 7,033) found that vitamin D supplementation reduced the risk of preeclampsia, gestational diabetes, and low birth weight but made little or no difference in the risk of preterm birth. The quality of the studies ranged from moderate to very low.[47] A review article in 2020 discussed five high-quality masked randomized clinical trials that each included at least 500 enrolled women. None of these five trials demonstrated a beneficial effect of vitamin D supplementation on pregnancy outcomes. However, there was benefit in some subgroup analyses and longer-term follow-up studies.[48] A review of 13 systematic reviews (including 204 primary studies) in 2020 found better pregnancy outcomes in the longitudinal studies. The randomized clinical trials showed benefit only on small for gestational weight, not on other pregnancy outcomes. The overall quality of the studies was low.[49]

Based on the updated evidence, the World Health Organization revised its recommendation in 2020. Although it did not recommend oral vitamin D supplementation for all pregnant patients to improve maternal and perinatal outcomes, it recommended that vitamin D supplementation could be given to pregnant patients with suspected vitamin D deficiency. It also recommended advising pregnant patients that sunlight was the most important source of vitamin D.[50] Obviously, this is not an option for patients with SLE.

Levels of 25(OH)D are low in patients with SLE at the time of diagnosis.[51] Our analysis dealt with the actual 25(OH)D level, regardless of the source. Sources of vitamin D in our patients with SLE could include some UV sun exposure, dietary sources, prenatal vitamins, and additional supplementation. A 25(OH)D level greater than 60 ng/mL was likely due to oversupplementation. These higher levels were not due to biotin, as we avoid biotin administration (because it interferes with the vitamin D assay). Based on our results, we recommend measurement of 25(OH)D in pregnancy (both the first and second trimester), not just to achieve the ideal level, but to avoid oversupplementation. Oversupplementation was likely more common in adherent patients (who then, unfortunately, had more adverse pregnancy outcomes). This contrasts with our previously published analysis of the benefits of 25(OH)D supplementation, in which we showed that although the benefit on proteinuria plateaued at 25(OH)D level of 40 ng/mL, there was no adverse effect of higher levels.[36]

We found an association between the 25(OH)D levels and adverse pregnancy outcomes, including preterm delivery in SLE, but a cause-and-effect relationship cannot be proven. It is possible that low vitamin D levels could simply be a marker for generally poor prenatal health behaviors that could have confounded the results. In addition, the small number of pregnancies also led to

instability in some of the analyses. We could not adjust for parity because the parity of the index pregnancy was not known. Finally, the analysis included clinically identified pregnancies. Chemical pregnancies and very early miscarriages not known to the patient would have been missed. However, despite these limitations, the conclusions of our analyses clearly contradict the recommendations of the Endocrine Society Clinical Review Guidelines[52] that support "empiric vitamin D supplementations during pregnancies, given its potential to lower risk of pre-eclampsia, intra-uterine mortality, preterm birth, SGA birth and neonatal mortality." In pregnant patients with SLE, a vitamin D replacement should be targeted to the 25(OH)D level range from 40 to 59 ng/mL because both high and low levels are a concern.

Based on our findings, we recommend the monitoring of maternal serum 25(OH)D levels throughout SLE pregnancies and supplementing patients with vitamin D insufficiency or deficiency aiming for a 25(OH)D level range from 40 to 59 ng/mL. Oversupplementation should be avoided.

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AUTHOR CONTRIBUTIONS

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

Study conception and design. Madanchi, Fava, Goldman, Magder, Petri.

Acquisition of data. Madanchi, Goldman, Petri.

Analysis and interpretation of data. Madanchi, Fava, Magder, Petri.

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Limitations in Activities of Daily Living Among Individuals With Systemic Lupus Erythematosus

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Objective. We aimed to estimate the burden and identify potential correlates of limitations in activities of daily living (ADLs) among persons with systemic lupus erythematosus (SLE).

Methods. Individuals with SLE were recruited from a population-based cohort (October 2019 to May 2022) and reported their ability to independently perform various instrumental ADLs (IADLs) and basic ADLs (BADLs) via survey. Limitations were defined as having at least some difficulty performing at least one of the IADLs or BADLs. Descriptive statistics were calculated, and associations (adjusted odds ratios [aORs]) of various participant characteristics with IADL and BADL limitations were assessed with logistic regression adjusting for age, sex, and race.

Results. The mean age of the 436 participants was 46.2 years; most were female (91.7%) and Black (82.8%). More than half (56.2%) reported limitations in IADLs, most commonly housekeeping (50.7%), laundry (37.2%), and shopping (33.0%); 43.8% reported limitations in independently performing BADLs, most commonly transferring (26.6%), bathing (25.3%), dressing (24.4%), and continence (22.0%). Higher disease activity (greater than or equal to vs less than the median) was strongly associated with IADLs (aOR 6.49, 95% confidence interval [CI] 4.15–10.2) and BADLs (aOR 7.35, 95% CI 4.70–11.5), along with higher depression and perceived stress scores, lower educational attainment and income, and older age.

Conclusion. IADL and BADL limitations may be common in individuals with SLE and more prevalent among those who report higher disease activity, depressive symptoms, and lower income and among those who are older. Research to support evidence-based strategies for improvement in quality of life and maintenance of independence in the older SLE population is warranted.

INTRODUCTION

With increasing life expectancy among those with systemic lupus erythematosus (SLE),[1] a primary goal of SLE care providers should be maintaining patient independence among their patients as they age. To address this, we first need to understand the current state of limitations in the essential, routine tasks known as activities of daily living (ADLs) among an adult population with SLE and the factors associated with these limitations. ADLs include instrumental ADLs (IADLs), which meet personal needs for independent community living (eg, food preparation and household chores),[2] and basic ADLs (BADLs), which meet basic personal physical needs (eg, bathing and dressing)[3]; limitations in either can lead to poor quality of life and loss of independence.

ADL limitations are most frequently associated with older populations. However, in 2019, 6% of US adults aged 18 to 64 years reported a lot of difficulty or inability to perform in at least one functional domain, and these limitations were more common among those who were Black (7%) or living below the poverty level (15%).[4] Further, for those with chronic conditions, such as arthritis, the prevalence of ADL limitations can be much higher, regardless of age.[5] Given that SLE is a complex, chronic, and

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SIGNIFICANCE & INNOVATIONS

- Maintaining patients' independence should be a priority for systemic lupus erythematosus (SLE) care providers who treat increasing numbers of older patients with SLE.
- We sought to understand the current state of activity limitations among an adult population with SLE and the factors associated with these limitations by exploring instrumental activities of daily living (IADLs; or tasks to support independent community living) and basic activities of daily living (BADLs; or tasks to support personal care) among a population-based cohort of primarily Black and female adults with SLE.
- We found that IADL and BADL limitations were common (56% and 44% reporting at least some difficulty, respectively) and that these limitations were more likely among those who were older and those who reported higher disease activity, depressive symptoms, and lower income.
- Future research to develop and implement targeted interventions to maintain independence among individuals with SLE as they age is warranted.

heterogeneous disease that disproportionately affects the underserved and socioeconomically disadvantaged, understanding the prevalence of and factors associated with IADL and BADL limitations in these patients is even more important for maximizing independence and minimizing disability.

Although there is some evidence suggesting that ADL limitations may be highly prevalent in individuals with SLE,[6,7] less is known about the specific measures of IADLs and BADLs in individuals with SLE. To address this gap, we sought to characterize the burden and correlates of limitations in IADLs and BADLs in a population-based cohort of individuals with SLE.

PATIENTS AND METHODS

Study population and data sources. The Approaches to Positive, Patient-Centered Experiences of Aging with Lupus (APPEAL) study recruited participants with validated SLE[8] from the population-based Georgians Organized Against Lupus (GOAL) cohort in metropolitan Atlanta[9,10]; exclusion criteria were being inactive in GOAL, being unable to speak English, having insufficient vision and hearing to undergo study testing, being unable to consent, or living outside Georgia at the time of recruitment. The Emory Institutional Review Board approved the APPEAL (IRB00110977) and GOAL (IRB00003656) study protocols. APPEAL participants provided informed consent before completing study visits.

A total of 451 participants completed the APPEAL study visit between October 8, 2019, and May 12, 2022. For this analysis, we excluded participants whose overall survey response patterns were potentially invalid (n = 4) or who did not have complete IADL and BADL assessments (n = 11). Study data were obtained from performance tests and self-administered questionnaires and additionally linked to data from the GOAL survey closest to the APPEAL visit date.

Variables. *Limitations in ADLs.* Participants were asked about their limitations in the following IADLs[2]: using the phone, shopping, food preparation, housekeeping, laundry, transportation, managing medications, and managing finances (Table 1). BADLs[3] assessed included bathing, dressing, toileting, transferring, feeding, and continence (Table 1). For primary analyses, IADL and BADL limitations were defined as any difficulty (some or more difficulty) versus no difficulty performing at least one of the IADL and BADL tasks independently.

Other variables. Sociodemographics included age, sex (at birth), race, ethnicity, and education, all self-reported by the participant via the National Institutes of Health (NIH) Toolbox from a fixed set of categories. Race was categorized as Black (single or multiple race), other, and White. Education was the highest level attained and categorized as high school graduate or high school equivalency or lower, some college or associate's degree, and college graduate or higher. Current working status was assessed with the Work Productivity and Activity Impairment

Table 1. Study assessment of BADLs and IADLs*

Domain/ measure	Wording of item
Overall question	How much difficulty do you have doing the following activities on your own?
Possible responses	No difficulty
	Some difficulty
	A lot of difficulty
	Unable to do
	Could do it, but don't[a]
	Don't know or refuse[b]
IADLs	
Phone	Using the phone
Shopping	Shopping
Food	Preparing food
Housekeeping	Housekeeping
Laundry	Laundry
Transportation	Traveling (car, taxi, public transportation)
Medications	Managing your medications
Finances	Managing your finances
BADLs	
Bathing	Bathing or showering
Dressing	Getting dressed
Toileting	Using the toilet
Transferring	Moving in and out of bed and chairs
Feeding	Feeding yourself
Continence	Controlling your bowel and/or bladder

* BADL, basic activity of daily living; IADL, instrumental activity of daily living.
[a] Treated as "no difficulty."
[b] Treated as missing.

Questionnaire.[11–13] Current income (categorized as <$20,000, $20,000–$59,999, and ≥$60,000), receipt of Social Security disability benefits, and disease duration (adjusted for the date of the APPEAL visit) were self-reported at the closest GOAL assessment. Current SLE activity was assessed via the Systematic Lupus Activity Questionnaire (SLAQ; range 0–44; higher scores indicate greater SLE-related disease activity).[14] The Brief Index of Lupus Damage (BILD) score (range 0–46; higher scores indicate greater cumulative SLE-related organ damage)[15,16] was obtained from linked GOAL data. Cumulative damage to individual systems was defined by BILD items, as were comorbid heart, cerebrovascular, and pulmonary disease. Currently taking steroids was self-reported by the participant at the study visit. Body mass index (BMI) was calculated from height and weight; obesity was defined as BMI ≥ 30. Physical activity was assessed with the International Physical Activity Questionnaire Short Form.[17] Depressive symptoms were assessed via the validated 8-item Patient-Reported Outcomes Measurement Information System (PROMIS) depression short form 8a (T scores; mean 50, SD 10).[18,19] Finally, perceived stress was assessed using the 10-item Perceived Stress Scale (range 0–40; higher scores indicate greater perceived stress).[20,21] Other potential indicators of disability included the following: physical performance (Short Physical Performance Battery [range 0–12; higher scores indicate better performance])[22,23]; physical functioning T score (PROMIS physical functioning short form 12a [mean 50, SD 10; higher scores indicate better functioning])[24]; composite age-corrected standard fluid cognition score (NIH Toolbox Fluid Cognition Battery [mean 100, SD 15; higher scores indicate better performance])[25–28]; and community mobility score (University of Alabama at Birmingham Study of Aging Life-Space Assessment [range 0–120; higher scores indicate greater community mobility]).[29]

Statistical analysis. Characteristics of participants were described overall, and percentages with limitations in IADLs and BADLs were described overall and by selected participant characteristics. Patterns in limitations were explored using Venn diagrams and UpSet plots. Adjusted odds ratios (aORs) for associations of any limitation in IADLs or BADLs with selected characteristics were obtained with multivariable logistic regression, adjusting for demographics (age, sex, and race). In sensitivity and additional analyses, we explored the following: (1) associations of IADL and BADL limitations with characteristics, with additional adjustment for socioeconomic indicators (education and income), SLE-related factors (SLAQ and BILD scores), and comorbid conditions (heart, cerebrovascular, and pulmonary disease); (2) associations of IADL and BADL limitations with characteristics among subgroups of those not receiving disability benefits, those who were Black, and those who were White; (3) associations of IADL and BADL limitations with individual disease damage domains; (4) number of limitations in IADLs and BADLs, defined as the number of individual tasks in which individuals reported at least some difficulty; (5) severe limitations in IADLs and BADLs, defined as reporting a lot of difficulty with or being unable to do at least one of the IADL or BADL tasks; and (6) limitations in individual IADL and BADL tasks. Complete case analysis was used. All analyses (statistical significance threshold of 0.05) were conducted using Stata v. 18.5.

RESULTS

Characteristics of study participants. Study participants (N = 436) had a mean age of 46.2 years; 41.3% were ≥50 years old (Table 2). Most were female (91.7%), Black (82.8%), and non-Hispanic (94.5%). About one-quarter (23.4%) had a high school diploma or less, and 35.2% had an annual household income of less than $20,000. Nearly half (44.9%) reported receiving disability benefits. The median duration of SLE was 14.8 years, with median SLAQ and BILD scores of 11 and 2, respectively. Cumulative SLE damage was most frequently reported for the ocular (30.7%), cardiovascular (24.3%), and peripheral vascular and musculoskeletal (19.7% each) systems. About half (47.5%) had obesity, and 73.7% reported low physical activity (Table 2).

Reported limitations in ADLs among individuals with SLE. More than half reported at least some limitations in at least one IADL (n = 245, 56.2%), whereas 43.8% (n = 191) reported at least some limitations in at least one BADL. Most individuals (79.4%) were concordant in their limitations: 39.6% reported no limitations in either IADLs or BADLs, and 39.6% reported limitations in both; however, 16.6% had IADL limitations without BADL limitations, and 4.2% had BADL limitations without IADL limitations (Figure 1).

Overall, 43.8%, 9.4%, 9.6%, and 37.2% had limitations in zero, one, two, or three or more IADL tasks, respectively (Figure 2). Among those with any IADL limitations, 16.7%, 17.1%, and 66.2% had limitations in one, two, or three or more tasks, respectively. For BADLs, 56.2%, 16.5%, 7.6%, and 19.7% had limitations in zero, one, two, or three or more tasks, respectively (Figure 2); for those with any BADL limitations, 37.7%, 17.3%, and 45.0% had limitations in one, two, or three or more tasks, respectively. The numbers of IADL and BADL limitations were strongly positively correlated with each other ($\rho = 0.74$) and strongly negatively correlated with physical functioning ($\rho = -0.70$ for IADL limitations, and $\rho = -0.64$ for BADL limitations), whereas correlations of these limitations with physical and cognitive performance, receipt of disability benefits, and community mobility were low to moderate (Supplementary Table 1). Severe limitations (a lot of difficulty with or inability to do any of the tasks) in IADLs and BADLs were seen in 16.3% and 7.8%, respectively, and severe limitations in both IADLs and BADLs were seen in 5.3%.

The prevalence of ADL limitations varied widely by individual task. Among the IADLs (Figure 3A), limitation prevalence ranged from 2.5% (using the phone) to 50.7% (housekeeping); about one-third each reported limitations in shopping (33.0%) and doing laundry (37.2%). Among the BADLs (Figure 3B), limitation prevalence ranged from 2.8% (feeding) to 26.6% (transferring); about one-quarter each reported limitations in bathing (25.3%), dressing (24.4%), and continence (22.0%). Most with limitations reported some difficulty for each of the tasks (Figure 3). The most common patterns of limitations among those with any IADL limitations were in housekeeping only (11.8%) and in housekeeping, preparing food, shopping, doing laundry, and transportation (11.8%) (Supplementary Figure 1A). The most common patterns of limitations among those with any BADL limitations were in continence only (19.4%) and in bathing, dressing, toileting, and transferring (10.5%) (Supplementary Figure 1B).

Table 2. Selected characteristics of study participants with systemic lupus erythematosus*

Characteristic	Value
Sociodemographic	
Age, mean (SD), y	46.2 (11.8)
Age category, n (%)	
18–34 y	88 (20.2)
35–49 y	168 (38.5)
≥50 y	180 (41.3)
Sex,[a] n (%)	
Female	400 (91.7)
Male	36 (8.3)
Race, n (%)	
Black	361 (82.8)
Other	51 (11.7)
White	24 (5.5)
Hispanic ethnicity, n (%)	
Hispanic	24 (5.5)
Not Hispanic	411 (94.5)
Level of education completed, n (%)	
High school diploma or less	102 (23.4)
Some college/associate's degree	164 (37.6)
College graduate or higher	170 (39.0)
Currently working, n (%)[b]	
No	221 (52.1)
Yes	203 (47.9)
Annual household income, n (%)	
<$20,000	149 (35.2)
$20,000–$59,999	168 (74.9)
≥$60,000	106 (25.1)
Receiving disability benefits,[c] n (%)	
Yes	194 (44.9)
No	238 (55.1)
Clinical	
Disease duration, median (IQR), y	14.8 (9.2–22.3)
SLAQ score, median (IQR)	11 (6–16)
BILD score,[c] median (IQR)	2 (1–4)
Cumulative system damage (from BILD[c]), n (%)	
Ocular	134 (30.7)
Neuropsychiatric	74 (17.0)
Renal	37 (8.5)
Pulmonary	66 (15.1)
Cardiovascular	106 (24.3)
Peripheral vascular	73 (19.7)
Gastrointestinal	103 (23.6)
Musculoskeletal	86 (19.7)
Dermatologic	36 (8.3)
Currently taking steroids, n (%)	
Yes	185 (42.5)
No	250 (57.5)
BMI, mean (SD)	30.2 (8.2)
Obesity (BMI ≥ 30), n (%)	
Yes	202 (47.5)
No	223 (52.5)
Physical activity,[d] n (%)	
Low	317 (73.7)
Moderate	66 (15.4)
High	47 (10.9)
Depression T score,[e] mean (SD)	48.2 (9.2)
PSS score,[f] mean (SD)	15.2 (7.3)

* Overall N = 436, except for the following: ethnicity (n = 435), income (n = 423), disease duration (n = 435), SLAQ score (n = 417), BMI (n = 425), physical activity (n = 430), depressive symptoms score (n = 418), perceived stress score (n = 403), medications (n = 435), SPPB score (n = 435), fluid cognition (n = 197; in-person visits only), self-reported physical functioning (n = 435), and work status (n = 424). BILD, Brief Index of Lupus Damage (range 0–46; 46 is maximum damage); BMI, body mass index; GOAL, Georgians Organized Against Lupus (parent study); IQR, interquartile range; PSS, Perceived Stress Scale; SLAQ, Systemic Lupus Activity Questionnaire (range 0–47; 47 is maximum activity); SPPB, Short Physical Performance Battery (range 0–12; higher scores indicate better performance).
[a] Represents sex assigned at birth.
[b] From the Work Productivity and Activity Impairment Questionnaire: General Health v. 2.0.
[c] From the closest GOAL assessment.
[d] From the International Physical Activity Questionnaire Short Form.
[e] From the Patient-Reported Outcomes Measurement Information System depression short form 8a.
[f] From Cohen's 10-item PSS (range 0–40; higher scores represent greater perceived stress).

Factors associated with limitations in ADLs. Prevalence of any IADL limitation was higher in older participants (59.4% vs 45.4% in those aged ≥50 vs 18–34 years). After adjustment for sex and race, age ≥50 versus 18 to 34 years was associated with 78% higher prevalence odds (Table 3); this association was consistent with further adjustment but was not statistically significant after adjustment for SLAQ and BILD scores (Supplementary Table 2). Although IADL limitations were more prevalent in female versus male (57.3% vs 44.4%) and Black versus White (57.6% vs 47.1%) participants, the differences were not statistically significant (Table 3); the associations for Black versus White race were null after adjustment for education and income (Supplementary Table 2). Lower educational attainment was also associated with higher prevalence of IADL limitations, with 2.2- and 1.8-fold higher adjusted prevalence odds for those with a high school diploma or less and some college versus those with a college degree (Table 3), but the associations

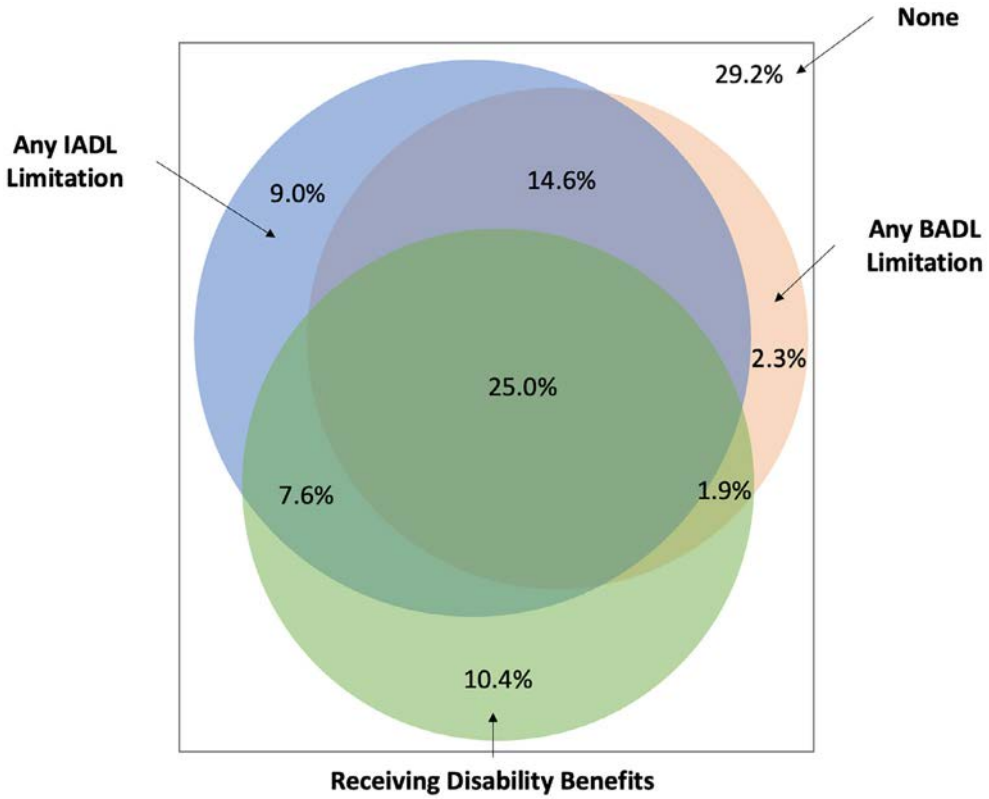

Figure 1. Venn diagram showing overlap of any limitation in IADLs, any limitation in BADLs, and self-reported receipt of disability benefits among individuals with systemic lupus erythematosus. BADL, basic activity of daily living; IADL, instrumental activity of daily living.

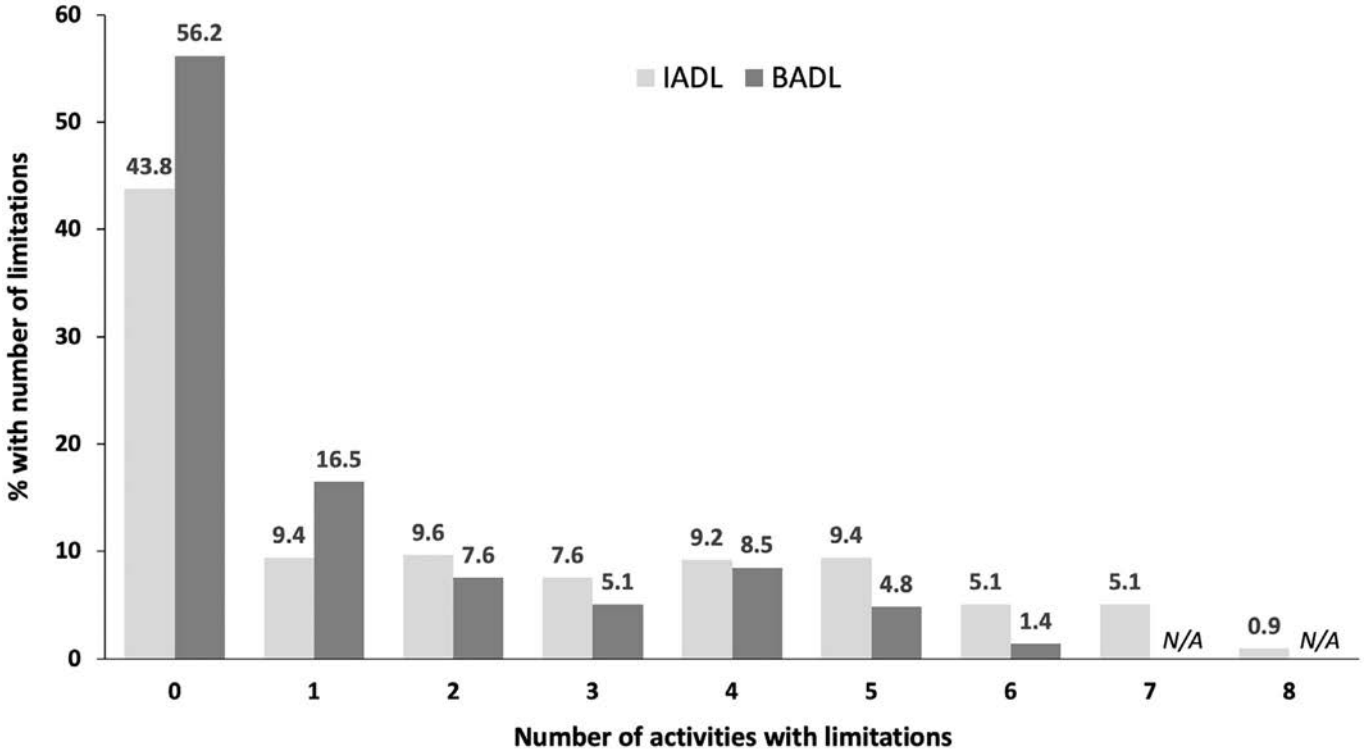

Figure 2. Distribution of the number of limitations in IADLs and BADLs among individuals with systemic lupus erythematosus. BADL, basic activity of daily living; IADL, instrumental activity of daily living; N/A, not applicable.

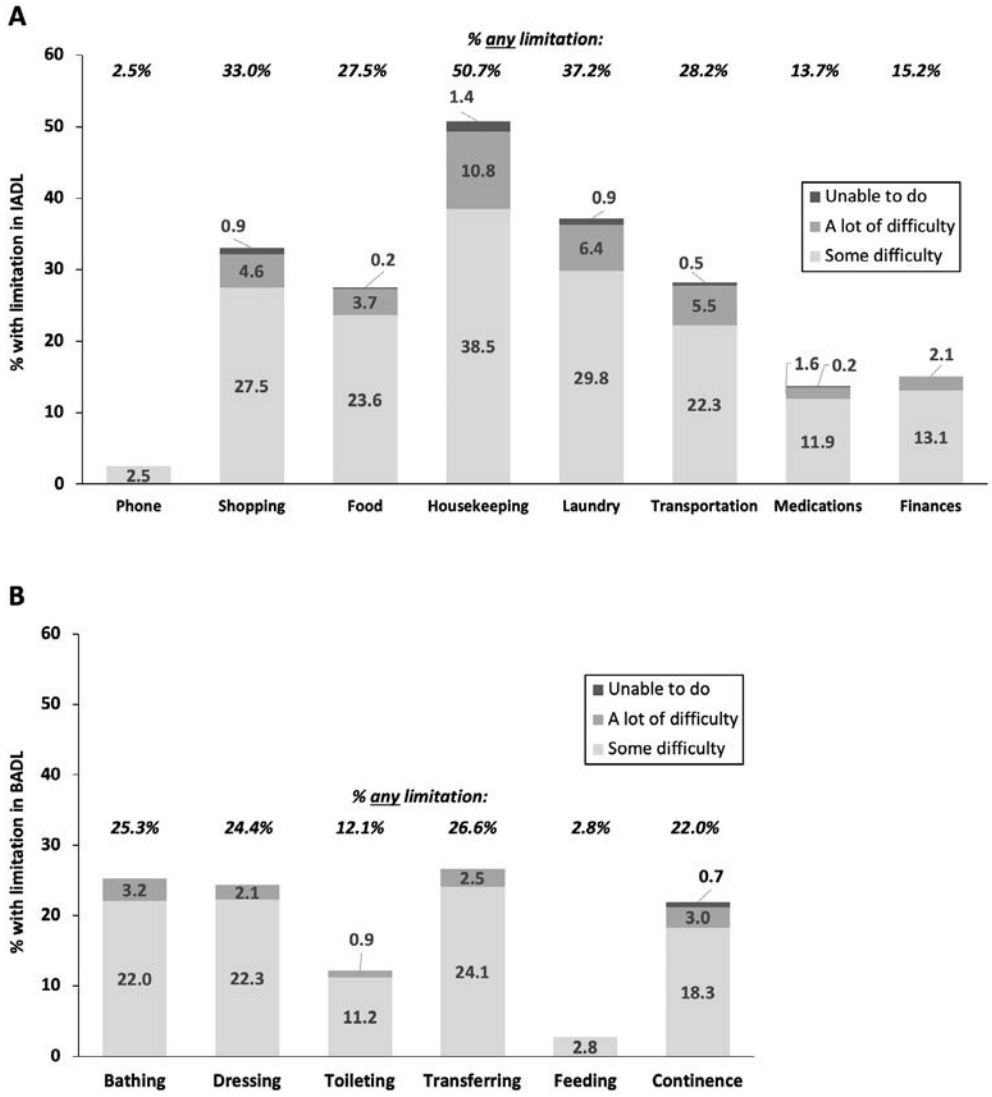

Figure 3. Percentage of individuals with systemic lupus erythematosus with limitations in (A) IADLs and (B) BADLs. Stacked bars show percentages within each level of difficulty (some difficulty, a lot of difficulty, and cannot do); overall percentages with any difficulty are shown above the stacked bars. BADL, basic activity of daily living; IADL, instrumental activity of daily living.

were attenuated after adjustment for socioeconomic factors (Supplementary Table 2). Lower income levels (<$20,000 and $20,000–$59,999 vs ≥$60,000) were associated with 3.2- and 2.1-fold higher odds of IADL limitations and were consistent with adjustment. Receipt of disability benefits was associated with 3.5-fold higher odds of limitations in IADLs (Table 2); further, of those with any IADL limitations, 58.0% were receiving disability benefits (Figure 1). Higher scores for disease activity (SLAQ; 6.5-fold), depression (3.4-fold), perceived stress (2.7-fold), and disease damage (BILD; 1.8-fold) were all associated with higher odds of IADL limitations (Table 3); only higher disease activity and higher depressive symptom scores remained statistically significantly associated with IADL limitations after further adjustment for socioeconomic and SLE-related factors and comorbid conditions (Supplementary Table 2). High and moderate physical activity versus low physical activity were associated with 60% and 79% lower odds of IADL limitations, respectively. Currently taking steroids and obesity were not associated with prevalence of IADL limitations (Table 3). Although underweight status (BMI < 18.5) was associated with higher odds of limitations (unadjusted odds ratio 2.05, 95% confidence interval [CI] 0.61–6.85) in separate analyses, the results were not statistically significant. Subgroup analyses showed that associations were similar in those not receiving disability benefits, with slightly stronger effects for lower income, higher disease activity, and higher perceived stress; there were no notable differences between those who were Black and those who were White, except the association of disease damage with IADL limitations was stronger in the White (aOR 6.79, 95% CI 1.80–25.7) versus Black (aOR 1.54, 95% CI 1.00–2.37) participants (*P* for interaction = 0.04; Supplementary Table 3).

Table 3. Any limitations in IADLs and BADLs among individuals with systemic lupus erythematosus, by selected participant characteristics*

Characteristic	Any limitation			
	IADLs		BADLs	
	No. (%)	aOR[a] (95% CI)	No. (%)	aOR[a] (95% CI)
Age category				
18–34 y	40 (45.4)	1.00 (ref.)	28 (31.8)	1.00 (ref.)
35–49 y	98 (58.3)	1.65 (0.98–2.79)	77 (45.8)	1.74 (1.01–3.02)
≥50 y	107 (59.4)	1.78 (1.06–2.99)	86 (47.8)	1.94 (1.13–3.34)
P[b]	<0.001		0.04	
Sex				
Female	229 (57.3)	1.00 (ref.)	180 (45.0)	1.00 (ref.)
Male	16 (44.4)	0.60 (0.30–1.21)	11 (30.6)	0.53 (0.25–1.11)
P[b]	0.1		0.1	
Race				
Black	208 (57.6)	1.00 (ref.)	169 (46.8)	1.00 (ref.)
Other	13 (54.2)	0.92 (0.40–2.12)	6 (25.0)	0.40 (0.15–1.04)
White	24 (47.1)	0.63 (0.35–1.14)	16 (31.4)	0.49 (0.26–0.93)
P[b]	0.4		0.02	
Hispanic ethnicity				
Hispanic	12 (50.0)	0.94 (0.38–2.33)	7 (29.2)	0.79 (0.29–2.12)
Not Hispanic	233 (56.7)	1.00 (ref.)	184 (44.8)	1.00 (ref.)
P[b]	0.5		0.1	
Level of education				
Less than high school	66 (64.7)	2.20 (1.31–3.71)	50 (49.0)	2.11 (1.25–3.55)
Some college	101 (61.6)	1.88 (1.21–2.93)	88 (53.7)	2.51 (1.59–3.97)
College graduate or higher	78 (45.9)	1.00 (ref.)	53 (31.2)	1.00 (ref.)
P[b]	0.002		<0.001	
Annual household income				
<$20,000	99 (66.4)	3.20 (1.80–5.68)	80 (53.7)	2.88 (1.60–5.18)
$20,000–$59,999	95 (56.6)	2.06 (1.19–3.57)	77 (45.8)	2.09 (1.18–3.70)
≥$60,000	43 (40.6)	1.00 (ref.)	30 (28.3)	1.00 (ref.)
P[b]	<0.001		<0.001	
Receiving disability benefits				
Yes	141 (72.7)	3.53 (2.31–5.39)	116 (59.8)	3.10 (2.05–4.69)
No	102 (42.9)	1.00 (ref.)	73 (30.7)	1.00 (ref.)
P[b]	<0.001		<0.001	
SLAQ score				
Greater than or equal to the median	149 (79.3)	6.49 (4.15–10.2)	130 (69.2)	7.35 (4.70–11.5)
Less than the median	85 (37.1)	1.00 (ref.)	53 (23.1)	1.00 (ref.)
P[b]	<0.001		<0.001	
BILD score				
Greater than or equal to the median	107 (65.2)	1.76 (1.17–2.66)	88 (53.7)	1.73 (1.16–2.60)
Less than the median	138 (50.7)	1.00 (ref.)	103 (37.8)	1.00 (ref.)
P[b]	0.003		0.001	
Taking steroids				
Yes	110 (59.5)	1.39 (0.93–2.08)	84 (45.4)	1.24 (0.83–1.86)
No	134 (53.6)	1.00 (ref.)	106 (42.4)	1.00 (ref.)
P[b]	0.2		0.5	
Obesity				
Yes	120 (59.4)	1.17 (0.78–1.74)	98 (48.5)	1.22 (0.82–1.83)
No	119 (53.4)	1.00 (ref.)	88 (39.5)	1.00 (ref.)
P[b]	0.2		0.06	
Physical activity				
Low	204 (64.4)	1.00 (ref.)	161 (50.8)	1.00 (ref.)
Moderate	27 (11.1)	0.41 (0.23–0.71)	20 (30.3)	0.48 (0.27–0.87)
High	13 (5.3)	0.21 (0.11–0.43)	9 (19.2)	0.25 (0.12–0.54)
P[b]	<0.001		<0.001	
Depression T score				
Greater than or equal to the mean	154 (69.5)	3.41 (2.26–5.15)	125 (56.1)	2.98 (1.97–4.51)
Less than the mean	81 (41.1)	1.00 (ref.)	61 (31.0)	1.00 (ref.)
P[b]	<0.001		<0.001	
PSS score				
Greater than or equal to the mean	141 (69.1)	2.72 (1.80–4.11)	115 (56.4)	2.47 (1.64–3.74)

(Continued)

Table 3. (*Cont'd*)

Characteristic	Any limitation			
	IADLs		BADLs	
	No. (%)	aOR[a] (95% CI)	No. (%)	aOR[a] (95% CI)
Less than the mean	90 (45.2)	1.00 (ref.)	68 (34.2)	1.00 (ref.)
P[b]	<0.001		<0.001	

* SLAQ median 12 (n = 188 had SLAQ scores ≥12, n = 229 had SLAQ scores <12); BILD median 3 (n = 164 had BILD scores ≥3, n = 272 had BILD scores <3); depression T score mean 48.2 (n = 223 had T scores ≥48.2, n = 197 had T scores <48.2); PSS score mean 16 (n = 204 had PSS scores ≥16, n = 199 had PSS score <16). aOR, adjusted odds ratio; BADL, basic activity of daily living; BILD, Brief Index of Lupus Damage; CI, confidence interval; IADL, instrumental activity of daily living; PSS, Perceived Stress Scale; ref., reference; SLAQ, Systemic Lupus Activity Questionnaire.
[a] Age-, sex-, and race-adjusted odds ratio.
[b] By χ^2 or Fisher's exact test, as appropriate.

Neuropsychiatric (3.0-fold), pulmonary (2.2-fold), cardiovascular (1.9-fold), and peripheral vascular (1.9-fold) damage were all associated with higher odds of IADL limitations, whereas the association of musculoskeletal damage with higher odds of IADL limitations (1.6-fold) was not statistically significant (Supplementary Table 4).

BADL limitations were less frequently reported, but associations of these limitations with characteristics were similar to those seen with IADL limitations. For example, prevalence of any BADL limitation was higher in older participants (47.8% vs 31.8% in those aged ≥50 vs 18–34 years); after adjustment for sex and race, age ≥50 versus 18 to 34 years was associated with 1.9-fold higher prevalence odds (Table 3); this association was consistent with further adjustment (Supplementary Table 5). Lower educational attainment and lower income were also associated with higher odds of BADL limitations. Unlike IADLs, White versus Black race was associated with 51% lower odds of BADL limitations (Table 3), but this association was attenuated after adjustment for socioeconomic factors (Supplementary Table 5). Receipt of disability benefits was associated with 3.1-fold higher odds of limitations in BADLs (Table 3), with 61.4% of those with IADL impairments receiving disability benefits (Figure 1). As with IADL limitations, higher scores for disease activity (7.4-fold), depression (3.0-fold), perceived stress (2.5-fold), and disease damage (1.7-fold) were all associated with higher odds of BADL limitations, whereas high and moderate physical activity versus low physical activity were associated with 52% and 75% lower odds of BADL limitations, respectively (Table 3); the associations of oldest versus youngest age, higher disease activity, higher depressive symptom scores, and high versus low physical activity all remained statistically significant after full adjustment (Supplementary Table 5). Currently taking steroids and obesity were not associated with prevalence of BADL limitations (Table 3), nor was underweight status in separate analyses. Associations were similar among those not receiving disability benefits and between those who were Black and those who were White (Supplementary Table 6). Neuropsychiatric (2.5-fold), pulmonary (2.4-fold), peripheral vascular (1.9-fold), and musculoskeletal (1.7-fold) damage were all associated with higher prevalence of BADL limitations (Supplementary Table 4).

The number of tasks in which there were limitations also differed by characteristic (Supplementary Tables 7 and 8). Black participants were more likely than White participants to report three or more IADL task limitations (41.3% vs 19.6%; Supplementary Table 7) or three or more BADL task limitations (22.7% vs 5.9%; Supplementary Table 8). Those with a high school diploma or less or some college were also more likely to report three or more IADL limitations (44.1% and 44.5% vs 25.9%) or three or more BADL limitations (25.5% and 25.0% vs 11.2%) than those who graduated college, as were those with lower versus higher income (52.4% and 33.9% vs 20.8%; 28.2% and 19.1% vs 7.6%, respectively). Those with higher scores for disease activity, disease damage, depression, and perceived stress also had statistically significantly higher prevalence of greater numbers of limitations (Supplementary Tables 7 and 8). Severe limitations in IADLs and BADLs, although less frequent than any limitations, followed similar patterns of associations with characteristics (Supplementary Table 9).

Participant characteristics were also associated with individual IADL (Supplementary Table 10) and BADL (Supplementary Table 11) tasks. For example, older age was associated with higher prevalence of limitations in using the phone, food preparation, housekeeping, doing laundry, and managing finances, whereas Black versus White race was associated with higher prevalence of limitations in shopping, food preparation, doing laundry, and transportation (Supplementary Table 10). Lower income, higher disease activity, and higher scores for depression and perceived stress were associated with higher prevalence of limitations in most IADL tasks (Supplementary Table 10). Except for continence, older age was not associated with a higher prevalence of limitations in individual BADL tasks, whereas Black versus White race was associated with a higher prevalence of limitations in bathing, toileting, and transferring (Supplementary Table 11). Higher disease activity and perceived stress were both associated with higher prevalence of limitations in all BADL tasks (Supplementary Table 11).

DISCUSSION

In this population-based adult SLE cohort, we found that more than half (56%) and nearly half (44%) reported limitations in

independently performing at least one IADL and BADL, respectively. Additionally, limitations in multiple tasks were common: 37% and 66% of those with any limitations in IADLs and BADLs, respectively, had limitations in three or more of the tasks. Further, although most of the reported limitations might be considered mild or moderate (with participants reporting some difficulty), 16% and 8% reported severe limitations in performing at least one IADL or BADL, respectively.

Although data on the prevalence of IADL and BADL difficulty are sparse in the setting of SLE, we can make indirect comparisons of our estimates to the general adult population. For example, 6% of the 2019 US adult population (18–64 years) reported severe limitations in at least one ADL, well below our prevalence of severe limitations (16% and 8% for IADLs and ADLs, respectively); in fact, our estimates were more similar to the prevalence in those aged ≥65 to 74 years (19%).[4] Among adults aged ≥60 years in the National Health and Nutrition Examination Survey (NHANES) 2011–2018, any IADL limitations (some or more difficulty in managing medications, doing household chores, or food preparation) and any BADL limitations (some or more difficulty eating, dressing, getting in and out of bed, or walking between rooms) were reported by 28% and 21%, respectively[30]; in a slightly younger population (2018 Health and Retirement Study participants aged ≥50 years), 17% reported any BADL limitations.[31] These estimates, using definitions similar to our primary analyses, all fall well below our estimates of 56% and 44% in our younger population. Further, our prevalence estimates for IADL and BADL limitations were lower than those among middle-aged (50–64 years) adults (NHANES 2011–2014) with congestive heart failure (58% and 56%) but were comparable to or higher than those for stroke (52% and 53%), cardiovascular disease (43% and 40%), chronic obstructive pulmonary disease (40% and 35%), arthritis (37% and 36%), chronic kidney disease (30% and 29%), and cancer (31% and 26%).[32] Together, our results suggest that adults with SLE may experience more difficulty with both IADLs and BADLs than similarly aged and older adults and adults with other common chronic diseases.

In the setting of aging, we generally consider limitations in IADLs (tasks that foster independent living) to precede limitations in BADLs (tasks for basic self-care). Here, we found that 17% had IADL limitations only, and 40% reported limitations in both IADLs and BADLs, suggesting that some individuals with SLE may have lived with unrecognized or unaddressed IADL limitations for some time before the development of BADL limitations. Alternatively, the same underlying issues (eg, profound fatigue) might have led to the simultaneous development of IADL and BADL limitations. Overall, these patterns suggest that the conceptualization of aging-related gradual loss of ability to perform IADLs independently, followed in time by limitations in BADLs, may not apply in the setting of SLE.

Certain IADL and BADL tasks were more frequently affected in our population. For IADLs, more than half (51%) reported limitations in doing household chores independently. Other common limitations were also in tasks that require both physical and cognitive labor—laundry (37%), shopping (33%), transportation (28%), and food preparation (28%)—and these limitations often clustered together within individuals. Limitations in IADLs that arguably require primarily cognitive labor—managing medications (14%) and finances (15%) and using the phone (3%)—were less commonly reported. Within the BADLs, reported limitations in transferring (27%), bathing (25%), and dressing (24%) were common, perhaps partially reflecting mobility issues, whereas limitations in feeding (3%) were rarely reported. Surprisingly, limitations in continence were commonly reported (22%; 23% of women and 13% of men), and the most common pattern of BADL limitations seen in our population was limited continence alone. For comparison, 28% and 14% of women and men aged ≥50 years in NHANES reported some level of either urinary or fecal incontinence.[33] Limitations in getting on and off the toilet were less common (12%), suggesting that limitations in continence may be more related to bladder symptoms than functional limitations that interfere with toileting. Further epidemiologic exploration of incontinence in SLE is warranted.

Although older age was associated with higher prevalence of limitations in IADLs and BADLs in our cohort, as expected, several other factors were strongly associated with these limitations. Higher disease activity was associated with approximately seven-fold higher odds of both IADL and BADL limitations. Related variables, including scores for depression and perceived stress, were also associated with substantially higher odds of these limitations. Lower educational attainment and income, but not sex or race, were generally statistically significantly associated with higher odds of limitations. However, White versus Black race was associated with 50% lower odds of BADL limitations only. Higher physical activity was associated with lower odds of limitations, whereas obesity was not associated with IADL or BADL limitations. Overall, these results suggest that observed limitations in ADLs among those with SLE may be driven by emotional functioning as much as by physical and cognitive functioning. Interestingly, the receipt of disability benefits was associated with higher odds of limitations, as expected, but the overlap of these limitations with receipt of disability benefits was far from complete: 42% and 39% of those with IADL and BADL limitations were not receiving disability benefits, and 23% of those receiving disability benefits had no ADL limitations. Further, associations of characteristics with IADL and BADL limitations among those who were not receiving benefits were similar to those in the overall cohort.

Of course, BADLs and IADLs are imperfect measures of limitations. IADLs and BADLs do not measure individuals' value for being able to perform the task. The Valued Life Activities (VLA) measure accounts for both the ability to perform an activity and the importance that the respondent places on the activity. Using the VLA measure, Katz et al[7] found that most (91%) of their cohort (>800 individuals) had at least one VLA that was affected

by their SLE, and VLA disability was associated with fold-fold higher odds of fair or poor self-rated health.[6] Additionally, the measured tasks may differ across individuals. For example, limitations in laundry may be more likely for people who need to go to a laundromat or navigate stairs with laundry. Similarly, limitations in transportation may depend on whether an individual has a car or whether public transportation is available, adequate, and easy to use. Our results showing that income was associated with higher odds of IADL limitations support the potential for increased difficulty of tasks in the setting of fewer resources. Finally, at least one IADL task, using the phone, may be outdated. This task originally captured the ability to hear the phone ringing and get to the phone in time to answer it, as well as dialing, remembering phone numbers, and standing for long periods while speaking. Now it is likely that limitations in using the phone reflect cognitive issues that make it difficult to navigate complex modern phones or issues with vision.

Other potential limitations of our study deserve mention. First, causal inference is limited in this cross-sectional study, and factors associated with limitations cannot be considered definitive risk factors. For example, limitations in ADLs might lead to reductions in income rather than, or in addition to, low income creating or exacerbating ADL limitations. Second, although our cohort was population-based, it might not represent individuals with SLE in other geographic regions. Further, the participants we recruited into the APPEAL study may have represented a group with fewer IADL and BADL limitations than the GOAL cohort or even the general SLE population in metropolitan Atlanta, which would suggest we may be underestimating the true prevalence of ADL limitations. Third, although we had data from a large cohort, there was likely a lack of power in certain small subgroups (eg, subgroups of White participants), which limited our ability to examine stratified analyses and interaction terms. Finally, there are other unmeasured individual factors that might be important for IADL and BADL limitations, particularly, fatigue and sleep quality. In this study of patient-reported measures, we also did not have an objective measure of disease activity, such as the SLE Disease Activity Index.[34] Although we adjusted for comorbid conditions extracted from the BILD score, these represent only severe and SLE-related damage; thus, there is likely suboptimal capture of comorbidity. Because we did not administer the Stanford Health Assessment Questionnaire Disability Index,[35] we cannot compare our results to those obtained with this more clinically used instrument. Information on environmental or household factors might also contribute to individuals' experiences of limitations, for example, presence of ramps, wide aisles, and accessible parking, along with availability and affordability of delivery or pick-up services, could support independent shopping, and walk-in access, bars, and/or seats in the shower could support independent bathing.

Our results suggest that limitations in both IADLs and BADLs are common in individuals with SLE. This burden may match or exceed the burden among older adults and those with other chronic diseases. ADL limitations may be more likely among those who report more SLE activity, depressive symptoms, and perceived stress, in addition to those who are older. Further study on the risk factors and outcomes of ADL limitations, as well as specific barriers and facilitators to performing IADLs and BADLs in the setting of SLE, is warranted. Such research will inform evidence-based strategies for improvement in quality of life and maintenance of independence in the aging SLE population.

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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 Plantinga 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.

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Clinical Presentation, Care Pathways, and Delays in Access to Specialized Care in Patients With Systemic Lupus Erythematosus: A Study From Lupus Midwest Network (LUMEN)

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Objective. We aimed to characterize presentation and care pathways of patients with systemic lupus erythematosus (SLE), and delays in access to SLE-specialized care.

Methods. We included patients with incident SLE from the Lupus Midwest Network registry. Time from the first medical encounter for SLE clinical manifestation to access to SLE-specialized care, physician diagnosis, and treatment was estimated. Delays were defined as ≥6 months to access specialized care. We compared SLE manifestations, disease activity, and Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage indexes (SDI) between patients with and without delays. Logistic regression models assessed associations with delays.

Results. The study included 373 patients with SLE. The median time to access SLE-specialized care was 1.1 (95% confidence interval [CI] 0.9–1.5) months, time to diagnosis was 30.6 (95% CI 18.9–48.1) months, and time to treatment initiation was 4.7 (95% CI 3.9–8.4) months. Approximately 25% of patients (93 out of 373) experienced delays accessing specialized care, which were associated with fewer SLE manifestations at first SLE-related encounter (fewer than two SLE domains; 92% vs 72%, $P < 0.001$). Patients with mucocutaneous or musculoskeletal manifestations were less likely to experience delays, whereas hematologic (odds ratio [OR] 1.71, 95% CI 1.03–2.84) or antiphospholipid antibodies domains (OR 6.05, 95% CI 2.46–14.88) were associated with delays. Delays were associated with damage at first access to SLE-specialized care (SDI ≥1; 30% vs 7%, $P < 0.001$).

Conclusion. Patients follow a heterogeneous pathway to receive care. One-fourth of patients experienced delays accessing SLE-specialized care, which was associated with disease-related damage. Fewer manifestations, hematologic manifestations, or antiphospholipid antibodies were associated with delays.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that can affect any organ system.[1] Because of its clinical heterogeneity, making a diagnosis, particularly during the initial stages, can be difficult.[2,3] Patients with more recognizable manifestations are likely to be referred earlier to SLE specialists,[4] but insidious and nonspecific features frequently precede a clinical diagnosis, leading to delayed referrals to specialized health care. Among patients with SLE, a delayed diagnosis may

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SIGNIFICANCE & INNOVATIONS

- The care pathways for patients with systemic lupus erythematosus (SLE) and related delays were strongly influenced by the disease's clinical presentations. Specifically, the initial severity or sudden onset of clinical manifestations determined which health care providers were involved and the settings in which patients received care.
- Rheumatology emerged as the main specialty by the time patients first accessed SLE-specialized care. However, as many as one fourth of patients were initially seen by nephrology or dermatology.
- One in four patients experienced delays in access to SLE-specialized care, and these delays were associated with damage.
- Presentations characterized by hematologic or antiphospholipid antibodies domains, as well as fewer SLE manifestations at first SLE-related encounter, were associated with delays accessing SLE-specialized care.

translate into an increased risk of irreversible damage and poor outcomes.[2,5] Therefore, minimizing delays in access to specialists could lead to better outcomes. However, little is known about how initial SLE presentations may influence the pathways patients experience to receive treatment and be diagnosed in the US health care system.

A study conducted in Greece that used a combined approach of medical chart reviews and interviews revealed that it took patients a median of 24 months to receive a diagnosis after symptom onset.[3] An analysis of US administrative insurance data reported that young patients with SLE who had diagnostic codes of thrombocytopenia and venous thromboembolism had the longest delay in receiving an SLE diagnosis.[6] However, the generalizability of these findings across different health care systems or countries remains uncertain. Furthermore, studies relying on interviews may be prone to recall bias, and reports from administrative databases could contain misclassified patients with SLE.

With these considerations, using a population-based registry, we performed a cohort study of patients with incident SLE, with detailed clinical data predating SLE diagnosis. We explored the pathways of patients with SLE, tracking their journey from the first SLE-related manifestation until first encounter with specialized SLE care. We aimed to study risk factors associated with delays in accessing care, and the associations among delays, disease activity, and damage accrual.

PATIENTS AND METHODS

Study population. The Lupus Midwest Network (LUMEN) is a population-based registry of a 27 county region in southeast Minnesota and southwest Wisconsin, nested in the Rochester Epidemiology Project (REP), a medical records linkage system.[7–9] 9 The REP allows ready access to the medical records from health care providers for the local population, including the Mayo Clinic, Olmsted Medical Center, their affiliated health systems and hospitals, local nursing homes, and so on. The demographics, distribution of morbidity, and mortality rates in the REP region are similar to those in the upper Midwest.[10] The characteristics and strengths of the REP, as well as its generalizability, have been described elsewhere.[11–13] This study was approved by the institutional review boards of the Mayo Clinic (20–006485) and the Olmsted Medical Center (036-OMC-20). The data are available after reasonable request and ethical approval.

Case definition and ascertainment. Patient identification and ascertainment of the LUMEN registry have been previously published.[7,8,14] Briefly, ascertainment of a potential SLE case was identified via two strategies: (1) through International Classification of Diseases (ICD), Ninth Revision and ICD, Tenth Revision codes for SLE, cutaneous lupus erythematosus, and other associated diseases, and (2) through laboratory measures associated with SLE—antinuclear antibodies (>1:80), low complement, anti–double stranded DNA, anti-Sm, lupus anticoagulant, anticardiolipin (IgG, IgM, and IgA), and anti–β 2 glycoprotein 1 (IgG, IgM, and IgA) antibodies. We identified all the potential patients with SLE in the REP 27 county region, from 1976 to 2018 for Olmsted County, and from 2010 to 2018 in the other 26 counties. We included patients with SLE who fulfilled the 2019 EULAR/American College of Rheumatology (ACR) classification criteria.[15] We used the 2019 EULAR/ACR criteria because they perform better than other classification criteria at identifying patients in population-based studies.[16] To be considered incident, patients needed to be residents of the 27 county region on the date of criteria fulfillment.

Data collection. We electronically retrieved demographic variables and self-reported race and ethnicity (Hispanic; non-Hispanic White, Asian, and Black). Educational level and disease manifestations based on the definitions of the 2019 EULAR/ACR classification criteria were manually abstracted from medical records. To understand how patients seek medical care, we identified the medical encounters that were related to SLE and abstracted the dates they occurred. We defined an SLE-related encounter as inpatient or outpatient medical visits during which care for SLE manifestations was provided. Encounters wherein clinical findings could be better explained by conditions other than SLE were not counted (eg, joint swelling related to trauma, a dermatology visit for a mole check). We considered that a patient received care for SLE if disease manifestations were documented in the medical history, physical examination, or clinical interventions. Inpatient encounters were defined as those requiring at least one overnight stay, and each hospitalization was considered

a single encounter. We abstracted the medical specialties of the clinicians involved in SLE-related encounters and grouped them as SLE-specialized (rheumatology, dermatology, and nephrology), internal medicine and subspecialties (excluding SLE specialized), family medicine, emergency medicine, surgical specialties, and other specialties.

We abstracted the dates of the medical encounters wherein a physician diagnosis of SLE and SLE treatment were given for the first time. SLE treatment was based on prescriptions for antimalarials (chloroquine or hydroxychloroquine), or conventional (azathioprine, cyclophosphamide, methotrexate, mycophenolate, or tacrolimus) or biologic immunosuppressants (rituximab or belimumab). Patients prescribed glucocorticoids, nonsteroidal anti-inflammatory drugs, or topical medications as monotherapy were not considered to have received SLE treatment. We determined the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)[17] and the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI)[18] at the time patients had an encounter with SLE specialties. If patients did not access SLE specialties, SLEDAI-2K and SDI were obtained when the patient fulfilled the classification criteria.

Three physician abstractors (ASR, JAMA, and JXY) underwent an initial calibration phase with a sample of 10% of patients. During several rounds of calibration, >95% agreement was considered reliable throughout the abstraction process. Variables subjected to judgment calibration were the dates of the first medical encounter, the number of medical encounters, characteristics of specialties seen, and the total number of encounters. The abstraction was completed using the REDCap online platform.[19,20]

Characterization of SLE care pathways. To outline the pathways in the journeys of patients with SLE, we tracked key events, specifically the first: SLE-related encounter, SLE-specialized encounter, SLE diagnosis encounter, and SLE therapy encounter. Patients were observed from the first SLE-related encounter until we identified these three key events: migration out of the 27-county region, death, or until February 11, 2020. We measured the time in months and summarized all encounters between the first SLE-related encounter and the other key events in care.

Outcomes. We defined a delay in access to SLE-specialized care as a period of 6 months or more between the first SLE-related encounter and the first SLE-specialized encounter. Delays were dichotomized at 6 months based on prior evidence showing that patients diagnosed within six months from symptom onset have improved prognosis.[5]

Statistical analysis. Descriptive statistics were used to summarize demographic and clinical variables. SLE manifestations seen up to the first SLE-specialized care encounter were presented overall and according to the type of specialized care received. Among patients who never received specialized care, SLE manifestations through the most recent encounter were reported. Using chi-square and rank-sum tests, we compared characteristics identified during the initial encounter and assessed differences in the SLEDAI-2K and SDI between patients with and without delays in accessing specialized care. Fisher's exact tests were used to compare categorical variables with expected cell counts less than five. We used Kaplan–Meier methods to estimate median time from the first SLE-related encounter to reaching each additional key event, to appropriately account for patients who had not yet reached a key event at last follow-up. Log-rank tests were used to compare median times. Logistic regression models were used to estimate associations between characteristics and delays in access to specialized care, adjusted for age, sex, and calendar year of SLE incidence, with results summarized as odds ratios (ORs) and 95% confidence intervals (CIs). Cox models were not used because dichotomizing delays at 6 months was considered to be clinically relevant, and all patients had at least 6 months of follow-up, so there was no censoring. Complete patient analysis was used for all patients. Values of $P < 0.05$ were considered statistically significant for all analyses. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

The study included 373 patients with incident SLE. At the time of their first SLE-related encounter, the mean ± SD age was 42.8 (18.5) years, with 80% being female, 82% identifying as non-Hispanic White, and 61% having at least some college education. The first SLE-related encounter occurred in the outpatient setting for 83% of patients, whereas 17% were hospitalized. During the first SLE-related encounter, the most frequent clinical domains from the EULAR/ACR criteria were hematologic (31%), musculoskeletal (25%), and mucocutaneous (18%) (Table 1). At first access to SLE specialty care, the median (25th–75th percentile) SLEDAI-2K was 4 (2–8), with 13% having an SDI of ≥1.

The specialties involved in this initial encounter included 34% of patients seen by internal medicine (or its branches) and 32% by family medicine. Additionally, 12% of patients (44 of 373) were seen by SLE-specialized physicians during the first encounter, primarily by dermatology. Patients presenting at first SLE-related encounter with musculoskeletal domain manifestations were predominantly seen in primary care, including both internal medicine (34%, 31 of 92) and family medicine (43%, 40 of 92). Meanwhile, those with mucocutaneous symptoms were more frequently seen by SLE-specific specialties, mainly dermatology (35%, 23 of 66). Patients exhibiting symptoms in the serositis domain were more likely to be seen in emergency medicine (Supplementary Table 1).

Table 1. Demographics and clinical characteristics of patients with SLE at first SLE-related encounter*

Characteristic	Value[a]
Age, mean ± SD), y	42.8 ± 18.5
Sex	
Female	300 (80)
Male	73 (20)
Race and ethnicity	
Non-Hispanic White	305 (82)
Asian	27 (7)
Hispanic	17 (5)
Non-Hispanic Black/African American	14 (4)
Other/unknown	10 (2)
Educational level[b]	
High school or less	140 (39)
Some college or greater degree	223 (61)
First SLE domains[c]	
Constitutional	11 (3)
Hematologic	114 (31)
Neuropsychiatric	1 (<1)
Mucocutaneous	66 (18)
Serosal	22 (6)
Musculoskeletal	92 (25)
Renal	8 (2)
Antiphospholipid antibodies	24 (6)
Complement proteins	31 (8)
Specific autoantibodies	100 (27)
Number of SLE domains	
One domain	288 (77)
Two or more domains	85 (23)
Health care setting	
Outpatient care	308 (83)
Inpatient care	65 (17)
Specialty during first SLE-related encounter	
Internal medicine and subspecialties[d]	126 (34)
Family medicine	121 (32)
Emergency medicine	49 (13)
Surgical specialties[e]	19 (5)
SLE-specialized[f]	44 (12)
Other[g]	14 (4)
SLEDAI-2K, median (25th–75th percentile)[a]	4 (2–8)
SDI, median (25th–75th percentile)[a]	0 (0)
SDI ≥1[a]	47 (13)

* Characteristics are presented as n (%) unless otherwise noted. Unless otherwise noted, N = 373. SDI was measured at the time of access to SLE-specialized care. ACR, American College of Rheumatology; SDI, SLICC/ACR damage index; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC, Systemic Lupus International Collaborating Clinics.
[a] All characteristics were measured at first SLE-related encounter except SLEDAI-2K and SDI, which were measured at first access to SLE-specialized care.
[b] N = 363.
[c] Per the 2019 EULAR/ACR classification criteria for SLE.[15]
[d] Includes hematology-oncology, infectious diseases, pulmonary medicine, cardiovascular diseases, community internal medicine, internal medicine hospitalists, occupational medicine, and women's health.
[e] Includes general surgery, orthopedic surgery, transplant medicine, vascular medicine, gynecology and obstetrics, ophthalmology, and urology.
[f] Includes dermatology, nephrology, and rheumatology.
[g] Includes psychiatry, neurology, and pediatrics.

Time to access to SLE-specialized care, SLE diagnosis, and SLE treatment. Among the 373 patients included in this study, 2% (n = 8) had no access to SLE-specialized care during follow-up (median 55, range 8–114 months). Of the remaining 365 patients, 274 (75%) had their first SLE-specialized care with rheumatology, 59 (16%) with dermatology, and 32 (9%) with nephrology. However, as previously mentioned, 44 patients (12%) accessed SLE-specialized care during their first SLE-related encounter, whereas the remaining 329 patients (88%) required multiple consultations before first accessing SLE-specialized care. The median time to access SLE-specialized care was 1.1 (95% CI 0.9–1.5) months, with patients typically requiring a median of three encounters (interquartile range [IQR] 2–4) to achieve this access (Supplementary Table 2).

SLE manifestations (by EULAR/ACR domains) seen up to the first SLE-specialized care encounter are outlined in Table 2. Patients first visiting rheumatology exhibited musculoskeletal manifestations (46%), patients visiting dermatology more frequently had mucocutaneous manifestations (59%), and patients who first visited nephrology had more renal manifestations (34%). The rest of the clinical domains were more evenly distributed across the three SLE-specialized care services.

A total of 284 patients received an SLE diagnosis by a physician during follow-up, whereas the rest received other diagnoses including undifferentiated connective tissue disease or inflammatory arthritis (23%), yet all fulfilled the EULAR/ACR criteria for SLE. The median time from the first SLE-related encounter to receiving an SLE diagnosis was 30.6 (95% CI 18.9–48.1) months; those diagnosed with SLE had a median of 6 (IQR 3–12) encounters between these two times. Moreover, 338 patients received SLE treatment during follow-up. The median duration from the first SLE-related encounter to the initiation of SLE treatment was 4.7 (95% CI 3.9–8.4) months, involving 5 (IQR 3–9) encounters (Supplementary Table 2).

Care pathways between initial inpatient and outpatient care. When comparing the first SLE-related encounters between inpatient and outpatient settings, patients initially assessed in inpatient care more frequently presented with the following domains: constitutional (11% vs 1%, $P < 0.001$), hematologic (42% vs 28%, $P = 0.035$), serosal (22% vs 3%, $P < 0.001$), and renal (8% vs 1%, $P = 0.005$; Supplementary Table 3). Patients initially assessed in outpatient care more frequently presented with musculoskeletal domain manifestations (28% vs 11%, $P = 0.004$). Additionally, half of the patients (52%) in inpatient care for their first SLE-related encounter were seen by a specialist in emergency medicine. Patients hospitalized at first SLE-related encounter also showed higher disease activity at first access to SLE-specialized care compared to those who had their first SLE-related encounter in an outpatient setting (median SLEDAI-2K 8 [IQR 5–14] vs 4 [IQR 2–7], $P < 0.001$) and were

Table 2. SLE manifestations up to the first access of SLE-specialized care*

Domain	Total who reached specialized care (N = 365), n (%)	Rheumatology (n = 274), n (%)	Dermatology (n = 59), n (%)	Nephrology (n = 32), n (%)	Never reached specialized care (n = 8), n	*P* value[a]
Constitutional	15 (4)	14 (5)	1 (2)	0	0	0.371
Hematologic	124 (34)	95 (35)	15 (25)	14 (44)	3	0.188
Neuropsychiatric	3 (1)	3 (1)	0	0	0	1.000
Mucocutaneous	93 (25)	56 (20)	35 (59)	2 (6)	0	<0.001
Serosal	32 (9)	25 (9)	2 (3)	5 (16)	2	0.117
Musculoskeletal	130 (36)	126 (46)	2 (3)	2 (6)	3	<0.001
Renal	19 (5)	8 (3)	0	11 (34)	1	<0.001
Antiphospholipid antibodies	42 (12)	35 (13)	1 (2)	6 (19)	3	0.008
Complement proteins	79 (22)	59 (22)	8 (14)	12 (38)	2	0.030
Specific autoantibodies	161 (44)	134 (49)	12 (20)	15 (47)	6	<0.001

* Per the 2019 EULAR/ACR classification criteria for SLE.[15] ACR, American College of Rheumatology; SLE, systemic lupus erythematosus.
[a] *P* values are from chi-square tests (or Fisher's Exact tests when counts less than five are present) comparing rheumatology versus dermatology versus nephrology.

more likely to present with damage at first access to SLE-specialized care (SDI ≥1 in 20% vs 11%, $P = 0.048$). Although the time needed to access SLE-specialized care did not differ statistically, the median time for receiving an SLE diagnosis (40.8 [95% CI 28.9–60.2] vs 3.4 [95% CI 1.2–11.1] months, $P < 0.001$) and starting SLE treatment (6.9 [95% CI 4.1–10.2] vs 2.3 [95% CI 1.0–4.8] months, $P = 0.021$) was significantly shorter for those who were initially hospitalized (Supplementary Table 2).

Access to SLE-specialized care and delays. A total of 75% of the patients with SLE (280 of 373) gained access to SLE-specialized care within 6 months, whereas 25% (93 of 373) experienced a delay in access or never achieved access during follow-up. As detailed in Table 3, there were no differences in demographics or education levels among those with or without delay in access to SLE-specialized care. More patients with delay had manifestations in the hematologic and antiphospholipid antibody domains and were affected in only one SLE domain at the first SLE-related encounter, compared with patients without delay (92% vs 72%, $P < 0.001$). More patients without delay had manifestations in the mucocutaneous, musculoskeletal, specific autoantibodies, and complement domains. The delay in access to SLE-specialized care was associated with a five-fold increased likelihood of presenting with at least one point on the SDI score at first access to SLE-specialized care (30% vs 7%, adjusted OR 5.30, 95% CI 2.71–10.37, data not tabulated). However, a delay in access to SLE-specialized care was not associated with increased disease activity at the time the patient first accessed SLE-specialized care.

After adjusting for age, sex, and calendar year, an initial presentation involving the hematologic domain was associated with a nearly two-fold increase in odds of experiencing a delay in SLE specialty care (OR 1.71, 95% CI 1.03–2.84), and the antiphospholipid antibodies domain was associated with a six-fold increase in odds for delay (OR 6.05, 95% CI 2.46–14.88). Conversely, those who initially presented with mucocutaneous (OR 0.17, 95% CI 0.06–0.44), musculoskeletal (OR 0.47, 95% CI 0.25–0.88), specific autoantibodies (OR 0.44, 95% CI 0.23–0.82), or two or more SLE domains (OR 0.23, 95% CI 0.10–0.52) were associated with a decreased likelihood of delay. We observed a decreased likelihood of delays over time; specifically, each 10-year increase at the initial SLE-related encounter was associated with a lower risk of delays (OR 0.73, 95% CI 0.60–0.88), and the median time to gain access, which was 2.7 (95% CI 0.7–8.6) months during 1989 to 1998, decreased to 1 (95% CI 0.8–1.5) month during 2009 to 2018 (Supplementary Table 2). Age, sex, race and ethnicity, education level, initial care received in an inpatient or outpatient setting for the first SLE-related encounter, or the type of medical specialties at the first SLE-related encounter were not associated with delays (Table 4).

DISCUSSION

In this study, we characterized the clinical presentation of patients with SLE at key time points early in their disease course, carefully delineated the care pathways of patients with SLE, and assessed the impact of delayed access on disease activity and damage. In agreement with prior findings,[3,21,22] patients with SLE primarily sought care for musculoskeletal and mucocutaneous symptoms. Rheumatology emerged as the predominant first contact within SLE-specialized care, although some patients were seen first by nephrology or dermatology. We observed that the time to initiate SLE treatment was shorter than the time to receive an SLE diagnosis. The trajectory toward specialized care, diagnosis, and treatment was notably influenced by disease severity and presentation. A minority of patients initially required inpatient management, characterized by a higher SLEDAI-2K score and more severe manifestations, leading to more prompt diagnosis and treatment compared with outpatient counterparts. Many patients experienced delays accessing SLE-specialized care, leading to significantly greater damage accrual, despite similar levels of disease activity as those without delays.

Table 3. Demographics, clinical manifestations, disease activity, and specialties according to delay in access to SLE-specialized care in a population-based cohort from a 27 county region of the American upper Midwest*

Characteristic	Delayed access to specialized care (n = 93)[a]	Without delays (n = 280)	*P* value[b]
Age, mean ± SD, y	42.7 ± 18.1	42.9 ± 18.7	0.965
Sex			0.252
Female	71 (76)	229 (82)	
Male	22 (24)	51 (18)	
Race and ethnicity			0.245
Non-Hispanic White	79 (86)	226 (81)	
Non-Hispanic Black/African American	2 (2)	12 (4)	
Asian	9 (10)	18 (6)	
Hispanic	1 (1)	16 (6)	
Other/unknown	2 (2)	8 (3)	
Educational level[c]			0.284
High school or less	39 (43)	101 (37)	
Some college or greater degree	51 (57)	172 (63)	
First SLE domain[d]			
Constitutional	3 (3)	8 (3)	1.000
Hematologic	36 (39)	78 (28)	0.049
Neuropsychiatric	0 (0)	1 (<1)	1.000
Mucocutaneous	5 (5)	61 (22)	<0.001
Serosal	8 (9)	14 (5)	0.201
Musculoskeletal	14 (15)	78 (28)	0.013
Renal	0 (0)	8 (3)	0.209
Antiphospholipid antibodies	15 (16)	9 (3)	<0.001
Complement proteins	3 (3)	28 (10)	0.049
Specific autoantibodies	14 (15)	86 (31)	0.003
Number of SLE domains			<0.001
One domain	86 (92)	202 (72)	
Two or more domains	7 (8)	78 (28)	
SLEDAI-2K, median (25th–75th percentile)	5 (4–8)	4 (2–8)	0.204
SDI, median (25th–75th percentile)	0 (0–1)	0 (0)	<0.001
SDI ≥1	28 (30)	19 (7)	<0.001
Specialties seen before SLE-specialized care, median (25th–75th percentile)	2 (1–3)	1 (1–2)	<0.001

* Characteristics reported as n (%) unless otherwise noted. All characteristics measured at first SLE-related encounter except SLEDAI-2K, SDI, and specialties seen before SLE-specialized care which were measured at first access to SLE-specialized care. ACR, American College of Rheumatology; SDI, SLICC/ACR Damage Index; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC, Systemic Lupus International Collaborating Clinics.
[a] Delays were defined as 6 months or more to reach access for specialized care.
[b] Categorical variables are compared using chi-square or Fisher's exact tests. Continuous variables are compared using rank-sum tests.
[c] n = 90 and n = 273 for the group with delayed access to specialized care and the group without delays, respectively.
[d] Per the 2019 EULAR/ACR classification criteria for SLE.[15]

The median lag time to be seen by an SLE-specialized physician in our cohort was approximately 1 month. Keeping in mind that universal access to health care and the particularities of the country's system play a significant role in access to care, this finding could be compared with a study from Greece, which reported an average time of 3 months from the first physician visit to rheumatology assessment.[3] Our shorter time could be partially due to patients presenting with skin manifestations being promptly seen at first encounter by dermatology, which is considered as SLE-specialized for the purposes of this study. In addition, these results have to be understood in the proper context; our study included newly diagnosed patients until 2018, before the COVID-19 pandemic and during the peak of the US rheumatology workforce.[23,24] Future studies will need to assess the impact of the US rheumatology workforce shortages on access to care for patients with incident SLE.

Our findings underscore that the care pathways for patients with SLE are significantly influenced by the disease's clinical presentations. Specifically, the initial severity or sudden onset of systemic manifestations often dictates the health care providers involved and the settings in which patients receive care. Those requiring inpatient care typically presented with higher SLEDAI-2K scores, frequently had conditions characterized by serositis and renal manifestations, and received a diagnosis and treatment more swiftly than their outpatient counterparts. This observation is closely aligned with the study from Greece, which found that

Table 4. Factors at the first SLE-related encounter associated with a delay in access to SLE-specialized care (≥6 months) in patients with new-onset SLE from the LUMEN registry*

Characteristic	OR (95% CI)[a]
Calendar year (per 10 years increase)	0.73 (0.60–0.88)
Demographics	
Age (per 10 years increase)	1.03 (0.90–1.18)
Male sex	1.53 (0.84–2.78)
Non-White race (n = 371)	0.86 (0.43–1.72)
College or greater degree (n = 363)	0.79 (0.48–1.29)
First SLE domains*	
Constitutional	1.00 (0.25–3.96)
Hematologic	1.71 (1.03–2.84)
Neuropsychiatric	–
Mucocutaneous	0.17 (0.06–0.44)
Serosal	2.10 (0.82–5.38)
Musculoskeletal	0.47 (0.25–0.88)
Renal	–
Antiphospholipid antibodies	6.05 (2.46–14.88)
Complement proteins	0.35 (0.10–1.21)
Specific autoantibodies	0.44 (0.23–0.82)
Number of SLE domains	
≥2 domains	0.23 (0.10–0.52)
Health care settings	
Inpatient care (vs outpatient)	0.87 (0.45–1.68)
Specialty seen	
Family medicine	(Reference)
Emergency medicine	1.20 (0.55–2.62)
Internal medicine[b]	0.98 (0.53–1.81)
Surgical specialties[c]	1.99 (0.71–5.59)

* Per the 2019 EULAR/ACR classification criteria for SLE.[15] ACR, American College of Rheumatology; CI, confidence interval; LUMEN, Lupus Midwest Network; OR, odds ratio; SLE, systemic lupus erythematosus.
[a] Estimates and *P* values are from adjusted univariable logistic regression assessing the association between the given variable of interest and delay after adjusting for age, sex and calendar year of SLE incidence.
[b] Internal medicine and subspecialties include hematology-oncology, infectious diseases, pulmonary medicine, cardiovascular diseases, community internal medicine, internal medicine hospitalists, occupational medicine, women's health.
[c] Surgical specialties include general surgery, orthopedic surgery, transplant medicine, vascular medicine, gynecology and obstetrics, ophthalmology, and urology.

approximately 20% of patients were hospitalized due to their initial SLE manifestations.[25] Although our study's approach to abstracting and classifying SLE manifestations differed (for instance, we did not abstract cerebrovascular or thrombotic events because they do not fall under the EULAR/ACR SLE criteria), both studies concur that hematologic, renal, or serosal manifestations were prevalent among patients hospitalized early in their diagnostic journey.

Although the median time to access SLE-specialized care was short, the journey to receive a physician diagnosis and SLE treatment initiation was notably longer. Interestingly, although all the patients fulfilled the EULAR/ACR SLE criteria, some patients never received a definitive physician diagnosis of SLE. This discrepancy can be attributed to the application of the novel EULAR/ACR criteria to historical medical records. These criteria have been recognized for classifying a greater number of patients as having SLE compared with previous criteria.[16,26] In our study, it became apparent that many patients received a diagnosis of nonspecific conditions, such as inflammatory arthritis or undifferentiated connective tissue disease, before a definitive SLE diagnosis. A diagnosis of lupus is complex, and as the condition evolves, the diagnosis may change over time. Interestingly, the time needed for diagnosis changed after 2009 to 2018. During this period, the time taken for diagnosis notably decreased, arguably due to advances in SLE care and increased awareness. Reassuringly, the absence of a definitive SLE diagnosis by a physician did not preclude treatment; clinicians frequently initiated treatment based on the patient's clinical presentation.

In our study, many patients experienced a delay of 6 months or longer in accessing a specialist. Currently, there is no universally accepted definition of what constitutes a delay in access to specialized care for patients with SLE. We adopted a 6 month benchmark based on its demonstrated clinical relevance in prior research.[3,5] Using this benchmark, we found that the patients who presented with antiphospholipid antibodies or hematologic manifestations were more likely to have delayed access to care. Patients with antiphospholipid antibodies often had a history of unexplained thrombosis or, less frequently, a false-positive syphilis test. Conversely, patients with more conventional symptoms such as musculoskeletal and mucocutaneous manifestations, or patients with multiple domains involved, were at a lower risk of experiencing delays. Our findings contrast with the study done in Greece in which patients having mucocutaneous manifestations had delays.[3] A likely difference between these studies was that we looked at patients in the population as a whole and patients seen by dermatology and nephrology in addition to rheumatology, versus patients seen in a rheumatology referral center as per the study in Greece. A study by Chang et al,[6] which used administrative diagnostic codes to investigate health care usage among patients with SLE in the year before their diagnosis, found the longest delays among those with diagnostic codes for "primary thrombocytopenia, unspecified" and for "other venous embolism and thrombosis." These findings align with the pattern of delay we observed in our study. Clinicians should be aware of the association between hematologic and antiphospholipid syndrome (APS) manifestations and a potential delay in SLE care. These might include assessing for SLE biomarkers such as anti-DNA, anti-Sm, or low complement in people with APS, cytopenias, or both.

Our study has several key strengths. Using a population-based cohort alongside a record linkage infrastructure enabled comprehensive tracking of all SLE manifestations from the earliest recorded classification criterion across various providers and care settings. This approach not only minimized referral bias but also ensured inclusion of patients across the entire severity spectrum, thereby reducing the risk of misclassification. Unlike studies based on surveys, our method was not susceptible to recall bias.

However, it is important to acknowledge certain limitations. First, our findings may not be generalizable to clinical settings outside the American Midwest. Individuals from more diverse backgrounds or from other geographic regions may experience different disease trajectories. Second, the rarity of some disease manifestations within our study's time frame may have resulted in insufficient statistical power for certain comparisons. Third, due to our study's retrospective design, we were constrained by the completeness of clinical documentation. Although not all manifestations of SLE were abstracted—limiting our focus to those listed in the EULAR/ACR SLE criteria—we believe this approach is justified by identifying the manifestations (and using the standardized definitions) that classify a patient as having SLE. These criteria involved a process to identify manifestations most representative of SLE, thereby supporting the robustness of our methodology and assuring generalizability. Fourth, our study spanned four decades, and assessing dynamic changes in social determinants of health longitudinally was not feasible. Although we incorporated educational and demographic characteristics into the analysis, not all the social determinants of health were available.

In conclusion, our study provides valuable insights into the initial SLE manifestations and the care pathways of patients with new-onset SLE. We uncovered significant heterogeneity in patients' care pathways, revealing that one-fourth of patients first sought SLE-specialized care outside of rheumatology, and about one-fifth required initial hospitalization. Nearly one-quarter of patients experienced delays in access to SLE-specialized care; delays were associated with damage accrual. These findings underscore the need for future research aimed at optimizing patient pathways and coordinated care strategies. Specifically, early identification of patients with the risk factors outlined in our study could lead to interventions designed to prevent irreversible damage.

AUTHOR CONTRIBUTIONS

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

Study conception and design. Sanchez-Rodriguez, Meade-Aguilar, Figueroa-Parra, Duarte-García.

Acquisition of data. Sanchez-Rodriguez, Meade-Aguilar, Yang.

Analysis and interpretation of data. Sanchez-Rodriguez, Meade-Aguilar, Yang, Figueroa-Parra, Hanson, Langenfeld, Thanarajasingam, Chamberlain, Greenlund, Barbour, Crowson, Duarte-García.

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REVIEW ARTICLE

Does Higher Compliance With American College of Sports Medicine Exercise Prescription Guidelines Influence Exercise Outcomes in Knee Osteoarthritis? A Systematic Review With Meta-Analysis

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Objective. We wanted to determine if higher compliance with American College of Sports Medicine (ACSM) exercise prescription guidelines influences exercise outcomes in knee osteoarthritis (OA).

Methods. We conducted a systematic review. We searched the Cochrane Central Register of Controlled Trials, MEDLINE, and Embase up to January 4, 2024, for randomized controlled trials evaluating resistance and/or aerobic exercise for knee OA. Interventions were classified as higher compliance (meeting ≥60% of ACSM guideline recommendations for frequency, intensity, and duration) or lower compliance (meeting <60% of recommendations). Effects on pain and function were evaluated via meta-analysis, stratified by compliance.

Results. Twenty-five trials (3,290 participants) evaluated combined resistance and aerobic programs, with no differences in outcomes between those with higher and lower compliance (standardized mean difference [SMD] pain: −0.38 [95% confidence interval (CI) −0.59 to −0.17] vs −0.31 [95% CI −0.45 to −0.16], respectively; SMD function: −0.43 [95% CI −0.64 to −0.21] vs −0.36 [95% CI −0.58 to −0.14]). Sixty-six trials (5,231 participants) evaluated resistance exercise, with no differences between interventions with higher and lower compliance (SMD pain: −0.60 [95% CI −0.81 to −0.39] vs −0.93 [95% CI −1.27 to −0.59]; SMD function: −0.64 [95% CI −0.83 to −0.44] vs −0.85 [95% CI −1.20 to −0.49]). Twelve trials (958 participants) evaluated aerobic exercise, with no differences between interventions with higher and lower compliance (SMD pain: −0.79 [95% CI −1.20 to −0.38] vs −1.00 [95% CI −2.52 to 0.53]; SMD function: −0.83 [95% CI −1.27 to −0.38] vs −0.76 [95% CI −2.02 to 0.50]).

Conclusion. Higher or lower compliance with ACSM exercise prescription guidelines did not influence exercise outcomes. Given there was substantial heterogeneity and many publications were at risk of bias, our results should be interpreted with caution.

INTRODUCTION

Knee osteoarthritis (OA) affects hundreds of millions of people worldwide.[1] All clinical guidelines advocate exercise for management of knee OA, irrespective of age, comorbidity, pain severity, or disability.[2–6] However, although numerous studies support the effectiveness of exercise in the short term, benefits are only small to moderate and diminish over time.[7,8] Finding ways to optimize exercise programs to maximize their effectiveness is an important area of ongoing research.

Land-based exercise interventions tested in randomized controlled trials (RCTs) for knee OA vary substantially in terms of

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SIGNIFICANCE & INNOVATIONS

- Finding ways to optimize land-based exercise programs to maximize their effectiveness for knee osteoarthritis (OA) is an important area of ongoing research. The American College of Sports Medicine (ACSM) provides guidelines for exercise prescription for people with arthritis, including the optimal frequency, intensity, and duration of both resistance and aerobic exercise. This review aimed to determine whether higher compliance with ACSM guidelines influences exercise outcomes in knee OA across different types of exercise.
- We found that higher or lower compliance with ACSM exercise prescription guidelines did not influence change in knee pain or physical function in resistance, aerobic, and mixed (aerobic and resistance) programs.
- However, there was substantial heterogeneity, some evidence of publication bias, and many included trials were of low quality. As such, our results should be interpreted with caution.

exercise dosage.[9] Determining the optimal exercise dosage that is most beneficial for OA symptoms may help enhance benefits. The American College of Sports Medicine (ACSM) provides evidence-based guidelines for health care providers who prescribe exercise for people with arthritis, including guidance regarding the optimal frequency, intensity, and duration of both resistance and aerobic exercise for health benefits (eg, weight control, improved physical capacity, reduced risk of fall, reduced joint pain, and management of comorbidities).[10] For resistance exercise, a frequency of two to three days per week is recommended at an intensity of 50% to 80% of 1 repetition maximum, aiming for between 8 to 12 repetitions and 1 to 3 sets of each exercise. For aerobic exercise, a frequency of three to five days per week is recommended at a moderate (defined as 40%–59% volume of O_2 [VO_2] reserve) or vigorous (≥60% VO_2 reserve) intensity, aiming to accumulate 150 minutes per week of moderate intensity or 75 minutes per week of vigorous intensity.

Two previous systematic reviews in knee OA found that exercise interventions that had high compliance with the ACSM guidelines (ie, met ≥60% of dosage recommendations) were no more effective at improving pain or physical function than interventions that had low compliance.[11,12] However, one of these reviews found that higher ACSM compliance was associated with a greater increase in muscle strength.[12] In contrast, another review in hip OA found that higher compliance with ACSM guidelines was associated with greater improvements in pain and function.[13] All of these prior systematic reviews pooled all different types of exercise together in their analyses (ie, aerobic, resistance, and programs that involve a combination of aerobic and resistance), which may potentially explain why some differences in outcomes were not detected. Separating analyses by exercise type is important given there is some suggestion that effects of exercise on knee OA symptoms varies according to exercise type.[14] As such, the aim of this review is to determine if higher compliance with ACSM exercise prescription guidelines influences exercise outcomes in knee OA in aerobic, resistance, and mixed (aerobic plus resistance) exercise programs.

PATIENTS AND METHODS

This review used data extracted as part of an update to a Cochrane Systematic Review evaluating the effectiveness of exercise for knee OA.[9] We followed the Cochrane Handbook for Systematic Reviews of Interventions,[15] and this manuscript is written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[16] Data are available upon reasonable request to the corresponding author.

Literature search. Three databases (MEDLINE OvidSP, Embase OvidSP, and The Cochrane Central Register of Controlled Trials) were searched from inception to January 4, 2024. No language restrictions were applied, and gray literature was not searched. The search strategy can be found in Supplementary Material 1.

Eligibility criteria. Trials involving adults with knee OA (according to accepted clinical criteria[4,17,18] or who self-reported knee OA on the basis of chronic joint pain, with or without radiographic confirmation) were included. Trials with participants who had OA in other joints were included if outcomes for those with knee OA were presented separately (or were provided by the authors) or if >80% of participants in the trial had knee OA. To be eligible, trials were required to include outcomes of self-reported knee pain severity and/or self-reported physical function.

Any land-based exercise RCTs that involved either resistance exercise (as per the definition provided in ACSM guidelines, ie, programs involving voluntary muscle contractions against a resistance, such as machines, free weights, resistance bands, or body weight[10]) and/or aerobic exercise (ie, cardiovascular activities with "low joint stress," such as walking or cycling[10]) were eligible. Eligible interventions were allowed to incorporate education and/or behavior change strategies that were designed to help participants adhere to the exercise program (eg information about benefits of exercise and mobile app to maximize adherence), could be supervised or unsupervised, and could include other nonsurgical cointerventions (provided that these cointerventions were provided similarly in the comparator group). Eligible exercise interventions were permitted to use other types of exercise (eg, stretching) only in a warm-up or warm-down. Any three-arm trials with two exercise arms using different types of exercise (eg, Group A: aerobic exercise; Group B: resistance exercise; and Group C: control) were included in both relevant meta-analyses. Any three-arm trials using

the same type of exercise at the same ACSM dosage (eg, Group A: resistance exercise delivered via individual session; Group B: exact same resistance program but delivered via group session; and Group C: control) were included, and exercise arms were pooled in the meta-analysis.

Exercise interventions were ineligible if they were perioperative (ie, specifically recruited all participants from surgical waiting lists and/or evaluated outcomes postsurgery), included whole-body vibration or gait retraining as the intervention, or included any type of exercise that was not either resistance exercise or aerobic exercise (eg, mind–body [such as yoga or Tai Chi], balance, and stretching). Any three-arm trials with two exercise arms using the same type of exercise but at a different ACSM dosage (eg, Group A: resistance exercise at low intensity; Group B: resistance exercise at high intensity; and Group C: control) were excluded so that they would not be counted in the meta-analysis twice. Comparator groups eligible for inclusion were as follows:

- Placebo, sham, or attention control (ie, an intervention that was designed to control for contextual or placebo effects and was described as "placebo/sham" and/or an "attention control" intervention involving ≥1 bout of synchronous interaction with a care provider [not including contact from study personnel to obtain outcome measures]);
- No treatment, usual care (ie, stated that participants could receive normal care but not controlled by the trial), or minimal education (ie, participants were provided with a one-off information resource), and
- Any nonexercised and nonsurgical intervention that was also offered or provided equally as a cointervention in the exercise group (eg weight loss diet, manual therapy, or physical therapy [not including any kind of exercise component]).

Study selection. Teams of two review authors (involving all study authors) independently screened titles and abstracts for inclusion before retrieving the full-text publication. Teams of two authors independently screened full texts and identified studies for inclusion. A third author adjudicated if agreement was not achieved at any stage.

Quality assessment. To assess potential bias, the Cochrane Collaboration's Risk of Bias 1 tool for assessing risk of bias in RCTs was used.[19] Two authors (BJL and MH) independently assessed risk of bias for each included study. Any disagreements were resolved through discussion or by involving a third review author. Each risk of bias domain (random sequence generation [selection bias]; allocation concealment [selection bias]; blinding of participants and personnel [performance bias], blinding of outcome assessment [detection bias], incomplete outcome data [attrition bias], and selective outcome reporting [reporting bias]) was judged as adequate (low risk of bias), inadequate (high risk of bias), or unclear (insufficient information).

Data collection. Teams of two authors independently extracted outcome data from included studies. We used a data collection form in Covidence, which was pilot tested on at least two eligible studies. Any potential disagreements were resolved by consensus or by involving another review author. Data relating to study participants (number randomized to each group, mean age, percentage female, OA diagnostic criteria, and body mass index [BMI]) was extracted, as well as details relating to comparison and exercise interventions and outcomes of knee pain and physical function.

For outcomes, we extracted means and standard deviations (SD) immediately at the end of the treatment (posttreatment). If authors used more than one pain or function outcome, we used a hierarchy of outcomes (described in the prior Cochrane review of exercise for knee OA[7]). If authors reported both end score and change from baseline values, we extracted the end score values. If reported, we extracted intention-to-treat (ITT)–analyzed data. If we needed to obtain missing outcome data (eg, when data were not available for all participants), we contacted the trial authors. If no response was received after two attempts to contact (at least one month apart), data were considered irretrievable. If necessary, we calculated missing SDs from other statistics (eg, standard errors, confidence intervals [CIs], or *P* values), according to the methods recommended in the Cochrane Handbook for Systematic Reviews.[20]

Evaluating compliance with ACSM guidelines. Exercise interventions were categorized into two groups: high and low prescription compliance with the ACSM recommendations (Table 1). Two authors (LS and AJK) independently followed a grading system (Table 1; based on those used by prior similar reviews[11,13]) to assess whether each study complied to ACSM recommendations for the variables of intensity, time, and frequency. One point was given if the dose had been met, and zero points were given if the dose had not been met, was not reported, or was unclear. If the two authors could not agree, a third author (BJL) adjudicated. Points were then added for each dosage variable (intensity, time, and frequency), divided by the total possible score, and multiplied by 100 to give an overall compliance ratio (in percentage) for each trial. A compliance ratio of ≥60% was defined as "higher compliance" (based on a prior similar review[11]), whereas a compliance ratio of <60% was rated as "lower compliance."

Data analysis. We used the Cochrane Collaboration Review Manager[21] to calculate standardized mean differences (SMDs) with 95% CIs. We calculated the SMD based on the number of participants randomized at baseline and entered data with a consistent direction of effect across studies. We pooled all comparator groups together as we anticipated that there would not be enough trials in each category to enable separate analyses.

Table 1. Scoring rules for whether exercise programs were deemed to be compliant or noncompliant with the American College of Sports Medicine guidelines for exercise prescription*[10]

	Guidelines for aerobic programs	Guidelines for resistance programs
Frequency	3–5 days/week[a]	2–3 days/week[a]
Intensity	Moderate (described by authors as being moderate; 40–59% VO_2R or HRR; 12 on original Borg RPE) to vigorous (≥60% VO_2R or HRR)[a]	50–80% 1-RM or 5–8 on the Borg CR-10 scale or 10–15 on the original Borg RPE[a]
Duration	Accumulate 150 min/week of moderate intensity or 75 min/week of vigorous intensity or an equivalent combination of the two[a]	8–12 reps[a] or 1–3 sets[a]
Total possible points	3	4

* Compliance ratio was calculated by dividing each point scores out of total possible points and multiplying by 100 to give a percentage. If programs involved both aerobic and resistance exercise, both elements were scored as previously described, with the final score being out of 7. If programs exceeded the recommendations (eg, prescribed 6 days/week aerobic exercise), we deemed this as being noncompliant and awarded 0 points. If programs prescribed a range (eg, resistance exercise 1–2 days/week), we deemed this as compliant if the upper or lower range was within the recommendations. If clinician discretion was used for specific prescription, we deemed that as being unclear in compliance and awarded 0 points. 1-RM, one rep maximum; CR-10, category-ratio 10; HRR, heart rate reserve; RPE, rating of perceived exertion; VO_2R, volume of O_2 reserve.
[a] Indicates that this element was scored 0 to 1. 1 point indicates criteria was met. 0 points indicates criteria was not met, was not reported, or was unclear.

We performed separate meta-analyses in SPSS (Version 29, IBM Statistics, USA) for each type of exercise (ie, mixed programs of resistance plus aerobic exercise, resistance exercise alone, and aerobic exercise alone), subgrouped by whether trials were deemed to have higher or lower compliance with the ACSM guidelines. Study heterogeneity was assessed by using the I^2 statistic. To examine publication bias, we conducted Egger's regression test[22] and inspected funnel plots. We also conducted sensitivity analyses:

- We increased the ACSM compliance ratio defined to be "higher compliance" from ≥60% to 100%.
- As we anticipated that a substantial number of trials would not report some dosage variables, we explored treatment effects when including only trials that reported every dosage variable.
- We examined compliance to individual dosage variable (ie, frequency, intensity, and duration) to explore effects on pain or function according to each attribute.
- We explored treatment effects when including only trials at overall low risk of bias (ie, were judged to have low risk of bias on at least three of six bias domains, as per our Cochrane review[9]).

RESULTS

Study selection. The literature search resulted in 10,314 articles, with 10,262 being screened on title and abstract after removal of duplicates. After screening 768 records in full text, 100 trials, with 9,364 participants, were included in the final analyses (Figure 1).

Study characteristics. Supplementary Material 2 provides an overview of the study characteristics. Twenty-five trials (25%; 3,290 participants) involved interventions evaluating combined aerobic and resistance exercises.[23–47] Sixty-six trials (66%; 5,231 participants) involved resistance exercise only.[48–113] Twelve trials (12%; 958 participants) involved aerobic exercise only.[62,92,103,114–122] Three trials were included in analyses for both resistance exercise and aerobic exercise[62,92,103] because they were all three-arm trials with one arm receiving aerobic exercise and one arm receiving resistance exercise. Participants were, on average, 63.0 years old (SD 6.0; range 40.6–80.5), with a mean BMI of 29.6 (SD 3.1; range 22.4–37.9). The proportion of women ranged from 13% to 100% (mean 71%; SD 17%). The mean intervention duration was 14.9 weeks (SD 17.1 weeks; range 2–104 weeks).

The mean compliance ratio with the ACSM guidelines was 57% (SD 29%; range 0%–100%; Supplementary Material 2 and 3). Of the 25 trials (3,290 participants) evaluating interventions with combined aerobic and resistance exercises,[23–47] eight (32%) were ≥60% compliant with the ACSM guidelines.[26,34,42–47] The most poorly reported element was intensity of resistance exercise (not reported in 10 of 25 trials). Of the 66 trials (5,231 participants) involving resistance exercise only,[48–113] 36 (55%) were ≥60% compliant with the ACSM guidelines.[49–53,55–58,60–63,65,67,70,71,74,76,77,80,82,86,88,92–96,98,101,104,109,111–113] The most poorly reported element was intensity (not reported in 25 of 66 trials). Of the 12 trials (958 participants) involving aerobic exercise only,[62,92,103,114–122] 7 (58%) were ≥60% compliant with the ACSM guidelines.[62,92,103,114,117–119] The most poorly reported element was duration (not reported in 3 of 12 trials).

Pain was measured by all but four studies (4%).[35,72,79,94] Forty-two studies (42%) measured pain using visual analog scale (VAS)/ numeric rating scale (NRS).[25–28,30,32,36,37,40,41,48,49,52–54,58,59,61,64,66,67,69,71,74–76,80–83,92,98–101,103,106,110,112,114,122,123] Forty-six studies (46%) measured pain using the Knee Injury and OA Outcome Score (KOOS)/ Western Ontario and McMaster Universities OA Index (WOMAC).[23,24,29,31,33,38,39,42,43,45,47,50,51,55–57,63,65,68,70,73,77,78,84–87,89–91,93–95,97,102,105,107–109,111,113,116–120,124] Three studies (3%) measured pain using the Arthritis Impact Measurement Scale (AIMS).[34,46,115] One study (1%) used a 1 to 6 scale,[62] two

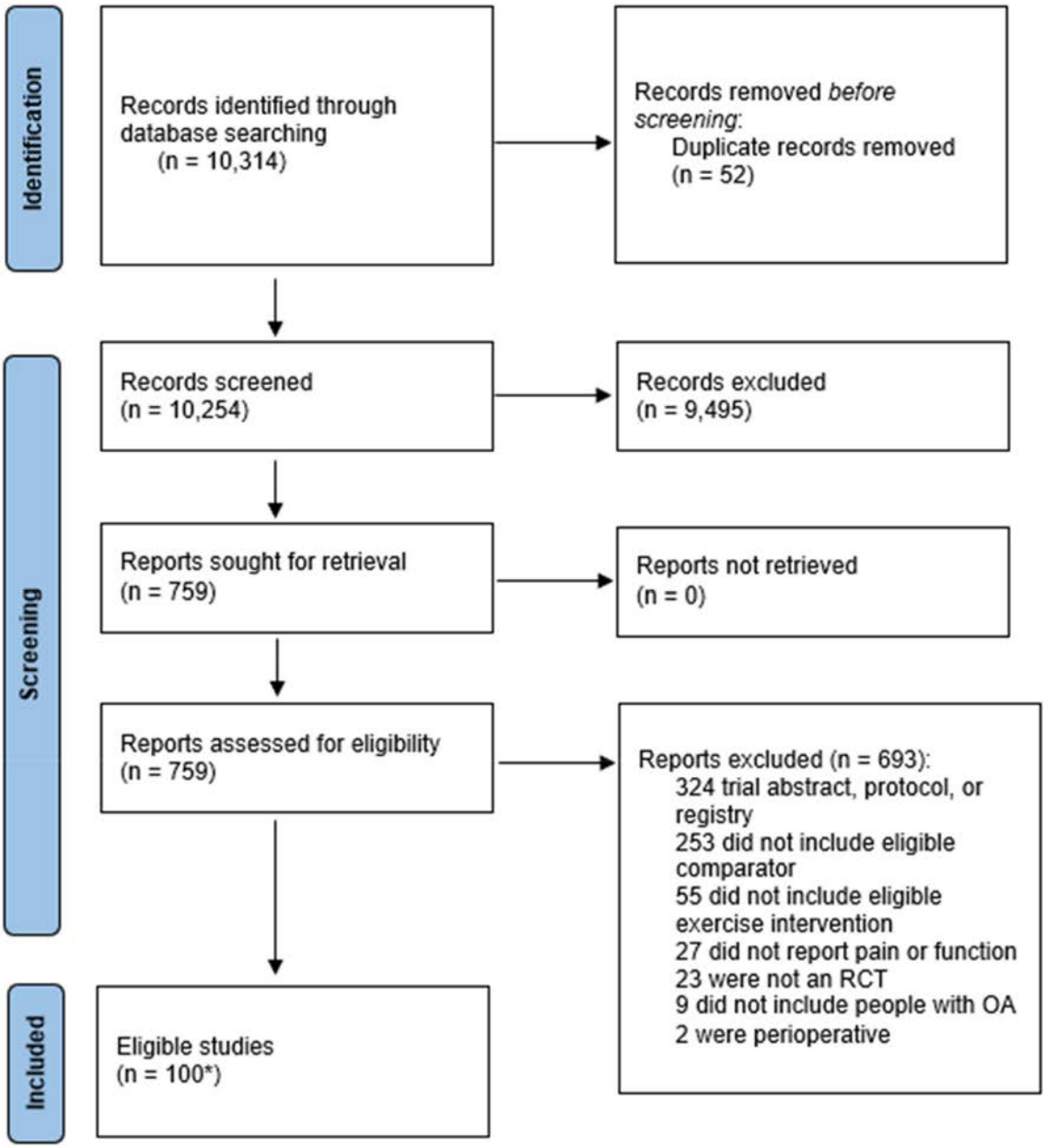


Figure 1. Flow chart of randomized controlled trials included in the systematic review and meta-analysis. *Chart includes an additional 34 trials from the prior version of the Cochrane review.[7] OA, osteoarthritis; RCT, randomized controlled trial.

(2%) used the Lequesne index,[60,88] one (1%) used the McGill Questionnaire,[121] and one (1%) used the OA Screening Index (OASI).[104]

Physical function was measured by all but eight studies (8%).[34,40,49,80,82,88,112,121] Seventy-seven studies (77%) measured function using the KOOS activities of daily living or WOMAC physical function subscale.[23,24,26–33,35–39,41–43,45,47,48,50–57,61,63–66,68,70,72–75,77–79,81,83–87,89–95,97,99–103,105–109,111,113,114,116–120,122,124] Two studies (2%) used the Lequesne index,[58,60] three (3%) used the AIMS,[25,46,115] two (2%) used global disability score,[59,76] two (2%) used the Impact of Rheumatic Diseases on General Health and Lifestyle scale,[69,110] one (1%) used the Algofunctional Index,[98] one (1%) used a 1 to 6 scale,[62] one (1%) used VAS/NRS,[67] one (1%) used the OASI,[104] one (1%) used a patient-specific functional scale,[96] and one (1%) used the Short Form 36.[71]

Risk of bias. Supplementary Material 4 shows risk of bias for included trials. Forty-four studies (44%) adequately generated a random sequence and concealed the sequence until allocation; thus, we considered these studies at low risk of selection bias.[23,26,27,29,32,33,36,37,43,47,49–53,58–60,62,64–66,68,70,73,74,78,80,83–85,92,93,97,100,106,107,110–112,116,118,122,124] Fifty-six studies (56%) did not report their method of randomization, and we judged their risk

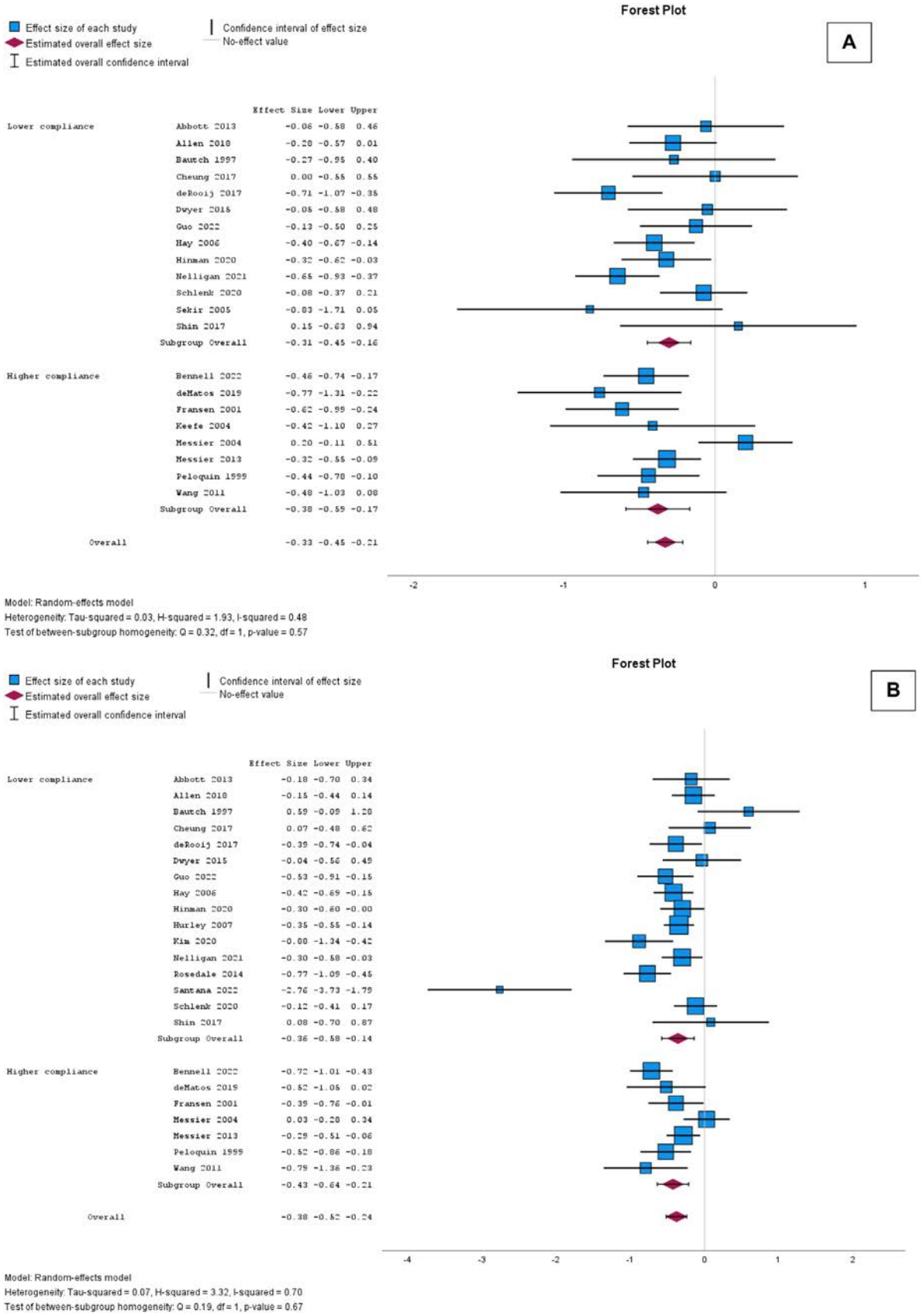


Figure 2. Forest plot of effects (standardized mean differences) of mixed programs (comprising resistance and aerobic exercise) on (A) pain and (B) physical function. Negative values favor exercise. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25451/abstract.

of selection bias as unclear.[24,25,28,30,31,34,35,38–42,45,46,48,54–57,61,63,69,71,72,75–77,79,81,82,86–91,94–96,98,99,101–105,108,109,113–117,119–121]

Six studies (6%) adequately blinded participants and investigators to their treatment by using limited disclosure and/or an adequate comparison intervention that enabled blinding.[30,32,36,50,53,57] Thus, we considered these studies at low risk of performance bias. The nature of the interventions in the remaining 94 studies (94%) precluded blinding of participants to treatment allocation, and therefore, we judged them at high risk of performance bias. All outcomes were self-reported by participants. Six studies (7%) adequately blinded outcome assessors via limited disclosure,[30,32,36,50,53,57] and these were therefore considered to have a low risk of detection bias. As participants were unblinded in the remaining 94 studies (94%), we considered them to be at high risk of detection bias.

Attrition bias was unlikely in 50 studies (50%) because the number of drop outs were small (<20%) and consistent across interventions and/or authors used ITT analyses.[23,24,26–29,31,32,35,36,40,43,45,47–55,59,62,65,72–74,77,78,80–85,90,92,100–102,104,105,107,108,110,111,116,122,124] There was a high risk of bias in 50 studies (50%) as the number of drop outs was large (>20%) and/or authors did not use ITT analyses.[25,30,33,34,37–39,41,42,46,56–58,60,61,63,64,66,68–71,75,76,79,86–89,91,93–99,103,106,109,112–115,117–121]

Reporting bias was unlikely in 35 studies (35%) because these were prospectively registered, and results for all outcomes in the trial registry were reported.[23,26,27,29,31–33,36,37,39,51–53,56,60,61,63,66,68,80,84,86,92–95,97,99,105,106,114,116,118,119,122] Reporting bias was unclear in 65 studies (65%) because the trial registry was inaccessible.[25,30,34,35,38,40–43,45–48,50,54,55,57–59,62,64,65,69–79,81–83,85,87–91,95,98,100–104,107–113,115,117,120,121,124] Reporting bias was likely in five studies (4%) because they were unregistered or did not report all outcomes reported in their registry.[24,28,49,58]

Results of meta-analyses. Of the 25 trials (3,290 participants) evaluating interventions with combined aerobic and resistance exercises,[23–47] 8 (32%) were ≥60% compliant with the ACSM guidelines.[26,34,42–47] There were no differences in pain (higher compliance SMD: −0.38 [95% CI −0.59 to −0.17]; lower compliance SMD: −0.31 [95% CI −0.45 to −0.16]; I^2 = 48%; Figure 2) or physical function (higher compliance SMD: −0.43 [95% CI −0.64 to −0.21]; lower compliance SMD: −0.36 [95% CI −0.58 to −0.14]; I^2 = 70%; Figure 2).

Of the 66 trials (5,231 participants) involving resistance exercise only,[48–113] 36 (55%) were ≥60% compliant with the ACSM guidelines.[49–53,55–58,60–63,65,67,70,71,74,76,77,80,82,86,88,92–96,98,101,104,109,111–113] There were no differences in pain (higher compliance SMD: −0.60 [95% CI −0.81 to −0.39]; lower compliance SMD: −0.93 [95% CI −1.27 to −0.59]; I^2 = 89%; Figure 3) or physical function (higher compliance SMD: −0.64 [95% CI −0.83 to −0.44]; lower compliance SMD: −0.85 [95% CI −1.20 to −0.49]; I^2 = 89%; Figure 3). Egger's test indicated there was risk of publication bias (Supplementary Material 5).

Of the 12 trials (958 participants) involving aerobic exercise only,[62,92,103,114–122] 7 (58%) were ≥60% compliant with the ACSM guidelines.[62,92,103,114,117–119] There were no differences in pain (higher compliance SMD: −0.79 [95% CI −1.20 to −0.38]; lower compliance SMD: −1.00 [95% CI −2.52 to 0.53]; I^2 = 93%; Figure 4) or physical function (higher compliance SMD: −0.83 [95% CI −1.27 to −0.38]; lower compliance SMD: −0.76 [95% CI −2.02 to 0.50]; I^2 = 93%; Figure 4). Results were comparable in our sensitivity analyses (Supplementary Material 6–9).

DISCUSSION

The aim of this systematic review was to determine if higher compliance with ACSM exercise prescription guidelines influences exercise outcomes in knee OA. We found no difference in exercise effects between programs with higher and lower compliance to ACSM prescription parameters, suggesting that exercise dosage may not be an important factor driving symptom improvement in knee OA. However, given the heterogeneity and overall poor quality of included publications, our results should be interpreted with caution.

Our review is the first to examine whether exercise outcomes differ according to high and low compliance with ACSM prescription guidelines across different types of exercise (ie, aerobic, resistance, and combined aerobic and resistance programs). Our findings reflect similar prior research in knee OA. Another meta-analysis, pooling data from 15 RCTs involving resistance, aerobic, or flexibility exercise, found that there were no differences in effects on pain or function between trials with higher and lower ACSM compliance.[11] Similarly, two other meta-analyses comparing effects of resistance exercise programs that were and were not ACSM compliant found no difference in pain or function.[12,125] Interestingly, this contrasts with a similar meta-analysis in hip OA,[13] which included 12 RCTs and found interventions with higher ACSM compliance resulted in larger improvements in pain and function. This may be because the authors of that review used a slightly different compliance scoring system to ours, in which they used a scoring scale from 0 to 2 and awarded one point to trials that did not report a relevant dosage variable. Our scoring system was more stringent in that we awarded zero points when dosage variables were not reported.

Our sensitivity analyses found that compliance and noncompliance with each individual ACSM dosage variable (frequency, intensity, and duration/sets/reps) made no difference to effects of exercise on pain and function. These findings are supported by RCTs[126–129] and meta-analyses[9,125,130–132] that found effects of exercise on pain and function do not vary based on intensity, frequency, or duration of the prescribed program. The collective evidence suggests that a dose-response relationship between exercise and symptoms of pain and function may not exist in knee OA. The exact mechanisms behind the effect of exercise on symptoms of pain and function are unclear,[133] with recent

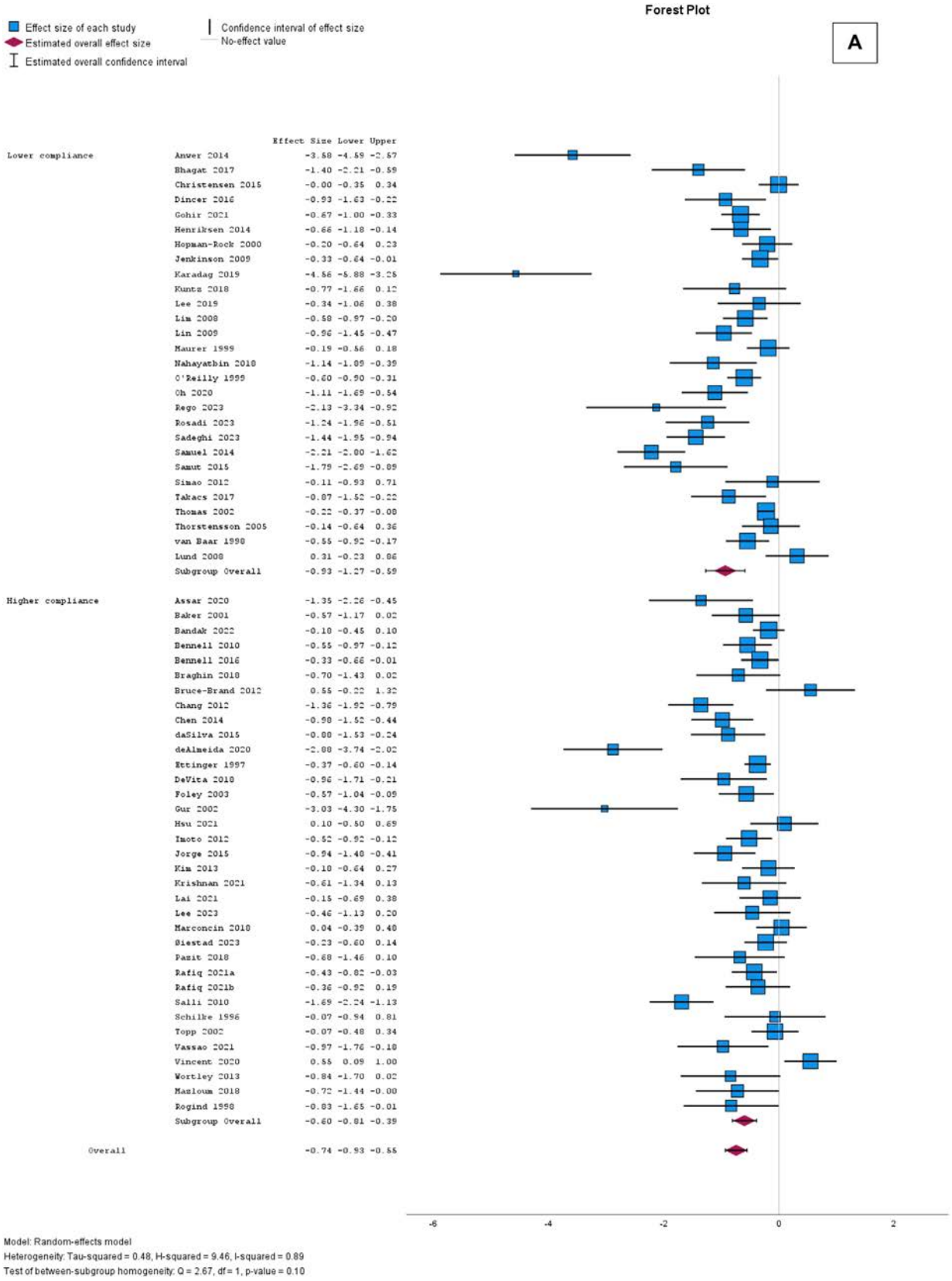
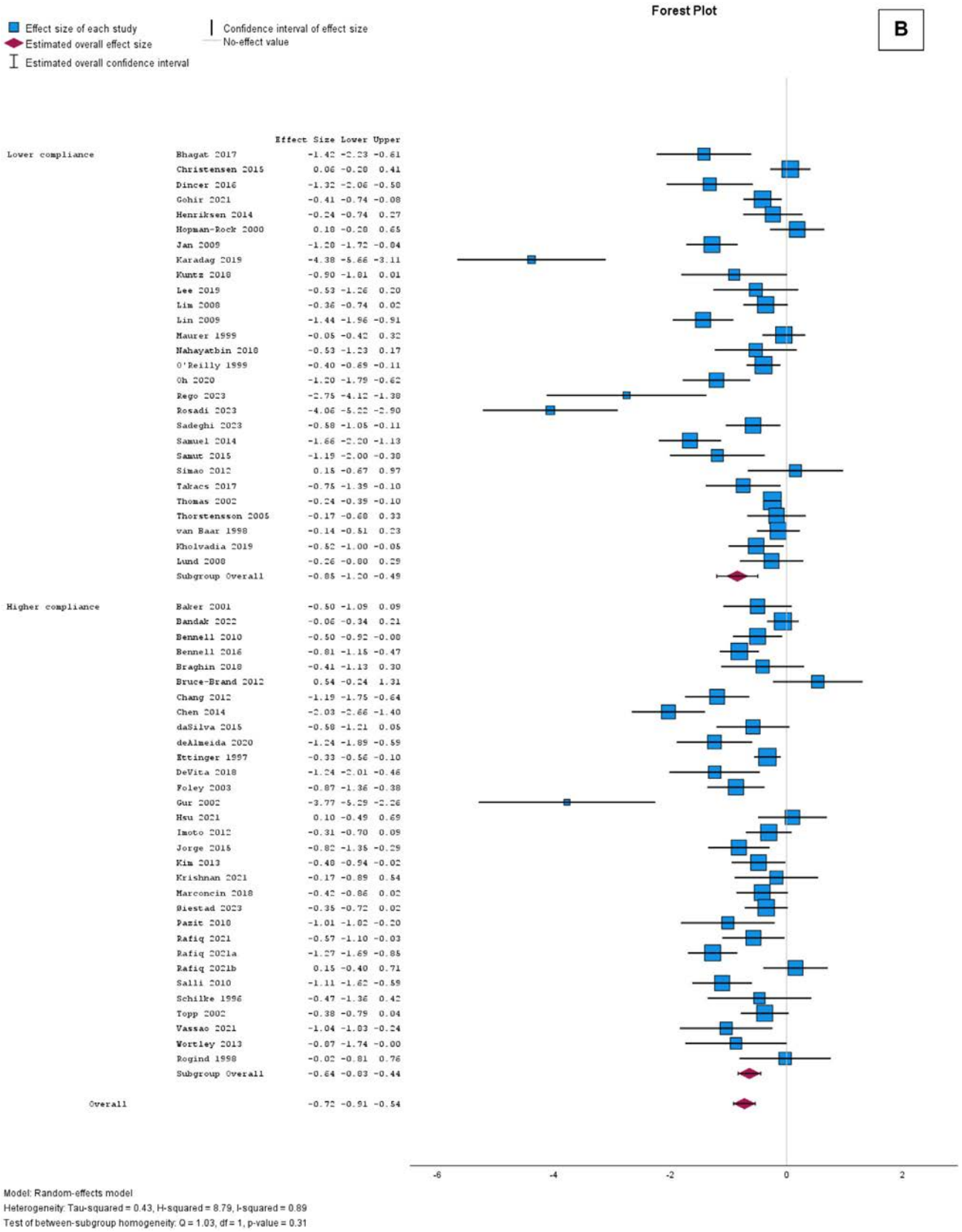


Figure 3. Forest plot of effects (standardized mean differences) of resistance exercise on (A) pain and (B; next page) physical function. Negative values favor exercise. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25451/abstract.

Figure 3 (Continued)



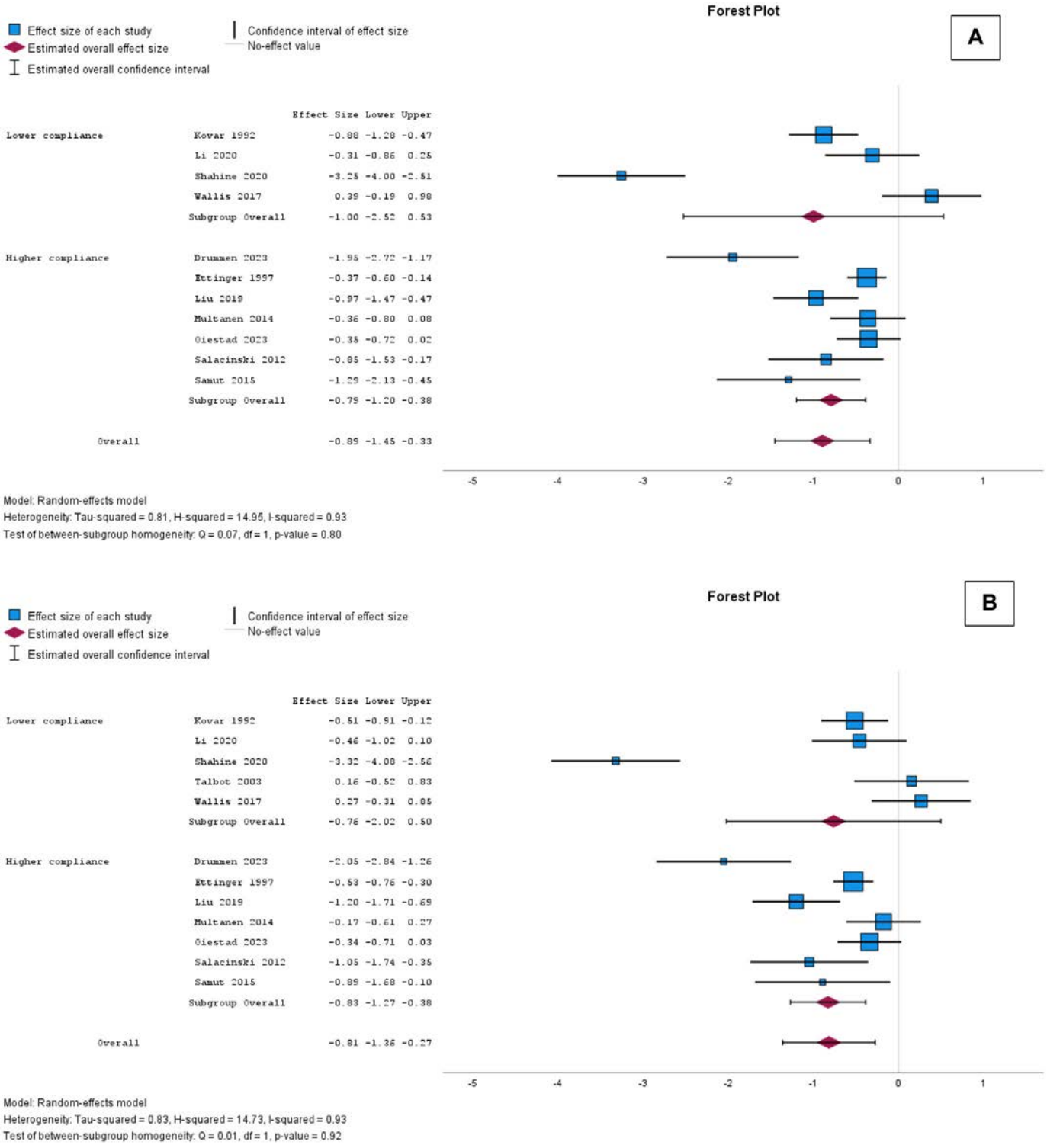


Figure 4. Forest plot of effects (standardized mean differences) of aerobic exercise on (A) pain and (B) physical function. Negative values favor exercise. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25451/abstract.

evidence suggesting that physiologic mechanisms (including change in muscle strength, proprioception, and range of motion) may play no, or only a minimal, role.[134] Psychosocial factors, including self-efficacy, pain beliefs, and fear of movement, may play a more substantial role.[135,136] Further, some of the improvements in pain and function observed with exercise are likely driven by contextual factors and placebo response.[51,137,138]

Our findings suggest that, for improvements in pain and function, people with knee OA can engage with an exercise program with either high or low ACSM compliance. Health care

providers may not need to focus on prescribing knee OA programs at a specific dosage and instead may use a more individualized approach based on a dosage that is feasible for the patient. However, as per the ACSM guidelines,[10] exercise programs that are compliant with recommendations may enhance other health outcomes that our review did not assess, such as muscle strength or cardiovascular health. There is some evidence from non-OA populations that aerobic exercise programs that are compliant with ACSM guidelines may have additional benefits for cardiovascular health[139,140] and systemic inflammation,[141,142] as well as decreased risk of comorbidities.[143] A prior meta-analysis in people with knee OA found that resistance exercise programs that are ACSM compliant are associated with greater benefits for muscle strength.[12] However, a recent meta-analysis of 178 trials in healthy adults found that all types of resistance exercise prescription (in terms of loads, sets, and frequency) were better than no exercise for improving muscle strength and hypertrophy,[144] suggesting any dosage of resistance exercise may be sufficient for muscle benefits.

We have low certainty in our findings, and they should be interpreted with caution. Between-study heterogeneity was substantial, indicated by the large I^2 values (range 48%–89%). This is likely explained by differences between trials regarding participant demographics, comparator group, exercise setting (eg, gym-based vs home-based, supervised vs unsupervised, and delivered in-person vs remotely via technology), and duration of the intervention. We also found evidence of publication bias among resistance exercise trials, suggesting potential overestimation of treatment effects. The majority of included trials were of poor quality (86% were deemed to be at overall unclear or high risk of bias, where ≥3 of 6 domains were at unclear or high risk of bias), and 39% of trials comprised small sample sizes (<50 participants). In addition, ACSM prescription variables were generally not well reported among included trials, with 43% not reporting at least one variable. Future trials should ensure that all elements of exercise intervention dosage are adequately described.[145]

Our review has limitations. Firstly, when evaluating ACSM compliance, we scored any dosage variables that were not reported (or were unclear) as being noncompliant. This may have resulted in misclassification, and potential differences may have been attenuated. However, results remained comparable in our sensitivity analyses in which only trials that had no missing or unclear data were included. Secondly, we do not know whether the exercise programs prescribed to participants accurately reflects what participants actually did during the intervention. Only 51% of included trials used some kind of measure of adherence, and because there was substantial heterogeneity in how this was measured, we did not use this data to inform our analyses. Finally, we pooled relevant exercise programs together regardless of their comparator group. This may have had an influence on the size of effect that was observed because the type of comparator used in OA exercise trials has been shown to influence effect size.[146]

Higher or lower compliance with ACSM exercise prescription guidelines did not influence exercise outcomes. However, given there was substantial heterogeneity and many publications were at risk of bias, our results should be interpreted with caution.

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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 Lawford 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.

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Evaluating Criteria for Symptoms Suggestive of Early Osteoarthritis Over Two Years Post–Anterior Cruciate Ligament Reconstruction: Data From the New Zealand Anterior Cruciate Ligament Registry

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Objective. The objectives were to determine the prevalence of meeting criteria for symptoms suggestive of early osteoarthritis (OA) after anterior cruciate ligament reconstruction (ACLR) and to characterize the longitudinal changes in these symptoms during the first two years post-ACLR.

Methods. We analyzed data from 10,231 patients aged 14 to 40 years in the New Zealand ACL Registry who completed the Knee Injury and Osteoarthritis Outcome Score (KOOS) at 6, 12, and 24 months post-ACLR. Symptoms suggestive of early OA were defined as scoring ≤85% on at least two of four KOOS subscales. Longitudinal patterns of change were categorized as persistent, resolution, new, inconsistent, or no symptoms across the three visits. Prevalence and odds ratios (ORs) of symptoms were compared across visits, sex, and age groups using generalized estimating equations, and longitudinal patterns of symptom change were analyzed using multinomial logistic regression.

Results. Prevalence of meeting criteria of symptoms suggestive of early OA was 68% at 6 months, 54% at 12 months, and 46% at 24 months post-ACLR. Longitudinally, 33% had persistent symptoms, 23% had no symptoms, 29% showed symptom resolution, 6% developed new symptoms, and 9% had inconsistent symptoms. Women consistently showed higher odds of symptoms (OR range 1.17–1.52). Older age groups demonstrated higher odds of symptoms, particularly at 6 months (OR range 1.64–2.45).

Conclusion. Symptoms suggestive of early OA are highly prevalent within two years post-ACLR, with one third of patients experiencing persistent symptoms. These findings indicate that symptoms are more likely to persist rather than newly develop, emphasizing the importance of early identification and targeted interventions.

INTRODUCTION

Knee osteoarthritis (OA) is a common and debilitating condition that frequently develops after anterior cruciate ligament reconstruction (ACLR).[1,2] Approximately one in three people will demonstrate radiographic knee OA within 10 years after an ACLR.[3] The onset of knee OA often manifests as subtle and insidious knee symptoms and functional deterioration in the absence of detectable joint space narrowing on radiographs.[4–6] Recent efforts have proposed an early OA classification criteria that operationally defines symptoms suggestive of early OA based on a combination of scores on the subscales of a patient-reported questionnaire.[7–10] Although these symptoms alone do not definitively indicate early OA, they represent an important aspect of potential early OA development that can be assessed using widely available patient-reported outcome measures. It is crucial to assess these symptoms because they may act as early markers of OA and significantly affect a patient's quality of life and ability to function. At six months after ACLR—when postsurgical pain should be classified as chronic pain[11,12]—one third of

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SIGNIFICANCE & INNOVATION

- This study demonstrates a high prevalence of participants meeting a criteria of symptoms suggestive of early osteoarthritis (OA) within the first two years after anterior crucial ligament reconstruction (ACLR), using data from the New Zealand ACL Registry. The prevalence decreases from 68% at 6 months to 46% at 24 months, indicating a persistent issue despite some improvement over time.
- Our findings reveal that about one third of the patients persistently met a criteria of symptoms suggestive of early OA throughout the two years post-ACLR. This underscores the chronic nature of symptoms post-ACLR and the necessity for ongoing management.
- The research highlights significant sex- and age-related differences in the prevalence and persistence of symptoms suggestive of early OA, with women and older age groups being more susceptible.
- This study offers valuable insights into the patterns of symptom development and persistence post-ACLR, emphasizing the need for early identification of at-risk individuals and targeted interventions to optimize long-term joint health and prevent disability.

people exhibit significant symptoms that meet this classification criteria's definition of symptoms suggestive of early OA.[9] Although people commonly assume that symptoms at six months post-ACLR are attributable to the surgery and will continue to improve over time, it is unclear how a patient's symptom status on this criteria changes during the first two years after ACLR. Therefore, it is crucial to understand how a patient's status on this criteria for symptoms suggestive of early OA evolves during the first two years after ACLR to determine whether symptoms at six months typically resolve, persist, or fluctuate over this period.

A recent review compiled data across multiple cross-sectional and longitudinal studies to highlight that patient-reported outcomes often do not return to normative levels after ACLR,[13] even after rehabilitation. Prior studies typically use continuous Knee Injury and Osteoarthritis Outcome Score (KOOS) scores to understand overall group means over time,[13] which may obscure individual patient experiences. Using classification criteria may better identify the number of patients who meet a threshold for symptoms suggestive of early OA.[8] Recently, a study used the symptoms suggestive of early OA classification criteria to investigate the longitudinal change in meeting this symptom criteria from 6 to 12 months after ACLR.[14] This study found that 22% of participants persistently meet the criteria for symptoms suggestive of early OA at consecutive visits from roughly 6 to 12 months after ACLR, whereas only 9% of participants progressed from not meeting to meeting the symptom criteria across the two visits.[14] However, results from the aforementioned study have limited generalizability because they were from a single center and a relatively short-term follow-up period.[14] Larger-scale, population-based studies are needed to confirm the prevalence and change in meeting this symptom criteria in the first two years after ACLR. Studying longitudinal data in a national registry will delineate recovery patterns of this criteria for symptoms suggestive of early OA in a real-world sample.

Additionally, the large and robust data set in a population-based study will allow us to better understand how important factors may influence how patients change in meeting this criteria for symptoms suggestive of early OA after ACLR. Because factors such as sex and age can influence symptoms or the onset of OA after ACLR,[15–18] these represent important factors that may affect whether or not a patient may meet this symptom criteria across visits after ACLR. This information will be valuable for identifying people with symptoms suggestive of early OA after ACLR, who likely need additional interventions to alleviate pain and facilitate secondary prevention efforts to optimize long-term joint health after ACLR.[19–21]

Therefore, we aim to build upon prior research by using population-based New Zealand ACL Registry data. Specifically, we evaluated the performance of the criteria for symptoms suggestive of early OA by determining the prevalence at 6, 12, and 24 months after ACLR and characterized the longitudinal change in early OA symptom status across all visits. Given previous findings that factors such as sex and age can influence the onset of OA after ACLR,[15–18] we used regression models to analyze how meeting the criteria for symptoms suggestive of early OA differed across sex, age groups, visit time points, and their interactions. The initial Luyten classification criteria to define early OA use clinical examination findings and symptoms, as well as radiographs, to rule out someone with radiographic signs of OA.[8] We focused on their operational definition of symptoms similar to prior ACLR studies.[9,14,22] We have elected only to use symptoms because young patients during this time after ACLR generally lack radiographic evidence of OA,[23] and industry stakeholders have expressed major concerns about using clinical examination data for multicenter studies (eg, national registries, clinical trials) because of lack of reliability across sites and investigators.[24] We hypothesized that at least one third of people would present with symptoms suggestive of early OA at 6, 12, and 24 months post-ACLR and that a substantial proportion would experience persistent symptoms across each visit. We also expected a higher prevalence of symptoms suggestive of early OA in female patients compared with male patients, as well as older age groups compared with younger age groups.

PATIENTS AND METHODS

This study uses data from the New Zealand ACL Registry, an ongoing nationwide cohort study that prospectively collects outcomes in patients after ACLR across New Zealand.[25,26]

The registry began in 2014, and data submission has been mandatory for all surgeons performing ACLR in New Zealand since 2017. From 2014 to 2022, the registry captured 89% of all ACLR procedures performed nationally.[26] All patients provide informed consent for voluntary participation and use of their data for research and audit purposes. The registry has ethical approval as a quality assurance initiative endorsed by the New Zealand Ministry of Health. Patient demographic information was gathered through a preoperative form. The operating surgeon completed a surgical data form outlining the specifics of each reconstruction procedure. Patients were emailed, texted, or mailed to complete follow-up surveys assessing patient-reported outcomes at standard intervals of 6, 12, and 24 months after ACLR. Patients received up to three reminders to encourage survey completion.

Patients. We first selected participants from the New Zealand ACL Registry who were between 14 and 40 years of age based on a recent consensus statement on the secondary prevention of knee OA after ACL injury.[27] The upper limit of 40 years was chosen to minimize the inclusion of individuals with pre-existing OA, ensuring our focus on post-traumatic OA in a younger population. We then excluded participants who did not have KOOS data available from at least one of the visits at 6, 12, or 24 months post-ACLR. None of the patients were excluded based on operative findings. For a separate subset analysis, we also identified participants with complete KOOS data across all study visits to specifically examine within-participant patterns of change in meeting the criteria for symptoms suggestive of early OA from 6 to 12 to 24 months post-ACLR.

KOOS. The KOOS is a knee-specific patient-reported outcome measure designed to evaluate the effects of knee injuries across the lifespan.[28] The KOOS consists of five subscales: pain, symptoms, activities of daily living (ADL), sport, and quality of life (QoL). However, only the pain, symptoms, ADL, and QoL subscales are proposed to define symptoms suggestive of early OA status.[8] Each subscale includes items rated on a 5-point Likert scale from 0 (extreme problems) to 4 (no problems). Subscale scores are calculated and transformed to a 0 to 100 scale, with 0 representing severe knee problems and 100 no knee problems. The KOOS subscale scores are subsequently used to make a dichotomous determination of whether a patient meets the classification criteria for symptoms suggestive of early OA.[8]

Classification criteria for defining symptoms suggestive of early OA. We operationally defined the presence of symptoms suggestive of early OA using the symptoms portion of the 2018 Luyten early OA classification criteria.[8] As per the Luyten classification criteria, symptoms suggestive of early OA were identified when a participant scored ≤85% on a minimum of two of the four KOOS subscales: pain, symptoms, ADL, or QoL.[8] These classification criteria for symptoms suggestive of early OA have been employed in assessing participants after ACLR[9,14,22] and specifically in the New Zealand ACL Registry but only at 6 months after ACLR.[29] In the current study, symptoms suggestive of early OA were defined using this Luyten early OA classification criteria at 6, 12, and 24 months post-ACLR. We selected the Luyten criteria over similar Englund KOOS criteria for their greater sensitivity in detecting early OA symptoms (requiring fewer subscales to be below threshold) and their specific design for identifying initial early OA symptoms,[8,30] both of which align well with our goal of capturing a wider range of individuals with potential early OA symptoms in our post-ACLR population.[9] Additionally, we used the original subscale threshold values from the Luyten KOOS criteria rather than the threshold values corresponding to the patient acceptable symptom state because prior research indicated no significant differences in the prevalence and progression of symptoms suggestive of early OA between these two criteria.[14] It is important to note that our operational definition of "symptoms suggestive of early OA" represents only the patient-reported aspect of the full Luyten early OA classification criteria,[8] which also include clinical examination (ie, joint line tenderness or crepitus) and radiographic assessments (ie, Kellgren-Lawrence grade 0 or 1).

Determining longitudinal patterns of change in criteria of symptoms suggestive of early OA. One of the objectives of this study was to determine the longitudinal patterns in a participants' change in meeting a criteria of symptoms suggestive of early OA at 6, 12, and 24 months after ACLR. To define longitudinal change in meeting a criteria of symptoms suggestive of early OA across all three visits, we created a composite variable based on all potential combinations of a participant's symptom status at 6, 12, and 24 months after ACLR. We then summarized these combinations into five groups (Table 1): 1) no symptoms—not meeting the criteria for symptoms suggestive of early OA at any visit; 2) new symptoms—transitioning from not meeting the criteria to meeting the criteria at a later visit; 3) resolution of symptoms—transitioning from meeting the criteria to not meeting the criteria at a later visit; 4) inconsistent symptoms suggestive of early OA; or 5) persistent symptoms—meeting the criteria for symptoms suggestive of early OA at all visits. Table 1 provides a detailed explanation of how the groups are defined based on all possible combinations of meeting the criteria for symptoms suggestive of early OA across the 6-, 12-, and 24-month visits.

Operational definition of sex and age groups for analysis. We used variables to determine how additional factors affected the prevalence of meeting a criteria of symptoms suggestive of early OA after ACLR: 1) sex and 2) age group. Sex assigned at birth was dichotomized as male and female. Age at the time of surgery was stratified into the following age groups: a) ≤18 years, b) 18.1 to 22 years, c) 22.1 to 30 years, and d) 30.1 to 40 years. These age ranges were chosen to reflect

Table 1. Defining the groups for longitudinal change in early knee OA symptom across visits at 6, 12, and 24 months after ACLR*

Longitudinal pattern of symptoms suggestive of early OA	Symptoms suggestive of early OA across all visits (6, 12, or 24 months)
No symptoms suggestive of early OA	0, 0, 0
New early symptoms	0, 1, 1 or 0, 0, 1
Resolution of symptoms suggestive of early OA	1, 0, 0 or 1, 1, 0
Inconsistent symptoms suggestive of early OA	0, 1, 0 or 1, 0, 1
Persistent symptoms suggestive of early OA	1, 1, 1

* The three numbers indicate their longitudinal change in meeting a criteria of symptoms suggestive of early OA at 6, 12, and 24 months post-ACLR. 0, not meeting the criteria of symptoms suggestive of early OA; 1, meeting the criteria of symptoms suggestive of early OA. ACLR, anterior cruciate ligament reconstruction; OA, osteoarthritis.

distinct stages of life and activity levels: the ≤18 years group represents adolescents typically in high school, the 18.1 to 22 years group corresponds to young adults likely in college or early adulthood, and the 22.1 to 30 years and 30.1 to 40 years groups represent two phases of early adulthood, allowing for an even distribution and meaningful comparison of outcomes across different stages of adult life. This stratification helps in understanding how age-related factors influence recovery and symptom development post-ACLR.

Statistical analysis. *Prevalence and odds of symptoms suggestive of early OA.* We began our analysis by descriptively examining the prevalence of symptoms suggestive of early OA across each visit time point after ACLR. Subsequently, we employed a generalized estimating equation (GEE) model with an exchangeable correlation to determine how sex and age were related to the prevalence of these symptoms at 6, 12, and 24 months post-ACLR, as well as how they were associated with changes in meeting the criteria for early OA across visits. The outcome variable was defined as the presence/absence of symptoms suggestive of early OA. Predictor variables included sex, visit time points, and age, with male sex, 6 months, and the youngest age group as reference categories, respectively. The model included interaction terms for sex × visit and age × visit to examine how the effects of sex and age group on symptom prevalence and changes in early OA status varied across visits. Using a logit link function, we modeled the log odds of the presence of symptoms suggestive of early OA. This approach allowed us to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for each predictor, as well as the ratios of longitudinal ORs. These ratios of longitudinal ORs indicate the differences in change in odds between the levels of sex and age group from 6 to 12 months and 12 to 24 months post-ACLR. We used contrast statements to assess these differences in changes of early OA status. This quantified how sex and age were associated with the likelihood of changing symptom status over time, expressed as ratios of longitudinal ORs. The analysis, performed using SAS software (SAS Institute Inc., Cary, NC), accounted for the correlated nature of repeated measures within participants and provided detailed insights into the associations among sex, age, and both the prevalence and longitudinal changes of symptoms suggestive of early OA at each time point. To ensure robust findings and evaluate the impact of missing data, we conducted the analysis using both the full sample and the subset with complete KOOS data at all three visits (6, 12, and 24 months).

Within-participant longitudinal pattern of change in symptoms suggestive of early OA. Using the subset of participants who had complete data across all time points, we analyzed the within-participant longitudinal patterns of change in symptoms suggestive of early OA after ACLR. We first conducted a descriptive examination to determine the prevalence of different within-participant longitudinal patterns: no symptoms (reference category), new symptoms, resolution of symptoms, inconsistent symptoms, and persistent symptoms. We then employed multinomial logistic regression to assess the associations of sex and age with these within-participant patterns of symptoms suggestive of early OA. Predictor variables included sex (referenced to male patients) and age group (categorized with "<18 years" as the reference). We used the generalized logit link function to model the log odds of each category of longitudinal pattern relative to the reference category (no symptoms). This approach allowed us to calculate ORs and 95% CIs for each predictor, providing insights into how sex and age group were associated with the odds of experiencing different within-participant longitudinal patterns of symptoms suggestive of early OA compared with having no symptoms over the 24-month period post-ACLR.

RESULTS

Prevalence and odds of symptoms suggestive of early OA. Of the 10,231 participants with KOOS data available at any visit post-ACLR, 3,693 had complete data across all three visits (6, 12, and 24 months). Table 2 highlights that participants with complete data were similar in age (26.7 vs 26.1 years) and time to surgery (8.4 vs 8.2 months) compared with the larger cohort but had a slightly higher proportion of female patients (52% vs 46%) and hamstring tendon autografts (69% vs 64%). Our analysis revealed a decreasing trend in the overall prevalence of symptoms suggestive of early OA over time post-ACLR (Table 3). At 6 months post-ACLR, 68% of patients met the criteria for symptoms suggestive of early OA. This prevalence decreased to 54% at 12 months and further reduced to 46% at 24 months post-ACLR. Despite this decreasing trend, the overall prevalence remains alarmingly high at 24 months. Notably, the results were consistent in the smaller subset analysis with

Table 2. Demographic and surgical characteristics of participants with data at all visits compared with those with data at any visit post-ACLR*

Variable	Participants with data at all visits (n = 3,693)	Participants with data at any visit (n = 10,231)
Age, mean ± SD, y	26.7 ± 7.2	26.1 ± 7.1
Months to surgery, mean ± SD	8.4 ± 17.6	8.2 ± 17.0
Sex, n (%)		
Female	1,916 (52)	4,722 (46)
Male	1,777 (48)	5,509 (54)
Autograft, n (%)		
Bone patellar tendon bone	967 (26)	2,249 (30)
Hamstrings tendon	2,540 (69)	4,807 (64)
Quadriceps tendon	94 (3)	267 (4)
Missing	92 (2)	201 (2)
Chondroplasty, n (%)		
No	3,545 (96)	9,800 (96)
Yes	148 (4)	431 (4)
Microfracture, n (%)		
No	3,609 (98)	9,984 (98)
Yes	84 (2)	247 (2)

* This table presents a comparison of demographic and surgical characteristics between participants who had complete data at all follow-up visits (n = 3,693) and those who had data at any visit (n = 10,231) after ACLR. The table includes mean ± SD for continuous variables (age and months to surgery) and frequencies (percentages) for categorical variables (sex, autograft type, chondroplasty, and microfracture). This comparison allows for an assessment of potential differences between the complete case cohort and the larger sample with any available data. ACLR, anterior cruciate ligament reconstruction.

complete data across all visits when compared with the larger group (Supplementary Table 1).

Table 3 presents detailed ORs and 95% CIs for all analyses of the prevalence of symptoms suggestive of early OA at each time point. To avoid redundancy, the specific statistics are not repeated in the text below. Compared with male patients, female patients consistently demonstrated higher odds of experiencing symptoms suggestive of early OA across all time points, with the difference being most pronounced at 6 months post-ACLR and slightly attenuated at 12 and 24 months. When examining the ratio of longitudinal ORs for changes in meeting the criteria for symptoms suggestive of early OA, female patients showed lower odds of change compared with male patients from 6 to 12 months post-ACLR, but no significant difference from 12 to 24 months (Table 4). These results were similar in the smaller subset with complete data across all visits (Supplementary Tables 1 and 2).

Age-related differences were also observed, with comparisons made relative to the reference group of ≤18 years (Table 3). At 6 months post-ACLR, all older age groups showed significantly higher odds of symptoms suggestive of early OA compared with the adolescent group (≤18 years). At 12 months, the differences persisted but were less pronounced, with significantly higher odds in the 22.1 to 30 years and 30.1 to 40 years groups, whereas the 18.1 to 22 years group showed nonsignificant elevated odds. By 24 months, only the 30.1 to 40 years group maintained significantly higher odds, whereas the younger adult groups did not show statistically significant differences compared with adolescents. Longitudinal analysis of changes in symptoms suggestive of early OA revealed that all older age groups had lower ratios of longitudinal odds of changing symptom status compared with the adolescent group, with this effect being more pronounced from 6 to 12 months than from 12 to 24 months post-ACLR (Table 4). These results were consistent in the smaller subset with complete data across all visits (Supplementary Tables 1 and 2).

Within-participant longitudinal pattern of change in symptoms suggestive of early OA. Descriptive analysis revealed the following distribution of longitudinal patterns of symptoms suggestive of early OA across all 3,693 participants (Table 5): no symptoms (23%, n = 859), new symptoms (6%, n = 226), resolution of symptoms (29%, n = 1,055), inconsistent symptoms

Table 3. Prevalence and ORs of symptoms suggestive of early OA at 6, 12, and 24 months post-ACLR stratified by sex and age group*

	6 months (n = 8,275)		12 months (n = 7,224)		24 months (n = 5,372)		Visit × group interaction
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	*P* value
All (n = 10,231)	5,638 (68)		3,890 (54)		2,496 (46)		
Sex							
Male (n = 5,509)	2,789 (65)	REF	1,963 (52)	REF	1,222 (44)	REF	<0.0001
Female (n = 4,722)	2,849 (72)	1.52 (1.38–1.67)	1,927 (56)	1.19 (1.09–1.31)	1,274 (49)	1.17 (1.06–1.30)	
Age							
≤18 y (n = 1,581)	701 (55)	REF	474 (45)	REF	339 (43)	REF	<0.0001
18.1–22 y (n = 1,734)	888 (64)	1.64 (1.41–1.92)	582 (49)	1.27 (1.08–1.49)	394 (46)	1.13 (0.94–1.36)	
22.1–30 y (n = 3,796)	2,179 (72)	2.34 (2.05–2.68)	1,481 (55)	1.58 (1.37–1.82)	898 (45)	1.16 (0.99–1.36)	
30.1–40 years (n = 3,120)	1,870 (72)	2.45 (2.13–2.81)	1,353 (59)	1.86 (1.61–2.15)	865 (49)	1.33 (1.14–1.57)	

* This table presents the prevalence and ORs with 95% CIs for symptoms suggestive of early OA at 6, 12, and 24 months post-ACLR. Data are stratified by sex and age groups, with comparisons made to the reference categories (male patients and ≤18 years age group) at each time point. Significant interaction effects between visit time points and groups (sex and age) are noted with *P* values <0.0001. This table highlights the variations in early OA symptom prevalence and risk across different demographic groups over time. ACLR, anterior cruciate ligament reconstruction; OA, osteoarthritis; OR, odds ratio; REF, reference; 95% CI, 95% confidence interval.

Table 4. Ratio of longitudinal ORs of change in symptoms suggestive of early OA across visits post-ACLR, stratified by sex and age group*

	6 to 12 months ratio of longitudinal OR (95% CI)	12 to 24 months ratio of longitudinal OR (95% CI)
Sex		
Male	REF	REF
Female	0.79 (0.71–0.87)	0.98 (0.88–1.09)
Age		
≤18 y	REF	REF
18.1–22 y	0.77 (0.64–0.93)	0.89 (0.73–1.09)
22.1–30 y	0.67 (0.57–0.79)	0.73 (0.62–0.87)
30.1–40 y	0.76 (0.64–0.90)	0.72 (0.60–0.86)

* This table presents the group comparisons of longitudinal changes (6 to 12 months, and 12 months to 24 months) in meeting the criteria for symptoms suggestive of early OA after ACLR. Ratios of longitudinal ORs with 95% CIs are provided for comparisons among groups, using male patients and the ≤18 years age group as references. Data are stratified by sex and age groups, highlighting the differential risks of developing symptoms suggestive of early OA over time across demographic categories. Female patients showed lower odds of change in symptom status compared with male patients from 6 to 12 months, but no significant difference from 12 to 24 months. All older age groups demonstrated lower odds of change in symptom status compared with the adolescent group, with this effect being more pronounced from 6 to 12 months than from 12 to 24 months post-ACLR. ACLR, anterior cruciate ligament reconstruction; OA, osteoarthritis; OR, odds ratio; REF, reference; 95% CI, 95% confidence interval.

(9%, n = 342), and persistent symptoms (33%, n = 1,211). This distribution indicates that persistent symptoms are the most common and newly developed symptoms are the least common longitudinal patterns for meeting the criteria of symptoms suggestive of early OA symptoms across 6, 12, and 24 months post-ACLR. Supplementary Table 3 highlights the prevalence of the longitudinal pattern of change in symptoms suggestive of early OA across all eight potential combinations of symptom status across all visits.

Table 5 presents detailed ORs and 95% CIs for all analyses of the longitudinal patterns of symptoms suggestive of early OA. To avoid redundancy, the specific statistics are not repeated in the text below. Compared with male patients, female patients had significantly higher odds of experiencing resolution, inconsistent, and persistent symptoms relative to having no symptoms. The proportion of female patients with persistent symptoms (36%) was higher than that of male patients (30%). Interestingly, the odds of new symptom development relative to no symptoms were not significantly different between sexes.

Compared with adolescents (≤18 years), all other age groups had a greater chance of resolution and persistent symptoms instead of having no symptoms (Table 5). The proportion of participants with persistent symptoms increased with age, from 26% in the ≤18 years group to 37% in the 30.1 to 40 years group. Conversely, the proportion of participants with no symptoms decreased from 33% in the youngest age group to 20% in the oldest. Notably, the odds of incident symptoms relative to no symptoms were not significantly different across age groups.

Table 5. Longitudinal patterns of symptoms suggestive of early OA and corresponding ORs at 6, 12, and 24 months post-ACLR, stratified by sex and age group in patients with complete follow-up data*

	No Sx n (%)	New n (%)	Resolution n (%)	Inconsistent n (%)	Persistent n (%)	No Sx vs new OR (95% CI)	No Sx vs resolution OR (95% CI)	No Sx vs inconsistent OR (95% CI)	No Sx vs persistent OR (95% CI)
All (n = 3,693)	859 (23)	226 (6)	1,055 (29)	342 (9)	1,211 (33)				
Sex									
Male (n = 1,777)	469 (26)	126 (7)	487 (27)	167 (9)	528 (30)	REF	REF	REF	REF
Female (n = 1,916)	390 (20)	100 (5)	568 (30)	175 (9)	683 (36)	0.94 (0.70–1.27)	1.54 (1.28–1.85)	1.30 (1.01–1.68)	1.71 (1.43–2.05)
Age									
≤18 y (n = 521)	171 (33)	48 (9)	104 (20)	62 (12)	136 (26)	REF	REF	REF	REF
18.1–22 y (n = 575)	150 (26)	50 (9)	158 (27)	50 (9)	167 (29)	1.17 (0.74–1.85)	1.87 (1.34–2.61)	0.96 (0.62–1.49)	1.54 (1.12–2.11)
22.1–30 y (n = 1,336)	287 (21)	64 (5)	433 (32)	114 (9)	438 (33)	0.79 (0.52–1.20)	2.68 (2.01–3.58)	1.15 (0.80–1.66)	2.11 (1.61–2.78)
30.1–40 y (n = 1,261)	251 (20)	64 (5)	360 (29)	116 (9)	470 (37)	0.90 (0.58–1.37)	2.61 (1.94–3.51)	1.36 (0.94–1.96)	2.67 (2.02–3.52)

* This table presents the longitudinal patterns of symptoms suggestive of early OA at 6, 12, and 24 months post-ACLR for patients who have KOOS data available at all three time points. The data is stratified by sex and age groups, showing the prevalence of each symptom category (no symptoms, new, resolution, inconsistent, persistent). ORs with 95% CIs are provided for comparisons among groups, using "no symptoms" as the reference category. This table highlights the differences in symptom patterns and risk factors for early OA across different demographic groups, specifically for patients with complete follow-up data at all three visits. ACLR, anterior cruciate ligament reconstruction; KOOS, Knee Injury and Osteoarthritis Outcome Score; OA, osteoarthritis; OR, odds ratio; REF, reference; Sx, symptom(s); 95% CI, 95% confidence interval.

DISCUSSION

This study reveals a substantial prevalence of symptoms suggestive of early OA throughout the first two years after ACLR in 10,231 patients from the New Zealand ACL Registry. We observed a decreasing trend in prevalence from 68% at 6 months to 46% at 24 months post-ACLR, although the prevalence remains alarmingly high even 2 years after surgery. Longitudinal analysis showed 33% of participants persistently met the symptom criteria across all visits, whereas 23% never met the criteria. Significant sex- and age-related differences were observed. Female participants showed higher odds of experiencing symptoms across all time points, yet lower odds of changing symptom status from 6 to 12 months post-ACLR. Age-related differences were most pronounced at 6 months post-ACLR, with older groups demonstrating higher odds of meeting the criteria but lower odds of changing status over time compared with adolescents.

Although symptoms at 6 months post-ACLR are often attributed to postoperative recovery, our data show that these symptoms persist in a substantial proportion of patients through 24 months. This observation is important given that 6 months postsurgery is when postsurgical pain is typically reclassified as chronic.[11,12] The persistence of these symptoms in our study period raises questions about the nature of recovery after ACLR and highlights the need for continued monitoring and potential intervention beyond the immediate postoperative phase. Therefore, patients presenting with symptoms suggestive of early OA, especially those with persistent symptoms, constitute an important at-risk group that could benefit from targeted interventions to alleviate symptoms and potentially prevent progression to established OA.

Our results provide important insights into the prevalence of symptoms suggestive of early OA after ACLR, revealing the persistence of these symptoms over time. Our findings demonstrated that 68% of participants met the criteria for symptoms suggestive of early OA at 6 months post-ACLR, significantly higher than the previously reported 36% at 5 to 7 months.[9] This variation could be due to differences in average age (26.1 vs 20.0 years) and study populations,[9] with the previous study focused on high-volume orthopedic clinics in the United States, whereas the current used national registry data from New Zealand. Future research could explore regional or cultural adjustments to KOOS thresholds for more accurate assessment. Our results also extend previous work by highlighting the decreasing prevalence of symptoms at 12 (54%) and 24 (46%) months. This trend aligns with previous data indicating a decrease in unacceptable symptoms from 1 (43%) to 2 (33%) years post-ACLR.[31] Although the decline may reflect symptom resolution due to rehabilitation, it is concerning that 46% of participants still meet the criteria for symptoms suggestive of early OA at 24 months post-ACLR, indicating persistent issues with pain, function, and QoL.

Our longitudinal analysis provides insights into the natural history of symptom reporting over 2 years post-ACLR, revealing a low prevalence of new symptom development (6%) from 6 to 24 months post-ACLR. Instead, we observed that 33% of participants exhibited persistent symptoms across all visits, whereas 23% reported no symptoms and 29% experienced symptom resolution between visits. These findings indicate that symptoms are more likely to persist rather than newly develop within the first two years post-ACLR, emphasizing the importance of early identification and targeted interventions for those experiencing symptoms at six months postsurgery. Notably, we found that 57% of individuals with symptoms at 6 months continued to have symptoms at 24 months, compared with only 18% of those without symptoms at 6 months developing symptoms at 24 months (Supplementary Table 3). This persistence highlights the chronic nature of symptoms for many participants and underscores the importance of early identification and intervention at six months, when many patients are discharged from care. Although some individuals benefit from rehabilitation and natural recovery, a significant proportion continue to experience chronic symptoms, necessitating a proactive approach and additional therapeutic strategies to manage long-term outcomes effectively. Future studies should focus on understanding how these symptoms relate to the onset of symptomatic knee OA and developing targeted interventions for those at highest risk of persistent symptoms, potentially reducing the risk of long-term issues.[7,32]

Our analysis revealed significant sex-related differences in the prevalence and patterns of symptoms suggestive of early OA. Female patients consistently demonstrated higher odds of experiencing symptoms compared with male patients across all time points post-ACLR (Table 3). This aligns with prior evidence that women generally have worse patient-reported outcomes and higher rates of OA after ACLR.[6,15,16,33,34] Longitudinally, female patients showed higher odds of experiencing resolution, inconsistent, and persistent symptoms relative to having no symptoms. Notably, 36% of female patients exhibited persistent symptoms compared with 30% of male patients. However, our longitudinal GEE analysis revealed an intriguing paradox: Despite higher overall symptom prevalence, female patients had lower odds of changing symptom status from 6 to 12 months post-ACLR, with no significant difference between sexes from 12 to 24 months. This suggests that, although female patients may be more likely to experience symptoms, their symptom status tends to be more stable over time compared with male patients, particularly in the early postoperative period.

Age-related differences were also observed, with older age groups generally showing higher odds of symptoms suggestive of early OA (Table 3). These differences were most pronounced at 6 months post-ACLR, with all older age groups showing significantly higher odds than those ≤18 years. By 24 months, only the 30.1 to 40 years group maintained significantly higher odds. Longitudinally, we observed a clear trend of increasing persistent

symptoms with age, from 26% in the ≤18 years group to 37% in the 30.1 to 40 years group. Conversely, the proportion of participants with no symptoms decreased from 33% in the youngest age group to 20% in the oldest. These findings suggest that older individuals may require more intensive or prolonged rehabilitation strategies to mitigate the risk of persistent symptoms. However, it is important to note that at least one quarter of all age subgroups exhibited persistent symptoms, indicating that age alone does not determine long-term outcomes and that individualized approaches are necessary across all age groups. Our longitudinal GEE analysis further revealed that all older age groups had lower odds of changing symptom status compared with adolescents, particularly from 6 to 12 months post-ACLR. This suggests that, although older individuals are more likely to experience symptoms initially, their symptom status tends to be more stable over time.

This study has several limitations to consider. The use of registry data may introduce selection bias because male patients more commonly experienced missing KOOS data, resulting in a larger proportion of female patients (52%) with complete data at all visits compared with the broader cohort with any data (46%). The generalizability of our findings to other geographic regions is unclear, necessitating similar studies in different cohorts or population-based registries. Although the registry achieved >55% patient-reported outcome follow-up at 2 years post-ACLR,[26] incomplete follow-up data may affect the observed prevalence of symptoms suggestive of early OA at later visits. Continued longitudinal tracking is needed to determine long-term symptom trajectories and predict future symptomatic OA incidence. Additionally, the New Zealand ACL Registry is limited to operative information and patient-reported outcomes, lacking detailed data on concomitant injuries and other factors that could influence post-ACLR outcomes. Similar to prior studies in patients after ACLR,[9,14,22,29,35] our classification of symptoms suggestive of early OA is based solely on patient-reported outcomes using KOOS. However, the full Luyten classification criteria for early OA also include clinical examination and radiographic findings, which were not available in the New Zealand ACL Registry data. Future research should incorporate a multifaceted assessment, including clinical evaluation, structural imaging, biomechanics, and more detailed injury classifications (eg, meniscal involvement) to provide a comprehensive understanding of post-ACLR alterations.[27,32] We acknowledge that excluding patients with incomplete follow-up data for the within-participant longitudinal pattern analysis may introduce selection bias. However, supplementary tables indicate that there were no meaningful differences between this subset and the larger cohort with missing data. Future studies using statistical approaches to impute data could help include a broader sample and further validate our findings. Despite these limitations, this study characterizes symptoms suggestive of early OA in a real-world sample, providing valuable insights into the prevalence and patterns of these symptoms after ACLR.

Our study offers critical insights into the prevalence and change overtime in meeting a criteria for symptoms suggestive of early OA in a large cohort of participants post-ACLR. We found a high prevalence (46%–68%) of symptoms suggestive of early OA, with one third of participants showing persistent symptoms across all study visits. Female patients and older individuals were more likely to experience persistent symptoms suggestive of early OA. These results underscore the importance of improved care and secondary prevention of knee OA, including routine screening and targeted interventions post-ACLR. The study highlights the need for ongoing research and clinical efforts in symptom recovery and OA prevention, especially for those with persistent symptoms post-ACLR.

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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 Harkey 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.

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Prevalence of Clinically Relevant Findings on Magnetic Resonance Imaging in Middle-Aged Adults With Knee Pain and Suspected Meniscal Tear: A Follow-Up

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Objective. Radiographs are frequently obtained for patients with knee osteoarthritis (KOA), with magnetic resonance imaging (MRI) reserved for those with complex KOA. There are few data on how often subsequent MRI reveals clinically actionable but unanticipated findings. The purpose of this study is to estimate the prevalence of these findings on MRI for patients managed nonoperatively for suspected meniscal tears.

Methods. The Treatment of Meniscal Problems and Osteoarthritis (TeMPO) study enrolled patients aged 45 to 85 years with knee pain, osteoarthritis (Kellgren–Lawrence [KL] grades 0–3), and suspected meniscal tear. We reviewed baseline MRI and recorded notable findings, including subchondral insufficiency fractures of the knee (SIFKs), avascular necrosis (AVN), tumors, and nonsubchondral fractures. Other baseline data included demographic characteristics, Knee Injury and Osteoarthritis Outcome Score, duration of knee symptoms, and KL grade.

Results. Study-ordered MRI was performed on 760 patients, with 61 concerning findings identified (8.03%, 95% confidence interval 6.09%–9.96%). A total of 25 participants had SIFKs, 10 had nonsubchondral fractures, 4 had AVN, 8 had benign tumors, and 14 had other clinically relevant findings.

Conclusion. We estimated the prevalence of clinically relevant incidental findings on MRI to be 8.03% in middle-aged adults with mild to moderate KOA and suspected meniscal tear. These data may prompt clinicians to be more aware of the range of findings that can underlie knee symptoms, some of which could change management but may require different modalities of imaging to detect. Future research is needed to pinpoint factors associated with these concerning findings so that patients who are at risk can be identified and referred for advanced imaging.

INTRODUCTION

Conventional radiography is the most commonly used imaging method for assessing knee osteoarthritis (KOA) because it is widely accessible and relatively inexpensive and allows clinicians to assess features of osteoarthritis (OA) including osteophytes and joint space narrowing.[1] Although rarely used for the initial diagnosis or routine monitoring of KOA because of its substantially higher cost, magnetic resonance imaging (MRI) offers several advantages over plain radiography.[1,2] MRI of the knee is a widely accepted imaging modality due to its multiplanar imaging capabilities and excellent soft-tissue contrast resolution that allows for accurate evaluation of cartilage, menisci, ligaments, synovium, and bone.[1]

First-line standard treatment for patients with KOA with or without concomitant meniscal tear includes physical therapy (PT) to strengthen quadriceps, hamstrings, and proximal hip muscles and improve range of motion and functional capacity. These changes, along with a reduction in inflammation, are thought to mitigate OA pain.[3] However, other causes of knee pain in middle-aged and older adults are more readily diagnosed with

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SIGNIFICANCE & INNOVATIONS

- Within the population of patients with mild to moderate knee osteoarthritis and a suspected meniscal tear, we estimated the prevalence of unsuspected clinically relevant findings to be 8.03%, which can be further broken down into estimates of prevalence for those with subchondral insufficiency fracture of the knee (SIFK; 3.29%), other fracture (1.32%), avascular necrosis (AVN; 0.53%), tumor (1.05%), and other findings including bone edema, contusions, and osteochondral lesions (1.84%).
- The results of the present study refined the estimate of SIFK prevalence in this patient population from our initial report published in 2020, which was the first reported estimate of SIFKs in adults with knee pain and suspected meniscal tear (2.94%).
- This estimate may prompt clinicians to be more aware of other findings, such as SIFKs, tumors, fractures, and AVN, that could contribute to patients' symptoms and may prompt a different management approach but that also require advanced imaging to detect.

MRI than with conventional radiography, including subchondral insufficiency fractures of the knee (SIFKs), avascular necrosis (AVN; also known as osteonecrosis), and tumors. It is important to distinguish these pathologic processes because they often require distinct clinical management. For example, although KOA with meniscal tear is often treated with a course of PT that includes weight-bearing exercises, SIFK is sometimes managed with a period of reduced weight bearing to allow the fracture to heal.[4,5] AVN, arising from ischemia of the distal femur or proximal tibia, is often initially managed with reduced weight bearing and may be treated surgically in advanced stages.[6] Finally, benign and malignant tumors of the bone typically require additional imaging, and malignant-appearing tumors may require biopsy or surgical resection.[7] Because initial management and decisions regarding imaging of KOA and suspected meniscal tear may vary depending on site and patient factors, SIFKs, AVN, and tumors may go undiagnosed, or their diagnoses may be delayed substantially.

The Treatment of Meniscal Problems and Osteoarthritis (TeMPO) study is a randomized controlled trial (RCT) that compares the efficacy of two in-clinic PT interventions and two protocolized home exercise programs for the treatment of symptomatic meniscal tears in adults 45 to 85 years old with mild to moderate KOA (Kellgren–Lawrence [KL] grades 0–3).[8] The study design of TeMPO offers an opportunity to collect data on the incidence of patients with undiagnosed SIFKs, AVN, and tumors in a cohort of middle-aged and older adults with knee pain referred for PT. The protocol required all patients to undergo MRI confirmation of meniscal tear and OA before randomization. The study-ordered MRI allowed us to obtain advanced imaging data for patients who normally would not have undergone MRI as part of their routine clinical care and likely would have been referred to PT for treatment of a suspected meniscal tear in the setting of mild to moderate OA.[8] In a preliminary study, Huizinga et al[9] reported on the prevalence of SIFKs in the TeMPO cohort from the first 22 months of study enrollment and found 10 instances of SIFKs of 340 study-ordered MRI (prevalence of 2.9%, 95% confidence interval [CI] 1.2%–4.7%). Enrollment for the TeMPO study was completed in October 2022, providing an even larger cohort of patients for whom MRI is available. The purpose of this study is to expand on our previous report by (1) estimating the prevalence of unsuspected SIFKs in a large cohort of study participants, and (2) estimate the prevalence of other findings on MRI (including AVN and tumors) that could potentially impact clinical management for patients being managed nonoperatively for knee pain and suspected meniscal tear.

PATIENTS AND METHODS

Setting. The TeMPO study is a four-arm multicenter RCT investigating combinations of nonoperative therapies (eg, in-clinic PT and at-home exercises) for the treatment of degenerative meniscal tear in adults 45 to 85 years old with mild to moderate KOA. Although the TeMPO study enrolled from four clinical sites, this analysis includes patients from the centers with the most research MRI available: Brigham and Women's Hospital, University at Buffalo, and University of Pittsburgh. The TeMPO study was approved by the Mass General Brigham Institutional Review Board.

Sample. The TeMPO study enrolled patients aged 45 to 85 years old with knee pain, KL grade 0 to 3 OA (on standing bilateral radiographs no older than one year),[10,11] no history of inflammatory arthritis, and a physician-suspected meniscal tear.[8] Patients experiencing knee pain associated with acute trauma (<21 days ago) were excluded. The suspected meniscal tear had to be demonstrated on MRI before a potentially eligible participant could be randomized. This MRI could be obtained in two ways according to clinician preference and practice style. First, the patient's physician could order the MRI for clinical reasons. Alternatively, if the physician did not order MRI, the study team ordered MRI to confirm eligibility. This second group of MRI scans form the sample for this study. This MRI likely would not have been obtained had the patient not agreed to participate in the TeMPO trial. Figure 1 provides a flow diagram describing how the sample for this report was identified from the larger TeMPO cohort; further explanation for how this sample was determined is described in the Results section. Because this MRI was used to assess eligibility, not all of the participants included in this report were ultimately randomized and included in the TeMPO study.

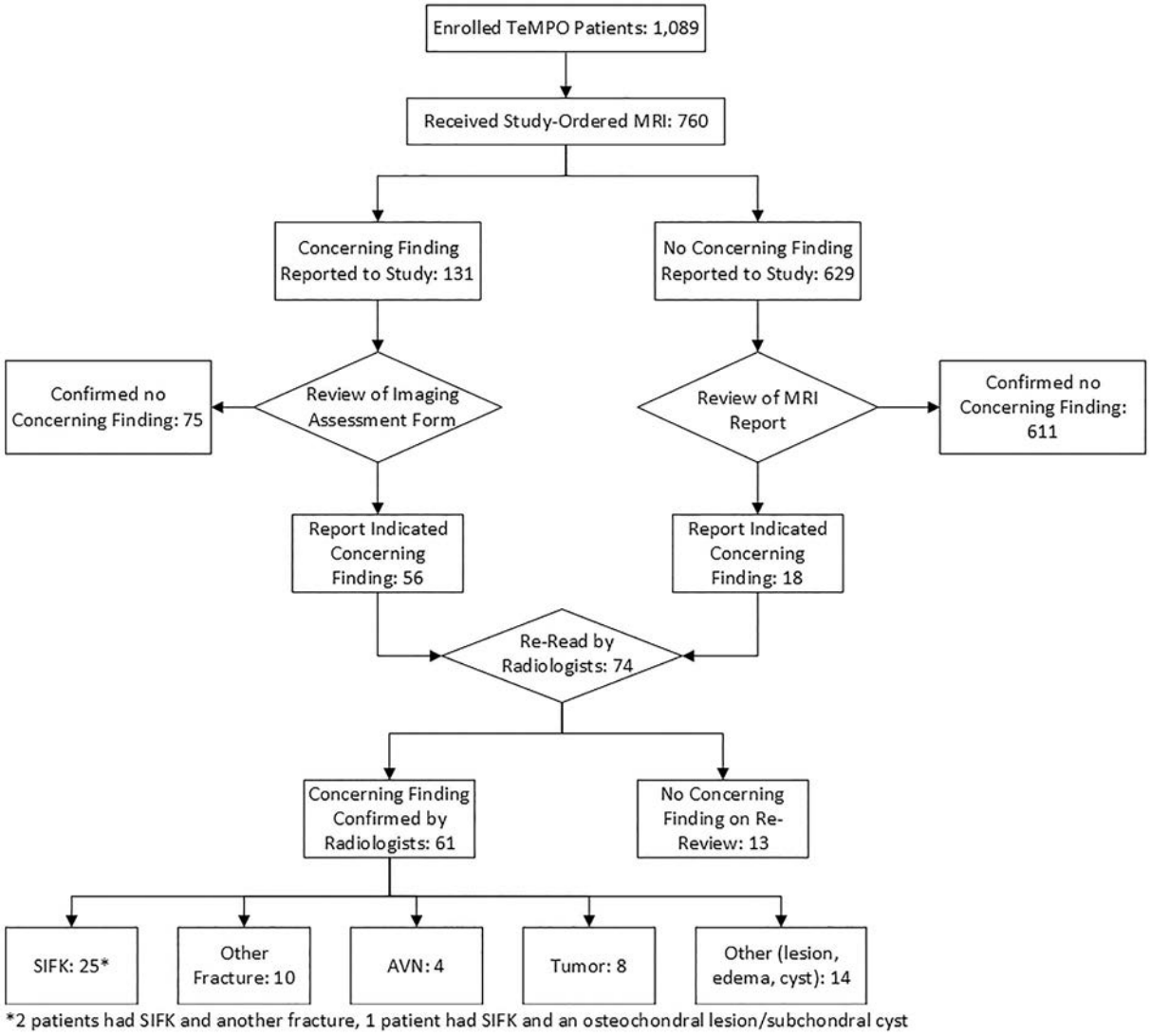

Figure 1. Flow diagram of concerning finding review. AVN, avascular necrosis; MRI, magnetic resonance imaging; SIFK, subchondral insufficiency fracture of the knee; TeMPO, Treatment of Meniscal Problems and Osteoarthritis.

Data collection. We identified study-ordered MRI with concerning findings in two ways. First, for all study-ordered MRI, a clinician at each site performed an imaging assessment in the day or two following study acquisition to document the existence and location of the meniscal tear (if present) on an imaging report form. The imaging report form provided an option for the clinician to select if a concerning finding was present and to identify the type of concerning finding. We obtained the MRI scans that noted concerning findings that were deemed clinically relevant for review.

A second mechanism to identify potential patients involved a review of the formal radiology report in the medical record. Each MRI had a formal reading at the study sites done for safety purposes. Study staff at each site searched these radiology reports for words or descriptors that indicated a potential concerning finding: mass, tumor, neoplasm, SIFK, stress fracture, fracture, insufficiency, cortical collapse, collapse, serpiginous/serpentine, osteonecrosis, AVN, spontaneous osteonecrosis of the knee, and enchondroma. This list encompasses some of the most common concerning findings on knee MRI determined by consensus between two fellowship-trained musculoskeletal radiologists (NS and SES).

All flagged MRI, identified by either method, was read at one institution by two musculoskeletal radiologists (NS and SES). Features were scored together in real time until consensus was reached and recorded using REDCap, which is a secure web platform that supports data collection and management for research studies.[12] For each concerning finding (SIFK, other fracture, AVN, tumor, or other finding), the radiologists recorded the type, laterality (medial/lateral), location on the bone (weight-bearing or non–weight-bearing femoral; anterior, central, or posterior tibial; patellar), presence of subchondral collapse, and

presence of bone edema. Bone marrow edema was further categorized as a percentage of the femoral condyle or proximal tibial plateau (<25%, 25%–50%, 50%–75%, and >75%). Additionally, for patients with SIFKs and other fractures, the radiologists recorded the fracture length (<10, 10–20, and >20 mm) as well as the location of each lesion (subchondral [SIFK], intra-articular, epiphyseal, diaphyseal, metaphyseal) and whether fractures were displaced or nondisplaced. We also collected data on the presence, location, and morphology of meniscal tear (medial or lateral; complex, radial, or no tear), degree and location of degenerative cartilage changes, and presence of bone marrow lesions/cysts. Meniscal extrusion and morphology were scored using the MRI Osteoarthritis Knee Score grading system for these features.[13] In addition to scoring participants' MRI, we collected data including demographic characteristics (age, sex, race, body mass index [BMI]), Knee Injury and Osteoarthritis Outcome Score (KOOS; scored from 0 to 100; 100 is no pain), and duration of symptoms from patients' baseline questionnaires as well as KL grade from radiographs taken before study enrollment.

Statistical analysis. Baseline KOOS, BMI, and age are reported as mean and 95% CIs for participants with concerning findings, as well as for participants who underwent study-ordered MRI without any concerning findings. Categorical patient characteristics (sex, race, and KL grade) and MRI characteristics (presence and laterality of meniscal tear, cartilage degenerative changes, subchondral collapse, edema, and bone marrow lesions/cysts) are reported as whole numbers and percentages of the total sample size. We estimated the prevalence of each type of concerning finding (SIFK, other fracture, AVN, and tumor) and concerning findings as a percentage of the total number of study-ordered MRI with a 95% CI using Microsoft Excel. We counted participants who exhibited multiple concerning findings, including SIFKs, in the SIFK category alone, so that sample sizes for each category were mutually exclusive.

RESULTS

Total concerning findings. From 2018 through 2022, 760 study-ordered MRI scans were performed for the TeMPO study at the three institutional sites. Of these MRI scans, 131 were flagged as having potential concerning findings, including SIFKs. For these records, we reviewed the study imaging assessment form and excluded 75 patients because the finding was not clinically concerning. Keeping in mind that these individuals had no acute knee injury, we excluded meniscal root tears, loose bodies, chronic anterior cruciate ligament/medial collateral ligament pathology, and other findings that would not affect immediate clinical management. The remaining 56 records were reviewed by the study radiologists. Local study staff also reviewed the text of the MRI reports located in the medical record for the 629 study-ordered MRI scans the imaging assessment forms of which did not report a concerning finding at the time of study enrollment. In this manner, we identified an additional 18 MRI scans as having potential concerning findings.

Together, two fellowship-trained musculoskeletal radiologists reviewed 56 records flagged by the review of imaging assessment form and 18 records identified from review of MRI reports. By consensus, they determined that 13 MRI scans did not have any concerning findings to note, leaving 61 MRI scans with a confirmed concerning finding. Figure 1 provides a flow diagram of the process of image review, identification, and classification of concerning findings. Table 1 provides the baseline and MRI characteristics for patients by concerning finding status. Among those without a concerning finding, the mean age was 58.7 (95% CI 58.1–59.3) years, mean BMI was 29.9 (95% CI 29.4–30.4) kg/m^2, mean KOOS was 53.1 (95% CI 52.0–54.3), 61% of participants were female, 86% were White, 29% had KL 3 KOA, and 44% reported that their symptoms had been present for one to five months.

Subchondral insufficiency fractures. Of the 760 patients who received study-ordered MRI, we identified 25 patients with SIFKs. This resulted in an estimated prevalence of unsuspected SIFK of 3.29% (95% CI 2.02%–4.56%). The mean age of these participants was 61.6 (95% CI 59.1–64.2) years and mean KOOS was 53.7 (95% CI 47.2–60.3). A total of 20 participants (80% of those with SIFKs) had fractures that were located medially, and 5 participants (20%) had lateral fractures. Seven participants with SIFKs had both tibial and femoral fractures (four had anterior tibial/weight-bearing femoral fractures, two had central tibial/weight-bearing femoral fractures, and one had anterior and central tibial/weight-bearing femoral fracture). A total of 14 more participants had weight-bearing femoral fractures alone, and the remaining 4 participants had tibial fractures alone (3 central and 1 posterior tibia). One participant (4%) exhibited subchondral collapse. A total of 14 of 25 participants with SIFKs (56%) had either a medial meniscal tear or both medial and lateral meniscal tears. A total of 5 of 14 tears were vertical, 3 were horizontal and/or radial, 7 were complex, 6 were root tears, and 6 exhibited partial maceration (types of tears were not mutually exclusive).

Other fractures. Ten participants had other, nonsubchondral fractures (estimated prevalence 1.32%, 95% CI 0.51%–2.13%). Of these, four fractures (40%) occurred in the lateral compartment, five (50%) in the medial compartment, and one (10%) involved both compartments. Six were fractures of the tibia alone, one was of the femur, one was of the patella, and two patients had fractures of both the femur and tibia. Four fractures were epiphyseal, three involved the epiphysis and metaphysis, one was metaphyseal alone, one was intra-articular, and one was both intra-articular and epiphyseal. In all 10 patients, the study physician could not see the fracture on plain radiographs.

Table 1. Patient and MRI characteristics for TeMPO study concerning findings*

Characteristic	SIFK (n = 25), n (%)[a]	Other fracture (n = 10), n (%)	AVN (n = 4), n (%)	Tumor (n = 8), n (%)	Other (n = 14), n (%)	Remainder participants (n = 699), n (%)
Age, mean (95% CI), y	61.6 (59.1–64.2)	63.6 (57.8–69.4)	61.8 (54.7–68.8)	57.5 (52.6–62.4)	53.6 (49.8–57.5)	58.7 (58.1–59.3)
Sex						
Male	13 (52)	3 (30)	2 (50)	0 (0)	5 (36)	252 (36)
Female	12 (48)	7 (70)	2 (50)	8 (100)	9 (64)	423 (61)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	24 (3)
Race						
White	20 (80)	10 (100)	3 (75)	6 (75)	12 (86)	601 (86.0)
Black	1 (4)	0 (0)	1 (25)	0 (0)	1 (7)	35 (5.0)
Asian	1 (4)	0 (0)	0 (0)	1 (13)	0 (0)	10 (1.4)
Native American	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.6)
Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.3)
Unknown/other	3 (12)	0 (0)	0 (0)	1 (13)	1 (7)	47 (6.7)
KL grade						
0	7 (28)	4 (40)	0 (0)	3 (38)	6 (43)	216 (30.9)
1	6 (24)	0 (0)	2 (50)	2 (25)	3 (21)	185 (26.5)
2	3 (12)	0 (0)	0 (0)	1 (13)	1 (7)	92 (13.2)
3	9 (36)	6 (60)	2 (50)	2 (25)	4 (29)	203 (29.0)
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.4)[b]
Duration of symptoms						
Zero to four weeks	8 (32)	2 (20)	0 (0)	3 (38)	4 (29)	152 (21.7)
One to five months	11 (44)	4 (40)	1 (25)	2 (25)	6 (43)	307 (43.9)
Six or more months	4 (16)	4 (40)	3 (75)	3 (38)	3 (21)	216 (30.9)
Unknown	2 (8)	0 (0)	0 (0)	0 (0)	1 (7)	24 (3.4)
Body mass index, mean (95% CI), kg/m^2	30.2 (27.6–32.8)	28.9 (23.9–34.0)	31.8 (14.2–49.4)	28.6 (23.5–33.7)	28.0 (23.8–32.3)	29.9 (29.4–30.4)
KOOS (100-point scale, 100 being best), mean (95% CI)	53.7 (47.2–60.3)	59.2 (47.2–71.1)	48.6 (4.6–92.6)	52.8 (39.1–66.4)	55.8 (47.8–63.7)	53.1 (52.0–54.3)
Laterality of meniscus tear						
No tear	11 (44)	3 (30)	1 (25)	2 (25)	7 (50)	124 (17.7)
Medial only	11 (44)	4 (40)	1 (25)	6 (75)	6 (43)	413 (59.1)
Lateral only	0 (0)	0 (0)	1 (25)	0 (0)	1 (7)	54 (7.7)
Both	3 (12)	3 (30)	1 (25)	0 (0)	0 (0)	108 (15.5)
Cartilage degenerative changes						
None	1 (4)	2 (20)	1 (25)	1 (13)	1 (7)	16 (2.3)
Partial thickness only	12 (48)	6 (60)	0 (0)	6 (75)	9 (64)	455 (65.1)
Partial and full thickness	12 (48)	2 (20)	3 (75)	1 (13)	4 (29)	228 (32.6)
Subchondral collapse						
Yes	1 (4)	0 (0)	0 (0)	0 (0)	1 (7)	N/A
No	20 (80)	10 (100)	4 (100)	8 (100)	11 (79)	N/A
Unknown	4 (16)	0 (0)	0 (0)	0 (0)	2 (14)	N/A
Edema						
<25%	0 (0)	2 (20)	1 (25)	0 (0)	6 (43)	N/A
25%–50%	6 (24)	1 (10)	0 (0)	0 (0)	2 (14)	N/A
50%–75%	10 (40)	4 (40)	0 (0)	0 (0)	2 (14)	N/A
>75%	9 (36)	3 (30)	0 (0)	0 (0)	0 (0)	N/A
Unknown	0 (0)	0 (0)	3 (75)	8 (100)	4 (29)	N/A
Bone marrow lesions/cysts						
Yes	14 (56)	6 (60)	2 (50)	5 (63)	8 (57)	N/A
No	11 (44)	4 (40)	2 (50)	3 (38)	6 (43)	N/A

* AVN, avascular necrosis; CI, confidence interval; KL, Kellgren–Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; MRI, magnetic resonance imaging; N/A, not applicable; SIFK, subchondral insufficiency fracture of the knee; TeMPO, Treatment of Meniscal Problems and Osteoarthritis.

[a] Two participants had SIFKs and other fractures, one participant had SIFK and other finding (osteochondral lesion).

[b] Because the TeMPO study only included patients with mild to moderate osteoarthritis (KL grades 0–3), these three patients were excluded from the study after baseline imaging and were not randomized.

AVN. Four participants' MRI revealed AVN of the knee (estimated prevalence 0.53%, 95% CI 0.01%–1.04%). Of the four patients, the first involved the medial, epiphyseal non–weight-bearing portion of the femur. The second was also epiphyseal and medial but involved the weight-bearing femur. The third was lateral, both epiphyseal and diaphyseal, and involved both the weight-bearing femur and central tibia. The fourth was both medial and lateral, affecting both weight-bearing and non–weight-bearing portions of the epiphyseal and diaphyseal femur. None of the four patients' AVN was visible on plain radiographs.

Tumors/ossific lesions. Eight participants had intramedullary ossific lesions on MRI, all of which were nonaggressive-appearing cartilage lesions in keeping with enchondromas. Locations included one lateral, four medial, and three central. Seven of the ossific lesions were in the non–weight-bearing femur, and one was in the central tibia. All eight patients with enchondroma were female. The resulting estimated prevalence of intramedullary ossific lesions within the TeMPO cohort was 1.05% (95% CI 0.33%–1.78%). Importantly, all of these lesions had no aggressive features, and no further treatment or intervention was indicated.

Other concerning findings. The 14 remaining MRI scans contained clinically relevant concerning findings but did not fit into the aforementioned categories (estimated prevalence 1.84%, 95% CI 0.89%–2.80%). These findings included bone contusion or edema without a fracture line (n = 7), osteochondral lesion (n = 3), soft-tissue lesion (n = 1), old fracture (nonacute; n = 1), bipartite patella (with cystic changes and edema; n = 1), and intraosseous ganglion (n = 1). A total of 2 findings were in the lateral compartment, 10 were medial, and 2 were not classified by laterality.

DISCUSSION

Standard treatment for KOA with or without concomitant meniscal tear often includes a course of PT. However, other causes of knee pain in middle-aged and older adults, including those with SIFKs, AVN, and tumors, are often not detectable on plain radiographs. The TeMPO trial, which required a baseline MRI for enrollment into the study to confirm meniscal tear, offered a unique opportunity to estimate the prevalence of SIFKs, AVN, and tumors, as well as other clinically relevant findings, in patients with mild to moderate KOA and a suspected meniscal tear who likely would otherwise not have undergone initial MRI. Within this population, we estimated the prevalence of unsuspected clinically relevant findings to be 8.03%, which can be further broken down into estimates of prevalence for SIFK (3.29%), other fracture (1.32%), AVN (0.53%), tumor (1.05%), and other findings including bone edema, contusions, and osteochondral lesions (1.84%).

The results of the present study agree with those findings from our initial report published in 2020, which was the first reported estimate of SIFKs in adults with knee pain and suspected meniscal tear.[9] In the original report, we identified 10 patients with SIFKs of 340 total study-ordered MRI scans for an estimated prevalence of unsuspected SIFK of 2.94%, which is very close to the present estimate of 3.29%. In addition to refining the estimate of SIFK prevalence with a larger sample size from a complete trial cohort (760 study-ordered MRI scans, compared to the original 340), we also built on our previous findings by describing other unsuspected MRI findings that carry important consequences for clinical management, including other fractures, AVN, and tumors.

With just 25 patients with SIFKs, we cannot assess formally whether participants with SIFKs differed from those without concerning findings in their initial presentation. Table 1 suggests that the group with SIFKs is similar to those without concerning findings in terms of age, KL grade, and baseline pain. Of note, in our small sample, the group with SIFKs were more often male (52% vs 36%) and more likely to not have a meniscal tear (44% vs 18%) compared to those without a concerning finding on MRI. This differs from the small existing literature on risk factors for SIFK, which has so far reported either no sex difference or a higher prevalence of SIFK in female patients.[5] These findings should be pursued in larger studies designed to elucidate features associated with SIFK among persons with knee pain.

These are the only reported prevalence estimates of fractures, AVN, and tumors among adults with knee pain and suspected meniscal tear to our knowledge. Our study has several important limitations. First, the small sample size for the different concerning finding types prevented us from being able to identify patient or MRI characteristics associated with a concerning finding. Because many of the patients with concerning findings also had concomitant meniscal tears, it is unclear which condition was the primary contributor to their pain. We did not have complete data on patients with clinically ordered MRI who did not have a meniscal tear or cartilage damage, and thus, we cannot comment on whether those with clinically ordered or study-ordered MRI differed with respect to other variables. Finally, the study was conducted with a cohort of clinical trial participants from three academic medical centers in the Northeastern United States, with a notable lack of racial diversity. Given these limitations, the generalizability of the reported results is limited to adults with knee pain and suspected meniscal tear.

In conclusion, we estimated the prevalence of clinically relevant unsuspected findings on MRI to be 8.03% in middle-aged adults with suspected meniscal tear. This estimate may prompt clinicians to be more aware of other findings, such as SIFKs, tumors, fractures, and AVN, that could contribute to patients' symptoms and may prompt a different management approach but that also require advanced imaging to detect. Future research is needed to pinpoint factors associated with these concerning findings so that patients at highest risk can be identified and referred for advanced imaging without delay.

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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 Smith 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.

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Building the OAChangeMap to Improve the Service Delivery of the New South Wales Osteoarthritis Chronic Care Program: A Worked Example of Using a Codesign Framework

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Objective. The Osteoarthritis Chronic Care Program (OACCP) has been implemented in Australian public hospitals to deliver best evidence osteoarthritis (OA) care. It is important to ensure that the OACCP continues to deliver evidence-based OA care as intended. We aimed to identify barriers and enablers to delivering the OACCP, prioritize the barriers, and generate strategies to address them.

Methods. This study provides a worked example of a seven-step theory-informed codesign framework. We invited OACCP coordinators to participate in semistructured interviews (analyzed thematically) and complete a questionnaire to identify barriers and enablers to delivery of the OACCP. We then invited a broader group of stakeholders (OACCP coordinators, health managers, policy makers, consumers, and researchers) to prioritize the barriers via a short survey (survey 2). We held five codesign workshops in which we mapped the priority barriers to the Theoretical Domains Framework and developed strategies to address them.

Results. Sixteen coordinators were interviewed, and the main barriers identified were as follows: (1) patients often have beliefs that are inconsistent with best evidence care, (2) there are aspects of clinical care that are not delivered optimally, and (3) system-level factors are a barrier to optimal patient care and sustainability of the OACCP. We codesigned a plan for action with patient educational materials, shared decision-making tools, and health professional education and training.

Conclusion. Our worked example of codesign used a theory-based, data-driven approach with key stakeholders, identified and prioritized barriers to the delivery of the OACCP, acknowledged enablers, and generated a plan for feasible strategies to improve the program.

INTRODUCTION

Osteoarthritis (OA) affects more than 500 million people worldwide and is a major contributor to years lived with a disability.[1] We have known for more than a decade that best evidence first-line care for this painful, disabling condition includes education for self-management, exercise, and weight management,[2] yet many people are still not offered this care.[3]

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SIGNIFICANCE & INNOVATIONS

- This study provides a worked example of a theory-informed seven-step codesign framework used to explore gaps in the delivery of an osteoarthritis (OA) management program and plan strategies to improve the program.
- The framework was used to identify and understand the barriers and enablers associated with delivering the OA management program from the perspective of the coordinators and to leverage broader stakeholder expertise to plan data-driven strategies designed to improve the program at a health system level.

There are many factors limiting the delivery of first-line OA care. It is often easier for health professionals to refer for surgical opinion than to deliver first-line care,[4,5] and there is a lack of knowledge and skills for first-line care.[6,7] To address this, structured OA management programs have been implemented,[8,9] and although this is encouraging, it is important to monitor the quality of care being delivered by these programs[10] because it is recognized that programs often fail to deliver full benefit because they are not optimally implemented at scale.[11] Continuous evaluation of OA management programs is needed to ensure they deliver evidence-based care as intended.[12]

The Osteoarthritis Chronic Care Program (OACCP) is an OA management program implemented by the Agency for Clinical Innovation (ACI) from 2011 that operates in 26 public hospitals across New South Wales (NSW), Australia.[13] The OACCP is a 9- to 12-month program delivered over several visits that aims to reduce pain and improve function and quality of life for people with OA. Key features include the provision of tailored OA interventions delivered by a multidisciplinary health care team, with a focus on the first-line treatments and adjunctive treatments when appropriate.[14] The OACCP is led by a coordinator (usually a physiotherapist) who conducts a holistic assessment, provides OA education, supports participants with self-management, and prescribes exercise programs. The OACCP coordinator may refer patients for consultation with other health professionals (eg, dietitian, occupational therapist) and other services according to their individual clinical needs.[15]

A process evaluation report found OACCP sites were implemented with good fidelity to the OACCP model of care (MoC).[16] The OACCP MoC is flexible in the way sites are operationalized within their local context.[15] The report showed large differences in how the sites were structured, particularly in terms of the multidisciplinary teams.[16] Evaluations revealed that some OACCP sites demonstrated greater improvements in participant pain and function outcomes, such as the Knee Injury and Osteoarthritis Outcome Score and the Hip Disability and Osteoarthritis Outcome Score, than others.[14,16,17] In response to these data, we aimed to explore gaps in the OACCP and develop strategies codesigned with stakeholders to improve delivery of the program and facilitate more consistent participant outcomes across sites.

Codesign refers to approaches in which end users as "experts by experience" become part of the design team.[18] Although codesign is increasing in popularity in general, the "how to" of codesign is often poorly described[19]; however, this is changing in the field of OA.[20–25] The goal of this study was to provide a worked example of a theory-informed codesign framework to understand the factors impacting delivery of the OACCP from the perspective of OACCP coordinators, prioritize with a broader group of stakeholders (coordinators, consumers, policy makers, and managers), and generate a list of potential strategies to address the barriers.

PATIENTS AND METHODS

Design and participants. This was a mixed-methods participatory research study. Participatory research describes systematic inquiry that involves the collaboration of stakeholders to facilitate change.[26] We used the seven-step codesign framework established by Trischler et al[27] in public service design to inform our methodology (Figure 1). The study was approved by the Northern Sydney Local Health District Human Research Ethics Committee (RESP/18/128-HAWKE-RESP/18/128). The Consolidated Criteria for Reporting Qualitative Research checklist was used to ensure complete and transparent reporting.[28]

Steps 1 and 2: Resourcing and planning (data collection to understand the barriers). We invited NSW OACCP coordinators to participate in face-to-face semistructured interviews to identify barriers and enablers to the delivery of the OACCP. Invitations were issued via email, and written consent was obtained before the interviews. We used a systematic theory-driven approach. The interview guide (Supplementary File) was informed by a systematic review on staff-reported barriers and enablers to implementing hospital-based interventions across three domains: (1) system level, (2) staff level, and (3) intervention level.[29] The interviews were undertaken by JPE, a female researcher who practiced as a physiotherapist in the NSW Health system until 2015 but did not work in the OACCP. JPE was trained to interview by GD, an experienced independent qualitative researcher who had no contact with participants. Each interview was approximately 60 minutes, conducted 1:1 in the participants' workplace, and audio recorded and transcribed verbatim. Field notes were kept to record the interviewer's observations.[30] Interviews were conducted until theoretical saturation was achieved,

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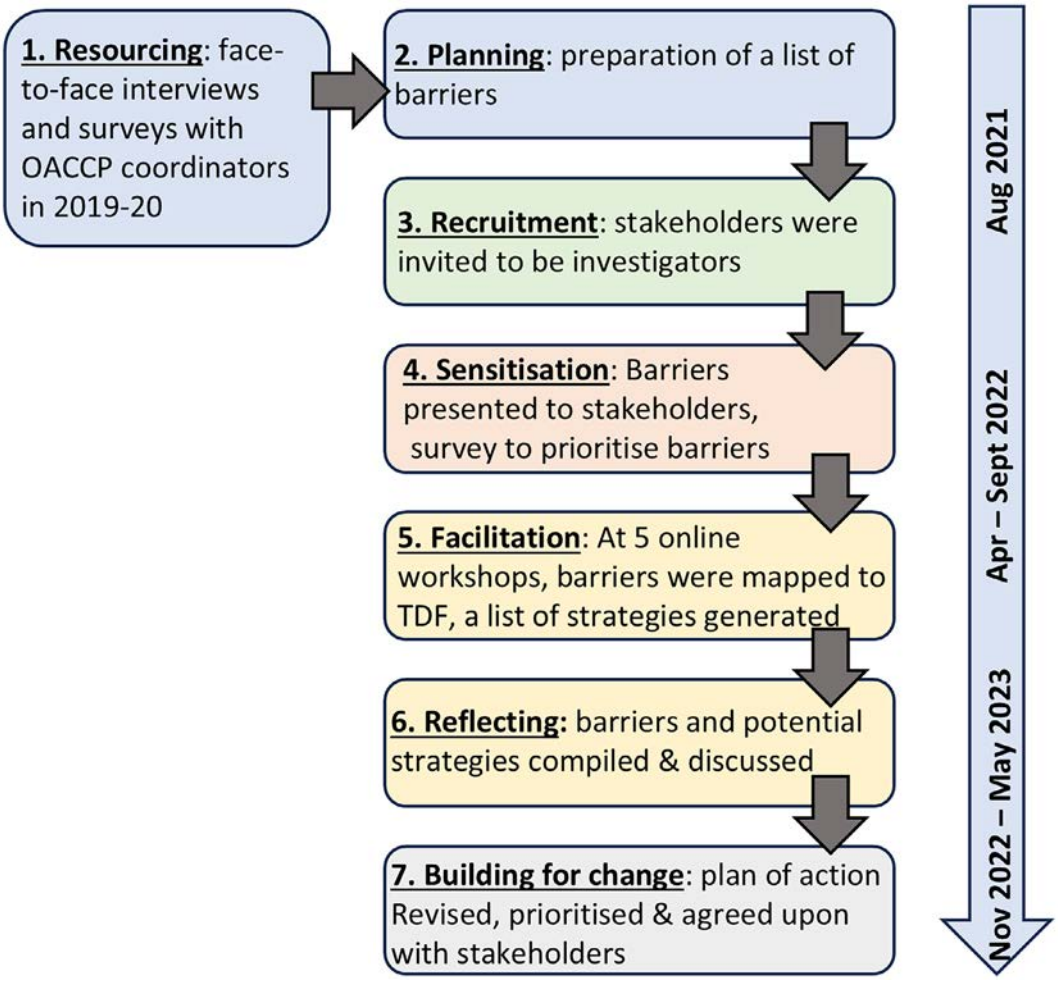

Figure 1. Seven-step codesign framework adapted from the study by Trischler et al.[27] OACCP, Osteoarthritis Chronic Care Program; TDF, Theoretical Domains Framework.

defined as the point at which no new themes or subthemes were constructed from the data.[31]

Survey 1 was emailed to participants one week following the interview via REDCap.[32] The survey included demographic questions and the modified *Hennessy-Hicks Training Needs Analysis Questionnaire*.[33,34] It asked coordinators about the key functions in their roles, their training needs, and how they used research evidence to inform their practices[35] (Supplementary File). Participants were asked to rate the importance of 28 activities to their roles (7-point scale: 1 = not at all important, 7 = very important), how well they performed these roles (1 = not very well, 7 = very well), and how important training and the work environment were to their performance (1 = not at all important, 7 = very important). They were also asked to list the areas they needed further training on and the preferred format (eg, workshop, online). The results of the qualitative and quantitative analyses were combined and synthesized into a complete list of barriers and enablers.

Step 3: Recruitment (for broad engagement). OACCP stakeholders associated with Sydney Health Partners (SHP) were invited to take part as investigators (Figure 1). Back in 2021, SHP was a collaboration between five major health districts, the University of Sydney, and 11 medical research institutes. The roles of the stakeholder investigators were to provide perspectives to represent OACCP coordinators, health managers, policy makers, and consumers (patients) so that we could best use the data we had collected and to propose solutions to improve OACCP delivery as described in steps 4 to 7.

Step 4: Sensitization (discussing and prioritizing barriers with stakeholders). The stakeholder investigators were presented with the results from the interviews and survey 1 at an online meeting and were asked to reflect on the results. The investigators completed survey 2 to rate the importance of each barrier to OACCP delivery using a 5-point Likert scale (0 = not important at all, 4 = extremely important). A list of prioritized barriers was developed from this survey.

Steps 5 and 6: Facilitation and reflecting (making sense of the barriers and identifying strategies). Over the following months (May to September 2022) we held a series of five online codesign

workshops with the stakeholder investigators. JPE facilitated the workshops with assistance from JLB, SK (both nonclinician OA researchers), and VD (researcher and physiotherapist). At these workshops, the seven top-ranked barriers were discussed in depth. We combined barriers that were related to each other and used the Theoretical Domains Framework (TDF) to identify factors that influence health professional and patient behaviors to make sense of the barriers.[36] At the workshops, we further mapped the barriers to the TDF domains and used the Theory and Technique Tool[37] to identify and select potential behavior change techniques and strategies to address the barriers.

Step 7: Building for change. A full list of strategies was developed iteratively by the whole investigator group. We held another investigator meeting to discuss each of the strategies and make a final decision on which to prioritize. These decisions were based on strategies considered feasible to act on immediately, strategies that duplicated existing initiatives, or those that would require further funding and were considered future projects (Figure 1). The list of strategies was circulated for final reflections until all investigators approved the plan.

Analyses. The primary qualitative outcomes were the barriers and enablers identified at system, staff, and intervention levels that were key to OACCP delivery. Secondary outcomes were (1) professional education and training requirements of OACCP coordinators, (2) prioritized barriers, (3) strategies to address the barriers, and (4) prioritized strategies to address the barriers.

Data were analyzed and summarized using theoretical thematic analysis, following the process described by Braun and Clarke.[38] Interviews were analyzed as each was completed to ensure that data saturation was reached. Individual transcripts were read through by the primary investigator (JPE) soon after transcription and shared with interviewees for checking. JPE and GD read and coded the transcripts to identify topics and initial patterns of ideas emerging from the data. Because the interview questions were framed using a structured approach according to the three domains of barriers and enablers identified by Geerligs et al (system, staff, intervention),[29] these domains were used in our initial codebook. We then moved to a more inductive approach to developing the codes under these headings. Codes were organized into categories and combined with similar or related ideas from across all participant data to form themes and subthemes. These analytical steps were conducted using qualitative analysis software NVivo (NVivo 14, Lumivero). The themes and subthemes were reviewed and discussed iteratively by JPE, GD, and the other investigators until they made the decision that no new themes and subthemes were emerging from the data. Standard word processing was used in the final steps of organizing subthemes and consideration of associations between domains.

The demographic and survey data were analyzed with descriptive statistics (medians and interquartile ranges [IQRs] for skewed data) using SPSS 27. The results of the qualitative and quantitative analyses were combined by mapping the barriers identified in themes and subthemes from the qualitative analysis to the topics identified as areas of training need from the survey. This complete list of barriers was used to prioritize the barriers in survey 2.

RESULTS

Participant characteristics. Sixteen physiotherapists from 14 OACCP public hospital sites were interviewed. These were from 9 of 15 local health districts across NSW (five regional and four metropolitan). Nine participants were female (mean ± SD age 41 ± 10.3 years) and had worked as an OACCP coordinator for a mean ± SD of 40 ± 28.2 months (range 9–90 months). Given the confidentiality issues associated with identifying individuals among the small group of OACCP coordinators, we do not provide detailed interviewee characteristics. The results from the semistructured interviews are summarized in Table 1 with illustrative quotes.

Barriers and enablers to the delivery of the OACCP (steps 1 and 2). *Theme 1: Pre-existing beliefs inconsistent with best evidence OA care*. Barriers. People with OA often hold misconceptions about their condition. OACCP coordinators reported that it was necessary to address common misconceptions about OA with participants, such as the following: nothing can be done about OA apart from surgery, which is inevitable, pain indicates damage, and weight-bearing through joints would cause further damage. OACCP coordinators believed that these misconceptions were reinforced by family, friends, and mainstream media. Coordinators noted that negative descriptors (eg, "bone-on-bone") were often, and other health professionals made treatment recommendations that conflicted with best evidence care. OACCP coordinators reported that patients often believed the only effective treatment available was surgery. OACCP participants who had seen an orthopedic surgeon and were waitlisted for joint replacement surgery were reluctant to delay the surgery, even when it was obvious that they did not need it.

Patients have unhelpful attitudes to OA treatments and the health professionals who provide them. OACCP coordinators often had difficult conversations with participants about uncomfortable subjects such as excess body weight and mental health issues. These topics were confronting for people who had bad past experiences with health professionals or who felt stigmatized about their weight or mental health. This led to their reluctance to follow up on lifestyle changes, especially weight loss recommendations with a dietitian or seeing a social worker or psychologist for support.

Table 1. Themes and subthemes with quotes from OACCP coordinators regarding barriers and facilitators to OACCP delivery*

	Quotes
Theme 1: patients often have pre-existing beliefs that are inconsistent with best evidence OA care	
Barriers	
People with OA often hold misconceptions about their condition	"There's a lot of fear avoidance and a lot of catastrophizing that they pick up from all angles. Whether it's Dr Google, primary care, their family - there's a lot of damaging, scary linguistics associated with osteoarthritis."
	"They still use the old terminology of 'bone-on-bone' and sort of almost scare the patients into 'I can't do anything, I must sit down and do nothing.'"
Unhelpful attitudes to OA treatments and the health professionals who provide them	"Often there's the people that you talk about dietician and losing weight and they go, 'Yeah, but I don't want to see the dietician.' A lot of people say, 'I know what I have to do. I know what I've got to do, it's just doing it, so there's no point in me coming.'"
	"I think it's very stigma related still. Seeing a psychologist is a big step for a lot of people. Even taking antidepressants or antianxiety medication, there's still a real stigma associated with that. People don't want to admit that they've got a mental health problem."
Some patients are less willing to invest time and money into improving their health	"Quoting one of our surgeons…you try and promote someone to take control of their own joint pain and be actively engaged in improving their weight and their exercise, it costs them money. I can give them a joint replacement for nothing… they're just passively riding this train towards surgery."
	"Most patients who probably do decline are ones that are working so they can't get to us…we only might see them a total of four times but they're just a bit - well a lot of the time they're saving up for - saving all their sick leave and annual leave ready for the surgery…. So they don't want to take any extra basically."
Poor adherence to first-line treatments	"Once they know they've got a date [for surgery], they don't - some of them don't want to come back in because they're having their surgery anyway, so they don't really see the need to come back."
	"There are the people that come back and go, 'No, I haven't done any of those things'…usually most of the whys are 'I've been too busy,' wasn't motivated…. Or it was too painful."
Enablers	
Group exercise, weight management, and education programs bring secondary benefits related to peer support	"I've had quite a few comments saying the group exercise, it's good to talk to like-minded people who are going through the same thing, they feel like they can share with them. I suppose they have a bit more empathy from the other people that are going through the same joint pain."
	"That they found that [sharing their experiences] really useful at the time, it was great, and they would like the idea to have something going like that in the future."
Educational resources were helpful for OACCP patients	"We've introduced our education booklet and things, so we've got a bit more material to give out to patients, which is good, because we had really nothing before that."
	"We have a booklet that we give out to patients that we developed this year. It's like an educational booklet and a little exercise diary. So, every patient gets that. There's another sheet in there that has a summary of how the OACCP runs at the hospital, so it's like a bit of a flowchart…. So, that's going well…."
Theme 2: there are aspects of clinical care that are not covered at an optimal level by the programs	
Barriers	
Variation in resourcing across the sites has led to reduced capacity in management of comorbid chronic conditions, including pharmacotherapies	"I know that the classic OACCP model probably has a bit more time and ability to focus more on other chronic conditions, other issues, be it uncontrolled diabetes or something of the like and that we probably aren't covering as thoroughly. You're trying to get through everything that you're trying to do as a one-man band."
	"More medication management. So having a little course where that maybe came from a pharmacist or a medical person would be good. Because I mean I know that I'm wary about giving too much advice on that because it might not be in my - so I give fairly general stuff."
Some program elements are challenging to implement	"Oh I think it's hard sometimes with goal setting with certain people. I think that it's really tough to come to find something really tangible or smart focused or functionally orientated of what people want to achieve, because I find that hard, yeah."
	"I think in terms of supporting long-term behavior change I think it can get better."

(Continued)

Table 1. (*Cont'd*)

	Quotes
	"I always think there's not enough - to really get patients to lose weight, we don't have enough dietician involvement. It's not regular enough. Because all the studies that I've read, they've had a dietician one-on-one follow-ups weekly to really get a good weight loss result. So, I don't think there's enough support around helping patients reduce their weight."
	"Pain science and chronic pain management skills are not something we've really got the capacity to support at one day every three months."
Enablers	
Clinician education, training, and mentoring improves care	"I've done the Health Change Australia course, the behavior change stuff, but I think that's something that I should do - or we all should do regularly in OACCP because that's such a big part of it."
	"That helped going to the peer mentoring day at the ACI. That helped me when I first started, because I didn't really know anyone else doing it. So, that was good. I guess the resources at the ACI have, model of care and all that. All that's very helpful...."
Transdisciplinary care that involved sharing roles across different disciplines was very helpful	"They're very open minded...sometimes you meet clinicians and they're in their box and they're not sticking their head out of the box...the people that I have been lucky enough to have got in my team, they're happy to stick their heads out of that box and have a look around into the box next door."
	"The OT, physio and dietician and the social worker - have just learned heaps about each other's professions in this cohort...We actually do a pretty good job... [there's a] Huge amount of crossover... Recognizing our boundaries."
Theme 3: system-level factors are a barrier to optimal patient care and sustainability of the OACCP	
Referral to OACCP from orthopedic surgery departments	"It's a real challenge to get somebody off the waitlist, even if it's pretty obvious they could...it's that language too. Some of our doctors are still using the 'bone-on-bone' and it's not going to get any better.... You're trying to undo those thoughts and fears."
	"They've waited 12 months to see him.... He looks at their x-rays...he spends a minute with them, they tell me.... He certainly doesn't ask them about their pain and function in depth. He puts them on the list and then they wait another year.... They've been waiting a year but these people - but in their heads - in their heads they need this surgery because the doctors said I need the surgery...I'm bone-on-bone...I'm going to need an operation.... How's my word against that doctor's word, hello. I'm a physio, like.... We haven't got very far."
The most appropriate referral pathway is from primary care	"That should be a prerequisite to going on the waiting list. The GP should send them straight here and then we refer to the orthopedic surgeon."
	"I'd love to engage with the GPs and get them referring. Really, I think in terms of the model of care, the whole pathway should be GP, physio/OACCP then on to an orthopedic surgeon. But that's not feasible in the limitations that we have currently."
OACCPs are underresourced for the work that they do	"It's great that people come up with these concepts and these models of care.... That's fantastic. But you can't implement something that's not resourced appropriately. Or you can't sustain that."
	"So, none of them are funded. All come from existing resources.... None of our positions are funded in OACCP, but we do have a half day clinic once a week with the multidisciplinary team. That's the registered nurse, occupational therapist and the dietician. Which kindly the heads of department and the Patient Admissions Manager support basically out of the goodness of their hearts really."

* ACI, Agency for Clinical Innovation; GP, general practitioner; OA, osteoarthritis; OACCP, Osteoarthritis Chronic Care Program; OT, occupational therapist.

Some patients are less willing to invest time and money into improving their health. OACCP coordinators felt some patients were less willing to invest time and/or money into engaging with OA treatments such as exercise. This was exacerbated by publicly funded joint replacement surgery being available at a minimal cost. Also, people who had to take sick leave to attend appointments were often reluctant to attend the OACCP. This is a system-level barrier because OACCP services are usually restricted to business hours.

OACCP participants have poor adherence to first-line treatments. Although OACCP coordinators recognized that some people were very engaged, many lacked the internal motivation to do the prescribed amount of exercise and other recommended treatments, despite active efforts to engage them. People who were already booked in for joint replacement surgery were particularly challenging to engage.

Enablers. Group exercise, weight management, and education programs bring benefits related to peer support. The OACCP coordinators who ran group education, exercise, and weight management sessions at their site believed it enhanced their program, provided an important social outlet, and improved their adherence with diet and exercise recommendations.

Educational resources were helpful for OACCP patients. Some OACCP coordinators used educational resources with patients (eg, exercise diaries, care plans, healthy eating leaflets) and found them helpful. The resources were locally developed and not consistently used across OACCP sites.

Theme 2: Aspects of clinical care not delivered optimally by the programs. Barriers. Variation in resourcing has led to reduced capacity in management of comorbid chronic conditions, including use of pharmacotherapies. OACCP sites that had physicians or nurses on their multidisciplinary teams were able to review, discontinue, or prescribe medications and provide advice on comorbidity management according to their scope of practice. Sites that lacked these professionals had reduced capacity to review medications and manage comorbid conditions and were reliant on participants' general practitioners to undertake these aspects of care.

Some program elements are challenging to implement. Goal setting was seen as a key to the OACCP; however, the coordinators found it difficult. The person-centered approach to goal setting described in the OACCP MoC places the patients in charge of making their own goals. Although coordinators attempted to use a person-centered approach, their patients struggled to set realistic goals, and the coordinators felt they often took over. Goal setting to support long-term health behavior change was seen as an area that could be improved.

There was recognition by coordinators that weight loss is challenging, and sometimes the goal was to stop patients gaining weight rather than reducing it. There were concerns that the OACCP weight management interventions were not intensive enough to achieve the weight loss needed to improve OA symptoms.

Chronic pain management strategies were seen as something that was needed but could not be delivered. The coordinators felt patients would benefit from chronic pain management strategies, such as such as cognitive behavioral therapies, but most sites were underprepared to deliver these because of lack of staff training.

Enablers. Clinician education, training, and mentoring improves care. The coordinators had taken part in professional development through the ACI, such as training in person-centered care and behavior change techniques and peer mentoring. These activities were seen to improve care.

Transdisciplinary care that involved sharing roles across different disciplines was very helpful. OACCP sites in regional areas experienced reduced capacity due to a chronic shortage of health professionals. Coordinators from regional sites reported that a strategy to address this was to work in a transdisciplinary manner whereby members of the OACCP multidisciplinary team were trained to deliver key components that were out of their traditional scope of practice. For example, the physiotherapist was trained to provide dietary advice for times when a dietitian was unavailable.

Theme 3: System-level factors as a barrier to optimal patient care and OACCP sustainability. Referral to OACCP from orthopedic surgery departments is not the ideal pathway. All OACCP coordinators agreed that recruiting participants from joint replacement waitlists was "too late" in their care pathway and not as beneficial as referral earlier in the course of their condition. Once people with OA were told they needed surgery, they were reluctant to try first-line treatments. The coordinators strongly believed that if people experienced the full benefits of first-line treatments before seeing the surgeon, it would reduce the need for costly joint replacements.

There was a strong belief among coordinators that people should be referred into the program from primary care. Changing this arrangement was seen as problematic for OACCPs funded through orthopedic surgery departments in public hospitals. This was because the OACCP was positioned as a strategy to address overly long waitlist times for joint replacement surgeries, rather than as definitive OA management.

OACCPs are underresourced for the work that they do. Most OACCP coordinators felt they were inadequately funded to run their programs. Unmet staffing needs were commonly identified for physiotherapists, dietitians, and administrative support staff. Coordinators from two sites that lacked funding for a multidisciplinary OACCP team expressed that this was a huge barrier to the sustainability of their program. There were also perceptions of inequitable resourcing particularly in regional areas.

Results of survey 1: OACCP coordinator training needs analysis (steps 1 and 2). The results of survey 1 are summarized in Table 2. Nine of 28 activities were rated as very important to the OACCP coordinator role (median 7). They performed three of nine of the important activities very well, including the following: establishing a supportive relationship with participants (median 7, IQR 1), communicating face-to-face (median 7, IQR 1), and providing evidence-based care (median 7, IQR 1). The coordinators performed well (median 6) across the remaining six of nine activities identified as very important.

Two activities OACCP coordinators saw as important to their role (median 6) but gave a rating of their performance as neutral or fairly well (median 4 or 5) were identifying areas worthy of investigation for quality improvement or research and critically evaluating published research. Because the coordinators regarded these areas as important to improving their performance (median 6), these were flagged as opportunities for future training, along with other topics listed in Table 3. The most frequently reported topics for future training were the following: (1) medications and supplements for OA, (2) person-centered care and supporting behavior change, (3) extracting OACCP data for activity and performance reporting, (4) pain coping and cognitive behavioral therapy, and (5) accessing and interpreting research evidence. Preferences for delivery of professional education were for online modules, completed at their own pace with recorded presentations, and online interactive workshops.

Table 2. Survey 1: Training needs of OACCP coordinators: modified Hennessey Hicks survey*

	Importance of these activities to successful performance of your job[a]	How well you are performing these activities in your role[b]	Importance of training to improving performance of these activities[c]	Importance of changes in the working environment to improving performance of activities[d]
1. Establishing a supportive relationship with patients	7 (0)	7 (1)	5 (4)	5 (3)
2. Paperwork, inputting accurate assessment data into records	6 (1)	6 (2)	4 (1)	6 (2)
3. Interpreting patient data: surveys, functional measures, etc	6 (1)	6 (1)	4 (2)	4 (2)
4. Applying the patient data collected into your own practice	6 (1)	5 (1)	5 (3)	5 (3)
5. Critically evaluating published research in OA management	6 (1)	5 (1)	6 (2)	4 (2)
6. Appraising your performance in implementing the OACCP	6 (1)	5 (0)	4 (2)	5 (2)
7. Getting on with your allied health and medical colleagues	6 (1)	6 (1)	4 (3)	6 (4)
8. Communicating with patients face-to-face	7 (1)	7 (1)	4 (4)	6 (2)
9. Identifying areas of clinical practice for investigation	6 (1)	5 (1)	5 (2)	5 (3)
10. Case coordination, education, exercise, weight control, etc	7 (0)	7 (1)	6 (2)	6 (2)
11. Introducing new ideas into your OACCP work	6 (1)	5 (1)	5 (2)	6 (3)
12. Finding information that can inform your clinical work	6 (1)	5 (1)	5 (2)	4 (1)
13. Providing feedback to colleagues working in the OACCP	6 (0)	5 (1)	5 (2)	5 (3)
14. Providing correct information to patients and/or carers	7 (1)	6 (0)	5 (2)	4 (2)
15. Teaching colleagues and/or students how to do things in the OACCP	6 (2)	6 (1)	5 (2)	5 (3)
16. Planning and organizing an individual OACCP patient's care	7 (1)	6 (1)	5 (1)	6 (2)
17. Evaluating OACCP patients' psychological and social needs	7 (1)	6 (1)	5 (2)	5 (2)
18. Organizing your own time effectively	7 (1)	6 (1)	4 (2)	6 (2)
19. Using technical equipment, including computers	6 (2)	6 (1)	5 (3)	6 (3)
20. Education and health promotion around comorbidities	6 (1)	5 (1)	5 (1)	5 (2)
21. Making do with limited resources	6 (2)	6 (2)	4 (2)	5 (3)
22. Assessing patients' clinical needs	7 (1)	6 (1)	5 (1)	5 (1)
23. Collecting and collating relevant research for use	5 (1)	5 (1)	5 (3)	5 (3)
24. Identifying areas for quality improvement or research	6 (1)	4 (1)	6 (2)	5 (2)
25. Working as a member of a multidisciplinary OACCP team	7 (1)	6 (1)	4 (2)	6 (2)
26. Locating and accessing relevant equipment and resources	6 (2)	5 (1)	4 (2)	5 (2)
27. Undertaking administrative activities	5 (1)	6 (2)	4 (3)	6 (2)
28. Coping with changes to the OACCP and broader health service	6 (1)	6 (1)	3 (2)	5 (2)

* Values are median (interquartile range). OA, osteoarthritis; OACCP, Osteoarthritis Chronic Care Program.
[a] 1 = not at all important; 7 = very important.
[b] 1 = not well; 7 = very well.
[c] 1 = not at all important; 7 = very important.
[d] 1 = not at all important; 7 = very important.

Results of survey 2: Prioritization of the barriers (steps 3 and 4). The SHP stakeholder investigators participated in the next steps. We recruited six physiotherapists (five were OACCP coordinators) and one health manager across three large and diverse local health districts in metropolitan NSW. We also recruited one consumer with lived experience with OA and two policy makers from the ACI. Ten investigators completed survey 2, in which they ranked the barriers identified in the interviews and survey 1 in order of importance (Table 4). The two top-ranked barriers were reduced capability of OACCP coordinators to (1) support long-term behavior change and (2) set goals with participants. Both are important aspects of person-centered care.

Plan to address the prioritized barriers. A full description of the barriers, mapped to the TDF, with proposed strategies, classified according to feasibility (can do now, already being done, or needs funding to do later), is in Table 4. Each barrier was mapped to the domains and constructs of the TDF across the three levels: i) OACCP intervention (including acceptablility to participants), ii) staff and iii) health system. The proposed plan of action to address the most important barriers determined as

Table 3. Survey 1: Open-ended questions on topics where further training was needed (weighted according to priority level)*

Topics identified to meet the specific training needs of individual OACCP coordinators	Priority 1	Priority 2	Priority 3	Priority 4	Priority 5	Total count
Person-centered care and supporting behavior change	6	–	–	–	2	8
Medications and supplements	2	4.5	–	1	1	8.5
Accessing and interpreting the latest evidence	2	3	–	–	–	5
Pain coping/cognitive behavioral therapy	4	–	2	–	–	6
Extracting OACCP data for activity reporting and performance appraisal	4	3	–	1	–	8
Managing comorbidities	4	–	–	–	–	4
Assessment and treatment techniques for hip/knee	2	–	–	–	–	2
Use and interpretation of outcome measures	2	–	–	1	–	3
Chronic pain management	2	–	–	–	–	2
Effective group exercise	2	–	–	–	–	2
Productivity training	–	3	–	–	–	3
Sleep hygiene	–	1.5	–	–	–	1.5
Telehealth	–	1.5	–	–	–	1.5
Managing a team (providing feedback)	–	1.5	1	–	–	2.5
Research skills	–	1.5	1	–	–	2.5
Psychosocial assessment and management	–		1	–	–	1
Interpretation of imaging	–	–	2	–	–	2
Staying up to date on programs available in primary care	–	–	1	–	–	1
Professional performance self-assessment	–	–	1	–	–	1
Use of bracing and orthotics	–	–	–	1	–	1
Exercise prescription for OA	–	–	–	1	–	1
Promoting the OACCP service	–	–	–	1	–	1

* To assist with the interpretation, the results were weighted according to the priority level. Topics indicated as priority 1 were assigned 2 points, priority 2 topics were assigned 1.5 points, and priority 3, 4 and 5 topics were assigned 1 point. OA, osteoarthritis; OACCP, Osteoarthritis Chronic Care Program.

feasible for immediate action in the OAChangeMap included the following: patient education materials to address misconceptions about OA, when joint replacement is needed, and whether exercise is safe and healthy for joints; shared decision-making tools to assist patients with goal setting and developing a management plan; training in person-centered care for health professionals in interactive workshops; and access to an evidence-based comprehensive OA eLearning program designed for health professionals of any discipline. Recommended modules for OACCP health professionals will be evidence-based OA practice, using positive language around OA and other topics as needed (eg, pharmacotherapies). These strategies will be used in the next phase of our work, when we will develop, implement, and evaluate the strategies, which will be reported in a subsequent article.

DISCUSSION

We adopted a seven-step codesign framework[27] to identify and understand the barriers and enablers associated with delivering the OACCP from the perspective of the coordinators and to leverage broader stakeholder expertise to plan data-driven strategies designed to improve the program. Our analysis of the semi-structured interviews and survey 1 revealed themes that were consistent with important barriers reported in current literature.[5–7,39–42] Priority barriers related to OACCP patients were around the common misconceptions people hold about their OA. These misconceptions can affect their uptake of best evidence care, which is an issue highlighted in previous studies,[7,39] as is the notion that misconceptions may be compounded when people are exposed to health professionals with differing opinions.[5,42] Further, the importance of avoiding negative descriptors when taking about OA is a growing area of concern.[40–42] Our OAChangeMap strategies include patient educational resources and OACCP staff training that will be implemented to address these priority barriers.

Our strategies resonate with international work led by Keele University researchers and the OA Research Society International Joint Effort Initiative, which aims to change the way society thinks and talks about OA by using the biopsychosocial framework and by supporting positive lifestyle changes for joint health.[41] Further, policy makers recently released the Australian Commission for Safety and Quality in Health Care *Osteoarthritis of the Knee Clinical Care Standard*, which aims to educate health professionals, patients, and the public about taking an evidence-based, biopsychosocial approach to OA management and avoiding negative descriptors of OA.[43]

Our priority barriers related to OACCP staff were perceived knowledge and skills gaps in supporting long-term behavior change, goal setting, chronic disease management, evidence-based practice, weight management, medications, and other areas, consistent with previous studies.[6,7] We will address these knowledge and skills-related barriers by delivering bespoke OACCP workshops and our Arthritis Training Learning and up-Skilling eLearning program.[44]

Table 4. Survey 2: Top eight barriers and groups of barriers ranked according to importance, mapped to TDF and potential strategies to address the barriers*

Barriers or group of barriers to delivery of the OACCP, median (IQR)	TDF domains and constructs mapped to the barriers (or group of barriers)	Potential strategies to address the barriers
Group of barriers: reduced capacity/capability to support participants in achieving long-term behavior change, 4 (1); reduced capacity/capability to provide optimal goal setting with participants, 4 (2); reduced capacity/capability to provide chronic disease management (care is fragmented/siloed), 3.5 (1)		
Participant level	Knowledge; beliefs about consequences; social influences; emotion; optimism; beliefs about capabilities; memory, attention, and decision processes	OA patient education materials (P) Tools to support shared decision-making, goal setting, and management planning (P) Walking or exercise groups for social support and improved adherence to physical activity recommendations (PFA)
Staff level	Skills; belief about capabilities; knowledge; professional role; social influences; environmental context; emotion (burnout)	Advanced training in person-centered care and behavior change for OACCP health professionals (P) Reminders in the electronic medical record to check in with participants about their ability to change their health behaviors, eg, "readiness to change" (U) Peer mentoring with audit and feedback to rate the quality and performance of goal setting and person-centered care (P) Training on common comorbidities and their management (PFA)
System level		Flag indicator in medical record to indicate several teams are involved in the care of participants with chronic conditions to reduce fragmented care (U) Stratified care so that participants can receive different levels of care intensity depending on clinical needs (PFA) Multidisciplinary team case conference to support better interclinician communication and more consistent messaging (U) Service maps: information about readily available services and referral pathways (U)
Reduced capability to translate research evidence into practice, 3.5 (1)		
Staff level	Skills; belief about capabilities; knowledge	Training to support development of evidence-based practice skills such as critical appraisal of evidence to decide if it should be incorporated into practice (P)
Inadequate funding available for OACCP staffing, 3.5 (1)		
Staff level	Outcome expectancies; professional identity; professional role; professional boundaries; group identity; perceived competence; social pressure; emotion (burnout)	
System level		Bundle payments for hip and knee OA; bundle up surgery with all of the activities around it to incentivize providing quality care (U) Evaluate OACCP impact on health care use: reducing complicated long stayers (following joint replacement surgery), admissions to rehabilitation, discharge destination, clinical outcomes, etc (PFA) Assessing delays to surgery or complaints about joint replacement waitlists across NSW related to uptake

(Continued)

Table 4. (*Cont'd*)

Barriers or group of barriers to delivery of the OACCP, median (IQR)	TDF domains and constructs mapped to the barriers (or group of barriers)	Potential strategies to address the barriers
		of the OACCP program: does the OACCP reduce these problems? (PFA) Longer-term data linkage for health care use, including presentations to hospital EDs; not related to OA necessarily (PFA) Map the holistic pathways of care for the person: Where are there opportunities for change? Who is involved? How does the funding flow? Where are the barriers? (PFA) Develop and evaluate a model of virtual OACCP care: determine who this might suit (stratified care) (PFA) Optimize use of existing programs that support the aims of the OACCP, eg, Get Healthy generic education and programs https://www.gethealthynsw.com.au/ (U)
Referral to OACCP from orthopedic surgery departments, 3.5 (1)		
Participant level	Knowledge; beliefs about consequences; pessimism; outcome expectancies; social influences; social comparison	Tools to support shared decision-making, goal setting, and management planning (P)
Staff level	Outcome expectancies; professional identity; professional role; professional boundaries; group identity; perceived competence; social pressure; knowledge; skills	Training on use of shared decision-making tools developed for participants (P)
System level		Implement and evaluate an extended scope of practice model for physiotherapists to assess the need for joint replacement surgery before referral to an orthopedic surgeon (PFA) Conduct a cohort study comparing different sites to demonstrate the superior outcomes of OACCPs that recruit participants from primary care and medical specialists (PFA) Surgery deferral system: mechanism to support the ability to defer surgery twice after completion of the OACCP (U)
Group of barriers: people with OA often hold misconceptions about their condition, 3.5 (1); unhelpful attitudes to OA treatments and the health professionals who provide them, 3 (1)		
Participant level	Knowledge; beliefs about consequences; social influences; emotion; optimism; beliefs about capabilities	Patient educational resources to address misconceptions about OA; when joint replacement is needed, and exercise is safe and healthy for joints (P)
Staff level	Knowledge; beliefs about consequences; professional confidence; outcome expectancies; optimism	Health professional education and training communicating with patients with a special focus on using positive language around OA (avoiding terms such as "bone-on-bone" and "joints are worn out") (P)

* Rating: 0 = not important at all; 4 = extremely important. ED, emergency department; IQR, interquartile range; NSW, New South Wales; OA, osteoarthritis; OACCP, Osteoarthritis Chronic Care Program; P, strategies that were considered priorities because they were feasible for immediate action; PFA, strategies that were considered priorities but were not immediately feasible and needed support through a funding application; TDF, Theoretical Domains Framework; U, strategies that are already underway at a system level or one or more OACCP sites and could be leveraged at all NSW sites.

The priority system-level barrier to OACCP delivery was related to the perception that OACCP patients referred from joint replacement surgery waitlists came into the program too late, having already been told they "needed" surgery. This barrier was specific to the NSW context and is difficult to address because the evaluation of surgical throughput by NSW Health encourages a surgical optimization model for OACCP versus a prewaitlist model. However, we will attempt to address this with patient

educational materials and shared decision-making tools to help OACCP patients make informed decisions about first-line nonsurgical management options for OA.

There were strengths and limitations to using the seven-step codesign framework in our study. Although using the codesign framework was a strength, it provided a clear guideline that we adapted to suit our context and, similar to other codesign methods described in the OA literature, involved mixed methods, several steps, and broad consultation with various stakeholder groups[20–25]; it was also resource intensive. It is recognized that codesign research often takes longer than expected and is expensive, and sometimes participating health professionals are too busy treating patients to participate in the study activities.[45] It may have been more efficient to extract barriers to the implementation of best evidence OA care from systematic reviews for step 1 instead of conducting interviews and/or a survey. Although the Trischler framework allows for this approach,[27] it risks missing important locally relevant barriers that may only be uncovered with a more intensive, tailored approach.

Our approach was limited in some respects because we only involved OACCP coordinators in our interviews and surveys (step 1) even though there are other stakeholders who are key to the OACCP. Further, JPE, who is a physiotherapist, conducted the interviews and led the analyses. These factors may have influenced the results by placing greater emphasis on barriers affecting physiotherapists and not focusing as much on the issues affecting other stakeholders. This was mitigated through having a nonphysiotherapist researcher (GD) as a second coder. We also recruited a broader group of stakeholders for steps 3 to 7 to round out the perspectives represented. Our stakeholder investigators were a convenience sample taken from the SHP catchment. This potentially limited the perspectives represented in steps 3 to 7 to stakeholders from large Sydney metropolitan health districts; however, we interviewed coordinators from five regional health districts and four metropolitan districts back in step 1, so the views of regional coordinators were included. Limitations in the generalizability of perspectives are common to other OA codesign studies[20,22–24] because people involved in these activities by nature are often highly educated and motivated to contribute to finding solutions to the problems being explored. To mitigate this, we will consult with OACCP health professionals and people living with OA from across NSW to inform the development of our OAChangeMap strategies for the next phase of this work.

We identified key barriers to delivering the OACCP. We used our findings as a platform to engage stakeholders and develop codesigned solutions. We found this was a powerful way to create buy-in from key stakeholder groups, and although the findings are yet to be embedded into practice, this process has created stronger pathways through which we can drive improvements to OACCP delivery. The novel contribution of this article is in the way it describes the codesign methodology we used to identify and prioritize the barriers and generate strategies to address them. This methodology can potentially be transferred to other contexts in different regions and countries and for different health conditions and health services.

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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 Eyles 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.

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Comparing Rituximab and Cyclophosphamide in Induction Therapy for Childhood-Onset Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: An ARChiVe Registry Cohort Study

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Objective. Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are chronic life-threatening vasculitides requiring substantial immunotherapy. Adult trials identified rituximab (RTX) as an alternative to cyclophosphamide (CYC) for remission induction of GPA and MPA. Disease rarity has limited feasibility of similar trials with pediatric patients. We aim to evaluate the relative efficacy and toxicity of CYC and RTX for patients with childhood GPA and MPA through registry-based comparative evaluation.

Methods. From A Registry of Childhood Vasculitis, we identified patients with GPA and MPA who received induction with RTX or CYC. Pediatric Vasculitis Activity Score (PVAS) and Pediatric Vasculitis Damage Index (pVDI) score evaluated disease activity and damage. Descriptive statistics summarized patient characteristics. RTX and CYC comparisons used logistic regression for primary outcomes of postinduction remission (PVAS = 0) or low disease activity (PVAS ≤ 2). Hospital admission for adverse events and pVDI scores were compared using logistic regression and ordinal regression, respectively.

Results. Among 104 patients, 43% received RTX, 46% CYC, 11% both. Treatment groups did not significantly differ for diagnosis PVAS and onset age. There was no difference in remission among the groups (63% overall; odds ratio [OR] 1.07, 95% confidence interval [CI] 0.45–2.52). Hospitalizations occurred in 22% of patients receiving RTX versus 10% patients receiving CYC (OR 2.27, 95% CI 0.73–7.05). The median 12-month pVDI score was 1 in both groups (OR 0.98, 95% CI 0.43–2.22).

Conclusion. This is the first study comparing CYC and RTX for induction in pediatric GPA and MPA. No significant differences were shown in rates of remission, severe adverse events, or organ damage. Limitations included lack of standardized treatment regimens, retrospectivity, and lack of longitudinal adverse drug-related event data.

INTRODUCTION

Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) comprises a group of rare, systemic inflammatory diseases that include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA. Given the rarity of pediatric MPA and GPA,[1] data on treatments and outcomes are limited, and the majority of pediatric knowledge is extrapolated

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SIGNIFICANCE & INNOVATIONS

- This study is the first of its size to compare rituximab and cyclophosphamide for remission induction in childhood-onset antibody-associated vasculitis (AAV).
- In this study, rituximab was noninferior to cyclophosphamide in achieving remission or low disease activity in patients with childhood-onset AAV.
- The results of this study will assist pediatric rheumatologists with clinical decision-making as well as to help guide future comparative effectiveness studies within this patient population.

from adult studies. AAV can cause severe, often rapidly fatal or organ-threatening manifestations such as necrotizing pulmonary capillaritis or glomerulonephritis. Early recognition and therapy are essential, but treatments carry their own toxicity burden.

Before 2011, the mainstay of treatment for severe AAV in adults and children was receiving high-dose glucocorticoids (GCs) in conjunction with cyclophosphamide (CYC), an alkylating agent frequently used for remission induction in systemic autoimmune diseases.[2,3] CYC is effective but carries a number of risks including severe infection, malignancy, and infertility that are dependent on cumulative dose, limiting the extent of treatment particularly in teenagers and young adults in their child-bearing years.[4,5] Rituximab (RTX), a chimeric anti-CD20 biologic medication initially prescribed for the treatment of certain hematologic cancers, emerged as a potential alternative to CYC for remission induction treatment of adult AAV when two landmark trials in 2010 demonstrated noninferiority compared with CYC.[6–9] RTX is perceived to have a more favorable side effect profile although it still carries a risk of allergic reaction, prolonged hypogammaglobulinemia, and severe infections.[10] RTX has become more widely used for treatment of adult AAV,[7–9] however, it was not until 2018 following the small, 25 patient Pediatric Polyangiitis Rituximab Study safety trial that RTX was approved for treatment for pediatric AAV.[11]

Previous data from pediatric registries have demonstrated high rates of remission for pediatric AAV. In a French registry of 66 pediatric patients with GPA or MPA published in 2015, approximately 74% of patients achieved remission and 25% of patients had refractory disease.[1] Unfortunately, 41% of the patients in the French registry cohort had disease relapse and 4% died. A similar study from the international Pediatric Vasculitis (PedVas) initiative in 2017 examined 12-month outcomes of 105 pediatric patients with GPA or MPA[12] who had been recruited to A Registry of Childhood Vasculitis (ARChiVe). In this study, 42% of patients achieved remission by 12 months, and 24% of patients had a disease relapse, but no deaths were observed. Notably, the majority of patients in both the French (67%) and PedVas (70%) studies initially received CYC, and in each study, only 13% initially received RTX. There have been no subsequent treatment-related outcome studies of pediatric AAV. The limited studies in pediatric AAV outcomes include the French registry[1] and PedVas[12] studies described above and a comparative study of children (n = 35) and adults (n = 151) with AAV.[13] The last study suggests that there may be more cumulative damage and a higher frequency of relapse in the pediatric patients, but none of the studies systematically review treatment specific outcome.

In this study, we describe data from ARChiVe with the primary objective of comparing early outcomes in pediatric patients with GPA or MPA who receive induction treatment with either CYC, RTX, or both medications. Specifically, our aims were evaluating the noninferiority of RTX when compared with CYC with respect to the (1) proportion of patients with inactive or low disease activity or clinically important improvement postinduction, (2) proportion of patients with significant adverse drug-related hospitalizations, and (3) comparison of disease and treatment-related damage at 12 and 24 months.

PATIENTS AND METHODS

Registry and data collection platform. All retrospective clinical data were obtained from the ARChiVe, an international registry established in 2007. In 2012, the registry became incorporated into a prospective PedVas Initiative collecting both clinical and biologic follow-up data that uses REDCap as its data management platform. Patient eligibility criteria and the registry data set have been described previously.[14] Data collected in the registry include demographic data (including self-reported parental race and ethnicity from a fixed set of categories), diagnosis, presenting features and specific organ involvement, laboratory testing results, diagnostic investigations, medication dosing (including GCs), and standardized disease activity and damage measures. Visits are categorized as time of diagnosis,

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postinduction (4–6 months after diagnosis), 12 months after diagnosis, 24 months after diagnosis, relapse or flare, and unscheduled hospitalizations. Patients and the public were not involved in any steps of the design, conduct, analysis, and results dissemination of this study.

Disease measurement tools. Disease activity was recorded according to the Pediatric Vasculitis Activity Score (PVAS), adapted from the adult Birmingham Vasculitis Activity Score.[15] PVAS is a validated scoring metric for disease activity in chronic childhood vasculitis, measuring disease-related manifestations in nine organ systems.[12] The score ranges from 0 to 65, with higher scores suggesting greater disease activity. The cumulative score is responsive to changes in disease activity with therapy and is a useful tool to measure treatment response as opposed to disease-related damage.

Disease damage was recorded according to the Pediatric Vasculitis Damage Index (pVDI). The Vasculitis Damage Index (VDI) is a validated tool, that measures both disease and treatment-related damage in patients with chronic vasculitis. VDI scores and summates changes in multiple individual items across 10 system sections that have been sustained beyond 3 months as permanent damage. The score ranges from 0 to 72, with higher scores suggesting greater accumulated damage. ARChiVe collects data on damage using an adapted VDI for use in pediatric patients, termed pVDI. Details on the pVDI and how it was adapted from the VDI have been described previously.[12]

Patients. For the purpose of this study, patients were included from ARChiVe if they were diagnosed with either GPA or MPA before their 18th birthday, received either CYC (intravenous or oral), RTX, or both medications for induction therapy, and had data for the diagnosis and postinduction visits, collected between 2011 and 2020. Figure 1 details the selection of patients used for each aim.

Outcomes. *Framework for measuring outcomes.* In this study, we were guided by the EULAR recommendations for conducting clinical trials in AAV and their definitions of remission and damage[16] with adaptations for pediatrics, notably using PVAS and pVDI. The primary outcome was achievement of remission, or significant clinical improvement, with >50% reduction in disease activity at the postinduction visit. Secondary outcomes include rates of drug-related hospitalization between the

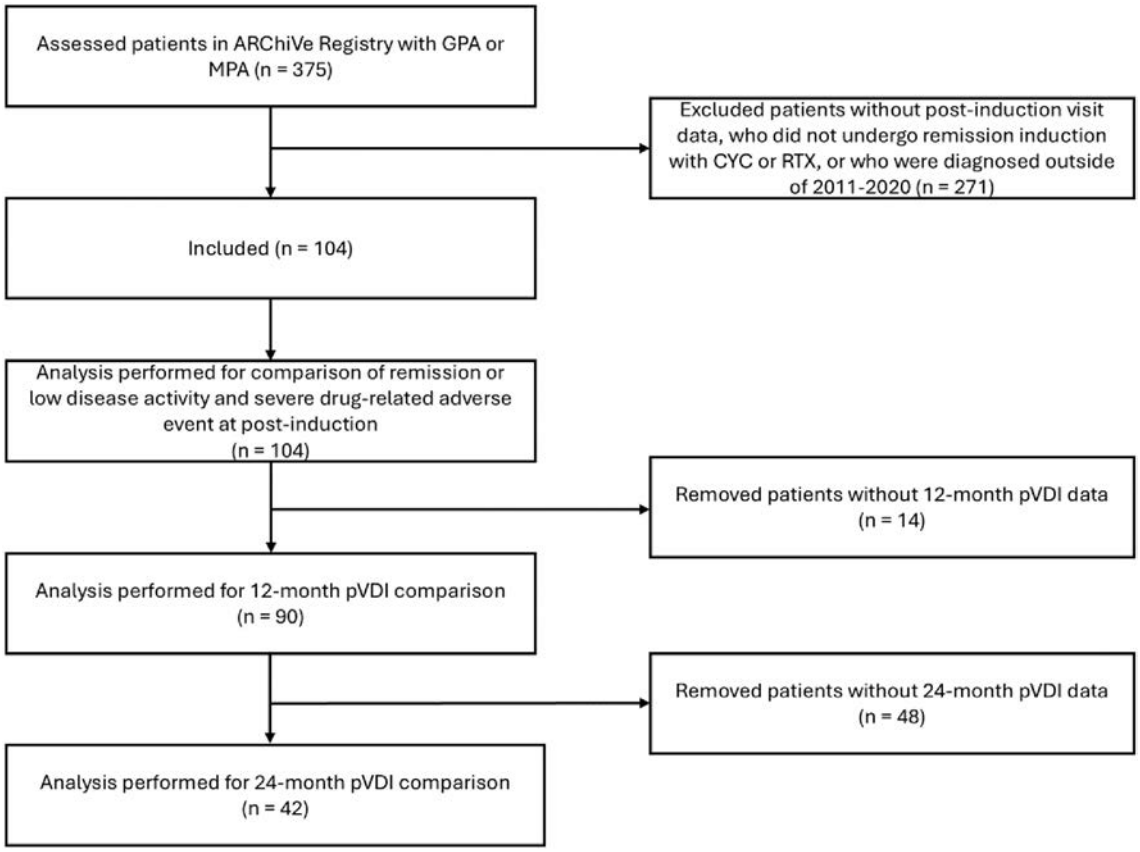

Figure 1. Strengthening the Reporting of Observational Studies in Epidemiology flow chart for cohort selection. ARChiVe, A Registry of Childhood Vasculitis; CYC, cyclophosphamide; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; pVDI, Pediatric Vasculitis Damage Index; RTX, rituximab.

diagnosis and postinduction visits and the degree of disease-related damage at the 12- and 24-month visits. Additionally, changes in some definitions were required to accommodate some of the limitations of available registry data consistent with other recent studies in AAV.[12,17]

Primary outcome. Primary outcome was determined at the postinduction visit and was defined by remission (PVAS = 0) or low disease activity (PVAS ≤2). The EULAR definition of remission is also qualified by inclusion of a stable low GC dose ≤7.5mg of prednisone or prednisolone for longer than three months; however, such dosing details during the three months before remission were not available. Therefore, the primary analysis at the postinduction visit was without attention to GC dosing. To partially account for this, a secondary analysis was performed that included a prednisone or prednisolone dosage of ≤0.2 mg/kg/day (equivalent to an adult dose of 7.5 mg) at the postinduction visit. In previous studies using this registry, clinically relevant improvement with a PVAS decrease of 75% was more meaningful than 50% described by EULAR, and therefore we included an analysis for both measures.[12]

Secondary outcomes. Damage was defined by pVDI scores and was assessed at both the 12- and 24-month visits. Severe adverse drug-related events were defined as any hospitalization occurring between diagnosis and the postinduction visit secondary to either infection or a drug-related cause. Admissions for routine medication administration were excluded. The registry was not previously structured to collect adverse drug-related events that did not require hospitalization, although the ability to collect more specific data regarding adverse drug-related events was added recently.

Statistical analysis. Descriptive statistics were used to report demographics, baseline disease characteristics, rates of low disease activity, remission, rates of hospitalization, and damage. Comparisons between treatment groups were made using Fisher's exact test and Pearson's chi-square test for categorical data and Kruskal-Wallis rank sum test for quantitative data.

Logistic regression was used to model the primary outcome of remission or low disease activity and the secondary outcome of hospital admission. Proportional odds ordinal regression was used to model the secondary outcomes of pVDI at 12 and 24 months. For all regression models, sex, diagnosis PVAS, pulmonary involvement, and the need for dialysis were included as covariates to address confounding factors. Odds ratios (ORs) were estimated with the respective 95% confidence intervals (CIs) for each outcome measure. The proportional odds assumption was checked by fitting a corresponding multinomial model and comparing the two models using a likelihood ratio test. Complete case analysis was used for all results. Analyses were performed using R version 4.3.1.

Consistent with adult studies,[8,18] we specified a noninferiority margin of –0.25 for the difference in proportion of remission, hospitalization, and damage. Noninferiority would be achieved if the lower bound of the two-sided 95% CI for the difference in proportion between RTX and CYC was above –0.25.

RESULTS

Patient characteristics. In total, 104 patients fulfilled study inclusion criteria, with 90 patients also having a 12-month follow-up visit, and 42 patients having a 24-month follow-up visit. Table 1 summarizes patient demographics according to induction treatment: 45 patients (43%) received RTX, 48 patients (46%) received CYC, and 11 patients (11%) received a combination of RTX and CYC. The majority had a diagnosis of GPA (81%), were female (67%), were White (62%), and had a median age at diagnosis of 14 years. Most patients were from either the United States (38%) or Canada (34%), with a wide geographic distribution including patients from Europe, Asia, and South America. Patients receiving combination therapy had a higher age of diagnosis (median 16 years old, $P = 0.033$) and patients in the United States were more likely to receive RTX or combination RTX and CYC for induction treatment compared with other countries (74% vs 42%, respectively, $P < 0.001$). We also note a nonsignificant trend (Table 1) for treatment with CYC over RTX alone in the presence of renal or pulmonary involvement.

The median PVAS at diagnosis for all patients was 19 (interquartile range 16–24). Patients receiving combination therapy had a slightly higher median PVAS at diagnosis than patients receiving RTX or CYC (21 vs 19, $P = 0.4$). The majority of patients also had renal disease (87%). More patients receiving CYC or combination therapy had renal disease (94% and 91%, respectively) compared with patients receiving RTX (76%, $P = 0.066$). Because glomerular filtration rate at diagnosis was incompletely captured in the registry, we used the need for dialysis as a surrogate of severe renal disease. Overall, 23% of patients required dialysis at diagnosis, and dialysis requirements were similar among treatment groups ($P = 0.9$).

Primary outcome: remission at postinduction. Overall, 63% of patients achieved remission or low disease activity by the postinduction visit (Table 2). Active PVAS items for patients who did not achieve remission by the postinduction visit may be found in Supplementary Table 1. Patients who received RTX had a similar proportion of remission or low disease activity to those who received CYC (64% vs 62%, respectively, $P > 0.9$). Of the 90 patients who had data for the 12-month visit, 72% achieved remission or low disease activity by the 12-month visit. Notably, patients who received RTX had a significantly lower median steroid dosage (0.13 mg/kg/day) at the postinduction visit compared to the patients receiving CYC (0.3 mg/kg/day) and the group receiving combination therapy (0.3 mg/kg/day; $P < 0.001$). A significant majority of patients achieved at least a 75% reduction in PVAS (82%) or a 50% reduction in PVAS (91%) by the

Table 1. Patient characteristics by induction medication*

Characteristics	Rituximab, n (%)	Cyclophosphamide, n (%)	Combination, n (%)	Overall, n (%)	*P* value[a]
Sample size, n	45	48	11	104	
Sex					0.7
Female	31 (69)	33 (69)	6 (55)	70 (67)	
Age at diagnosis, median (IQR) y	14.0 (11.0–16.0)	14.0 (12.0–15.0)	16.0 (15.0–17.0)	14.0 (12.0–16.0)	**0.033**
Parents' race and ethnicity					0.3
White	31 (69)	25 (52)	8 (73)	64 (62)	
Other	6 (13)	10 (20)	0 (0)	16 (15)	
Asian	4 (8.9)	9 (19)	1 (9.1)	14 (14)	
Hispanic/Latinx	3 (6.7)	4 (8.3)	1 (9.1)	8 (7.7)	
Black	1 (2.2)	0 (0)	1 (9.1)	2 (1.9)	
Place of residence					<0.001
United States	22 (49)	10 (21)	7 (64)	39 (38)	
Canada	12 (27)	23 (48)	0 (0)	35 (34)	
Europe	11 (24)	9 (19)	4 (36)	24 (23)	
Asia	0 (0)	4 (8.3)	0 (0)	4 (3.8)	
Argentina	0 (0)	2 (4.2)	0 (0)	2 (1.9)	
Diagnosis					0.077
Granulomatosis with polyangiitis	37 (82)	41 (85)	6 (55)	84 (81)	
Microscopic polyangiitis	8 (18)	7 (15)	5 (45)	20 (19)	
Antibody status					
pANCA	14 (31)	12 (25)	6 (55)	32 (31)	0.15
Anti-MPO	13 (29)	14 (29)	7 (64)	34 (33)	0.079
cANCA	24 (53)	26 (54)	4 (36)	54 (52)	0.5
Anti-PR3	30 (67)	31 (65)	3 (37)	64 (62)	0.053
ANCA negative	0 (0)	3 (6.3)	0 (0)	3 (2.9)	0.9
Time between symptom onset and diagnosis, median (IQR), d	41 (16–119)	35 (23–78)	55 (14–100)	36 (22–94)	0.7
Renal involvement	35 (78)	45 (94)	10 (91)	90 (87)	0.066
Required dialysis	10 (22)	11 (23)	3 (27)	24 (23)	0.9
Pulmonary involvement	21 (47)	24 (50)	8 (73)	53 (51)	0.3
PVAS at diagnosis, median (IQR)	19 (14–24)	19 (17–24)	21 (18–26)	19 (16–24)	0.4

* Bolded *P* values are considered statistically significant. ANCA, antineutrophil cytoplasmic antibody; cANCA, cytoplasmic ANCA; IQR, interquartile range; MPO, myeloperoxidase; pANCA, perinuclear ANCA; PR3, proteinase 3; PVAS, Pediatric Vasculitis Activity Score.
[a] Kruskal-Wallis rank sum test; Pearson's chi-square test.

postinduction visit. This was also similar across treatment groups (75% reduction, $P = 0.5$ and 50 % reduction, $P = 0.2$).

Patients receiving RTX had a slightly higher odds of remission at six months (OR 1.07; 95% CI 0.45–2.52; Table 3). The predicted probability of remission or low disease activity (PVAS ≤2) for patients receiving RTX was 0.015 (95% CI –0.216 to 0.246), greater than that of the patients receiving CYC, which was within the predefined noninferiority margin. When including the steroid dose in the definition of remission, the OR for patients receiving RTX increased (OR 2.34; 95% CI 0.94–5.84).

Secondary outcomes: hospitalizations and damage. Hospitalization occurred between the diagnosis and postinduction visits in 18% of patients (Table 4). A greater percentage of patients receiving RTX required hospitalization compared with patients receiving CYC (22% vs 10%, respectively; OR 2.27,

Table 2. Patient outcomes at postinduction by treatment groups*

Outcome	Rituximab, n (%)	Cyclophosphamide, n (%)	Combination, n (%)	Overall, n (%)	*P* value[a]
Sample size, n	45	48	11	104	–
PVAS at postinduction visit, median (IQR)	1 (0–4)	1.5 (0–4)	1 (0–6.5)	1 (0–4)	0.8
Remission or low disease activity[b]	29 (64)	30 (62)	7 (64)	66 (63)	>0.9
Remission or low disease activity[c]	20 (47)	12 (27)	1 (11)	33 (34)	0.060
Unknown[d]	2	4	2	–	–
Remission or 75% reduction in PVAS	36 (80)	41 (85)	8 (73)	85 (82)	0.5
Remission or 50% reduction in PVAS	40 (89)	46 (96)	9 (82)	95 (91)	0.2

* IQR, interquartile range; PVAS, Pediatric Vasculitis Activity Score.
[a] Kruskal-Wallis rank sum test; Pearson's chi-square test.
[b] Remission or low disease activity defined as PVAS ≤2.
[c] Remission or low disease activity defined as PVAS ≤2 and steroid dose ≤0.2 mg/kg/day.
[d] Number of patients for whom there is insufficient follow-up data to determine post-induction disease activity status; Sample sizes shown on the first row do not apply to this case.

Table 3. Regression model results for primary outcome at postinduction visit*

Outcome	n	Rituximab, OR (95% CI)	Combination, OR (95% CI)
Remission or low disease activity[a]	104	1.07 (0.45–2.52)	1.12 (0.28–4.44)
Remission or low disease activity[b]	96	2.34 (0.94–5.84)	0.48 (0.07–3.36)
Remission or 75% reduction in PVAS	104	0.80 (0.26–2.42)	0.30 (0.06–1.53)
Remission or 50% reduction in PVAS	104	1.06 (0.16–6.78)	0.14 (0.01–1.51)

* Each model adjusted for sex, diagnosis PVAS, pulmonary involvement, and the need for dialysis. All ORs use cyclophosphamide as reference. CI, confidence interval; OR, odds ratio; PVAS, Pediatric Vasculitis Activity Score.
[a] Remission or low disease activity defined as PVAS ≤2.
[b] Remission or low disease activity defined as PVAS ≤2 and steroid dose ≤0.2 mg/kg/day.

Table 4. Secondary outcomes by treatment groups*

Outcome	Rituximab	Cyclophosphamide	Combination	Overall	*P* value[a]
Infection or drug-related hospitalization, n (%)	10 (22)	5 (10)	4 (36)	19 (18)	0.084
pVDI score at 12-month visit, median (IQR)	1 (0–2)	1 (0–2)	0 (0–2)	1 (0–2)	>0.9
pVDI score at 24-month visit, median (IQR)	0 (0–2)	0 (0–1)	0.5 (0–1)	0 (0–1)	>0.9

* IQR, interquartile range; pVDI, Pediatric Vasculitis Damage Index.
[a] Kruskal-Wallis rank sum test; Pearson's chi-square test.

95% CI 0.73–7.05; Table 5). Notably, the number of patients requiring multiple hospitalizations for drug or infection related causes was higher for patients receiving RTX (11%) than for CYC (2%). The majority of patients receiving RTX (61%) or CYC (56%) had disease-related damage at the 12-month visit (denoted by pVDI score >0, Table 4). However, the degree of reported damage was low overall. The median pVDI score at 12 months was 1 in both groups; patients receiving RTX had a slightly lower odds of a greater pVDI score (OR 0.98, 95% CI 0.43–2.22; Table 5). There was no significant evidence of nonproportionality in ORs (χ^2 = 15.2; df = 12; P = 0.23).

DISCUSSION

This retrospective multicenter international study evaluated the noninferiority of RTX compared with CYC with respect to remission, hospitalizations, and disease- or treatment-related damage in pediatric AAV. This is the largest study to date comparing induction regimens in pediatric patients with these diseases. Consistent with prior descriptive studies evaluating pediatric AAV, the majority of the patients in our cohort were female (67%), had GPA (81%), and had renal (87%) or lung (51%) involvement. Our cohort, however, had a higher proportion of patients who received RTX (43%) or combination RTX and CYC treatment (11%) for induction compared with prior studies in which CYC was used for induction in the majority of patients, concordant with the increasing treatment with RTX for adult patients over the same time period.

Our findings are consistent with adult studies demonstrating noninferiority of RTX compared to CYC for induction therapy in AAV, albeit our pragmatic registry study did not have the rigor of a clinical trial. Of note, a significant number of adult studies have shown RTX to be superior to CYC in achieving remission, including a post hoc analysis of the Rituximab versus cyclophosphamide for ANCA-associated vasculitis (RAVE) trial that noted that patients with proteinase 3-positive AAV were significantly more likely to achieve remission by six months when treated with RTX (65% vs 48%, P = 0.04).[19] Recently, a large comparative effectiveness study from the French Vasculitis Study Group registry noted significantly higher rates of remission for patients receiving RTX compared with those receiving CYC (risk ratio 1.82, 95% CI 1.22–2.73).[20] This effect was maintained in the subgroup analysis. In the most recent guidelines from the American College of Rheumatology and Vasculitis Foundation (ACR/VF),[21] RTX was conditionally recommended over CYC for remission induction in patients with active, severe GPA or MPA, regardless of organ manifestations. This recommendation was made based on trial results, the comparatively lower toxicity for RTX compared with CYC, and a patient panel expressing a preference for RTX.[21]

Table 5. Regression model results for secondary outcomes*

Outcome	n	Rituximab, OR (95% CI)	Combination, OR (95% CI)
Infection or drug-related hospitalization	104	2.27 (0.73–7.05)	3.92 (0.85–18.1)
pVDI score at 12-month visit	90	0.98 (0.43–2.22)	0.84 (0.20–3.28)
pVDI score at 24-month visit	42	1.31 (0.30–5.57)	1.73 (0.26–10.6)

* Each model adjusted for sex, Pediatric Vasculitis Activity Score at diagnosis, pulmonary involvement, and the need for dialysis. All ORs use cyclophosphamide as reference. CI, confidence interval; OR, odds ratio; pVDI, Pediatric Vasculitis Damage Index.

Pediatric treatment recommendations for AAV currently do not parallel ACR/VF guidelines. The European Single Hub and Access Point for Paediatric Rheumatology in Europe recommendations for treatment of pediatric vasculitides[22] published in 2019 recommend CYC as first-line induction therapy for severe AAV, citing an absence of studies evaluating the efficacy and toxicity of RTX in pediatric patients. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) AAV Workgroup recently published consensus treatment plans (CTPs) for childhood-onset AAV.[23] In this CTP, both RTX and CYC were offered as potential induction medications. However, there was no preference stated between the two induction regimens, citing similar questions regarding the safety and efficacy of RTX in treating pediatric-specific disease. Although our study was not powered appropriately to determine whether RTX or CYC was superior in achieving remission induction, we were able to demonstrate noninferiority of RTX, which should serve to satisfy some of the questions regarding the efficacy of RTX in pediatric AAV. The comparative effectiveness study of the use of the CTP as well as the newest iteration of ARChiVe will be better able to evaluate safety and efficacy concerns between induction regimens.

Our study has significant strengths. As previously mentioned, this study uses ARChiVe, the largest registry for chronic childhood vasculitides in the world. As a result, we were able to analyze a comparatively large and diverse cohort of pediatric patients. Although disease rarity limits the possibility of randomized control trials to study these treatment alternatives, in this pragmatic study the treatment groups were well-balanced in terms of demographics, initial disease characteristics, antineutrophil cytoplasmic antibody specificity, and treatment choice.

Preference for prescribing RTX over CYC in the United States versus other sites is noted, but it is not clear how this would influence the standardized outcomes after the treatment choice was made. A nonsignificant trend for preferential prescription of CYC over RTX for renal and pulmonary involvement might potentially influence relative outcomes, but there were too few patients to consider reviewing subsets of patients. This study has some limitations. Although there was a significant difference in GC dose among patients at the postinduction visit, there was no information available about cumulative steroid dose through induction or steroid dosing between visits, limiting the ability to draw conclusions about the GC dose difference. We have previously described a wide variation in GC dosing for pediatric patients with AAV with renal disease.[24] The lack of control of GC dosing may have impacted the odds of achieving remission. However, it is worth noting that, although induction GC dose was controlled in the previously mentioned landmark AAV trials, GC tapers were similarly left up to the discretion of the treating physician. Also, considering the differences in adverse side effects between standard and rapid dose tapers of prednisone in the large plasma exchange and glucocorticoids in severe ANCA-associated vasculitis study in adult AAV, the difference in steroid dose between the induction regimens will need to be evaluated in further studies.

Although this study was able to compare short-term adverse events, most notably infections requiring hospitalization, the absolute number of events was low, which limited the comparison between treatment groups. Previous studies have suggested that RTX was associated with a greater number of infections than CYC.[25] Our study similarly showed twice the number of events in the group receiving RTX compared with the group receiving CYC, although this difference was not statistically significant. Additionally, this study was not able to compare adverse effects not requiring hospitalizations because those data were not captured by the registry.

This study was not able to evaluate for longer-term adverse effects of these induction medications such as persistent hypogammaglobulinemia, cancer, and fertility issues given the inherent limitations of the registry. Notably, pediatric AAV registry studies suggest the increasing treatment with RTX versus CYC over time.[12,14,26] We speculate that this shift in treatment is primarily influenced by the potential treatment toxicity burden perceived by both physicians and patient families. The risks of CYC for malignancy and infertility in general are dose and age dependent.[27] A recent study of long-term outcomes in 293 patients with GPA receiving CYC demonstrated no increased risk of cancer for patients who received ≤36 g of CYC during treatment. Additionally, a systemic review of patients with pediatric cancer noted that there was a low risk of fertility loss for male patients and female patients cumulatively receiving > 7.5 gm/m^2 of CYC.[28,29] The risks of RTX therapy for prolonged immune suppression are higher in children than in adults[30] and perhaps more than perceived; recent studies suggest 4% of children require regular intravenous immunoglobulin replacement therapy one year after receiving RTX.[30–32] Persistent hypogammaglobulinemia will be evaluated in the future as the newest iteration of ARChiVe collects data on Ig levels. This will be part of a current and ongoing CARRA prospective comparative pragmatic evaluation of CYC versus RTX as induction therapy for AAV (both using GCs) in standardized regimens according to CTPs.[24] However, given the time course between receiving CYC and cancer or fertility issues and the rarity of these diseases, some of these adverse events may remain difficult to capture rigorously.

This study demonstrates the noninferiority of RTX compared to CYC in achieving remission or low disease activity in childhood-onset AAV. The findings also suggest no difference in adverse events or damage between patients who received RTX or CYC. The results of this study may assist with current clinical decision-making regarding the choice of induction medications in childhood-onset AAV and will complement the ongoing CARRA prospective CTP study.

AUTHOR CONTRIBUTIONS

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

Study conception and design. Gagne, Sivaraman, Bosman, Klamer, Morishita, Cabral.
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Analysis and interpretation of data. Gagne, Sivaraman, Bosman, Klamer, Morishita, Cabral.

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Transcriptional Profiling of Tofacitinib Treatment in Juvenile Idiopathic Arthritis: Implications for Treatment Response Prediction

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Objective. To assess changes in gene expression following tofacitinib treatment and investigate transcription patterns as potential predictors of treatment response in patients with active juvenile idiopathic arthritis (JIA).

Methods. Whole-blood samples were collected from patients with JIA at baseline and after 18 weeks of open-label tofacitinib treatment. Patients who achieved a JIA–American College of Rheumatology (ACR) response of 70% or above at week 18 were classified as treatment responders (TRs), whereas those with at most a JIA–ACR30 were classified as poor responders (PRs). Differential gene expression and gene ontology overrepresentation analyses were performed to compare RNA expression between week 18 and baseline samples, as well as between PR and TR samples at baseline.

Results. Samples from 67 patients at baseline and 60 patients at week 18 were analyzed. After 18 weeks of tofacitinib treatment across all patients with JIA, 883 genes showed significant differential expression (week 18 to baseline). The most strongly down-regulated genes were overrepresented within interleukin-7 (IL-7) and type I and type II interferon pathways, whereas up-regulated genes were enriched in ontologies related to neuronal cell processes and cell signaling. Comparing PRs and TRs at baseline, 663 genes showed differential expression. Up-regulated genes were overrepresented within ontologies including activation of MAPK activity ($P = 9.40 \times 10^{-5}$), myeloid cell development ($P = 8.13 \times 10^{-5}$), activation of GTPase activity ($P = 0.00015$), and organelle transport along microtubules ($P = 0.00021$).

Conclusion. Tofacitinib treatment in JIA down-regulated genes in interferon and IL-7 signaling pathways regardless of effectiveness. Furthermore, baseline up-regulation of MAPK signaling may predict poor response to tofacitinib treatment in JIA.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) comprises a group of immune-mediated diseases characterized by chronic arthritis, with disease onset occurring before 16 years old.[1] Current treatment strategies for JIA are based on the subtype of JIA and subsequent clinical response to anti-inflammatory therapies.[2] However, despite advancements in understanding JIA pathophysiology, achieving and maintaining clinical remission remains challenging, with only a minority of children attaining optimal outcomes.[3]

The management of JIA in patients with polyarticular joint involvement relies on treatment with conventional disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs, or small-molecule DMARDs, either alone or in combination. Although markers such as C-reactive protein, erythrocyte

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SIGNIFICANCE & INNOVATIONS

- Gene expression analysis could enhance medical decision-making and improve treatment strategies for juvenile idiopathic arthritis (JIA), leading to more personalized approaches in clinical practice.
- In this study, tofacitinib treatment in JIA down-regulated genes associated with interferon and interleukin-7 signaling pathways.
- Baseline up-regulation of the MAPK signaling pathway may serve as a potential biomarker for predicting poor response to tofacitinib.
- The findings may encourage further research and potential clinical trials exploring MAPK inhibitors as alternative therapies for patients with JIA with an up-regulated MAPK pathway.

sedimentation rate, antinuclear antibody positivity, and HLA-B27 are commonly used, additional blood-based biomarkers could significantly enhance the medical decision-making process and improve JIA treatment strategies.

Previous studies investigating candidate biomarkers measured in the serum (donated by Pfizer) or plasma for predicting treatment response to conventional and biologic DMARDs in JIA have demonstrated limited success. S100 proteins have been the most extensively explored.[4–7] Our own pilot study indicated a potential association between the response of patients with JIA treated with the JAK inhibitor (JAKi) tofacitinib and levels of S100A12, resistin, monocyte chemotactic protein 1, and their temporal changes in serum.[8]

The emergence of "omics" has made gene expression profiling an appealing approach for discovering and evaluating blood-based biomarkers. Initial research suggests that whole-blood gene-expression patterns may be predictive of treatment response in patients with systemic JIA.[9] Furthermore, studies in rheumatoid arthritis (RA) indicate that prescription of JAKi leads to a dose-dependent reduction in the expression of STAT3 and its target genes.[10] However, it remains unclear whether similar gene expression changes occur in patients with JIA undergoing treatment with a JAKi.

Therefore, the primary aim of this study was to investigate how gene expression changes in patients with JIA after treatment with tofacitinib. We additionally sought to identify potential gene expression biomarkers that could predict treatment response and thereby aid in personalizing therapeutic approaches for patients with JIA.

MATERIALS AND METHODS

Patients and study design. We retrospectively analyzed the gene expression profiles of patients with JIA who participated in a phase 3 randomized clinical trial evaluating the efficacy of tofacitinib (NCT02592434).[4] The trial enrolled patients between 2 and 17 years old that were diagnosed with polyarticular course JIA, including polyarticular rheumatoid factor–positive and polyarticular rheumatoid factor–negative arthritis, extended oligoarticular arthritis, enthesitis-related JIA (ERA), juvenile psoriatic arthritis, and systemic JIA. All patients received oral open-label tofacitinib from baseline until week 18. Patients who achieved a JIA–American College of Rheumatology (ACR) response of at least 30% at week 18 were randomized to either continue tofacitinib or initiate placebo for up to 26 weeks.[4] Additional details on study design, including eligibility criteria, can be found elsewhere.[4] Our analysis used all available whole-blood RNA samples collected at baseline (ie, just before the initiation of tofacitinib) and again at week 18.

Response measures. Response to tofacitinib from baseline to week 18 was measured per the provisional JIA–ACR criteria for treatment response.[11] Improvement with treatment is evaluated based on percentage changes (week 18 to baseline) of the six JIA core response variables (CRVs), which include the number of joints with active arthritis, the number of joints with limited range of motion, physician global assessment of disease activity, parent and patient assessment of overall well-being, functional ability as measured by the Child Health Assessment Questionnaire, and erythrocyte sedimentation rate or C-reactive protein levels.[11] A JIA–ACR30, JIA–ACR50, or JIA–ACR70 response is defined as at least 30%, 50%, or 70% improvement (from baseline to week 18) in three of the six CRVs, with no more than one remaining CRV worsening by more than 30%.[11]

For this analysis, patients were further classified as poor responders (PRs) if they had at most a JIA–ACR30 response by week 18 and classified as treatment responders (TRs) if they achieved at least a JIA–ACR70 response. This classification strategy (PRs or TRs) aligns with other studies of biomarkers in JIA[9] and allows for a clear demarcation between response groups.

Covariates. Age and disease duration were collected through chart review, reflecting the time since diagnosis and the patient's age at the time of study enrollment. The JIA category, as defined by the International League of Associations for Rheumatology classification criteria, was used to categorize patients into subtypes including polyarticular rheumatoid factor–positive and polyarticular rheumatoid factor–negative arthritis, extended oligoarticular arthritis, ERA, juvenile psoriatic arthritis, and systemic JIA. These covariates (age, disease duration, and JIA category), along with the patient groups that were compared, which was either the study time point (values of either baseline or week 18) or the combination of timepoint and treatment response class (values of PR at baseline, TR at baseline, PR at week 18, or TR at week 18), were included in the statistical models to control for

potential confounding factors and to assess differential gene expression patterns.

Laboratory assays. Whole-blood samples were collected at baseline and at week 18 using PAXgene Blood RNA tubes (PreAnalytiX). Upon collection, the samples were treated with DNase I, and then RNA was extracted using Zymo's Quick-RNA Whole Blood kit. RNA quality was assessed using a Bioanalyzer (Agilent Technologies). To deplete globin messenger RNA and ribosomal RNA (rRNA), the NEBNext Globin and rRNA Depletion Kit (New England BioLabs) was used. Next, complementary DNA libraries were generated using the NEBNext Ultra II Directional RNA Library Preparation Kit (New England BioLabs) with eight cycles of polymerase chain reaction amplification. Library quality control and quantification were performed using Qubit quantification (Thermo Fisher Scientific). Paired-end (2 × 150bp) directional polyA RNA sequencing was conducted by the Genomics, Epigenomics, and Sequencing Core at the University of Cincinnati using established protocols[12,13] on an Illumina NovaSeq 6000 sequencer (Illumina).

Statistical analysis. Pseudoquantification was performed using kallisto (version 0.48.0, GRCh38 release 94 index) to generate a count matrix from RNA-sequencing read data. The variancePartition R package (version 1.28.9)[14] was used to quantify the variation in expression attributable to sample characteristics and for mixed-effect differential expression analyses using the Dream workflow.[15] These differential analyses modeled for age, disease duration, patient identity, JIA category, and group identity, which was the study time point (baseline or week 18), treatment response class (PR or TR), or the combination of time point and treatment response class (PR or TR).

These two groupings were used to assess the effects of tofacitinib on gene expression (week 18 to baseline) and to compare gene expression of PR to TR at both time points. For comparisons between response groups, patients with a JIA–ACR50 response were excluded from the analysis.

Differentially expressed genes were identified as those with a false discovery rate (FDR) of <0.05 calculated using the Benjamini-Hochberg method. For the comparison between week 18 and baseline samples, we focused our analysis on differentially expressed genes with the largest effect size (absolute logFC >0.7, equivalent to a >1.6-fold difference). Gene ontology (GO) overrepresentation analysis was performed separately for up- and down-regulated genes using the dseqr R package (version 0.35.0).[16] For GO terms where the set of up- or down-regulated genes had a Jaccard similarity >0.7, only the GO term with the smallest *P* value was reported. The pathview R package (version 1.38.0) was used to visualize differentially expressed genes in the MAPK signaling pathway from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database.[17] Ethics approval for the study was obtained from Cincinnati Children's Hospital Medical Center (Institutional Review Board 2021-0465).

RESULTS

Patients. The clinical trial enrolled 225 patients with polyarticular course JIA (184) and psoriatic arthritis or ERA (41). By week 18, 52 patients had discontinued the study, primarily because of a lack of treatment response, resulting in no week 18 samples for these 52 patients. We had access to a total of 127 whole-blood samples from the 173 patients who completed the first 18 weeks, with 67 collected at baseline and 60 at week 18. None of these samples were excluded because of poor sample quality (Supplementary Figure 1). Consequently, at baseline there were 47 TR samples and 20 PR samples, whereas at week 18, there were only 38 TR samples and 8 PR samples. The remaining 14 samples, which were collected at week 18 from patients with a JIA–ACR50 response, were included in analyses that explored changes in gene expression from baseline to week 18. A summary of the demographic and clinical characteristics at baseline, along with an overview of the available samples for analysis, can be found in Tables 1 and 2.

Differential gene expression associated with tofacitinib treatment. After filtering out lowly expressed genes, 31,799 genes were considered for further analysis. Among the sample metadata variables collected, patient identity and treatment time point explained the largest percentage of genome-wide gene expression variance (Supplementary Figure 2). A total of 883 genes were significantly differentially expressed after tofacitinib treatment at FDR <0.05 and absolute log fold change >0.7 (equivalent to a >1.6-fold difference). Among these 883 genes, 286 genes were significantly up-regulated and 597 genes were significantly down-regulated at week 18 as compared with baseline (Figure 1A).

Among the 597 down-regulated genes (Figure 2), several significant GO terms were identified. Noteworthy among these were the following: (1) epigenetic negative regulation of gene expression, which predominantly encompassed genes encoding histones, including those targeted by interleukin-7 (IL-7) signaling; (2) negative regulation of IL-10 production (indoleamine dioxygenase 1, X-C motif chemokine ligand 1 [XCL1], TYRO protein tyrosine kinase-binding protein, tribbles pseudokinase 2, CD274, and interferon [IFN]-stimulated gene 15 [ISG15]); (3) type I IFN signaling pathway (IFN-inducible protein 6 [IFI6], IFI27, IFN-induced protein with tetratricopeptide repeats 1 [IFIT1], IFIT3, IFN-induced transmembrane protein 1 [IFITM1], ISG15, and radical S-adenosyl methionine domain containing 2 [RSAD2]); and (4) response to IFNγ (Fcγ receptor Ia [FCGR1A], guanylate binding protein 1 [GBP1], CCL3, CCL23, XCL1, XCL2, GBP5, and IFITM1). Additional terms identified among genes down-regulated by tofacitinib included those involved in the regulation of

Table 1. Patient characteristics and available samples at baseline*

Demographics	Baseline (n = 67)		*P* value
	Treatment responders, (n = 47)	Poor responders, (n = 20)	
Sex, female, n (%)	39 (83)	14 (70)	0.325
Age, mean ± SD, y	12.0 ± 4.0	13.0 ± 3.0	0.320
White, n (%)	40 (85)	18 (90)	0.714
Hispanic ethnicity, n (%)	11 (23)	4 (20)	>0.9999
JIA category, n (%)			
PJIA-RF+	11 (23)	2 (10)	0.325
PJIA-RF−	25 (53)	8 (40)	0.425
Extended oligo-JIA	4 (9)	3 (15)	0.418
JPsA	6 (13)	2 (10)	>0.9999
ERA	1 (2)	4 (20)	0.025

* ERA, enthesitis-related arthritis; JIA, juvenile idiopathic arthritis; JPsA, juvenile psoriatic arthritis; oligo-JIA, oligoarticular JIA; PJIA-RF+, polyarticular JIA rheumatoid factor–positive; PJIA-RF−, polyarticular JIA rheumatoid factor–negative.

lymphocyte chemotaxis, proliferation, and cellular responses to cytokines, as well as other immune-mediated pathways (Table 3). For GO terms identified among up-regulated genes after treatment, please refer to Supplementary Table 1.

On further analysis of the gene expression changes in response to tofacitinib within the TR group of patients, a significant portion of these genes represented a subset of the broader gene expression changes observed with the treatment in the entire group. Specifically, out of the total 6,679 genes that showed differential expression, 6,229 genes overlapped with the overall gene expression profile induced by tofacitinib within the TR group.

Differences in gene expression at baseline between PRs and TRs. When comparing transcriptional profiles at baseline between PRs (n = 20) and TRs (n = 47), we identified 663 differentially expressed genes (Figure 1B). For genes that were up-regulated at baseline in PRs, the most significantly overrepresented GO terms were (1) myeloid cell development, (2) activation of MAPK activity, (3) activation of GTPase activity, and (4) organelle transport along microtubule. Supplementary Table 2 provides a listing of the GO terms that were significantly overrepresented (FDR ≤0.02) among genes up-regulated in PR versus TR at baseline. For genes that were up-regulated, on comparing TR versus PR at baseline, the most significantly overrepresented GO terms included those related to positive regulation of viral genome regulation followed by those related to viral transcription (Supplementary Table 3). Of note, GOs related to the type I IFN signaling pathway (IFI6, IFI27, IFIT1, IFIT3, IFITM1, ISG15, and RSAD2), response to IFNγ (FCGR1A, GBP1, CCL3, CCL23, XCL1, XCL2, GBP5, and IFITM1), and the JAK/STAT signaling pathway (JAK1, JAK2, JAK3, Tyk2, STAT1, STAT3, STAT4, STAT5A/B, STAT6, suppressor of cytokine signaling 1 [SOCS1], SOCS3, protein inhibitor of activated STAT 1 [PIAS1], PIAS3, IL-6 receptor, IL-6 cytokine family signal transducer, IFNγ receptor 1 [IFNGR1], IFNGR2, tumor necrosis factor receptor superfamily 1A [TNFRSF1A], and TNFRSF1B) were not significantly up-regulated in TR when compared with PR at baseline.

Genes of the MAPK signaling pathway. Figure 3 depicts the expression of genes in the activation of MAPK activity ontology (GO: 0000187) that were significantly up-regulated at baseline in PRs (arrestin β 1 [ARRB1], IL-1 receptor–associated kinase [IRAK1], MAPKKK10, protein kinase N1 [PKN1], MAPKK1, MAPKK7, teratocarcinoma derived growth factor 1 [TDGF1], MAPK activated protein kinase 2 [MAPKAPK2], TAO kinase 2 [TAOK2], and MAPK 8 interacting protein 3 [MAPK8IP3]). All these genes were also up-regulated in PR as compared to TR at

Table 2. Core response variable between treatment responders and poor responders at baseline and week 18 of tofacitinib treatment*

Core response variables	Total n = 127	Treatment responders		Poor responders	
		Baseline, n = 47	Week 18, n = 38	Baseline, n = 20	Week 18, n = 8
Joints with active arthritis, n	7 ± 7	11 ± 6	0.6 ± 1	11 ± 7	3 ± 4
Joints with limited range of motion, n	4 ± 5	7 ± 6	0.5 ± 0.9	6 ± 7	4 ± 4
VAS of PGA[a]	4 ± 3	6 ± 2	0.8 ± 1	6 ± 2	3 ± 2
VAS of patient overall well-being[b]	3 ± 2	4 ± 2	1 ± 1	4 ± 2	4 ± 2
ESR, mm/hr	17 ± 17	22 ± 19	11 ± 9	19 ± 20	11 ± 9
CRP, mg/dL	0.6 ± 1.6	0.8 ± 1.5	0.3 ± 0.8	1.3 ± 2.7	0.8 ± 1.2

* Values are the mean ± SD unless otherwise indicated. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PGA, physician global assessment of juvenile idiopathic arthritis activity; VAS, visual analog scale.
[a] 0, inactive; 10, very active.
[b] 0, very well, 10, very poor.

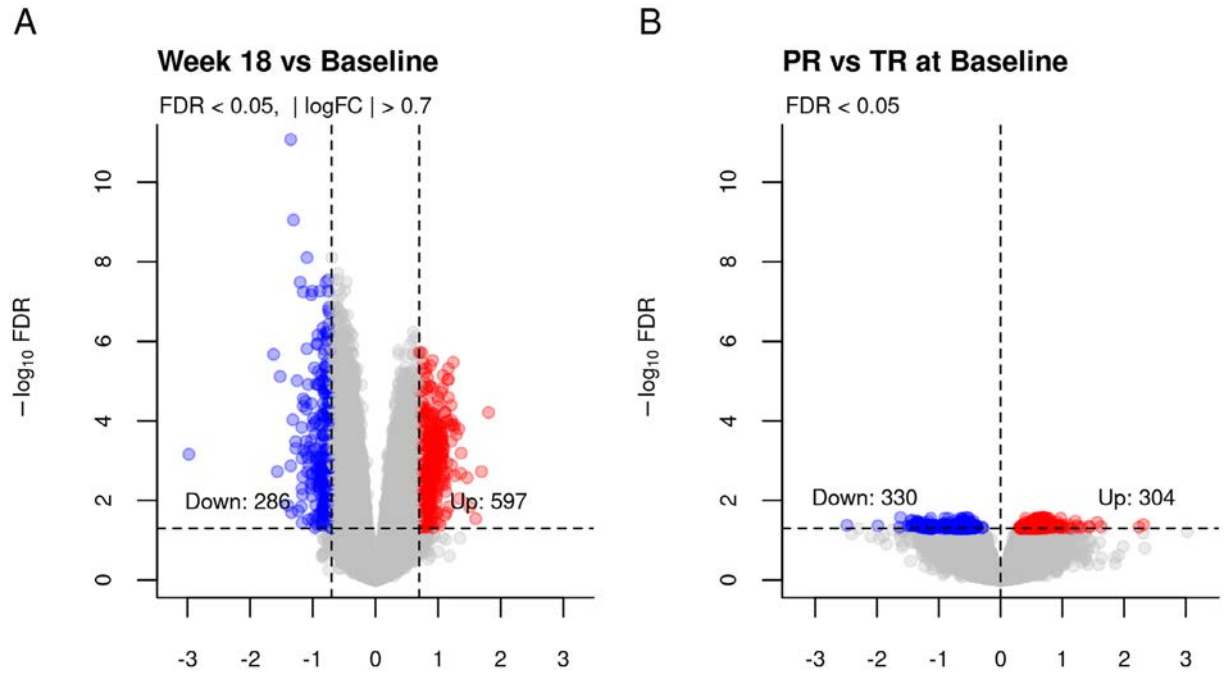

Figure 1. Volcano plots showing significantly up- and down-regulated genes after applying corresponding logFC and FDR thresholds for the two primary comparisons: (A) week 18 as compared with baseline samples and (B) PRs as compared with TRs at baseline. FDR, false discovery rate; PR, poor responder; TR, treatment responder.

week 18 (logFC > 0), but these differences did not reach statistical significance (comparisons indicated in Figure 3 as not significant). Supplementary Figure 3 provides a visualization of the significantly differentially expressed genes of the MAPK signaling pathway as defined in the KEGG database.

When investigating baseline patient characteristics, neither age, gender, nor JIA category were found to be predictive of treatment response. The ERA subgroup demonstrated a notably poor response to tofacitinib treatment. Nevertheless, further large-scale studies are necessary to explore this finding in greater detail.

DISCUSSION

Our analysis indicates that tofacitinib treatment in JIA leads to significant changes in the expression levels of hundreds of genes across various GOs. Our results also indicate that, despite overall significant improvement of JIA activity with tofacitinib, a subset of patients with JIA with elevated expression of genes that are part of the MAPK signaling pathway seem to benefit less from this treatment.

Tofacitinib, a first-generation JAKi, is expected to inhibit the production of various cytokines, chemokines, and growth factors regulated through the JAK/STAT signaling pathways.[18] In agreement with these expectations, we found that 18 weeks of tofacitinib treatment in patients with JIA led to significant down-regulation of genes in known JAK/STAT pathways, including those regulated by type I and type II IFNs. The IFN-driven Th1 polarization of T lymphocytes has long been considered a disease-promoting mechanism in JIA.[19] In oligoarticular JIA in particular, higher levels of IFN-γ–driven chemokines in synovial fluid predict progression to polyarticular disease.[20] Our findings are consistent with prior research suggesting that IFN-driven pathways are important in the pathogenesis of JIA[19,20] and demonstrate that tofacitinib effectively targets these pathways. However, further investigation is needed to determine whether tofacitinib can truly modify the disease course of JIA.

Notably, our finding that tofacitinib down-regulates IFN gene expression in JIA aligns with studies in adults with RA. In RA, tofacitinib treatment has been shown to reduce IFN-induced STAT1 phosphorylation in peripheral blood monocytes and T cells.[21] Moreover, a recent study found that JAKi reduced the gene expression of cytokines and their receptors, as well as intracellular signaling molecules such as STAT1, IFN regulatory factor 1 (IRF1), and IRF7 in patients with RA,[22] confirming the similarities of the response to JAK inhibition between RA and the nonsystemic forms of JIA included in our study.

Among the genes down-regulated with treatment, the most significantly enriched ontologies were epigenetic negative regulation of gene expression (GO: 0045814) and ribosomal DNA heterochromatin assembly (GO: 0000183). These ontologies were composed predominantly of down-regulated histone genes, which were also identified in several ontologies associated with

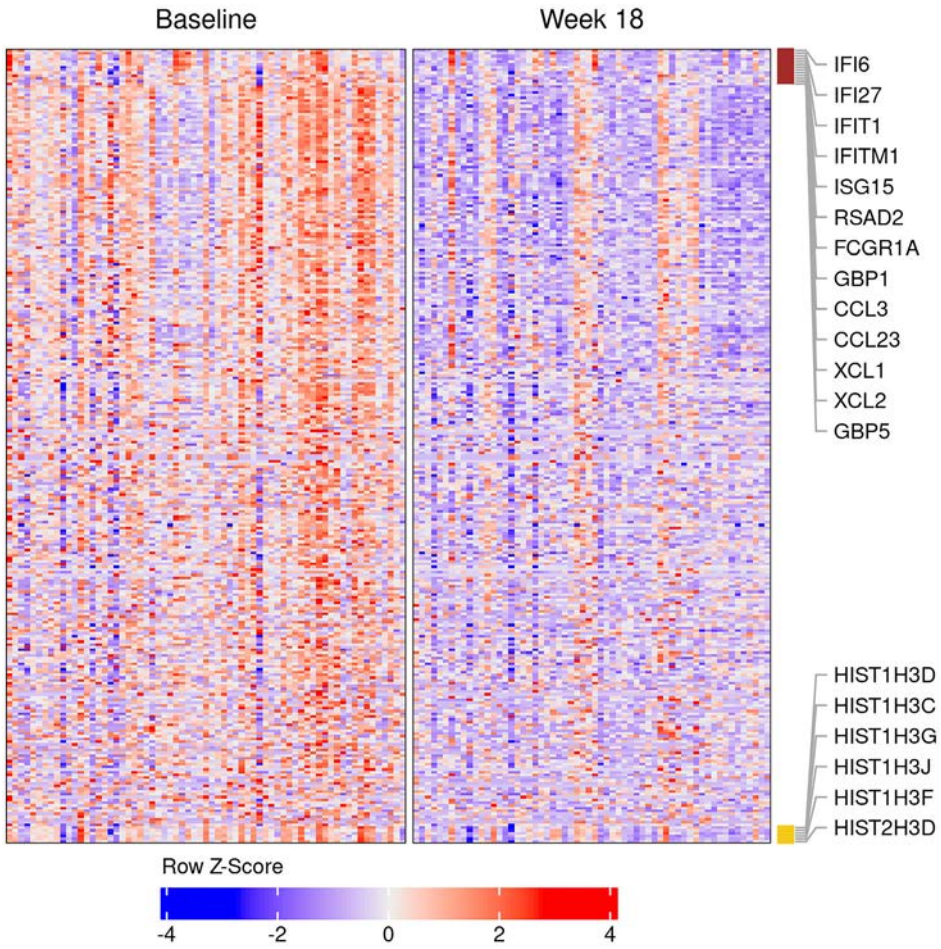

Figure 2. Heatmap showing *z* scores of genes that were down-regulated after 18 weeks of tofacitinib treatment in patients with juvenile idiopathic arthritis (false discovery rate <0.05 and logFC less than −0.7). Annotated genes are from ontologies related to type I and type II interferon activity (brown) as well as interleukin-7 signaling (yellow). FCGR1A, Fcγ receptor Ia; GBP, guanylate binding protein; HIST, histone; IFI, IFN-inducible protein; IFIT, IFN-induced protein with tetratricopeptide repeats; IFITM, IFN-induced transmembrane protein; IFN, interferon; ISG, interferon-stimulated gene; RSAD2, radical S-adenosyl methionine domain containing; XCL, X-C motif chemokine ligand.

IL-7 signaling.[23] IL-7 is known to signal through the JAK/STAT pathway,[24] making it a potential target of tofacitinib treatment. Again, our findings are consistent with prior research in RA, in which elevated levels of IL-7 in the synovial fluid distinguished RA from osteoarthritis,[25] and it has been suggested that IL-7 mediates joint destruction through fibroblast activation.[26]

The finding from our analysis with the greatest potential for clinical translation may be that a gene expression signature reflective of activation of MAPK signaling pathways was associated with an unfavorable response to tofacitinib in JIA. This observation aligns with similar findings in RA, which led to clinical trials that tested MAPK inhibitors for the treatment of RA.[27,28] Thus, the future availability of MAPK inhibitors may offer an appealing therapeutic option for patients with JIA with up-regulated MAPK signaling, particularly in those who have not responded to JAKi.

The MAPK pathway comprises a signaling cascade that plays a crucial role in regulating physiologic cell functions, such as proliferation, differentiation, survival, and apoptosis.[29] Components of the MAPK family, such as p38, ERK, and JNK, are believed to contribute to synovial cell activation in RA.[30] In previous research, we observed that treatment-naive children with oligoarticular JIA who later developed polyarticular joint involvement exhibited more prominent activation of ERK/MAPK signaling in their peripheral blood cells.[31] Because the MAPK signaling pathway is not directly affected by JAK/STAT signaling, the effect of tofacitinib on the MAPK pathway is expected to be limited. Thus, despite JAK/STAT signaling blockade, the MAPK pathway can remain activated, potentially explaining why patients with an activated MAPK pathway were less likely to respond to JAK inhibition. Consistent with this notion, our study found that genes from the MAPK signaling pathway (ARRB1, IRAK1, MAPKKK10, PKN1, MAPKK1, MAPKK7, TDGF1, MAPKAPK2, TAOK2, and MAPK8IP3) remained up-regulated in PRs at week 18, although the differences did not reach statistical significance, possibly because of a loss of statistical power.

Table 3. Gene ontologies overrepresented among down-regulated genes at week 18 as compared with baseline*

GO identifier	Term	N	Up-regulated, n	Down-regulated, n	*P* value	FDR
0045814	Negative regulation of gene expression, epigenetic	120	0	16	1.3×10^{-14}	$<1 \times 10^{-4}$
0000183	rDNA heterochromatin assembly	39	0	11	3.1×10^{-14}	$<1 \times 10^{-4}$
0032613	Interleukin-10 production	57	0	6	1.2×10^{-5}	$<1 \times 10^{-4}$
0032693	Negative regulation of interleukin-10 production	18	0	4	1.8×10^{-5}	$<1 \times 10^{-4}$
0060337	Type I interferon signaling pathway	93	0	7	2.1×10^{-5}	$<1 \times 10^{-4}$
1901623	Regulation of lymphocyte chemotaxis	26	0	4	8.1×10^{-5}	2×10^{-4}
0070936	Protein K48-linked ubiquitination	57	0	5	0.00016	3×10^{-4}
0045071	Negative regulation of viral genome replication	59	1	5	0.00019	4×10^{-4}
0034341	Response to interferon-γ	199	2	8	0.00045	8×10^{-4}
0006342	Chromatin silencing	72	0	5	0.00048	9×10^{-4}
0072676	Lymphocyte migration	114	1	6	0.00058	0.001
0050672	Negative regulation of lymphocyte proliferation	77	1	5	0.00065	0.001
0071347	Cellular response to interleukin-1	177	2	6	0.0054	0.007
0002440	Production of molecular mediator of immune response	209	1	6	0.012	0.01
0051153	Regulation of striated muscle cell differentiation	101	0	4	0.013	0.02
0002367	Cytokine production involved in immune response	104	0	4	0.014	0.02
0001909	Leukocyte-mediated cytotoxicity	107	0	4	0.016	0.02
0032526	Response to retinoic acid	108	0	4	0.016	0.02
0051100	Negative regulation of binding	166	1	5	0.017	0.02
0070374	Positive regulation of ERK1 and ERK2 cascade	202	1	5	0.036	0.04
0031396	Regulation of protein ubiquitination	206	1	5	0.039	0.04

* FDR, false discovery rate; GO, gene ontology; rDNA, ribosomal DNA.

On the other hand, although GOs in the IFN and JAK/STAT signaling pathway were down-regulated by week 18 of tofacitinib treatment, our study did not identify these pathways as up-regulated in the TR when compared with PR at baseline. Although such a finding could have added invaluable insights into predicting treatment response to tofacitinib, larger-scale studies may be able to identify such a correlation. Moreover, after 18 weeks of tofacitinib treatment, no specific subset of differentially expressed genes was found in the TR group compared with the whole cohort with 6,229 out of 6,679 genes overlapping with the overall cohort gene expression changes. This substantial overlap indicates that the therapeutic effects of tofacitinib in TR are largely driven by a core set of genes that are consistently modulated across the treated population, underscoring the drug's targeted and widespread impact on gene expression in these patients. The use of serum biomarkers in predicting treatment

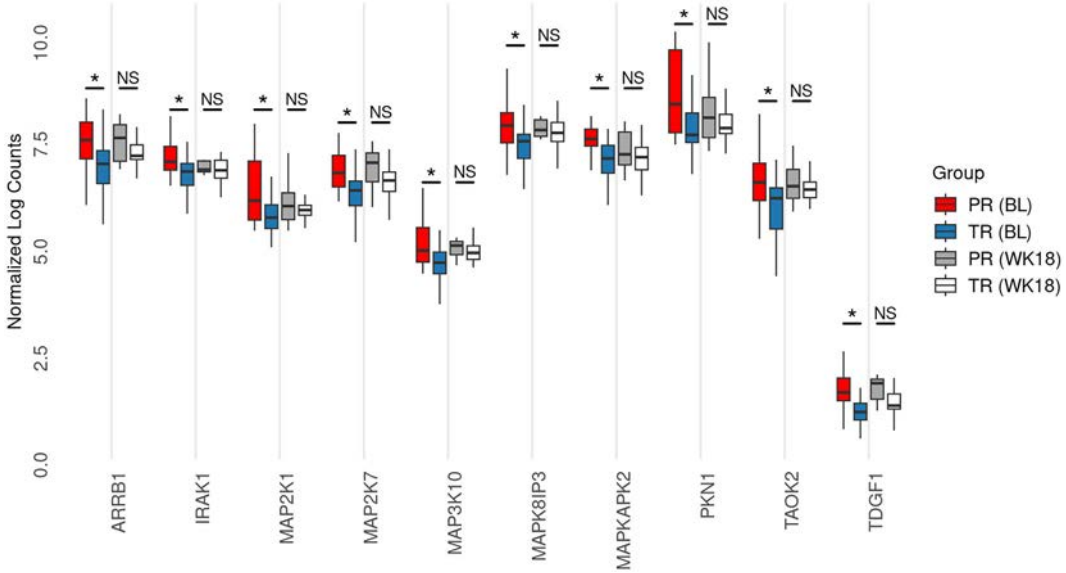

Figure 3. Comparison of MAPK gene expression between PRs and TRs at BL and WK18. *, false discovery rate <0.05. AARB1, arrestin β 1; BL, baseline; IL, interleukin; IRAK1, IL-1 receptor–associated kinase; NS, not significant; PKN1, protein kinase N1; PR, poor responder; TAOK2, TAO kinase 2; TDGF1, teratocarcinoma derived growth factor 1; TR, treatment responder; WK18, week 18.

response to conventional and biologic DMARDs in JIA has been limited thus far. This includes our own research of serum biomarkers that might predict or at least correlate closely with the response to tofacitinib treatment.[8] Our results support the notion that biomarkers that could assist with the personalization of JIA treatment should not rely only on downstream blood-based biomarkers but should also consider gene expression. This is consistent with other studies in JIA aimed at identifying biomarkers that anticipate response to methotrexate[32–34] and tumor necrosis factor inhibitors.[35,36] The main strength of this study was the unique opportunity to use a relatively large number of samples obtained from patients whose clinical phenotypes had been thoroughly characterized as a part of a phase III clinical trial. The main limitation, on the other hand, was that the available samples allowed only for measurements of gene expression rather than direct functional assessments of activation of the MAPK signaling pathway.

Moreover, because of the use of PAXgene tubes, peripheral blood mononuclear cells were not collected, and hence, detailed information on leukocyte counts, differentiation, or fluorescence-activated cell sorting (FACS) analysis of white blood cell populations were not feasible. As a result, the potential influence of varying blood cell compositions on gene expression could not be fully explored in our analysis. Future studies should consider incorporating leukocyte counts, differentiation, or cell-sorting techniques such as FACS to better characterize the cellular composition of blood samples and refine the interpretation of gene expression data.

The administration of tofacitinib to patients with JIA induces widespread alterations to blood transcriptional profiles. Notably, tofacitinib treatment resulted in the down-regulation of genes related to type I and type II IFNs, as well as IL-7 signaling pathways. Moreover, it was observed that the presence of MAPK activation before the initiation of tofacitinib correlated with an unfavorable response to this JAKi. This association could be explored as a potential biomarker for tailoring personalized treatment approaches for JIA.

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AUTHOR CONTRIBUTIONS

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

Study conception and design. Ruperto, Brunner, Grom, Thornton.
Acquisition of data. Dhakal.
Analysis and interpretation of data. Eloseily, Pickering, Grom.

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Improving Identification of At-Risk Behaviors in Adolescents With Rheumatic Disease

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Objective. Many adolescent patients view their rheumatologist as their primary physician, and therefore it is important to screen youth for sexual activity and substance use as recommended by the American Academy of Pediatrics. We implemented an electronic social history questionnaire (SHQ) and alert system to identify at-risk behaviors in adolescents with rheumatic disease.

Methods. The SHQ was administered to adolescents 14 years and older with a goal to survey patients' sexual activity and alcohol, tobacco, and drug use. The SHQ was given via tablet at each rheumatology outpatient visit. A positive response triggered a best practice advisory (BPA) alert when the chart was opened to remind the clinician to discuss these results privately.

Results. A total of 877 unique patients were surveyed. Ninety patients (12%) reported being sexually active, and sexually active patients were significantly older than those who were not (17.2 vs 15 years; $P < 0.001$). Seventy-two percent of patients were female, and the mean age was 15.8 years. Sexually active patients were more likely to be smokers, to drink alcohol, and to use other drugs ($P < 0.001$). Strong associations were observed between alcohol use and male sex ($P = 0.0227$), White race ($P = 0.0052$), and public insurance ($P = 0.0021$).

Conclusion. Overall, 12% of patients reported being sexually active, underscoring the need to screen adolescents for sexual activity given many rheumatology patients take teratogenic medication. A smaller proportion used substances. Implementing an electronic medical record–based SHQ can help identify patients most at risk, and the BPA serves as a useful tool to remind clinicians to discuss the SHQ privately.

INTRODUCTION

Adolescence is a unique and pivotal time in childhood development that involves transitioning from childhood to adulthood. During this time, adolescents and young adults (AYA) may become sexually active and experiment with licit and illicit substances.

The American Academy of Pediatrics (AAP) recommends pediatricians screen for sexual activity and substance use yearly, as well as perform risk screening for sexually transmitted infections (STIs).[1] Although pediatric rheumatologists acknowledge the importance of sexual and substance use discussions, most assume their patients' pediatricians are addressing these topics.[2] Many rheumatologic patients, however, view their subspecialists as their primary care providers, making the subspecialty clinic visit an important opportunity to effectively screen and counsel AYAs on sexual activity and licit and illicit substance use.[3,4]

Literature confirms AYA patients and their families desire to have reproductive health discussions with their rheumatologists.[5] Moreover, concurrent use of licit and illicit substances with certain teratogens in rheumatologic patients may result in additional health problems, such as cardiovascular and liver disease.[6] Although the American College of Rheumatology acknowledges a need for reproductive and sexual health education in patients with rheumatic disease, there are no clear guidelines for screening pediatric patients for sexual activity and licit and illicit substance use.[5,7] Research demonstrates that AYAs with chronic disease are as sexually active as their peers; however, data specific to AYA rheumatology patients are lacking.[8,9] Rheumatology AYA patients need to be screened for sexual activity and licit and illicit substance use to reduce their risk for harm.

Our goal is to use a survey as a tool to identify those who are participating in such behaviors. Phase 1 of this study includes implementing a social history questionnaire (SHQ) and alert

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SIGNIFICANCE & INNOVATIONS

- Adolescents and young adults with rheumatic disease are as sexually active as their peers.
- As pediatric rheumatologists, we should be screening our patients for risky behaviors, but we assume our patients' pediatricians are doing this.
- By implementing an electronic medical record (EMR)–based social history questionnaire (SHQ), we were able to identify that a significant number of our patients are sexually active and a smaller number use substances.
- Using an EMR alert system is a helpful tool for clinicians to identify which patients may need counseling or intervention based on SHQ responses.

system, and future phases may explore outcomes and possible solutions.

PATIENTS AND METHODS

Context. This study was conducted at a single-center specialty outpatient clinic in an urban city. The project team included a rheumatology fellow as team lead, a rheumatology physician, an adolescent medicine physician, a research coordinator, a medical assistant (MA), and electronic medical record (EMR) specialists. This study was approved by the institutional review board, and a quality improvement consent was obtained. This study was conducted from December 2020 to October 2022 and is ongoing.

Design and intervention development. The intervention included implementing an adolescent SHQ that was provided to rheumatology patients confidentially. The project team met and selected the questionnaire, which included questions regarding sexual activity and drug, alcohol, and tobacco use (Table 1). The SHQ was already built into our institution's EMR and was provided in English only. The initial concerns raised by the project team involved patient confidentiality. Texas law was reviewed with the project team, and per Texas Family Code 32.003-004, minors can legally give consent to diagnosis and treatment of STIs and counseling of substance use, and providers are legally required to maintain the confidentiality of care provided to a minor.[10]

At every visit during the rooming process, all patients 14 years and older being seen in the rheumatology clinic were given the survey. The adolescent was given a tablet with a privacy screen to allow for optimal confidentiality and was instructed to complete the questionnaire without adult assistance or supervision. The MA on the team was trained on providing the SHQ to patients, discussing confidentiality, and releasing the SHQ into the EMR. If the SHQ was not completed by the patient by the time the patient completed rooming, the MA would receive a best practice advisory (BPA) to remind them to provide the tablet to the patient. This same SHQ was given at every rheumatology visit. The results were automatically inputted in the EMR questionnaire section and were not viewable by guardians unless specifically requested.

After discussion with the AYA specialist, it was decided to start screening youth 14 years and older because that is the age youth can legally have sex in Texas, although the age of consent is 17 years old. In the state of Texas, the Romeo and Juliet Statute may protect minors from prosecution provided that both participants are within three years of age, over the age of 14, and willingly engage in sexual conduct.[11]

If the patient had completed the SHQ previously, the responses were carried over from the previous visit, and patients could change their responses if warranted. If the patient were to select "yes" to any of the mentioned behaviors, the clinical staff would be notified by a BPA upon opening the patient chart. Clinical staff included attendings, fellows, pediatric residents, medical students, and registered nurses. The BPA would then notify the clinician of the positive result and direct them to review the questionnaire. The BPA would fire only once per clinical encounter to prevent BPA fatigue. After the BPA was triggered, the clinician would need to acknowledge the alert and click to verify that they will take action. If there were no identified risky behaviors, the clinical staff would not be notified of completion of the questionnaire and would need to review the results unprompted.

Following a positive survey response, the clinician would then interview the youth privately during the clinic encounter as appropriate. If there were concerns for substance use disorder or mental health issues, an in-clinic social worker could meet with the patient.

Study of intervention. We evaluated the intervention with executed tests of change to improve staff awareness, the SHQ completion rate, and the BPA firing rate. The first issue we came across during this implementation was remembering to provide a patient with a survey and transferring the responses electronically into the EMR. The BPA alert was an important tool to remind the MA to give the patient a survey and upload responses.

In the following weeks during data review, we realized the positive response BPA was only firing for attending physicians and not for the trainees in the clinic. The project team met, and the EMR specialist was able to add subspecialty fellows, pediatric residents, and medical students to the BPA alerts for positive SHQ responses. Given the outpatient clinic was especially busy, a decision was made to add registered nurses to the BPA alerts to help prompt clinicians to review SHQ responses when positive. A review of positive SHQ responses and the BPA firing rate was done quarterly to ensure the project was working effectively.

Statistical measures. Measures were analyzed by a biostatistician. Responses to sexual activity and drug, alcohol, or tobacco use were compared to patient sex, body mass index, insurance status, race, and ethnicity. These data were extracted

Table 1. Social history questionnaire questions and responses*

	Responses
Smoking questions	
What is your smoking status?	Heavy smoker Current everyday smoker Light smoker Current some day smoker Former smoker Passive Never
If response is yes, select all types of tobacco	Cigarettes, pipe, cigars Optional: packs per day, years, start date, quit date
Do you use smokeless tobacco?	Current user Former user Never used Optional: quit date
Drug use questions	
Do you use drugs?	Yes Not currently Never Optional: use per week
What types of drugs? (Select all that apply)	IV Cocaine Marijuana Methamphetamines Amyl nitrate Barbiturates "Crack" cocaine Fentanyl Amphetamines Anabolic steroids Benzodiazepines Codeine Heroin Solvent inhalants Hydromorphone PCP Nitrous oxide Other
Alcohol use questions	
Do you use alcohol?	Yes Never Not currently
Alcohol use per week	Glasses of wine: 1, 2, 3, 4, other Cans of beer: 1, 2, 3, 4, other Shots of liquor: 1, 2, 3, 4, other Standard drinks or equivalent: 1, 2, 3, 4, other
Sexual activity questions	
Are you sexually active?	Yes Not currently Never
If yes, select type of partner	Female Male
If yes, select birth control/ protection. Select all that apply	Condom Pill Diaphragm IUD Surgical Spermicide Implant Rhythm method Injection Sponge Inserts Abstinence Coitus interruptus Cervical cap Ring Emergency contraception Other

(Continued)

Table 1. (*Cont'd*)

* IUD, intrauterine device; IV, intravenous; PCP, phencyclidine.

from the EMR, and the chi-square test, Fisher's exact test, and the Kruskal-Wallis test were used to evaluate differences in patients who did and did not have a positive response, as appropriate. Given the small number of positive responses, analysis stratified by covariates was unattainable. Considering some patients may have taken multiple SHQs and changed their answer, if they ever responded "yes" to a risky behavior, this was included in our analysis. Only one response per patient was recorded. Positive responses were consolidated over this study and are included in Table 2. Tablets were already in use, so no additional funds were needed to secure technology.

Table 2. Positive SHQ responses*

SHQ parameter	Positive responses, n	Percentage, %
Sexual activity	107	12.2
Type of contraception		
Abstinence	2	1.87
Condoms	56	52.3
Diaphragm	1	0.93
Emergency contraception	1	0.93
IUD	10	9.3
Implant	6	5.6
Injectable contraception	7	6.5
Patch	2	1.87
Pill	25	23.4
Spermicide	1	0.93
None	6	5.6
Drug use	28	3.19
Marijuana	20	71.4
Anabolic steroids	1	3.57
Tobacco use	8	0.91
Cigars	2	25
Pipe	1	12.5
Alcohol use	29	3.31
Average drinks per week	2.1	–

* All positive responses were consolidated over the course of the study and are depicted once per patient. Type of contraception, drug type, and average number of drinks per week were optional SHQ responses. IUD, intrauterine device; SHQ, social history questionnaire.

Privacy screens were purchased at a low cost to help with patient confidentiality.

RESULTS

Eight hundred seventy-seven unique patients were provided the SHQ and seen in the rheumatology clinic for a total of 2,673 individual surveys during the specified time period. During the first year (December 2020 to December 2021) there were 1,563 total visits, and all but 186 surveys were completed, making our screening rate 88% for the first year. During our second year (December 2021 to December 2022) the screening rate increased to 91%.

Patient demographics are depicted in Table 3. Most patients identified as being non-Hispanic White (73%). More than 75% of clinic patients were female. The mean age overall was 15.8 years, and the mean age for those who reported being sexually active was 16.9 years. Overall, 12% of surveyed patients reported being sexually active. Three percent of patients reported using illicit drugs, 3% reported using alcohol, and 1% responded yes to tobacco use (Table 2). Notably, patients who reported use of alcohol, tobacco, and/or drugs were more likely to be sexually active ($P < 0.0001$). Patients were given the option to select a type of alcohol, tobacco, and drug, and responses are delineated in Table 2. There was no association between sexual activity and insurance status, although there was an association found for White race ($P < 0.0001$). Two-group comparisons for alcohol use, smoking status, and drug use were conducted using the chi-square test or Fisher's exact test. Strong associations were observed between alcohol use and male sex ($P = 0.0227$), White race ($P = 0.0052$), and public insurance ($P = 0.0021$). Similarly, significant associations were found between smoking and White race ($P = 0.0002$), as well as private insurance ($P = 0.0121$), and between drug use and private insurance ($P = 0.0157$).

Table 3. Demographics of rheumatology patients surveyed in the clinic*

Parameter	Total no. of patients	Percentage of patients, %
Sex		
Male	572	24.11
Female	1,800	75.89
Body mass index		
Underweight (<5th percentile)	102	4.41
Healthy weight (5th–85th percentile)	1,313	56.77
Overweight (85th–95th percentile)	424	18.33
Obese (>95th percentile)	474	20.49
Race		
White	1,738	73.27
Black or African American	309	13.03
Asian or Asian American	125	5.27
American Indian or Alaskan Native	41	1.73
Other	159	6.70
Ethnicity		
Hispanic	796	33.56
Non-Hispanic	1,571	66.23
Did not respond	5	0.21
Insurance status		
Private commercial insurance	1,338	56.41
Government funded	876	36.93
None	158	6.66

* Demographics include all patients who completed the social history questionnaire in the clinic over the course of the study.

DISCUSSION

In this study, we implemented an SHQ into our outpatient rheumatology clinic and increased surveying risky behaviors from a baseline of 0% to 88% in the first year. Of the reasons for a survey not being completed, we found the biggest issue to be in the first few weeks, when the staff was learning a new task. Reminders by word of mouth from the team and BPA instructions were essential.

We found that a significant number of our patients are sexually active, and a smaller portion are using illicit substances that pose a potential health risk. This is an important finding given we were not assessing such behaviors regularly before this study. Further data and chart review are needed to quantify by diagnosis the number of patients who are sexually active and/or using teratogenic medications. These findings mimic the literature and raise concerns regarding the need for more discussions surrounding reproductive health, substance use, and chronic disease. Although our rate of sexually active AYAs is less than reported by the Centers for Disease Control and Prevention (12.2% vs 29%), a similar percentage of our patients reported condom use (52.3%). Twenty-five percent of our surveyed patients documented contraceptive use, which is lower than the national average of 33%, although many patients did not disclose any contraceptive use.

Our cohort demonstrated a lower rate of sexual activity (12% vs 21%) and alcohol use (3% vs 38%) compared with a study of adolescents with lupus diagnosed in Brazil.[12] Although our group was substantially larger than the Brazilian cohort, the discrepancy could also be contributed to the difference in culture and legal drinking and smoking age. However, we feel that underreporting was likely the case, especially in the beginning, when the survey was first rolled out.

Barriers to providing the survey included hesitant patients or caregivers, time constraints, and confidentiality. In the beginning, many patient caregivers were accustomed to completing preappointment surveys for the adolescent, and the same was true when introducing this SHQ. Therefore, in the beginning and likely without our knowledge, the patient's caregiver was completing

the survey in place of the patient. To deter caregivers from doing this, our MA was provided with a prompt to discuss the survey with families and instructed the patient to complete the survey independently. After a few initial cycles, we found this prompt worked for families, and most AYA patients became accustomed to completing the SHQ independently, with low rates of noncompletion.

Clinic disruption was also a barrier in the beginning of this implementation. The addition of another survey to complete before their visit caused slight delays to clinic flow. Once our team was familiar with the survey distribution and discussing with families, this time constraint became less burdensome. There were a few occasions when the patient did not complete the survey before the provider visited with them, and the BPA would not fire until after the clinic visit, potentially missing an opportunity to discuss risky behaviors.

Another limitation was the possibility of the patient not answering truthfully or copying forward their previous responses. An SHQ can be a successful screening measure, but it is imperative that the patient is aware of their confidentiality. Alone time with the adolescent without parental supervision is essential to effective AYA care and is supported by the AAP, among other groups.[1] Unfortunately, many youths may not disclose information about sexual activity or drug use in front of parents given fear of being judged or retaliated against by a guardian, leading to unreliable or withheld information.[13,14] During primary care visits to discuss preventive care with adolescents, physicians spent a mean of 22 minutes in the examination room, and only 31% of physicians discussed confidentiality.[15] The same study reported the majority of physician and AYA conversations lasted less than 36 seconds.[15] We attempted to avoid this issue of youth not responding truthfully by using a privacy screen on the tablet, which prevented caregivers from viewing the answers, and ensuring the patient was aware their responses would be kept confidential. Additionally, while the youth was completing the SHQ on the tablet, the caregiver would be filling out additional clinic surveys simultaneously.

Unfortunately, the language used in the SHQ may not have been appropriate for the age range and therefore could have led to underreporting. It is likely that AYAs do not know terms such as coitus interruptus, diaphragm, or the rhythm method. This could be considered a study limitation, and future efforts will be made to change the language. Furthermore, because SHQ responses were carried forward to future encounters, this allowed for responses to be overwritten and potentially introduced bias and an underestimation of risk.

Legal protections in certain states also confound the difficulties clinicians and AYA patients face regarding confidentiality and the right to make autonomous medical decisions.[16] Most physicians are comfortable addressing sexual health and substance use with their patients, but the majority felt they needed more training on confidentiality laws.[17] Current research further discloses this issue in a study revealing that young people find confidentiality extremely important and may forego care if it is not achieved.[14,18]

The study team raised concerns regarding who would be responsible for addressing positive responses to sexual activity or substance use. Our clinic has a designated social worker who was able to visit with the patient for concerns of sexual abuse or substance use if needed. They were also able to file legal reports if required. At the time of this study, we did not have a dedicated clinic psychologist, but there were psychology staff available if there were immediate needs such as suicidal or homicidal ideation. Although this study did not focus on counseling rates, our team decided that the provider should be counseling patients confidentially on sexual health, especially if they are on a prescribed teratogen. For patients desiring additional sexual and reproductive health counseling, and specifically contraception, we made referrals to our local AYA clinic.

Albeit this study was focused on pediatric rheumatology, we do feel its use would be beneficial to other subspecialties and pediatricians, especially for those that use teratogens. Therefore, the outcomes of this study are generalizable, and the study design can be repeated for use at other centers. Keys to success included consistent project leadership and involvement of an invested team, participant engagement and buy-in, and support from the institution.

Further directions for this study include evaluating documented counseling rates, collecting feedback from AYAs on the SHQ language, and testing for trends between disease activity measures and at-risk behaviors. This is especially important given that the data show a rate of documented contraception counseling to be only 46% in women on teratogens.[19] Other studies suggest that federal surveillance systems have the potential to improve contraceptive discussions and potentially relieve adverse effects of teratogens.[20]

In conclusion, adolescents with chronic disease are using licit and illicit drugs and are as sexually active as their peers. In-clinic screening using an EMR tool such as a BPA can help clinicians identify patients who are at high risk for substance use disorder or unplanned pregnancy.

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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 Ciaglia 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.

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BRIEF REPORT

Factors for Consideration by Pediatric Rheumatologists When Scoring the Physician Global Assessment of Disease Activity in Juvenile Idiopathic Arthritis: First Step Toward an Internal Consensus

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Objective. The physician global assessment of disease activity (PhGA) is a tool used nearly ubiquitously by pediatric rheumatologists for the assessment of patient disease activity status. However, this tool lacks standardization in its scoring. This survey aimed to identify score influencing factors, along with inclusion or exclusion of extra-articular manifestations and imaging, when scoring the PhGA in juvenile idiopathic arthritis (JIA).

Methods. Electronic surveys were sent to Paediatric Rheumatology International Trials Organisation and Pediatric Rheumatology Care and Outcomes Improvement Network members who completed a previous survey on scoring of the PhGA. Respondents were asked to rank their top seven factors for inclusion in the PhGA for nonsystemic JIA (nsJIA) and systemic JIA (sJIA), along with ranking extra-articular manifestations and imaging for inclusion. Frequency and percentage of rank and Likert responses were analyzed, and geographic regions as well as level of experience were compared using the chi-square test and Fisher's test.

Results. A total of 276 respondents from 54 countries and six continents participated. For nsJIA, factors selected by >50% included number of swollen joints, active uveitis, duration of morning stiffness, and number of tender joints. For sJIA, factors selected by >50% were presence and duration of fever, laboratory tests, number of swollen joints, serositis, rash, hepatomegaly, lung disease, and lymphadenopathy. Agreement on the inclusion of extra-articular factors, such as uveitis, macrophage activation syndrome, and sJIA-associated lung disease, had >70% moderate or strong agreement for inclusion, whereas psoriasis had only 50.5% agreement for inclusion and imaging had 64.7% agreement for inclusion. Variations in rank between different geographic regions or level of experience were minor.

Conclusion. This survey identifies factors that pediatric rheumatology providers find important for PhGA scoring of disease activity, documents varying agreement on inclusion of extra-articular manifestations of disease, and lays the framework for further consensus work.

INTRODUCTION

The physician global assessment of disease activity (PhGA) is a tool used nearly ubiquitously by pediatric rheumatologists for the assessment of patient disease activity status. It is integrated into numerous disease activity tools to aid in the evaluation of patients with inflammatory arthritides. In the juvenile idiopathic arthritis (JIA) population it has been used in the coreset of the

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[Correction added on 27 November 2024, after first online publication: The affiliations of Paula Vähäsalo and Beth S. Gottlieb have been corrected.]

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SIGNIFICANCE & INNOVATIONS

- The similarities in frequencies of ranks and the rank priorities for nonsystemic juvenile idiopathic arthritis (JIA) or systemic JIA (sJIA) demonstrated progress toward the standardization of scoring of the physician global assessment of disease activity (PhGA) tool.
- Pediatric rheumatology providers generally agreed on the inclusion of active uveitis, presence of macrophage activation syndrome, and sJIA-associated lung disease in PhGA scoring. Psoriasis inclusion and imaging presented mixed agreement for inclusion.
- Provider perspective on factor ranking for inclusion in PhGA scoring did not meaningfully differ by geographic region or level of experience.

American College of Rheumatology (ACR) JIA response criteria,[1] the ACR criteria for clinically inactive disease,[2] and the Juvenile Arthritis Disease Activity Scores.[3]

The PhGA has shown predictive value in models with other baseline variables, including failure to achieve remission, functional disability, and joint damage,[4] and is central in all trials with biologic disease modifying antirheumatic drugs and small molecules. Furthermore, PhGA scores at the onset of disease predicted disease trajectory five years from onset, among other parameters.[5]

However, there is a lack of detailed description of content of the PhGA score or guidance for use and scoring in clinical practice. This gap has led to heterogeneity in both inter- and intrarater scoring of JIA disease activity[6–8] and differences between PhGA scoring among JIA categories.[9] However, it remains a widely used and accepted tool among pediatric rheumatologists internationally, demonstrating the importance of standardization of the use and scoring of the tool.

The aim of this study was to conduct a survey to collect detailed data on the priority of different factors influencing the providers' assessment of PhGA in both nonsystemic JIA (nsJIA) and systemic JIA (sJIA) and which extra-articular manifestations, if any, should be included in the scoring of the assessment tool. Further, we evaluated whether the provider's geographic region or level of experience are associated with factors selection and compared our survey results to previous work on this topic.

MATERIALS AND METHODS

Members of the Paediatric Rheumatology International Trials Organisation (PRINTO) and Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) who completed the first survey on factors affecting the PhGA assessment by pediatric rheumatologists described by Backström et al[8] were recontacted by electronic communication and asked to complete a second survey. A reminder email was sent at two and four weeks to improve response rates.

The second survey was revised and approved by members of the PRINTO–PR-COIN PhGA standardization task force. The survey asked respondents to rank their top seven factors for inclusion in a standardized provider global assessment of disease activity tool from a total of 17 factors for nsJIA and 18 factors for sJIA. Number one referred to the highest rank, and number seven referred to the lowest rank. Separate ranks were included for nsJIA and sJIA because these categories present with disparate clinical pictures. Given the elevated level of importance of extra-articular factors in the first survey, these items were directly considered outside the ranking system, and respondents were asked to consider five factors that may affect the PhGA assessment, including uveitis activity, psoriasis activity, imaging, consideration of macrophage activation syndrome (MAS), and presence of lung disease in sJIA, using a Likert scale of agreement. The full survey is available in the supplemental materials.

Ethics and statistical analysis. The Seattle Children's Institutional Review Board (IRB) determined that this study was exempt from IRB review, in accordance with applicable regulations and Seattle Children's Hospital institutional policy (no. STUDY00004379). Ranking responses were evaluated by frequencies and percentages of respondents ranking the factor within their top seven, median ranks of each factor, and frequencies and percentages of respondents who ranked each factor in any of the top three positions. Mean factor relevance, as calculated in survey[8] 1, was also presented for comparison of factor importance (Table 1). Of note, survey 1 data were based on participants using a graphic cursor to rate from 0 to 100 the relevance of 17 factors potentially affecting the PhGA scoring.[8] Likert scale responses were evaluated for frequencies and percentages at each level of agreement for extra-articular manifestations and imaging. Differences among geographic regions and level of experience when available were compared with Pearson's chi-square test or Fisher's test, when appropriate. For multiple

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Table 1. Rank and frequency of item selection for standardized inclusion in physician global assessment of disease activity*

	n (%)	Median rank	Item ranked 1–3, n (%)	Factor type	Mean factor relevance
Nonsystemic juvenile idiopathic arthritis (n = 276)					
Number of swollen joints	252 (91)	1	201 (73)	Clinical	86.8
Presence of active uveitis	206 (75)	4	92 (33)	Clinical	67.5
Duration of morning stiffness	188 (68)	4	67 (24)	PRO	64.0
Number of tender joints	152 (55)	3	93 (34)	Clinical	74.5
Results of laboratory tests	136 (49)	4	43 (16)	Laboratory/imaging	59.5
Type of affected joints	118 (43)	4	53 (19)	Clinical	46.1
Presence and severity of dactylitis	110 (40)	4.5	34 (12)	Clinical	63.9
Degree of inflammation in the active joints as assessed by ultrasound	111 (40)	5	35 (13)	Laboratory/imaging	60.0
Number of joints with limited range of motion	95 (34)	3	49 (18)	Clinical	63.6
The level of patient's well-being as reported by the patient or the parent or caregiver	98 (36)	5	29 (11)	PRO	46.9
The level of patient's pain as reported by the patient or the parent or caregiver	97 (35)	5	27 (10)	PRO	48.8
The result of functional ability questionnaire	80 (29)	5	22 (8)	PRO	53.2
Presence of psoriatic skin manifestations	68 (25)	6	17 (6)	Clinical	48.7
Degree of inflammation in the active joints as assessed by MRI	56 (20)	4.5	15 (5)	Laboratory/imaging	60.8
Presence of erosions on imaging tests	38 (14)	5	13 (5)	Laboratory/imaging	52.8
Presence of fever	25 (9)	4	12 (4)	Clinical	46.5
Presence and severity of fatigue	28 (10)	5	8 (3)	PRO	N/A
Systemic onset juvenile idiopathic arthritis (n = 276)					
Presence and duration of fever	255 (92)	1	207 (75)	Clinical	89.2
Results of laboratory tests (including signs of macrophage activation syndrome)	238 (86)	3	151 (55)	Laboratory/imaging	82.6
Presence and severity of serositis	207 (75)	4	68 (25)	Laboratory/imaging	81.0
Number of swollen joints	196 (71)	3.5	98 (35)	Clinical	79.7
Presence and severity of evanescent erythematous rash	198 (72)	4	81 (59)	Clinical	70.1
Presence and severity of hepatomegaly and/or splenomegaly	160 (58)	5	30 (11)	Clinical	71.4
Presence and severity of lung disease	141 (51)	4	57 (21)	Laboratory/imaging	N/A
Presence and severity of lymphadenopathy	102 (37)	5	22 (8)	Clinical	64.3
The level of patient's well-being as reported by the patient or the parent	88 (32)	6	20 (7)	PRO	53.0
Number of tender joints	69 (25)	5	25 (9)	Clinical	70.3
Duration of morning stiffness	46 (17)	6	10 (4)	PRO	59.6
Type of affected joints	38 (14)	5	8 (3)	Clinical	43.8
Presence and severity of fatigue	37 (13)	5	10 (4)	PRO	N/A
The level of patient's pain as reported by the patient or the parent	32 (12)	6	6 (2)	PRO	51.9
The result of functional ability questionnaire	27 (10)	5	7 (3)	PRO	52.6
Number of restricted joints	18 (7)	5	4 (1)	Clinical	59.3
Degree of inflammation in the active joints as assessed by MRI	15 (5)	6	2 (1)	Laboratory/imaging	57.5
Presence of erosions on imaging	10 (4)	4	2 (1)	Laboratory/imaging	48.2

* Factor type: clinical evaluation, laboratory, or imaging value. Type of affected joint: for example, due to their function, some joints, when affected, should weigh more than others. Rank number 1 refers to participants' most important factor when scoring the physician global assessment. The mean factor relevance was calculated from survey 1 data based on participants rating from 0 to 100 with a graphic cursor the relevance of 17 factors potentially affecting the physician global assessment of disease activity scoring. MRI, magnetic resonance imaging; N/A, not applicable; PRO, patient-reported outcome.

comparisons, Bonferroni corrections were conducted. Statistical analyses were performed with Microsoft Excel version 16.54 or IBM SPSS version 28.0.0.0 (190) (IBM).

RESULTS

Of the 491 respondents who completed the first survey, 276 (56%) completed the second survey. Respondents spanned 54 countries from six continents (Africa and Middle East, 20 [7.2%]; Asia and Australia, 16 [5.8%]; Europe, 155 [56.2%]; North America, 47 [17.0%]; and South America 27 [9.8%]), with 11 (4.0%) respondents for whom the region of origin was unknown. For 194 respondents, the duration of experience in pediatric rheumatology was known. Of these, 62 (32.0%) had less than 10 years of experience and 132 (68.0%) had more than 10 years of experience.

Frequency of factor selection for both nsJIA and sJIA and the median rank are included in Table 1. Factors selected by more

Table 2. Level of agreement on inclusion of extra-articular manifestation and imaging in physician global assessment scoring*

Level of agreement	Uveitis activity, n (%) (n = 274)	Psoriasis activity, n (%) (n = 275)	MAS, current episode, n (%) (n = 276)	sJIA-associated lung disease, n (%) (n = 276)	Available imaging, n (%) (n = 275)
Strongly or moderately agree	202 (73.7)	139 (50.5)	223 (80.8)	194 (70.3)	178 (64.7)
Neutral	11 (4.0)	53 (19.2)	4 (1.4)	38 (13.7)	32 (11.6)
Strongly or moderately disagree	61 (22.2)	83 (30.1)	49 (17.8)	44 (15.9)	65 (23.6)

* Two respondents did not respond to uveitis activity, and one respondent did not respond to both imaging availability and psoriasis activity. MAS, macrophage activation syndrome; sJIA, systemic onset juvenile idiopathic arthritis.

than 50% of respondents for nsJIA in order of frequency include number of swollen joints, presence of active uveitis, duration of morning stiffness, and number of tender joints. These factors were also placed in the top three ranks at the highest frequencies for nsJIA. For sJIA, a wider pool of factors collected more than 50% of rankings, including presence and duration of fever; results of laboratory tests; number of swollen joints; and presence and severity of serositis, rash, hepatomegaly, lung disease, and lymphadenopathy.

The level of agreement for inclusion in the PhGA score of potential extra-articular manifestations is reported in Table 2. Uveitis, MAS, or sJIA-associated lung disease all reached 70% moderate or strong agreement (73.7% [202 of 274], 80.8% [223 of 276], and 70.3% [194 of 276], respectively). Responses were mixed for inclusion of psoriasis activity, with 50.5% (139 of 275) of respondents moderately or strongly agreeing. The inclusion of available imaging reached 64.7% (178 of 275) moderate or strong agreement.

There were minor differences in factor rankings between geographic regions. For sJIA, respondents from North America tended to prioritize swollen joint count more often than respondents from other regions, whereas hepatosplenomegaly was ranked more often in Europe than in Asia and Australia or North America. The results from functional ability questionnaires were ranked more often in Asia and Australia than in Europe (Supplemental Tables 1 and 2).

Factor importance ranking was somewhat similar for respondents with different levels of experience. In nsJIA, those with more experience ranked duration of morning stiffness higher than those with less experience (Supplemental Tables 3 and 4). Furthermore, providers with less than 5 years of experience put less importance on swollen joint count in nsJIA and result of laboratory markers in sJIA when compared with those with more than 10 years of experience (data not shown).

DISCUSSION

In this survey, conducted among pediatric rheumatology providers, the number of swollen joints, presence of active uveitis, duration of morning stiffness, and number of tender joints were ranked most frequently for inclusion in the PhGA score for patients with nsJIA. For PhGA scoring of patients with sJIA, ranking was more heterogeneous, with presence and duration of fever, results of laboratory tests, and presence and severity of serositis being most prominently ranked. Survey respondents were geographically diverse, which is representative of the international pediatric rheumatology community, with similar representation to the previous survey, reflecting the collaborative importance of this work.

Consideration for inclusion of extra-articular manifestations, such as uveitis and psoriasis in the PhGA score, presents an ongoing discussion. These factors require the rheumatologist to rely on other subspecialty providers, such as an ophthalmologist and dermatologist, for disease activity evaluation. Further, at point-of-care, they may require interpretation of manifestation specific activity scores, such as the Standardization of Uveitis Nomenclature (SUN) criteria for uveitis[10] activity and the Psoriasis Area and Severity Index score (PASI)[11] for psoriasis activity. Inclusion of such factors into a point-of-care global assessment by the treating provider, which the PhGA is intended to be, brings to point the reliance on availability of external information from such providers. Similarly, inclusion of available imaging presents the question of timeliness and relevance of recent imaging to the patient's current disease activity level along with reliance on outside sources for data.

Notably, respondents of this survey ranked presence of active uveitis highly within the inclusion factors, and the majority reported moderate to strong agreement on its inclusion as an extra-articular manifestation of nsJIA disease activity. This is consistent with findings noted on the first survey by Backström et al,[8] in which uveitis demonstrated a normalized score of >75% for factors affecting PhGA scoring in nsJIA. However, considerations for psoriasis inclusion were more mixed in our survey and did not approach the consensus threshold, at 50.5% demonstrating moderate to strong agreement, with 19.2% remaining neutral. This finding may indicate similarities to the findings reported by Alongi et al,[12] in which psoriasis was not reported to be a significant driver of nonzero global assessment scores in their population analysis. Imaging inclusion leaned toward inclusion at 64.7% moderate or strong agreement and additionally may require specific guidance for use in the PhGA score.

Uveitis and psoriasis activity both likely represent extra-articular factors associated with nsJIA, and within this survey appear to demonstrate a division among providers for inclusion in PhGA scoring. These findings suggest that these topics will require further evaluation, and discussion to achieve group consensus for inclusion or exclusion, the method of evaluation for

such manifestations and guidance for providers on use, if included in the PhGA.

Regarding sJIA-specific extra-articular factors, there was overall moderate to strong agreement for inclusion of both a current MAS episode (80.8%) and sJIA-associated lung disease (70.3%) in our survey, demonstrating more homogeneous agreement for such factors. MAS activity is likely analogous to the "results of the laboratory findings" presented by Backström et al,[8] which neared a 100% normalized score with a narrow interquartile range and coincides with this survey's high ranking of results of laboratory testing (including signs of MAS) as the second highest ranked item for sJIA. sJIA-associated lung disease was not directly addressed in the first survey, and thus our findings offer further insight into the importance of lung manifestations of disease to providers. However, inclusion of associated lung disease, again, presents reliance on outside providers for assessment of disease status and will require guidance on definition of activity versus damage in affected patients.

An additional notable finding in this survey is that factors that include patient-reported outcomes, such as well-being scores, and reports of fatigue, pain, and functional ability ranked lower overall for both nsJIA and sJIA and tended to cluster in ranking when considered for inclusion in the PhGA. However, it's undeniable that patient-reported outcomes represent the patient experience of disease and are an imperative part of the overall patient assessment. Interestingly, for the patient cases reported in the study by Backström et al,[8] the patients with the highest values for patient-reported outcomes were among the top three median scores of PhGA. We interpret the results of this survey to indicate that providers are in agreement with assessment of such outcomes outside of the PhGA tool and note that these factors may be best evaluated in individual measurement tools aimed at the patient experience of disease activity and within composite scoring systems. We recommend this as an avenue for future research endeavors, such as those being undertaken within the Outcome Measures in Rheumatology JIA working group[13] and within the Childhood Arthritis and Rheumatology Research Alliance outcomes workgroup project focusing on burden of illness assessments.[14]

Finally, an important finding of this survey is the overall homogeneous ranking of factor importance between regions without significant differences for patients with nsJIA. For this population, the number of swollen joints approached significance for sJIA and near significance for nsJIA, which we attribute to the high importance of swollen joint count present in the North American respondents.

For patients with sJIA, there was more heterogeneity between regions. We feel this demonstrates the weight of different measures and availability of accurate evaluation for specific factors. Furthermore, access to treatment regimens may affect how respondents value the severity of each factor in their ranking. However, these findings may also indicate the need for more consensus building on sJIA factors in the future between regions.

The group showed homogeneity in terms of importance of the factors based on their expertise. For the most experienced providers, swollen joint count and duration of morning stiffness in nsJIA, and laboratory test results in sJIA were more important than for those with less experience.

We acknowledge potential limitations in this study, first being the relatively low response rate to the survey instead of the classic 80% suggested for Delphi process.[15] Further, because of IRB limitations, level of experience information for the North American respondents was not available (13% of the respondent population). We note that resource availability may not be equal globally and that inclusion of particular study recommendations, such as imaging or laboratory testing, in a proposed PhGA scoring mechanism may instill bias toward higher resource centers. Lastly, participants were aware that a standardization process was underway for the PhGA scoring, and repeat respondents may be biased by the Hawthorne effect influencing their responses.

Taken as a whole, these observations demonstrate that although the pediatric rheumatology community is a diverse global entity with variation in experience, training, access to technologies, and varying patient populations, providers across regions generally take similar factors into account when scoring the PhGA. This indicates a solid foundation for forward movement of this standardization process.

The aim of this survey was to further understand factors most important to rheumatology providers when scoring the PhGA in JIA, with the ultimate goal of consensus for inclusion of pertinent factors in this assessment tool. Although ongoing detailed consensus building is still required, this survey has allowed for a narrowing of the field of factors and an improved understanding of the importance of extra-articular manifestations and imaging in the point-of-care physician assessment of global disease activity. This work will continue through the PRINTO–PR-COIN collaborative PhGA task force, which aims to create recommendations for the PhGA tool to improve provider assessments of patient global disease activity and allows for standardized education of the tool's use for pediatric rheumatology providers.

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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 Balay-Dustrude 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.

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American College of Rheumatology
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REVIEW ARTICLE

Determinants of Self-Management Behavior in Gout: A Scoping Review

Jeffrey van der Ven,[1] Bart J. F. van den Bemt,[1] Marcel Flendrie,[2] Johanna E. Vriezekolk,[2] and Lise M. Verhoef[2]

Objective. This study aimed to identify modifiable determinants of self-management behavior in patients with gout.

Methods. Four databases (Medline, Embase, PsycINFO, and CINAHL) were searched using terms related to gout, self-management, and determinants of behavior as described in the Theoretical Domains Framework (TDF). Two reviewers independently selected relevant studies via screening of title/abstract and full text. Thematic synthesis was performed for qualitative data; quantitative data were summarized using cross-tabulation displaying the investigated associations of determinants with self-management behavior. The TDF facilitated identification and grouping of determinants.

Results. From 2,087 unique articles found, 56 studies were included in this review, of which there were 27 qualitative and 29 quantitative studies. Eight themes were identified: knowledge and skills for self-management, acceptance of disease, beliefs about necessity of self-management to improve gout-related health, resistance and reluctance for medication adherence and dietary alteration/changes, negative emotions influencing self-management, social support and interactions, environmental context, and self-regulation of behavior. Quantitative determinants associated with self-management behavior, predominantly medication adherence, were mapped to 12 of the 14 domains of the TDF. No determinants regarding skills and goals have been identified in quantitative research.

Conclusion. Intervention targets for self-management behavior in patients with gout mainly included determinants related to knowledge, implicit and explicit beliefs and attitudes, the environmental context and resources, and (social) support and reinforcement.

INTRODUCTION

Gout is a chronic disease caused by deposition of monosodium urate crystals in joints and soft tissue, which can occur in a state of hyperuricemia. These crystals trigger an immune response that results in painful arthritis. Despite available and effective management options, gout treatment is often suboptimal, with cited ranges of approximately 20% to 36 % of all patients with gout treated in primary care being under the target serum uric acid (sUA) levels of ≤36 mmol/L, therefore causing patients to continue experiencing flares.[1–3] This poor result has various causes, such as insufficient knowledge about the disease and its management among patients and health professionals and nonadherence to (non)pharmacological interventions.[4–6] Inadequate treatment and subsequent flares decrease quality of life and functioning, increasing burden on patients, the health care system, and society through higher health care resource use and work productivity losses.[7–9]

Given the suboptimal treatment and expected rise of patients with gout without a proportionate rise in health care resources and personnel, stimulating self-management is a promising solution to improve care.[8,10–14] Self-management concerns an individual's ability to manage symptoms, treatment, physical and psychological consequences, and lifestyle changes inherent to living with a chronic illness.[14] Self-management in patients with gout is important because it enables individuals to effectively treat flares and adhere to long-term medication and lifestyle adjustments. However, several studies indicate suboptimal self-management behavior, such as a lack of lifestyle changes and treatment adherence.[4–6,15–17]

Previous research has investigated nurse-guided self-management programs in patients with gout, demonstrating increased adherence to long-term medication and improved

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SIGNIFICANCE & INNOVATIONS

- Modifiable determinants were identified for almost all domains of the Theoretical Domains Framework, which can act as targets for interventions.
- Most studies on determinants of self-management behavior in patients with gout assess medication adherence as self-management outcome.
- Results on determinants of self-management behavior concerning lifestyle and care-seeking behavior are scarce.

clinical outcomes.[2,18,19] However, being labor intensive, these types of interventions will not be feasible in the future due to staff shortages.[11,20] eHealth-based interventions delivered through applications (apps) or websites may provide an efficient solution to promote self-management, for example by providing education and support in an automated manner. These interventions, efficient in terms of labor, look promising in stimulating self-management to a certain extent, but effects on clinical outcomes, if any, remain small.[21–23] Studies, also efficient in terms of labor, have shown improved adherence behavior and clinical outcomes when patients self-monitor sUA levels and use interactive voice-response systems.[24,25] However, evidence on large and persistence of adherence behavior effects induced by (digital) interventions, taking into account labor efficiency, remains scarce.

According to the Capability, Opportunity, Motivation, and Behavior (COM-B) model, behavior will only be performed when patients have the capability, opportunity, and motivation to do so. The aforementioned interventions may enhance knowledge and opportunities but might not foster the necessary skills and motivation for desired behavior. It's crucial to target interventions at the right determinants to ensure patients have all influencing factors, increasing the likelihood of behavioral change and improved treatment outcomes. Finding out what factors affect self-management is an important first step, and many studies have looked into this.[4,5,16] However, no studies to date have created a comprehensive overview of determinants associated with gout self-management behavior, which can consequently be used to inform evidence-based interventions. Therefore, this scoping review aimed to identify and describe determinants associated with self-management behavior in patients with gout.

MATERIALS AND METHODS

The protocol of this review was registered in Open Science Framework at the January 25, 2023 (doi:10.17605/OSF.IO/4PQFX). This study used the five-step scoping review methodology described by Levac et al.[26] The Preferred Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews guideline was used to ensure quality and transparency of reporting (Supplementary S1).[27] Due to the nature of this work being a scoping review, ethical approval from an institutional review board or ethics committee was not required.

Step 1: identify the research question. The research question was defined by the research team as, "What are determinants associated with self-management behavior in gout?"

Step 2: identifying relevant studies. A literature search was performed in four databases: Medline (PubMed), Embase (Ovid), PsycINFO (Ovid), and CINAHL. The searches were performed on November 16, 2022. The Sample, Phenomenon of Interest, Design, Evaluation and Research type (SPIDER) tool was used to specify the inclusion criteria for literature and guide the search strategy development (Table 1).[28] The search strategy included the use of mapped subject headings and key terms, using wildcards/truncations when applicable (ie, various spellings and verb forms). The search strategies combined terms related to (1) gout, (2) self-management behavior, and (3) determinants of behavior based on the Theoretical Domains Framework (TDF; Supplementary Material 2).[14,29] The TDF, a more detailed version of the COM-B model, was used to identify and categorize modifiable determinants that can be targeted using behavior change interventions.[30] We operationalized self-management behavior for gout by translating the definition by Barlow et al[14] to the context of gout (care) as following: (1) adherence to medication (urate-lowering therapy [ULT] and medication to treat

Table 1. Study inclusion and exclusion criteria based on the SPIDER tool*

Criterium	Justification
Sample	Adult patients with a diagnosis of gout Not studies related to cells/animals/models or healthy individuals, health care providers, etc
Phenomenon of interest	Determinants based on the TDF domains and constructs (Supplementary Material 2)
Design	Cross-sectional, longitudinal, observational and intervention studies, questionnaires, RCT Interviews, focus group (discussion or nominal group technique) Not case reports, literature reviews, editorials, commentaries
Evaluation	The association of determinants with self-management behavior defined as: • adherence to receiving medication (ULT and medication to treat acute gout flares) • adherence to diet recommendations (eg, alcohol restriction, purine low diet, and staying hydrated) • adherence to recommendations for physical activity, exercise, and losing weight (training programs) • care-seeking behavior • self-monitoring of disease status
Research type	Quantitative, qualitative, and mixed methods; peer-reviewed original research articles; conference abstracts 2020 to 2022; published in English

* RCT, randomized controlled trial; SPIDER, Sample, Phenomenon of Interest, Design, Evaluation and Research type; TDF, Theoretical Domains Framework; ULT, urate-lowering therapy.

acute gout flares); (2) adherence to diet recommendations (eg, alcohol restriction, purine low diet, and staying hydrated); (3) adherence to recommendations for physical activity, exercise, and losing weight (training programs); (4) care-seeking behavior; and (5) self-monitoring of disease status. Search terms for each database are shown in Supplementary Material 3.

Step 3: selecting studies. First, duplicate articles were removed. Studies were screened by title and abstract for relevance independently by two authors (JvdV and LMV), and disagreements were discussed until consensus was reached over inclusion or exclusion. This approach was repeated after full-text screening. From the included articles, references were screened for potential relevance, as well as the articles that cited the included articles (snowballing).

Step 4: charting the data. Relevant data, using a predefined extraction format developed by the research team, were retrieved from the included articles by JvdV and verified by LMV through comparison with full-text articles.

Step 5: collating, summarizing, and reporting the results. To analyze and report the findings from included qualitative studies, a thematic synthesis was performed using Atlas.ti (version 23).[31] One author (JvdV) performed the steps of analysis, which were discussed with two other authors (BJFvdB and LMV). Statistical associations reported between determinants, and different types of self-management behavior were mapped in a cross-table and categorized according to the 14 TDF constructs and the domains of the COM-B model, which represents a simplified version of the TDF.[30] Associations that were only reported descriptively were narratively reported.

RESULTS

The search strategy yielded 2,087 unique articles, of which 62 articles were included for full-text screening. In total, 56 studies (52 full-text articles and 4 conference abstracts) were included in our scoping review (Figure 1).

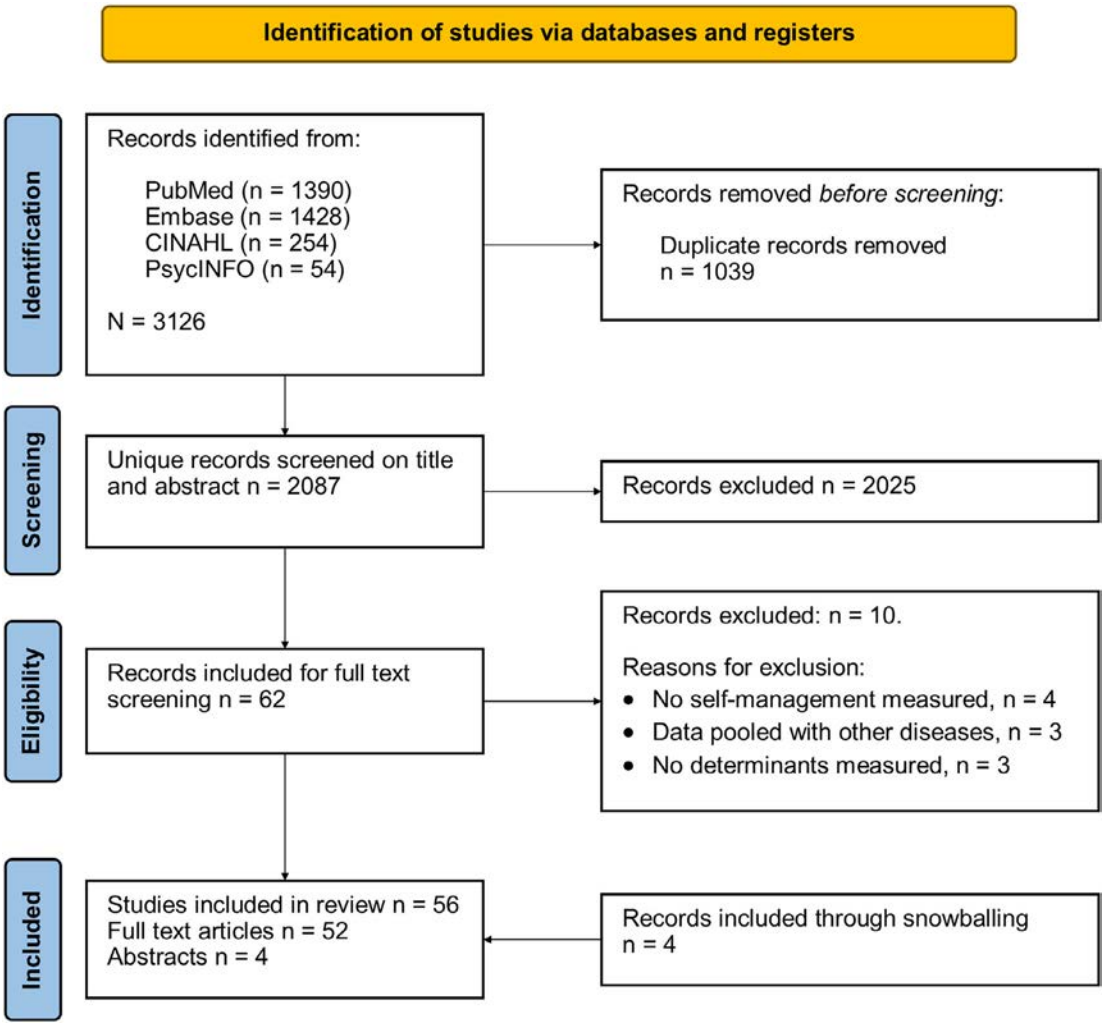

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram of the scoping review.

Overview. The characteristics (first author, year of publication, country, setting, study aims, sample size, and study design/methods) of all included studies are reported in Supplementary Material 4. The studies were published between 2008 and 2023 in 16 different countries and spread over all continents except South America and Africa. Studies were performed in many settings but mostly in secondary care (n = 28; 50%). Of 29 quantitative studies, 20 were observational studies (18 cross-sectional and 2 longitudinal), 8 were interventional studies, and 1 involved a secondary data analysis from the GOSPEL cohort.[32] The median sample size for quantitative studies was 298 (interquartile range [IQR] 77–1,352). A total of 27 qualitative studies (interviews and focus groups) were included, with a median sample size of 24 (IQR 17–43).

Thematic synthesis of qualitative studies. The thematic analysis yielded eight themes describing determinants related to self-management behavior, but mainly adherence to medication and dietary recommendations, and are described below. Supporting quotes can be found in Table 2.

Knowledge and skills for self-management. Patients adhered to gout-specific medication when they gained knowledge about the causes of gout, the consequences of having gout, the goals of ULT treatment, and knowing that flares can occur more frequently during the up-titration of ULT.[33–37] Likewise, not knowing or receiving a warning for this initial increase in flares was reported as a barrier for ULT adherence.[36,37] Also, nonadherence to ULT was attributed to a lack of awareness regarding the necessary ULT regimen and its significance in treating gout.[37–39] Some patients thought they should only take ULT when having a flare and used medication accordingly.[40,41] Furthermore, patient skills were reported as a barrier for self-management. Patients experienced issues with getting medication refills,[37] planning their medication regimen ahead when traveling, or had trouble reading labels.[42] Finally, patients accidentally forgot to take medication,[37–39,43–45] for example when traveling or due to having too many pills and forgetting to collect prescriptions.[40,42] In terms of diet, gaining more knowledge led to avoidance of trigger foods and alcohol.[39,46]

Acceptance of disease. Patients reported that acceptance of having gout led to improved medication adherence and lifestyle modification.[35,41,47,48] In contrast, not accepting the disease led to resistance to ULT.[36–38] Finally, masculinity caused reluctance to seek medical attention because men wanted to avoid the embarrassment of admitting severe pain in a small body part.[49]

Beliefs about necessity of self-management to improve gout-related health. Patients adhered to ULT when they felt the need to prevent or reduce disease symptoms (eg, to prevent flares and associated pain).[33,34,37,38,42,43,45,47,50] Other reasons to adhere to ULT included the prevention of disease progression; disability; surgery; avoiding additional hospital visits; improving quality of life, mobility, and daily functioning; and being able to care for others and not having to change their diet.[34,35,37,38,42,48,51] For the latter, some patients elaborated that lifestyle modification was difficult to adhere to in the long run.[48] On the contrary, the identification of dietary triggers for gout and the subsequent belief that gout could be prevented through diet acted as a barrier to receiving ULT.[37,48,51] Additional barriers to receiving ULT included preferences for alternative medicine, perception that other medication is more effective,[42] and only receiving ULT when sUA levels increase.[48] Some patients preferred to treat flares only receiving short-term treatment instead of long-term ULT[35–37] if flare frequency was acceptable to them. After quitting, patients were motivated to restart receiving ULT when recently experiencing a

Table 2. Quotes supporting each of the themes described*

Theme	Quote
Knowledge and skills for self-management	"For one participant, forgetting seemed to be connected to lacking knowledge, with the belief that ULT is: 'built up after, you know, a week of taking it straight, missing it one day is probably not going to be detrimental, right?'"[38]
Acceptance of disease	"Just my eating, my drinking, and I guess the attitude that I had to realize that I had this problem and I just have to deal with it and had to change my whole routine, way of thinking."[47]
Beliefs about necessity of self-management to improve gout-related health	"And, the medicine [ULT] works for me. I haven't had a flare since coming out of the study. I never fail to take it, because I know what will happen to me if I don't, I think about it, oh did I take my tablet [ULT], so it's, religiously I take that tablet [ULT]."[33]
Resistance and reluctance for medication adherence and dietary alteration/changes	"So I know gout's never going to kill me, right. So I don't want to be taking—I don't want to be rattling around full of tablets all the time."[36]
Negative emotions influencing self-management	"Fear. Because … when I get an attack, it's debilitating … before I was on the allopurinol. You know, I would call it a great preventer."[37]
Social support and interactions	"I was really well looked after. It depends on familiarity, on how used to being in contact with it [gout] they [family or friends] are. It is all relative, if they know you and you have persisted in having to stick to a diet, then they are more on your side."[48]
Environmental context	"Copay was $20—I have to ration the pills; I go with the pill I need the most, when I do that."[42]
Self-regulation of behavior	"Make sure that you take your meds on time. Get in a regimen of taking certain meds at a certain time. If you are a military person, you know how to discipline yourself. So, get in that regimen, watch what you eat, make sure you take your meds on time."[47]

* ULT, urate-lowering therapy.

recurrent flare.[37] Regarding lifestyle, patients adjusted their diet by either consuming foods they believed to be beneficial or avoiding foods believed to be detrimental to alleviate symptoms and reduce (the frequency of) flares.[35,43,47,51,52] Patients generally believed that changing dietary habits and being physically active were necessary to reduce sUA levels.[41,46–48] Limitations in daily activities and the desire to accomplish life plans were also motivators for lifestyle modification.[35,46]

Resistance and reluctance for medication adherence and dietary alteration/changes. Patients resisted receiving ULT when they were not convinced of its necessity,[38,45] mostly due to absence of pain or frequent flares,[42,47] sometimes believing their gout was cured[49] and disliking the long-term commitment.[33,35–37,39,52] Patients reported experimenting with diet and medication during an asymptomatic period.[34,37,38,45,46,49] Many patients experienced initial flares when starting ULT, leading to feelings of negative experiences and subsequent nonadherence.[34,37,38,42,43] Other factors contributing to nonadherence to receiving ULT included side effects[42,44,46] and lack of symptom improvements.[43,53] Patients felt they were receiving too many pills,[33,42,45,54] which for some, felt detrimental to their body or led to feelings of frustration.[42,53] Other negative attitudes toward receiving medication included a feeling of being dependent,[37] disliking receiving multiple medications, resistance due to side effects,[41] and general resistance toward medication,[36,51] even though some did not have specific concerns receiving ULT.[35] Patients were resistant toward making dietary changes because of the restrictiveness of diet and long-term commitment,[39,48,51] but poor dietary compliance could also originate as part of a "resistance to authority" reaction to the feeling being forced into lifestyle adaptations by the health care professional (HCP).[46] Diet modification was also perceived to be unrealistic, unmanageable, and irrelevant.[51] Some patients were reluctant to seek care,[46,49,55,56] although they were in severe pain.[45] Sometimes, gout was not considered severe enough to seek care,[39] whereas others were reluctant to seek care due to their belief that gout was not curable and seeking care was therefore not helpful.[46]

Negative emotions influencing self-management. Feelings of insecurity (eg, with receiving a [generic] substitution),[45] impatience for treatment effectiveness[36] and concerns and fear for (long-term) side effects of receiving ULT negatively impacted adherence to ULT[33,37,41,46,49,50] Fear of a gout flare and associated pain led to adherence to ULT[35] and lifestyle modification.[46,47,51] Feelings of shame or embarrassment led patients to avoid seeking help from a general practitioner (GP) because they perceived gout as self-inflicted.[35] Finally, feelings of depression or desperation negatively impacted self-management.[35,47]

Social support and interactions. Support from others could facilitate self-management behavior.[46] Family members reminded patients to take medication[37,45] and to maintain a diet or stop drinking alcohol.[46–48] Patients were motivated to change their self-management behavior to unburden their family.[42,46] Positive experiences shared by other patients prompted patients to modify their lifestyle or medication regimen.[37,44,51] On the other hand, negative stories from others led to nonadherence to ULT.[56] Social occasions made it difficult for patients to adhere to restrictions regarding alcohol and diet,[41,46] impacting their social lives.[51] Engagement and regular contact with an HCP improved adherence to ULT[33] and trust in the HCP and their recommendations.[34,37,42,48] Many patients were adherent to ULT or stopped drinking alcohol because the doctor told them to or told them about the importance and consequences.[42,43,47,52] A lack of guidance and attention were barriers to ULT adherence or seeking care.[37,46] A lack of confidence in the GP caused patients to prefer seeking treatment in a hospital over treatment by a GP.[6]

Environmental context. Patients experienced problems with pill size and picking up prescriptions, which acted as barriers for ULT adherence.[42] Patients reported limited access to HCPs and long wait times, delaying care seeking.[55,56] Financial constraints delayed care seeking[55,56] and hindered ULT adherence.[42,43,52] Receiving incorrect, conflicting, or unclear advice regarding food and medication[35,57] led to patients not modifying their diet and resulted in nonadherence to ULT.[37,45,51] However, receiving digital lifestyle advice was considered an important digital feature that motivated patients to lose weight.[58] Patients described strategies, tools, and interventions to improve self-management behavior. These included stocking on ULT, placing it in a convenient location,[45] and including ULT in a regimen with other medicines.[37,42,47] Patients found (digital) reminders or calendars helpful for remembering to take their medications,[37,44,58] pick up prescribed medications,[40] and stick to their exercise routine.[37,44] Pill boxes also supported medication adherence.[42,43,47] An app facilitating communication with HCPs could help to seek care from a rheumatologist, according to patients.[44] Finally, patients mentioned that an individual treatment approach can overcome medication resistance by adjusting the medication dose and addressing individual needs and concerns.[33,44]

Self-regulation of behavior. Patients described that establishing habits and routines for receiving medication or lifestyle adjustments positively influenced adherence to medication and lifestyle recommendations.[34,37,38,42,45,46,48,51,52] Likewise, lack or interruption of routine decreased adherence to ULT.[34,37,42] Patients believed that self-discipline was necessary for good adherence to ULT and dietary recommendations.[34,37,44,47] Patients made self-directed decisions such as adjusting physical activity[38] and altering ULT doses,[52,56] sometimes based on how they were feeling.[37,42,46] Additionally, patients used opioids to cope with pain,[52] self-increased doses of colchicine,[54] and adjusted diet instead of taking medication[51] to gain a sense of control. Insight into sUA levels served as motivator for patients to adjust their diet and adhere to medication[33,37,58]; it allowed them to assess the effectiveness of ULT and informed lifestyle modifications by identifying dietary triggers.[37] In

Table 3. Associations between determinants and adherence to medication*

Determinants	Association (reference)
Psychological capability	
Knowledge	
• Awareness of gout management strategies	+[15]
• Understanding/Knowledge about the disease	+[65,66]
Behavioral regulation	
• Patience	+[67]
• Compliance with diet advice	+[67]
• Compliance with exercise advice	+[67]
Memory, attention and decision making	
• Preferring ULT vs lifestyle modification only, both ULT and lifestyle modification and others	+[15]
• Performing dietary modification	ns[15]
Social opportunity	
Social influences	
• Perceived social support	ns[68]
• Relationship with hospital doctors	ns[68]
Physical opportunity	
Environmental context and resource	
• No provider visits for gout before ULT initiation vs 3 or more visits[a]	–[69a]
• Initiation of ULT in a hospital setting vs GP and private rheumatologist	–[70]
• Number of hospitalizations before ULT initiation	ns[69]
• Number of physician visits prior to ULT initiation	ns[69]
• Prescriber specialty rheumatologist vs non-rheumatologist prescriber	+[71,72]
• Prescriber specialty non-rheumatologist/nephrologist vs rheumatologist or nephrologist	–[73]
• Digital education and monitoring flares, logging information using an app vs regular care	ns[21]
• Education using story telling with DVD's in culturally matching language vs regular care	ns[74]
• Care in community-based outpatient clinic and other type clinic vs veterans affairs medical center[b]	+[72b]
• Care in a combination of community-based clinic/veterans affair medical center vs veterans affairs medical center[b]	–[72b]
• Rural residence vs urban residence	+[72]
• Performing regular measurements of sUA	+[67]
• Receiving information on lifestyle changes	+[67]
• Low vs average socio-economic status[c]	–[75c]
• Higher/unknown socio-economic status vs average socio-economic status[c]	+[75c]
Reflective motivation	
Role and identity	
• Experiencing symptoms believed to be related to illness (Identity)	–[65]
Beliefs capabilities	
• Self-efficacy	ns[79]
• Confidence to keep serum urate under control	+[66]
• Confidence to have blood tests at recommended frequency	+[66]
• Confidence to take gout medications regularly	+[66]
• Personal control (over disease)	ns[65]
Optimism	
• Good perception of one's illness	ns[68], –[67]
• Satisfaction with long-term treatment	+[67]
• Optimistic status	–[80]
• Perceived susceptibility	+[79]
• Satisfaction with effectiveness of ULT	+[66]
• Global satisfaction	+[66]
Beliefs consequences	
• Positive beliefs about medication	+[68]
• Higher consequences of the disease	–[65]
• Timeline (how long will symptoms continue)	ns[65]
• Higher perceived severity of disease	+[79]
• Treatment control (helpfulness of treatment)	ns[65]
• Higher perceived benefits ULT	+[79]
• Low perceived barriers to ULT	+[79]

(Continued)

Table 3. (*Cont'd*)

Determinants	Association (reference)
Intentions	
• Obedience	+[67]
Automatic motivation	
Reinforcement	
• Interactive voice-response system to assess adherence, alert pending prescriptions and provide encouragement vs regular care	+[25]
• Digital education and reminders vs regular care	+[22]
• Self-monitoring sUA using a PoCT device vs regular care	+[24]
Emotions	
• Emotional response	–[65]
• Concerns	ns[65]
• Mental status	+[66]
• Depression	ns[66]

* Determinants are mapped to the corresponding theoretical domains framework construct, specified in bold, which were in turn mapped to the capability, opportunity, motivation and behaviour model domains, specified in italic, in the outer left column. Statistically significant associations between determinants and adherence to medication are reported as a plus sign (+) when positively associated, and as a minus sign (-) when negatively associated. Ns indicates no significant association was found. Between brackets are the studies in which a finding was reported. For associations between determinants and other self-management behaviours, see Supplementary Table S1.
[a] (69) = The variable provider visits before ULT initiation consisted of 4 categories; 0 visits, 1 visit, 2 visits and 3 or more visits. 3 or more visits was the reference category, 1 visit or 2 visits were not associated with adherence compared to 3 or more visits.
[b] (72) = The outpatient clinic type variable consisted of four categories, "Veterans Affairs Medical Center" as the reference category, "community-based outpatient clinic", A combination of the first two categories and "Other" clinic type.
[c] (75) = The variable of socioeconomic status consisted of 6 categories; < 8, 9-11, 12-13 (reference category), 14-16, 17-20, unknown. We named <8 as lower SES than average (the reference category) and 14-16, 17-20 and unknown as higher than average. The latter 3 categories were all significantly associated with the reference category. Only 9-11 was not associated with the reference category.

terms of possibly self-monitoring sUA levels, patients preferred to own and use a point-of-care device for gout to prevent blood tests.[37] Laziness caused nonadherence to medication, not getting refills in time, and delaying care seeking.[38,39,42] Finally, patients believed in the need for an active role in treatment,[37] such as knowing when to take colchicine,[38,54] changing diet,[48] and proactively seeking care.[38,44] However, self-diagnosis and treatment led to delay in care seeking.[55]

Descriptive determinants of self-management of quantitative research. A subset (n = 6) of quantitative studies provided descriptive reports on determinants of self-management. Reasons for discontinuing ULT included patients feeling it was no longer required or becoming fed up with the medication.[59] In a cross-sectional observational study, intentional nonadherence was driven by desires for a normal life, perceiving oneself as healthy, and testing the necessity of treatment. Medication-related concerns encompassed dislike for side effects, worry about dependence, belief in decreasing efficacy, perceived harshness on the body, high doses, and doubts about treatment efficacy.[60] An eight-year retrospective study revealed ULT discontinuation in 46.8% of 282 patients, with determinants including poor health literacy, perceived inefficacy, and adverse events.[61] Other patient-reported nonadherence reasons included remission, concerns about side effects, inadequate education, receiving alternative medicine, forgetting to receive medication, and inconvenience in obtaining medication.[62] Improved patient understanding of the disease and treatment seemed to increase adherence.[63] Finally, physicians can influence patients' dietary behavior by addressing and proposing lifestyle interventions.[64]

Associations of determinants with self-management behavior of quantitative research. The majority of statistical associations reported between TDF determinants and self-management behavior related to adherence to medication (19 of 23 studies), shown in Table 3. For adherence to dietary recommendations, physical activity recommendations, and care-seeking behavior, five, three, and two studies were found, respectively, which can be found in Supplementary Table 1[21,22,76,77,78,81,82]. No studies were found investigating determinants of self-monitoring of disease status.

DISCUSSION

In this comprehensive scoping review, we included studies investigating modifiable factors of self-management behavior using the TDF to guide our search. A thematic synthesis of 27 qualitative studies resulted in eight themes: knowledge and skills for self-management, acceptance of disease, beliefs about necessity of self-management to improve gout-related health, resistance and reluctance to medication adherence and dietary alteration/changes, negative emotions influencing self-management, social support and interactions, environmental context, and self-regulation of behavior. Most studies addressed medication adherence. Several studies described lifestyle and care seeking, and one study described self-monitoring of disease. Both quantitative and qualitative findings support the importance

of knowledge, skills, preference for receiving ULT as opposed to other self-management options, and positive beliefs about medication in influencing adherence to receiving ULT. Contradicting results were found regarding acceptance of the disease in association with adherence to ULT in quantitative and qualitative findings.

The results of this review provide practical, evidence-based targets for systematically developing interventions to stimulate self-management behavior. Although the results described in this study are related specifically to patients with gout, many of the determinants of medication adherence are also found in patients with other chronic diseases (eg, diabetes or hypertension). The similarities include, for example, the stimulating effect of social support and positive beliefs, whereas hindering effects were found for limited care access, information and communication problems, problems experienced with medication, and negative beliefs.[83] Thus, our findings regarding medication adherence align with other chronic diseases, which supports validity of our results and suggests that the findings may be transferable to other chronic diseases.

To develop successful interventions, a thorough understanding of the target behavior and its underlying determinants is required. We have used the TDF to identify behavior determinants. An important question remains: What should effective interventions entail? The Behaviour Change Wheel (BCW) offers various intervention functions targeting TDF constructs and COM-B domains. The latter presents a simplified version of behavioral factors in which three interacting domains—capability, opportunity, and motivation—determine whether a behavior is performed or not.[30] Additionally, interventions should target determinants with highest impact potential, with an additional potential for spillover effects to other COM-B domains. To illustrate, education targeting psychological capability may be important for medication adherence but may not create additionally motivation opportunity to actually perform the behavior. Therefore, the *Education* and *Persuasion* intervention functions could aim to increase motivation by cultivating appropriate beliefs and creating positive expectations within the motivation domain regarding medication adherence behavior, which were determinants identified in this study. To directly provide more opportunities for correct medication use, an *Enablement* intervention function can facilitate (digital) reinforcement and access to appropriate care and increase (social) support. The EULAR self-management recommendations also suggest a role for (social) support, and previous research stresses the importance of reinforcing patients.[2,12,24] Finally, interventions could focus on fostering habitual behavior, which is more likely to persist over time.[84]

Regarding mode of delivery, eHealth can play an important role because it facilitates delivery of intervention functions in a cost-efficient manner. A combination of eHealth supported by HCP guidance could be most optimal due to promised efficiency of the former and proven effectiveness of the latter.[2,18] The use of eHealth is supported by the 2021 EULAR recommendations for implementing self-management in patients with inflammatory arthritis because eHealth can allow patients to acquire a more active role in their health as well as facilitate use of relevant patient-reported outcome domains.[12] Guidance on development of eHealth apps for rheumatic diseases is described in the EULAR points to consider for the development, evaluation, and implementation of mobile health.[85] An important factor to bear in mind when implementing eHealth for patients with rheumatic diseases is that it should complement care rather than serve as a replacement.[86,87]

The use of the scoping review methodology approach allowed us to capture both qualitative and quantitative data relevant to the research question, providing a comprehensive and detailed overview of determinants that influence self-management. Also, mapping of determinants to the TDF and COM-B model allows for identification of suitable interventions to positively influence self-management behavior. A few limitations may be acknowledged. Quality appraisal of included studies was considered not feasible due to the large number of studies and heterogeneity in study type and design. Due to this, biased results from studies with lower methodologic rigor could have impacted our findings. For example, of the eight included interventional studies, six were randomized controlled trials (RCTs), one was a prepost study, and another one was quasi-experimental. Arising from their design, the latter two studies have a higher risk of bias compared to the RCTs. In general, the RCTs were considered of good quality. However, in two studies, blinding was not possible due to the nature of the intervention, possibly leading to performance and/or detection bias.[24,25] Additionally, we cannot provide conclusions on the strength and causality of the associations that were reported.

This study identified determinants for self-management behavior in gout and provides targets for researchers and policy makers to select and develop evidence- and theory-based interventions targeting patients with gout and their context. Subsequently, implementing these interventions is expected to increase self-management behavior and thereby improve clinical outcomes. This study also reveals the complexity and the quantity of determinants that could be targeted to improve and support self-management. Although a complex intervention targeting the specific barriers for self-management of individuals may be most effective, a general intervention could target the COM-B domains by using the *Education*, *Persuasion*, and *Enablement* intervention functions according to the BCW.[30] More information on determinants of self-management behavior other than adherence to receiving ULT, such as lifestyle modifications, care-seeking behavior, and self-monitoring of disease status in gout, are needed to get a complete picture of determinants associated with self-management behavior. To, conclude, we identified various modifiable determinants of self-management behavior in patients with gout, which can

function as targets for interventions aiming to improve gout care through increased self-management.

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, Mr van der Ven 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.

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Cost-Related Medication Behaviors for Patients With and Without Systemic Autoimmune Rheumatic Diseases

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Objective. Medication nonadherence challenges the management of systemic autoimmune rheumatic diseases (SARDs). We investigated cost-related medication behaviors among patients with SARDs, and compared them to those of patients without SARDs, in a large diverse cohort across the United States.

Methods. As part of the *All of Us* (version 7), a nationwide diverse adult cohort with linked electronic health records begun in 2017, participants completed questionnaires concerning cost-related medication behaviors. Chi-square tests compared responses between patients with SARDs, by disease and medication type, and to those without SARDs. Logistic regression analyses were used to calculate odds ratios (95% confidence intervals [CIs]).

Results. We analyzed data from 3,997 patients with SARDs and 73,990 participants without SARDs. After adjustment, patients with versus without SARDs had 1.56 times increased odds of reporting unaffordability of prescription medicines (95% CI 1.43–1.70), 1.43 times increased odds of cost-related medication nonadherence (95% CI 1.31–1.56), and 1.23 times increased odds of using cost-reducing strategies (95% CI 1.14–1.32). Patients with SARDs who reported unaffordability were 16.5% less likely to receive a disease-modifying drug (95% CI 0.70–0.99) but 18.1% more likely to receive glucocorticoids (95% CI 0.99–1.42). In addition, unaffordability of prescription medicines was likely to have 1.27 times increased odds of one to two emergency room visits per year (95% CI 1.03–1.57) and 1.38-fold increased odds of three or more emergency room visits per year (95% CI 0.96–1.99).

Conclusion. In this large diverse cohort, patients with versus without SARDs had more self-reported cost-related medication behaviors, and those who reported medication unaffordability received fewer disease-modifying drugs and had more emergency room visits.

INTRODUCTION

Systemic autoimmune rheumatic diseases (SARDs), such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriatic arthritis (PsA), are chronic inflammatory disorders that mainly, but not exclusively, affect connective tissues like joints and muscles.[1,2] With the introduction of newer biologic agents, significant advances have been achieved in the treatments of SARDs in recent years.[3] However, the high cost of biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) has restricted their reception and can lead to care inequities.[4–6]

Medication nonadherence is a challenging issue in the management of chronic diseases, SARDs in particular.[7,8] The prevalence of medication nonadherence in patients with SARDs has varied widely, reported to range from 6% to 90% in past studies.[9–11] Suboptimal adherence has been associated with worse clinical outcomes, including higher disease activity, and increased hospitalization and emergency department visits, all of which can contribute to increasing health care cost and disease burden.[12–15] Many factors are reported to be associated with medication nonadherence, including patient-related factors (eg, age, gender, race, and ethnicity), therapy-related factors (eg, complexity, side effects), and condition-related factors (eg,

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SIGNIFICANCE & INNOVATIONS

- This large cross-sectional survey within the *All of Us* found that patients with systemic autoimmune rheumatic diseases (SARDs) reported more cost-related medication behaviors than did those without SARDs.
- When compared by type of SARDs, patients with systemic lupus erythematosus reported the highest cost-related medication nonadherence, whereas those with psoriatic arthritis reported using the most cost-reducing strategies.
- Among patients with SARDs, unaffordability of prescription medicines was more likely to have 1.27 times increased odds of having one to two emergency room visits per year in the same year. (95% confidence interval [CI] 1.03–1.57) and 1.38 times increased odds of having three or more emergency room visits per year in the same year. (95% CI 0.96–1.98).

mental health, prognosis); medication cost is one of the most important components contributing to poor adherence.[9,10,16,17] Thus, understanding cost-related medication nonadherence is important but has been less well studied among patients with SARDs in recent years. Several studies have been performed among individuals with RA or SLE[18–20] but not among those with other SARDs. Therefore, we aimed to investigate the prevalence of cost-related medication behaviors in patients with and without SARDs and their associations with prescription rates for DMARDs and glucocorticoids and health care use in a large, diverse cohort across the United States.

PATIENTS AND METHODS

Study population. The *All of Us* is a nationwide longitudinal cohort study aiming to enroll one million diverse participants across the United States. The procedures of *All of Us* have been previously described in detail.[21,22] The institutional review board of the *All of Us* approved the operational protocol, and all participants provided informed consent at the time of enrollment. Briefly, adults aged 18 years or older are eligible to participate through *All of Us*–affiliated health care provider organizations or directly through the *All of Us* website or certain events. After enrollment, participants were asked to complete several surveys, which are provided in both English and Spanish at a fifth-grade reading level. Each survey is intended to be completed in about 15 minutes. They were asked to agree to share their electronic health records (EHRs), undergo physical measurements, and donate biospecimens.

Among the participants with baseline survey and linked EHR data in *All of Us* version 7 (C2022Q4R9; released April 2023), participants who fully answered the seven questions on cost-related medication behaviors and who received at least one prescription of medications within one year of enrollment were included in the study. Among them, patients with SARDs, including those with RA, SLE, PsA, ankylosing spondylitis, Sjögren disease, systemic sclerosis, dermatomyositis/polymyositis, mixed/undifferentiated connective tissue diseases, and vasculitis, were identified if they had at least two International Classification of Diseases, Nineth Revision (ICD-9), International Classification of Diseases, Tenth Revision (ICD-10), and Systematized Nomenclature of Medicine (SNOMED) codes at least 60 days apart within two years before their enrollment.[23,24] The comparison group for the first part of the analysis consisted of those who did not have any code for SARDs before enrollment.

Questionnaires of cost-related medication behaviors. From the Health Care Access and Utilization survey in *All of Us*, derived from the National Health Interview Survey, we used the seven questions including three indices of cost-related medication behaviors: unaffordability of prescription medicine, cost-related medication nonadherence, and cost-reducing strategies.[25,26] Unaffordability of prescription medicine was assessed by asking whether there was a time when they needed prescription medication but did not get them because they could not afford them. Cost-related medication nonadherence, a binary variable, was defined as an indication of "yes" to any of three questions: (1) skipping medications, (2) receiving less medication than prescribed, and (3) delaying filling a prescription to save money. Following cost-reducing strategies was defined as answering "yes" to any of three questions: (1) asking their doctor for a lower-cost medication, (2) buying prescription drugs from another country, and (3) using alternative therapies to save money.

Variables. From the basic survey in *All of Us*, we extracted the following data: age, gender, race and ethnicity, household income, education level, insurance type, employment status, and smoking status. Data on primary spoken language were not available. Geographic region based on state of enrollment was categorized as Northeast, Midwest, West, and South. The area deprivation index was derived from the 2017 American Communities Survey measures and calculated by taking the population-weighted average of the index for the US census tracts based on their three-digit zip code.[27] Obesity was defined by body mass index ≥30 kg/m^2 from the baseline in-person physical measurement data. The Charlson Comorbidity Index (CCI) was assessed using ICD-9, ICD-10, and SNOMED codes from the EHRs within the year before the enrollment.[28] Medication history was collected using RxNorm from the EHRs within the year before the enrollment, and the number of medications was defined as the maximum number of prescribed medications on a single day and categorized into three groups: 1 to 4, 5 to 9 (ie, polypharmacy), and ≥10 (ie, excessive polypharmacy).[29] DMARD and

glucocorticoid reception was coded by their ingredients using RxNorm. Health care use, including inpatient visits, emergency room visits, and outpatient visits, were identified within the one year before the enrollment.

Statistical analysis. Chi-square tests first compared self-reported responses regarding cost-related medication behaviors. We compared responses among patients with and without SARDs, and additionally, we compared each type of SARD with those without. Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression for cost-related medication behaviors and analyzed in three models, the first adjusting for the number of medications, the second further adjusting for age, gender, race and ethnicity, and geographic region, and the last further adjusting for annual household income, education level, insurance type, employment status, area deprivation index score, and CCI score. A sensitivity analysis was conducted to recategorize patients with two or more SARDs into the SARD category for which they had the highest number of codes (ICD-9, ICD-10, or SNOMED). In this analysis, we excluded patients with an equal number of codes for more than one SARD because it was still difficult to distinguish which was the primary disease.

We used logistic regression models to examine unadjusted and adjusted associations of each cost-related medication behavior with the prescriptions of DMARDs (any vs none) and glucocorticoids (any vs none) among the patients with SARDs. Covariates were the number of medications including DMARDs and/or glucocorticoids, age group, gender, race and ethnicity, insurance type, CCI score, and types of SARDs. Among the patients with SARDs, we also compared annual health care use in those with or without each type of cost-related medication behavior. Here, in each model, the independent variable was the cost-related medication behavior and the dependent variable was (1) baseline annual inpatient visits (0 [referent], 1–2, and ≥3), (2) baseline annual emergency department visits (0 [referent], 1–2, and ≥3), or (3) baseline annual outpatient visits (0 [referent], 1–9, and ≥10). For these health care use outcomes, multinomial logistic regression analyses were performed. Models were adjusted for the number of medications, age group, gender, race and ethnicity, insurance type, CCI score, and types of SARDs. *P* of less than 0.05 was considered statistically significant. All statistical analyses were performed using R version 4.1.0 in a Jupyter Notebook contained in the *All of Us* workbench.

RESULTS

Among 185,902 participants with at least one prescription within one year of enrollment, 80,663 participants answered all seven questions of interest (Figure 1). Those who answered the survey tended to be older and more educated than those who did not, and more respondents were female and non-Hispanic White (Supplementary Table 1). Among them, we identified 3,997 patients with SARDs and 73,990 participants without any SARD diagnosis. Of them, 1,330 patients had RA (33.3%); 468 had SLE (11.7%), 373 had Sjögren disease (9.3%); 282 had PsA (7.1%); 279 had ankylosing spondylitis (7.0%); 441 had other SARDs (11.0%) including 72 with systemic sclerosis (1.8%), 41 with dermatomyositis/polymyositis (1.0%), 163 with mixed/undifferentiated connective tissue diseases (4.1%), and 165 with vasculitis (4.1%); and 824 had two or more types of SARDs (20.6%). The characteristics of the study population were described in Table 1. The patients with SARDs had a mean age of 57.5 years, and 78.4% were women, whereas the participants without SARDs had a lower mean age of 53.7 years and a lower percentage were women (63.3%). In both groups, approximately 71% self-identified as non-Hispanic White Americans, 10% as non-Hispanic Black Americans, and 11% as Hispanic Americans. Patients with SARDs were more likely than those without to have lower annual household income, be less educated, have public insurance, and be unemployed. Compared to those without SARDs, the patients with SARDs had higher mean CCI (1.5 vs 1.0), calculated without rheumatic disease (potential range 0–32). As expected, more patients with than without SARDs were prescribed conventional DMARDs (41.7% vs 2.8%), biologic and/or targeted synthetic DMARDs (19.0 % vs 0.7%), and glucocorticoids (45.9% vs 23.5%), along with five or more medications (56.6% vs 41.6%).

Table 2 shows the prevalence of cost-related medication behaviors among patients with and without SARDs. Patients with

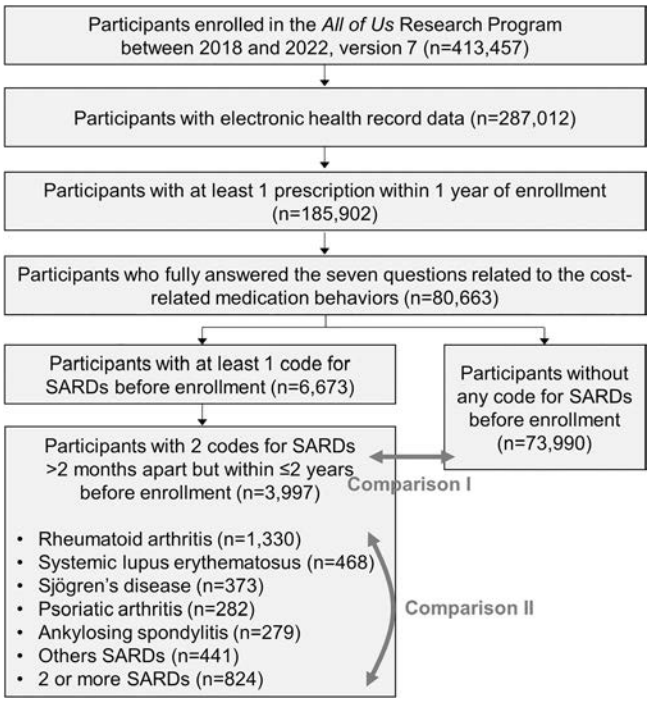

Figure 1. Flow chart of study population. SARD, systemic autoimmune rheumatic disease.

Table 1. Demographic and survey data of participants with and without SARDs in the *All of Us* who responded to the Health Care Access and Utilization survey (data release version 7)*

Characteristics	Participants with SARDs (n = 3,997), n (%)	Participants without SARDs (n = 73,990), n (%)
Age, y		
18–49	1,061 (26.5)	27,821 (37.6)
50–64	1,491 (37.3)	22,823 (30.8)
≥65	1,445 (36.2)	23,346 (31.6)
Self-reported Gender		
Women	3,133 (78.4)	46,830 (63.3)
Men	749 (18.7)	25,089 (33.9)
Other/prefer not to answer/missing	115 (2.9)	2,071 (2.8)
Self-reported race and ethnicity		
Hispanic American	424 (10.6)	7,917 (10.7)
Non-Hispanic Black American	437 (10.9)	7,307 (9.9)
Non-Hispanic White American	2,806 (70.2)	52,824 (71.4)
Non-Hispanic other/prefer not to answer/missing	330 (8.3)	5,942 (8.0)
Enrollment year		
2018	1,105 (27.6)	19,391 (26.2)
2019	1,336 (33.4)	24,767 (33.5)
2020	417 (10.4)	7,981 (10.8)
2021	701 (17.5)	13,606 (18.4)
2022	438 (11.0)	8,245 (11.1)
Annual household income, thousands of dollars		
<35	1,058 (26.5)	16,671 (22.5)
35–100	1,294 (32.4)	24,667 (33.3)
≥100	1,072 (26.8)	22,973 (31.0)
Prefer not to answer/missing	573 (14.3)	9,679 (13.1)
Education level		
High school graduate or less	657 (16.4)	11,183 (15.1)
Some college	1,163 (29.1)	18,318 (24.8)
College graduate or above	2,082 (52.1)	42,766 (57.8)
Prefer not to answer/missing	95 (2.4)	1,723 (2.3)
Insurance[a]		
Private	1926 (48.2)	39,045 (52.8)
Public	1,510 (37.8)	23,352 (31.6)
Uninsured	41 (1.0)	2011 (2.7)
Prefer not to answer/missing	520 (13.0)	9,582 (13.0)
Employment		
Employed/self-employed	1,559 (39.0)	38,397 (51.9)
Unemployed	163 (4.1)	3,659 (4.9)
Other[b]	2,160 (54.0)	30,051 (40.6)
Prefer not to answer/missing	115 (2.9)	1,883 (2.5)
Region		
Northeast	1,649 (41.3)	26,129 (35.3)
Midwest	1,102 (27.6)	23,373 (31.6)
West	733 (18.3)	14,998 (20.3)
South	≤513 (≤12.8)	9,453 (12.8)
Missing	<20	37 (0.1)
Area deprivation index, median (IQR)[c]	0.30 (0.07)	0.30 (0.06)
Smoking		
Ever	1,590 (39.8)	27,170 (36.7)
Never	2,344 (58.6)	45,558 (61.6)
Missing	63 (1.6)	1,262 (1.7)
BMI, kg/m^2		
≥30	1,799 (45.0)	29,950 (40.5)
<30	2,083 (52.1)	41,159 (55.6)
Missing	115 (2.9)	2,881 (3.9)
Charlson Comorbidity Index, mean ± SD[d]	1.5 ± 2.1	1.0 ± 1.9
Myocardial infarction	109 (2.7)	1,266 (1.7)
Congestive heart failure	264 (6.6)	2,569 (3.5)
Peripheral vascular disease	256 (6.4)	2,265 (3.1)
Cerebrovascular disease	253 (6.3)	2,282 (3.1)
Diabetes	681 (17.0)	9,820 (13.3)

(Continued)

Table 1. (*Cont'd*)

Characteristics	Participants with SARDs (n = 3,997), n (%)	Participants without SARDs (n = 73,990), n (%)
Chronic pulmonary disease	980 (24.5)	9,644 (13.0)
Liver disease	329 (8.2)	3,577 (4.8)
Renal disease	420 (10.5)	3,518 (4.8)
Number of medications		
1–4	1,736 (43.4)	43,247 (58.4)
5–9	983 (24.6)	14,598 (19.7)
≥10	1,278 (32.0)	16,145 (21.8)
Medications		
Conventional DMARDs[e]	1,666 (41.7)	2,070 (2.8)
Biologic DMARDs and/or targeted synthetic DMARDs[f]	760 (19.0)	540 (0.7)
Glucocorticoids[g]	1,834 (45.9)	17,362 (23.5)
SARDs		
Rheumatoid arthritis	1,330 (33.3)	–
Systemic lupus erythematosus	468 (11.7)	–
Sjögren disease	373 (9.3)	–
Psoriatic arthritis	282 (7.1)	–
Ankylosing spondylitis	279 (7.0)	–
Other SARD	441 (11.0)	–
Two or more SARDs	824 (20.6)	–

* According to *All of Us* data sharing policies, cells with less than 20 participants were suppressed. BMI, body mass index; DMARD, disease-modifying antirheumatic drug; IQR, interquartile range; SARD, systemic autoimmune rheumatic disease.
[a] Reports of both private and public insurance were considered as private. Reports of having only Indian Health Service coverage were considered uninsured.
[b] Other includes homemaker, student, retired, and unable to work (disabled).
[c] The area deprivation index was derived from the 2017 American Communities Survey based on their three-digit zip code. There were 33 participants with missing data.
[d] Charlson Comorbidity Index score was calculated using 16 comorbidities, excluding rheumatic disease.
[e] Conventional DMARDs included azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, mycophenolate/mycophenolic acid, sulfasalazine, and tacrolimus.
[f] Biologic DMARDs included abatacept, adalimumab, anakinra, belimumab, brodalumab, canakinumab, certolizumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, ocrelizumab, rilonacept, risankizumab, rituximab, sarilumab, secukinumab, tildrakizumab, tocilizumab, and ustekinumab. Target synthetic DMARDs included baricitinib, tofacitinib, and upadacitinib.
[g] Glucocorticoids included dexamethasone, methylprednisolone, prednisolone, and prednisone.

SARDs were significantly more likely than those without SARDs to report unaffordability of prescription medicines: 18.3% of patients with SARDs and 11.9% of those without ($P < 0.001$). Patients with SARDs were 1.5-fold more likely to experience cost-related medication nonadherence than those without (18.1% vs 13.1%, $P < 0.001$), and the following similar trends were observed in all items of cost-related medication nonadherence: skipping medication doses (9.9% vs 6.9%, $P < 0.001$), receiving less medication than prescribed (10.8% vs 7.7%, $P < 0.001$), and delaying filling a prescription (15.6% vs 11.0%, $P < 0.001$). The self-reported prevalence of using cost-reducing strategies was also significantly higher among patients with SARDs than those without

Table 2. Prevalence of cost-related medication behaviors in patients with and without SARDs in the *All of Us* (data release version 7)*

Patients reported cost-related medication behavior	Participants with SARDS (n = 3,997), n (%)	Participants without SARDs (n = 73,990), n (%)	*P* value[a]
Unaffordability of prescription medication	731 (18.3)	8,837 (11.9)	<0.001
Cost-related medication nonadherence	725 (18.1)	9,678 (13.1)	<0.001
Skipped medication doses	396 (9.9)	5,092 (6.9)	<0.001
Received less medication than prescribed	433 (10.8)	5,661 (7.7)	<0.001
Delayed filling a prescription	622 (15.6)	8,138 (11.0)	<0.001
Cost-reducing strategies for prescription medication	1,148 (28.7)	17,803 (24.1)	<0.001
Asked for a lower-cost medication	971 (24.3)	14,391 (19.4)	<0.001
Bought prescription drugs from another country	129 (3.2)	2,407 (3.3)	0.97
Used alternative therapies	322 (8.1)	5,251 (7.1)	0.02

* SARD, systemic autoimmune rheumatic disease.
[a] *P* values were calculated by chi-square test.

(28.7% vs 24.1%, $P < 0.001$). There were significant differences in the prevalence of requesting a lower-cost medication (24.3% vs 19.4%, $P < 0.001$) and using alternative therapies (8.1% vs 7.1%, $P = 0.02$), but there was no difference in buying prescription drugs from another country (3.2% vs 3.3%, $P = 0.97$).

The demographic and survey responses of the patients with SARD by disease are presented in Supplementary Table 2 and Figure 2. The prevalence of reporting unaffordability of prescription medicines was 16.3%, 22.2%, 16.1%, 17.7%, 17.9%, 15.4%, and 22.1% among patients with RA, SLE, Sjögren disease, PsA, ankylosing spondylitis, other SARDs, and two or more types of SARDs, respectively. For cost-related medication nonadherence, 16.7%, 20.1%, 18.2%, 16.3%, 17.9%, 15.4%, and 21.5% of patients with RA, SLE, Sjögren disease, PsA, ankylosing spondylitis, other SARDs, and two or more types of SARDs answered yes, respectively, whereas 25.8%, 30.3%, 33.5%, 34.8%, 23.3%, 27.4%, and 30.8% of patients with each disease reported yes for cost-reducing strategies. Among those with these diseases, the highest proportion of patients reporting unaffordability of prescription medicines were those with SLE (22.2%), followed by those with two or more types of SARDs (22.1%), ankylosing spondylitis (17.9%), and PsA (17.7%). Patients with two or more types of SARDs and those with SLE also reported the highest cost-related medication nonadherence (21.5% and 20.1%, respectively), whereas those with PsA reported the most cost-reducing strategies (34.8%).

Table 3 displays the results of univariable- and multivariable-adjusted logistic regression analyses for cost-related medication behaviors. After sequentially adjusting for the number of medications (minimally adjusted), adding demographic factors (demographics adjusted), and adding socioeconomic factors and CCI score (fully adjusted), the patients with SARDs had 1.56 times increased odds of unaffordability of prescription medications (95% CI 1.43–1.70), 1.43 times increased odds of cost-related medication nonadherence (95% CI 1.31–1.56), and 1.23 times increased odds of cost-reducing strategies (95% CI 1.14–1.32). When comparing types of SARDs to those without any SARD in unadjusted models, having any type of SARD significantly increased a patient's odds of having all three cost-reducing behaviors than for patients without SARDs, with the exception of cost-related medication nonadherence among those with PsA and cost-reducing among those with RA and ankylosing spondylitis, among whom the odds were not significantly elevated. After multivariable adjustment, all types of SARDs were seen to have increased odds of reporting unaffordability of prescription medications by at least 40%. Patients with PsA had the highest adjusted OR for medication unaffordability (adjusted OR 1.81, 95% CI 1.30–2.47), followed by those with two or more types of SARDs (adjusted OR 1.79, 95% CI 1.50–2.13). Having two or more types of SARDs was also most strongly associated with cost-related medication nonadherence (adjusted OR 1.62, 95% CI 1.36–1.93), followed by Sjögren disease (adjusted OR 1.57, 95% CI 1.18–2.05). PsA was the SARD most strongly associated with reporting cost-reducing strategies in our fully adjusted models (adjusted OR 1.68, 95% CI 1.30–2.15) but was less strongly associated with cost-related nonadherence (adjusted OR 1.39, 95% CI 0.99–1.91). Full adjustment reduced the odds of all three cost-related medication behaviors the most for those with SLE; after full adjustment, the OR for unaffordability of medication, cost-related medication nonadherence, and cost-

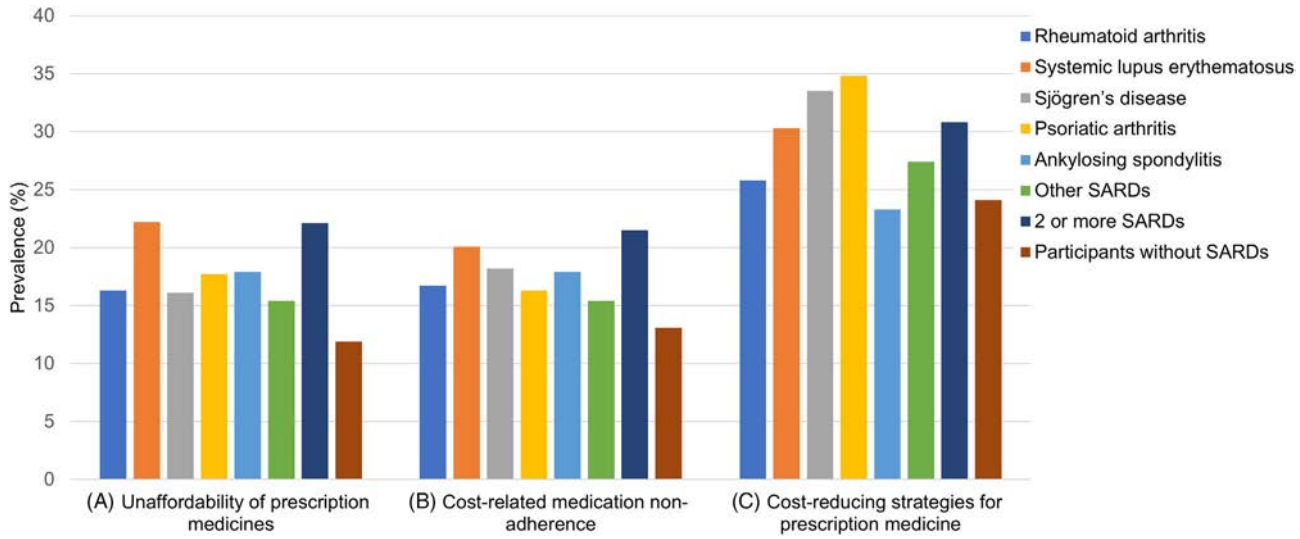

Figure 2. Prevalence of cost-related medication behaviors in patients with different types of systemic autoimmune rheumatic diseases (SARDs) in *All of Us* (data release version 7). Cost-related medication nonadherence included skipping medication doses, receiving less medication than prescribed, and delaying filling a prescription to save money. Cost-reducing strategies for prescription medication included asking for a lower-cost medication, buying prescription drugs from another country, and using alternative therapies to save money.

Table 3. Unadjusted and adjusted odds ratio (95% CI) for cost-related medication behaviors in patients with SARDs compared to patients without SARDs in the *All of Us* (data release version 7)*

Type of SARDs	Unadjusted odds ratio	Adjusted odds ratio		
		Minimally adjusted[a]	Demographics adjusted[b]	Fully adjusted[c]
Unaffordability of prescription medication				
Any SARD	1.65 (1.52–1.79)	1.56 (1.43–1.69)	1.64 (1.50–1.79)	1.56 (1.43–1.70)
Rheumatoid arthritis	1.44 (1.24–1.66)	1.36 (1.17–1.57)	1.54 (1.32–1.79)	1.43 (1.22–1.66)
Systemic lupus erythematosus	2.11 (1.68–2.61)	2.01 (1.61–2.49)	1.50 (1.19–1.87)	1.45 (1.15–1.82)
Sjögren disease	1.41 (1.06–1.85)	1.36 (1.02–1.78)	1.57 (1.17–2.07)	1.52 (1.12–2.01)
Psoriatic arthritis	1.59 (1.16–2.14)	1.52 (1.11–2.05)	1.86 (1.35–2.53)	1.81 (1.30–2.47)
Ankylosing spondylitis	1.61 (1.17–2.17)	1.55 (1.13–2.09)	1.65 (1.19–2.24)	1.58 (1.14–2.17)
Other SARD	1.34 (1.03–1.73)	1.27 (0.97–1.64)	1.51 (1.15–1.96)	1.54 (1.17–2.01)
Two or more SARDs	2.09 (1.77–2.46)	1.92 (1.62–2.27)	1.92 (1.61–2.27)	1.79 (1.50–2.13)
Cost-related medication nonadherence[d]				
Any SARD	1.47 (1.35–1.60)	1.41 (1.30–1.53)	1.47 (1.35–1.60)	1.43 (1.31–1.56)
Rheumatoid arthritis	1.33 (1.15–1.54)	1.27 (1.10–1.47)	1.43 (1.23–1.65)	1.37 (1.18–1.59)
Systemic lupus erythematosus	1.67 (1.32–2.09)	1.61 (1.28–2.01)	1.28 (1.01–1.61)	1.29 (1.01–1.62)
Sjögren disease	1.48 (1.13–1.92)	1.44 (1.10–1.86)	1.61 (1.22–2.10)	1.57 (1.18–2.05)
Psoriatic arthritis	1.30 (0.93–1.76)	1.25 (0.90–1.70)	1.44 (1.03–1.97)	1.39 (0.99–1.91)
Ankylosing spondylitis	1.45 (1.06–1.95)	1.41 (1.03–1.90)	1.48 (1.07–2.00)	1.44 (1.04–1.97)
Other SARD	1.21 (0.93–1.56)	1.16 (0.89–1.50)	1.31 (1.00–1.69)	1.36 (1.03–1.76)
Two or more SARDs	1.82 (1.53–2.14)	1.71 (1.44–2.01)	1.68 (1.41–1.99)	1.62 (1.36–1.93)
Cost-reducing strategies for prescription medication[e]				
Any SARD	1.27 (1.18–1.36)	1.24 (1.16–1.33)	1.25 (1.16–1.34)	1.23 (1.14–1.32)
Rheumatoid arthritis	1.10 (0.97–1.24)	1.07 (0.94–1.21)	1.09 (0.96–1.24)	1.07 (0.95–1.22)
Systemic lupus erythematosus	1.37 (1.12–1.67)	1.35 (1.10–1.64)	1.29 (1.05–1.57)	1.28 (1.05–1.57)
Sjögren disease	1.59 (1.28–1.97)	1.57 (1.26–1.94)	1.55 (1.24–1.92)	1.51 (1.21–1.87)
Psoriatic arthritis	1.68 (1.31–2.14)	1.65 (1.29–2.10)	1.71 (1.33–2.19)	1.68 (1.30–2.15)
Ankylosing spondylitis	0.96 (0.72–1.26)	0.94 (0.71–1.24)	0.94 (0.71–1.24)	0.92 (0.69–1.22)
Other SARD	1.19 (0.96–1.47)	1.17 (0.94–1.44)	1.19 (0.96–1.47)	1.21 (0.98–1.50)
Two or more SARDs	1.41 (1.21–1.63)	1.36 (1.17–1.57)	1.34 (1.15–1.56)	1.31 (1.13–1.53)

* CI, confidence interval; SARD, systemic autoimmune rheumatic disease.
[a] The minimally adjusted model was adjusted for the number of medications.
[b] The demographics-adjusted model was additionally adjusted for age, gender, race and ethnicity, and geographic region (based on four US census regions).
[c] The fully adjusted model III was additionally adjusted for annual household income, education level, insurance type, employment status, area deprivation index, and Charlson Comorbidity Index.
[d] Cost-related medication nonadherence included skipping medication doses, receiving less medication than prescribed, and delaying filling a prescription to save money.
[e] Cost-reducing strategies for prescription medication included asking for a lower-cost medication, buying prescription drugs from another country, and using alternative therapies to save money.

reducing strategies decreased from 2.11 to 1.45, from 1.67 to 1.29, and from 1.37 to 1.28, respectively, for those with SLE.

Results of a sensitivity analysis in which patients with two or more SARDs were categorized into the group with the highest number of codes (ICD-9, ICD-10, or SNOMED) are shown in Supplementary Figure 1 and Supplementary Table 3. As in the main analysis, patients with PsA had the highest adjusted OR for medication unaffordability (adjusted OR 1.87, 95% CI 1.40–2.46) after adjustment. For cost-related medication nonadherence, patients with Sjögren disease showed the highest adjusted OR (adjusted OR 1.49, 95% CI 1.15–1.90), whereas those with PsA had the highest adjusted OR for cost-reducing strategies (adjusted OR 1.65, 95% CI 1.32–2.06).

Figure 3 displays associations between cost-related medication behaviors and prescription rates for DMARDs and glucocorticoids and health care use among patients with SARDs. The odds of receiving DMARDs were similar or slightly lower among patients with SARDs who reported each of the cost-related medication behaviors compared to those who did not. However, the odds of receiving glucocorticoids were significantly higher among patients reporting each of the cost-related medication behaviors than those who denied these. After adjusting for the number of medications, age, gender, race and ethnicity, CCI score, and type of SARD, compared with reporting affordability of prescription medicines, unaffordability was significantly associated with 0.83 times decreased odds of a DMARD prescription (95% CI 0.70–0.99) but marginally associated with 1.18 times increased odds of a glucocorticoid prescription (95% CI 0.99–1.42). In terms of health care use, annual outpatient visits were not significantly different between patients reporting or not reporting each type of cost-related medication behavior. However, after adjustment, compared with reporting affordability of prescription medicines, patients reporting medication unaffordability were more likely to have 1.27 times increased odds of having one to two

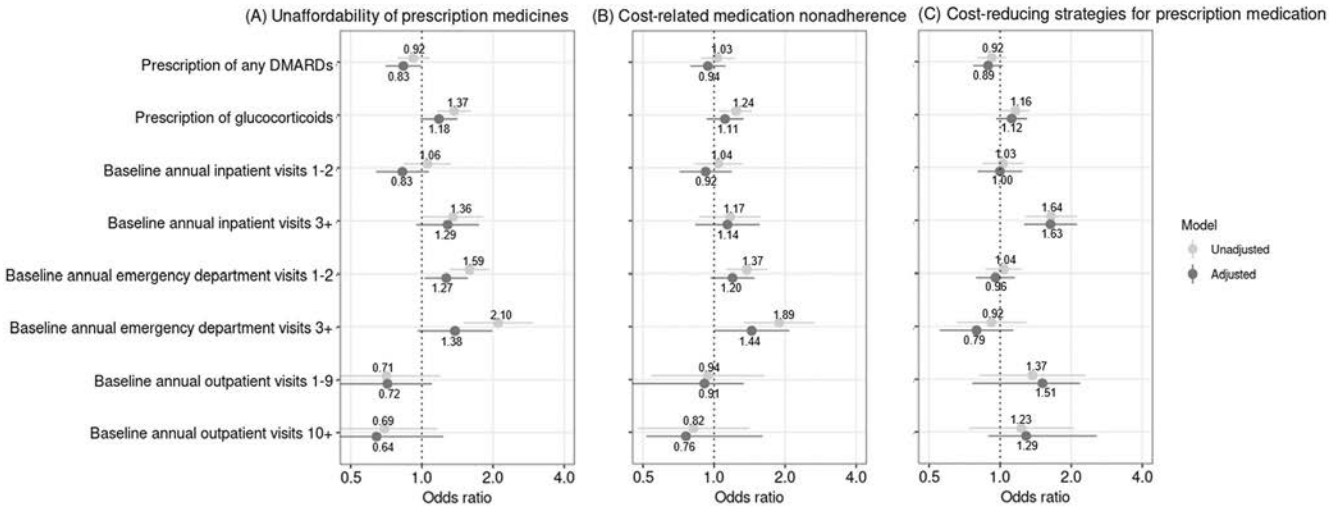

Figure 3. Associations between cost-related medication behaviors and baseline medication prescriptions and health care use in patients with systemic autoimmune rheumatic diseases in *All of Us* (data release version 7). For prescription of DMARDs (any vs none) and prescription of glucocorticoids (any vs none), unadjusted and adjusted logistic regression analyses were performed compared to the group of patients who did not receive any medications. For baseline annual inpatient visit (0 [referent], 1–2, and ≥3), emergency department visit (0 [referent], 1–2, and ≥3), and outpatient visit (0 [referent], 1–9, and ≥10), unadjusted and adjusted multinomial logistic regression analyses were performed. Adjusting factors included the number of medications, age group, gender, race and ethnicity, insurance type, Charlson's Comorbidity Index score, and types of systemic autoimmune rheumatic diseases. DMARD, disease-modifying antirheumatic drug.

emergency department visits per year (95% CI 1.03–1.57) and 1.38 times increased odds of three or more emergency department visits per year (95% CI 0.96–1.99). Experiencing cost-related medication nonadherence was marginally significantly associated with 1.44 times increased odds of having three or more emergency department visits per year (95% CI 0.99–2.08), whereas experiencing cost-reducing strategies was significantly associated with 1.63 times increased odds of having three or more inpatient visits per year (95% CI 1.26–2.11).

DISCUSSION

In this large, diverse cross-sectional study, the prevalence of cost-related medication behaviors among patients with SARDs self-reported on three survey domains, unaffordability of prescription medicines, cost-related medication adherence, and cost-reducing strategies, was higher than among those without SARDs. This large nationwide study reveals that approximately one in five patients with SARDs reported unaffordability of medication and cost-related medication nonadherence. This overall percentage of 18.1% of patients with SARDs reporting cost-related medication nonadherence, higher than among those without SARDs (13.1%) exceeds that previously reported in other disease populations such as hypertension (approximately 10.7%–12.7%), cardiovascular disease (approximately 12.6%–15.1%), and diabetes (approximately 15.9%–16.5%).[30–33]

Our study aligns with previous findings. According to Harrold et al[18] and Minhas et al,[20] the prevalence of cost-related medication nonadherence among patients with RA and SLE was 18.4% and 21.7%, respectively, compared to 16.3% and 22.2%, as reported in the current study. Specifically, in a past study by Minhas et al,[20] 13.4% of patients with SLE skipped medication doses to save money, 15.2% received less medication than prescribed to save money, and 16.2% delayed filling a prescription to save money. Similarly, in our study, we found that 13.0% of patients with SLE skipped medication doses to save money, 12.0% received less medication than prescribed to save money, and 16.7% delayed filling a prescription to save money.

The high prevalence of cost-related medication problems experienced by this population may be explained by both costly medications and the demographics of the populations with SARDs. Several past studies have found a large economic burden of medications in patients with SARDs. A recent systematic review of the economic burden of having RA found that the main component of the direct cost to patients with RA was that of their medications, which accounted for up to 87.2% of direct costs.[34] According to Clarke et al,[35] outpatient pharmacy cost was the third largest driver of high health care costs among patients with SLE. Similarly, Walsh et al[36] showed that patients with ankylosing spondylitis spent 8.1 times more on total outpatient pharmacy costs than the matched controls.

Among different types of SARDs, having PsA had the highest adjusted ORs for self-reported cost-related medication problems, particularly for unaffordability of medication and use of cost-reducing strategies, such as requesting a lower-cost medication or switching medications. This may point to the high costs of biologic DMARDs for patients with PsA, including newer biologics such as those targeting interleukin-17 and interleukin-12 and

-23, the median point-of-sale price per fill of which was up to $23,417 in the United States in 2020.[37,38] In our study, approximately half of patients with PsA (45.4%) were receiving a prescription of a biologic DMARD, the highest proportion of those with SARDs. According to a past study investigating Medicare plan coverage for PsA therapies, coverage for biologic DMARDs varied by drug, ranging from 10.0% to 99.8%, and only 2.4% to 5.5% of plans provided copay assistance plans for their medications.[38] Low coverage and use of copay assistance programs from pharmaceutical companies for some of these drugs may explain the high odds of reporting unaffordability and use of cost-reducing strategies but nonsignificantly elevated odds of medication nonadherence among patients with PsA.

We found the largest effect of adjustment for sociodemographic differences among those patients with SLE, who reported the most medication nonadherence and unaffordability of prescription medication. However, after sequentially adjusting for the number of medications, demographic factors, socioeconomic factors, and CCI score, the ORs for cost-related medication nonadherence decreased by 22.7% and for unaffordability of medications decreased by 32.3%. The younger, more non-White, and less insured populations most affected by SLE may thus explain the high prevalence of medication unaffordability and nonadherence among these patients, a very important consideration in their clinical care.[39,40]

Cost-related medication behaviors can affect patient outcomes. Recently, two studies have demonstrated significant associations between cost-related medication nonadherence and patient-reported outcomes among patients with SLE.[41,42] Patients with cost-related medication nonadherence or using cost-reducing strategies had worse patient-reported outcomes, not only for SLE disease activity and damage but also for depressive symptoms and health-related quality of life. Further studies are needed to determine how cost-related medication nonadherence influences clinical outcomes for those with other SARD diagnoses and to develop strategies to mitigate cost-related nonadherence for patients with SARDs.

Importantly, our cross-sectional analysis found that patients with SARDs who reported unaffordability of their medications were 16.5% less likely to be prescribed DMARDs and 18.1% more likely to receive glucocorticoids. Although DMARDs are standard treatment of SARDs, prescription drug unaffordability appears to be a barrier to receiving DMARDs. Glucocorticoids rapidly alleviate symptoms, but receiving them should be as limited as much as possible due to their many negative effects on patient outcomes, including increased risks of cardiovascular disease, infections, and osteoporosis.[43,44] However, because glucocorticoids are relatively inexpensive and readily accessible treatments, they appear to be overreceived for those patients with medication cost barriers. In addition, we observed that patients with SARDs who experienced unaffordability of their medications had similar outpatient visits but more frequent inpatient emergency department visits than those who did not. This finding is in line with previous studies that have observed that problems in medication adherence may increase acute health care use in those with chronic diseases, including SLE.[13,45–47] Our cross-sectional finding should be pursued in a longitudinal cohort study.

We acknowledge several limitations of this study. First, participants who did not answer the Health Care Access and Utilization survey with questions on cost-related medication behaviors were excluded in the study, which may affect the results. The "AoURP" has aimed to include underrepresented people in biomedical research, with 45% racial and ethnic minorities in the version 7 release studied here. However, 56.6% of enrolled participants did not answer the Health Care Access and Utilization survey on cost-related medication behaviors and thus were not included in our study. In the current study, 71.3% of participants were non-Hispanic White Americans, and those who were older, non-Hispanic White, female, and who had higher education levels were overrepresented with higher survey response rates. This trend may have led to underrepresentation of other sociodemographic groups and influenced results. It is likely in this case that our results are really an underestimate of medication cost-related nonadherence among patients with SARDs. Second, cost-related nonadherence rates among patients with SARDs may in fact be underestimated due to low response rates and uneven distribution of respondents and nonrespondents and the possibility of social desirability bias on self-reported questionnaires.[48] Third, because we identified patients by diagnosis codes, there may be misclassification errors, although these diagnostic algorithms have been developed and validated and are widely used in EHR datasets.[23,24] Similarly, drug prescriptions may be underestimated due to possible incomplete EHR records. Fourth, patients with and without SARDs were not matched but were adjusted for possible confounders in the analysis instead because we were specifically interested in how they affected cost-related nonadherence behaviors. There may be possibilities that more comorbidities in patients with SARDs could affect their cost-related behaviors. Further studies that match comorbid conditions are needed to validate our findings in more balanced cohorts. Last, we did not measure actual pill counts for adherence to antirheumatic medications or perform cost analyses. Due to the cross-sectional nature of the study, we could not determine causality. Despite these limitations, to our knowledge, this is the first large US survey study to investigate the prevalence of self-reported cost-related medication behaviors among patients with different types of SARDs and compared to patients followed for other diverse clinical indications. This study includes a nationally representative and diverse patient population with a large sample size, making the findings generalizable.

In summary, patients with SARDs reported 1.56 times increased odds of unaffordability of prescription medicines, 1.43 times increased odds of cost-related medication nonadherence, and 1.23 times increased odds of cost-reducing strategies than

did patients without SARDs. Among those with SARDs, we observed variation in these measures, with the highest prevalence of nonadherence among those with SLE and the highest prevalence of using cost-reducing strategies among those with PsA. Ongoing research is investigating how cost-related medication behaviors influence medication adherence and clinical outcomes for patients with SARDs. Clinicians and other stakeholders should take the financial burden of medications faced by patients with SARDs into account to enhance medication adherence and clinical outcomes.

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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 Yee 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.

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