# 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 guide-lines, health care economics, health care policy, educational, social, and public health issues, and future trends in rheumatology practice.

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# Arthritis Care & Research

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**Cover image:** The image on the cover (from McBride et al, page 6) shows hematoxylin and eosin staining of the aortic wall with prominent cystic medial necrosis (left) and elastin staining of the aortic wall highlighting loss of elastic fibers with the areas of cystic medial necrosis (right).

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American College of Rheumatology
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**EDITORIAL**

# Reexamining Remission Definitions in Rheumatoid Arthritis: Considering the Twenty-Eight–Joint Disease Activity Score, C-Reactive Protein Level, and Patient Global Assessment

David T. Felson,[1] Diane Lacaille,[2] Michael P. LaValley,[3] and Daniel Aletaha[4]

***Editors' Note:*** *The Editors of the 5 journals of the American College of Rheumatology and European Alliance of Associations for Rheumatology have been reminded by this editorial that ACR and EULAR have jointly agreed on various classification criteria, definitions, recommendations, or points to consider, which do not always find reflection in manuscripts submitted to the journals. Consequently, in the future, the Editors will enforce the use of the products obtained in the course of joint ACR/EULAR or EULAR/ACR activities in all respective papers. For rheumatoid arthritis this would mean use of the ACR/EULAR or EULAR/ACR classification criteria, remission definitions, recommendations on what to report in clinical trials, and others, as pertinent. The same applies to other diseases. There are valid and important reasons that these activities have been undertaken by ACR and EULAR, and therefore, the conclusions of the various task forces, which have been endorsed by ACR and EULAR, should be respected by investigators and study administrators. This does not mean other methods could not be used in a study, but at the least, the reports should address the methods agreed upon by the 2 organizations. Maintaining uniformity across major publications regarding rheumatoid arthritis remission or other definitions not only allows for more appropriate comparison across analyses, but also enhances readers' ability to interpret results. Author instructions across the 5 journals will more strongly reflect this requirement*.

Over the last 30 years, treatment for rheumatoid arthritis (RA) has improved dramatically. By the early 2000s, disease remission had become a realistic goal, although definitions of remission varied widely, making it difficult to compare treatment strategies and gauge how often remission occurred. In 2009, the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) created a joint committee whose charge was to recommend a definition of remission. Members of the committee suggested a large number of candidate definitions and, using a data-driven consensus process, statisticians and programmers tested these candidates in a bank of RA trial data to see which definitions performed best in predicting long-term good function and lack of radiographic progression. The committee endorsed a stringent definition using measures from the validated core set of outcome measures.

After reviewing analysis results, the committee selected 2 definitions of remission that were approved by the ACR and EULAR (1,2). The first was a Boolean version in which, to be classified as having attained remission, a patient had to have tender and swollen joint counts of ≤1, a C-reactive protein (CRP) level of ≤1 mg/dl, and a patient global assessment of arthritis activity of ≤1 (on a 0–10 scale). The second recommended definition was a score of ≤3 on the Simplified Disease Activity Index (SDAI) (3), a scoring system that is based on the same core set outcome measures. While designed and validated in trials, these definitions could help assess treatment "success" in clinical practice as well as in trials

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and, in practice, could serve as a "treat-to-target" goal for some patients.

Like all developed criteria, the ACR/EULAR 2011 RA remission criteria were labeled as provisionally approved and awaited validation in an independent sample for final approval. A revised validated version of the remission criteria is pending full approval by ACR/EULAR. Many concerns have arisen since the publication of the provisional remission criteria. Among them is the continuing use in trials of 28-joint Disease Activity Score (DAS28) thresholds (4) to define remission, questions about the use of CRP as an element of remission definitions, and questions about the appropriateness of including patient global assessment in defining RA remission. This editorial will address each of these issues.

## Using the DAS28: when "remission" is often not remission

The DAS28 is a widely used measure of disease activity. An ACR committee that critically evaluated RA disease activity measures for use in clinical settings found that the DAS28 met predefined criteria, including providing a score that stratified patients into at least 3 disease activity states, being measurable in the clinical setting, and having adequate psychometric properties. The DAS28 was one of 4 recommended RA disease activity measures (5).

The committee on RA remission considered several DAS28 thresholds as candidate definitions of remission, including the popular threshold of a DAS28 using the CRP level (DAS28-CRP) of <2.6 and an even lower threshold of <2.0. The DAS28 formula weights swollen joint count half as much as tender joint count and also underweights it relative to CRP (or erythrocyte sedimentation rate [ESR]). Therefore, a patient can achieve a low DAS28 score but still have a substantial number of swollen joints. The committee's analyses showed that 10% of patients with a DAS28 of <2.6 had ≥4 swollen joints, and 1 patient had >20 swollen joints. When a lower DAS28 threshold of <2.0 was used, swollen joint counts of 2 or 3 were common and scores of up to 6 possible. In fact, if the tender joint count is 0, values for the other components of the DAS28 become irrelevant (Figure 1). Values of up to 60 (of 100) for patient global assessment are consistent with remission according to the DAS28. Even if the tender joint count is 1, the DAS28 score can be in the remission range when other core set measures show active disease. DAS28-CRP thresholds differ substantially from those obtained with the DAS28 using the ESR (DAS28-ESR) (6), and with the DAS28-ESR, RA would be even more likely to be classified as being in remission when disease is in fact active.

One other major criterion was that patients whose disease was in remission at 6 months or 12 months in a 2-year trial should be likely to have both good and stable functional and radiographic outcomes later in the same trial. Patients in whom DAS28

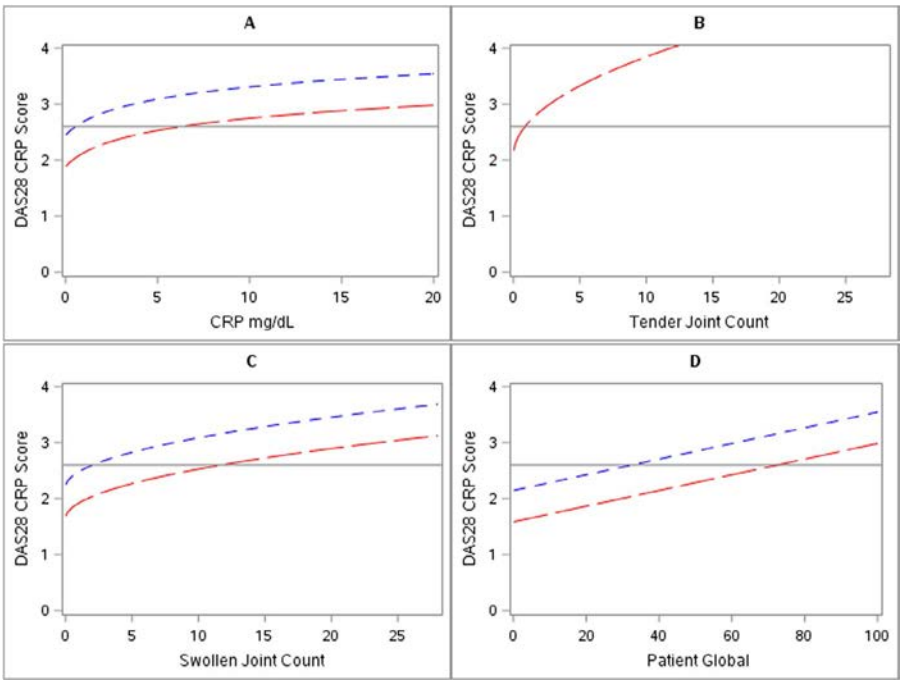


**Figure 1.** The contribution of each component of the 28-joint Disease Activity Score using the C-reactive protein level (DAS28-CRP) to remission (score <2.6 [solid horizontal line]) when other components are in the range of remission. The DAS28-CRP is composed of 4 components: CRP level (**A**), tender joint count (TJC) (**B**), swollen joint count (SJC) (**C**), and patient global assessment of arthritis activity (**D**). In each graph, it is assumed that the 3 components other than the one depicted met the threshold for remission (CRP 0.5, TJC 0 [red dashed lines] or 1 [blue dashed lines], SJC 0, patient global assessment 1). Note that when the TJC is 0, most values of CRP and patient global assessment yield a DAS28 of <2.6 ("remission"), and SJC values of <10 yield DAS28 "remission."

remission was achieved had worse radiographic outcomes than those achieving remission according to other definitions (no change in the Sharp score [7] or the Sharp/van der Heijde score [8]). Ultimately, the committee rejected DAS28 candidates as definitions of remission because swollen joint counts were too high to be consistent with clinical remission and because DAS28 "remission," even with the use of stricter thresholds, did not predict good combined functional and radiographic outcomes as well as the predictive ability that was observed using the remission definitions selected by the committee.

Other studies carried out since the publication of ACR/EULAR remission criteria provided additional evidence that the DAS28 should not be used to define remission. Saleem and colleagues (9) demonstrated that among patients whose RA was in remission according to the DAS28, power Doppler ultrasound showed considerable disease activity unless disease was also in remission according to the SDAI. Lee et al (10) reported that joint pain was present and persisted in patients whose disease was in remission according to the DAS28 but was absent if remission was classified according to the Boolean definition. Analyses from the AGREE trial of abatacept versus placebo (11) confirmed that patients in whom remission was achieved according to the DAS28 subsequently had worse mean scores on the Health Assessment Questionnaire (HAQ) (12) than those in whom remission was attained according to the SDAI. Schoels and colleagues reported, from an analysis of 3 large multicenter RA trials, that among patients with a DAS28 of <1.9, those whose disease was not in remission according to the ACR/EULAR criteria still had an average of 2–3 swollen joints (13).

Given the problems with use of the DAS28 to define remission, why is it so widely used? First, the DAS28 is a commonly used disease activity measure and it is easy to apply a threshold in data already being acquired, although the requisite elements of the ACR/EULAR definitions of remission are also acquired. Another potential reason relates to industry-sponsored RA trials. A definition based on a DAS28 of <2.6 yields remission rates far higher than definitions endorsed by the ACR/EULAR, and treatments therefore appear more efficacious with use of the DAS28. Further, use of a definition that yields a higher remission rate improves statistical power. The same absolute difference in remission rates between 2 drugs is more likely to reach statistical significance when remission rates are higher. Finally, DAS28 use is mandated by some regulatory agencies. Many reports do not even include data on other measures of remission.

## When remission definitions favor some treatments over others

Reliance on the CRP level to define RA remission is an emerging concern (14). CRP is the second most heavily weighted variable in the DAS28 formula. The armamentarium for treatment of RA includes effective biologic agents that have different effects on CRP; interleukin-6 and JAK inhibitors both directly reduce CRP, whereas abatacept and rituximab do not. If the DAS28-CRP is used in a trial comparing the efficacy of abatacept and JAK inhibitors, even if effects on joint counts and patient-reported outcomes are the same, JAK inhibitors would score better, as seen in one recent trial (15). In another trial comparing biologic agents, the authors acknowledged avoiding use of the DAS28-CRP because of this bias (16). The ACR/EULAR provisional criteria allow for remission definitions that exclude acute-phase reactants, using a 3-variable version of the Boolean definition and the Clinical Disease Activity Index (17) instead of the SDAI. Further, while the full ACR/EULAR remission definitions include acute-phase reactants, they are not weighted as heavily as in the DAS28-CRP (or the DAS28-ESR).

## Concerns about inclusion of the patient global assessment

Yet another concern about the provisional definitions of remission has been championed by Ferreira et al (18). They point out that a patient's global assessment of their arthritis activity often is based on considerations unrelated to current disease activity, such as pain from joint damage, and that this measure should not be included in definitions of remission. The factors that most influence the patient global activity measure are pain and fatigue. Ferreira and colleagues' analyses suggest that removing the patient global assessment would not compromise the ability to predict later radiographic outcomes in RA, although they acknowledge that patient

**Table 1.** Proportion of patients with good outcomes (both radiographic and functional) in 3 multicenter rheumatoid arthritis trials*

| | Candidate remission definition | |
|---|---|---|
| Patients with good outcomes† | TJC, SJC, and CRP level all ≤1 | TJC, SJC, CRP level, and patient global assessment all ≤1 |
| In remission, % | 46 | 66 |
| Not in remission, % | 17 | 17 |
| Positive likelihood ratio (95% CI) | 3.1 (1.9–5.3) | 7.2 (3.5–14.8) |

* Excluding patient global assessment compromises the ability to predict good outcomes (from ref. 1). TJC = tender joint count; SJC = swollen joint count; CRP = C-reactive protein; 95% CI = 95% confidence interval.
† Based on remission status at 6 months after baseline. Good radiographic outcome was defined as a change of 0 in the Sharp/van der Heijde score between 12 months and 24 months after baseline. Good functional outcome was defined as a change of 0 in the Health Assessment Questionnaire between 12 months and 24 months after baseline and a score of ≤0.5 at both the 12-month and 24-month time points.

global assessment is a powerful predictor of function (as measured by the HAQ). High patient global assessment scores not only correlate with poor concurrent physical function, but they identify patients whose physical function is worsening (19,20). If patient global assessment is removed, remission criteria no longer predict future patient function well.

In addition to its being the only patient-reported outcome measure included in remission definitions and the importance of including the patient perspective, there are other critical reasons to include patient global assessment as a component of remission. First, the patient global assessment reflects components of disease activity that are otherwise not captured, including fatigue and pain, as well as inflammation in joints not included in a 28-joint count, such as the feet and ankles. This may be why high patient global assessment scores, even when 28-joint counts are low, identify patients at high risk of later functional loss. Second, the patient global assessment is among the most sensitive, if not the most sensitive, outcome measure in RA (20). It improves much more with active RA treatment than with placebo, suggesting that it provides a window into disease activity related to systemic inflammation not detected by tender and swollen joint counts. Therefore, eliminating patient global assessments from RA trial outcomes would compromise the ability to distinguish the comparative efficacy of different treatments. This would occur at a time when, given the large armamentarium of treatments available, there is a particular need to maximize the ability to differentiate their efficacy. In addition, inclusion of patient global assessment markedly increases the likelihood that patients in whom remission is attained will have both good radiographic outcomes and good functional outcomes later (Table 1), and it ensures that the definition of remission captures nonradiographic outcomes that are important to patients.

## Conclusions

With remission achievable in RA, making the definition of remission stringent will ensure that patients benefit from comprehensive control of their disease. The DAS28 should not be used to define remission because, even with the use of low thresholds, many patients whose disease is in "remission" will still have a number of swollen joints and active disease. Also, given its dependence on the CRP value, use of the DAS28 makes it difficult to differentiate efficacious treatments with dissimilar effects on acute-phase reactant levels. Defining remission without asking patients to provide any information about their disease activity—not to mention failing to collect data on any patient-reported outcomes—risks losing valuable information on treatment efficacy.

### AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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CLINICOPATHOLOGIC CONFERENCE

# All in the Family: A Curious Case of Aortopathy

Erica McBride, Evan Stern, and Saira Bilal

## CASE PRESENTATION

### Chief symptoms

A 28-year-old African American man presented at an outside hospital with new-onset pain and swelling of the right leg.

### History of present illness

The patient had a history of intermittent headaches and presented at a hospital outside of our institution with a few days history of severe pain and swelling of the right leg and dyspnea. A venous ultrasound of the right leg revealed a large occlusive deep vein thrombosis (DVT) extending from the right common femoral vein to the right popliteal vein. A computed tomography (CT) angiogram of the chest revealed a mid ascending thoracic aortic aneurysm measuring 5.9 cm, a pulmonary artery dilatation measuring 3.2 cm, and no evidence of pulmonary embolus. The patient was started on a regimen of anticoagulation with intravenous heparin and was transferred to our institution for surgical management of the aortic aneurysm and evaluation for large vessel vasculitis.

### Past medical, social, and family history

The patient had a history of patent ductus arteriosus, which was surgically corrected as an infant, and a presumed diagnosis of gout. He also noted "poor vision" that required glasses but had not been followed closely by an ophthalmologist. He was a daily tobacco smoker, with less than one pack of cigarettes consumed daily, and occasionally smoked marijuana. He was sexually active with one partner. His family history was notable for early onset coronary artery disease in his father, who experienced his first myocardial infarction (MI) in his fifth decade of life.

### Review of systems

The patient noted blurry vision, intermittent headaches that resolved with acetaminophen, dyspnea on exertion, and pain and swelling of his right leg. The review of systems was otherwise negative.

### Physical examination

On physical examination, the patient's blood pressure reading was 100/51 mm Hg, with a heart rate of 89 beats per minute, respiration rate of 16/minute, temperature of 37°C, and oxygen saturation of 99% on room air. He had a body mass index of 32.6 kg/m$^2$. The patient was in no acute distress and was alert and oriented to person, place, and time with good insight into his medical issues. He was also noted to have a tall stature. His pupils were equal in size, fixed and dilated, nonreactive to light, and sclerae were anicteric. Lungs were clear to auscultation without presence of wheezing, rhonchi, or rales. Cardiovascular examination showed normal findings for S1 and S2, and no murmurs, rubs, or gallops were observed on examination. On examination of the skin, there was no evidence of palpable purpura, malar rash, livedo reticularis, erythema nodosum, translucent skin, or abnormal skin turgor. The patient had no abnormal scars, ulcers, or keloids. Abdominal examination was unremarkable. There was notable nonpitting edema of the right leg, extending up to the thigh. Dorsalis pedis and radial pulses were 2+ bilaterally. Full range of motion in all joints on musculoskeletal examination without evidence of synovitis was observed. On neurologic examination, cranial nerves 3–12 were noted to be intact, and the patient was able to move all his limbs with equal ability. There was no evidence of dysmetria of the upper and lower limbs. He was observed to have 5/5 strength with shoulder abduction, elbow flexion, elbow extension, and hand grip bilaterally. He had 4/5 strength with hip flexion in the right leg limited by pain. He had 5/5 strength with hip flexion in the left leg.

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**Laboratory investigations and imaging.** Complete blood cell count was consistent with mild leukocytosis of $12.5 \times 10^3$ µl. The patient had an erythrocyte sedimentation rate (ESR) of 0 mm/hour and a C-reactive protein (CRP) level of 37.1 mg/liter (Table 1). A fourth-generation HIV immunoassay was negative. Testing for rapid plasma reagin (RPR), hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody was nonreactive. Results for tuberculosis by QuantiFeron–TB Gold (QFT) testing, antinuclear antibodies (ANAs) by indirect fluorescence assay, anti–double-stranded DNA (anti-dsDNA), rheumatoid factor (RF), cyclic citrullinated peptide (CCP), myeloperoxidase (MPO), proteinase 3 (PR3), and human leukocyte antigens HLA–B27 and HLA–B51 were negative. Angiotensin-converting enzyme (ACE) and complements C3 and C4 were within normal limits. Hypercoagulable evaluation was unremarkable (Table 1).

A transthoracic echocardiogram revealed severe aortic insufficiency with an estimated ejection fraction of 35% with severe aortic root dilatation measuring 5.6 cm and mild mitral regurgitation; the tricuspid aortic valve and pulmonary artery appeared normal. Right ventricular systolic pressure was 24.65 mm Hg. Computerized angiography of the chest, abdomen, and pelvis revealed normal coronaries, no evidence of atherosclerosis, an ascending aortic aneurysm with a maximal diameter of 7.0 cm, and an aortic root enlargement measuring up to 4.7 cm in diameter (Figure 1). The pulmonary artery appeared normal. No other vascular abnormality was noted.

Positron emission tomography (PET) of the full body revealed increased radiotracer uptake of the right leg vasculature and of a small area of the ascending aorta (Figure 2). Magnetic resonance angiography (MRA) of the brain revealed fusiform dilatation of the bilateral cavernous portion of the internal carotid artery and corkscrew appearance of the bilateral M1 segments of the middle cerebral artery (Figure 3). Magnetic resonance imaging (MRI) of the brain with and without contrast and with diffusion-weighted imaging (DWI) revealed an acute lacunar infarct in the right corona radiata; T2/fluid-attenuated inversion recovery sequences revealed signal hyperintensity in the subcortical greater than periventricular white matter. Extensive dural calcifications were also noted as atypical for the patient's age (Figure 4).

**Table 1.** Laboratory results*

| Test | Value (normal value) |
|---|---|
| Initial laboratory evaluation | |
| Serum white blood cell count, µl | 12.5 (4.8–10.8 × $10^3$) |
| Hemoglobin, gm/dl | 14.6 (14.0–18.0) |
| Hematocrit, % | 44.9 (42–52) |
| Platelet count, µl | 111 (130–400 × $10^3$) |
| Erythrocyte sedimentation rate, mm/hour | 0 (0–15) |
| C-reactive protein, mg/dl | 37.1 (0–9.0) |
| Serum creatinine, mg/dl | 0.9 (0.8–1.5) |
| Serum total protein, gm/dl | 6.9 (6–8.0) |
| Serum albumin, gm/dl | 3.7 (3.5–5.0) |
| Total bilirubin, mg/dl | 3.6 (0.2–1.3) |
| Aspartate transaminase, units/liter | 26 (10–45) |
| Alanine transaminase, units/liter | 25 (20–70) |
| Hematology, rheumatology, and infectious laboratory evaluation | |
| Anticardiolipin IgA/IgM/IgG | All <10 (<10) |
| $\beta_2$–glycoprotein inhibitor IgA/IgM/IgG | All <10 (<10) |
| dRVVT screen, seconds | 37.8 (<47) |
| Antiprothrombin antibody IgG | Negative |
| Factor V Leiden mutation | Negative |
| *MTHFR* gene mutation | Negative |
| Protein C functional, % | 116 (60–160) |
| *PAI-1* gene mutation | 5G/5G (normal) |
| Rapid plasma reagin | Nonreactive |
| Hepatitis C antibody | Negative |
| Hepatitis B surface antigen | Negative |
| Hepatitis B core antibody | Negative |
| QuantiFeron-Gold | Negative |
| ANA by immunofluorescence assay | Negative |
| Anti-dsDNA, IU/ml | 2 (0–9) |
| RA latex turbid, IU/ml | 10.5 (0–13.9) |
| Anti-CCP, units | 3 (0–19) |
| Anti-MPO, units/ml | <9.0 (<9) |
| Anti-PR3, units/ml | <3.5 (<3.5) |
| Complement 3, mg/dl | 119 (80–200) |
| Complement 4, mg/dl | 37 (10–50) |
| HLA–B27 | Negative |
| HLA–B51 | Negative |
| Angiotensin-converting enzyme, units/liter | 22 (14–82) |

* ANA = antinuclear antibody; anti-CCP = anti–cyclic citrullinated peptide; anti-MPO = anti-myeloperoxidase; anti-PR3 = anti–proteinase 3; dRVVT = dilute Russell's viper venom time; dsDNA = double-stranded DNA.

## CASE SUMMARY

A 28-year-old African American man presented with right leg pain and dyspnea and was found to have an unprovoked DVT of the right leg on venous ultrasound in addition to an ascending aortic aneurysm measuring 7.0 cm and a dilated pulmonary artery on CT imaging. His examination was notable for fixed dilated pupils. His laboratory evaluations revealed mild leukocytosis, elevated CRP level, and normal ESR with negative findings for RPR, HIV, QFT testing, hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody. Additionally, results for ANAs by indirect fluorescence assay, anti-dsDNA, RF, CCP, MPO, and PR3 were within normal limits. Testing for both HLA–B27 and HLA–B51 was negative.

With a plan for surgical intervention of the ascending aortic aneurysm, a full body PET scan was performed that revealed increased metabolic activity in the vasculature of the right leg and the anterior wall of the ascending aorta, raising the suspicion for vasculitis. An MRI and MRA of the brain revealed acute lacunar infarcts of the brain parenchyma and dilatation of the internal carotid arteries and a portion of the middle cerebral artery. Prior to aortic aneurysm repair, the patient underwent an interventional radiology–guided thrombectomy and tissue plasminogen activator thrombolysis of the DVT, complicated by a pulmonary embolism requiring anticoagulation. Notably, the PET scan was performed after the thrombectomy was performed. The patient underwent

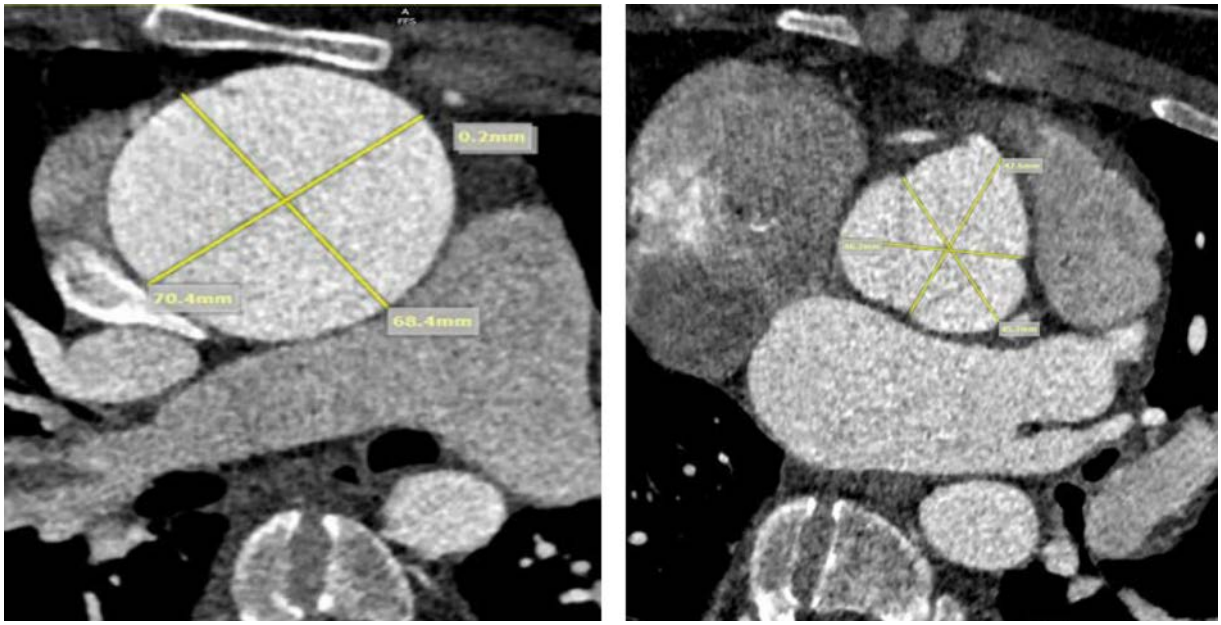


**Figure 1.** Thoracic computed tomography of the ascending aorta (left), with enlargement of the aortic root shown (right).

conventional angiography of the head and neck that confirmed findings on MRA of dilatation of the bilateral internal carotid arteries, and no further interventions were recommended from the neurosurgery service prior to aortic aneurysm and valve repair. Given the high clinical suspicion for vasculitis preoperatively, he was treated with 1 gram of intravenous methylprednisolone daily for 3 days.

## DIFFERENTIAL DIAGNOSIS

**Behçet's disease (BD).** Behçet's disease is a systemic vasculitis that affects both small and large vessels in venous and arterial systems. Men are affected more often than women, and disease typically presents between the third and fourth decade of life (1). BD is most commonly seen in Asia, the eastern

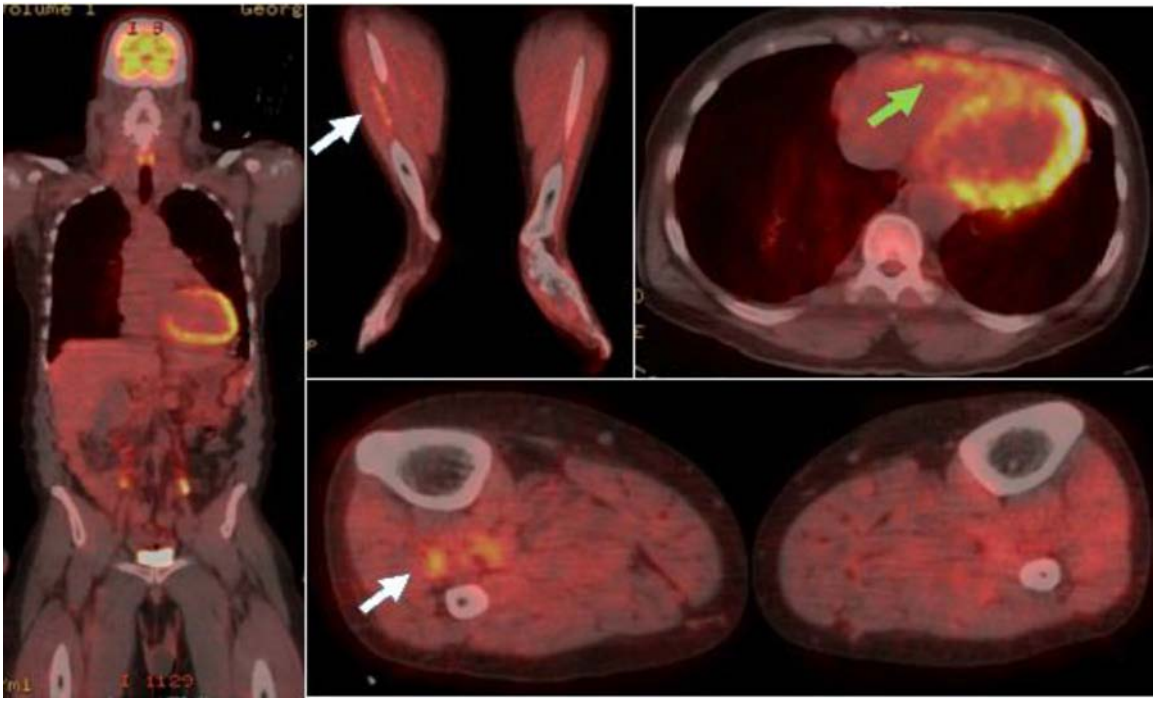

**Figure 2.** Positron emission tomography of the full body (left), lower limbs (middle top), and ascending aorta (top and bottom right), with increased radiotracer uptake of the right leg vasculature (white arrows) and of a small area of the ascending aorta (green arrow) shown.

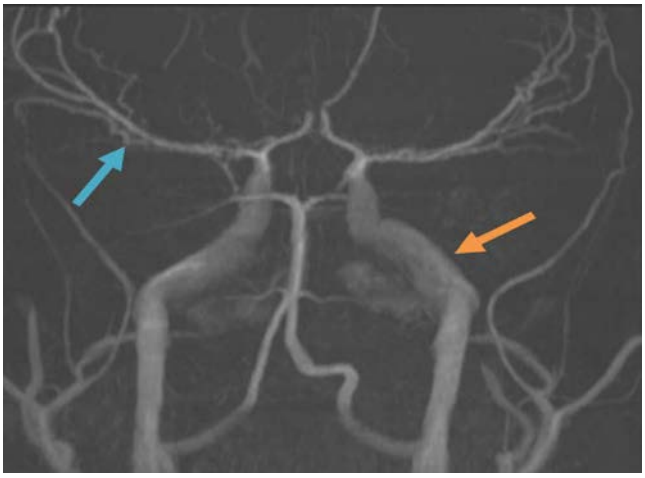

**Figure 3.** Magnetic resonance angiography of the head and neck. Fusiform dilatation of the bilateral cavernous portion (orange arrow) of the internal carotid artery and corkscrew appearance of the bilateral M1 segments of the middle cerebral artery (blue arrow) are shown. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24215/abstract.

Mediterranean, and the Middle East and is traditionally the most prevalent in the geographic areas that once comprised the old Silk Road (between latitudes 30 and 45 degrees north [1]). Unfortunately, the pathogenesis of BD is not well understood but is associated with the HLA–B51 haplotype, with a reported pooled odds ratio of 5.78 for susceptibility based on a meta-analysis of case–control studies (2). Though there are no standardized diagnostic criteria for BD, the International Study Group diagnostic criteria is widely used, though it does not include all the possible manifestations of BD, particularly vascular or gastrointestinal manifestations (3). Patients typically present with recurrent oral ulcers in addition to recurrent genital ulcers, ocular manifestations such as uveitis or retinal vasculitis, skin lesions that include acneiform nodules, erythema nodosum, or papulopustular lesions, and positive results on pathergy testing (1). Often, patients can present with more aggressive disease that includes neurologic manifestations such as brain stem or parenchymal lesions, sinus venous thrombosis, arterial vasculitis, or aseptic meningitis (4). Vascular manifestations of BD may also include pulmonary arterial aneurysms, aortitis, superficial thrombophlebitis, and DVTs in addition to cardiac valve lesions, pericarditis, and myocarditis (4). Hughes-Stovin syndrome, a disease characterized by venous thromboembolism and pulmonary arterial aneurysms, has also been associated with BD (5).

Given the presence of an ascending aortic aneurysm, dilated pulmonary artery, unprovoked DVT, parenchymal brain lesions, dilated internal carotid arteries, and increased uptake on PET scan in our patient, BD was considered high on the differential. However, in the setting of a normal ESR, presence of fixed and dilated pupils, increased PET uptake in the right leg vasculature post-thrombectomy, and lack of characteristic symptoms such as oral ulcers, genital ulcers, fevers, and uveitis, we considered other causes for his symptoms, particularly noninflammatory vasculopathies.

**Large vessel vasculitis.** When encountering a case of thoracic aortic aneurysms in a young individual, vasculitic aortitis is a pathologic mechanism that must be considered. The most common rheumatic causes of aortitis are the large vessel vasculitides, giant cell arteritis (GCA) and Takayasu arteritis (6). Aortitis can also be associated with other systemic rheumatic diseases such as systemic lupus erythematosus, rheumatoid arthritis, BD,

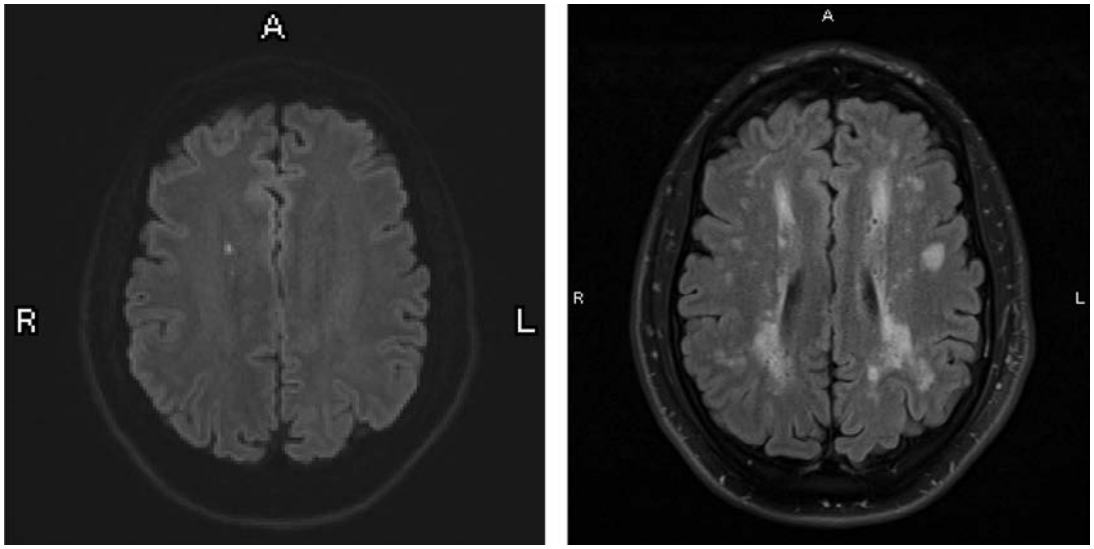


**Figure 4.** Magnetic resonance imaging of the brain transeverse section, with diffusion weighted imaging (left) and T2 flair (right). Imaging revealed an acute lacunar infarct in the right corona radiata, while T2/fluid-attenuated inversion recovery sequences revealed signal hyperintensity in the subcortical greater than periventricular white matter. Extensive dural calcifications were also noted as atypical for the patient's age.

HLA–B27–associated spondyloarthropathies, Cogan's syndrome, sarcoidosis (6), IgG4-mediated disease, and chronic periaortitis.

It is important to recognize IgG4-mediated disease as a cause for aortitis, given the recent recognition and growing body of knowledge of this disease process. IgG4 is a systemic inflammatory disease characterized by elevated serum levels of IgG4 and IgG4-positive lymphoplasmacytic infiltration that cause fibrosclerotic change in affected organs (7). Common presentations involve salivary and parotid gland enlargement, in addition to type 1 autoimmune pancreatitis (8). Inflammatory abdominal aortic aneurysms are one of the most common vascular lesions of IgG4-mediated disease and inflammatory aneurysms, in addition to arteritis, and are also reported in other medium- and large-sized vessels such as the aortic arch, thoracic aorta, coronary artery, and other arteries (7).

Takayasu arteritis is most commonly observed in young women between the ages of 25 and 30 years. GCA is also more commonly seen in women, but with an older median age of 75 years (6). Both GCA and Takayasu arteritis involve infiltration of the arterial wall with an inflammatory population of cells including lymphocytes, macrophages, and multinucleated giant cells with unknown pathogenesis (6). Over time, these patients are at an increased risk of developing aortic aneurysms and subsequent aortic dissections (6). GCA most commonly involves branches of the external carotid arteries, and less commonly the aorta and its branches, including the subclavian and axillary arteries, with increased risk of developing thoracic aortic aneurysms later in life (6). Takayasu arteritis is well known for its predilection for the large vessels, including the aorta, with cases involving both the thoracic and abdominal aorta (6). Takayasu arteritis also commonly affects the aorta branch vessels, including the subclavian, innominate, renal, common carotid, vertebral, and mesenteric arteries, and rarely the pulmonary arteries—though presentation typically shows stenotic lesions versus aneurysmal lesions (6).

Cogan's syndrome is a rare systemic autoimmune-mediated disease with unknown pathophysiology (9). Pathognomonic manifestations include intraocular inflammation (nonsyphilitic interstitial keratitis) and vestibulo-auditory dysfunction (neurosensory deafness, tinnitus, and vertigo) (9). Cases of aortitis with Cogan's syndrome have been reported (10).

Diagnosis of the large vessel vasculitides is facilitated through imaging, most commonly CT/CTA, MR/MRA and fluorodeoxyglucose (FDG)–PET. Classic findings for both Takayasu arteritis and GCA include mural thickening and enhancement with vascular stenosis and surrounding tissue edema (11). The sensitivity and specificity of imaging performed by CT/CTA and MR/MRA for Takayasu arteritis are both 100% when compared to conventional angiography (11). Sensitivity and specificity for FDG-PET in diagnosing Takayasu arteritis is reported as 81% and 74%, respectively, based on meta-analysis data (12). Reported sensitivity and specificity with CT/CTA in diagnosing GCA is 73% and 78%, respectively. With MR/MRA imaging, sensitivity and specificity is 73% and 88%, respectively, when compared to a clinical diagnosis of GCA (11). FDG-PET is reported to have a sensitivity and specificity of 67–77% and 66–100%, respectively, for diagnosing extracranial GCA when compared to temporal artery biopsy (11).

Infectious causes of aortic aneurysms are another important diagnostic consideration, affecting less than 1% of surgically repaired aortic aneurysms (13). Mycotic aneurysms tend to affect men and are more likely to occur in the aorta compared to other arteries (13). Previously, mycotic aneurysms were associated with endocarditis, with cases of β-hemolytic group A *Streptococcus*, *Pneumococcus*, and *Haemophilus influenzae* being more prevalent (13). However, *Salmonella* and *Staphylococcus aureus* are more likely to cause mycotic aneurysms and, in the modern age, are infections associated with intravascular intervention and intravenous drug abuse (13). Though rare, syphilitic aortitis is another consideration given its manifestations, which include aortic wall thickening and aneurysmal dilatation involving the ascending and thoracic aorta (13). Mycobacterial aortitis, though rare in the developed world, can occur from direct seeding of aortic tissue from neighboring infected lymph nodes with mycobacterial organisms (14).

Takayasu arteritis was considered on the differential for this patient with aortic aneurysm who had an increased uptake on FDG-PET; however, the lack of vessel stenosis and wall thickening, as well as a pattern of alternating areas of stenosis with post-stenotic dilatation on imaging, suggested another underlying etiologic cause. GCA was a less likely diagnosis considering the patient's young age and in the absence of temporal headaches and ocular involvement. His absence of peripheral inflammatory arthritis or inflammatory back pain suggests against a HLA–B27–associated disease process. Additionally, the lack of uveitis, lymphadenopathy, or pathognomonic skin lesions such as erythema nodosum or lupus pernio observed in the patient led to sarcoidosis being a less likely cause of his symptoms.

Infection was considered less likely given our patient's lack of fevers, systemic signs of infection, absence of recent endovascular repair or surgical intervention, and negative results on QuantiFeron-TB Gold, RPR, and blood cultures.

**Congenital vascular disease.** Given our patient's young age and extensive vascular involvement, a number of congenital collagen vascular diseases were considered during the diagnostic evaluation. Loeys-Dietz syndrome is an autosomal-dominant connective tissue disease caused by mutations in the *TGFBR1* and *R2* gene families, with these patients developing widespread aortic aneurysms and arterial tortuosity (15) that are not only isolated to the aortic root, but also aortic side branches and cerebral vessels (16). These patients can also develop extravascular manifestations similar to Marfan syndrome, including pectus deformity, scoliosis, and pes planus (15), but differ in the presence of hypertelorism, cleft palate, or abnormal uvula (16). Additionally, they may develop early osteoarthritis, osteochondritis dissecans, and characteristic craniosynostosis (15).

Conversely, Marfan syndrome is an autosomal-dominant condition caused by a mutation in the *FBN1* gene that causes not only thoracic aortic aneurysms and dissection, but characteristic features such as ectopia lentis and marfanoid body habitus due to excessive elongation of the upper and lower limbs (17). The most characteristic aortic aneurysm is a result of aortic root dilatation at the level of the aortic sinuses of Valsalva, which could evolve to aortic dissections and rupture (16). These patients also rarely have arterial aneurysms beyond the aorta, as compared to Loeys-Dietz syndrome (16). Patients with Marfan syndrome also develop skeletal abnormalities such as scoliosis and pectus excavatum.

Ehlers-Danlos syndrome is a heterogenous group of disorders caused by several different mutations in a group of genes coding for fibrillar collagen and collagen proteins classified into 6 subtypes based on clinical features and associated genetic abnormality (18). Common features between subtypes typically include joint hypermobility based on Beighton Score for Joint Hypermobility and skin hyperextensibility (18). The vascular subtype of Ehlers-Danlos syndrome is most closely associated with premature aortic aneurysms and arterial rupture and is caused by mutations in the *COL3A1* gene encoding type III collagen (18). Interestingly, the vascular subtype of this syndrome is characterized by skin manifestations, which includes thin translucent skin with visible veins without hyperextensibility (18). These patients tend to develop arterial rupture in the absence or presence of aneurysms predominantly involving the medium-sized vessels of the abdomen such as the renal, iliac, femoral mesenteric, and hepatic arteries (16). This is in contrast with the hypermobile subtype of Ehlers-Danlos syndrome with an as-of-yet unknown molecular genetic cause (16). These patients must meet the criteria of the hypermobile subtype of Ehlers-Danlos syndrome, which includes widespread joint hypermobility and only mild connective tissue hyperextensibility such as striae or atrophic scarring, with the exclusion of other underlying heritable or acquired connective tissue diseases (16).

It is also important to consider a series of genetic mutations grouped together as familial thoracic aortic aneurysms and dissection (TAAD), which cause issues with the aorta and may or may not cause other systemic signs or symptoms of disease. Mutations in these genes lead to a varying degree of risk for aortic dissections, as well as differing extraaortic mutations (19). Specific mutations of *ACTA2* are estimated to account for 12–21% of nonsyndromic familial TAAD (19).

Fibromuscular dysplasia is another consideration as a vasculitis mimicker and in cases of vascular dissection. Fibromuscular dysplasia is a nonatherosclerotic vascular disease that causes abnormal development of the arterial cell wall (most commonly the vessel media) and less commonly, the vessel intima (20). A genetic cause is attributed to the development of fibromuscular dysplasia; however, the specific genetic mechanism behind this condition has yet to be identified (20). More recent studies suggest a group of genetic factors involved in the pathogenesis of fibromuscular dysplasia, including the genes *PHACTR1* and *EDN1* (21). Fibromuscular dysplasia can present with multifocal involvement, a "string-of-beads" appearance, or a focal area of stenosis; fibromuscular dysplasia typically involves the renal and extracranial carotid arteries (20). However, disease has been identified in many medium-sized vessels of the body including the mesenteric, external iliac, and brachial arteries (20). Arterial aneurysms and dissections and arterial redundancy and tortuosity are manifestations of fibromuscular dysplasia that have been identified (20). Patients with fibromuscular dysplasia tend to be young or middle-aged women (20).

Given our patient's thoracic aortic aneurysm and in addition to dilated internal carotid arteries and middle cerebral artery, presence of fixed and dilated pupils, and absence of an elevated ESR or other pathognomonic signs of systemic inflammatory illness, the team pursued further genetic testing in the patient.

## CLINICAL COURSE

The patient underwent successful surgical aortic aneurysm graft repair and mechanical aortic valve replacement. Aortic tissue surgical pathology was revealing for cystic medial necrosis without evidence of significant vasculitis (Figure 5).

Cystic medial degeneration necrosis is a disorder of the large arteries, particularly the aorta, characterized by an accumulation of basophilic, ground substance in the media with cyst-like lesions (22). Degenerative disruptions of collagen, elastin, and smooth muscle cells in the media may result in weakening of the arterial wall (22). Cystic medial necrosis tends to be associated with a higher risk for various aortic complications, including aortic dissection and dilation (23). Cystic medial necrosis is also considered one of the histologic markers for congenital vascular diseases, including Marfan syndrome, Loeys-Dietz syndrome, and Ehlers-Danlos syndrome (23).

Gene-Seq testing for a cardiofamilial aortopathy profile (Labcorp) for the following genetic mutations was performed: *ACTA2*, *COL3A1*, *FBN1*, *MYLK*, *MYH11*, *SLC2A10*, *SMAD3*, *TGFB2*, *TGFBR1*, *TGFBR2*, and *MED12* (c3020 > G). Genetic testing results came back positive for a heterozygous dominant missense mutation in the *ACTA2* gene (C.535C > T, p. Arg179Cys). Based on pathologic features and genetic testing, a rapid prednisone taper was completed. The patient's postoperative course was complicated by pulmonary hypertension and right-sided heart failure requiring diuresis and ionotropic support. His clinical condition gradually improved, and he was ultimately discharged to an acute rehabilitation center. Our patient was referred to a specialized center for further surveillance of his *ACTA2* mutation and disease manifestations.

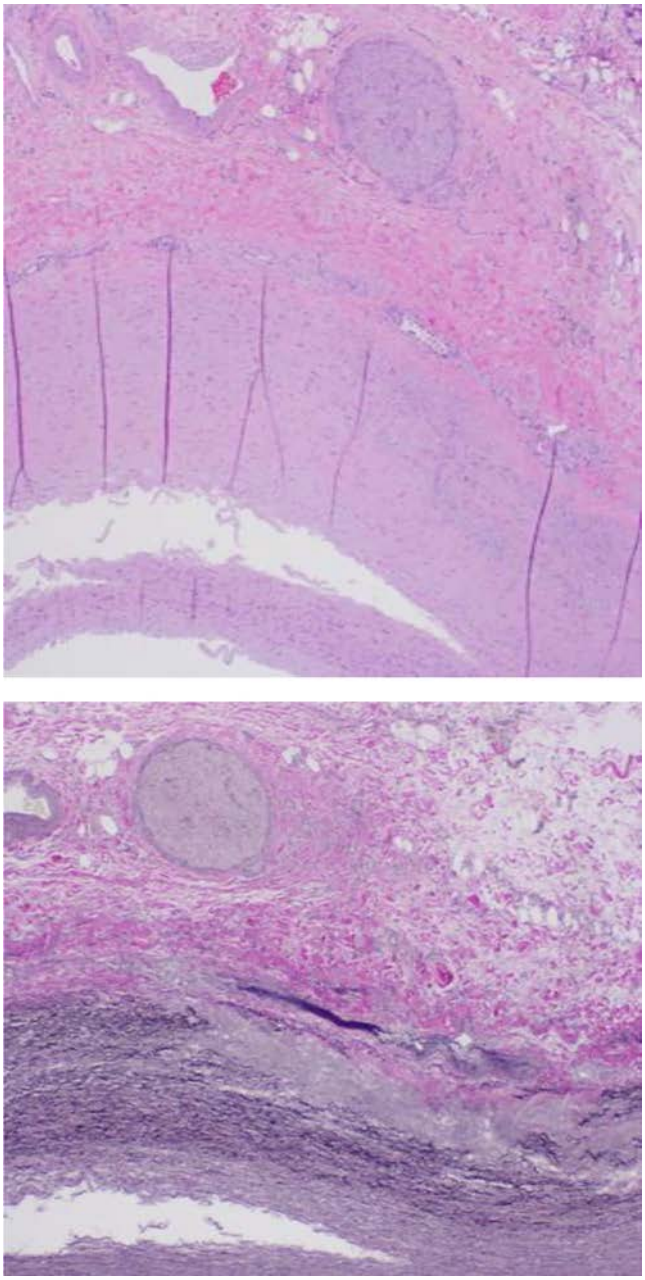

**Figure 5.** Hematoxylin and eosin staining of the aortic wall with prominent cystic medial necrosis (top) and elastin staining of the aortic wall highlighting loss of elastic fibers within the areas of cystic medial necrosis (bottom). Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24215/abstract.

## DISCUSSION

The *ACTA2* gene encodes an α-2 actin protein found in smooth muscle cells and is the most abundant protein in smooth muscle cells that serves not only a contractile function, but also to synthesize extracellular matrix components such as collagen, elastin, and proteoglycans similar to fibroblasts (24). Mutations in this protein cause decreased contractility in response to the stretch resulting from pulsatile blood flow, which is the proposed mechanism for arterial aneurysm development in these patients (25). *ACTA2* heterozygous missense mutations are extremely rare, yet account for the major genetic cause of familial TAAD, affecting 14% of documented families (24). Milewicz and colleagues have previously described 5 cases of de novo *ACTA2 R179H* mutation in a single-family cohort in which all affected members developed ascending aortic aneurysms and patent ductus arteriosus (26). Interestingly, other studies report incomplete penetrance, as low as 50% despite the mutation having a dominant mode of transmission (25,27).

Cerebrovascular disease is also an important manifestation in patients with *ACTA2* mutations that can cause significant morbidity and early mortality. Fusiform dilatation of the internal carotids, as well as stenoses into the M1 segments of the middle cerebral arteries, has been previously described (26). Though initially thought to be similar to Moyamoya disease, the neurologic manifestations of disease associated with *ACTA2* mutation represent a distinct entity (27). Pathologically, patients with *ACTA2* mutation have fibrosis and smooth muscle cells proliferation of the intimal and medial layers on arterial pathology, distinct from Moyamoya disease, as well as an absence of compensatory small vessel collaterals observed in Moyamoya disease (27). Additionally, parenchymal abnormalities, such as T2 hyperintensity on MRI in the periventricular white matter, is another important feature of this disease attributed to progressive ischemic damage (26,27). The ischemic small vessel disease observed in patients with *ACTA2* mutation is attributed to the hyperproliferation of mutant smooth muscle cells in vitro causing occlusive disease compared to the aneurysmal activity in larger vessels (25). This is the same mechanism proposed to explain the early onset coronary artery disease that is also observed in these patients.

The fixed and dilated pupils observed in the patient can be attributed to congenital mydriasis, a rare condition characterized by aplasia of the iris sphincter muscle and hypofunction or hypoplasia of the dilator muscles observed in patients with the *ACTA2* mutation (26). Hypoplasia of smooth muscle cells can also affect the bladder and gastrointestinal tract, manifesting as hypotonic bladder and congenital intestinal malrotation, respectively (26). Venous thromboembolism has been described in pediatric case series of patients with *ACTA2* mutation (28) and may explain the unprovoked venous thromboembolism observed in the patient.

If there is high suspicion for congenital vascular disease in a particular case, then clinicians should consider genetic testing for Loeys-Dietz syndrome, Marfan syndrome, Ehlers-Danlos syndrome, and familial TAAD. Labcorp has an available genetic panel, the Gene-Seq cardiofamilial aortopathy profile, that can be used for initial screening and can identify common genetic causes for congenital vascular disease. Once identified, families of the patient who underwent screening should be counseled on obtaining genetic testing to enhance disease identification and surveillance in the case of vascular malformations.

The patient presented a diagnostic challenge with aortic aneurysms, DVT, dilated pulmonary artery, dilated pupils, cerebral aneurysms, and ischemic white matter changes raising concern for vasculitis. This patient highlights the importance of a broad differential when encountering aortic aneurysms accompanied with other organ manifestations in younger patients, and that congenital vascular disease needs to remain on the differential for variable vessel vasculitis. In particular, differentiating large vessel vasculitides from congenital vascular disease is a necessary skill for the practicing rheumatologist. Knowledge of the findings on imaging of large vessel vasculitis including vascular stenosis, vessel wall thickening, and alternating areas of stenosis with post-stenotic dilatation is imperative when comparing the manifestations of genetic collagen vascular disease such as aneurysms, stenosis, and dissections in the absence of vessel inflammation or imaging enhancement. Knowledge of systemic disease processes can also aide in the diagnostic considerations by allowing the clinician to recognize extravascular manifestations that are unique to the disease in question.

## FINAL DIAGNOSIS

Familial thoracic aortic aneurysm disease caused by a missense *ACTA2* mutation.

### 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 submitted for publication. Dr. McBride 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.** McBride.
**Acquisition of data.** McBride, Stern.
**Analysis and interpretation of data.** Bilal.

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**EDITORIAL**

# Introduction to the Special Theme Section: Rehabilitation Sciences and the Rheumatic Diseases

Kelli D. Allen[1] and Daniel K. White[2]

In this issue of *Arthritis Care & Research* (AC&R), we highlight articles focused on rehabilitation in the context of rheumatic diseases. This topic is of particular interest because of the well-documented impact of rheumatic diseases on pain, physical function, physical activity, disability, and other key outcomes that can be addressed through rehabilitative interventions. Manuscripts covering a broad range of topics were considered for this theme issue, including the effects and consequences of rehabilitation interventions in rheumatic diseases, rehabilitation as linked with symptoms and conditions, and intervention studies addressing improvement in the mechanics of rehabilitation levels, cost-benefit analyses, and outcomes. Chronic disease management and/or public-health strategies in the population that address rheumatic diseases and rehabilitation were also considered. Manuscripts submitted for theme issues of AC&R undergo the same peer-review procedures as other scientific manuscripts in the journal and therefore meet the same rigorous standards as articles in any other issue.

The call for submissions for this theme issue generated 40 submissions. We are pleased to highlight in this issue 10 manuscripts of high relevance to the topic of Rehabilitation Science and the Rheumatic Diseases. Notably, these manuscripts address a range of rheumatic diseases, including rheumatoid arthritis, spondyloarthritis, systemic sclerosis, inflammatory arthritis (as a broad group), and osteoarthritis. This highlights the importance of rehabilitation across the spectrum of rheumatic diseases, as well as the ongoing high-quality, rehabilitation-focused research in each of these disease areas. We would like to highlight some key themes that emerged among the theme issue manuscripts.

First, several manuscripts highlight various barriers that people with rheumatic disease experience in trying to engage in exercise and rehabilitation programs. These include a range of physical symptoms that need to be considered when designing and delivering programs for individuals with rheumatic conditions. However, participants in these studies also described key internal and external facilitators to engaging in exercise and rehabilitation programs. We need to learn more about how to best capitalize on these facilitators in clinical situations, as well as in the research context, when developing new programs.

Second, some studies highlight the expansion of telehealth for delivering rehabilitation and exercise programs for people with rheumatic diseases; growth in this delivery approach was accelerated by COVID-19. The delivery of rehabilitation through telehealth has tremendous capacity for enhancing the reach and access of specialty rehabilitation to those who need it most. However, studies, including those in this theme issue, also highlight that telehealth may not be an optimal substitute for in-person programs in some situations. We still need to gain understanding about how to best utilize telehealth strategies and in what situations they are most appropriate.

Third, significant challenges remain with respect to long-term maintenance of exercise following completion of formal programs; as a result, the benefits that patients experience often attenuate over time. We need better models and strategies for enhancing long-term maintenance to exercise and rehabilitation strategies. This is perhaps one of the most important areas for additional research in the context of rehabilitation in the rheumatic diseases, as the adage of "use it or lose it" rings true for many rehabilitation-based interventions. Finally, studies in this issue highlight a need for more research on rehabilitation interventions for some rheumatic diseases, including psoriatic arthritis, spondyloarthritis, and systemic sclerosis. These studies will help address the urgent need to understand the impacts of different exercise and rehabilitation interventions for these health conditions.

Although challenges and gaps in our knowledge remain, the articles in this theme issue illustrate the wide scope of ongoing

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No potential conflicts of interest relevant to this article were reported.

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research in the area of rehabilitation and the rheumatic diseases. AC&R published a theme issue on exercise in arthritis in 1994, and at that time this body of literature was in very early phases with a limited number of rigorous trials (1). Our knowledge in this area has grown tremendously in the past few decades. The rheumatology community has many clinicians and researchers who are dedicated to improving the lives of patients through rehabilitation, and we look forward to continued advances in this research area.

## AUTHOR CONTRIBUTIONS

Both authors were involved in drafting the article or revising it critically for important intellectual content, and approved the final version to be submitted for publication.

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REHABILITATION SCIENCES AND THE RHEUMATIC DISEASES

# Association of Disease Activity and Disability With Rehabilitation Utilization in African American Adults With Rheumatoid Arthritis

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**Objective.** To examine the association of disease activity and disability with rehabilitation utilization in African American adults with rheumatoid arthritis (RA).

**Methods.** We analyzed cross-sectional baseline data from the Consortium for the Longitudinal Evaluation of African Americans with RA (CLEAR) I and CLEAR II registry. Disease activity was quantified with the Disease Activity Score in 28 joints using the C-reactive protein level. Disability was measured with the Health Assessment Questionnaire. Rehabilitation utilization was determined by self-reported recall of physical therapy or occupational therapy visits in the prior 6 months or ever. We examined the association of disease activity and disability with rehabilitation utilization using separate binary logistic regression models to estimate odds ratios and 95% confidence intervals and adjusted for potential confounders. We repeated the analyses with the sample stratified by disease duration (early RA and established RA).

**Results.** Of 1,067 participants, 14% reported utilizing rehabilitation in the prior 6 months, and 41% reported ever utilizing rehabilitation. Rehabilitation utilization in the prior 6 months was similar among those with early and established RA (12% versus 16%). A greater proportion of those with established RA reported any past rehabilitation utilization (28% versus 50%). Among those with established RA but not early RA, worse disability was associated with rehabilitation utilization in the prior 6 months. Disease activity was not associated with either outcome.

**Conclusion.** Among African American adults with RA, rehabilitation utilization in the 6 months prior to assessment was low and associated with disability but not disease activity. Factors driving rehabilitation utilization are unclear.

## INTRODUCTION

Considerable advances in pharmacologic care for adults with rheumatoid arthritis (RA) over the last 25 years, including emphasis on a treat-to-target approach and the introduction of biologic drugs, have resulted in lower disease activity and less joint destruction (1,2). However, disability has not improved to the same extent (1–3). Functional limitation remains a prevalent consequence of RA (1,3). Rehabilitation, including physical therapy (PT) and occupational therapy (OT), is recommended to address disability and functional limitations in adults with RA (4), yet utilization of rehabilitation for adults with RA in the US is low (5).

The current understanding of why and when rehabilitation is used among patients with RA in the US is limited. Factors associated with OT utilization in the US are unknown, and there is a single study that investigated factors associated with PT utilization (5). Using data from a registry of patients with RA, Iversen et al (5) observed that 15% of adults with RA utilized PT in a 6-month period. Factors associated with utilization of PT were greater disease activity, higher levels of formal education, stronger social networks, and receiving disability pension. While this study provided novel insight into which patients with RA are more likely to receive PT, generalizability was limited, as the sample was predominantly White (98%) and insured (98%), with higher socioeconomic status (67% with income >$50,000; 26% with a graduate degree or some graduate education) (5).

Racial and ethnic disparities exist in rehabilitation utilization for musculoskeletal conditions. African American and Hispanic

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**SIGNIFICANCE & INNOVATIONS**

- This is the first report on rehabilitation utilization among African American adults with rheumatoid arthritis (RA) in the US.
- Rehabilitation utilization was low among African American adults with RA.
- Rehabilitation utilization was associated with disability but not disease activity, particularly in adults with established RA.

adults with a musculoskeletal condition, including arthritis, have lower odds of receiving outpatient rehabilitation services compared to White adults (6). In RA, lower disease activity and disability were associated with less utilization of rehabilitation services in White adults with RA, but it is unclear if associations are similar in African American adults. The purpose of this study was to examine the association of disease activity and disability with rehabilitation utilization in African American adults with RA, adjusting for other potential confounders. We hypothesized that greater disease activity and disability would be associated with rehabilitation utilization. A secondary purpose of the study was to examine if these associations differed among adults with early or established RA.

## MATERIALS AND METHODS

**Design.** We conducted a cross-sectional analysis of data from the Consortium for the Longitudinal Evaluation of African Americans with RA (CLEAR) I and CLEAR II registries. CLEAR I was a longitudinal cohort of African American adults with early RA (disease duration <2 years). Data from the baseline visit of CLEAR I were included in this analysis. CLEAR II was a cross-sectional cohort of African American adults with RA with no restriction on disease duration. Participant data for both CLEAR I and CLEAR II were collected at 1 of 5 southeastern US institutions (University of Alabama at Birmingham; Emory University, Atlanta, Georgia; Medical University of South Carolina, Charleston; University of North Carolina at Chapel Hill; Washington University, Saint Louis, Missouri).

**Sample.** The shared inclusion criteria for the CLEAR I and CLEAR II cohorts were as follows: 1) self-identified as African American; 2) met the American College of Rheumatology 1987 criteria for RA (7); 3) ability and intent to provide informed consent; and 4) no concurrent diagnosis of rheumatic diseases other than osteoarthritis. Additional inclusion criteria for the CLEAR I cohort were RA disease duration <2 years and willingness to regularly participate in follow-up visits at years 3 and 5 of disease duration. CLEAR I recruitment occurred from 2002 to 2005, and CLEAR II recruitment occurred from 2006 to 2011. Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24797/abstract, depicts a flow diagram to describe the analytic sample.

**Measures.** The primary variables of interest were disease activity and disability. Disease activity was defined using the Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP). The DAS28-CRP is a validated measure of RA disease activity and includes 28 tender and swollen joint counts, a patient assessment of disease activity on a visual analog scale, and serum levels of CRP with a range of 0–9.4 (8,9). Disability was assessed using the Health Assessment Questionnaire (HAQ) disability index. The HAQ is a valid, sensitive, and commonly used self-reported measure of physical function in adults with RA (10,11). The HAQ addresses 8 functional domains including dressing, arising, eating, walking, hygiene, reaching, gripping, and usual activities.

Other participant characteristics were collected as potential confounders, including age (years), sex, body mass index (kg/m$^2$;

**Table 1.** Participant characteristics*

| Characteristic | Full sample (n = 1,067) | Early RA (n = 445) | Established RA (n = 622) | *P*† |
|---|---|---|---|---|
| Age, mean ± SD years | 54.2 ± 12.2 | 51.3 ± 13.0 | 56.3 ± 11.2 | <0.001 |
| Sex, female | 916 (85) | 373 (84) | 543 (87) | 0.10 |
| BMI, mean ± SD kg/m$^2$ | 31.6 ± 7.6 | 31.6 ± 7.8 | 31.6 ± 7.5 | 0.95 |
| Education, more than high school | 465 (44) | 191 (43) | 273 (44) | 0.77 |
| Employed, yes | 322 (30) | 184 (41) | 139 (22) | <0.001 |
| Household income, >$30,000 | 262 (25) | 130 (30) | 132 (21) | 0.002 |
| Comorbidities, median (IQR) number | 3 (2–5) | 3 (2–4) | 3 (2–5) | <0.001 |
| Disease duration, median (IQR) months | 37 (13–138) | 11 (6–17) | 117.5 (60–213) | NA |
| DMARD use, yes | 904 (85) | 365 (82) | 539 (87) | 0.04 |
| Disease activity (DAS28-CRP) score, mean ± SD | 3.9 ± 1.4 | 4.0 ± 1.5 | 3.8 ± 1.3 | 0.10 |
| Disability (HAQ) score, mean ± SD | 1.4 ± 0.8 | 1.5 ± 0.9 | 1.3 ± 0.7 | 0.002 |
| Rehabilitation utilization in the prior 6 months, yes | 150 (14) | 53 (12) | 97 (16) | 0.10 |
| Rehabilitation utilization ever, yes | 434 (41) | 126 (28) | 308 (50) | <0.001 |

* Values are the number (%) unless indicated otherwise. BMI = body mass index; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; DMARD = disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; IQR = interquartile range; NA = not applicable; RA = rheumatoid arthritis.
† Comparison of early RA and established RA using independent *t*-test, Mann-Whitney U test, or chi-square test.

calculated from measured height and weight), disease duration (months from self-reported date of diagnosis to date of study entry), current use of conventional (e.g., methotrexate and leflunomide) or biologic disease-modifying antirheumatic drugs (DMARDs; self-reported yes/no), comorbidities (number of self-reported comorbid conditions from a list), household income (>$30,000 versus ≤$30,000), current employment (yes/no), and education (more than high school versus high school graduate or less). The list of comorbidities were as follows: anemia; asthma, bronchitis, or emphysema; back or spine problems; depression; diabetes mellitus; fibromyalgia; heart disease such as angina, heart attack, or hardening of arteries; high blood pressure or hypertension; inflammatory bowel disease (Crohn's disease or ulcerative colitis); kidney stones or kidney disease; liver disease; osteoporosis; parathyroid disease; psoriasis; stomach ulcer, stomach or intestinal surgery; tumor, cyst, or cancer; and vascular disease or stroke. In addition, participants could report any unlisted comorbidities.

**Outcomes.** The primary outcomes were rehabilitation utilization in the 6 months prior to the study visit and any prior rehabilitation utilization. Participants were asked if they had seen a physical therapist or occupational therapist for help with their arthritis or other problems in the prior 6 months or ever. A response of "yes" was classified as rehabilitation utilization in each time frame, respectively.

**Multiple imputation.** Data were missing for 227 participants (21.3%), primarily due to missing values for DAS28-CRP score (n = 157, 14.7% missing). Thus, we used the multiple imputation procedure (SAS, version 9.4; PROC MI) to impute the relevant missing variables. We included all measures in Table 1

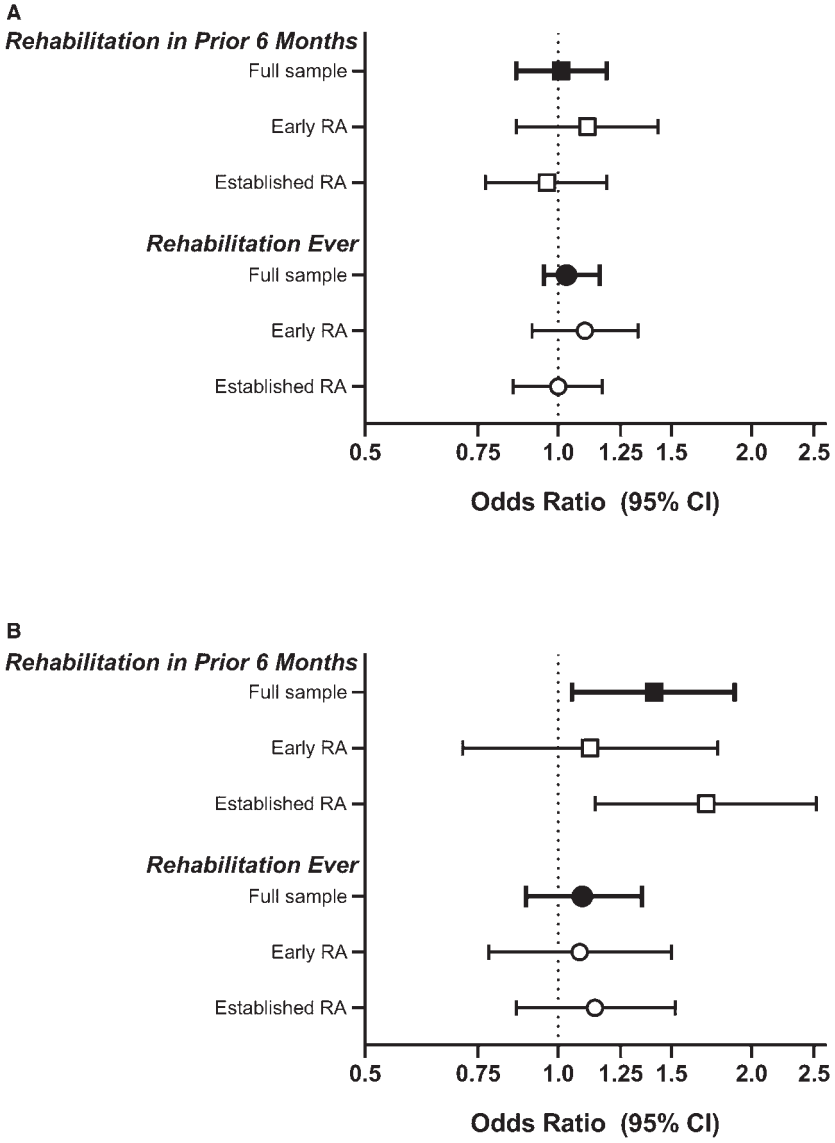


**Figure 1.** Association of disease activity (**A**) and disability (**B**) with rehabilitation utilization in the prior 6 months (squares) and ever (circles) in the full sample (solid square or circle) and in the stratified samples (open square or circle). 95% CI = 95% confidence interval; RA = rheumatoid arthritis.

as variables in the imputation models. Twenty imputed data sets were created with 20 burn-in iterations before each imputation. The multiple imputation was conducted by fully conditional specification (FCS) logistic methods for binary covariates and using FCS regression predicted mean matching method, which does not assume normality, for continuous variables. FCS was used because it performs well for assumptions for data missing at random and missing proportions lower than 0.5 (http://www2.sas.com/proceedings/sugi30/113-30.pdf).

**Statistical analysis.** We calculated summary statistics for all participant characteristics and outcomes of interest. We examined the association of disease activity and disability with rehabilitation utilization using separate binary logistic regression models to estimate odds ratios and 95% confidence intervals. We adjusted for the potential confounders and also reported the association of these variables with the outcome. We repeated the analyses with the sample stratified by disease duration (early RA [<2 years] and established RA [≥2 years]). Separate analyses were carried out in each of the 20 imputed data sets, and then estimated parameters from all imputed data sets were synthesized to generate a single estimate according to Rubin's rules. All tests were 2-sided and considered statistically significant at the 0.05 level. All analyses were conducted using the statistical software package SAS, version 9.4.

## RESULTS

Of 1,067 participants, 14% reported utilizing rehabilitation in the prior 6 months, and 41% reported ever utilizing rehabilitation (Table 1). The proportion of the sample reporting rehabilitation utilization in the prior 6 months was similar among those with early and established RA (12% versus 16%); however, a greater proportion of those with established RA reported any past rehabilitation utilization (28% versus 50%; $P < 0.001$).

In the full sample, disease activity was not associated with rehabilitation utilization in the prior 6 months or ever in unadjusted and adjusted models (Figure 1 and Table 2). Worse disability was associated with higher odds of rehabilitation utilization in the prior 6 months or ever in unadjusted models, but only the association with rehabilitation utilization in the last 6 months persisted in the adjusted model. Among the other factors, older age was associated with higher odds of rehabilitation in the prior 6 months in adjusted models, while older age, higher number of comorbidities, and current employment were associated with higher odds of any prior rehabilitation utilization.

When the results were stratified by disease duration, the association of disability with rehabilitation utilization in the prior 6 months was magnified among those with established RA and was not present in those with early RA (Figure 1 and Table 2). Disease activity remained not associated with rehabilitation utilization in both groups and in either time frame. Among participants with early RA, older age was associated with rehabilitation utilization in the prior 6 months and any prior rehabilitation utilization in unadjusted and adjusted models. In addition, higher number of comorbidities was associated with any prior rehabilitation in the unadjusted model only, while longer disease duration, DMARD use, and more than high school graduation were associated with higher odds of any prior rehabilitation utilization in the adjusted model only. Among participants with established RA, a higher number of comorbidities and current employment were associated with both outcomes in the unadjusted models and remained associated with any prior rehabilitation utilization in the adjusted model. Older age was associated with any prior rehabilitation utilization in the unadjusted model only.

## DISCUSSION

Contrary to our hypothesis, disease activity was not associated with rehabilitation utilization in the prior 6 months or any prior rehabilitation utilization in the full sample. In partial support of our hypothesis, worse disability was associated with rehabilitation utilization in the prior 6 months or ever; however, only the association with utilization in the prior 6 months persisted in the adjusted model. This remained true among those with established RA but not among those with early RA. Iversen et al (5) also previously reported that worse function and disability were associated with higher odds for physical therapy utilization in the prior 6 months. In contrast to our findings, Iversen et al reported that greater disease activity was associated with rehabilitation utilization, although they used a different measure of disability (i.e., the Rheumatoid Arthritis Disease Activity Index), which may have contributed to the discrepancy (5). Additionally, function was not significantly associated when considered alongside disease activity and disability (5). Considerable differences in sample characteristics may also account for some of the discrepancy, as their sample population was predominantly White with higher socioeconomic status and less comorbidity (5). Taken together, it remains unclear why and when rehabilitation is utilized for African American adults with RA, although disability is a contributor in those with established disease.

Beyond a description of factors associated with rehabilitation utilization, this analysis was the first to shed light on rehabilitation utilization reported among African American adults with RA. In the CLEAR I and II cohorts, 14% of participants reported utilizing either PT or OT in the prior 6 months. It remains unclear if this rehabilitation utilization is different than for White adults with RA. Iversen et al (5) reported that 15% of adults with RA utilized PT in the 6-month period; OT utilization was not included in the estimate. Thus, it is unclear how overall rehabilitation utilization compares between the samples, differences in sample characteristics notwithstanding. Sandstrom et al reported that Black adults with arthritis were 34% less likely to utilize office-based therapy compared to non-Black/non-Hispanic adults with arthritis; however, the type of arthritis (RA versus osteoarthritis) and type of office-based therapy (PT versus OT versus other) was not specified in this analysis (6). Further

**Table 2.** Factors associated with rehabilitation utilization in the prior 6 months or ever in the full sample and stratified by rheumatoid arthritis (RA) disease duration*

| | Utilization in the last 6 months | | Utilization ever | |
|---|---|---|---|---|
| | Unadjusted model | Adjusted model | Unadjusted model | Adjusted model |
| Full sample | | | | |
| Disease activity (per unit increase in DAS28-CRP score) | 1.07 (0.94–1.22) | 1.01 (0.86–1.19) | 1.04 (0.95–1.14) | 1.03 (0.92–1.16) |
| Disability (per unit increase in HAQ score) | 1.40 (1.12–1.74) | 1.41 (1.05–1.88) | 1.18 (1.01–1.38) | 1.09 (0.89–1.35) |
| Age (per year) | 1.03 (1.02–1.05) | 1.03 (1.01–1.05) | 1.03 (1.02–1.04) | 1.02 (1.01–1.03) |
| BMI (per 1 kg/m$^2$) | 1.02 (0.99–1.04) | 1.02 (0.99–1.04) | 1.02 (1.00–1.03) | 1.02 (1.00–1.03) |
| Sex (ref.: female) | 0.91 (0.70–1.18) | 1.04 (0.78–1.37) | 0.87 (0.73–1.04) | 1.02 (0.83–1.24) |
| Disease duration (per year) | 1.00 (1.00–1.00) | 1.00 (1.00–1.00) | 1.01 (1.00–1.01) | 1.00 (1.00–1.01) |
| Comorbidities (per increase in number) | 1.18 (1.09–1.27) | 1.07 (0.98–1.17) | 1.30 (1.22–1.39) | 1.20 (1.11–1.29) |
| DMARD use (ref.: yes) | 1.08 (0.86–1.36) | 1.06 (0.83–1.35) | 0.94 (0.80–1.12) | 0.95 (0.79–1.15) |
| Household income (ref.: <$30,000) | 1.02 (0.83–1.24) | 1.19 (0.94–1.50) | 0.97 (0.84–1.12) | 1.14 (0.96–1.36) |
| Employed (ref.: no) | 1.39 (1.12–1.73) | 1.18 (0.93–1.52) | 1.41 (1.23–1.63) | 1.21 (1.02–1.43) |
| Education (ref.: more than high school) | 0.88 (0.74–1.05) | 0.84 (0.69–1.02) | 0.89 (0.79–1.01) | 0.88 (0.76–1.02) |
| Early RA subsample | | | | |
| Disease activity (per unit increase in DAS28-CRP score) | 1.08 (0.88–1.31) | 1.11 (0.86–1.43) | 1.06 (0.92–1.22) | 1.10 (0.91–1.33) |
| Disability (per unit increase in HAQ score) | 1.04 (0.75–1.44) | 1.12 (0.71–1.77) | 1.08 (0.85–1.37) | 1.08 (0.78–1.50) |
| Age (per year) | 1.04 (1.02–1.07) | 1.05 (1.02–1.08) | 1.04 (1.02–1.05) | 1.05 (1.03–1.07) |
| BMI (per 1 kg/m$^2$) | 1.01 (0.97–1.05) | 1.02 (0.98–1.06) | 1.02 (0.99–1.04) | 1.01 (0.98–1.04) |
| Sex (ref.: female) | 1.14 (0.78–1.65) | 1.21 (0.80–1.21) | 0.94 (0.71–1.26) | 1.02 (0.74–1.40) |
| Disease duration (per year) | 0.96 (0.92–1.01) | 0.97 (0.92–1.01) | 1.03 (1.00–1.07) | 1.04 (1.01–1.08) |
| Comorbidities (per increase in number) | 1.06 (0.91–1.24) | 0.98 (0.82–1.16) | 1.17 (1.04–1.31) | 1.08 (0.95–1.22) |
| DMARD use (ref.: yes) | 0.85 (0.56–1.28) | 0.80 (0.52–1.23) | 0.76 (0.56–1.02) | 0.72 (0.52–0.99) |
| Household income (ref.: <$30,000) | 1.21 (0.89–1.64) | 1.23 (0.83–1.82) | 1.12 (0.89–1.40) | 1.12 (0.85–1.50) |
| Employed (ref.: no) | 1.10 (0.81–1.48) | 1.00 (0.69–1.45) | 1.07 (0.86–1.33) | 0.91 (0.70–1.19) |
| Education (ref.: more than high school) | 0.80 (0.60–1.07) | 0.76 (0.54–1.08) | 0.81 (0.66–1.00) | 0.76 (0.60–0.98) |
| Established RA subsample | | | | |
| Disease activity (per unit increase in DAS28-CRP score) | 1.08 (0.90–1.29) | 0.96 (0.77–1.19) | 1.07 (0.94–1.21) | 1.00 (0.85–1.17) |
| Disability (per unit increase in HAQ score) | 1.93 (1.41–2.66) | 1.70 (1.14–2.52) | 1.46 (1.16–1.82) | 1.14 (0.86–1.52) |
| Age (per year) | 1.02 (1.00–1.04) | 1.02 (0.99–1.04) | 1.02 (1.01–1.03) | 1.00 (0.99–1.02) |
| BMI (per 1 kg/m$^2$) | 1.02 (0.99–1.05) | 1.02 (0.99–1.05) | 1.02 (1.00–1.04) | 1.02 (0.99–1.04) |
| Sex (ref.: female) | 0.76 (0.52–1.11) | 0.86 (0.57–1.29) | 0.86 (0.68–1.09) | 1.01 (0.77–1.31) |
| Disease duration (per year) | 1.00 (1.00–1.01) | 1.00 (1.00–1.00) | 1.00 (1.00–1.01) | 1.00 (1.00–1.01) |
| Comorbidities (per increase in number) | 1.22 (1.11–1.34) | 1.11 (1.00–1.24) | 1.34 (1.23–1.45) | 1.26 (1.15–1.38) |
| DMARD use (ref.: yes) | 1.28 (0.96–1.70) | 1.23 (0.91–1.68) | 1.17 (0.93–1.48) | 1.19 (0.92–1.54) |
| Household income (ref.: <$30,000) | 0.91 (0.69–1.21) | 1.11 (0.81–1.51) | 0.95 (0.78–1.15) | 1.14 (0.90–1.44) |
| Employed (ref.: no) | 1.73 (1.21–2.48) | 1.43 (0.97–2.10) | 1.54 (1.26–1.88) | 1.40 (1.10–1.77) |
| Education (ref.: more than high school) | 0.94 (0.75–1.16) | 0.89 (0.69–1.14) | 0.94 (0.80–1.11) | 0.95 (0.78–1.14) |

* Values are the odds ratio (95% confidence interval). BMI = body mass index; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; DMARD = disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; ref. = reference.

research is needed to understand the extent to which disparities exist regarding rehabilitation utilization for adults with RA.

Despite consistent recommendations for rehabilitation and exercise in the management of RA (4), rehabilitation utilization was low. In the CLEAR I and II cohorts, lifetime rehabilitation utilization (i.e., any prior utilization) was 41% and 48% among those with established RA and a median disease duration of nearly 10 years. These are likely overestimates of actual rehabilitation utilization for RA, as participants may have reported rehabilitation utilization for problems that were unrelated to RA, such as after a sport injury. Overall, these results are consistent with previous reports that rehabilitation utilization over 1 year is lower in the US (24% [5,12]) compared to other countries (40–46% [13,14]). Reasons for this difference in rehabilitation utilization are unclear.

The results of this study and prior studies suggest that rehabilitation is potentially underutilized in RA management for adults in the US. Disability and functional limitation remain a prevalent issue among adults with RA, despite considerable improvements in disease management and joint preservation, with the proliferation of DMARDs and biologic drugs (1–3). As a complement to pharmacologic strategies, rehabilitation is needed to address disability and functional limitation. Prior analyses in CLEAR indicated that socioeconomic disparities in disease activity, disability, and other self-reported health outcomes exist among African American adults with RA (15). Higher household income was associated with rehabilitation utilization in the prior 6 months, and current employment was associated with any prior rehabilitation utilization in this analysis (Table 2), which may further contribute to

these health disparities. Future research must consider barriers to accessing rehabilitation and advance approaches to integrating rehabilitation into routine RA care in the US to preserve function and delay disability in adults with RA.

The results should be considered in light of several limitations. First, rehabilitation utilization estimates used self-reported recall, combined PT and OT, and were not necessarily specific to RA, as the participants may have seen a rehabilitation professional for problems other than RA. Analyses of administrative and electronic medical record data are needed to estimate PT and OT utilization more accurately for clinical issues related to RA. Other variables, such as comorbidities and medications, were also based on self-reported recall. This analysis was cross-sectional, so causality cannot be inferred. Rehabilitation utilization preceded the measures of disease activity and disability, so we cannot exclude the possibility that these clinical measures improved following rehabilitation. The CLEAR cohort includes participants recruited from academic medical centers in the southeastern US in the early 2000s, which may limit generalizability beyond the region and practice type as well as to current clinical practice. Biologics were an emerging treatment in the early 2000s, and their use was likely not consistent across institutions or across the enrollment period. It is unclear how this could affect referral to rehabilitation, although we know that functional limitations remain a prevalent consequence of RA in the era of biologics (1,3). Finally, we did not have information regarding insurance coverage, location, and transportation availability, which may impact rehabilitation utilization.

In conclusion, among African American adults with RA, rehabilitation utilization was low (14%) in the 6 months prior to enrollment into CLEAR, was not associated with disease activity, and was only associated with disability among those with established disease. Factors driving rehabilitation utilization in African American adults with RA remain unclear and should be a focus of future research to facilitate delivery of appropriate and effective rehabilitation services.

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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 submitted for publication. Dr. Thoma 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.** Thoma.
**Acquisition of data.** Cleveland, Jonas, Bridges, Callahan.
**Analysis and interpretation of data.** Thoma, Cleveland, Callahan.

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REHABILITATION SCIENCES AND THE RHEUMATIC DISEASES

# Exploring the Associations Among Occupational Balance and Health of Adults With and Without Inflammatory Arthritis

Flora To-Miles,[1] Carita Håkansson,[2] Petra Wagman,[3] and Catherine L. Backman[1]

**Objective.** Occupational balance is a person's subjective perception of the amount and variation of their everyday activities. Evidence suggests an association between occupational balance and health. However, the impact of arthritis on occupational balance and its association with health is unclear. This exploratory study was undertaken to examine associations between occupational balance and measures of health and between-group differences in adults with and without inflammatory arthritis (IA).

**Methods.** In a cross-sectional study, participants completed the 11-item Occupational Balance Questionnaire (OBQ-11) and the Short Form 36 (SF-36) health survey (physical and mental component summary scores) and provided demographic information. Telomere lengths were analyzed from dried blood spots.

**Results.** A total of 143 adults participated (67 with IA, 76 from the healthy comparison [HC] group). Occupational balance was higher in the HC group than in the IA group (mean difference 3.5 [95% confidence interval 1.0, 5.9; $P = 0.01$]), but this difference was not statistically significant when adjusted for physical health. The association between occupational balance and physical health was stronger in the IA group ($R^2 = 0.17$, $P = 0.001$) than in the HC group ($R^2 = 0.05$, $P = 0.05$). Occupational balance was associated with mental health ($R^2 = 0.26$, $P < 0.001$) but not associated with telomere length ($R^2 = 0.02$, $P = 0.24$).

**Conclusion.** Occupational balance is associated with mental health for all participants and associated with physical health and disease activity in participants with IA. Attention to assessment of and strategies for improving occupational balance in rehabilitation practice and arthritis self-management programs may contribute to sustaining physical and mental health.

## INTRODUCTION

Occupations are the tasks and activities of daily life that people do to occupy themselves and fulfill specific purposes such as self-care, productivity, and leisure (1). In this context, occupations encompass both activities and participation in a life role as defined in the International Classification of Functioning (2); therefore, we use the term "occupation" throughout this paper. Occupational balance is the subjective perception of having "the right amount of occupations and the right variation between occupations" (3). Occupational balance is dynamic: people's perception of what feels right fluctuates depending on the occupations they need or want to do and how the social and physical environment supports or disrupts their occupations. Occupational balance is a composite of at least 3 personal judgments: the degree to which one views their occupations as congruent with their values; having the ability and resources to manage their occupations; and that the overall mix of occupations is harmonic (4).

Individuals with inflammatory types of arthritis (including but not limited to rheumatoid arthritis [RA], spondyloarthritis [SpA],

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**SIGNIFICANCE & INNOVATIONS**

- This study is among the first to compare occupational balance between individuals living with inflammatory arthritis and a healthy comparison group using the 11-item Occupational Balance Questionnaire.
- Occupational balance is associated with disease activity and physical health in adults with inflammatory arthritis, and occupational balance explains more than one-fourth of the variance in mental health scores for participants with and without arthritis.
- Targeting occupational balance (aiming for a satisfying amount and mix of occupations) in arthritis rehabilitation and self-management programs may be an avenue to supporting physical and mental health.

psoriatic arthritis [PsA], systemic lupus erythematosus [SLE], and juvenile idiopathic arthritis [JIA]) experience symptoms that limit their occupations (5). Arthritis symptoms are known to disrupt daily occupations, including leisure, household work, caregiving, and employment (6). A qualitative study exploring the factors important for maintaining employment among 9 men with arthritis found that adjusting leisure, rest, and household occupations was a way to sustain employment and a balance among occupations (7). Therefore, engaging in an appropriate mix of important or meaningful occupations can help manage arthritis and support well-being (8), suggesting a need to further examine occupational balance.

Several observational studies have demonstrated a relationship between occupational balance and health and well-being. For example, occupational balance is related to self-reported measures of stress (9,10), life satisfaction, and self-rated health (11) among healthy adults. Occupational balance was associated with life satisfaction in a survey of 686 adults with RA (12) and with general health status in another cross-sectional survey of 169 adults with RA (13). Occupational balance was crucial to perceptions of good health for 9 women with RA or JIA participating in a qualitative interview study (8). Another qualitative study (14) exploring occupational balance in 10 participants (8 women, 2 men) with RA found that a mix of challenging and relaxing occupations was beneficial for health. To better assess the benefits and gain a deeper understanding of occupational balance, those authors proposed that future studies compare experiences of individuals with and without RA and generate potential interventions (14). While promoting occupational balance shows promise for supporting arthritis self-management in the presence of occupational disruption (15), there is little evidence on whether occupational balance differs between individuals with and without arthritis, which presents a knowledge gap.

Dür and colleagues (16) reported correlations between an occupational balance questionnaire and cytokines, C-reactive protein (CRP) levels (biologic markers of inflammation), and Short Form 36 (SF-36) health survey (17) subscale scores among people with and without RA. In the RA group, engaging in little or no variety of different activities was weakly associated with higher CRP and interleukin-6 levels. The study of Dür et al (16) is unique in seeking evidence on the relationship between occupational balance and biologic indicators of health comparing adults with and without arthritis. Another biologic indicator of health that may supplement self-reported health measures is telomere length (TL). TL shortens with age (18) and is a marker of immunity and inflammation (19,20); previous research has found shorter telomeres in individuals with RA than in the general population (21). Body mass index (BMI) and smoking are also associated with shorter TL (22,23). Stamm and colleagues (14) suggested that a comparative study including people with and without arthritis using both biomarkers and self-reported measures of health may advance understanding of the ways that occupational balance interventions could contribute to arthritis self-management.

This study explored associations among occupational balance and health measures in adults with and without inflammatory arthritis (IA). The specific research questions were as follows: 1) Does occupational balance differ between individuals with and without arthritis? 2) If there is a difference in occupational balance between groups, do differences remain after controlling for covariates? 3) Does occupational balance predict self-reported physical and mental health and TL in the full sample and/or IA and healthy comparison (HC) groups?

## SUBJECTS AND METHODS

We conducted an exploratory, cross-sectional study with multiple research questions; the present analysis is limited to the questions listed above. The clinical research ethics board at the University of British Columbia approved the study procedures, and all participants provided informed consent.

**Participant recruitment and eligibility criteria.** Participants were recruited via rheumatology clinic and community advertising and word-of-mouth, as participants shared recruitment notices with friends and family. Inclusion criteria were being an adult (≥19 years of age) and being able to read and write English. Participants in the IA group required a rheumatologist-confirmed diagnosis of an inflammatory type of arthritis, such as RA, PsA, SpA, SLE, or JIA, and being on a stable drug regimen for at least 3 months. Exclusion criteria were cancer in the last 5 years, current smoking status (defined as smoking >100 cigarettes in one's lifetime and having smoked >1 cigarette during the past 30 days) because cancer and smoking affect telomere biology (23,24), and long-term neurologic conditions (e.g., stroke) and respiratory conditions (e.g., chronic obstructive pulmonary disease) that restricted daily occupations. Participants reporting common medical conditions (e.g., diabetes mellitus, depression, and hypertension) were not

excluded if they confirmed that the condition was controlled by medication and/or self-management strategies and did not restrict engagement in daily occupations. Diagnosis and medication were recorded when applicable.

**Procedures.** A researcher (FTM) explained the study to potential participants, screened for eligibility by telephone interview, and obtained informed consent. Data collection sessions were scheduled for participants in small groups. Because acute illness may affect participation in typical occupations or perceptions of health, 2 days prior to data collection, participants were reminded via email to reschedule if they were ill (e.g., cold) so they would feel well when collecting health and occupational balance measures. Data collection took place from October 2018 to December 2019 in group sessions of up to 15 participants, taking 60–120 minutes for participants to complete all study procedures. Participants completed questionnaires individually (each packet prelabeled with a unique ID code), and a researcher (FTM) completed blood draws 1 participant at a time throughout the session. A lancet was used to prick a fingertip and fill 5 blood spots on Whatman blotting papers and left to dry for a minimum of 4 hours or overnight. Once dried, papers were placed in individual biohazard foil bags labeled with participants' ID codes, along with a desiccant, and stored in a freezer at –80°C until analysis for TL.

**Measures.** *The 11-item Occupational Balance Questionnaire (OBQ-11).* The OBQ-11 (25,26) is an 11-item scale with a score range of 0–33 and assesses respondents' perceptions of the amount and variety of their everyday occupations. Higher scores indicate greater balance. It has demonstrated adequate test–rest reliability in healthy adults (25,26), good construct validity, reliability (26), and internal consistency in the IA population (12). We used the English version (10). In our sample, the 11-item scale had a Cronbach's α of 0.93.

*SF-36 health survey.* The SF-36 health survey (17) has 36 items organized into 8 subscales, with 2 summary scores for physical and mental health, respectively. The physical component summary (PCS) score and mental component summary (MCS) score are derived from weighted formulas of survey items. Normalized scores range from 0 to 100, with higher scores indicating better health. The SF-36 has demonstrated reliability and validity in both arthritis and general populations. The PCS and MCS are composite scales for which internal consistency is not reasonably applied (27) because they use weighting and aggregation of the 8 subscales. Cronbach's α in the present sample for the 8 subscales ranged from 0.78 to 0.92.

*TL.* TL was measured from dried blood spots with intrarun and interrun coefficients of variation for the internal controls at 5–10% (28). DNA was extracted from participants' blood and then analyzed for TL in bundles of 40 samples, all completed at one time. TL is measured as a T/S ratio (relative telomere to single copy gene).

*Demographic data.* Demographic data collected included age, sex, BMI, education, employment status, household income, and comorbidities for all participants, and arthritis diagnosis, disease duration, and disease activity for the IA group (using the Rheumatoid Arthritis Disease Activity Index [RADAI] [29], with a score range 0–10, where greater scores indicate higher disease activity). We measured height and weight during the study session to calculate BMI.

**Data analysis.** Two participants each missed 1 item on the OBQ-11, and this was dealt with by mean substitution (30). Disease duration was missing for 3 participants, and 2 people from the IA group did not complete the RADAI. For the SF-36, 2 participants each missed a single item, which did not affect the subscale scores because they are an arithmetic mean.

We used SPSS for Windows (Microsoft), version 27, for all analyses, beginning with descriptive statistics for all variables and correlational analyses (Pearson's r) for occupational balance, physical health, mental health, TL, disease activity, and disease duration. Chi-square and independent *t*-tests were used to assess between-group differences for demographic variables and occupational balance (research question 1). Analyses of covariance (ANCOVAs) were used to determine between-group differences in occupational balance while controlling for 5 covariates (research question 2). PCS scores, age, sex, and employment status were chosen as covariates in the ANCOVAs because they were associated with occupational balance in prior studies (10,12,16), and income was associated with health (31). Additionally, because the IA group has lower PCS scores than the HC group, the ANCOVA helps to determine if occupational balance differs between groups after controlling for physical health status. Multiple linear regression analyses were conducted for each of PCS scores, MCS scores, and TL as the dependent variable (research question 3), using occupational balance and diagnosis (IA/HC) as predictor variables. When diagnosis was a significant variable in the regression, an interaction term of occupational balance and diagnosis was added.

For detecting between-group differences (*t*-tests), the estimated sample size was 64 participants per group using the parameters $\alpha = 0.05$, $\beta = 0.8$, and a moderate effect size $d = 0.5$. Minimum sample size estimates for regression analyses were 5–10 times as many cases as the variables (32); with 3–4 variables in each equation, the sample required for between-group comparisons exceeded the minimum sample size needed for regression analyses.

## RESULTS

A total of 273 individuals expressed interest in the study. Fifty-nine declined participation after receiving more information and were not screened. Of the 214 individuals screened, 37 eligible persons declined to participate, and 34 were ineligible, leaving

**Table 1.** Participant characteristics*

| Characteristic | Overall sample (n = 143) | IA group (n = 67) | HC group (n = 76) |
|---|---|---|---|
| Sex† | | | |
| Male | 32 (22) | 11 (16) | 21 (28) |
| Female | 111 (78) | 56 (84) | 55 (72) |
| Age, mean ± SD years | 50.42 ± 16.31 | 53.01 ± 15.88 | 48.13 ± 16.45 |
| Education level | | | |
| High school graduate or less | 19 (13) | 8 (12) | 11 (15) |
| Trade, vocational, or community college graduate | 30 (21) | 16 (24) | 14 (18) |
| University bachelor's degree | 58 (41) | 25 (37) | 33 (43) |
| Master's or doctoral degree | 36 (25) | 18 (27) | 18 (24) |
| Marital status | | | |
| Married/living with partner | 85 (60) | 41 (61) | 44 (58) |
| Widowed/separated/divorced | 19 (13) | 10 (15) | 9 (12) |
| Single | 39 (27) | 16 (24) | 23 (30) |
| Employment status | | | |
| Part-time | 22 (15) | 9 (13) | 13 (17) |
| Full-time | 58 (41) | 31 (46) | 27 (36) |
| Retired | 34 (24) | 12 (18) | 22 (29) |
| Other | 29 (20) | 15 (22) | 14 (18) |
| Household income, $ (Canadian) | | | |
| <40,000 | 37 (26) | 14 (21) | 23 (30) |
| 40,000–59,999 | 18 (13) | 7 (11) | 11 (15) |
| 60,000–79,999 | 10 (7) | 9 (13) | 1 (1) |
| 80,000–99,999 | 22 (15) | 14 (21) | 8 (11) |
| 100,000–119,999 | 20 (14) | 9 (13) | 11 (15) |
| ≥120,000 | 35 (25) | 14 (21) | 21 (28) |
| Ethnicity | | | |
| White/Caucasian | 105 (73) | 56 (85) | 49 (65) |
| Chinese | 13 (9) | 3 (4.5) | 10 (13) |
| Mixed race | 9 (6) | 2 (3) | 7 (8) |
| Latin American | 5 (4) | 3 (4) | 2 (3) |
| South Asian | 4 (3) | 1 (2) | 3 (4) |
| Other | 7 (5) | 2 (3) | 5 (7) |
| No. of comorbidities/health conditions | | | |
| 0 | 60 (42) | 17 (25)‡ | 43 (57) |
| 1 | 41 (29) | 19 (28) | 22 (29) |
| 2 | 20 (14) | 15 (22) | 5 (7) |
| 3 | 12 (8) | 10 (15) | 2 (3) |
| ≥4 | 10 (7) | 6 (9) | 4 (5) |
| BMI, mean ± SD (median) | 25.22 ± 5.33 (23.96) | 25.76 ± 5.31 (24.9) | 24.75 ± 5.33 (23.30) |

* Values are the number (%) unless indicated otherwise. BMI = body mass index; HC = healthy comparison; IA = inflammatory arthritis.
† Nonbinary was an option; no participants selected it.
‡ Other than IA.

143 eligible individuals who agreed to participate, 67 with IA and 76 in the HC group. Participant characteristics are presented in Table 1. Participants were primarily female, with a mean ± SD age of 50 ± 16 years, and two-thirds had a university degree. The mean ± SD disease duration of the IA group was 12.86 ± 13.10 years; 57% had RA, 16% PsA, 13% SLE, 10% SpA, 6% JIA, and 3% polyarthritis (precise diagnosis not yet confirmed). The mean ± SD RADAI score was 3.1 ± 2.1. There were no statistically significant differences in age and sex between the IA and HC groups.

In the total sample (n = 143), occupational balance was significantly correlated with PCS score (r = 0.25, $P < 0.01$) and MCS score (r = 0.51, $P < 0.01$). Even after controlling for age and BMI, which were predictors of TL in prior studies, there was no relationship between occupational balance and TL. Occupational balance was inversely correlated with disease activity in the IA group (n = 67; r = –0.38, $P = 0.002$), but not correlated with disease duration (r = 0.08, $P = 0.54$).

For comparison purposes with prior studies using the OBQ-11, the median (interquartile range) for the overall sample was 18.00 (10.00); and it was 16.00 (12.00) and 20.50 (10.75) for the IA and HC groups, respectively. Both occupational balance and PCS mean scores were lower in the IA group than in the HC group, but no statistically significant between-group differences were present for MCS scores and TL (Table 2).

**Table 2.** Between-group differences in health measures*

| Measures | IA group (n = 67) | HC group (n = 76) | Mean difference | 95% CI of mean difference | | t | *P* |
|---|---|---|---|---|---|---|---|
| | | | | Lower | Upper | | |
| OBQ-11 | 15.89 ± 7.50 | 19.37 ± 7.37 | 3.48 | 1.02 | 5.94 | 2.80 | 0.01 |
| PCS | 40.23 ± 11.44 | 52.97 ± 7.14 | 12.74 | 9.63 | 15.85 | 8.09 | <0.001 |
| MCS | 47.70 ± 9.76 | 48.76 ± 9.58 | 1.06 | −2.14 | 4.26 | 0.66 | 0.51 |
| TL | 7.89 ± 1.51 | 8.21 ± 1.41 | 0.32 | −0.17 | 0.80 | 1.29 | 0.20 |

* Values are the mean ± SD unless indicated otherwise. 95% CI = 95% confidence interval; HC = healthy comparison; IA = inflammatory arthritis; MCS = mental component summary score from the Short Form 36 health survey; OBQ-11 = 11-item Occupational Balance Questionnaire; PCS = physical component summary score from the Short Form 36 health survey; TL = telomere length.

Occupational balance remained statistically significantly different between groups when controlling for each of age, sex, income, and employment status (Table 3) but was not statistically significantly different between groups when controlled for PCS score ($P = 0.18$) or for all 5 covariates together ($P = 0.11$).

In the full sample, occupational balance and diagnosis explained 33% of the variance in PCS score ($P < 0.001$); however, diagnosis contributed most of the variance (32%). An interaction term of occupational balance and diagnosis was statistically significant ($P < 0.001$) in predicting PCS score (Figure 1). We therefore conducted regression analyses for the 2 groups separately (Table 4); occupational balance predicted 17% of the variance in PCS score in the IA group and 5% of the variance in PCS score in the HC group.

In the full sample, occupational balance and diagnosis explained 27% of the variance in MCS score, with occupational balance contributing 26% of the variance ($P < 0.001$) (Table 5). Occupational balance did not explain variance in TL, nor did diagnosis (Table 5).

## DISCUSSION

We explored relationships between occupational balance and health measures in individuals with and without IA and discovered some important differences. Occupational balance was higher in the HC group compared to the IA group; of the 3 health measures studied (PCS score, MCS score, and TL), occupational balance was most strongly related to mental health; occupational balance predicted physical health for the IA group but not the HC group, and occupational balance was not associated with telomere length.

Both the IA and HC groups had greater occupational balance scores compared to a prior study of Swedish women ages 30–55 years (33). However, occupational balance is not a static construct as it fluctuates based on current occupations. Our sample may have reported higher occupational balance than other samples due to a wider age range, differing occupations, or language or cultural differences, each of which could be explored in future studies. The between-group difference in occupational balance is consistent with a prior study in which individuals with chronic health problems reported lower occupational balance compared to those without health conditions (10). A possible explanation for between-group differences is that individuals with chronic illness engage in different occupations. However, a prior analysis of occupations in our study participants (34) showed that the 2 groups engaged in the same kinds of occupations at the same frequency despite differences in PCS score. It is not known if the way they engaged in the occupations was similar (e.g., with adjusted expectations or adaptations by IA participants). Therefore, occupational balance may differ between groups because of specific unidentified elements of occupations, which raises questions for future research.

Because diagnosis explained a large proportion of variance in PCS score in the present sample, we explored the association between occupational balance and physical health separately in the 2 groups. Occupational balance was associated with physical health in the IA group but not in the HC group, which could be a result of arthritis symptoms reducing occupational experiences.

**Table 3.** Between-group differences (inflammatory arthritis [IA] versus healthy comparison [HC]) and analysis of covariance results in occupational balance controlled for covariates*

| Covariate(s) adjusted for | Mean OBQ-11 IA group (n = 67) | Mean OBQ-11 HC group (n = 76) | F | *P* |
|---|---|---|---|---|
| PCS | 16.66 | 18.69 | 1.84 | 0.18 |
| Age | 15.59 | 19.62 | 10.81 | 0.001 |
| Sex | 15.71 | 19.52 | 9.41 | 0.003 |
| Income | 15.85 | 19.24 | 7.59 | 0.01 |
| Employment status | 16.17 | 19.11 | 5.77 | 0.02 |
| PCS, age, sex, income, and employment status | 16.43 | 18.73 | 2.59 | 0.11 |

* HC = healthy comparison; IA = inflammatory arthritis; OBQ-11 = 11-item Occupational Balance Questionnaire; PCS = physical component summary score from the Short Form 36 health survey.

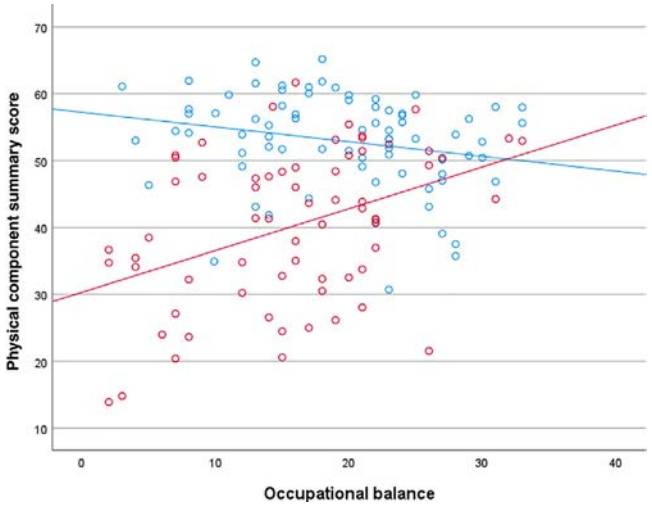


**Figure 1.** Scatter plot of 11-item Occupational Balance Questionnaire scores and Short Form 36 health survey physical component summary scores for inflammatory arthritis (red) and healthy comparison (blue) diagnostic groups. Each circle represents 1 participant.

That is, the inverse correlation between disease activity scores and occupational balance, along with the presence of pain, fatigue, and decreased mobility, may explain why occupational balance and PCS score are correlated in the IA group but not the HC group. This hypothesis is reinforced by our finding that once controlled for physical health, there was no between-group difference in occupational balance.

Previous studies demonstrate how arthritis symptoms may contribute to the differences in occupational balance between groups. Activity limitations due to IA can affect patients' occupational balance (35). Arthritis symptoms like pain can also impact participation in everyday activities and subsequently, an imbalance among occupations (36). Lower disease activity scores (representing arthritis symptoms) were associated with higher occupational balance in a survey of 682 adults with RA (12). Dür et al (16) found associations between inflammatory markers (also related to arthritis symptoms) and occupational balance in a sample of individuals with and without RA. In line with the above studies, we found that disease activity was inversely correlated with occupational balance in the IA group; however, disease duration was not correlated with occupational balance. Further research using more rigorous designs is needed to investigate the mechanisms through which IA symptoms impact occupational balance.

Among the variables explored in the current study, occupational balance was most strongly correlated with MCS scores for the total sample. In fact, OBQ-11 scores explained 26% of variance in MCS score, with diagnosis adding only 1%, in contrast to the findings for PCS score (diagnosis explaining 32% of the variance in PCS score, and OBQ-11 score contributing 1%). One explanation for this finding is the congruence between aspects of occupational balance and MCS score elements in the SF-36, such as items in the subscales energy/fatigue and role limitations due to emotional problems. Previous studies demonstrate that occupational balance is associated with mental health as measured by the SF-36 MCS score (10) and a 1-question self-rated health item ("How do you rate your health in general?") (11). Not being continuously stressed was associated with higher occupational balance among a sample of 682 people with RA (12). None of the preceding studies have confirmed the directionality of associations, which would strengthen suggestions for practice. For example, assessing occupational balance and offering strategies toward achieving a more satisfactory amount and variation of occupations that make up people's day-to-day lives may complement current self-management approaches and better support mental health outcomes for individuals with arthritis.

Since occupational balance and stress are related (10,37), it was expected that occupational balance would be associated with TL via the stress pathway (38). However, occupational balance was not significantly associated with TL in this sample; nor did TL differ between groups, which was also unexpected given

**Table 4.** Regression models predicting physical health (PCS scores)*

| Coefficients | $R^2$ | Unstandardized coefficients | | Standardized coefficients | t | *P* | 95% CI for B | |
|---|---|---|---|---|---|---|---|---|
| | | B | SE | | | | Lower | Upper |
| Total sample (n = 143) | | | | | | | | |
| Constant | – | 49.43 | 2.31 | – | 21.39 | <0.001 | 44.86 | 54.00 |
| Diagnosis | 0.32 | −12.10 | 1.61 | −0.54 | −7.53 | <0.001 | −15.28 | −8.93 |
| Diagnosis and OBQ-11 score | 0.33 | 0.18 | 0.11 | 0.12 | 1.73 | 0.09 | −0.03 | 0.39 |
| IA group (n = 67) | | | | | | | | |
| Constant | – | 30.31 | 3.03 | – | 10.01 | <0.001 | 24.27 | 36.36 |
| OBQ-11 score | 0.17 | 0.62 | 0.02 | 0.41 | 3.62 | 0.001 | 0.28 | 0.97 |
| HC group (n = 76) | | | | | | | | |
| Constant | – | 57.23 | 2.27 | – | 25.21 | <0.01 | 52.70 | 61.75 |
| OBQ-11 score | 0.05 | −0.22 | 0.11 | −0.23 | −2.01 | 0.05 | −0.44 | 0.00 |

* 95% CI = 95% confidence interval; HC = healthy comparison; IA = inflammatory arthritis; OBQ-11 = 11-item Occupational Balance Questionnaire; PCS = physical component summary score from the Short Form 36 health survey.

**Table 5.** Regression models predicting mental health (MCS scores) and telomere length (TL) (n = 143)*

| Coefficients | $R^2$ | Unstandardized coefficients | | Standardized coefficients | t | *P* | 95% CI for B | |
|---|---|---|---|---|---|---|---|---|
| | | B | SE | | | | Lower | Upper |
| Predicting MCS | | | | | | | | |
| Constant | – | 35.75 | 2.06 | – | 17.37 | <0.001 | 31.68 | 39.82 |
| OBQ-11 score | 0.26 | 0.67 | 0.09 | 0.53 | 7.13 | <0.001 | 0.49 | 0.86 |
| OBQ-11 score and diagnosis | 0.27 | 1.28 | 1.43 | 0.07 | 0.89 | 0.37 | −1.56 | 4.11 |
| Predicting TL | | | | | | | | |
| Constant | – | 8.56 | 0.36 | – | 23.78 | <0.001 | 7.85 | 9.27 |
| OBQ-11 score | 0.01 | −0.02 | 0.02 | −0.10 | −1.12 | 0.27 | −0.05 | 0.01 |
| OBQ-11 score and diagnosis | 0.02 | −0.38 | 0.25 | −0.13 | −1.51 | 0.13 | −0.87 | 0.12 |

* 95% CI = 95% confidence interval; MCS = mental component summary score from the Short Form 36 health survey; OBQ-11 = 11-item Occupational Balance Questionnaire.

prior research showing shorter telomeres in patients with arthritis (21,39,40). Research has shown stress as a pathway through which lifestyle influences telomere biology. Engaging in mindfulness or meditative activities or physical activities can reduce stress, which in turn, preserve TL (41,42). However, the different factors and mechanisms that influence TL are still largely unknown (43). The absence of associations between occupational balance and TL, and MCS score and TL, may be sample specific given that the present sample did not replicate the between-group difference in TL found in other studies (21,39,40). The mechanism through which occupational balance and TL may be associated is complex and requires replication before concluding that there is no relationship.

Our findings have clinical implications for practitioners. The OBQ-11 is easy to administer, reliable, and valid. Rehabilitation professionals can measure occupational balance and, when applicable, consider interventions to help patients choose or adjust occupations toward a more satisfying balance regarding the amount and kinds of occupations in which they engage. Interventions to balance different kinds of occupations may bolster physical and mental health and add to patients' repertoire of coping strategies and potentially promote overall health.

This study adds to the conceptual understanding of occupational balance. Our study used the OBQ-11 to compare occupational balance in participants with and without IA, which had not been tested previously and offers a better understanding of the impact of arthritis on occupational balance. When controlled for physical health (as measured by the SF-36 PCS score), there was no difference in occupational balance between groups, illustrating that physical health, as a consequence of arthritis, has an impact on perceptions of occupational balance. These findings call for further exploration on the interrelationships among physical health, arthritis symptoms, and occupational balance. Previous studies have reported that occupational balance is associated with general health in individuals with RA (13). Our study extends these findings by showing that occupational balance contributes more strongly to mental health than physical health and is inversely associated with arthritis disease activity, providing a more nuanced understanding of how occupational balance contributes to various facets of health.

Comparing occupational balance between adults with and without IA contributes to the literature on this concept and is a strength of the current study. Additionally, this study explored the relationship between occupational balance and biomarkers. To our knowledge, only 1 prior study (16) investigated associations between occupational balance and biologic markers, and our study adds to this small body of literature. By measuring several variables (physical health, mental health, TL, and occupational balance), this study built upon prior qualitative studies to explore the complex relationships between occupational balance and health constructs.

Our findings are limited to the perspectives of adults with similar characteristics (e.g., White adults, many of whom were highly educated and urban dwelling); the privileges of these groups may afford the choice and ability to select certain occupations, impacting occupational balance. For example, individuals with lower socioeconomic status (44,45), or those who identify as a racialized group (46), face greater barriers engaging in desired occupations. Study participants were English-speaking residents in the metropolitan area of Vancouver, Canada. Occupations and occupational balance may manifest differently in non-Western cultures (47), and findings should be applied cautiously. Future studies should investigate how occupational balance presents in more diverse groups, and specifically, how occupational balance differs between IA and HC groups from larger, representative samples, using occupational balance assessments in other languages when applicable (48,49). A strength of the OBQ-11 is its focus on the respondent's perception of the amount, variety, and impact of occupations, not their specific occupations; therefore, the actual occupations that comprise a person's ratings is their own interpretation in their own context. As an exploratory study, we are unable to attribute directionality among variables. For example, while we found associations between occupational balance, IA disease activity, and

physical health, future longitudinal and intervention studies are needed to elucidate the causal directions between these variables.

In conclusion, occupational balance was associated with mental health, accounting for more than one-fourth of its variance. This finding suggests that attention to the assessment of and strategies for improving occupational balance be considered in rehabilitation practice and arthritis self-management programs. Participants with inflammatory arthritis reported lower occupational balance compared to the healthy comparison group. However, this difference did not remain statistically significant after controlling for physical health. Occupational balance was a predictor of physical health only in the IA group and was inversely associated with disease activity. Finally, occupational balance was not associated with TL; however, the mechanism through which occupational balance and TL are associated is likely complex and multifaceted and requires further investigation. Overall, occupational therapists and others working with individuals with IA should consider assessing and enhancing occupational balance as a way to maintain physical and mental health.

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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 submitted for publication. Dr. Backman 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.

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REHABILITATION SCIENCES AND THE RHEUMATIC DISEASES

# Inflammatory Arthritis and the Effect of Physical Activity on Quality of Life and Self-Reported Function: A Systematic Review and Meta-Analysis

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**Objective.** Although physical activity is an evidence-based intervention that reduces disease-related symptoms and comorbidity in rheumatoid arthritis (RA), the effect of physical activity on self-reported function and quality of life (QoL) has not yet been analyzed. The present study synthesizes the evidence for the effectiveness of physical activity on QoL and self-reported function in adults with RA, spondyloarthritis (SpA), and psoriatic arthritis (PsA).

**Methods.** The databases PubMed, Embase, CINAHL, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to identify relevant randomized controlled trials (RCTs). Screening, risk of bias assessment (using the RoB 2.0 tool), and data extraction were independently performed by 2 or more of the authors. Meta-analyses were conducted with a random-effects model.

**Results.** Systematic review included 55 RCTs, and meta-analysis included 37 RCTs. Of the 55 studies included, 76%, 20%, and 4% were designed to investigate RA, SpA, and PsA, respectively. In the RA studies, effects of physical activity on QoL and function were found compared to the group of inactive controls; no effects were found compared to the group of active controls. In the SpA studies, the effects of physical activity on QoL were in favor of the control group. Effects of physical activity on function were found compared to the group of inactive controls and sustained in fatigue and pain when compared to the group of active controls. In the PsA studies, no effects on QoL were found, but effects on function were noted when compared to the group of inactive controls. The effect size was below 0.30 in the majority of the comparisons.

**Conclusion.** Physical activity may improve QoL and self-reported function in individuals with RA, SpA, and PsA. However, larger trials are needed, especially in SpA and PsA.

## INTRODUCTION

Throughout the past several decades, high-quality evidence has accumulated on the effectiveness of aerobic and muscle strengthening physical activity to reduce disease-related symptoms such as pain and comorbidity risk in people with rheumatoid arthritis (RA) (1). Nevertheless, more studies are needed to determine whether physical activity can improve quality of life (QoL) and self-reported function for patients with inflammatory arthritis. Emphasizing self-reported measures will capture how the patient experiences the effect of physical activity interventions. Patients' experiences and engagement in rehabilitation are known to be of utmost importance for successful outcomes. Using knowledge about the effects of physical activity in terms of

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**SIGNIFICANCE & INNOVATIONS**

- Summarized evidence shows that physical activity can lead to less pain, less fatigue, and improved mental and activity performance in inflammatory arthritis, with the most comprehensive information available on rheumatoid arthritis and spondyloarthritis. These findings add new important knowledge to the total benefits of physical activity.
- Knowledge of the effects of physical activity on self-reported health is of great importance to motivate the patient and is important for health professionals to bear in mind when promoting physical activity to patients.
- There is a need for further research in regard to the specific effects of physical activity in patients with psoriatic arthritis as related to both self-reported function and quality of life.

self-reported measures in everyday practice enables patient-centered care and also adherence to physical activity interventions (2,3). Since physical activity is effective and safe with few reported adverse effects, it should be a part of standard care for patients with inflammatory arthritis.

The World Health Organization (WHO) defines physical activity as "any bodily movement produced by skeletal muscles that requires energy expenditure, including activities undertaken while working, playing, carrying out household chores, traveling, and engaging in recreational pursuits." Exercise, on the other hand, is defined as "a subcategory of physical activity that is planned, structured, repetitive, and aims to improve or maintain one or more components of physical fitness" (4). Both the WHO and the American College of Sports Medicine (5) have provided internationally accepted recommendations for physical activity. The definitions essentially state the same target: everyone should engage in moderately intensive aerobic physical activity 150 minutes per week and at least twice a week, perform muscular strength and endurance physical activity. These recommendations are for all people, including people with inflammatory arthritis, who are generally less physically active than healthy controls (6,7).

The most common chronic types of systemic inflammatory arthritis are RA, spondyloarthritis (SpA), and psoriatic arthritis (PsA), all of which significantly impact patients' health. Despite better pharmacologic management and inflammation control, patients with inflammatory arthritis have disabilities and reduced QoL and are at an increased risk for cardiovascular disease (CVD) and CVD-related mortality (8). While these different diseases might be biologically different, and thus respond differently to pharmacologic treatment, there is strong reason to believe that the effects of physical activity on patient-reported outcomes in individuals with RA, SpA, and PsA are similar. Also, it has been shown that levels of function, fatigue, and pain are similar in these diseases (9). Patient-reported outcomes such as pain, fatigue, activity performance, and QoL are the most important outcomes for patients living with inflammatory arthritis (10–13). Previous systematic literature reviews have mainly focused on benefits of physical activity on objectively assessed outcomes, and there is a paucity of information in the literature on how physical activity can improve patient-reported outcomes and more patient-relevant outcomes in inflammatory arthritis. The present study is the first to synthesize evidence of effectiveness of physical activity on patient-reported outcomes such as QoL and self-reported function in adults with RA, SpA, and PsA. This study, which is called ENHANCE (Effectiveness Of Physical Activity Inflammatory Rheumatic Disease), will add synthesized knowledge about patient-experienced effects of well-characterized physical activity interventions.

## PATIENTS AND METHODS

This systematic review and meta-analysis is based on the items outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (14), which is registered in the International Register of Systematic Reviews (PROSPERO 2020: CRD42020175569) (See the PRISMA checklist in Supplementary Materials, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract).

**Data source and search strategy.** A comprehensive literature search was conducted in PubMed, Embase (Elsevier), CINAHL (EBSCO), and the Cochrane Central Register of Controlled Trials (CENTRAL) through September 21, 2020. The following search subject headings and search key terms were used: rheumatoid arthritis, RA, arthritis, rheumatoid, arthritis, inflammatory arthritis, inflammatory joint diseases, inflammatory rheumatic diseases, psoriatic, psoriatic arthritis, ankylosing spondylitis, spondyloarthritides, ankylosing, axial spondylarthritis, pelvospondylitis, spondyloarthropathies, Morbus Bechterew, physical activity, physical exercise, exercise training, muscle strength exercises, resistance training, aerobic fitness, cardiorespiratory exercise, and controlled trial. We also used the Cochrane Highly Sensitive Search Strategy (HSSS) to identify randomized trials in the above databases (https://work.cochrane.org/rct-filters-different-databases). A detailed description of the search strategy per database is presented in Documentation of Search Strategy in the Supplementary Materials (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract). The search strategy was augmented with manual searches of relevant reviews and reference lists of included articles. Two investigators (MB and ED) independently searched titles/abstracts and full texts for eligible articles. If agreement was not achieved, a third investigator (NB) adjudicated.

**Eligibility and participants.** Eligibility for study inclusion was determined using the PICOS (participants, interventions,

comparators, outcomes, and study design) approach. Adults ages 18 years or older who had a clinical diagnosis of RA, SpA (including ankylosing spondylitis [AS], undifferentiated SpA), axial SpA, pelvospondylitis, and spondyloarthropathy, or PsA based on established criteria (American College of Rheumatology or modified New York Criteria) were selected for study inclusion. We excluded trials of different types of arthritis that did not provide separate data for participants with RA, SpA, and PsA.

**Interventions, comparators, and outcome measures.** We included studies assessing physical activity or exercise as a stand-alone intervention using the previously cited WHO definitions (4). We excluded non–randomized controlled trial (RCT) studies, studies with fewer than 75% of RA, SpA, or PsA participants, studies that did not provide clear information of duration and dose (frequency/intensity) of the intervention, studies with treatment period of <2 weeks, studies that included a diagnosis of juvenile idiopathic arthritis, and studies without patient-reported outcome measures. We also excluded interventions that did not fulfill the WHO definition of physical activity or exercise, such as manipulation, balneotherapy, or passive movement. Multimodal interventions were also excluded unless the effect of physical activity/exercise could be assessed separately.

The following comparators were included: passive controls who were on a waiting list to receive treatment or who had not received treatment and active controls who had received usual care, another intervention, or a combination of treatments (as long as the effect of physical activity and exercise interventions could be measured distinctly from each other).

Studies reporting at least one of the following patient-reported outcome measures were included: 1) QoL and 2) self-reported function as defined by the International Classification of Functioning, Disability and Health (ICF) (15). QoL is defined as an individual's perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. QoL was the primary outcome measure, and self-reported function was the secondary outcome measure. Outcomes were extracted at the end of the intervention (i.e., posttreatment effects) regardless of the treatment duration.

**Study design.** We included only RCTs with a parallel-randomized or a cluster-randomized design published in peer-reviewed journals in English, Swedish, Norwegian, or Danish, and excluded studies with a quasi-experimental or cross-over study design.

**Data extraction.** The data extraction was performed by two investigators (MB and ED) and validated by a third investigator (NB). We recorded first author, year of publication, features of the interventions (e.g., type and dose frequency/intensity), comparator (active or inactive control), participant characteristics (e.g., mean age, percentage of female participants, condition treated, criteria used for diagnosis, sample size, and disease duration), and outcomes (time of assessment, instrument used, mean, SD, median, range, or any other data used to compute standardized mean difference [SMD] and SE).

**Study quality.** We assessed risk of bias within individual studies using the revised Cochrane Risk of Bias (RoB 2.0) tool for RCTs (16). This tool rates the potential for study bias arising from the randomization process, deviations from the intended intervention, missing outcome data, and measurement of outcomes and selective reporting. Overall risk of bias for each study was designated as "low," "some concerns," or "high." The risk of bias assessment was performed independently by 9 members of the author team, with 2 members (MB and NB) assessing each paper, and an extra assessment by another investigator (ED) performed in case of disagreement. We used the kappa statistical test to ascertain the consistency between assessors.

**Data analysis.** Data from the eligible RCTs were extracted and used to estimate the SMD or mean difference (MD) and the 95% confidence intervals (95% CIs) per outcome of interest. We calculated the mean ± SD for the outcomes of interest, which were reported as the median and interquartile range (IQR) using a specific formula (17). RCTs with inadequate data for synthesis were excluded from the meta-analysis. Given the heterogeneity in study designs and populations, the meta-analyses were conducted with the random-effects model (18) using Stata software, version 17.0, with the "metan" routine. We performed stratified meta-analyses by outcome and by condition treated (RA, SpA, and PsA). Heterogeneity was tested using chi-square, $\tau^2$, and $I^2$ statistics (19,20). $I^2$ index values of 25–50%, 51–75%, and >75% were considered as low, moderate, and high heterogeneity, respectively (20). Publication bias was analyzed using regression asymmetry test and visually inspecting the funnel plot (21) when >10 studies were included (22). A two-sided *P* value of less than 0.05 was considered statistically significant for all analyses. We assessed the overall quality of the evidence for each outcome of interest using the GRADE approach as recommended by the Cochrane Handbook (23).

When feasible, sensitivity analyses were performed on risk of bias and subgroup analysis on physical activity type (cardiorespiratory training, strength training, and mixed training) and intensity (high, moderate, and low). High intensity was defined as 60–89% of $V_{O_2}R$, 75–94% of maximum pulse, or rating of perceived exertion of 14–17, and moderate intensity was defined as 40–59% of $V_{O_2}R$, 60–74% of max pulse, or rating of perceived exertion of 12–13.

## RESULTS

**Search results.** The database search identified 11,376 articles. During the screening process, 3,835 duplicate articles were

excluded. After examining titles and abstracts, 7,431 additional articles were excluded. Thereafter, 110 full-text articles were retrieved and read; 55 articles were excluded because they did not meet the inclusion criteria (Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract). Thus, 55 studies were included in the analysis, though 18 were excluded from the quantitative synthesis because lack of data did not allow for calculation of the SMD/SE or because only follow-up data were reported, but not immediate postintervention effects (See Supplementary References 1–18 of excluded studies from meta-analysis). Hence, the final meta-analysis included 37 studies (Figure 1) (24–60).

**Characteristics of included studies.** The characteristics of the included studies are presented in Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract. The majority of studies were conducted in Brazil (n = 6), Sweden (n = 6), The Netherlands (n = 6), the UK (n = 5), the US (n = 5), and Norway (n = 4). Of the 55 RCTs, 42 investigated RA, 11 investigated SpA, and 2 investigated PsA. The median sample size per study was 60 participants with an IQR of 36–100 and a range of 17–490. The mean age ranged from 36.2 to 73.7 years, and 70% of the participants were female. The mean disease duration ranged from 0.8 to 24.9 years.

Cardiorespiratory training was examined in 19 RCTs, mixed cardiorespiratory and strength training in 24 RCTs, and strength training in 12 RCTs. The median duration of treatment was 3 months, with a range from 15 days to 2 years (Supplementary Table 2).

**Quality of included studies.** In the risk of bias analysis, the evaluators obtained a concordance index of 89.8% (Supplementary Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract). In domain 1 (the randomization process criterion), 61% of the studies presented a low risk of bias. In domain 2 (deviations from intended intervention criterion), 68% of the studies presented a low risk of bias, and 25% showed some concern of bias. In domain 3 (missing outcome

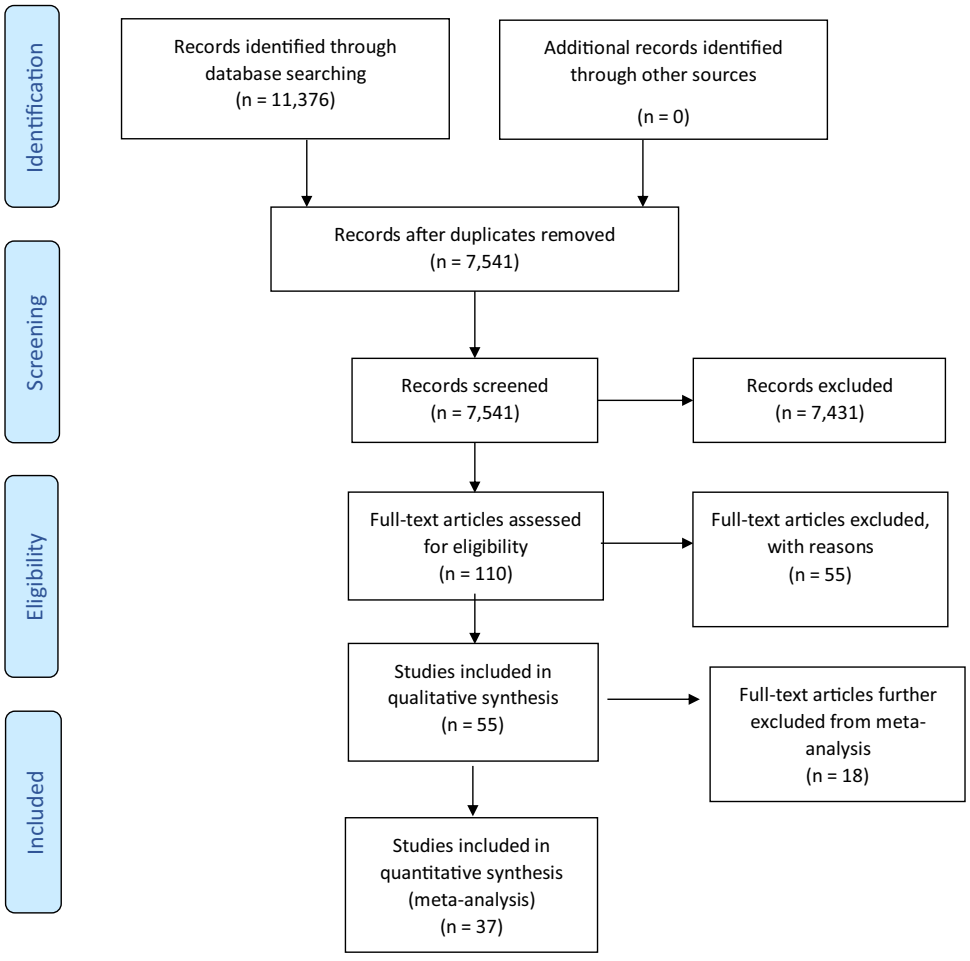


**Figure 1.** Flowchart of the selection process of included studies.

**Table 1.** Analysis of the effects of physical activity interventions on the overall and summary components of QoL in patients with RA*

| Outcomes of quality of life in RA | No.† | Intervention | Comparator‡ | ES (95% CI) | $I^2$ | *P* | Publication bias (*P* by Egger's test) | Quality of evidence |
|---|---|---|---|---|---|---|---|---|
| Overall QoL | 5 | Any physical activity (cardiorespiratory training + mixed cardiorespiratory and strength training) | Inactive control | 0.50 (0.10, 0.90) | 66 | 0.01§ | NA | Low |
| Physical component | 1 | Mixed cardiorespiratory and strength training | Inactive control | −0.10 (−0.77, 0.58) | NA | 0.78 | NA | Very low |
| Mental component | 2 | Mixed cardiorespiratory and strength training | Inactive control | 0.22 (−0.45, 0.89) | 47 | 0.52 | NA | Very low |
| Overall QoL | 7 | Any physical activity (cardiorespiratory training + mixed cardiorespiratory and strength training) | Active control | 0.00 (−0.19, 0.20) | 29 | 0.97 | NA | Low |
| Physical component | 3 | Any physical activity (cardiorespiratory training + mixed cardiorespiratory and strength training) | Active control | −0.18 (−0.52, 0.15) | 0 | 0.28 | NA | Low |
| Mental component | 2 | Any physical activity (cardiorespiratory training + mixed cardiorespiratory and strength training) | Active control | −0.09 (−0.49, 0.32) | 0 | 0.67 | NA | Low |

* 95% CI = 95% confidence interval; ES = effect size (standardized mean difference) from random effects meta-analysis; $I^2$ = heterogeneity; NA = not applicable; QoL = quality of life; RA = rheumatoid arthritis.
† Number of studies included in the meta-analysis.
‡ Inactive controls were defined as individuals who were on a waiting list to receive treatment, were receiving treatments as usual, or who had not received medical intervention. Active controls were defined as individuals who had received another type of treatment or exercise.
§ Statistically significant.

data criterion), 84% of the studies had a low risk of bias. In domain 4 (measurement of the outcome criterion), 84% of the studies presented a low risk of bias, and 15% presented some concerns. In domain 5 (selection of the reported result criterion), 52% of the studies presented a low risk of bias, and 46% presented some concerns of bias. The overall risk of bias showed that 18 (33%) of the 55 included studies were at low risk for bias, and 12 (32%) of the 37 studies included in the meta-analysis studies were at a low risk for bias (Supplementary Table 2).

**Effectiveness of physical activity on QoL and function in RA.** Regarding QoL, 12 studies met the inclusion criteria and provided adequate data for synthesis. Data on QoL were extracted from the studies using patient-reported outcome measures assessing general health, overall physical health, mental health, well-being, emotional aspects, vitality, or social aspects. The patient-reported outcome measures included the following instruments: EuroQol Health, Short-Form 36 health survey (SF-36), SF-12, RAND-36 score, Arthritis Impact Measurement Scale (AIMS) Psychological Health and Components, and Life Orientation Test. The SF-36 and SF-12 do not evaluate the general QoL, but the SF-36 and SF-12 domains were merged to the level of physical and mental component to harmonize the analysis across studies, which presented only summary components. In these instruments, improvement corresponded to increased scores; positive scores indicate improvement in favor of physical activity interventions.

Compared to the control group (i.e., treatment-as-usual/waiting list/no treatment), the physical activity interventions (i.e., cardiorespiratory training plus mixed cardiorespiratory and strength) had a significant postintervention improvement in the overall self-reported QoL (SMD 0.50 [95% CI 0.10, 0.90]; $P < 0.01$, $I^2 = 66\%$) (Table 1) (Supplementary Figure 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract). In the meta-analysis comparing the effect of physical activity interventions to an active control group (e.g., other training programs, home exercises, and medications), no significant between-group differences were found (Table 1) (Supplementary Figure 3). The overall quality of evidence was moderate to low (Table 1).

Regarding function, 26 studies met the inclusion criteria and provided adequate data for synthesis. The outcomes on function were extracted from the studies that presented self-reported data from questionnaires measuring function, such as the Health Assessment Questionnaire (HAQ), the Multidimensional Health Assessment Questionnaire (MD-HAQ), and pain or fatigue on the visual analog scale (VAS). In these instruments, negative scores indicate improvement due to physical activity interventions. Outcomes were categorized as follows: disease activity and disease symptoms, pain, fatigue, sleep, self-efficacy, depression, anxiety, mental aspects, physical function, and activity performance. The effects of physical activity interventions on function in patients with

**Table 2.** Analysis of the effects of physical activity interventions on outcomes of function in patients with RA

| Outcomes of function in RA | No.† | Intervention | Comparator‡ | ES (95% CI) | $I^2$ | *P* | Publication bias (*P* by Egger's test) | Quality of evidence |
|---|---|---|---|---|---|---|---|---|
| Activity performance | 29 | Any physical activity (cardiorespiratory training + strength + mixed cardiorespiratory and strength) | Inactive control | −0.25 (−0.37, −0.13) | 12 | <0.001§ | 0.45 | Moderate |
| Pain | 14 | Any physical activity (cardiorespiratory training + strength + mixed cardiorespiratory and strength) | Inactive control | −0.24 (−0.43, −0.05) | 44 | 0.01§ | 0.48 | Moderate |
| Fatigue | 12 | Any physical activity (cardiorespiratory training + mixed cardiorespiratory and strength) | Inactive control | −0.28 (−0.49, −0.08) | 59 | 0.006§ | 0.12 | Moderate |
| Sleep | 1 | Mixed cardiorespiratory and strength training | Inactive control | 0.22 (−0.23, 0.66) | NA | 0.33 | NA | Very low |
| Disease activity and disease symptoms | 1 | Mixed cardiorespiratory and strength training | Inactive control | −0.65 (−0.11, −0.19) | NA | 0.005§ | NA | Low |
| Self-efficacy | 7 | Any physical activity (cardiorespiratory training + mixed cardiorespiratory and strength) | Inactive control | 0.05 (−0.41, 0.50) | 84 | 0.85 | NA | Low |
| Depression, anxiety, and mental aspects | 3 | Cardiorespiratory training | Inactive control | −0.40 (−0.84, 0.03) | 60 | 0.07 | NA | Low |
| Physical function | 2 | Strength training + mixed cardiorespiratory and strength | Inactive control | −0.41 (−0.61, −0.20) | 0 | <0.001§ | NA | Low |
| Activity performance | 43 | Any physical activity (cardiorespiratory training + mixed cardiorespiratory and strength) | Active control | −0.01 (−0.14, 0.12) | 20 | 0.88 | 0.79 | Moderate |
| Pain | 17 | Any physical activity (cardiorespiratory training + mixed cardiorespiratory and strength) | Active control | −0.08 (−0.29, 0.14) | 43 | 0.50 | 0.06 | Moderate |
| Depression, anxiety, and mental aspects | 3 | Any physical activity (cardiorespiratory training + mixed cardiorespiratory and strength) | Active control | 0.02 (−0.35, 0.39) | 0 | 0.91 | NA | Moderate |

* 95% CI = 95% confidence interval; ES = effect size (standardized mean difference) from random effects meta-analysis; $I^2$ = heterogeneity; NA = not applicable; QoL = quality of life; RA = rheumatoid arthritis.
† Number of studies included in the meta-analysis.
‡ Inactive controls were defined as individuals who were on a waiting list to receive treatment, were receiving treatments as usual, or who had not received medical intervention. Active controls were defined as individuals who had received another type of treatment or exercise.
§ Statistically significant.

RA are presented in Table 2 and in Supplementary Figures 4 and 5, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract.

Compared to the control group (treatment-as-usual/waiting list/no treatment), any physical activity intervention had a significant postintervention improvement in the following areas: activity performance (SMD −0.25 [95% CI −0.37, −0.13]; $P < 0.001$, $I^2 = 12\%$), pain (SMD −0.24 [95% CI −0.43, −0.05]; $P < 0.05$, $I^2 = 44\%$), fatigue (SMD −0.28 [95% CI −0.49, −0.08]; $P = 0.006$, $I^2 = 59\%$), disease activity and disease symptoms (SMD −0.65 [95% CI −0.11, −0.19]; $P = 0.005$), and physical function (SMD −0.41 [95% CI −0.61, −0.20]; $P < 0.001$, $I^2 = 0\%$) (Table 2 and Supplementary Figure 4, at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract). However, no significant difference for any functional outcome was found for the effect of physical activity interventions with an active control group (e.g., other training programs, home exercises, medications) (Table 2 and Supplementary Figure 5). For pain, there was evidence of publication bias and small study effects, as indicated by Egger's test and funnel plot assessment (Supplementary Figures 6–10). The overall quality of evidence was moderate to low (Table 2).

**Effectiveness of physical activity on QoL and function in SpA.** Overall, five studies met the inclusion criteria and were included in the analysis. The effects of physical activity interventions on QoL of patients with SpA are illustrated in Figure 2 and Supplementary Figure 11, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract. In relation to the meta-analysis of QoL, a significant postintervention improvement in overall QoL (MD 3.22 [95% CI 1.99, 4.45]; $P < 0.001$) was found for the control group (i.e., treatment-as-usual/waiting list compared to the physical activity intervention cardiovascular training) (Figure 2). No other significant results were found for the effects of physical activity interventions on QoL of patients with SpA compared to active or inactive controls (Figure 2 and Supplementary Figure 11). In general, the overall quality of evidence was low.

Nine studies met the inclusion criteria and were included in the meta-analysis. The postintervention effects of physical activity interventions on function for patients with SpA are illustrated in Figure 3 and Supplementary Figure 12 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract). The outcomes were categorized as described in the RA section above. Again, an improvement was indicated by decreased scores except for sleep, self-efficacy, and physical function.

The following significant improvements were found in the group that performed physical activity interventions (strength training alone, mixed cardiorespiratory, strength training) compared to an inactive control group (treatment-as-usual): activity performance (SMD −0.60 [95% CI −1.09, −0.12]; $P < 0.02$,

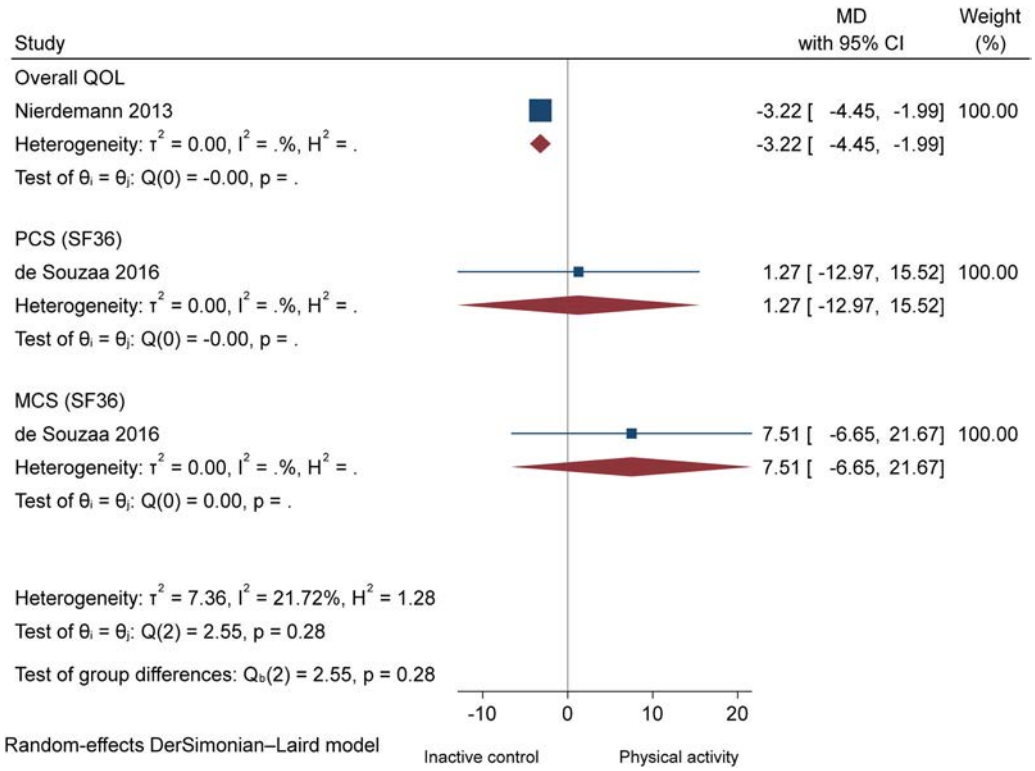


**Figure 2.** Analysis of the effects of physical activity interventions versus inactive control for quality of life in patients with spondyloarthritis. 95% CI = 95% confidence interval; MCS = mental component summary; MD = mean difference; PCS = physical component summary; QoL = quality of life; SF-36 = Short Form 36. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract.

$I^2 = 57\%$), disease activity and disease symptoms (SMD −0.67 [95% CI −0.91; −0.42]; $P < 0.001$, $I^2 = 53\%$), fatigue (SMD −0.87 [95% CI −0.65, −0.09]; $P < 0.03$), depression, anxiety, and mental aspects (SMD −1.02 [95% CI −1.82, −0.23]; $P < 0.01$), and pain (SMD −0.74 [95% CI −1.02, −0.45]; $P < 0.001$, $I^2 = 0\%$) (Figure 3).

Compared to an active control group (e.g., other training programs, home exercises, medications), physical activity interventions (cardiorespiratory, mixed cardiorespiratory, strength training) showed acute significant improvements postintervention only for fatigue (SMD −1.97 [95% CI −2.44, −1.51]; $P < 0.001$) and pain (SMD −1.12 [95% CI −2.12, −0.12]; $P < 0.03$, $I^2 = 94\%$)

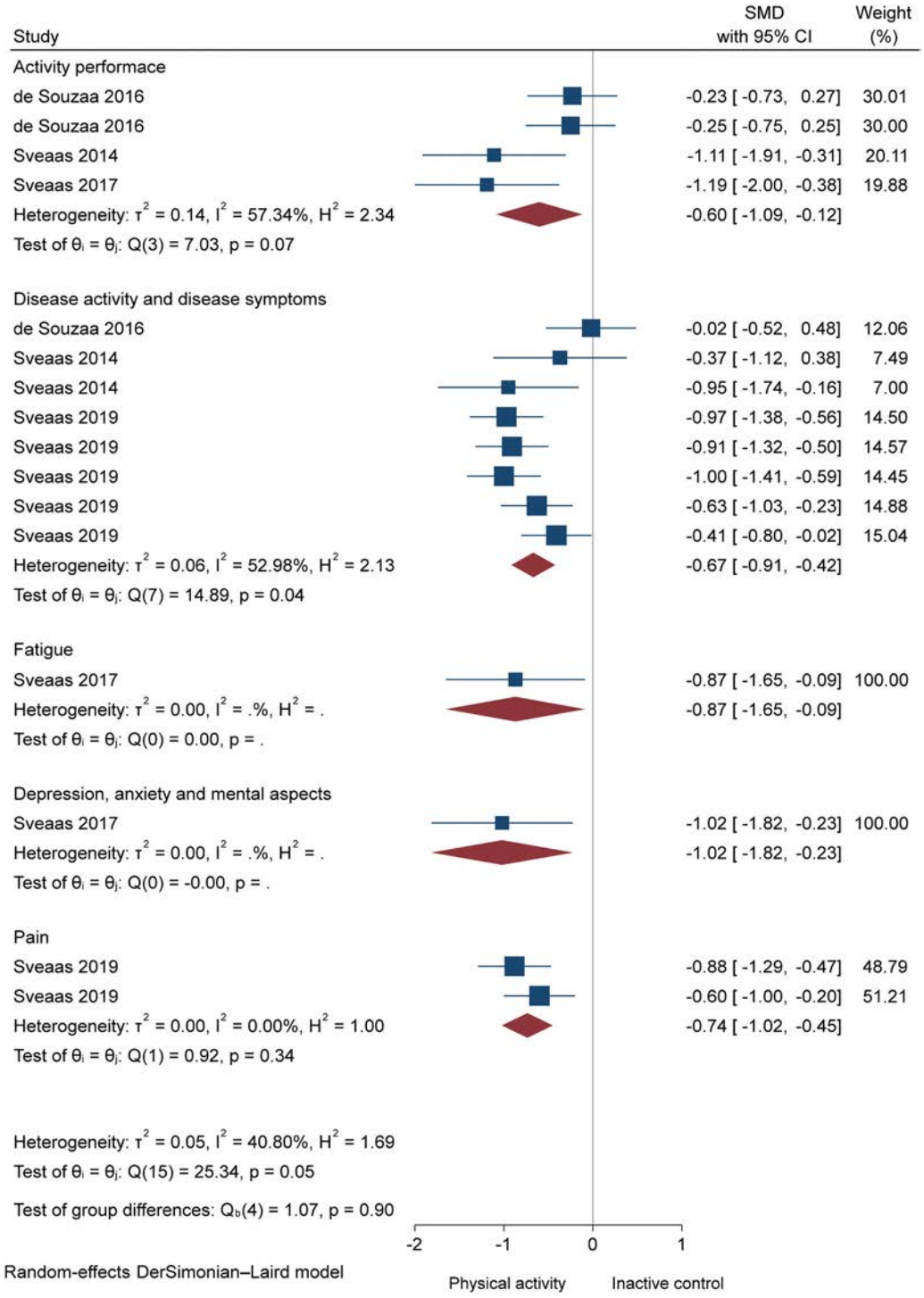


**Figure 3.** Analysis of the effects of physical activity interventions versus inactive control for function in patients with spondyloarthritis. 95% CI = 95% confidence interval; SMD = standardized mean difference. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract.

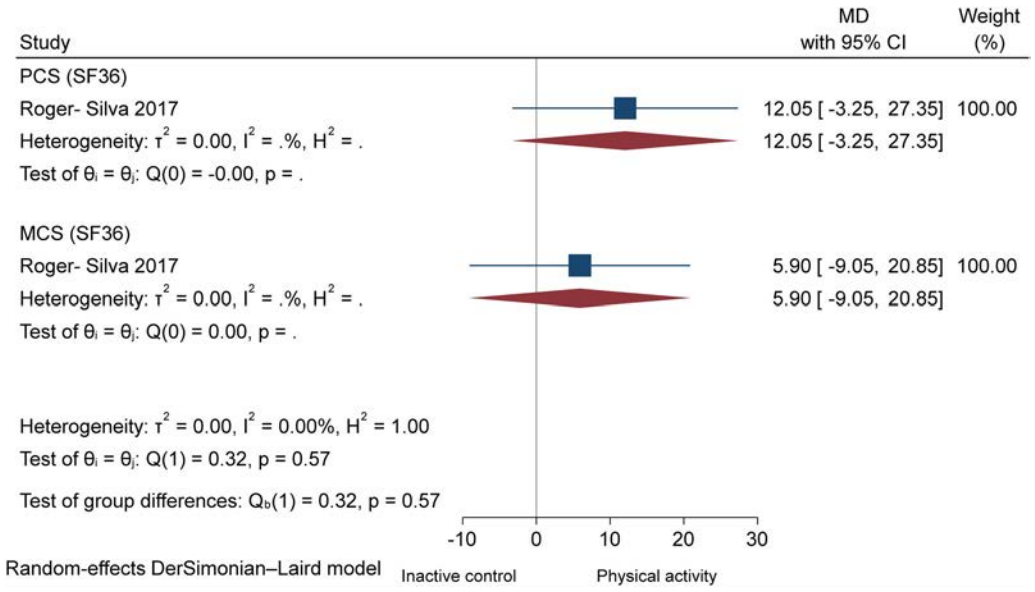


**Figure 4.** Analysis of the effects of physical activity interventions versus inactive control for quality of life in patients with psoriatic arthritis. 95% CI = 95% confidence interval; MCS = mental component summary; MD = mean difference; PCS = physical component summary; SF-36 = Short Form 36. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract.

(Supplementary Figure 12, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract). Egger's test and funnel plot assessment found no evidence of publication bias or small study effects for activity limitation (Supplementary Figure 13). The overall quality of evidence was moderate to low.

**Effectiveness of physical activity on QoL and function in PsA.** For PsA, two studies met the inclusion criteria, but only one was included in the analysis. Figure 4 depicts the postintervention effects of physical activity interventions on QoL of patients with PsA. No significant results were found for physical activity interventions (strength training) on QoL in patients with PsA. Generally, the overall quality of evidence was very low. The analysis using the SMD as effect size produced identical results.

The posttreatment effects of physical activity interventions on function in patients with PsA are illustrated in Supplementary Figure 14 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract), using the same method as previous for categorizing the outcomes.

Results from one study showed significant improvements in activity performance (SMD −0.57 [95% CI −1.01, −0.13]; $P < 0.01$, $I^2 = 0\%$) in the group that performed physical activity interventions (strength training) compared to a control group (waiting list) (Supplementary Figure 14). No data were available on physical activity versus an active control intervention. The overall quality of evidence was low.

**Sensitivity analysis.** Planned sensitivity and subgroup analyses were feasible only for RA. These results are illustrated in Supplementary Figures 15–36, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract. Sensitivity analyses limited to low risk of bias did not identify any significant postintervention effect on QoL but confirmed the significant postintervention improvement in activity performance (SMD −0.26 [95% CI −0.40, −0.12]; $P < 0.001$, $I^2 = 0\%$) and physical function (SMD −0.41 [95% CI −0.61, −0.20]; $P < 0.001$, $I^2 = 0\%$) for the group that performed any physical activity intervention. No other outcome remained significant in the analyses (Supplementary Figures 15–18).

Compared to an inactive control group, cardiorespiratory physical activity showed significant effects on overall QoL (SMD 0.55 [95% CI 0.05, 1.04]; $P = 0.03$, $I^2 = 75\%$) (Supplementary Figure 19). Cardiorespiratory, strength, and combined physical activity interventions showed effects on various aspects of function (Supplementary Figures 20–28).

Subgroup analyses of high-intensity physical activity showed significant effects on overall QoL and self-efficacy compared to inactive control (Supplementary Figures 29 and 33, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24805/abstract). In studies with moderate intensity, significant effects were found for many outcomes on function irrespective of physical activity type versus inactive control (i.e., activity performance, pain, fatigue, physical function) (Supplementary Figures 31–35), whereas significant effect was found for pain versus active control (Supplementary Figure 36).

## DISCUSSION

Overall, the results showed small and somewhat inconsistent positive effects of physical activity on QoL and different aspects of

function at the end of the intervention for patients with inflammatory arthritis. One reason is that the majority of studies included in the meta-analysis were single small studies, and there is also a possibility that the largest study might drag the overall effect size and vice versa (61). Our somewhat strict selection of only studies with a clear description of dose was chosen to enhance direct transfer to clinical practice. As we did not include other types of physical activity, such as low-intensity activities and range of motion exercise, we cannot draw any conclusions about their effect on QoL or self-reported function.

We found no evidence that physical activity was specifically more effective for any of the three diagnoses examined in the present study. The largest number of studies were on RA, where the results showed that any type of physical activity led to improved QoL compared to inactive controls, an effect that was no longer seen when compared against an active control intervention. A similar result was found regarding outcomes of function where the effects on activity performance, pain, fatigue, disease activity, disease symptoms, and physical function were found only when compared to inactive control groups. As physical activity has played a central role in the treatment of RA for a long time, the active control interventions could be too similar to the ones investigated here to lead to differences in effectiveness. As most studies had rather small sample sizes, similar results could also have been due to under-powered studies.

In SpA, positive effects were found for QoL in the inactive control group. Effects in favor of physical activity were found for activity performance, disease activity, disease symptoms, fatigue, depression, anxiety, mental aspects, and pain compared to inactive controls. The effects on pain and fatigue also remained when physical activity was compared to active controls. This could be explained by the physical activity performed by the intervention groups probably being more intensive than the physical activity performed by the active control groups. Pain and fatigue are likely driven by inflammation in patients with SpA.

In previous studies of inflammatory arthritis as well as systemic disorders, intensive exercise has contributed to less inflammation and disease activity (62,63). Furthermore, the intervention groups' ability to optimize exercise intensity and reduce fear of increasing pain and fatigue may have been due to attention from health care professionals. In SpA, we were not able to analyze axial, peripheral, and nonradiographic subgroups separately. Six of the studies included patients with AS according to the modified New York criteria, and five of the studies included patients with axial SpA according to the Assessment of SpA International Society classification criteria. This might indicate that the AS group is more severely affected by their disease than the axial SpA group as the diagnosis of AS requires radiographic evidence of sacroiliac and/or spinal involvement. However, disease activity was varied among included studies in both disease groups, indicating an overall similar state among all patients. Knowledge on the effects of physical activity on different diagnostic subgroups is essential for the individual tailoring of physical activity interventions and is therefore encouraged in future studies.

In PsA, only one study was available to be included in the meta-analysis, which indicates a huge lack of research including this diagnostic group. The included study investigated strength training and showed small effects on activity performance, which is promising. However, more studies are needed to enhance the understanding of the effect of physical activity in PsA.

Patients with inflammatory arthritis are less physically active than the general population (6,7) and at higher risk for CVD (64,65) and other health-related comorbidities, such as diabetes mellitus and osteoporosis. One important part of treatment is to promote regular physical activity to reduce cardiovascular risk factors (66) or other lifestyle-related diseases. Changes in sedentary behaviors require motivation (67). This motivation, in part, can come from the knowledge that physical activity not only improves oxygen uptake and muscle strength, but also can lead to less pain and fatigue and improved mental and activity performance. To optimize adherence and to achieve the best effect on an individual level, there is a need to tailor physical activity interventions to every patient's goals and their existing conditions—for example, level of pain and fatigue and other factors such as sedentary behavior or health literacy—in order to achieve the best effect on an individual level.

In the sensitivity analysis, low risk of bias confirmed the post-intervention effects on activity performance and physical function in RA, highlighting the importance of well-designed studies to achieve solid findings. Subgroup analyses indicate that cardiorespiratory physical activity improves QoL in RA, but the results are similar for the different physical activities regarding function. In addition, moderate intensity physical activity seems to confer more benefits than high intensity physical activity regarding both QoL and function in patients with RA. However, this finding might be due to the lower number of studies with high-intensity physical activity. Overall, there is a need for future RCTs in this field to include similar reporting in regard to control group, study period, comorbidities, and adherence. There is also a need for high-quality and homogeneous longitudinal data with a larger sample size in forthcoming RCTs in this field. Such research will allow for subgroup analyses related to aspects of disease severity, comorbidity, or coexisting symptoms as well as sedentary behavior or disabilities. Of the 55 RCTs, 18 (33%) were low risk for bias, an expected result as blinding in regard to physical activity intervention is impossible.

Our study had several limitations. First, the number of studies as well as the sample size were small for most of the outcomes, especially for SpA and PsA. Therefore, neither sensitivity analyses nor any subgroup analyses were possible. However, sensitivity analysis was possible in RA, as there were more studies with larger sample sizes and more clearly detailed intervention descriptions. Another limitation is the low granularity of adequately reported data, which reduced the number of

studies in the meta-analysis. Furthermore, the physical activity interventions had great variability in terms of duration of treatment and time of outcome assessment, which is not reflected in the present analyses. Many more studies would have been needed to adequately include duration in the subgroup analyses. We also did not assess the long-term effect of physical activity, only the postintervention effects based on outcomes eligible at the end of intervention periods. The effects from interventions not targeting maintenance or not including behavioral change strategies could have diminished over weeks to a few months after the intervention. Finally, the restricted number of studies comparing physical interventions with other active controls or follow-up assessments underscores the necessity for further research into physical activity intervention for various inflammatory arthritis subtypes. Given these limitations, our results should be considered with caution.

Nevertheless, the synthesized evidence shows that physical activity can lead to less pain, fatigue, and improved mental and activity performance in inflammatory arthritis with the most comprehensive information on RA and SpA. Clinical implications support the use of instruments capturing the patient-reported outcomes to assess a larger variety of effects of physical activity in inflammatory arthritis in addition to commonly used objective outcome measures. This might improve both short-term and long-term compliance to physical activity interventions with health benefits for the individual. Patient-reported aspects of health are as important as objective measures of disease activity and function in the care of patients with inflammatory arthritis. Future research should focus on the effects of physical activity in PsA, as well in larger, powered studies with standardized protocols to understand the effects of different kind of physical activity interventions.

## 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 submitted for publication. Dr. Björk 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.** Björk, Dragioti, Alexandersson, Appel Esbensen, Boström, Friden, Hjalmarsson, Hörnberg, Kjeken, Regardt, Sundelin, Sverker, Welin, Brodin.

**Acquisition of data.** Björk, Dragioti, Boström, Kjeken, Sundelin, Brodin.

**Analysis and interpretation of data.** Björk, Dragioti, Alexandersson, Appel Esbensen, Hörnberg, Kjeken, Sundelin, Brodin.

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REHABILITATION SCIENCES AND THE RHEUMATIC DISEASES

# The Future of Axial Spondyloarthritis Rehabilitation: Lessons Learned From COVID-19

Rosemarie Barnett and Raj Sengupta

**Supervised physical therapy and rehabilitation are vital for effective long-term management of axial spondyloarthritis (SpA). However, the unprecedented year of 2020 and the COVID-19 pandemic has prompted a drastic change in health care provision across all disease areas. In this review, we summarize changes that have been introduced to support rehabilitation in axial SpA during the pandemic and considerations for the future of axial SpA rehabilitation in the wake of COVID-19. We have witnessed the launch of online virtual physical therapy and education, in addition to an emphasis on remote monitoring. We have been propelled into a new era of digital service provision; not only providing a temporary stop-gap in treatment for some patients, but in the future, potentially allowing for a wider reach and provision of care and resilience of vital services. Unique collaboration between patients, health care professionals, and researchers will be key to fostering relationships and trust and facilitating wider evaluation and implementation of digital services at each stage in a patient's journey, which is imperative for relieving pressure from health care providers. Despite the potential of such digital interventions, it is important to highlight the maintained critical need for face-to-face services, particularly for vulnerable patients or during diagnosis or a flare of symptoms. It is also vital that we remain vigilant regarding digital exclusion to avoid further widening of existing health inequalities. Optimization of digital infrastructure, staff skills, and digital education alongside promoting accessibility and engagement and building trust among communities will be vital as we enter this new age of blended in-person and digital service provision.**

## Introduction

Physical therapy and rehabilitation are cornerstones of nonpharmacologic treatment for axial spondyloarthritis (SpA) and are critical for adequate long-term disease management (1,2). There is extensive evidence to suggest that physical activity is effective at reducing symptoms and disease activity in axial SpA, with a corresponding increase in spinal mobility, physical function, and cardiorespiratory fitness (1,3–8). As such, European treatment guidelines highlight the importance of a combination of nonpharmacologic and pharmacologic treatment modalities, including an emphasis on physical therapy, to optimize management of the condition (9). However, the most effective protocol for physical activity in axial SpA remains unclear (1,10).

Recent evidence suggests that physical therapy for axial SpA should be prescribed based on the individual, while covering aerobic, flexibility, resistance, and neuromotor training (1). While unsupervised home-based exercises have been found to be efficacious for patients, supervised physical therapy has been suggested to be more effective (2,11–14). Furthermore, recent research has highlighted the potential paradoxical role of biomechanical stress and entheseal microdamage in the radiologic progression of axial SpA through potential development of tissue-specific inflammation and complex interactions between proinflammatory pathways, including the likely role of cytokines, growth factors, and

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tissue-resident cells (10). Therefore, evidence-based exercises provided in a one-to-one or group setting guided by a highly experienced, specialized physical therapist may be preferable initially, whereby the specialist can gauge the capabilities of the patient and recommend appropriate stretches and exercise accordingly on a case-by-case basis. This supervised mode of delivery by a specialist has also been identified as important to patients (13).

The unprecedented year of 2020, however, and the COVID-19 pandemic have prompted a drastic change in health care provision across all disease areas. Patients have been unable to attend face-to-face appointments or supervised physical therapy, and a widening of existing gaps in health care have been highlighted (15). In the international REUMAVID study, of 1,707 patients with rheumatic musculoskeletal diseases (RMDs) surveyed from 15 European countries (47.5% of patients with an axial SpA diagnosis), 45.0% reported worsening health during the pandemic (16). In REUMAVID, patients also reported increased alcohol consumption, smoking, weight gain, and reduced physical activity, including an inability to continue rehabilitation exercises or physical therapy programs (17). Individuals participating in REUMAVID received poor access to care, 60.6% being unable to keep their rheumatologist appointment, 92.5% of which were canceled by their health care provider. More than one-half of participants perceived their health status to be "fair to very bad" and reported poor well-being as indicated by the World Health Organization Five Well-Being Index. Similar results have been reported in the UK specifically, where in a survey of health care professionals and patients conducted by the National Axial Spondyloarthritis Society (NASS), almost one-half of the patients reported a worsening of symptoms and deterioration of both general and mental health during lockdown (15). In the US, a study of 1,692 rheumatology patients from New York demonstrated that difficulties with medication access and flares were common during the peak of the pandemic (18). Furthermore, difficulty with medication access and COVID-related distress were both strongly associated with patient-reported flare and disease activity in this patient group.

As described by the NASS in the UK, although the COVID-19 pandemic has highlighted existing gaps in service provision for patients with axial SpA, it has also accelerated change, with the introduction of virtual and remote consultations, including care for flares, and an increased interest in digital service provision and the importance of remote monitoring (15). Indeed, it has required a rapid adaptation of both patients and clinicians' practices to embrace new ways of working. The pandemic has also highlighted the need for imminent changes and prioritization of initiatives to revolutionize both the resilience and efficiency of our current health care systems to ultimately provide optimal support and the best possible care for patients with axial SpA (15). In the present article, we discuss changes that have been introduced to support rehabilitation in axial SpA during the pandemic and considerations for the future of axial SpA rehabilitation in the wake of COVID-19.

## Change in axial SpA rehabilitation services during COVID-19

At the Royal National Hospital for Rheumatic Diseases (RNHRD) in Bath, the unique 2-week inpatient physical therapy rehabilitation program has been integral to axial SpA care since the 1970s. The course provides individuals with the tools that they need to confidently self-manage their condition, placing an emphasis on education, self-management, physical therapy, and hydrotherapy, with input from a multidisciplinary team of physical therapists, a consultant rheumatologist, occupational therapist, counsellors, pharmacist, dietician, and health care assistants. There are no strict entry criteria for program referral. However, it is thought to be particularly beneficial for newly diagnosed patients, those in flare and who are struggling to manage their condition, postsurgery (e.g., following hip replacement), or to maximize outcomes of biologic therapy. To cater to differing levels of disease activity, function, and mobility, the program is delivered at 3 levels of intensity depending on spinal mobility (according to the Bath Ankylosing Spondylitis Metrology Index [BASMI]): fast (BASMI score 0–3), fast/moderate (BASMI score 3–5), and moderate (BASMI score ≥5). Patients may attend the course more than once on an as- and when-appropriate basis.

Significant short- and long-term improvements in disease activity, spinal mobility, and function have been observed following course attendance (19,20). The social element of the course, including meeting others with the condition, is also a critical element of the program's success. Participants have been known to forge long-lasting relationships following the course and to form critical support networks of mutual understanding. Although yet to be explored in detail in the context of the course, relatedness indeed forms 1 of the 3 basic psychological needs as detailed in self-determination theory. Self-determination theory proposes that when 3 innate basic psychological needs for autonomy, competence, and relatedness are fulfilled, positive outcomes are achieved, with these 3 factors suggested to be the most predictive and reliable mediators of motivation, engagement, and well-being (21). The impact of the course on such outcomes is currently being explored in ongoing analysis.

During the pandemic, the importance of maintaining some form of supervised axial SpA rehabilitation delivery was recognized very early on at the RNHRD. As such, a group of highly skilled specialist physical therapists and rheumatologists, with input from a team of academics and behavioral scientists, was able to develop an online course to be delivered remotely via Zoom. While some services were obviously not available virtually (e.g., hydrotherapy), the core components of the course (education, self-management, and physical therapy) remained or could be reproduced, to an extent, online.

Similarly, we have seen organizations such as the NASS migrate from in-person to online educational events, enabling

a much wider reach for axial SpA education (22). The NASS has been hosting regular live online self-management sessions, with a wealth of legacy resources now available across its platforms, including recorded physical therapy sessions delivered live by specialist physical therapists.

## Introduction of remote data collection for axial SpA services

At the RNHRD, not only are participants now able to attend the Bath axial SpA rehabilitation course from their own home, but standard patient-reported outcome measures collected pre- and post-course (and at each clinic appointment) have been migrated to an online system called Meridian. This includes measures such as disease activity (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]), function (Bath Ankylosing Spondylitis Functional Index [BASFI] patient global assessment), quality of life, fatigue (Functional Assessment of Chronic Illness Therapy), anxiety and depression (EuroQol 5-domain instrument), work productivity (Work Productivity and Activity Impairment questionnaire), and sleep (Jenkins sleep scale). Patients enter data via a unique online Meridian portal, and these data are then automatically integrated into the hospital system. This has facilitated the previously unforeseen efficiency of data collection both for research and for clinical use in axial SpA. Clinicians can now access individual patient-level graphical representations of, for example, disease activity (BASDAI) over time via Meridian during a clinic appointment, while approved researchers can access anonymized, aggregated data for patients who consented to the Bath Spondyloarthritis Research Biobank. More than 30 years' worth of paper records have also been digitized and integrated into Meridian. This includes additional measures such as spinal mobility (BASMI) and laboratory results such as C-reactive protein level. Furthermore, additional digitized information for research, such as coded Margolis Pain Diagrams (specifying regional or chronic widespread pain) and occurrence of significant life events, is available for a subset of ~200 patients.

Although traditional patient-reported outcome measures are critical for understanding overall changes in disease activity and quality of life over time, they are subject to recall bias and may fail to capture a significant proportion of day-to-day disease information. In chronic, inflammatory conditions such as axial SpA where there may be fluctuating periods of disease activity and flare, these subtle daily changes in symptoms could be of critical importance for gaining a better understanding of the condition and for optimizing and personalizing treatments such as physical therapy. In 2017, the European Alliance of Associations for Rheumatology produced a "research roadmap to transform the lives of people with RMDs," often referred to as Rheuma-Map, which highlighted the need to better explore the impact of physical activity and lifestyle on the progression of axial SpA. Implementation of remote monitoring and digital technologies such as wearable devices and smartphones for granular, daily remote monitoring of symptoms and activity could be critical to meet this outlined need. Monitoring of lifestyle and physical activity and symptom data may also allow patients to gain a better understanding of their condition, while allowing them to gauge the level of physical activity that feels good for them and implement lifestyle changes accordingly. Since the start of the pandemic, we have seen an increased interest in remote monitoring both for research and clinical purposes. At the RNHRD, >350 patients are now registered with the RNHRD Project Nightingale study (www.projectnightingale.org), whereby individuals can use a smartphone app to track daily self-reported data in between clinical appointments, as well as before, during, and after course attendance. This includes variables such as pain, mood, stress, sleep, fatigue, flare, use of antiinflammatory drugs, and recommended exercise in addition to less explored variables such as menstrual cycle, caffeine intake, and screen time. The app can also be linked with an individual's wearable device if they have one to collect data on steps, heart rate, and sleep. Since September 2020, all patients invited to attend the virtual rehabilitation program have been invited to participate in Project Nightingale when referred to the course. This will form a larger piece of validation work to determine the capabilities of smartphone technologies to support both assessment of rehabilitation outcomes and potentially self-management. Indeed, enthusiastic patients at the RNHRD have expressed how Project Nightingale has helped them better self-manage and understand their disease while providing them motivation to exercise independently following intensive, supervised rehabilitation (23). However, until the platform has been evaluated scientifically, we cannot make firm recommendations for its use in health care.

## Considerations for future axial SpA rehabilitation delivery

In terms of rehabilitation specifically, as suggested in feedback from RNHRD patients' post-virtual course, the future will likely involve a blended combination of in-person and online physical therapy with complementary remote data collection pre- and post-course. Online therapy could be implemented either as a "top up" between in-person appointments or as an alternative for patients who may not have the time to commit to an intensive rehabilitation program, such as the 2-week inpatient course delivered at Bath. Indeed, axial SpA often develops in the second or third decade of a patient's life, which is a critical time for establishing relationships and careers. Therefore, some individuals may prefer a shorter online course, whereby they can fit their initial education and physical therapy around their daily routine. This could also potentially be beneficial in terms of incorporating patients' habits into their usual environment, which may be trickier to implement and adjust to if they are coming from an immersive program away from day-to-day life.

In Bath, while feedback on the axial SpA virtual rehabilitation program has been overwhelmingly positive, we need further

robust evidence to ensure the acceptability, accessibility, and efficacy of digital rehabilitation interventions, and in particular, their comparative effectiveness alongside in-person rehabilitation. While there is some published evidence to suggest telerehabilitation as a suitable substitution for face-to-face interventions in chronic nonmalignant musculoskeletal pain, including some forms of arthritis, we should be cautious about generalizing these results to axial SpA specifically, and methodologic limitations have been described (e.g., small sample size, short follow-up) (24). Research has been conducted assessing the effectiveness of telerehabilitation in RMDs more broadly. These studies have found that real-time telerehabilitation can improve physical function and pain and is comparable to face-to-face intervention in terms of this improvement (25). A recent systematic review in rheumatoid arthritis identified 5 randomized controlled trials reporting a positive impact of telehealth interventions on factors such as disease activity, medication adherence, physical activity, and self-efficacy (26), although there was high heterogeneity in the interventions described. Similarly, a recent rapid review identified 14 systematic reviews exploring the effectiveness of telerehabilitation in musculoskeletal conditions, whereby, despite contradictory results, telerehabilitation could be comparable with in-person rehabilitation or better than no rehabilitation for conditions such as osteoarthritis, low back pain, and hip and knee replacement (27). These findings suggest that telerehabilitation may be effective in improving symptoms in RMDs. However, evidence is still limited, and there is an imperative need for better quality clinical trials and systematic reviews to provide sufficient evidence on efficacy and effectiveness (27). Analyses of the virtual rehabilitation program for axial SpA are currently ongoing in Bath, while similar web-based physical therapy interventions are also being tested for axial SpA in Glasgow (28).

Input and considerations from physical therapists will also be critical when considering implementation of telerehabilitation for axial SpA. Key challenges currently identified are difficulties assessing patient mobility via Zoom or when observing and instructing patients, particularly while monitoring their performance of instructed exercises or if needing to provide discrete, individualized feedback during group activities (which is much easier in person, e.g., taking someone to one side to adjust their movement, and not so feasible in an online setting). Smaller groups of patients were also preferable with remote delivery, as it was harder to monitor multiple patients' movement via a screen.

Over time, the format of the digital course can be tweaked based on further feedback from patients and the unique experience and expert knowledge of the contributing health care professionals. Economic evaluations could also be useful to determine the cost-effectiveness of digital versus in-patient rehabilitation. Future wider implementation of digital rehabilitation for axial SpA could be critical in terms of relieving pressure from the health services, reducing wait times, and reducing travel burden for patients. However, we foresee that some form of in-person, supervised delivery will still be vital, particularly for those individuals who are newly diagnosed, fearful of movement, or who may have more severe disease and need closer supervision to prevent injury during exercise. Future studies to identify those patients who may most benefit from an in-person versus virtual rehabilitation program will be useful to refine these parameters, as will collaborations between patients, health care professionals, and researchers from multidisciplinary fields (biomechanics, human–computer interaction, health psychology) to assess the impact of such interventions and the best way to implement them. An initial in-person first-contact visit should also be considered to fully triage a patient's capabilities before prescription.

The immersive element of the 2-week inpatient program may also have greater benefits in terms of improving or maintaining motivation for exercise in the long term. Spurring or maintaining motivation may be more difficult when being guided over a monitor versus an immersive experience with peers and physical therapists who are living and breathing the rehabilitation together in a socially supportive environment away from other commitments and worries in day-to-day life. Even in terms of the pandemic, many of us have experienced dull motivation and focus, described as languishing (29), when attempting to work from home all day behind a monitor; similar feelings could be experienced with the virtual course. It must therefore be ensured that we do not simply abandon invaluable in-person follow-up visits and rehabilitation completely, as certain aspects simply cannot be replicated virtually. Furthermore, loss of in-person follow-up or initiation of patient-initiated, in-person follow-up may be particularly detrimental to those patients who are more stoic in nature. Indeed, in a clinic, it is not unusual for a physician to notice a sign or symptom that has not otherwise been raised by a patient. In a recent service evaluation in Bath involving interviews with rheumatology patients and clinicians at the RNHRD, the importance of in-person interaction for reassurance was highlighted (both for patients, that they have been assessed holistically, and for staff, that they have not missed key signs of disease progression) to build patient trust in what was going to be a long-term therapeutic relationship.

While digital interventions such as virtual rehabilitation potentially offer an array of benefits in terms of accessibility, relieving pressure on health services, and economic implications, digital exclusion is another key factor that must be considered. The term digital exclusion refers to those who lack the access, capacity, skills, motivation and/or trust to confidently go online (30). Indeed, digital exclusion exists at the intersection of multiple inequalities, whereby studies have shown that nonusers of the internet, devices, and online services are increasingly in vulnerable groups and may be older, less educated, and more likely to be unemployed, disabled, or socially isolated (31). In a recent study of 548 rheumatologists from 64 countries, although 82% of rheumatologists had switched to telehealth video during the pandemic, 17% estimated that approximately one-fourth of patients did not have access to telehealth video, especially those patients living below the poverty line (32). Respondents expressed a concern

for these more socially and economically vulnerable patients, whereby wide implementation of telehealth could further widen existing health inequalities and differences in health literacy. During the pandemic, interruption of disease-modifying antirheumatic drugs without recommendation by a physician was also shown to be associated with lower socioeconomic status (33). The identification of vulnerable patients at risk of digital exclusion should be considered when beginning to implement telehealth. These patients should perhaps be prioritized for in-person, face-to-face health care delivery. In the context of rehabilitation, however, for individuals who may be more economically vulnerable and unable to take considerable time off work for an immersive rehabilitation program such as the 2-week course at the RNHRD, an online course to complete around other commitments may be preferable if provided with the appropriate resources and support.

Other considerations are provision of digital education and optimization of health services, which will be critical for suitable implementation. In a recent survey of patients and clinicians, although >70% of patients and rheumatologists believed that digital health applications were useful in the management of RMDs, patients and rheumatologists respectively highlighted lack of information on suitable applications (58.5% of patients; 41.9% of rheumatologists) and poor usability (42.1% of patients) as key barriers to implementation (34). Rheumatologists also highlighted the importance of research evidence to support the implementation of such digital services.

In the UK, a survey study of patients with axial SpA and rheumatologists during the pandemic highlighted some key areas requiring urgent attention, including upskilling of digital service provision (embedding good digital practice) and addressing gaps in digital infrastructure and staff skills (15). For example, in terms of patient coding, just 58% of health care professionals surveyed in the aforementioned study were able to identify the cohort of patients at high-risk of COVID-19 under their care in 2 weeks or less. Furthermore, 10% of respondents were still unable to identify high-risk patients 4 months after shielding guidance was first issued by the UK government. Coding challenges were often the cause of these delays and the huge variation in times to identify high-risk patients. Interestingly, similar coding concerns throughout other rheumatology services prompted in Leeds the development of a strategy to communicate with patients online and enable them to self-assess their COVID-19 risk (35). The authors described the flexibility and agility of the NHS in the UK for introducing drastic change rapidly when pressured on such an unprecedented scale, in addition to describing the encouraging level of engagement of patients when it came to self-assessment and self-education.

## Conclusions

Physical therapy and rehabilitation are key in the management of axial SpA. Despite the challenges faced, the pandemic has also fostered an environment for adaptation and development of creative solutions to provide continued care. Indeed, all services have been tested and as such have been propelled into a new era of digital service provision. We have witnessed the launch of online virtual physical therapy and education in addition to an emphasis on remote monitoring. Not only has this provided a temporary stop-gap in treatment for some patients, but in the future, it may allow for a wider reach and provision of care and resilience of vital services. Unique collaboration between patients, health care professionals, and researchers will be key to fostering relationships and trust and facilitating wider evaluation and implementation of digital services at each stage in a patient's journey (from diagnosis to rehabilitation and long-term condition management), which are imperative to relieve pressure from health care providers. Despite the potential of such digital interventions, it is important to highlight the maintained critical need for face-to-face services, particularly during diagnosis or during a flare of symptoms. We must ensure that digital interventions are evaluated rigorously before widespread implementation in clinical practice. It is also vital that we remain vigilant regarding digital exclusion and that we avoid a further widening of existing health inequalities. Optimization of digital infrastructure, staff skills, and digital education alongside promoting accessibility, engagement, and building trust among communities will be vital as we enter this new age of blended in-person and digital service provision.

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## AUTHOR CONTRIBUTIONS

Both authors were involved in drafting the article or revising it critically for important intellectual content, and both authors approved the final version to be submitted for publication.

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REHABILITATION SCIENCES AND THE RHEUMATIC DISEASES

# Motivators, Barriers, and Opportunity for E-Health to Encourage Physical Activity in Axial Spondyloarthritis: A Qualitative Descriptive Study

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**Objective.** Physical activity is fundamental in the management of axial spondyloarthritis (SpA); however, evidence suggests that patients with axial SpA are not adhering to physical activity recommendations. E-health technology (e.g., telephone reminders and mobile text messaging) can increase participation in physical activity. The aims of this study were as follows: 1) to understand perspectives of the importance of physical activity in the management of axial SpA; 2) to describe factors associated with physical activity adherence; and 3) to explore the role of e-health technology to facilitate physical activity in patients with axial SpA.

**Methods.** Semistructured interviews were conducted with axial SpA patients attending an urban academic rheumatology clinic. Interviews were audio recorded and transcribed verbatim. Data were analyzed using thematic principles. Systematic labeling of the data set was completed using an inductive approach until saturation of emergent themes.

**Results.** Twelve patient interviews were completed. Most respondents were male (83.3%) with a mean ± SD age of 45.5 ± 12.5 years and a mean ± SD disease duration of 21.5 ± 14.9 years. Participants defined physical as any activity involving physical exertion. The role of physical activity in axial SpA management was well recognized and included symptom relief, pharmacologic synergy, and impact on general health. Motivators included a growth mindset, social support networks, and facility access. Barriers included fear of disease progression, life demands, and environmental restrictions. Feedback, electronic reminders, and virtual support networks were key components of e-health technology to facilitate engagement in physical activity.

**Conclusion.** The results of this study provide a foundation to guide development of patient-centered e-health technology interventions to increase physical activity uptake in patients with axial SpA.

## INTRODUCTION

Physical activity is defined as "any bodily movement produced by skeletal muscles that requires energy expenditure" and includes activity associated with work, play, travel, and leisure time (1). Exercise is an important subcomponent of physical activity and refers to planned, structured, and repetitive activity aimed at improving 1 or more components of physical fitness. Current guidelines for optimal physical activity suggest that "adults aged 18–64 years accumulate at least 150 minutes of moderate- to vigorous-intensity aerobic physical activity per week" (2). The benefits of physical activity are well established and include increased musculoskeletal and cardiorespiratory fitness, improved general function, and reduction in the risk of developing chronic disease, including hypertension, cardiovascular disease, type 2 diabetes mellitus, and depression (3).

Axial spondyloarthritis (SpA) is a chronic autoimmune disease that primarily affects the spine and manifests in pain, progressive stiffness, involvement of peripheral joints, and extraarticular manifestations affecting the ocular, gastrointestinal, and dermal systems

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**SIGNIFICANCE & INNOVATIONS**

- Leveraging the internal drivers of physical activity in adults with axial spondyloarthritis such as the reinforcement of symptom relief, the importance of a moderate approach, and the development of self-efficacy can lead to increased participation in physical activity that meets established guidelines.
- Feedback, electronic reminders, and virtual support networks are considered key components of e-health technology to facilitate engagement of physical activity in adults with axial spondyloarthritis.
- Targeting e-health interventions with an aim to integrate patient perspectives, address barriers, capitalize on existing knowledge, and fill knowledge gaps can promote physical activity uptake in axial spondyloarthritis.

(4). It is well established that exercise and physical activity are fundamental in the optimal management of patients with axial SpA (5–7). To date, however, there have been no explicit guidelines focused on the prescription of exercise or physical activity in this patient population, with the exception of recently published recommendations from the European Alliance of Associations for Rheumatology advocating physical activity as "an integral part of the standard care" in patients with inflammatory arthritis (8). Inclusion of physical activity in the treatment of axial SpA is critical given recent findings that patients with axial SpA are at higher risk of developing cardiovascular disease (9). Furthermore, it is well established that patients with ankylosing spondylitis, the major subset of axial SpA, are at higher risk of developing osteoporosis (10) and vertebral fracture (11) and are at increased risk of falls (12), all of which physical activity is known to reduce in the general population (3).

Despite the established benefits of physical activity in the optimal management of axial SpA, the evidence suggests that patients with axial SpA are not adhering to either exercise recommendations or physical activity guidelines (13–16). A number of studies have examined barriers to physical activity adherence and include concerns around worsening symptoms, prior negative experiences with exercise, and lack of knowledge of appropriate physical activity in axial SpA (17–19). Other studies have explored perspectives regarding uptake of physical activity in patients with ankylosing spondylitis and proposed strategies to enhance participation in physical activity that included improved social support systems, monitoring of health care professionals, and adoption of health-focused technology (17,20).

Understanding how to leverage technology for disease management and health promotion has gained momentum over the last several years as technology has become more accessible and user friendly (21,22). Specifically, the integration of e-health technology has been established in several studies as an adjunctive form of disease management in patients with chronic disease (23–25). Several recent approaches to increase physical activity in the general population and in patients with chronic disease have demonstrated e-health interventions such as telephone reminders; mobile text messaging and web-based interventions have a positive effect on participation in physical activity and overall health outcomes (26–29). Despite the known benefits of e-health interventions, there are few published studies examining the impact of e-health tools on physical activity in the axial SpA population. One pilot study examined the suitability of a web-based system to monitor symptoms, quality of life, and physical activity in patients with ankylosing spondylitis and demonstrated that health technology can positively impact participation in physical activity (30). A recent systematic review examined digital interventions to increase physical activity in inflammatory arthritis; however, this review did not include patients with axial SpA (31).

Given the importance of physical activity and exercise in the management of axial SpA and the known effect that e-health interventions can have on increasing uptake of physical activity in various chronic disease populations, the objectives of this study were as follows: 1) to understand patient perspectives of the importance of physical activity in the management of axial SpA; 2) to describe motivators and barriers associated with adherence to physical activity in patients with axial SpA; and 3) to explore the role of e-health technology in facilitating physical activity in patients with axial SpA with the aim of providing a foundation to guide development of patient-centered e-health technology interventions to increase uptake of physical activity in patients with axial SpA.

## PATIENTS AND METHODS

This qualitative descriptive (32) study leveraged the lived experience and opinions of individuals with axial SpA. Participants were recruited in-person during routine clinical visits at an urban academic spondylitis rheumatology clinic. Patients diagnosed with axial SpA based on Assessment of SpondyloArthritis international Society criteria (33), age ≥18 years, fluent in conversational English, and available to be interviewed over the telephone were eligible for study participation.

Semistructured individual telephone interviews were conducted by one member of the investigative team with knowledge and experience in qualitative research (LP or AC). Questions for the interview guide were informed by peer-reviewed literature on physical activity in chronic disease (including axial SpA) and the role of e-health technology in health behavior change. The interview guide was reviewed by the investigative team for content and clarity prior to study commencement. Questions aimed to solicit responses about the following: 1) participants' definition of physical activity and their understanding of physical activity relative to management of axial SpA; 2) what factors affect their physical activity levels (including motivators and barriers); and 3) their perceptions of technology's role in encouraging physical activity (e.g., reminders, feedback, etc.). Demographic and disease-related information were collected for each participant in addition

to information related to the participant's smart phone use when engaged in physical activity. Each interview lasted ~30 minutes.

Interview transcripts were reviewed upon completion and prior to interviewing the next participant to allow for identification of emergent themes and the need to modify the interview guide. Recruitment of study participants continued until saturation of emergent themes. For the purpose of this study, emergent themes were defined as common and repeated topics, ideas, and patterns related to the study objectives. Saturation was defined as no additional themes identified after review of each participant interview. Interviews were recorded and transcribed verbatim. Transcripts were analyzed using thematic analysis (34). Two investigators (LP and AC) independently reviewed interview transcripts and generated separate inductive coding schemes organized into emergent themes. LP and AC met to compare findings and to develop a unified coding scheme that was then applied to the interview transcripts. The coded data were imported into QSR, version 11.4 (NVivo), to assist with aggregation of codes into common themes. Themes were presented to the investigative team and discussed to allow for further comparison and reconciliation.

The methods of this study were reviewed by the Canadian Spondylitis Association, a not-for-profit, national patient association that supports and advocates for those diagnosed with ankylosing spondylitis and associated spondyloarthritides. This study was approved by the University Health Network's Research Ethics Board.

## RESULTS

Twelve patients with axial SpA completed interviews for this study. The majority of participants were male (83.3%) with a mean ± SD age of 45.5 ± 12.5 years and a mean ± SD disease duration of 21.5 ± 14.9 years. Approximately one-half were receiving biologic treatment (58.3%). The mean ± SD Bath Ankylosing Spondylitis Disease Activity Index score (35) was 2.5 ± 1.4, indicating low disease activity, and the mean ± SD Bath Ankylosing Spondylitis Functional Index score (36) was 1.8 ± 1.9, indicating high function.

**Perspectives of the role of physical activity in the management of axial SpA.** Participants thought of physical activity as any activity involving physical exertion, including exercise and other activities such as transportation, employment, housework, and seasonal activities (e.g., snow shoveling, lawn care, and gardening). Some participants exclusively defined physical activity as exercise and did not consider activity related to household chores or employment as part their definition of physical activity.

Participants recognized the importance of physical activity in the management of axial SpA and described direct benefits such as reduction of pain and stiffness, improved sleep quality, and less fatigue. Participants stressed that benefits of physical activity are not immediate and take time to develop. They highlighted the importance of education on anticipated time-to-effect of physical activity. Participants emphasized the need to manage patient expectations about benefit to ensure success in engagement of physical activity. Participants also identified indirect beneficial effects that led to adoption of other health behaviors such as diet optimization, smoking cessation, and prevention of other chronic diseases of which axial SpA patients are at risk (e.g., cardiovascular disease and osteoporosis). In addition, engagement in routine, structured physical activity allowed participants to experience improvements to their mental health and general well-being, which then translated into greater function and improved quality of life. Participants also described synergies that occur between physical activity and pharmacologic management, emphasizing

**Table 1.** Role of physical activity in managing axial spondyloarthritis*

| Theme | Illustrative participant quotes |
|---|---|
| Direct management effects | "It's almost mandatory in my case to be able to function properly on a daily basis. Without it, I'm in pain and very stiff. So, it's basically a different version of a medical treatment for me." (Participant 7) "For the most part. It's helped me improve my sleep, which I think improves activity, being recovered physically and mentally if you get enough sleep. I think there's a lot of downstream benefits to that." (Participant 12) "At the beginning it's hard to start and to see the benefit right away, but if (one is) willing to try and do it…for a period of time, and then (you) see the improvement, I think that's what will motivate…" (Participant 8) |
| Indirect management effects | "I know that if I'm active, I'm just in a better state of mind…I think my mood improves…no question, when I go for a bike ride, my mood improves…or when I play ball hockey. I'm exhausted but I'm in a great mood. So, I think mentally there absolutely is benefits to (physical activity)." (Participant 5) "…it was clear that physical activity and exercise brought about those happier, more balanced, mental, emotional affects." (Participant 7) |
| Integration with pharmacologic management | "…whether that's physical activity or other kinds of care that can work in concert with medication. Because without question, without my medication, I'd be a bit of a mess but it's everything working together." (Participant 5) |
| Evolution of benefits | "I think another thing that people need to understand is the physical activity part, it doesn't have a beginning and an ending. It's something that consistency is key, right? I guess that would be the biggest thing that you got to stay consistent with it. Because if you're not consistent with it, you just end up locking up and it's not a good thing." (Participant 3) "One of the things that I found in my experience was that it took a while, it took quite a while for the benefits to really (show) themselves…it took quite a few months before I started to realize, oh, hey wait, this is really working as a way of pain management and symptom management…I'm going to carve out this time for this. And after a while, it becomes just kind of part of your routine. But it takes time, it really takes time. And you have to kind of make the habit of it." (Participant 6) |

* Quotes provided are an example of participant narratives reflective of the corresponding theme.

the importance of maintaining nonsteroidal antiinflammatory and/or biologic therapies to gain greater effect through the addition of physical activity. See Table 1 for themes and supporting illustrative quotes.

**Factors affecting adherence to physical activity in patients with axial SpA.** Participants reported motivators (things that encouraged them to engage in physical activity) and barriers (things that prevented them from engaging in physical activity) that were intrinsic and extrinsic in nature. Intrinsic motivating factors for engagement in regular physical activity included symptom improvement. Experiencing symptom relief motivated participants to continue with regular and structured forms of physical activity to ensure continued symptom management. Other intrinsic drivers of physical activity included improvement in additional aspects of health including mental health, physical stamina, strength, and flexibility. Furthermore, prediagnosis physical activity was important in participants' ability to integrate exercise and physical activity into their daily routine after they received their diagnosis. This translated into improved self-efficacy or confidence in participants' ability to manage their disease through physical activity. Participants described perseverance in participating in regular physical activity, while accepting physical limitation. Finally, a positive outlook regarding physical activity was critical. Participants often reframed prediagnosis attitudes and beliefs about physical activity that would lead to incorporation of physical activity on a regular basis. This allowed for a growth mindset to adopt physical activity as part of their daily routine.

Extrinsic factors that facilitated physical activity were centered around the concept of social support networks. This included support from individuals including family, friends, and peers, in addition to professional guidance from health care providers. Other extrinsic facilitators included the ability to access facilities offering instruction on exercise and physical activity in convenient locations with affordable rates.

Intrinsic barriers included symptoms and physical limitations associated with axial SpA. The latter caused some participants to feel self-conscious, subsequently preventing them from participating

**Table 2.** Perceptions of physical activity (motivators)*

| Theme and subtheme | Illustrative participant quotes |
|---|---|
| Intrinsic motivating factors | |
| Symptom relief | "It's just the overall feeling, after I do it, I feel better." (Participant 8) "So, it's…about listening to your body, but also not listening to it a little bit, because I knew that when I was in pain, that's actually what I needed." (Participant 1) "It's all relative…, you're not judging yourself against somebody else. You judge it to you. If you see any progress…, like reduction of pain, better sleep…you can relate it to the physical activity, it will encourage you." (Participant 10) |
| Health impact | "…the more I'm working out, the more fit I feel, the more inclined I would be to eat healthy." (Participant 7) "If I know that something is good for me, good for my physical well-being, good for my mental well-being, that's enough encouragement for me." (Participant 3) "And it helps me therefore reduce the amount of pain I'm in, and the amount of medication I need, so those are really good pluses for me in terms of having that done." (Participant 9) |
| Self-efficacy | "You have a better sense of confidence about doing things, and that confidence correlates to your general well-being…" (Participant 10) "I started to feel stronger and better at it, which was encouraging." (Participant 1) "I can't make the AS go away, but I can manage it better. It makes my lifestyle, my quality of life immensely better by doing this. Immensely. That's a big motivation." (Participant 10) "Throughout my life I've always been involved in either some type of organized sport or I've always gone to the gym or things like that. So, I would venture to say that I've been pretty physically active my entire life in terms of sports and more so in the past." (Participant 3) |
| Moderation | "You really do have to know yourself, and you have to push yourself close to your limit but not past your limit." (Participant 10) "One of the goals I had for numerous years was to be able to touch my toes. So now I'm actually doing it, by doing yoga and doing forward folds all the time, I can actually touch my toes, which is, for me, it's something, when I started, I could barely go past my knees. It's quite an improvement." (Participant 11) |
| Reframing | "I think that at one point I didn't think that I was very, I don't know, sporty or something, but it's been cool engaging with exercise in a new way and totally changing the way I thought about that." (Participant 1) "Well, if you can't do any of the exercise and the other best thing that I would recommend is to be positive. That there's a lot worse disease out there, life-threatening. At least this you know you can live with it, to be positive mentally and not to let yourself down." (Participant 8) |
| Extrinsic motivating factors | |
| Social support networks | "I also had the support of my partner, like always. They would remind me when I needed to be reminded… like 'maybe you should go for a swim if you're feeling really sore', which was maybe something I needed at that time, when I started to do Pilates regularly, I would often go with my friend. I introduced her to Pilates, so that made it more of a social thing, too. We'd go together and hang out, which was…Yeah, that was a good thing to do, to have a bud." (Participant 1) "I think the people that you're with, your companions, the people that support you on an ongoing basis, are critical to your long-term health…they're the ones that are going to either motivate you or support you, or give you a kick in the butt and say you've got to get going…they see what you need sometimes better than what you do." (Participant 9) |
| Access | "It's probably access, even having my gym across the street from where I work is very helpful for encouraging, just trying to remove any (barrier)…" (Participant 12) |

* Quotes provided are an example of participant narratives reflective of the corresponding theme. AS = ankylosing spondylitis.

**Table 3.** Perceptions of physical activity (barriers)*

| Theme and subtheme | Illustrative participant quotes |
|---|---|
| Intrinsic barriers | |
| Disease-related factors | "...somebody with this disease is experiencing a lot of pain...it can be really difficult to feel motivated to move around when you're experiencing a significant amount of pain." (Participant 4) "Psychologically, you go to a class where it's a lot of jumping around, a lot of quick movements and stuff that you can't do. Maybe some people with AS can do it, I certainly can't. It's very discouraging not to be able to participate in the class, or participate in the exercise regime that you're going to benefit from." (Participant 10) |
| Fear of disease progression | "Because it's pretty intense when you get that diagnosis. I don't know for everyone else, but I was pretty young to get it, too. So it kind of shocked me to my core a little bit, which destabilized my willingness or understanding for physical activity. Really, like at the beginning I was like, 'Oh my God, I can't move'. Like I don't want to...I don't want to hurt myself more. I don't want to make it worse." (Participant 7) "Personally, you're afraid. You're self-conscious, these are hurdles you have to get over, and it hurts. It makes you feel worse if you don't do it right, or if you do too much. It's knowledge. If you don't have the knowledge to do it properly, and the help to do it properly, you're going to get hurt or you're not going to participate. The first time you're hurt, it's a downer, and you say, 'I'm not doing this." (Participant 10) |
| Extrinsic barriers | |
| Lack of time | "Yeah, 2 young children...sometimes they just need to be driven somewhere...sometimes that's what you end up doing after dinner, is you drive them to a dance class as opposed to going for a bike ride or getting some exercise or whatever. Probably time restraint is a major thing." (Participant 5) "But I can see myself slip into something where I'm very busy at work. Then I forgo one exercise this particular week, then next week I might forgo 2 types of exercise, and the slippery slope becomes fairly consistent in that it just deteriorates in terms of how much exercise to do." (Participant 9) |
| Access | "...getting to the gym, have it being open, having the space to do it, the weather cooperating." (Participant 6) |
| Environmental factors | "...living a certain distance away from work helps just if I'm walking, kind of like the 25 minutes, I usually target 25 minutes away from where I work, which is not long enough for me to take a bus, a cab, or drive. So, kind of being in that sweet spot of being able to walk to most of the things that I want to get to." (Participant 19) "... more people would ride their bike to work if they felt safe doing so. But we build our streets and our city for cars, not for people to use transit or actually get some exercise while they're commuting." (Participant 5) |

* Quotes provided are an example of participant narratives reflective of the corresponding theme. AS = ankylosing spondylitis.

in group activities such as exercise classes and team sports. Participants were also concerned that too much, or the wrong type of physical activity, could lead to increased symptoms and worsening disease activity. Participants discussed fear of experiencing atypical pain or relapse, particularly with vigorous activity, regardless of whether they were in remission or were managing their condition. Having difficulty finding the right balance caused apprehension in participating in physical activity when not advised by health care providers.

Lack of time was a commonly discussed extrinsic barrier to engaging in regular physical activity in participants with axial SpA. Daily obligations such as family responsibilities, work and social engagements often precluded participation in physical activity. Additionally, lack of access to structured forms of physical activity such as community recreational facilities and municipal programs made it more difficult to engage in regular physical activity. Access was identified as an extrinsic barrier from a financial perspective but also from a geographical perspective. Moreover, environmental factors such as extreme cold, heat, humidity, and precipitation prevented participants from engaging in outdoor physical activity. These seasonal effects disrupted routine physical activity for weeks or longer. Subsequent reengagement in activities was reported to be challenging due to deconditioning, apathy, and lack of time. Urban design was also a factor related to extrinsic barriers. Participants referred to the lack of parks, promenades, bike paths, walkability, and concern for personal safety as extrinsic barriers to physical activity. See Table 2 (motivators) and Table 3 (barriers) for themes and illustrative participant quotes.

**Role of e-health technology in facilitating engagement in physical activity.** The majority (75%) of participants reported using an iPhone (Apple) mobile digital device and reported high confidence using technology (mean ± SD 8.1 ± 1.7 on a 10-point scale). One-third (33.3%) of participants reported having their smartphone on their person when engaging in exercise or physical activity. The design of e-health technology was considered important in the context of physical activity and should incorporate uncomplicated visuals, simple layout, easy operation, and intuitive function. Technology considered overly complicated and challenging to navigate was thought to be a deterrent to uptake of physical activity. Performance feedback was an important component of e-health technology for increasing engagement in physical activity. Participants felt that tracking performance and comparing their activities to recommended guidelines would be helpful for maintaining sustained engagement in physical activity. The ability to visualize progress in relatable units of measurement (e.g., steps per day or minutes per day) was thought to allow for reflection on progress over time since the effects of regular physical activity are not immediately apparent. Other measures of performance and progress included numerical rating scales for symptoms (e.g., pain, stiffness, and fatigue) as well as composite measures such as disease activity or function. Gamification of physical activity was also described by participants to provide a sense of competitiveness with oneself or chosen peers.

Participants recognized the potential benefit of electronic reminders to encourage participation in structured and sustained physical activity; however, the risk of apathy to such reminders

**Table 4.** Role of e-health technology to facilitate engagement in physical activity*

| Theme | Illustrative participant quotes |
|---|---|
| Technology design | "Simple things, like your steps, your heartbeat, it's good." (Participant 10) "I think some (health technologies) are designed poorly, have poor navigation. Ones that are not intuitive. Some that may not be screened properly for the different types of phones. Some things are stretched here and there. Those, I would say, are some of the features that need to be taken into account." (Participant 2) "Legibility…simplicity on a given screen, I find is a big thing. If there's too many buttons or too many kinds of options on one screen, it gets a little bit convoluted. So easy navigation." (Participant 6) |
| Electronic reminders | "…reminders outside of your immediate circle would be very helpful…you need to go do this for you and your disease." (Participant 70) "People really get very apathetic to reminders or they disregard them, or if it's something that comes every day…(they) just disregard it…the purpose of the reminder may become less and less as the time goes on." (Participant 2) "…I think the notifications might help at the beginning. Until someone starts to pick up the habit…once the habit is ingrained, I think that it might really not make too much of a difference because …you don't think about it, you just know you got to do it…" (Participant 3) "…a friendly, upbeat text message something that would put people in a decent frame of mind. Just not something bland, blah media, nice text message with a smiley face or something, something encouraging." (Participant 3) |
| Performance feedback | "…it's kind of a game you start to play…where you're okay, let's see how much can I run this week? How much can I ride this week?" (Participant 6) "Like you get to see who walked the most steps in a day and I will go out and do an extra thousand steps if I can see that my buddy's beating me for the day". (Participant 5) "Maybe some type of support group, Facebook group, or something where people can share different exercises that they've done, or different ways that they've been able to engage in physical activity and be able to maybe guide some other people on making some small changes or small improvements in their lives, on specifically when it comes to physical activity." (Participant 2) |
| Virtual support | "Whereas if you get someone with a very similar case to yours who is living the benefits of physical activity, almost like a peer system or mentor system, then I think that could be very, very helpful." (Participant 7) "…you need encouragement, you might want to develop classes with people with similar ailments, and that's mutually supportive…I think people like community…it encourages you to do well either by joining other friends…people like to see it. It's not competitive, but it's community." (Participant 10) |

* Quotes provided are an example of participant narratives reflective of the corresponding theme.

was identified as a possible consequence. Some participants felt that frequent interruption caused by reminders would be frustrating and ultimately render the reminders ineffective. Having the ability to customize the frequency of reminders was one suggestion of how to make them more effective. The content of the reminders was also important. Participants expressed a preference for personalized messages of motivation and short text messages communicating the benefits of physical activity when sending reminders to engage in physical activity.

Virtual support networks with peers were considered important for providing encouragement and accountability. These support networks could be formed via social network platforms or group messaging applications. Participants suggested that online patient partnerships and mentorship programs could encourage and promote physical activity in patients with axial SpA. Direct electronic linkages (e.g., text messaging and email) with health care providers to answer questions regarding diagnosis and disease management were identified as a method of allaying apprehension about physical activity and thereby promoting engagement. Additionally, virtual lines of communication could provide instruction on appropriate frequency, duration, and intensity of specific physical activities for patients with axial SpA. Table 4 provides themes and illustrative participant quotes regarding the role of e-health technology in facilitating engagement in physical activity in patients with axial SpA.

## DISCUSSION

The results of this study provide a foundation of understanding to guide development of patient-centered e-health technology interventions to increase uptake of physical activity in patients with axial SpA. First, understanding factors that enable and inhibit physical activity engagement will help create targeted approaches to maximize physical activity in patients with axial SpA. Capitalizing on internal drivers of physical activity such as the reinforcement of symptom relief, the importance of a moderate approach, and the development of self-efficacy may lead to increased participation in physical activity that meets established guidelines. Second, the results of this study provide insight into the potential role of e-health technology in facilitating physical activity within the axial SpA population and may inform researchers and developers regarding key aspects of intervention and design as e-health strategies for improving adherence to physical activity continue to evolve.

The results of this study align with existing literature suggesting that engagement in physical activity can be positively or negatively influenced by internal and external drivers. The understanding of intrinsic and extrinsic motivators and barriers to change in health behavior is found throughout the literature on chronic disease management (37,38) and has similarly been explored in axial SpA (17,20). A recent study that examined determinants of change in exercise behavior in patients with axial SpA proposed intervention strategies such as education, goal-setting, feedback, and tailoring (39), many of which support the role of e-health in facilitating physical activity identified by this study. Future research into the application of these findings to e-health interventions targeted at improving physical activity is warranted.

The results of this study suggest that symptoms have a dual role as both motivators and barriers for uptake of physical activity. Participants identified symptom relief as a driver for ongoing physical

activity. This included pain reduction, improvement of mobility, less fatigue, and better sleep quality. However, participants also identified symptoms as a barrier to engaging in physical activity, whereby pain and fatigue could impede regular physical activity. A study examining perceptions of exercise in participants with rheumatoid arthritis demonstrated that regular physical activity leads to pain relief and improved mobility, fatigue, and sleep quality. But when these symptoms were unmanaged or undermanaged, it became difficult to engage in physical activity (40). These findings speak to the importance of following a moderate approach when participating in physical activity, using medication in tandem with physical activity, and ensuring that patients with axial SpA understand the difference between expected pain versus harmful pain that can lead to injury or worsening of their condition. Further research into the role of health care provider support, patient education, and feedback via e-health strategies may help to address this paradox.

It is well established that the effects of physical activity require specific exercise prescription and time allowance before physiologic benefits are achieved (41). Participants in this study noted that benefits resulting from physical activity evolve over time, which, based on review of the available literature, is an insightful and relatively unique patient perspective derived from this study. Patient education that emphasizes structured and consistent participation in physical activity is important and could be reinforced through digital feedback, a key aspect of e-health technology identified by participants in this study. Newly diagnosed patients may benefit from targeted education on exercise instruction and anticipated time-to-effect to ensure success in physical activity engagement.

There is a growing body of literature on e-health interventions aimed at measuring and improving adherence to physical activity in axial SpA and other forms of chronic disease (42). However, studies suggest that one-third of axial SpA patients are not fully adopting the use of e-health technology because of concerns around technical mastery (30). Further, a recent systematic review and metanalysis suggests that wearable devices in chronic disease management demonstrated insufficient evidence to improve health outcomes (43). The results of this study outline specific aspects of e-health technology design and operation as described by patients living with axial SpA. These include the need for personalized reminders, the role for feedback, and virtual support systems. Future development of e-health strategies should consider the incorporation of the results of this study to help optimize e-health adoption and efficacy aimed at change in health behavior in the axial SpA population.

The role of the physical environment was identified by participants as an important factor in physical activity engagement. This relationship is established in the literature on physical activity (44,45); however, it is a relatively novel finding specific to physical activity and axial SpA. These findings may be specific to a Canadian urban setting; however, the results suggest that physical environment and urban design may be an important contextual component when developing physical activity interventions. Consideration of seasonal adaptation, safety, walkability, and other physical environmental factors may enhance future e-health interventions to improve engagement in physical activity in the axial SpA population.

There are limitations to this study. First, participants were recruited from an urban academic rheumatology clinic, and therefore, the results may not reflect the opinions and experiences of patients with axial SpA in other settings. For example, access to structured physical activity programs may be limited for patients living in rural settings. Recruitment bias may also be at play given the nature of the study topic. For example, the mention of "physical activity" may have dissuaded patients who were less physically active from agreeing to participate. Second, since most participants were male with long-standing disease duration (>20 years), low disease activity, and high function, the results may not be transferrable to other populations. Factors that affect participation and views on the role of e-health in physical activity may be different in female patients with axial SpA, newly diagnosed patients, or patients with less function. Future research may benefit from purposive sampling to ensure multiple perspectives to understand the role of sex, disease duration, and function in physical activity and e-health technology. Last, the results did not undergo informant feedback to assess internal validity; however, the triangulation of results between participants and the 2 study investigators increases confidence in the accurate reflection of the perceptions of physical activity and e-health technology of patients with axial SpA.

In conclusion, patients with axial SpA acknowledged the important role of physical activity in the management of axial SpA and identified symptom reduction, a positive mindset, social support networks, and facility access as motivators to engagement in physical activity. In addition, patients with axial SpA identified a number of barriers to physical activity, including fear of disease progression, life demands, and environmental restrictions. Understanding patients' perception of motivators and barriers and the role of physical activity in the management of axial SpA will help to refine management approaches, including novel e-health interventions, to ensure adherence and maximize uptake of physical activity. Furthermore, elements of e-health tools to facilitate engagement in physical activity in the management of axial SpA should include digital feedback, electronic reminders, and integration of virtual support networks. Targeting e-health interventions with an aim of leveraging patient perspectives, addressing barriers, capitalizing on existing knowledge, and filling knowledge gaps will allow for a focused approach to optimizing care in axial SpA.

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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 submitted for publication. Ms. Passalent 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.

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**Analysis and interpretation of data.** Passalent, Cyr, Jurisica, Mathur, Inman, Haroon.

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REHABILITATION SCIENCES AND THE RHEUMATIC DISEASES

# Rehabilitation Interventions in Systemic Sclerosis: A Systematic Review and Future Directions

Susan L. Murphy,[1] Janet L. Poole,[2] Yen T. Chen,[3] Alain Lescoat,[4] and Dinesh Khanna[3]

**Objective.** To systematically review evidence of rehabilitation interventions for improving outcomes in systemic sclerosis (SSc) and to evaluate evidence quality.

**Methods.** Several electronic databases were searched to identify studies in which rehabilitation professionals delivered, supervised, or participated in interventions for individuals with SSc. Randomized controlled trials (RCTs) or non-randomized trials, one-arm trials, and prospective quasi-experimental studies with interventions were included if they had ≥10 participants. Quality appraisal was conducted by 2 independent raters using the Physiotherapy Evidence Database (PEDro) Scale.

**Results.** A total of 16 good or excellent quality studies (15 RCTs, 1 prospective quasi-experimental study) were included. Most rehabilitation interventions focused on hands/upper extremities, followed by multicomponent, orofacial, and directed self-management. Sample sizes varied between 20–267 participants (median 38). In 50% of studies, participants in intervention groups significantly improved compared to controls. Most studies demonstrated within-group improvements in intervention groups. Interventions varied in content, delivery, length, and dose and outcome measures collected.

**Conclusion.** Existing evidence provides some support for rehabilitation in SSc, such as interventions that focus on hand and upper extremity outcomes or are multicomponent, although there is high study heterogeneity. The evidence base would benefit from interventions testing similar replicable components, use of common outcome measures, and incorporation of delivery modes that enable larger sample sizes. There are challenges in recruiting participants due to the rarity of SSc and high disease burden, as participants' involvement in rehabilitation studies requires active participation over time. Intervention studies designed to reduce participation barriers may facilitate translation of effective interventions into practice.

## INTRODUCTION

Systemic sclerosis (SSc; scleroderma) is a rare, chronic, and progressive autoimmune disease characterized by skin fibrosis, vasculopathy, and visceral damage (1). SSc is often classified into 2 subtypes, including limited and diffuse cutaneous SSc, which provides a clinically useful profile of people who have different progression of skin thickening and survival rates (2). People with both limited or diffuse subtypes of SSc commonly experience Raynaud's phenomenon, pain, fatigue, decreased flexibility, reduced strength, and visceral involvement. People with diffuse cutaneous SSc are more likely to have significant skin disease burden with large joint contractures and to have severe disease involvement in internal organs with lung fibrosis and renal crisis, whereas those with limited cutaneous SSc are likely to have associated pulmonary arterial hypertension. Organ involvement, which can be life threatening, is a focus of clinical care in SSc, while less attention is paid to resultant disability and quality-of-life issues such as hand involvement, appearance changes, and fatigue (3–5). Yet, these symptoms are of significant concern to people with SSc (5). Regardless of subtype, there is high symptom burden

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**SIGNIFICANCE & INNOVATIONS**

- To the best of our knowledge, this is the first systematic review of rehabilitation literature in systemic sclerosis (SSc).
- Rehabilitation interventions demonstrate improvements in hand/upper extremity function, and health-related quality of life; however, the studies mainly involve small samples and vary in intervention content and dose.
- Multicomponent interventions and those that focus specifically on hands and upper extremities showed the most improvements in outcomes.
- Evidence-building in SSc will require attention to enhancing comparability across studies such as by testing similar interventions, using the same outcome measures, and reporting findings appropriately.

and disability that have significant effects on work and participation in life roles (6,7). There have been treatment advances, but no approved disease-modifying antirheumatic drugs for SSc. Without a cure, strategies that help individuals with SSc with chronic disease management are needed.

Rehabilitation is an important tool to help individuals manage SSc and potentially slow its disabling effects; however, there are difficulties in translating evidence-based rehabilitation strategies into practice. Less than 1 in 4 people with SSc across several countries reported using rehabilitation services (physical or occupational therapy) (8) and there are low referral rates to rehabilitation (9). Additionally, most rehabilitation professionals do not have clinical experience with SSc due to its rarity, and there is little clinical guidance available for rehabilitation professionals when encountering these patients.

There have been articles that have discussed the effectiveness of rehabilitation treatments in SSc; however, the literature has not been systematically reviewed for interventions specifically performed or supervised by rehabilitation professionals. Since 2001, and the updated definition of diffuse and limited cutaneous subtypes (10), there have only been 2 narrative reviews that have examined rehabilitation treatments, which were either limited to musculoskeletal impairments (11) or to describing local and generalized rehabilitation treatments (12); and neither review examined evidence based on study quality. Systematic reviews done in SSc encompass some rehabilitation studies but also included other nonpharmacologic treatments, such as nutrition and dental treatments (13), or examine effects of exercise but include studies that were not conducted as part of rehabilitation (14). A systematic review of rehabilitation treatments is still needed to provide a current understanding of the quality of this literature and provide the foundation to future directions to build evidence in this area. The objective of this systematic review was to examine the evidence for rehabilitation interventions in SSc. Therefore, the following was our primary research question: What is the effectiveness of rehabilitation interventions on clinical outcomes in individuals with SSc? Our secondary question was: What is the overall quality of the body of evidence in SSc rehabilitation literature?

## MATERIALS AND METHODS

**Search strategy.** The following databases were selected for the literature search: Medline through Ovid, Scopus, Embase, Cumulative Index to Nursing and Allied Health Literature, the Cochrane Central Register of Controlled Trials, OTseeker, and Physiotherapy Evidence Database (PEDro). These databases were selected in conjunction with our university library informationist along with guidance from the rehabilitation literature (15). In addition to searching these databases, we examined publication reference lists and other reviews for studies that would potentially meet study criteria. The informationist performed a literature search in these databases from the year 2001 and later because the diagnostic classifications of SSc (diffuse and limited cutaneous) were updated that year (10) and we wanted to ensure that we were including comparable patient samples. Searches involved subject headings unique to each database but similar to the Medline medical subject headings. The complete search strategy with terms used are provided (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24737/abstract). The protocol for this systematic review is published in an online registry (16) and was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

**Inclusion and exclusion criteria.** Because our intent was to select publications that examined rehabilitation practices, intervention studies were eligible for inclusion if the interventions included a rehabilitation professional (physical therapist/physiotherapist, occupational therapist, ergotherapist, rehabilitation specialist, or speech pathologist) for delivery or supervision. Interventions that were multidisciplinary and included rehabilitation were also considered within scope. Interventions were excluded if they were conducted by related but different disciplines (e.g., respiratory therapy, nursing, or dentistry) or if they were complementary and alternative treatments not conducted by rehabilitation (e.g., acupuncture or spa treatments). Interventions performed for the primary purpose of examining effects on a biomarker or physiologic outcome in a research environment and not a clinical treatment were also excluded. Publications that involved adult samples (ages ≥18 years) who had a diagnosis of SSc (limited or diffuse according to 1988 classification criteria and updated in 2001) (10) were included. Studies also needed to include samples that had ≥10 participants, which, similar to another review (13), excluded studies with a very low sample size given the heterogeneity of SSc. Given the state of the evidence, we felt it was important to consider all intervention studies with

designs in which participants were either randomized or not, including pre-post, single-arm studies and prospective studies that involved interventions. We also included published abstracts for the purpose of identifying additional research studies based on work reported in the abstracts. Because some team members were fluent in languages other than English, we also considered articles written in French or Chinese.

**Article selection.** Citations generated from the search were imported into Covidence systematic review software for title and abstract screening. A pair of reviewers (SLM, JLP, YTC, and AL) independently screened all titles and abstracts to determine if the articles met inclusion criteria. Conflicts were resolved by a third reviewer, who was a coauthor of the study. A full-text review of each eligible article was then conducted by the same pair of reviewers. These reviewers independently coded each full text for the inclusion criteria. Disagreements in the full-text evaluation were resolved through discussion, and misunderstandings were corrected to ensure consistency for the remainder of the article evaluation. After full-text evaluation, there were 33 articles to include in quality assessment and data extraction.

**Assessment of methodologic quality.** Quality appraisal was used to answer the secondary research question (regarding the quality of the body of evidence in the literature). The PEDro scale was used to assess article quality (17); it was developed for rehabilitation literature quality appraisal and has been shown to be a more comprehensive measure for rehabilitation evidence than the commonly used Jadad scale (18). The PEDro scale has a possible score of 10, in which 1 point is given for each quality metric that is met. Quality classifications are <4 = poor, 4–5 = fair, 6–8 = good, and 9–10 = excellent (19). Two independent raters, consisting of coauthors (SLM, JLP, YTC, and AL), trained in use of the PEDro scale independently rated each included article for quality. Any article for evaluation that was written by members of the study team did not include that member as a rater. We calculated interrater agreement of methodologic quality for 18% of the articles (i.e., 6 articles) using Cohen's kappa. After all raters reached a high level of agreement of articles by quality category (0.80 or above) (20), they completed evaluation of the remaining articles. Discrepancies on remaining articles were resolved through discussion.

**Data extraction.** We extracted data from articles that met a quality classification of ≥6 on the PEDro scale (good to excellent quality) (19). Data extraction was verified for 20% of articles. Data was independently extracted by a rater pair and then checked for consistency by a third rater. Only 1 discrepancy was found and resolved. Tasks for data extraction and verification were divided among coauthors Murphy, Poole, Chen, and Lescoat. One coauthor then extracted data from the remaining articles with data verification by a different coauthor.

**Evidence synthesis.** Studies were summarized by aspects of the intervention, such as intervention content, setting in which it was delivered (clinic, home, telehealth, or some combination), length, and dose. After a review of intervention content of included studies, interventions were categorized as hand/upper extremities (UE), orofacial, multicomponent, or directed self-management. Hand/UE included any treatments for hand or UE symptom reduction or increased mobility (like thermal treatments, manual therapy, or exercises). Orofacial included an exercise intervention addressing mouth opening. Multicomponent rehabilitation interventions involved >1 treatment for a specific body part such as hand or face, but also more generalized whole-body treatments, such as aerobic or water-based exercises. Directed self-management included a rehabilitation-involved, self-paced, symptom self-management program.

Sample characteristics were summarized by age, sex, ethnicity/race, subtype of SSc, and disease duration. Other elements of the synthesis included study design, timing of outcomes collection, assessment measures used, and whether study authors designated a primary outcome. Due to variability in outcome assessments, outcome domains were created to summarize findings.

## RESULTS

**Search results.** The systematic literature search yielded 3,478 publications in which titles and abstracts were screened by rater pairs. There was disagreement regarding eligibility among pairs in 79 (2%) of 3,478 cases, which was resolved by a third rater. The most common reason for exclusion was due to being an abstract with insufficient data on the involvement of a rehabilitation professional in the intervention (72% of those excluded). Ninety full texts were evaluated and 33 were selected for quality appraisal (Figure 1). There were 16 articles included in this review.

**Characteristics of studies.** The characteristics and main findings of each study are shown in Table 1. Of the 16 articles, 15 were randomized controlled trials (RCTs) and 1 used a prospective quasi-experimental study design (21). The sample sizes ranged from 20 to 267 people (median sample size 38). Thirty-eight percent of the articles (6 of 16) came from Italy (3 of which were by the same author), 3 were from the US, and remaining articles came from other countries. Most studies involved a high proportion of female to male participants (the lowest percentage of female participants was 47%, 15 of 16 studies ranged 65–100% female participants). In the US, the study by Yuen et al (22) had the highest proportion of minorities (52% African American participants, followed by Murphy et al [23] with 22%). The average age of participants across studies ranged from 50 to 65 years. Only 3 studies involved patients early in their disease process (average of 1–3 years since diagnosis [23,24], or median of 4 years since diagnosis [25]). The average disease duration of participants in

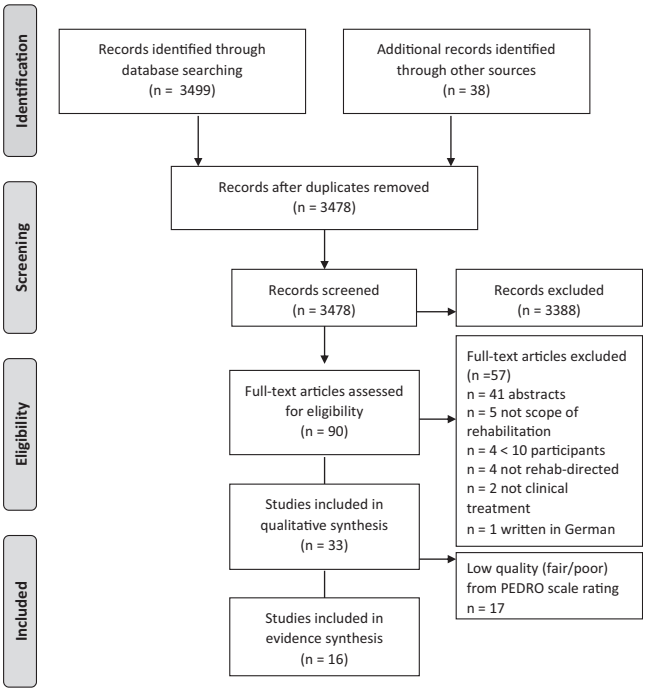


**Figure 1.** Flow diagram of studies of rehabilitation in systemic sclerosis. PEDro = Physiotherapy Evidence Database scale.

the remainder of articles was ≥6 years. With regard to disease subtype, 19% of articles did not specify a subtype. In terms of primary outcome, 6 (38%) of 16 articles did not specify a primary outcome.

**Quality.** Of potentially eligible articles reviewed, only 48% were considered of good quality or better on the PEDro scale and were included. Of these 16 articles, the mean ± SD PEDro score was 7.0 ± 0.97. Articles rated by each quality metric are demonstrated (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24737/abstract). Only 1 article was rated as excellent (26). The number of included articles by quality criteria on the PEDro scale are shown in Figure 2. The aspect of quality that was met by the fewest studies was blinding. More than half of articles (56%) used blinded outcome assessors, only 2 had participants that were blinded, and no articles had therapists who were blinded.

**Intervention delivery and content.** Of the interventions, which we classified by categories, including hand/UE, orofacial, multicomponent, and directed self-management (Table 1), hand/UE was the focus for more than half of the studies (9 of 16), followed by multicomponent interventions (5 of 16). All multicomponent interventions included treatments targeted to hands/UE, but other aspects such as orofacial exercises, general aerobic or resistance exercise, or supervision or check-in calls from therapists were also included. There was 1 intervention that focused only on orofacial exercises (22) and another that involved a rehabilitation-directed self-management program that had moderated online discussion boards with participants involving a rehabilitation professional (27). Intervention length ranged from 2 weeks to 12 months. Delivery mode was most often done in clinic either with a home component, such as an exercise program (n = 4), without a home component (n = 4), or with a telehealth component, which was an app-delivered exercise program with education (n = 1) (23). The remaining 7 studies were designed as home interventions with two having a telehealth component (27,28).

Investigators in almost all studies, regardless of intervention content, evaluated quality of life (Table 2). The most commonly used measures were the Health Assessment Questionnaire (HAQ and HAQ disability index [HAQ DI]) (n = 9) and the Short Form 36 health survey (SF-36; n = 11), which are reliable and valid outcomes in persons with SSc. Furthermore, since the majority of the studies were categorized as hand/UE or multicomponent, the other most frequent outcome measure was the Hand Mobility in Scleroderma test (n = 9), also validated for people with SSc. Other outcomes, grouped in domains, such as skin, pulmonary, and cardiac, were used less frequently and were specific to intervention content (Table 2).

Table 2 shows findings for articles based on between-group differences in outcomes measured (for more details, see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24737/abstract). Most effects from SSc interventions were in hand/UE function and health-related quality-of-life domains, followed by orofacial function. Interventions with the most effects had a hand exercise component or were multicomponent. In the hand/UE intervention category, findings varied as did interventions. The 2 studies that examined the effect of heat (warm water, paraffin) reported no significant difference between intervention and control groups (29,30), as did 2 studies that focused on hand exercises or massage with or without glove wearing (24,28). The exceptions were studies that incorporated manual lymph drainage (32) or negative pressure and stretching (23) reported significant between-group differences for some hand/UE outcomes. The only study that compared modality use (biofeedback, deep oscillation) to a control condition, found a significant improvement in biofeedback compared to the control group, while the oscillation group revealed a trend in improvement (25). Furthermore, within hand/UE interventions, in the intervention group, significant improvements were reported in 7 (78%) of 9 studies for hand/UE function outcomes and in 5 (71%) of 7 studies that had quality-of-life outcomes.

More positive group differences were reported in the multicomponent studies especially ones in which the interventions took place over a longer time period (33–35). In these studies, significant differences were reported between intervention and

**Table 1.** Characteristics of rehabilitation studies included in evidence synthesis (n = 16)*

| Author, year, country (ref.) | Sample, total no. (IG/CG) | Participants | Intervention duration/dose | Control/comparator description | Delivery mode | Intervention content |
|---|---|---|---|---|---|---|
| Hand/UE function studies | | | | | | |
| Gregory et al, 2019, UK (29) | 36 (17/19) | Female: IG = 76%, CG = 63%; % diffuse SSc: IG = 41%, CG = 42% | 9 weeks: paraffin wax baths, no less than 4 times/week; hand stretch exercises, 3–10 times/day | Hand stretch exercise only | Home | Paraffin wax baths |
| Kristensen et al, 2019, Denmark (30) | 86 (43/43) | Female: IG = 84%, CG = 63%; % diffuse SSc: IG = 60%, CG = 37% | 6 months: 30-minute sessions, 2 times/day | Lukewarm water hand immersion prior to hand exercises | Home | Paraffin wax baths |
| Maddali Bongi et al, 2009, Italy (31) | 40 (20/20) | Female: IG = 80%, CG = 70%; subtype NS | 9 weeks: massage and manipulation, 1-hour session 2 times/week; home exercise, 20-minute session daily | Home hand exercise program | Clinic/home | Hand massage, joint manipulation |
| Maddali Bongi et al, 2011, Italy (32) | 35 (20/15) | Female = 100%; subtype NS | 5 weeks: 1-hour session/week | Waitlist | Clinic | Manual lymph drainage (UE focus) |
| Murphy et al, 2021, US (24) | 32 (16/16) | Female = 72%; % diffuse SSc = 100% | 18 weeks: OT sessions, 1-hour session 1 time/week for 8 weeks; app-delivered hand exercises, daily | App hand exercises only | Clinic/telehealth | Thermal treatments (UE), negative pressure treatment, ROM, Home hand ROM exercises tailored by OT |
| Piga et al, 2014, Italy (28) | 20 (10/10) | Female = 100%; % diffuse SSc = 40% | 12 weeks: maximum of 50-minute sessions, 5 days/week | Home program of hand strength and mobility exercises using common objects | Telehealth | Hand exercises |
| Sporbeck et al, 2012, Germany (24) | 28 (10 [BF]/8 [DO]/10 [CG])† | Female (range across 3 groups) = 80–90%; % diffuse SSc (range across 3 groups) = 10–50% | 4 weeks: 3 times/week | Waitlist | Clinic | Biofeedback or deep oscillation to UE |
| Stephanantoni et al, 2016, Italy (25) | 31 (15/16) | Female: IG = 100%, CG = 94%; % diffuse SSc: IG = 47%, CG = 31% | 3 months: daily home exercise; weekly check-in calls between first and second assessments | General hand exercise | Clinic/home | Hand exercises tailored by OT |
| Vannajak et al, 2014, Thailand (23) | 28 (14/14) | Female: IG = 64%, CG = 25%; % diffuse SSc = 100% | 2 weeks: superficial heat 20- minute sessions daily; TTM 30-minute sessions daily; hand stretches 30-second sessions, each hand, daily; wearing gloves 6-hour sessions daily | Same daily home program as IG without gloves | Home | Traditional Thai massage to UE, joint manipulation, home hand ROM exercises, insulation gloves |
| Orofacial | | | | | | |
| Yuen et al, 2012, US (22) | 48 (26/22) | Female: IG = 81%, CG = 77%; % diffuse SSc = 44% | 6 months: 6-minute sessions, 2 times/day | Usual dental care | Home | Manual mouth-stretching and oral augmentation exercises with a wooden stick |

(Continued)

**Table 1.** (*Cont'd*)

| Author, year, country (ref.) | Sample, total no. (IG/CG) | Participants | Intervention duration/dose | Control/comparator description | Delivery mode | Intervention content |
|---|---|---|---|---|---|---|
| Multicomponent | | | | | | |
| Filippetti et al, 2020, Italy (33) | 44 (22/22) | Female: IG = 80%, CG = 79%; % diffuse SSc = IG = 44%, CG = 25% | 6 months: 3 times/week | Usual care with general recommendation to increase physical activity | Home | Aerobic exercise (bike), UE resistance exercise, hand stretching, PT calls |
| Horvath et al, 2017, Hungary (21) | 53 (31/22) | Female: IG = 93%, CG = 91%; % diffuse SSc = IG = 58%, CG = 50% | 3 weeks: 5 days/week for all therapies except for UE, mud baths every other day, and thermal baths daily | Mud baths, thermal baths, exercise for large joints, without treating hands | Clinic | Thermal treatments to UE, hand stretching, massage to trunk/UE, stretching and exercise to lower extremities |
| Maddali Bongi et al, 2009, Italy (50) | 20 (10/10) | Female = 65%; subtype NS | 9 weeks: hands, 1-hour session 2 times/week; face, 1-hour session, 2 times/week; global, 1-hour session/week | Educational advice and medical information about SSc | Clinic | Connective tissue massage, Kabat's technique, kinesitherapy, and a home exercise program |
| Rannou et al, 2017, France (34) | 220 (112/108)‡ | Female: IG = 86%, CG = 80%; % diffuse SSc: IG = 47%, CG = 50% | 12 months: PT/OT, 3 weekly, 3-hour sessions; splinting, 2-hour sessions daily; resting splints, nightly; home exercise daily | Usual care by physician with no restrictions on PT | Clinic/home | Multidisciplinary intervention (PT/OT) aerobic and resistance exercise, ROM for mouth, face, UE/LE and splinting |
| Schouffoer et al, 2011, Netherlands (35) | 53 (28/25) | Female: IG = 68%, CG = 84%; % diffuse SSc: IG = 54%, CG = 60% | 12 weeks: multidisciplinary weekly program; PT weekly; home exercise, 6 days/week | Usual care by physician with no restrictions on PT | Clinic/home | General exercise, hand/mouth exercises, education, PT supervised home exercise |
| Directed self-management | | | | | | |
| Khanna et al, 2019, US (27) | 267 (134/133) | Female: IG = 92%, CG = 90%; % diffuse SSc: IG = 43%, CG = 44% | 16 weeks: self-paced with weekly moderated discussion board | Received a copy of popular scleroderma resource | Telehealth | Self-paced web-based self-management program with rehab-directed discussion board |

* All study designs were randomized controlled trials except Horvath et al (21), which used a prospective quasi-experimental design. CG = control group; DASH = Disabilities of the Arm, Shoulder and Hand questionnaire; FIHOA = Functional Index for Hand Osteoarthritis; HAMIS = Hand Mobility in Scleroderma test; HAQ DI = Health Assessment Questionnaire disability index; IG = intervention group; LE = lower extremity; NS = not specified; PROMIS = Patient-Reported Outcomes Measurement Information System; PT = physical therapy; OT = occupational therapy; Ref. = reference; ROM = range of motion; SSc = systemic sclerosis; TTM = traditional Thai massage; UE = upper extremity; VAS = visual analog scale.
† The study by Sporbeck et al (24) consisted of 3 groups: biofeedback (BF), deep oscillation (DO), or waitlist control group (CG).
‡ A total of 218 participants were assessed in this study.

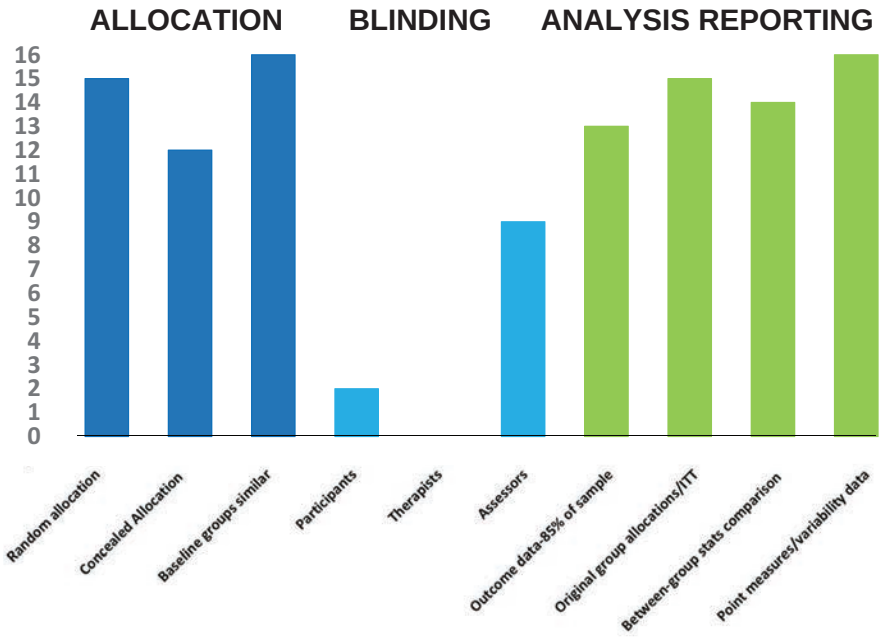


**Figure 2.** Articles rated by quality criteria on the Physiotherapy Evidence Database (PEDro) scale. ITT = intent-to-treat.

control groups for hand/UE function, orofacial, and quality of life (33–35). Specifically, 4 (80%) of 5 studies in the multicomponent category reported within-group improvements in the intervention group in hand/UE function outcomes and quality-of-life outcomes. In the 1 orofacial intervention, there were significant improvements in oral aperture (face/mouth function) in the intervention group, which were significantly different than the control group (22). The 1 directed self-management study did not report significant group differences (27). In general, many studies did report significant improvements in outcome measures within the intervention groups, but the improvements were not significantly different from changes observed in the control groups.

## DISCUSSION

We systematically reviewed the literature in SSc to examine the effectiveness of rehabilitation interventions. From the 33 studies identified, just less than half (48%) met the quality standard for inclusion. Sixteen studies that represented rehabilitation interventions focused on hand/UE or orofacial, were multicomponent, or involved rehabilitation-directed self-management were rated as good to excellent quality. Half of these studies showed between-group differences in which the intervention group had a statistically significant improvement compared to the control outcome (22,23,25,26,32–35). Most studies in this review had relatively small sample sizes, which may have resulted in lack of power to detect between-group interventions in studies with active comparator groups. However, the heterogeneity in studies and interventions make it difficult to synthesize the literature. These findings can be framed around the following 2 main challenges that have implications for translation of research into practice: evidence-building of rehabilitation research and conducting rehabilitation studies in the SSc population.

The complexity and patient-centered nature of rehabilitation contribute to the challenges of evidence-building and synthesizing results across rehabilitation trials. One problem is inconsistency in trial reporting, such as the lack of a predefined primary outcome measure, even among good-quality studies. There is a lack of consensus in reporting in rehabilitation RCTs in many areas, such as participant characteristics (36), randomization procedures, statistical analyses and power (37), and intervention description (38). Tools under development, such as checklists to extend the Consolidated Standards of Reporting Trials (CONSORT) group statement for rehabilitation trial reporting (39) should help increase study quality and the ability to synthesize findings. Many studies in this review had variable reporting of patient characteristics, intervention description, and comparator/control groups, and lacked power analyses. Blinding was not done frequently and is challenging in a real-world environment with therapists, outcome assessors, and participants. Despite challenges, some recommendations have been discussed to help ensure study rigor, such as blinding assessors and using active comparator groups where participants can be blinded to which intervention is hypothesized to be better (40).

Interventions tested in this review were difficult to synthesize even within a specific category. Hands and UE were most commonly addressed in interventions, but intervention content and dose were highly variable. Description of treatment rationale,

**Table 2.** Between-group differences by outcome in rehabilitation studies in systemic sclerosis (n = 16)*

| Outcome measure | No. of studies evaluating the outcome | Study (ref. number) with significant difference between intervention and control groups ($P < 0.05$) |
|---|---|---|
| Skin | | |
| MRSS, hand MRSS | 2 | – |
| Hand/UE function | | |
| HAMIS | 9 | 32, 35 |
| Durouz Hand Index/Cochin Hand Function test | 6 | 34 |
| QuickDASH or DASH | 2 | – |
| FIHOA | 1 | – |
| Kapandji index | 1 | 34 |
| Mobility (hand opening, hand abduction, fist closing, fingertips to palmer crease, total active motion, HAI) | 5 | – |
| Hand volume | 2 | 32 |
| VAS hand pain, interference | 2 | 32 |
| VAS hand edema, VAS interference edema | 1 | 32 |
| Pinch strength | 3 | 23 |
| Grip strength | 6 | 33, 35 |
| Biceps strength | 1 | 33 |
| Raynaud's phenomenon | | |
| Raynaud's phenomenon symptoms VAS | 2 | 25 |
| Digital ulcers | | |
| VAS digital ulcers | 1 | – |
| Orofacial | | |
| Oral aperture or mouth opening, MMO, microstomia, face involvement | 4 | 22, 34, 35 |
| Cardiac | | |
| 6MW | 2 | 33, 35 |
| Vo2 peak/max, aerobic capacity | 3 | – |
| Pulmonary | | |
| VAS shortness of breath | 1 | – |
| Gastrointestinal | | |
| VAS gastrointestinal symptoms | 1 | – |
| Musculoskeletal | | |
| Quadriceps strength | 1 | 33 |
| Global health | | |
| Global health VAS or questionnaire, general VAS | 3 | – |
| VAS overall disease severity | 1 | – |
| Health-related quality of life | | |
| PROMIS physical function | 1 | – |
| PROMIS-29 | 1 | – |
| Patient activation measure | 1 | – |
| Pain VAS | 2 | 34 |
| PROMIS self-efficacy for managing symptoms | 1 | – |
| Checklist individual strength | 1 | – |
| HAQ DI or HAQ, SHAQ | 9 | 32–35 |
| MACTAR | 1 | 34 |
| SF-36 | 11 | 32, 33 |
| VAS satisfaction with health | 1 | – |
| COPM | 1 | 26 |
| EQ-5D, QALYs, SWAP | 1 | – |

* 6MW = six-minute walk test; CHFT = Cochin Hand Function Test; COPM = Canadian Occupational Performance Measure; DASH = Disabilities of the Arm, Shoulder and Hand questionnaire; EQ-5D = EuroQol-5-domain questionnaire; FIHOA = Functional Index for Hand Osteoarthritis; HAI = Hand Anatomical Index; HAMIS = Hand Mobility in Scleroderma; HAQ = Health Assessment Questionnaire; HAQ DI = Health Assessment Questionnaire Disability Index; MACTAR = McMaster Toronto Arthritis Patient Preference Disability Questionnaire; MMO = maximum mouth opening; MRSS = Modified Rodnan Skin Thickness Score; PROMIS = Patient Reported Outcome Measure Information System; QALYs = quality-adjusted life-years; RP = Raynaud's phenomenon; SF-36 = Short Form 36 health survey; SHAQ = Scleroderma Health Assessment Questionnaire; SWAP = Brief Satisfaction with Appearance Scale; UE = upper extremity; VAS = visual analog scale.

goals and expected benefits, and underlying theory of interventions are recommended for reporting (41), and consistent information across studies could help build evidence and reduce variability. In addition, thought about the mechanism of action is critical. While SSc rehabilitation treatments incorporate specific elements, such as thermal modalities, massage, and stretching, few studies discuss why these components are essential or investigate how they work. For example, to examine if negative

pressure treatment affects skin thickness in SSc, Murphy and colleagues developed a protocol to use musculoskeletal ultrasound to examine changes in skin thickness after an occupational therapist–delivered treatment (42). Testing mechanism of action in rehabilitation treatments will help design and better target interventions in the future.

Most studies in the present review required participants to come to clinics to receive all or some of the intervention. Even for interventions designed to be done at home, participants had to travel to receive a device (wax or exercise machine) and/or instruction. Only 1 intervention was done completely via telehealth (27). Participation in interventions requiring in-person attendance may be prohibitive for those who do not live in urban areas or near scleroderma centers, or have transportation. Telehealth is an emerging mode of intervention delivery within rehabilitation. The recent global pandemic has led to massive changes in how health care and interventions are delivered. People have been forced to be more tech savvy and virtual interventions are becoming more accessible. The increased opportunity for virtual interventions helps to respond to the unmet need identified by people with SSc who want information delivered via the internet (43). Yet, virtual telehealth intervention delivery presents challenges to those with limited internet access, no video capabilities on their phones, and/or in areas with unstable connections. Further, telehealth is limited in its ability to provide hands-on treatment, like massage or stretching, by a rehabilitation professional that may reap greater benefits at least in the short term or be preferred by patients.

A further complication is that the reviewed studies were conducted in many countries with different health care systems and reimbursement structures. These differences have implications for how interventions could be translated into clinical practice outside of the study's country of origin. Becetti and colleagues (8) reported that use of rehabilitation was higher in Canada and France compared to the US and speculated that referral could be related to access to rehabilitation and health care costs. Other studies that surveyed providers reported referrals driven by costs (44) and a lack of understanding of the role of rehabilitation in management of SSc (45,46).

In the US, Black individuals have a higher prevalence of diffuse cutaneous SSc and more severe disease (47). However, the number of Black participants in research studies of SSc remains low. Although the 3 US studies reported on race and/or ethnic characteristics of samples, inclusion of diverse samples will be needed to better understand differences by race and ethnicity in the future.

For many studies in this review, outcome measures used have psychometric support for SSc. Stronger support exists for the HAQ DI, The Cochin Hand Function Test, and SF-36 than for the other outcomes (48). While these outcomes are largely self-reported and considered patient-centered, they do not measure what is important to patients or patients' goals. Only the COPM or MACTAR used in 2 studies (26,34) were truly patient-centered, and in one study, goals identified on the COPM guided the intervention (26). Engaging patient stakeholders as members of research teams may also help initiate use of goal identification as outcomes and to guide interventions thus improving adherence.

The design of future SSc rehabilitation trials may benefit from lessons inherited from recent RCTs evaluating pharmacologic treatments in SSc. Taking into account different subsets of the disease and impact of the natural history of SSc may help to include more homogeneous and comparable patient populations. Maddali Bongi and Del Rosso have recommended that rehabilitation treatments be tailored to individuals based on phase of disease (49), because individuals with early disease tend to have a higher symptom burden. Another strategy is to focus on just 1 SSc cutaneous subtype, such as diffuse (23,24). Specifying a clinically meaningful primary outcome measure that is tailored for a targeted disease subset (such as people in the edematous phase [32]) may help to improve statistical power of future RCTs. The coordination of centers of excellence with a multidisciplinary approach may also help expedite recruitment and ensure consistency of outcome measures. The use of web-based approaches for intervention delivery is a promising option to implement rehabilitation for daily SSc management as it may reduce some barriers to access, more readily allow for longer follow-up periods, and facilitate treatment adherence. The long-term impact of these techniques will also need to be demonstrated in RCTs as SSc remains a chronic disorder without available disease-modifying pharmacologic agents and without demonstration of improved quality of life with current medications. Rehabilitation may thus play an important role to improve such patient- reported outcomes with impact more of a holistic approach, including rehabilitation, on SSc patients' mental and social health as well as physical functioning.

The findings reported are limited by studies that are somewhat heterogeneous and consist of small sample sizes that may be underpowered to detect effects, even in this group of studies considered to be of good to excellent quality. However, understanding weaknesses in study design and reporting can help to build the evidence by increasing potency of interventions and consideration of how to best tailor them. Importantly, interventions were of low risk to participants and had effects on both physical and quality-of-life outcomes, supporting the need for inclusion as part of clinical care.

In conclusion, rehabilitation interventions have been recommended for people with SSc to address the musculoskeletal and systemic involvement leading to significant disability and reduction in meaningful activities (50). This comprehensive review of rehabilitation literature supports short-term efficacy of rehabilitation interventions and provides several future directions to further build the evidence and develop interventions that can reduce access barriers.

## 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 submitted for publication. Dr. Murphy 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.** Murphy, Poole, Chen, Lescoat, Khanna.

**Acquisition of data.** Murphy, Poole, Chen, Lescoat.

**Analysis and interpretation of data.** Murphy, Poole, Chen, Lescoat, Khanna.

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REHABILITATION SCIENCES AND THE RHEUMATIC DISEASES

# Muscle Strength and Osteoarthritis Progression After Surgery or Exercise for Degenerative Meniscal Tears: Secondary Analyses of a Randomized Trial

Bjørnar Berg,[1] Ewa M. Roos,[2] Nina Jullum Kise,[3] Lars Engebretsen,[4] Inger Holm,[1] and May Arna Risberg[5]

**Objective.** To evaluate muscle strength changes following partial meniscectomy or exercise therapy for degenerative meniscal tears and the relationship between baseline muscle strength and osteoarthritis progression.

**Methods.** Secondary analysis of a randomized trial (n = 140 participants). Isokinetic quadriceps and hamstrings strength (peak torque [Nm/kg] and total work [J/kg]) were assessed at baseline, 3-month, 12-month, and 5-year follow-up. Between-group differences were analyzed using intent-to-treat linear mixed models. The relationship between baseline muscle strength and osteoarthritis progression (Kellgren/Lawrence ≥1 grade increase) were assessed using logistic regression models.

**Results.** We found statistically significant between-group differences favoring exercise therapy at 3 months (quadriceps –0.30 Nm/kg [95% confidence interval (95% CI) –0.40, –0.20]; hamstrings –0.10 Nm/kg [95% CI –0.15, –0.04]) and 12 months (quadriceps –0.13 Nm/kg [95% CI –0.23, –0.03]; hamstrings –0.08 Nm/kg [95% CI –0.14, –0.03]). At 5 years, between-group differences were –0.10 Nm/kg (95% CI –0.21, 0.01) for quadriceps and –0.07 Nm/kg (95% CI –0.13, –0.01) for hamstrings. Quadriceps muscle weakness at baseline was associated with knee osteoarthritis progression over 5 years, with adjusted odds ratio of 1.40 for every 0.2 Nm/kg decrease (95% CI 1.15, 1.71). The adjusted odds ratio for hamstrings was 1.14 (95% CI 0.97, 1.35) for every 0.1 Nm/kg decrease.

**Conclusion.** Exercise therapy was effective in improving muscle strength at 3- and 12-month follow-up compared to partial meniscectomy, but the effect was attenuated at 5 years. Quadriceps muscle weakness at baseline was associated with higher odds of osteoarthritis progression over 5 years.

## INTRODUCTION

Knee muscle weakness is a typical feature of patients with symptomatic degenerative meniscal tears (1,2). Lower-extremity disuse and arthrogenic muscle inhibition are possible contributing factors (3,4). Following arthroscopic partial meniscectomy, surgery-induced trauma and postsurgery disuse may further augment muscular dysfunctions and prolong muscle weaknesses (1,3). A 2015 meta-analysis showed that partial meniscectomy patients had a moderate reduction in knee extensor muscle strength before surgery, at 6 months, and at 6 years postsurgery (1).

Muscle strengthening is suggested as one of the mechanisms underlying the beneficial effect of exercise therapy in knee osteoarthritis, with studies reporting a direct longitudinal association between increased knee muscle strength and reductions in activity limitations and pain (5,6). For degenerative meniscal tear patients, a 12-week exercise therapy program consisting of progressive neuromuscular and strengthening exercises significantly improved knee muscle strength (7). However, the course of

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**SIGNIFICANCE & INNOVATIONS**

- Twelve weeks of exercise therapy is effective in improving knee muscle strength up to 12 months compared to partial meniscectomy in middle-aged individuals with degenerative meniscal tears.
- Quadriceps muscle weakness at baseline is a risk factor for radiographic knee osteoarthritis progression over 5 years.
- Our results highlight the fact that early interventions targeting knee muscle strength should be recommended for degenerative meniscal tear patients, and the results support the ongoing shift in treatment strategy for this patient population, recommending exercise therapy over surgery.

knee muscle strength changes during the 5 years following arthroscopic partial meniscectomy or exercise therapy as treatments for degenerative meniscal tears remains unknown.

Knee muscle weakness may be an independent risk factor for radiographic knee osteoarthritis development or progression to more severe osteoarthritis changes in the general (8,9) and degenerative meniscus population (10,11). Identifying and targeting single pathways to osteoarthritis in early disease stages is likely more effective than when the disease has progressed and become more complex (12). Degenerative meniscal tears are part of the osteoarthritic process and a precursor to radiographic knee osteoarthritis (13). Subsequent radiographic changes, such as osteophyte formation and joint space narrowing, represent more significant joint damage. The presence and progression of these radiographic features are potentially clinically relevant, for both increased pain and the risk of incident disease (14,15). Ascertaining muscle strength as a potential risk factor has at least 2 important clinical implications: 1) to facilitate the shift toward a proactive treatment approach that allows for a greater chance to prevent or slow osteoarthritis progression (12,16); and 2) to support the ongoing shift in treatment strategy for degenerative meniscal tears recommending exercise therapy over surgical treatment (17).

In the Odense-Oslo Meniscectomy versus Exercise (OMEX) trial, arthroscopic partial meniscectomy was compared to exercise therapy for degenerative meniscal tears. Between-group differences in knee muscle strength changes have been previously reported at 3- and 12-month follow-up (18). However, no longitudinal analysis including muscle strength assessment at 5 years has been performed. Furthermore, the influence of muscle strength on osteoarthritis progression was not ascertained earlier in our trial. We also extend existing knowledge by reporting body weight–normalized muscle strength, within-group changes, and absolute knee muscle strength for the involved and uninvolved leg, and the proportions of patients with clinically relevant improvements in the 2 treatment groups.

Accordingly, the aim of this 5-year follow-up study of the randomized controlled OMEX trial was to evaluate normalized knee muscle strength and longitudinal changes following arthroscopic partial meniscectomy and exercise therapy as treatments for degenerative meniscal tears. We also examined the association between baseline knee muscle strength and osteoarthritis progression over 5 years.

## PATIENTS AND METHODS

**Study design and participants.** We conducted a randomized controlled trial involving participants ages 35–60 years with nontraumatic unilateral knee pain (>2 months), recruited from 2 orthopedic departments in Norway (October 2009 to September 2012). All participants had a degenerative medial meniscal tear verified by magnetic resonance imaging (MRI) and a Kellgren/Lawrence grade ≤2 and were considered eligible for surgery by 1 of 2 orthopedic surgeons based on patient history, physical examination, and MRI findings.

The sample size was calculated based on detecting a 10-point difference with an SD of 15 in the change in a composite score of 4 of 5 Knee injury and Osteoarthritis Outcome Score (KOOS) subscales ($KOOS_4$) at the primary endpoint (2-year follow-up) (18). Accounting for an estimated dropout rate of 15% and a 20% crossover rate, 140 participants were randomized (1:1 ratio). No a priori power calculations were performed for this 5-year follow-up study. An independent statistician determined the computer-generated randomization sequence, stratified by sex in blocs of 8, and concealed the allocations in sequentially numbered opaque envelopes. The test assessors were blinded to group allocation at baseline, 3 months, and 12 months. To preserve blinding, the participants wore long pants or neoprene sleeves. The trial was conducted according to the Declaration of Helsinki. The ethics committee of the Health Region of South-East Norway approved the trial (ref-no 2009/230). All participants gave written informed consent.

**Deviations from trial registration.** Muscle strength tests were registered at 3 and 24 months. Due to financial and logistic constraints, isokinetic muscle strength tests were conducted at 12 months instead of 24 months. Additionally, we included muscle strength tests at the 5-year follow-up because muscle weakness has been shown to persist for up to 4 years after partial meniscectomy (1).

**Interventions.** The 12-week exercise therapy program consisted of progressive neuromuscular and strengthening exercises. Experienced physical therapists at the Norwegian Sports Medicine Clinic or Gnist Trening og Helse AS followed a standardized protocol (19). The participants performed 2 to 3 sessions per week, and physical therapists supervised 1 of the weekly sessions.

Experienced surgeons performed the arthroscopic partial meniscectomy using anteromedial and anterolateral portals. A diagnostic procedure, including systematic probing of both menisci, was followed by resection of all unstable meniscal

tissue. Pre- or postoperative physical therapy was not part of the intervention, but the participants were given instructions for simple home exercises to regain range of motion and reduce swelling. Both interventions have been previously described in detail (18,19).

**Outcomes.** *Isokinetic muscle strength testing.* Quadriceps and hamstrings muscle strength was assessed using an isokinetic dynamometer (Biodex 6000) at baseline, 3 months, 12 months, and 5 years. Both legs were tested, and the testing order was determined by randomization. The same order was applied at all follow-ups. Trained assessors followed a detailed protocol to test concentric knee extension and flexion at 60°/second in the range from 90° flexion to full extension. Visual inspection and manual palpation were used to align the anatomical axis of rotation to the dynamometer axis. Baseline chair settings were recorded to duplicate the testing position at the subsequent follow-ups. Following a 10-minute warm-up on a stationary bike, the participants were placed in an upright seated position with shoulder and abdominal straps to minimize body movements. The participants performed 4 trial repetitions, followed by 1-minute rest and 5 maximal test repetitions. We used body weight normalized peak torque (Newton meters [Nm], Nm/kg) and total work (Joules [J], J/kg) in the data analyses. Peak torque represents the highest muscular force output at any moment during the test bout, and total work represents the amount of work accomplished during the 5 maximal repetitions (20). The reliability of isokinetic knee muscle testing is high (21–23). Based on the results from the test–retest studies, we defined participants as responders for normalized quadriceps and hamstrings strength at each follow-up if a change from baseline of at least 15% for quadriceps and at least 20% for hamstrings was

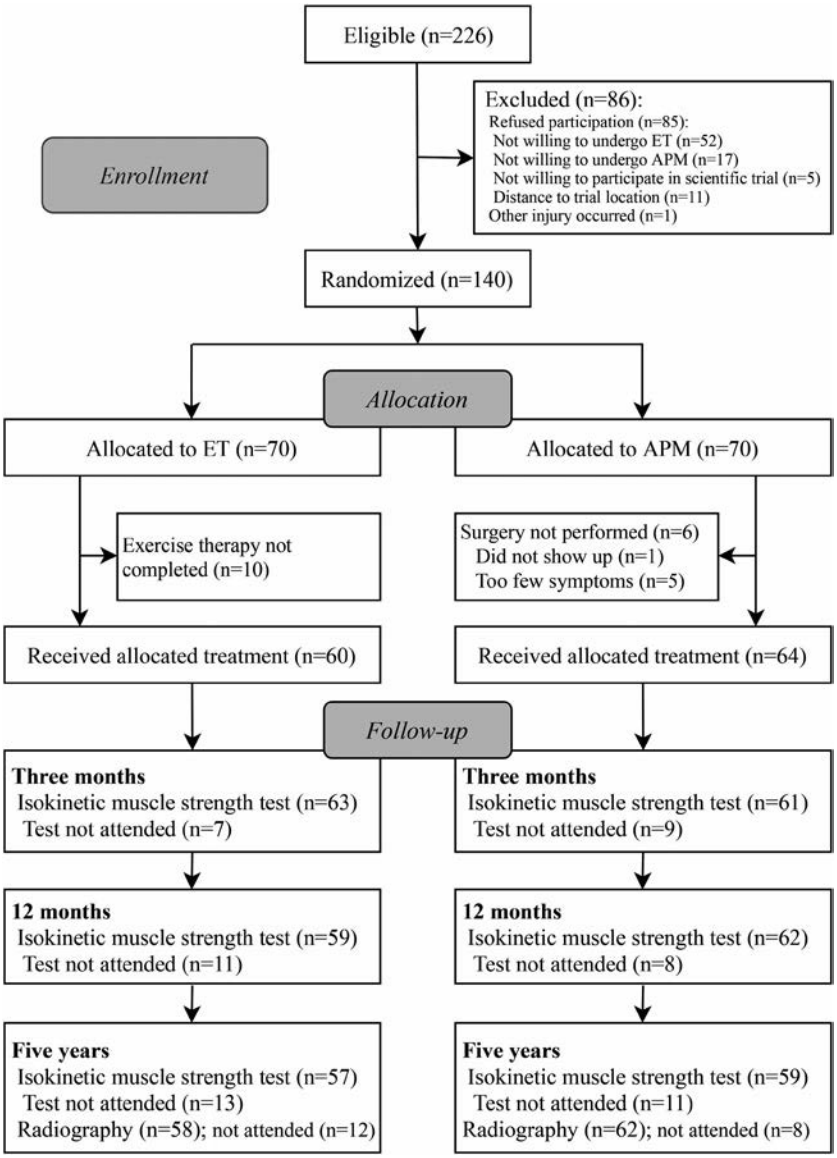


**Figure 1.** Study flow chart. APM = arthroscopic partial meniscectomy; ET = exercise therapy.

detected. A change of 15% for quadriceps strength has previously been used as a clinically important cutoff for knee osteoarthritis patients (24).

*Knee osteoarthritis progression.* Radiographs were acquired at baseline (recruiting hospitals) and 5 years (private radiology clinic) using a standardized protocol (25). The protocol included posteroanterior radiographs, 10° caudal x-ray beam angulation, and the use of a Synaflexer (Synarc) positioning frame (26). Two experienced radiographic readers, blinded to clinical data, graded all radiographs according to the Kellgren/Lawrence classification (0–4, normal to severe) (27). The radiographs were reread in cases of between-reader discrepancy and discussed until consensus was reached. Interrater reliability for the 2 readers has been previously evaluated for the Kellgren/Lawrence classification (weighted $\kappa = 0.67$) (28). We defined osteoarthritis progression as an increase of ≥1 grade from baseline to 5 years (dichotomous outcome: yes or no). Participants undergoing an osteotomy or total knee replacement were also considered to have progressed radiographically.

**Patient involvement.** There was no patient involvement in the planning or conduct of the study, but user involvement was included in implementation of the exercise therapy program. User experiences and results from the OMEX trial are disseminated to clinicians and patients through AktivA, a nationally implemented osteoarthritis treatment program (29).

**Statistical analysis.** The primary analyses of knee muscle strength changes were performed on an intent-to-treat basis. We used linear mixed models to analyze between-group differences in change from baseline to each follow-up. The outcomes were normalized quadriceps and hamstrings muscle strength (peak torque and total work) at 3 and 12 months and 5 years. The models were adjusted for sex (randomization stratification variable) and baseline value of the outcome. Participants were included as random effect with random intercept and slopes, and time point (baseline, 3 months, 12 months, and 5 years), time × treatment interaction, and sex as fixed effects. One outcome variable (hamstrings total work) was modeled with random intercept due to convergence difficulties. To adjust for baseline differences, we did not include a main effect for the treatment group in the model (30). From the fitted models, we present estimated mean change values and 95% confidence intervals (95% CIs) at each follow-up for both treatment groups and between-group differences in change from baseline. We also report absolute knee muscle strength in the involved and uninvolved leg at each time point for the 2 treatment groups.

Proportions in the 2 treatment groups with improvements >15% for quadriceps and >20% for hamstrings (responders) were compared at each follow-up using the chi-square test. For these analyses, participants with incomplete outcome data were excluded from the actual time point with missing data.

For our secondary aim, normalized quadriceps and hamstrings muscle strength (Nm/kg) at baseline were the exposures, and osteoarthritis progression (Kellgren/Lawrence increase of ≥1 grade) over 5 years was the outcome. A complete-case analysis was applied, excluding participants with missing outcome data at the 5-year follow-up (n = 20). We pooled data from both treatment groups because preliminary analyses showed no significant treatment × quadriceps interaction or treatment × hamstrings interaction. Separate logistic regression analyses were conducted for quadriceps and hamstrings peak torque to avoid multicollinearity. Models were adjusted for sex, baseline Kellgren/Lawrence grade, and the baseline pain subscale of the KOOS (31). Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test. Continuous variables were linearly related to the logit of the dependent variable (assessed using the Box-Tidwell approach). There were no standardized residuals with a value of ±2 SDs. Analyses were performed using Stata software, version 16.1.

## RESULTS

All 140 participants were included in the primary analyses (Figure 1). In the exercise group, 10 participants declined exercise therapy. Four of these participants and 10 participants who participated in the exercise therapy program crossed over to receive partial meniscectomy. Six participants in the partial meniscectomy

**Table 1.** Baseline characteristics of participants randomized to exercise therapy (ET) or arthroscopic partial meniscectomy (APM)*

| Characteristic | ET group (n = 70) | APM group (n = 70) |
|---|---|---|
| Men, no. (%) | 43 (61) | 43 (61) |
| Age, years | 50.2 ± 6.4 | 48.9 ± 6.3 |
| Body mass index, kg/m$^2$ | 26.5 ± 4.3 | 26.0 ± 3.7 |
| Pain duration, median [IQR] months | 9.5 [13.6] | 6.0 [7.0]† |
| Kellgren/Lawrence grade, no. (%) | | |
| 0 | 49 (70.0) | 48 (68.6) |
| 1 | 20 (28.6) | 19 (27.1) |
| 2 | 1 (1.4) | 3 (4.3) |
| Quadriceps peak torque, Nm/kg | | |
| Involved leg | 1.95 ± 0.57 | 2.03 ± 0.59 |
| Uninvolved leg | 2.22 ± 0.51 | 2.27 ± 0.51 |
| Quadriceps total work, J/kg | | |
| Involved leg | 9.57 ± 2.83 | 9.85 ± 2.91 |
| Uninvolved leg | 10.63 ± 2.44 | 10.89 ± 2.40 |
| Hamstrings peak torque, Nm/kg | | |
| Involved leg | 1.02 ± 0.32 | 1.10 ± 0.29 |
| Uninvolved leg | 1.07 ± 0.28 | 1.11 ± 0.28 |
| Hamstrings total work, J/kg | | |
| Involved leg | 5.50 ± 2.06 | 6.15 ± 1.9 |
| Uninvolved leg | 5.84 ± 1.81 | 6.22 ± 1.67 |

* Values are the mean ± SD unless otherwise stated. IQR = interquartile range; Nm/kg = Newton meter/kilogram; J/kg = Joule/kilogram.
† Missing data from 1 participant.

**Table 2.** Estimated change from baseline to follow-up and between-group differences in knee muscle strength for the exercise therapy (ET) and arthroscopic partial meniscectomy (APM) group*

| | 3 months' difference | | | 12 months' difference | | | 5 years' difference | | |
|---|---|---|---|---|---|---|---|---|---|
| | ET (n = 63) | APM (n = 61) | Δ | ET (n = 59) | APM (n = 62) | Δ | ET (n = 57) | APM (n = 59) | Δ |
| Quadriceps | | | | | | | | | |
| Peak torque | 0.26 | −0.04 | −0.30 | 0.24 | 0.12 | −0.13 | 0.13 | 0.03 | −0.10 |
| 95% CI | 0.19, 0.34 | −0.11, 0.04 | −0.40, −0.20 | 0.17, 0.32 | 0.04, 0.19 | −0.23, −0.03 | 0.05, 0.20 | −0.05, 0.10 | −0.21, 0.01 |
| Total work | 1.04† | −0.35 | −1.39 | 1.11 | 0.36 | −0.74 | 0.48 | 0.15 | −0.34 |
| 95% CI | 0.68, 1.40 | −0.70, 0.01 | −1.89, -0.88 | 0.74, 1.47 | 0.01, 0.72 | −1.25, −0.24 | 0.11, 0.86 | −0.22, 0.51 | −0.86, 0.18 |
| Hamstrings | | | | | | | | | |
| Peak torque | 0.16 | 0.06 | −0.10 | 0.14 | 0.06 | −0.08 | 0.04 | −0.02 | −0.07 |
| 95% CI | 0.12, 0.20 | 0.02, 0.11 | −0.15, −0.04 | 0.10, 0.19 | 0.02, 0.10 | −0.14, −0.03 | 0.00, 0.09 | −0.07, 0.02 | −0.13, −0.01 |
| Total work | 1.00† | 0.30 | −0.70 | 0.86 | 0.33 | −0.54 | 0.30 | −0.20 | 0.50 |
| 95% CI | 0.73, 1.27 | 0.03, 0.57 | −1.08, −0.32 | 0.59, 1.14 | 0.06, 0.60 | −0.92, −0.15 | 0.02, 0.58 | −0.47, 0.08 | −0.89, −0.11 |

* Values are the mean with the 95% confidence interval (95% CI). APM group is the reference. Δ = between-group difference in change; peak torque = Newton meter/kilogram; total work = Joule/kilogram.
† n = 62.

group did not undergo surgery. One participant who crossed over from the exercise group and 1 participant in the partial meniscectomy group received a high tibial osteotomy 4–6 months after the index partial meniscectomy. Three participants in the partial meniscectomy group underwent another partial meniscectomy at 12, 15, and 36 months after the index partial meniscectomy. One participant in the partial meniscectomy group received a total knee replacement 34 months after the index partial meniscectomy. Table 1 gives patient characteristics at baseline for the participants in the 2 treatment groups.

**Knee muscle strength change.** Table 2 shows estimated change in normalized quadriceps and hamstrings strength at 3 and 12 months and 5 years. Changes in normalized quadriceps and hamstrings peak torque are also shown in Figure 2. At 3 months, we found statistically significant between-group differences for change in normalized quadriceps (–0.30 Nm/kg [95% CI –0.40, –0.20]) and hamstrings peak torque (–0.10 Nm/kg [95% CI –0.15, –0.04]) favoring the exercise group (Table 2). A total of 44% of the exercise group participants were classified as responders for normalized quadriceps peak torque (≥15% change from baseline) compared to 16% in the partial meniscectomy group ($P \leq 0.001$ for between-group difference). The proportion of responders for normalized hamstrings peak torque (≥20% change from baseline) was 35% in the exercise group and 18% in the partial meniscectomy group ($P = 0.033$) (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24736/abstract).

At 12 months, the exercise group had maintained the improvements that were achieved at 3 months. Between-group differences at 12 months were statistically significant in favor of the exercise group for changes in normalized quadriceps (–0.13 Nm/kg [95% CI –0.23, –0.03]) and hamstrings peak torque (–0.08 Nm/kg [95% CI –0.14 to –0.03]) (Table 2). In the exercise group, 42% and 34% of the participants were responders for normalized quadriceps and hamstrings peak torque, respectively. The corresponding numbers for the partial meniscectomy group were 26% and 19% ($P$ for between-group difference 0.054 [quadriceps] and 0.070 [hamstrings]) (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24736/abstract).

At 5 years, we found a statistically significant between-group difference for change in normalized hamstrings peak torque in favor of the exercise group, but the difference was small (–0.07 Nm/kg [95% CI –0.13, –0.01]). We found no statistically significant between-group difference for normalized quadriceps peak torque (–0.10 Nm/kg [95% CI –0.21, 0.01]) (Table 2**)**. Muscle strength declined in both groups from 12 months to 5 years. However, normalized quadriceps strength at 5 years was higher compared to baseline in the exercise group (0.13 Nm/kg [95% CI 0.05, 0.20]) and equal in the partial meniscectomy group (0.03 Nm/kg [95% CI –0.05, 0.10]). For normalized hamstrings strength, differences were small compared to baseline; a slight improvement in the exercise group (0.04 Nm/kg [95% CI 0.00, 0.09]) and no difference for the partial meniscectomy group (Nm/kg –0.02 [95% CI –0.07, 0.02]). In all, 28% in the exercise group and 20% in the partial meniscectomy group were responders for normalized quadriceps peak torque ($P = 0.331$). The proportion of responders for normalized hamstrings peak torque was 23% (exercise group) and 10% (partial meniscectomy group) ($P = 0.066$) (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24736/abstract). Absolute knee muscle strength for the involved and uninvolved leg at all follow-ups is shown in Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24736/abstract.

**Association between baseline knee muscle strength and radiographic progression.** Of 120 participants, 65 (54%) were defined as having progressed radiographically: 31 in the exercise group and 34 in the

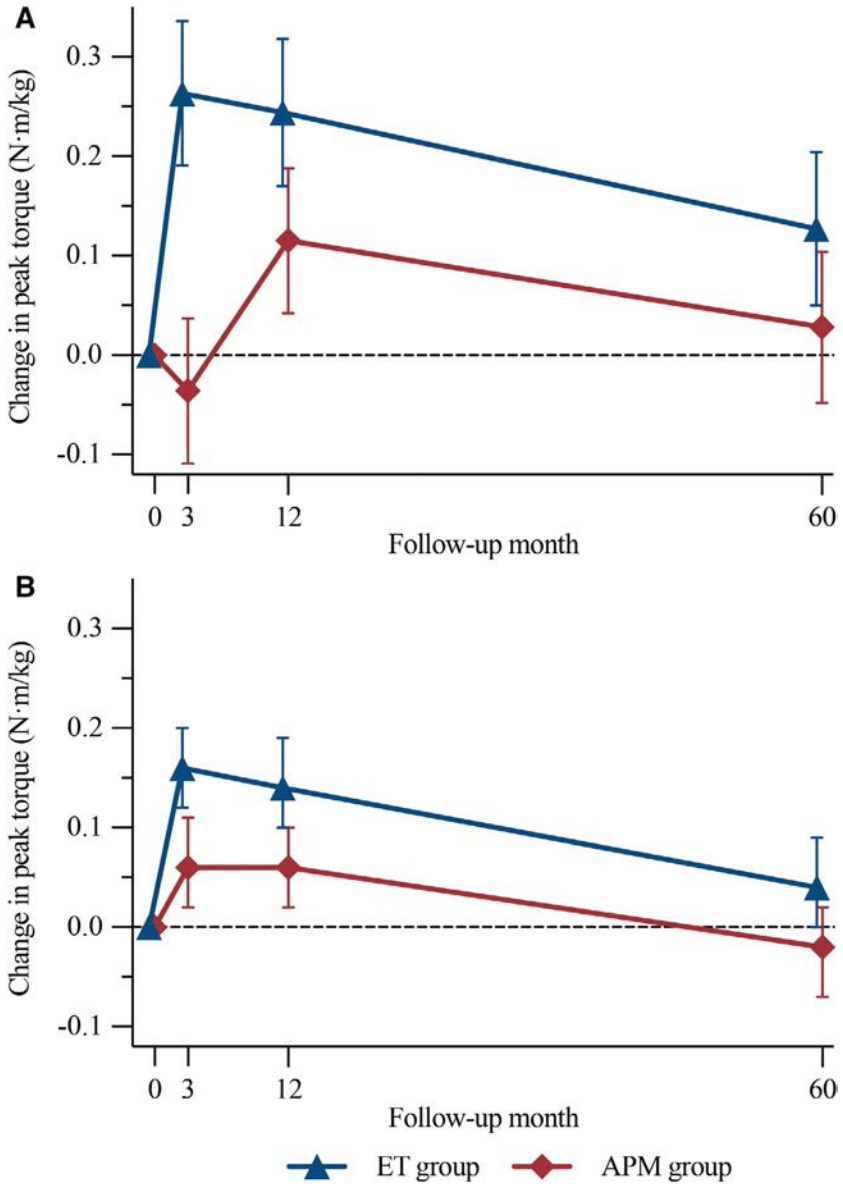


**Figure 2.** **A**, Change in normalized quadriceps peak torque; **B**, Change in normalized hamstrings peak torque (involved leg) for the exercise therapy (ET) and arthroscopic partial meniscectomy (APM) groups. Whiskers indicate 95% confidence intervals. The broken line indicates no change from baseline.

partial meniscectomy group. Overall, the proportion of women was higher in the progression group (43%) compared to the nonprogression group (33%). Participants with progression also had slightly higher body mass index and more knee pain at baseline (see Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24736/abstract). We found that quadriceps muscle weakness at baseline was significantly associated with increased odds of radiographic progression. In the crude model adjusted only for sex, the odds of radiographic progression increased by 33% for every 0.2 Nm/kg decrease in quadriceps strength (odds ratio [OR] 1.33 [95% CI 1.13, 1.58]). In the model adjusted for sex, knee pain, and Kellgren/Lawrence grade at baseline, the odds increased by 40% for every 0.2 Nm/kg decrease in quadriceps strength (OR 1.40 [95% CI 1.15, 1.71]). The crude and adjusted ORs for every 0.1 Nm/kg decrease in hamstrings strength were 1.14 (95% CI 0.99, 1.32) and 1.14 (95% CI 0.97, 1.35), respectively (Table 3). The goodness-of-fit test for crude and adjusted models for quadriceps and hamstrings showed that the models were adequate ($P > 0.05$).

## DISCUSSION

Twelve weeks of twice-weekly exercise therapy effectively improved quadriceps and hamstrings muscle strength in

**Table 3.** Association between baseline knee muscle strength (Nm/kg) and radiographic knee osteoarthritis progression over 5 years*

| | Knee osteoarthritis progression | | |
|---|---|---|---|
| | Progressors (n = 65) | Nonprogressors (n = 55) | *P* |
| Quadriceps strength (0.2 Nm/kg decrease) | | | |
| Crude odds ratio† | 1.33 (1.13, 1.58) | 1.0 (ref.) | 0.001 |
| Adjusted odds ratio‡ | 1.40 (1.15, 1.71) | 1.0 (ref.) | 0.001 |
| Hamstrings strength (0.1 Nm/kg decrease) | | | |
| Crude odds ratio† | 1.14 (0.99, 1.32) | 1.0 (ref.) | 0.073 |
| Adjusted odds ratio‡ | 1.14 (0.97, 1.35) | 1.0 (ref.) | 0.115 |

* Values are the odds ratio (95% confidence interval) unless indicated otherwise. Ref. = reference.
† Model adjusted for sex.
‡ Model adjusted for sex, baseline Kellgren/Lawrence grade, and baseline Knee Injury and Osteoarthritis Outcome Score pain subscale score.

degenerative meniscal tear patients compared to arthroscopic partial meniscectomy alone up to 12 months. While participants in the exercise group still had greater quadriceps strength at 5 years compared to baseline, there was no longer any statistically significant between-treatment group difference. We also found that for middle-aged individuals with degenerative meniscal tears and without radiographic osteoarthritis, lower quadriceps strength at baseline increased the odds of radiographic osteoarthritis progression over 5 years by 40% (for every 0.2 Nm/kg decrease).

Consistent with a previous investigation (2), muscle strength at baseline in the 2 treatment groups was 11–14% lower for quadriceps compared to the contralateral leg and 1–7% lower for hamstrings. Interestingly, muscle strength in the involved leg at baseline (Table 1) was equivalent to normative age-matched data for quadriceps peak torque (1.98 Nm/kg) but lower for hamstrings peak torque (1.17 Nm/kg) (32).

At 3 months, we found between-group differences of 15% for change in normalized quadriceps peak torque and 10% for normalized hamstrings peak torque. Following a slight decline in normalized quadriceps strength at 3 months, improvements were also seen for the partial meniscectomy group at 12 months, but between-group differences were still statistically significant. A previous investigation found no bilateral differences in quadriceps strength 12 months postoperatively (2). However, our partial meniscectomy group's affected leg was 6% weaker than the uninvolved leg at 12 months, and only 1 in 4 participants was defined as a responder (cutoff of 15% change).

Muscle strength declined from 12 months to 5 years in both treatment groups. This finding is expected because the mean age at inclusion was 50 years; the threshold when age-related declines in strength generally commence (33). We also saw a similar decline in the uninvolved leg, which corroborates the decline as age-related. Still, 5-year absolute muscle strength was 4–6% higher than baseline for the exercise group and between 1% higher to 3% lower for the partial meniscectomy group. Although this finding may partly be explained by disuse before study inclusion, our OMEX trial included highly physically active individuals; ~8 in 10 participated in sport or exercise activities ≥150 minutes/week before their knee problems (34). Moderate-to-vigorous physical activity is beneficially associated with lower-extremity muscle strength (35). In a previous study that also included individuals reporting a high physical activity level before diagnosis, no difference in muscle strength compared to healthy controls was found 2 years after partial meniscectomy or in changes from 2 to 4 years (36,37). In contrast, in persons not participating in any sporting activities, 24% lower quadriceps strength than matched controls has been found 4 years postsurgery (38). This finding may indicate that in physically inactive persons with potentially less spare muscle capacity at diagnosis, surgery and the extended period of inactivity could have more detrimental effects on muscle strength that are difficult to restore without a structured intervention program focusing on knee muscle strength.

Knee muscle weakness alters the mechanical environment and may affect cartilage integrity negatively (39). Our results support this idea and indicate that quadriceps muscle strength is important for the risk of progression to more severe osteoarthritis changes in middle-aged individuals with degenerative meniscal tears. A recent small study found that lower knee muscle strength 4 years after partial meniscectomy was associated with more severe osteoarthritis changes 11 years later (11). Our larger study complements these findings by identifying baseline muscle weakness as a risk factor for progression to more severe osteoarthritis changes 5 years later. Identification of a modifiable pathway to osteoarthritis in this patient population known to already be at increased risk for disease development indicates that early interventions addressing knee muscle strength should be recommended for all individuals with degenerative meniscus.

The mean difference in normalized quadriceps peak torque at baseline between participants with and without radiographic progression was almost 0.4 Nm/kg. For men and women, respectively, the deficit was 15% and 22% compared to those without

progression. The adjusted OR for every 0.2 Nm/kg decrease was 1.40 (95% CI 1.15, 1.71); the odds of radiographic progression increased by 40%. While we found improvements in the current study in quadriceps strength following 12 weeks of exercise therapy of >0.2 Nm/kg, participants with radiographic progression over 5 years were well balanced concerning treatment received (48% from the exercise group). Thus, participants in the exercise group with osteoarthritis progression probably did not achieve adequate quadriceps strength following the intervention to fully eliminate quadriceps muscle weakness as a risk factor for progression. For instance, progressors in the exercise group had a mean deficit of ~10% at 3 months compared to the uninvolved leg. In comparison, nonprogressors had equal quadriceps strength in the affected and uninvolved leg at the same time point. To achieve positive effects on muscle strength, adherence to exercise is essential. Clinicians are important facilitators to promote adherence through individually tailored exercises, patient education, and patient involvement (40).

The current study has limitations. No power calculations were performed a priori for this 5-year follow-up study. However, for between-group differences in knee muscle strength changes at 5 years, the CIs of the effect estimates do not include our predefined threshold for clinically relevant improvement, indicating that our results are conclusive (41). We evaluated peak torque and total work, but other parameters such as angle-specific torque may provide additional information in individuals with degenerative meniscus (42). Six participants in each group did not receive any treatment, and 14 (20%) crossed over from exercise to partial meniscectomy. However, we believe this result reflects clinical practice. We included middle-aged physically active individuals, and the results are not generalizable to older, less physically active individuals with concomitant osteoarthritis. Finally, the sample size prevented us from stratifying osteoarthritis progression analyses by sex.

In conclusion, 12 weeks of exercise therapy was effective in improving quadriceps and hamstrings muscle strength compared to arthroscopic partial meniscectomy for middle-aged patients with degenerative meniscal tears. We found statistically significant differences in change from baseline to 3 and 12 months in favor of the exercise group. At 5 years, between-group differences were attenuated and no longer statistically significant for quadriceps strength. We also found evidence to suggest that lower quadriceps strength at baseline is associated with radiographic knee osteoarthritis progression over 5 years.

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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 submitted for publication. Mr. Berg 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.** Berg, Roos, Holm, Risberg.
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REHABILITATION SCIENCES AND THE RHEUMATIC DISEASES

# Race Differences in Postacute Physical Therapy Utilization and Patient-Reported Function After Total Knee Arthroplasty

Allyn M. Bove,[1] Leslie R. M. Hausmann,[2] Sara R. Piva,[1] Jennifer S. Brach,[1] Allen Lewis,[3] and G. Kelley Fitzgerald[1]

**Objective.** This observational cohort study included patients of Black and White race and non-Hispanic ethnicity with end-stage knee osteoarthritis who were scheduled to receive total knee arthroplasty (TKA) surgery. Our objective was to examine whether race differences exist in the use of physical therapy (PT) across all postacute settings and to examine patient-reported physical function following TKA.

**Methods.** We collected pre- and postoperative physical function data and postoperative rehabilitation data on 104 Black and White individuals undergoing TKA. Regression analyses and independent samples *t*-tests were used to explore the predictive value of race on postoperative functional outcome and to compare PT utilization within each postacute setting and across all postacute rehabilitation settings.

**Results.** Total PT received was similar between White and Black participants, but significant race differences in PT utilization existed within specific settings. Race did not significantly predict function after TKA, but Black participants had slightly lower self-reported function both before and after surgery than White participants.

**Conclusion.** This is the first study to examine both PT utilization and functional outcomes in a sample of individuals undergoing TKA, and results indicate differences in where postoperative PT is received between Black and White patients.

## INTRODUCTION

Knee osteoarthritis (OA) is a common cause of disability affecting older adults. The most effective treatment for end-stage knee OA is total knee arthroplasty (TKA) surgery (1,2). More than one-half of people with knee OA will undergo TKA, which is effective and cost-effective at improving function and quality of life (3–10).

Outcomes following TKA are positive, with 85–90% of recipients experiencing significant improvements in pain, function, and quality of life (8,9). Thus, making TKA surgery available to all those in need is important. However, race disparities in knee OA surgery are well-documented. Studies consistently demonstrate that Black individuals are less likely to undergo TKA than non-Hispanic White individuals (11–19).

Recent research has explored disparities among those receiving TKA surgery. Several studies found that Black patients receive TKAs at lower-quality and low-volume hospitals and are more likely to experience postoperative complications and readmissions (20–25). Unfortunately, research regarding race disparities in functional outcomes following TKA is scant. Lavernia et al found that Black race and Hispanic ethnicity were associated with poorer self-reported physical function and health-related quality of life following arthroplasty (26). A recent study by Riddle et al noted clinically relevant postoperative race differences in function among participants in a clinical trial (27).

To maximize functional outcomes, patients undergoing TKA require high-intensity rehabilitation for weeks or months beyond the postoperative hospitalization to regain strength and physical function (28,29). This rehabilitation is particularly important for

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**SIGNIFICANCE & INNOVATIONS**

- This research adds to a very limited body of research regarding disparities in functional outcomes following total knee arthroplasty for end-stage knee osteoarthritis.
- This is the first study to examine race disparities in both rehabilitation utilization and physical function in the same cohort of patients.
- The results of this study support the findings of prior research that found a similar magnitude of differences in physical function after total knee arthroplasty between White and Black patients.

Black patients because they tend to exhibit poorer function preoperatively, which may be due to Black patients having lower expectations regarding recovery following TKA and delaying surgery in favor of nonsurgical treatments (12,30,31). Freburger et al demonstrated that non-White patients receive less intensive postacute rehabilitation care, receiving fewer hours of rehabilitation daily and weekly than White patients (32). However, studies investigating postoperative disparities in TKA have not examined the role of physical therapy (PT) in functional outcomes.

Overall, evidence suggests that race disparities may exist in functional outcomes after TKA, but this possibility has not been well studied. Knowledge is also lacking regarding disparities in postoperative PT utilization. Therefore, the purposes of this study were to determine whether race predicts functional recovery and to investigate race differences in utilization of postacute PT following TKA.

## MATERIALS AND METHODS

We employed a prospective observational cohort study design and recruited participants from 2015 to 2018 via advertisements in surgery offices, referrals from a research registry, and mailed advertisements. Participants provided informed consent prior to enrollment, and the study was approved by the University of Pittsburgh Institutional Review Board.

Inclusion criteria were a scheduled primary unilateral TKA, being White/Caucasian or Black/African American race and non-Hispanic ethnicity, and the ability to speak English. Potential participants were excluded if they were scheduled for simultaneous bilateral or revision TKA or if they failed to receive the scheduled surgery. Participants undergoing a staged bilateral TKA were eligible to participate in the study for their first TKA only.

**Research procedures.** Prior to surgery, participants completed questionnaires described below. After surgery, study personnel performed telephone or email check-ins monthly, but did not provide interventions or medical/rehabilitation advice. Follow-up questionnaires were collected 3 months postoperatively because research has demonstrated that most functional improvement occurs in the first 12 weeks (33). Participants were not required/encouraged to seek PT care from any particular clinic or provider.

**Outcomes.** Preoperatively, participants provided demographic/clinical information and a patient-reported outcome measure. Data collected included age, sex, race, ethnicity, marital status, educational attainment, income, health insurance, body mass index, TKA surgeon, TKA hospital, and medical comorbidities using the Functional Comorbidity Index (34). These variables were collected for evaluation as covariates because they have been shown in prior literature to correlate with outcomes following TKA (20–27,32,35–39).

The outcome measure for the primary aim (whether race predicts functional outcome at 3 months postoperatively) was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). This patient-reported measure assesses pain, stiffness, and physical function and is reliable, valid, and responsive in individuals with knee OA and TKA (40–44). We used the 5-point Likert scale version and calculated a total WOMAC score (ranging from 0 to 96, with higher scores indicating worse symptoms) (45).

At 3 months postoperation, participants completed a follow-up WOMAC questionnaire and a survey regarding their postoperative recovery, including hospital length of stay and postoperative complications. Participants self-reported the length of stay in any inpatient rehabilitation facility following discharge from the hospital and the number of home health PT visits received. Finally, participants reported the name/location of any outpatient PT facility attended. To minimize reporting bias, upon enrollment participants were given an informational sheet describing the items that would be asked at follow-up and a form to document these variables as they occurred. During check-ins after surgery, study personnel reminded participants to regularly record this information. Study personnel performed reviews of participants' outpatient PT charts to record the number of visits, duration of care, and number of units and/or minutes billed at each visit.

The primary outcome for this aim of the study was the total hours of postacute PT received. Time spent in each postoperative rehabilitation setting was calculated as follows: 1) acute rehabilitation: length of stay (days) $\times$ 90 minutes/day (46–48); 2) skilled nursing facility (SNF) or subacute rehabilitation facility: length of stay (days) $\times$ 45 minutes/day (46–48); 3) home: number of visits by home care therapist $\times$ 60 minutes/visit (49,50); 4) outpatient: total minutes (from billing/Current Procedural Terminology code sheet, sum of all outpatient visits); 5) summary outcome measure of TOTAL amount of PT received: sum of all settings (in minutes)/60. The summary of rehabilitation provided a total number of hours of postacute PT received, rounded to the nearest tenth of an hour.

**Statistical analysis.** We used WOMAC means $\pm$ SDs from Allen et al to determine target sample size (51). We

**Table 1.** Baseline participant demographic and clinical characteristics by race*

| Characteristic | White/Caucasian (n = 75) | Black/African American (n = 29) |
|---|---|---|
| Sex | | |
| Male | 28 (37.3) | 9 (31.0) |
| Female | 47 (62.7) | 20 (69.0) |
| Age, mean ± SD years | 64.3 ± 8.4 | 65.2 ± 6.2 |
| Marital status | | |
| Married/domestic partner | 57 (76.0) | 8 (27.6) |
| Divorced/separated | 7 (9.3) | 10 (34.5) |
| Widowed | 5 (6.7) | 8 (27.6) |
| Single, never married | 6 (8.0) | 3 (10.3) |
| Highest educational level completed | | |
| Less than high school | 0 (0.0) | 1 (3.4) |
| High school | 33 (44.0) | 23 (79.3) |
| College | 20 (26.7) | 4 (13.8) |
| Postgraduate degree | 22 (29.3) | 1 (3.4) |
| Annual household income, US$ | | |
| <25,000 | 8 (10.7) | 11 (37.9) |
| 25,000 to <50,000 | 16 (21.3) | 17 (58.6) |
| 50,000 to <100,000 | 28 (37.3) | 0 (0.0) |
| ≥100,000 | 20 (26.7) | 0 (0.0) |
| No response | 3 (4.0) | 1 (3.4) |
| Health insurance | | |
| Medicare | 36 (48.0) | 16 (55.2) |
| Medicaid | 1 (1.3) | 1 (3.4) |
| Dual Medicare/Medicaid | 4 (5.3) | 3 (10.3) |
| Private | 33 (44.0) | 8 (27.6) |
| Veterans | 1 (1.3) | 0 (0.0) |
| No insurance | 0 (0.0) | 1 (3.4) |
| Comorbidities | | |
| Arthritis | 75 (100.0) | 28 (96.6) |
| Osteoporosis | 16 (21.3) | 1 (3.4) |
| Asthma | 9 (12.0) | 6 (20.7) |
| Lung disease | 4 (5.3) | 1 (3.4) |
| Angina | 0 (0.0) | 0 (0.0) |
| Congestive heart failure | 8 (10.7) | 2 (6.9) |
| Myocardial infarction | 8 (10.7) | 1 (3.4) |
| Neurologic disease | 4 (5.3) | 0 (0.0) |
| Stroke or transient ischemic attack | 2 (2.7) | 0 (0.0) |
| Peripheral vascular disease | 4 (5.3) | 2 (6.9) |
| Diabetes mellitus I or II | 3 (4.0) | 6 (20.7) |
| Upper gastrointestinal disease | 29 (38.7) | 11 (37.9) |
| Depression | 9 (12.0) | 7 (24.1) |
| Anxiety/panic disorder | 10 (13.3) | 0 (0.0) |
| Visual impairment | 19 (25.3) | 6 (20.7) |
| Hearing impairment | 9 (12.0) | 1 (3.4) |
| Degenerative disc disease | 18 (24.0) | 12 (41.4) |
| Obesity | 44 (58.7) | 16 (55.2) |
| Preoperative WOMAC score, mean ± SD | 50.5 ± 15.1 | 54.1 ± 13.4 |

* Values are the number (%) unless indicated otherwise. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

calculated that 103 participants were needed to determine whether race is a moderate significant predictor of outcome, with alpha set at 0.05 and 80% power.

To explore the primary research question of whether race significantly predicts postoperative WOMAC score after adjusting for potential confounders, we first performed correlation analyses (continuous variables) and association analyses (categorical variables) to determine whether each potential demographic/clinical covariate was significantly related to both race and follow-up WOMAC. We set a threshold of *P* less than 0.10 for inclusion in regression analyses.

Next, we performed a series of linear regression analyses. We first performed a simple linear regression analysis (model 1) to examine the raw predictive value of race with respect to postoperative WOMAC score and then performed 3 different hierarchical linear regression analyses to adjust for covariates using information from the correlation/association analyses described above. We decided a priori to adjust for preoperative WOMAC

score in our regression model. Therefore, model 2 reflects the predictive value of race on postoperative function after adjusting for preoperative function. In model 3, we adjusted for preoperative WOMAC score and all covariates that were significantly correlated to both race and postoperative WOMAC score. In model 4, we adjusted for preoperative WOMAC score and all covariates that were significantly correlated to either race or postoperative WOMAC score. We also included total hours of postoperative PT in model 4 to allow us to see the impact of rehabilitation utilization on the relationship between race and functional outcomes. In models 2–4, we adjusted for covariates in the first step of the regressions. In the second step, race was added to determine the additional predictive value of race on postoperative WOMAC score. The importance of race as a predictor was determined based on change in $R^2$ when race was added to each model. SPSS statistics data analysis software, version 25, was used for all analyses.

To compare total postacute care PT utilization between Black and White participants, we performed an independent samples *t*-test comparing the mean total hours of postacute PT between the 2 groups. We also performed additional independent samples *t*-tests to compare utilization within each PT setting and chi-square analyses to compare the likelihood of receiving PT in each setting. In the small number of cases with any missing outcomes data (n = 8), we imputed the mean value of the participants' race group.

## RESULTS

We screened 135 participants by telephone. Of those screened, 104 met eligibility criteria, enrolled in the study, and completed baseline questionnaires. Ninety-six participants completed follow-up questionnaires; 8 participants (6 White and 2 Black) were lost to follow-up. Baseline demographic/clinical characteristics are described in Table 1. White and Black participants had similar average ages, and both groups skewed heavily female. White participants generally reported higher educational attainment and household income. Comorbidities differed somewhat between groups. White participants were more likely to have osteoporosis, hearing impairments, and anxiety or panic disorders. Black participants were more likely to have asthma, diabetes mellitus, depression, and degenerative disc disease.

Preoperatively, White participants had somewhat better total WOMAC scores (mean ± SD 50.5 ± 15.1) than Black participants (mean ± SD 54.1 ± 13.4) (Table 1). Both groups achieved substantial improvement pre- to postoperatively, but the magnitude of difference remained consistent at follow-up (Table 2). White participants' mean ± SD 3-month postoperative WOMAC score was 20.4 ± 16.6, compared to Black participants' mean ± SD WOMAC score of 25.2 ± 12.4, a 5% between-group difference in relation to the maximum possible score of 96. This finding does not meet the threshold of a clinically important difference of at least 6% (52).

**Table 2.** Postsurgical characteristics by race*

| Characteristic | White/Caucasian (n = 75) | Black/African American (n = 29) |
|---|---|---|
| Surgical complications | | |
| Yes | 15 (20.0) | 2 (6.9) |
| Wound infection, no. | 2 | 0 |
| DVT/PE, no. | 4 | 0 |
| Manipulation, no. | 4 | 1 |
| Other complication, no. | 7 | 1 |
| No | 52 (69.3) | 25 (86.2) |
| Unknown | 8 (10.7) | 2 (6.9) |
| Postoperative WOMAC, mean ± SD | 20.4 ± 16.6 | 25.2 ± 12.4 |

* Values are the number (%) unless indicated otherwise. DVT = deep venous thrombosis; PE = pulmonary embolism; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index (higher scores = worse symptoms).

Table 2 shows postoperative complications and outcomes by race. Complications were less common among Black participants. The most common complications included manipulation under anesthesia (to address severe stiffness) and blood clots. Several variables significantly correlated with either postoperative WOMAC score or race (Table 3). Variables related to postoperative WOMAC score included sex (r = 0.274, $P = 0.007$; women had worse function), preoperative WOMAC score (r = 0.331, $P = 0.001$), household income (r = 0.179, $P = 0.088$; lower income associated with poorer WOMAC scores), and surgeon (r = 0.186, $P = 0.069$). Variables significantly related to Black race included marital status (r = 0.403, $P < 0.001$; Black patients were more likely to be unmarried), educational attainment (r = 0.420, $P < 0.001$; Black patients generally reported lower educational attainment), and household income (r = 0.543, $P < 0.001$; Black patients reported lower incomes). Income was the only potential covariate correlated with both race and postoperative WOMAC. Two medical comorbidities, diabetes mellitus and degenerative disc disease, were significantly more common among Black participants and were associated with poorer postoperative WOMAC scores.

Table 4 shows the results of regression analyses. The unadjusted model (model 1) demonstrated that race was not a significant predictor of postoperative WOMAC score ($P = 0.071$, adjusted $R^2 = 0.024$). After adjusting for baseline WOMAC score (model 2), the overall model fit was statistically significant ($P = 0.001$), but $R^2$ (adjusted $R^2 = 0.12$) and $R^2_{change}$ (0.02) were both small when adding race into the model. Similar results were observed in model 3, adjusting for baseline WOMAC score, household income, and the presence of diabetes mellitus and/or degenerative disc disease ($P = 0.008$, adjusted $R^2 = 0.11$ [$R^2_{change}$ when adding race into the model = 0.01]). Finally, we expanded the model to adjust for postoperative rehabilitation utilization and additional sociodemographic variables, including sex, marital status, educational attainment, household income, and surgeon (model 4). Again, overall model fit was statistically significant ($P = 0.001$), but adjusted $R^2$ (0.30) and $R^2_{change}$ (0.003) when adding race into the model were both fairly small.

**Table 3.** Bivariate correlation matrix*

| | WOMAC Post | Age | Sex | Race | Marital | Education | Income | Insurance | Hospital | Surgeon |
|---|---|---|---|---|---|---|---|---|---|---|
| WOMAC Post | | | | | | | | | | |
| r | – | – | – | – | – | – | – | – | – | – |
| *P* | – | – | – | – | – | – | – | – | – | – |
| Age | | | | | | | | | | |
| r | 0.006 | – | – | – | – | – | – | – | – | – |
| *P* | 0.95 | – | – | – | – | – | – | – | – | – |
| Sex | | | | | | | | | | |
| r | 0.274† | 0.069 | – | – | – | – | – | – | – | – |
| *P* | 0.01 | 00.48 | – | – | – | – | – | – | – | – |
| Race | | | | | | | | | | |
| r | 0.185 | 0.053 | 0.059‡ | – | – | – | – | – | – | – |
| *P* | 0.07 | 0.59 | 0.56 | – | – | – | – | – | – | – |
| Marital | | | | | | | | | | |
| r | 0.018 | 0.080 | 0.209§ | 0.403§ | – | – | – | – | – | – |
| *P* | 0.86 | 0.42 | 0.03 | <0.001 | – | – | – | – | – | – |
| Education | | | | | | | | | | |
| r | 0.135 | 0.066 | 0.033‡ | 0.420§ | 0.234§ | – | – | – | – | – |
| *P* | 0.19 | 0.51 | 0.74 | <0.001 | 0.02 | – | – | – | – | – |
| Income | | | | | | | | | | |
| r | 0.179 | 0.202¶ | 0.028‡ | 0.543§ | 0.534§ | 0.572§ | – | – | – | – |
| *P* | 0.09 | 0.04 | 0.78 | <0.001 | <0.001 | <0.001 | – | – | – | – |
| Insurance | | | | | | | | | | |
| r | 0.022 | 0.547† | 0.143‡ | 0.091‡ | 0.026‡ | 0.026‡ | 0.250§ | – | – | – |
| *P* | 0.84 | <0.001 | 0.15 | 0.36 | 0.79 | 0.79 | 0.01 | – | – | – |
| Hospital | | | | | | | | | | |
| r | 0.118 | 0.049 | 0.197§ | 0.031‡ | 0.071‡ | 0.024‡ | 0.053‡ | 0.032 | – | – |
| *P* | 0.25 | 0.62 | 0.05 | 0.75 | 0.48 | 0.81 | 0.60 | 0.75 | – | – |
| Surgeon | | | | | | | | | | |
| r | 0.186 | 0.094 | 0.335§ | 0.044‡ | 0.022‡ | 0.058‡ | 0.064‡ | 0.188 | 0.622† | – |
| *P* | 0.07 | 0.34 | 0.001 | 0.66 | 0.84 | 0.56 | 0.52 | 0.06 | <0.001 | – |
| WOMAC Pre | | | | | | | | | | |
| r | 0.331† | 0.025 | 0.219¶ | 0.109 | 0.110 | 0.156 | 0.282† | 0.063 | 0.015 | 0.094 |
| *P* | 0.001 | 0.80 | 0.03 | 0.27 | 0.27 | 0.11 | 0.01 | 0.52 | 0.88 | 0.34 |

* r = Pearson's correlation coefficient; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; WOMAC Pre = preoperative WOMAC score; WOMAC Post = postoperative WOMAC score.
† Statistically significant.
‡ Chi-square analyses (not correlation analyses).
§ Chi-square analyses (not correlation analyses). Statistically significant.
¶ Statistically significant.

Overall model fit was strongest for model 4, but rehabilitation utilization plus all sociodemographic/clinical factors only accounted for 30% of variability in follow-up WOMAC scores. Race had a small effect in all models that we studied.

**Total postacute PT received.** All participants reported receiving acute care/hospital PT, and hospital length of stay was nearly identical between White and Black participants. Zero participants reported utilization of acute inpatient rehabilitation. Table 5 shows the aggregate hours of postacute PT received. The mean between-group difference was 2.6 hours, indicating that Black participants averaged 156 fewer minutes of PT care than White participants ($P = 0.36$).

**SNF PT.** More Black participants (27.6%) than White participants (17.3%) were admitted to skilled nursing facilities (Table 5). In the full cohort of Black and White participants, neither length of stay ($P = 0.45$) nor hours of PT received ($P = 0.49$) in these facilities was significantly different between racial groups. Results were similar in the subsample of 21 participants who were discharged to an SNF.

**Home health PT.** A majority of participants in both groups reported receiving home health PT, but a significantly larger proportion of Black participants received home health ($\chi^2 = 5.58$, $P = 0.02$). The number of visits received was also significantly higher among Black participants (average of 6.2 visits) than White participants (average of 4.7 visits, $P = 0.05$) (Table 5).

**Outpatient PT.** Most participants received outpatient PT (88.0% of White participants and 82.8% of Black participants). Duration of care was shorter for White participants (mean 56.8 days) than for Black participants (mean 71.2 days), but this difference was not significant ($P = 0.06$) (Table 5).

Although Black participants averaged longer outpatient PT duration of care, on average they received 1 fewer visit

**Table 4.** Regression models with race as a predictor of follow-up WOMAC score after adjusting for sociodemographic and clinical factors*

| Variable | Model 1 | Model 2 | Model 3 | Model 4 |
|---|---|---|---|---|
| Black | 0.72 (–0.07, 1.51) | 0.62 (–0.13, 1.37) | 0.22 (–0.75, 1.18) | 0.25 (–0.62, 1.1) |
| Baseline WOMAC score | – | 0.04 (0.02, 0.06) | 0.03 (0.002, 0.06) | 0.04 (0.02, 0.07) |
| Annual income | – | – | –0.10 (–0.52, 0.33) | –0.32 (–0.79, 0.15) |
| Presence of DM | – | – | 0.89 (–0.43, 2.20) | 0.51 (–0.67, 1.7) |
| Presence of DDD | – | – | 0.48 (–0.33, 1.29) | 0.72 (–0.02, 1.5) |
| Female | – | – | – | 0.63 (–0.15, 1.4) |
| Married or cohabitating | – | – | – | –0.26 (–0.52, –0.001) |
| College degree or higher | – | – | – | 0.05 (–0.21, 0.06) |
| Surgeon | – | – | – | 0.02 (–0.02, 0.06) |
| Postoperative PT, total hours | – | – | – | 0.01 (–0.02, 0.04) |
| Overall model fit | | | | |
| F (df) | 3.32 (1, 94) | 7.24 (2, 93)† | 3.34 (5, 86)† | 4.61 (10, 74)† |
| $R^2$ | 0.03 | 0.14 | 0.16 | 0.38 |
| Adjusted $R^2$ | 0.02 | 0.12 | 0.11 | 0.30 |
| $R^2_{change}$ from race term | 0.02 | 0.02 | 0.01 | 0.003 |

* Values are the beta coefficient (95% confidence interval [95% CI]) unless indicated otherwise. Beta coefficients and 95% CIs in Table 3 are difficult to interpret because the outcome variable (follow-up Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] score) had to be transformed to satisfy the normality assumption prior to running regression analyses. DDD = degenerative disc disease; df = degrees of freedom in regression models; DM = diabetes mellitus (type 1 or 2); PT = physical therapy.
† Statistical significance of overall model fit at $P < 0.05$.

(mean of 17.1 visits versus 16.1 visits; $P = 0.63$) and 5 fewer hours of outpatient PT (mean of 19.22 hours versus 14.08 hours; $P = 0.06$). This finding indicates that Black participants had less intensive outpatient PT, although neither between-group difference was statistically significant.

## DISCUSSION

In this study, race did not predict postoperative WOMAC score following TKA. This result held true in unadjusted regression models and after adjusting for rehabilitation utilization and relevant demographic and clinical variables. Black participants received an average of 2.6 fewer hours of total postacute PT following TKA than White participants. This difference was not statistically significant. Minor differences were present across treatment settings, with Black participants overall receiving more SNF and home health PT, but less outpatient and total PT.

A paucity of research investigates race disparities in functional outcomes after TKA, but some studies have identified Black race as a risk factor for other negative outcomes such as

**Table 5.** Postacute physical therapy (PT) utilization by race*

| | White/Caucasian, (n = 75) | Black/African American (n = 29) | Between-group *P* |
|---|---|---|---|
| Hospital/acute care: received PT? no. (%) | Yes: 75 (92.0); no: 0 (0.0); unknown: 0 (8.0) | Yes: 27 (93.1); no: 0 (0.0); unknown: 2 (6.9) | 0.86 |
| Hospital length of stay, days | 2.3 ± 0.8 | 2.3 ± 0.8 | 0.87 |
| Discharged to SNF? no. (%) | Yes: 13 (17.3); no: 56 (74.7); unknown: 6 (8.0) | Yes: 8 (27.6); no: 19 (65.5); unknown: 2 (6.9) | 0.25 |
| Length of stay in an SNF, days | 12.6 ± 6.8 | 11.0 ± 2.3 | 0.45 |
| Hours of SNF PT received† | 1.52 ± 0.46 | 2.44 ± 0.76 | 0.49 |
| Hours of SNF PT received‡ | 9.5 ± 5.1 | 8.3 ± 1.7 | 0.45 |
| Received home health PT? no. (%) | Yes: 52 (69.3); no: 17 (22.7); unknown: 6 (8.0) | Yes: 26 (89.7); no: 1 (3.4); unknown: 2 (6.9) | 0.02§ |
| No. of home PT visits | 4.7 ± 3.4 | 6.2 ± 3.4 | 0.05§ |
| Hours of home health PT received | 4.6 ± 0.44 | 6.2 ± 0.66 | 0.05 |
| Received outpatient PT? no. (%) | Yes: 66 (88.0); no: 3 (4.0); unknown: 6 (8.0) | Yes: 24 (82.8); no: 3 (10.3); unknown: 2 (6.9) | 0.22 |
| Duration of outpatient PT care, days | 56.8 ± 30.0 | 71.2 ± 37.7 | 0.06 |
| No. of outpatient PT visits | 17.1 ± 8.6 | 16.1 ± 9.0 | 0.63 |
| Outpatient PT, hours | 19.22 ± 1.55 | 14.08 ± 1.54 | 0.06 |
| Total hours of postacute PT received | 25.4 ± 1.7 | 22.8 ± 1.9 | 0.36 |

* Values are the mean ± SD unless indicated otherwise. SNF = skilled nursing facility.
† Analyzing all 104 patients.
‡ Analyzing the 21 patients who went to an SNF.
§ Statistically significant.

manipulation under anesthesia and lower Knee Society scores (indicating poorer range of motion, stability, and/or alignment) (53,54). We can reasonably hypothesize that patient-reported function may also be lower among Black patients after TKA. However, our findings do not support this hypothesis.

At both the preoperative and 3-month postoperative measurement points, White participants' total WOMAC scores were slightly better than those of Black participants. At follow-up, the between-group global WOMAC difference was 5% of the maximal score. Research by Angst et al has suggested that differences >6% of the maximal WOMAC score are clinically important in individuals with OA, so the between-group difference in the current study does not meet the threshold for clinical importance (52). In addition, the proportion of participants who would be classified as responders using Osteoarthritis Research Society International–Outcome Measures in Rheumatology criteria is very similar (72.0% of White participants and 72.4% of Black participants), which further supports the lack of a clinically important difference in function between Black and White patients in our sample (55).

However, physical therapists should still consider this information when treating patients post-TKA. A 4-point difference between 2 patients' global WOMAC scores could indicate that 1 patient experiences slightly more pain or difficulty on several functional tasks or substantially more pain or difficulty with 1 or 2 tasks. Physical therapists should therefore examine patient questionnaires to screen for difficulty with specific movements/tasks and tailor treatment plans to address tasks that are particularly problematic. Physical therapists should also consider supplementing patient-reported outcome measures (such as the WOMAC used in the current study) with performance-based measures of function because research is conflicting regarding the degree of correlation between the 2 types of measurement (56,57). One study noted that self-report measures, especially in the month after TKA, may significantly underestimate a patient's degree of functional deficits (57). Outpatient physical therapists are typically the final rehabilitation provider giving care to patients following TKA, so they are uniquely positioned to close the gap in postoperative function and maximize outcomes for all patients.

Our findings conflict with those of Lavernia et al, who noted that both Black race and Hispanic ethnicity were associated with poorer function and quality of life outcomes after TKA (26). In that single-surgeon study, Black patients were younger and had different preoperative diagnoses than White patients. Similar to our study, total WOMAC scores were higher (indicating worse symptoms) in Black patients preoperatively. In the current study, the difference was not clinically significant (between-group difference of 3.6 points in total average preoperative WOMAC score), but the difference was larger and clinically significant among participants in the Lavernia study (between-group difference of 8.6 points in total average preoperative WOMAC score). However, although the Lavernia study used a much larger overall sample size (n = 1,010 patients with TKA), ~90% of the sample was White (26). Our study involved a much smaller sample size (n = 104), but the race distribution was more equitable (28% Black and 72% White), and we investigated a larger number of demographic factors (e.g., insurance status, household income, and educational attainment). Both studies involved patients from a single urban region, and Black/White disparities in post-TKA function may differ by location due to geographic differences in health care utilization.

Our findings are consistent with those recently reported by Riddle et al (27). In a secondary analysis of 384 clinical trial participants, they noted that WOMAC function subscale scores were fairly similar at baseline between Black and non-Black participants. However, a larger gap in self-reported function was evident at a 2-month follow-up. This gap became smaller but persisted at 6- and 12-month follow-ups. These gaps are important because they demonstrate that the first 2 months after surgery, during which the large majority of postoperative PT services are delivered, may be an extremely important period in which to intervene to minimize race disparities. The participant sample in the study of Riddle et al was similar to ours with respect to age, sex, and comorbidities. However, all participants in their study demonstrated moderate or high pain catastrophizing at baseline, and two-thirds of the participants were randomized to receive interventions beyond usual clinical care (27).

Freburger et al found that 55% of patients were discharged home following total hip or knee arthroplasty surgery, compared to 72–80% of participants in the current study (32). This difference in the percentage of patients discharged may reflect differences in the samples because the current study included only patients receiving TKA, whereas Freburger et al included data from both knee and hip replacement recipients and did not report results separately by joint. Alternately, this difference with Freburger et al may reflect regional variation in postacute care patterns following joint replacement surgery. This difference may also reflect the time during which the data were collected. The Freburger study used a sample from 2005 and 2006, while the current study included data from 2015 to 2019; TKA care pathways have changed during that time.

Future research should investigate race disparities in long-term functional outcomes following TKA using validated measures of physical function over a longer time period (1 year or more) and using patients from a wider geographic region. In addition, future research should use large data sets that will provide the statistical power to detect differences between many different races and ethnicities rather than simply White and Black patients. Future work should use large data sets to track patients' PT utilization throughout all practice settings and explore the role of the various settings in functional recovery following TKA.

Overall, participants in our sample achieved similar functional outcomes on the WOMAC following TKA and received similar amounts of PT. These results support the hypothesis that when provision of rehabilitation is similar, disparities in function are minimal.

This study has several limitations. Most importantly, these results are based on analysis of 104 participants. Although we recruited the number of participants that were necessary for the primary aim per our power analysis, we were only powered to detect a moderate or larger relationship between race and functional outcomes. Some analyses in the secondary aim (postacute PT utilization) trended toward statistical significance, and a larger sample size may have increased power to detect differences that were statistically and clinically significant. However, a post hoc analysis indicated that we had 99% power to detect a significant between-group difference in total postoperative PT utilization.

In our sample, there were significant relationships between race and income, marital status, and educational attainment. By adjusting for these variables in our regression model, we possibly masked part of the effect of race on outcome. However, this masking is unlikely for 2 reasons. First, in the model where we only adjusted for income (the only demographic variable related to both race and WOMAC scores), the $R^2_{change}$ when adding race into the model was very low. Second, average WOMAC scores were similar between White and Black patients at both baseline and follow-up. Therefore, our statistical methods are unlikely to have masked a between-group difference in function. A related concern may be the potential collinearity among demographic variables that are known to be correlated in American society (such as race, income, marital status, and educational attainment). However, all of our regression models, whether including or excluding those variables, resulted in similar conclusions, so we feel that the relationship between these variables did not substantially impact the conclusions to be drawn from the data.

This study was conducted within a single geographic region. Participants in the study received their TKAs from 29 surgeons at 17 hospitals, which enhances generalizability. However, PT utilization patterns observed in this study may be different from those in other geographic areas. In addition, we included TKA surgeon and hospital as covariates in our analysis but did not include PT clinic or clinician because there were >50 unique PT facilities and providers giving care to the participants in the study. Although postoperative PT following TKA is largely based on the surgeon's protocol, differences possibly existed between clinics or clinicians that were not captured by our analysis.

Recall bias may be a concern because participants were asked to self-report some measures of postoperative PT utilization. However, we minimized this concern by providing instructional handouts preoperatively and reminders during postoperative contacts. Recall bias is not a concern for outpatient PT data because those data were gathered directly from each participant's chart. We estimated the length of each home health PT visit and average length of daily PT visits in skilled nursing facilities based on published norms (46–50), but practice patterns may vary within the actual facilities/agencies providing care to the participants in our study. Finally, the racial and ethnic demographics of our region only allowed us to include patients of Black and White race and non-Hispanic ethnicity. Therefore, we cannot generate any conclusions regarding functional outcomes in patients of other races and ethnicities.

In this sample of 104 participants undergoing TKA, race was not a substantial independent predictor of postoperative functional outcomes. Total postacute PT utilization did not significantly differ, but differences were present within specific care settings. Additional research is needed, using larger data sets, to fully illuminate race disparities in function and PT utilization after TKA.

## 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 submitted for publication. Dr. Bove 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.** Bove, Hausmann, Piva, Brach, Lewis, Fitzgerald.

**Acquisition of data.** Bove, Fitzgerald.

**Analysis and interpretation of data.** Bove, Hausmann, Piva, Brach, Lewis, Fitzgerald.

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## Errata

In the article by Lee et al published in the December 2010 issue of *Arthritis Care & Research* (A 44-Year-Old Woman With Cutaneous Bullae and Extensive Skin Necrosis [pages 1805–1811]), the title of the article should read as follows: A 44-Year-Old Woman With Cutaneous Bullae and Extensive Skin Necrosis: Levamisole-Contaminated Cocaine Causing a Drug-Induced Vasculitis.

In the article by Beltai et al published in the December 2018 issue of *Arthritis Care & Research* (Cardiovascular Morbidity and Mortality in Primary Sjögren's Syndrome: A Systematic Review and Meta- Analysis [pages 5–6]), the Results section contained an error. In the section entitled "Odds of heart failure," three articles were cited. Valvular disease outcomes were incorrectly considered as proxies for heart failure in the articles by Vassilou et al and Chiang et al. As a result, we decided to exclude these two studies. In the retained Bartoloni et al study, the prevalence of heart failure in the selected cohort of 788 female patients with primary Sjögren's syndrome in comparison with the control group was not higher ($P = 0.139$). As a result of excluding the two studies, our conclusion is now no increased likelihood of heart failure for patients with primary Sjögren's syndrome versus the general population. The other conclusions of the study are not affected.

We regret the error.

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REHABILITATION SCIENCES AND THE RHEUMATIC DISEASES

# Efficacy and Safety of Blood Flow Restriction Training in Patients With Knee Osteoarthritis: A Systematic Review and Meta-Analysis

Hao-Nan Wang, Yan Chen, Lin Cheng, Yi-Hui Cai, Wei Li, and Guo-Xin Ni

**Objective.** To evaluate the efficacy and safety of blood flow restriction training (BFRT) in the treatment of patients with knee osteoarthritis (OA).

**Method.** Seven electronic databases were searched to identify trials comparing BFRT and conventional resistance training in a population with knee OA. Studies were selected according to the inclusion and exclusion criteria. Standardized mean differences (SMDs) or risk ratios (RRs) with 95% confidence intervals (95% CIs) were calculated to compare outcome measures of the groups. The methodologic quality of selected studies and the quality of evidence were evaluated for included studies.

**Results.** A total of 5 studies were included in this meta-analysis, with very low to moderate risk of bias. The pooled results showed no significant difference between BFRT and conventional resistance training for knee OA, including pain (SMD –0.04 [95% CI –0.31, 0.24], $P = 0.79$), physical function performance (SMD 0.12 [95% CI –0.55, 0.78], $P = 0.73$), self-reported function (SMD 0.14 [95% CI –0.24, 0.52], $P = 0.48$), and adverse events (RR 0.45 [95% CI 0.20, 1.01], $P = 0.05$). In subgroup analysis, BFRT had a lower incidence of adverse events when compared with high-load resistance training (HLRT).

**Conclusion.** Data from pooled studies showed that BFRT may not have greater efficacy for treating patients with knee OA, and it is less likely to have a higher risk of adverse events. However, limited evidence supports the idea that BFRT is likely safer than HLRT. More evidence with high quality is needed in further research on efficacy and safety.

## INTRODUCTION

Osteoarthritis (OA) is the most common chronic degenerative bone and joint disease in the middle-aged and elderly worldwide (1). It is characterized by cartilage deterioration, joint space narrowing, and osteophyte formation (2). The knee is one of the most readily affected joints by OA (1,3). The prevalence of radiographic knee OA and symptomatic radiographic knee OA are estimated among older people in the US to be 37.4% and 12.1%, respectively (4). Patients with knee OA often suffer from chronic pain, impaired physical function, disability, and decreased quality of life (1,5,6). As a degenerative knee joint disease, the development of knee OA is strongly associated with a variety of factors, including age, sex, and obesity, as well as joint factors such as muscle weakness and joint morphology (7).

Exercise is commonly the first-line nonpharmacologic approach to treat knee OA and is recommended by the guidelines of various specialist societies (8,9). Resistance training is an important method of therapeutic exercise, which can decrease the risk of knee OA by increasing muscular strength and enhancing muscle hypertrophy (10). Weakness of the quadriceps muscle is regarded as a vital risk factor for the incidence (11) and progression (12) of radiographic knee OA and is highly related to the physical function and knee pain of knee OA patients (13). Additionally, poor limb muscle mass contributes to the severity of knee pain of knee OA (14) and is closely associated with present knee OA (15). According to the

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**SIGNIFICANCE & INNOVATIONS**

- Blood flow restriction training may have no advantages of clinical outcomes and safety versus conventional resistance training in treating patients with knee osteoarthritis.
- Blood flow restriction training has the feasibility of an alternative approach for knee osteoarthritis patients who are unable to tolerate the pain in high-load resistance training.
- We highlight the need for further investigation of efficacy and safety of blood flow restriction training with a lower degree of blood flow restriction and lower load (e.g., lower resistance training, walking, and aquatic exercise).

recommendations of the American College of Sports Medicine, the minimum mechanical load required to gain muscle strength and mass in resistance training is 60% and 70% of the 1-repetition maximum (16). However, high loads during the resistance training can increase the stress on the joints, which may lead to higher pain intensity and joint deterioration, as well as the decreased adherence of patients. For this reason, attention has recently been drawn to an ideal strategy of training, which can improve muscle strength and mass, while being more tolerable for individuals with knee OA.

Blood flow restriction training (BFRT), originating from the sport and exercise field, can decrease articular overload by exerting a lower resistance load while producing a similar gain in muscle strength and mass as in high-load resistance training (HLRT) (17). Typically, BFRT will block part of the arterial blood flow through the limbs by means of a pneumatized cuff or tourniquet and will be combined with low-load exercise, including low-load resistance training (LLRT) or walking (18). In addition to mechanical load, the benefits of BFRT to muscle strength and mass are considered to come from metabolic stress (19). Partial vascular occlusion causes an ischemic state in the limbs, resulting in promoted growth hormone (20,21) and increased recruitment of type II muscle fibers (22), which eventually activate the hypertrophic signaling pathways of skeletal muscle (23).

To date, trials of BFRT in patients with knee OA did not yield a consensus on the efficacy of BFRT because of their limited sample sizes and discrepant outcomes. Many previous reviews have focused mainly on the effectiveness of BFRT for building muscle strength or for improving clinical outcomes in musculoskeletal disorders (17,18,24,25). However, safety issues in individuals with knee OA must be considered because the majority of this population consists of older people who potentially have a variety of complications (26). Previous studies have highlighted the potential issue of BFRT in cardiovascular (27) and musculoskeletal systems (28,29) after this training. Therefore, we conducted a relatively comprehensive meta-analysis to assess the efficacy and safety of BFRT in patients with knee OA.

## MATERIALS AND METHODS

**Search strategy.** This systematic review and meta-analysis followed the guidelines set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24787/abstract, for the PRISMA Checklist) (30). The protocol of this study was registered in an international prospective register of a systematic review (PROSPERO #CRD42019130769) in April 2019. To identify relevant studies, a systematic literature search was performed by 2 review raters (HNW and YHC). Seven electronic databases were searched for articles published from January 1 to May 31, 2020, namely PubMed, CINAHL (EBSCO), Embase, Web of Science, SPORTDiscus (EBSCO), PEDro, and CENTRAL. The search string was created with 3 sections: the first encompassed synonyms for BFRT, the second was composed of synonyms for the knee joint, and the third referred to diseases. To ensure that at least 1 search term within each section was included in the results, all synonyms were connected with the operator OR and among sections were connected with the operator AND. We searched ClinicalTrials.gov and the International Clinical Trials Registry platform to identify additional unpublished records.

**Inclusion and exclusion criteria.** All studies were screened and assessed for eligibility with regard to our inclusion and exclusion criteria, which were based on the PICOS principle (i.e., extracting population, intervention, comparison intervention, outcome measures, and study design information). Studies were considered for inclusion if 1) subjects were diagnosed with knee OA or were at risk of knee OA; 2) the study allowed comparisons between BFRT and HLRT (≥60% 1 repetition maximum [RM]) or LLRT (<60% 1RM) or walking to waitlisting, placebo, or another intervention without blood flow restriction (BFR) (31); 3) each study contained at least 1 of the following outcomes: pain intensity, subject function score, functional performance examination, muscle mass/strength, or adverse events (AEs), assessed at pre- and posttraining; and 4) studies were published in English. Studies were excluded if 1) they were reviews, case reports, or observational investigations, 2) participants had received a surgical procedure or experienced lower-limb trauma, or 3) studies or data were duplicated.

**Data selection and extraction.** Two review raters (H-NW and YC) independently screened the titles and abstracts retrieved using the search strategy. The full texts of all studies considered potentially eligible for inclusion were then retrieved and read independently by the 2 review raters, who decided on the final selection. Any discrepancies were resolved through discussion and, where required, by the involvement of a third independent rater (LC). Data were independently extracted from the included studies by 2 authors (H-NW and YC), including author, year, patient characteristics,

intervention characteristics, duration of treatment, outcomes, and time points. Only the last time point value was considered when intervention effects were assessed at multiple time points. In the case of incomplete data from a published article, we contacted the corresponding author for the raw data of trials. Data were extracted from the studies identified for inclusion, and the extracted variables were revised and checked by H-NW and YC for accuracy.

**Assessment of risk of bias.** Following the instructions in the Cochrane Handbook for Systematic Reviews of Interventions (32), the risk of bias was individually rated for each study by 2 independent authors (H-NW and YC). Similarly, disagreements were resolved by discussion with a third reviewer (LC). Seven items were assessed, namely random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other source biases. Additionally, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods were used to evaluate the quality of evidence (33). The GRADE is a method to assess the quality of evidence based on the risk of bias, indirectness, inconsistency, imprecision, and risk of publication bias. The quality of evidence is graded as high, moderate, low, and very low.

**Statistical analysis.** This meta-analysis was carried out in Review Manager software (RevMan 5.2). The standardized mean difference (SMD) or mean difference with a 95% confidence interval (95% CI) were used to calculate all continuous data, and the risk ratio (RR) with 95% CI was calculated for the discontinuous data. The Higgins's ($I^2$) statistic was calculated to evaluate heterogeneity. The $I^2$ value was interpreted using the following cutoff values: <25% = low, 25–50% = moderate, and >50% = high (34). The random-effects model was applied if significant heterogeneity ($I^2 > 50\%$ or $P < 0.10$) existed, and the fixed model was adopted otherwise. The significance level was set at a $P$ value less than 0.05. Sensitivity analysis was performed to evaluate the quality and consistency of results by the sequential omission of each study. Additionally, publication bias was assessed by Egger's tests and funnel plots (32).

## RESULTS

**Search results.** A total of 464 records were identified, of which 302 published and unpublished records were retrieved for assessment after screening titles and abstracts. A total of 260 records were excluded because they did not meet the inclusion criteria. Subsequently, 42 full-text articles were assessed for eligibility, and 5 articles were included in this study. The agreement between the reviewers was evaluated by calculating the kappa coefficient ($\kappa = 0.816$). A flow diagram illustrating the process of article screening for this study is shown in Figure 1.

**Study characteristics.** Five articles (35–39) with 182 subjects were included to evaluate the efficacy and safety of BFRT for patients with knee OA. The detailed characterization of the 5 studies is summarized in Table 1. The 5 studies were randomized controlled trials published between 2015 and 2019. Of these 5, 3 (60%) were conducted in the US and 2 (40%) in Brazil. Three trials included patients diagnosed with knee OA, and 2 trials also included patients with radiographic or symptomatic knee OA (35,36). The age of the patients ranged from 49.9 to 69.1 years (median 60.4 years). The duration of the intervention ranged from 4 to 12 weeks, and the frequency of exercise was 2–3 times a week. All BFRT was combined with LLRT (20–30% 1RM), whereas the control group received resistance training (30–70% 1RM) alone. All studies involved resistance training, while 1 study adopted simultaneous stretching exercises. In the studies involving BFR, all reported the site and pressure applied, but only 3 studies described the size of the cuff in detail (35,36,38).

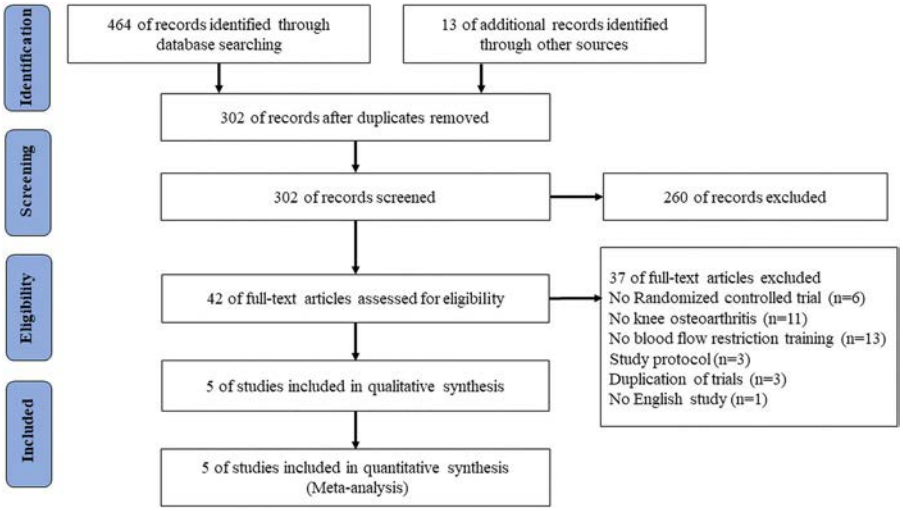


**Figure 1.** Flow diagram of the literature search and selection. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24787/abstract.

**Table 1.** Characteristics of included studies*

| Author, year (ref.) | Country | Sample size; participant ages | Diagnosis | Sex | Intervention | Cuff size; site; pressure | Duration; frequency | Outcomes | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|
| Segal et al, 2015a (35) | US | 42 participants: G1 = 20, G2 = 22; mean ± SD age (years): G1 = 58.4 ± 8.7, G2 = 56.1 ± 7.7 | Radiographic or symptomatic knee OA | Male | G1: BFR + LLRT (30% 1RM); G2: LLRT (30% 1RM) | 65 × 650 mm; proximal thigh; 160– 200 mm Hg | 4 weeks; 3 days/ week | Pain: KOOS pain subscale; muscle strength: isokinetic knee extensor strength, isotonic leg press strength | One patient withdrew because of intolerance of discomfort from pressure cuff |
| Segal et al, 2015b (36) | US | 45 participants: G1 = 21, G2 = 24; mean ± SD age (years): G1 = 56.1 ± 5.9, G2 = 54.6 ± 6.9 | Radiographic or symptomatic knee OA | Female | G1: BFR + LLRT (30% 1RM); G2: LLRT (30% 1RM) | 65 × 650 mm; proximal thigh; 160– 200 mm Hg | 4 weeks; 3 days/ week | Pain: KOOS pain subscale; muscle strength: isokinetic knee extensor strength, isotonic leg press strength; muscle size: quadriceps volume | One patient withdrew due to intolerance of pain from pneumatic cuff |
| Bryk et al, 2016 (37) | Brazil | 34 participants: G1 = 17, G2 = 17; mean ± SD age (years): G1 = 62.3 ± 7.0, G2 = 60.4 ± 6.7 | Knee OA | Female | G1: BFR + LLRT (30% 1RM); G2: HLRT (70% 1RM) | Unknown; upper third of thigh; 200 mm Hg | 6 weeks; 3 days/ week | Pain: NPRS; muscle strength: quadriceps strength; self-report function: Lequesne questionnaire; physical function performance: TUG | No patients withdrew; patients presented less knee discomfort in BFR + LLRT during training |
| Ferraz et al, 2017 (38) | Brazil | 48 participants: G1 = 16, G2 = 16, G3 = 16; mean ± SD age (years): G1 = 60.3 ± 3.0, G2 = 60.7 ± 4.0, G3 = 59.9 ± 4.0 | Knee OA | Female | G1: BFR + LLRT (30% 1RM); G2: LLRT (30% 1RM); G3: HLRT (70% 1RM) | 175 × 920 mm; inguinal fold; 70% LOP | 12 weeks; 2 days/ week | Pain: WOMAC pain subscale; muscle strength: leg press strength, knee extension strength; self-report function: WOMAC; physical function performance: TS, TUG; muscle size: quadriceps CSA | 4 patients from the HLRT group discontinued through the follow-up, exercise induced knee pain |
| Harper et al, 2019 (39) | US | 35 participants: G1 = 16, G2 = 19; mean ± SD age (years): G1 = 67.2 ± 5.2, G2 = 69.1 ± 7.1 | Knee OA | Female and male | G1: BFR + LLRT (20% 1RM); G2: HLRT (60% 1RM) | Unknown; proximal thigh; not specified | 12 weeks; 3 days/ week | Pain: WOMAC pain subscale; muscle strength: knee extensor strength; self-report function: LLFDI; physical function performance: gait speed, SPPB | 14 patients (G1: 3; G2: 11) reported adverse events of knee pain, of which 1 patient from the BFR group deemed possibly related to the study |

* BFR = blood flow restriction; CSA = cross-sectional area; HLRT = high-load resistance training; KOOS = Knee injury and Osteoarthritis Outcome Score; LLFDI = Late Life Function and Disability Instrument; LLRT = low-load resistance training; LOP = limb occlusion pressure; NPRS = numerical pain rating scale; OA = osteoarthritis; ref. = reference; RM = repetition maximum; SPPB = Short Physical Performance Battery; TS = timed stand-up test; TUG = timed up-and-go test; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

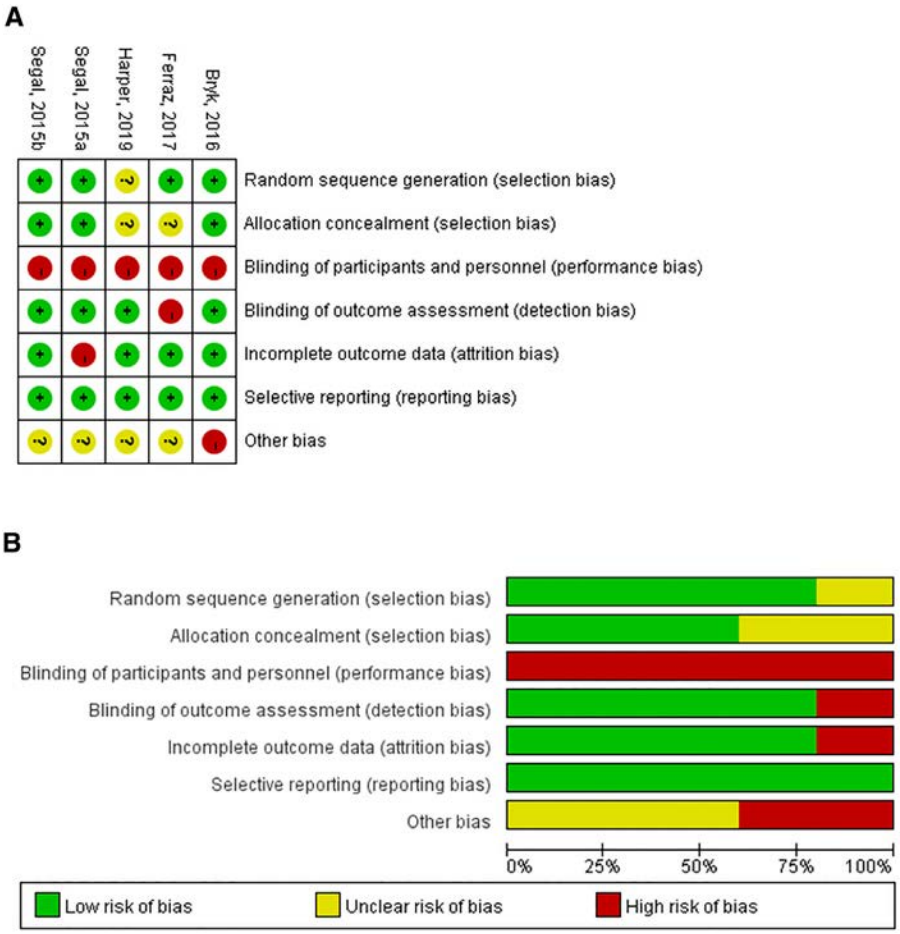


**Figure 2.** **A**, Summary of the risk of bias in included studies; **B**, The risk of bias as percentages across all included studies.

**Assessment of risk of bias.** The methodologic quality of the included studies as assessed by the GRADE method was very low to moderate. The risk of bias was assessed for all selected articles (Figure 2). All included trials used the random sequence generation method in their study design. Three trials mentioned allocation concealment (35–37), while the other 2 trials were at medium risk of selection bias (38,39). No study masked its participants or personnel successfully, which may be due to the challenges when using masking in trials with a BFR device. With regard to detection bias, all studies adopted blinding for the outcome assessor. Only 1 trial was considered as having a high risk of incomplete bias, and all articles had a low risk of selective reporting bias. Further, only 1 study was assessed to be at high risk of other bias (39) because the stretching exercise was used with participants in addition to BFRT and resistance training; other trials were unclear in the other biases.

**Outcome measures.** *Pain.* All 5 studies provided the data on the pain-related outcomes for BFRT compared with the control groups (35–39). Based on the fixed-effects model, participants in the BFRT groups had no better pain relief than those in the control groups in patients with knee OA (SMD –0.04 [95% CI –0.31, 0.24], $P = 0.79$, $I^2 = 0\%$) (Figure 3A and Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24787/abstract).

*Strength.* The 5 studies performed 9 strength tests to compare the effects of BFRT with the controls (35–39). Heterogeneity was found to exist among the included trials ($I^2 = 83\%$, $P < 0.01$). Therefore, a random-effects model was adopted. The results of this meta-analysis showed that there was no significant difference between the BFRT groups and the controls in improving the strength of patients with knee OA (SMD 0.30 [95% CI –0.31, 0.91], $P = 0.33$) (Figure 3B and Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24787/abstract).

*Physical function performance.* Among the 5 studies, 4 reported 8 examinations of physical function performance in both BFRT and control groups (35–39). Heterogeneity was found to exist among the included trials ($I^2 = 82\%$, $P < 0.01$). Therefore, a random-effects model was adopted in the meta-analysis. The results suggested that there was no significant difference between the BFRT groups and the controls in promoting the physical function performance of individuals with knee OA (SMD 0.12 [95% CI –0.55, 0.78], $P = 0.73$) (Figure 4A and

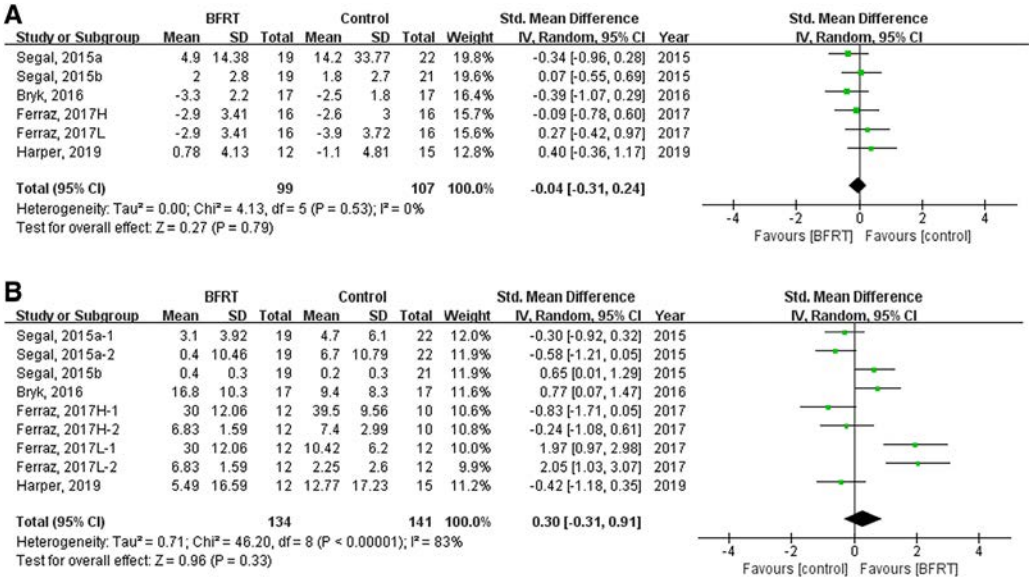


**Figure 3.** Forrest plots of comparisons of outcomes between blood flow restriction training (BFRT) and control groups for pain intensity (**A**) and strength (**B**). 95% CI = 95% confidence interval; IV = inverse variance; H = high-load resistance training; L = low-load resistance training.

Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24787/abstract).

*Self-reported function.* Three trials contributed to data on self-reported function in this meta-analysis (37–39). Based on the fixed-effects model, patients in the BFRT groups showed no improvement in their scores of self-reported functions when compared to the control groups (SMD 0.14 [95% CI –0.24, 0.52], $P = 0.48$, $I^2 = 0\%$) (Figure 4B and Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24787/abstract).

*AEs.* Four studies reported withdrawals of patients with knee OA owing to AEs (35,36,38,39). The main reason for AEs was exercise-induced knee pain. Figure 5 and Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24787/abstract, show the results of safety assessment, including the number of withdrawals due to AEs. Based on the fixed-effects model, the overall difference in AEs between the BFRT group versus the controls was not significant (RR 0.45 [95% CI 0.20, 1.01], $P = 0.05$, $I^2 = 0\%$), which indicated no significant difference in safety between the BFRT and resistance training groups.

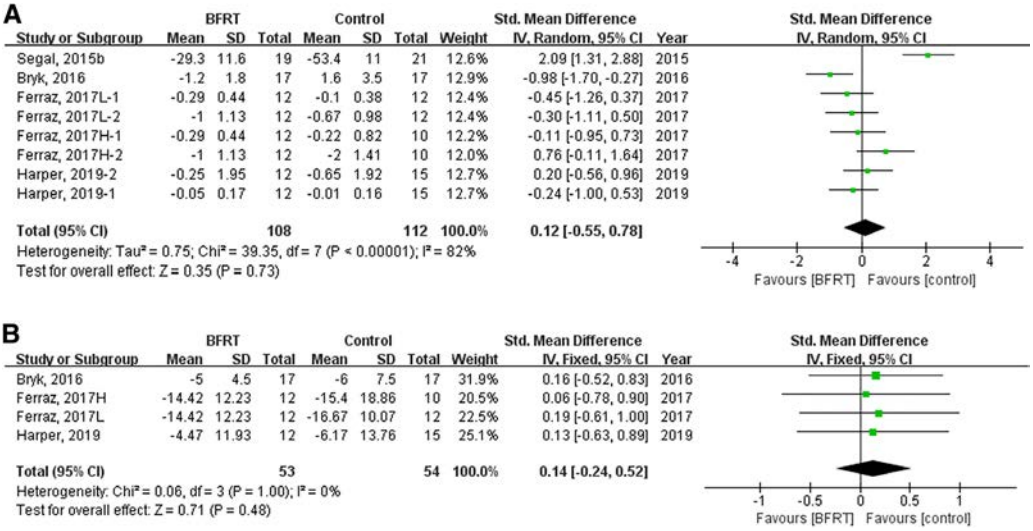


**Figure 4.** Forrest plots of comparisons of outcomes between blood flow restriction training (BFRT) and control groups for physical function performance (**A**) and self-reported function (**B**). 95% CI = 95% confidence interval; IV = inverse variance; H = high-load resistance training; L = low-load resistance training. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24787/abstract.

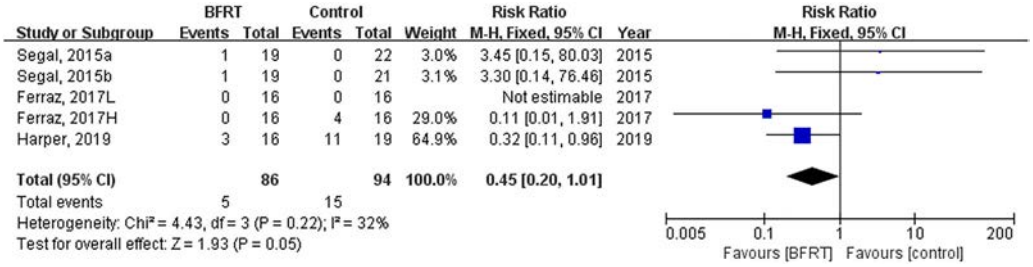


**Figure 5.** Forrest plot of comparisons of outcomes between blood flow restriction training (BFRT) and control groups for adverse events. 95% CI = 95% confidence interval; H = high-load resistance training; L = low-load resistance training; M-H = Mantel-Haenszel. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24787/abstract.

**Sensitivity analysis.** Sensitivity analysis was conducted by sequential omission of individual studies to assess the influence of each study on the overall outcomes. For physical function performance, sensitivity analysis indicated that the study by Segal et al (36) was the primary cause of the heterogeneity for the pooled data ($I^2 = 82\%$ versus $I^2 = 44\%$), but deleting this study did not change the significance of the pooled results ($P = 0.73$ versus $P = 0.37$). For the other outcomes, sensitivity analysis suggested that the results of heterogeneity and statistical significance were relatively robust.

**Subgroup analysis.** Subgroup analyses were performed based on the outcomes of the 5 studies, which included sex, load of resistance training, single- and multiple-joint strength, and type of physical function performance. The summary of relevant subgroup analyses is shown in Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24787/abstract, and Supplementary Figures 1–5, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24787/abstract.

According to the results of subgroup analyses, we found that the BFR with LLRT had a higher risk of AEs compared to HLRT (RR 0.26 [95% CI 0.09, 0.72], $P < 0.01$, $I^2 = 0\%$). The results of the other outcomes were unchanged in subgroup analyses.

**Publication bias.** The funnel plots and Egger's tests were conducted to estimate publication bias, as shown in Supplementary Figures 6–10, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24787/abstract. The funnel plots of outcomes suggested a possible publication bias in small trials. The *P* value of Egger's test was >0.05, indicating that publication bias was negligible in our meta-analysis.

## DISCUSSION

This meta-analysis was performed to analyze the efficacy and safety of BFRT in the treatment of knee OA. We found that BFR combined with LLRT had no advantage when compared with resistance training on pain, physical function performance, and self-reported function. Receiving BFR combined with LLRT resulted in no specific adverse effects. Moreover, the results showed that the effect of BFRT on strength seems to be inconclusive. Despite a different methodology and eligible criteria, these findings seemed to be consistent with findings of other studies that there was no difference between BFRT and conventional resistance training (25). Subgroup analyses of different control groups showed that BFR with LLRT had no better clinical outcomes than HLRT on pain and self-reported function. In contrast, BFRT seemed safer than HLRT.

Pain is a major concern for patients, and pain at the baseline is also relevant to the prognosis of knee OA (40). We did not find additional benefits in terms of pain relief in this review, which is consistent with the previous review of the effectiveness of BFRT in treating musculoskeletal disorders (18). Notably, the severity of knee OA may influence the effect of BFRT on pain. When comparing BFRT and LLRT alone, Ferraz et al (38) reported that BFRT had a better effect on pain alleviation for patients with knee OA, with a Kellgren/Lawrence grade of 2 or 3. In contrast, the other 2 studies (35,36), which also included symptomatic knee OA, found no significant results. Although pain and function are often reported together in knee OA, physicians tend to focus on pain, whereas function is considered to play an equal role in the treatment of knee OA (41). With regard to function, our pooled results demonstrated that BFRT produced no advantage over conventional resistance training in either physical function performance or self-reported function. Moreover, we were unable to investigate the efficacy of BFRT regarding quality of life owing to the limited number of studies. Future clinical studies of BFR are therefore recommended to evaluate the quality of life at the time points of baseline, postintervention, and follow-up.

Improvements of muscle hypertrophy and strength were considered to be the most important benefits of BFRT. Although not enough usable data were available in 2 trials to perform quantitative synthesis, those trials showed conflicting results. In terms of BFRT versus LLRT, 1 study found that BFRT yielded significantly higher increases in the quadriceps cross-sectional area (38), whereas another study showed that there was no difference between these 2 interventions (36). Moreover, that study illustrated the fact that BFRT affected quadriceps hypertrophy similar to the effect of HLRT (38). These results were in line with previous meta-analyses of studies in older individuals (17), who are more likely to develop knee

OA. For patients with knee OA, muscle size was strongly related to muscle strength (42), where only an increase >30% in knee extensor strength brought clinical benefit in terms of function (43). In this meta-analysis, the pooled data showed that the effect of BFRT on strength improvement seems to be inconclusive.

We further conducted subgroup analyses to investigate the effect of BFRT on strength compared to HLRT. The heterogeneity decreased by 15%, which indicated that the load of resistance training is a potential source of heterogeneity. Nevertheless, another important aspect to consider when evaluating the effect of BFRT on strength improvement is training duration. One pooled study investigated BFRT, LLRT, and HLRT for knee OA simultaneously for 12 weeks, finding that HLRT and BFRT produced a similar improvement in strength, and that these 2 methods of training were both better than LLRT alone (38). By contrast, another included trial showed that BFRT had no additional effect compared with LLRT (35). One possible explanation was that BFRT was just as effective as HLRT but that the training duration needed to be longer than 4 weeks to obtain a greater improvement than from LLRT in patients with knee OA.

Previous reviews have suggested that the risk from BFRT is not serious in musculoskeletal disorders and knee OA (24), but these studies did not synthesize results in a meta-analysis. Knee OA mainly occurs in older individuals, who often experience complications such as metabolic syndrome; therefore, safety is an important issue. Several studies have reported AEs in the cardiovascular and musculoskeletal systems (27,28). In our meta-analysis, the major AE was the inability to tolerate the discomfort of BFRT or knee pain during training. The pooled data demonstrated that BFRT had a lower risk of AEs compared with HLRT, suggesting the potential application in patients with knee OA. One included study did not clearly report the AEs, making it difficult to synthesize in this meta-analysis (37). Moreover, the pooled studies notably excluded serious comorbidities, which may reduce the risk of AEs. Therefore, developing an effective screening tool for BFRT is necessary to identify potential safety issues before it is applied to individuals in practice. Nevertheless, clinicians may also consider using a progressive model to enhance the tolerance of BFRT for patients from BFR combined with walking exercise, to BFR combined with LLRT, or BFR combined with HLRT (44).

In addition to resistance load, the degree of BFR influences the treatment response to BFRT. Clinically, a technique named relative percentage of limb occlusion pressure (LOP) is recommended to produce a similar degree of BFR for different individuals. Only 1 included trial in this review adopted this method, using 70% LOP (38), while the rest used the inflation pressure of cuffs. However, setting the same inflation pressure of cuffs to different individuals may not create a similar extent of restricted blood flow because a variety of factors likely contributed to the LOP, such as limb circumference, limb length, and cuff width (45,46). Additionally, different LOPs resulted in an altered acute response in terms of muscle activation, muscle strength, and tissue oxygenation in BFRT (47,48). Previous research has shown that BFR pressure with 40% LOP was sufficient for the effective acute response of muscle (48,49). But higher LOP promoted more pain and perception of pain during BFRT (50), which may decrease adherence and cause symptomatic participants to withdraw from the treatment. Future studies need to use the LOP to determine the degree of BFR and to investigate the effect of BFRT with lower LOP for patients with knee OA. Nevertheless, measuring LOP is suggested before each session to determine personalized pressure for accuracy and to select the same body position during measurement for reliability.

This study has several limitations. Only 5 trials were pooled, with a relatively small number of samples. The quality of evidence was rated very low when analyzing the strength and physical function performance of BFRT. The follow-up time points of all trials were 12 weeks or less in duration, so that evaluating the mid-term (6–12 months) to long-term (≥12 months) effect of BFRT in knee OA is impossible. Results were also limited to pooled homogeneous outcome measures, owing to different measurements used in the included studies, which may cause significant heterogeneity in several outcomes. Moreover, only studies in English were included in this review, which may have resulted in more potential studies not being included.

Furthermore, more research should investigate the mid-term to long-term outcomes and AEs of BFRT in knee OA. Future studies should pay close attention to the efficacy and safety of BFR combined with LLRT training, such as walking and aquatic exercise. Since the best program of BFRT has not been identified, more evidence is needed, especially regarding the different training volumes and degrees of BFR. Studies of BFRT should report more outcomes, such as quality of life, adherence, and cost-effectiveness.

The data of pooled studies show that BFRT does not seem to be more effective than conventional resistance training for patients with knee OA in relieving pain and in improving self-reported function. Regarding safety, BFRT has no higher risk of AEs compared with conventional resistance training. However, limited evidence supports the idea that BFRT is likely safer than HLRT. Further research is needed to evaluate its mid- and long-term effects as well as AEs of BFRT for patients with knee OA. It is also worth investigating the effectiveness of BFR combined with lower load resistance training and a low-degree BFR combined with resistance training.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all publication. Dr. Ni 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.** Wang, Chen, Ni.
**Acquisition of data.** Wang, Chen, Cheng.
**Analysis and interpretation of data.** Wang, Chen, Cheng, Cai, Li.

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REHABILITATION SCIENCES AND THE RHEUMATIC DISEASES

# Patient Perceptions of Physical Activity After a Diagnosis of Giant Cell Arteritis: Analysis of Multinational Qualitative Data

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**Objective.** To explore patient perceptions of physical activity in giant cell arteritis (GCA).

**Methods.** This was a multinational qualitative study, analyzing interview data collected from participants from the UK (n = 25) and Australia (n = 11) with a definitive diagnosis of GCA from imaging or biopsy. Interview transcripts were analyzed using thematic analysis to identify themes related to physical activity. This was secondary analysis of data collected to explore health-related quality of life in people with GCA.

**Results.** A total of 108 individual codes pertaining to physical activity were identified. These were grouped into 2 overarching themes: barriers to and facilitators of physical activity, each with 4 subthemes. Barriers were categorized into physical symptoms (including visual loss, fatigue, weakness, pain, and stiffness), perceptions of personal capability (including poor stamina, confidence, and mobility), negative perceptions of physical activity, and negative consequences. Facilitators of physical activity were categorized into external facilitators (including motivation from health care professionals and support groups), access to appropriate facilities, personal strategies (including pacing and goal-setting), and personal facilitators (including internal motivation to improve symptoms, and positive reinforcement).

**Conclusion.** A range of barriers and facilitators to physical activity were identified in relation to GCA. Future work could include development of an intervention to support physical activity in patients with GCA; ideally this intervention should be underpinned by an appropriate behavioral change framework and codesigned with patients.

## INTRODUCTION

Giant cell arteritis (GCA) is the most common vasculitis in the UK, with an incidence of 220 cases/million in adults age >50 years (1). GCA is a large- and medium-vessel vasculitis with a predilection for the branches of the external carotid artery, including the superficial temporal artery. This predilection for specific vessels accounts for the characteristic symptoms, which include temporal headache, jaw claudication, scalp tenderness, and visual disturbance or loss. Polymyalgic and constitutional symptoms may also feature, as well as a wide range of musculoskeletal manifestations (2). The spectrum of disease also includes large-vessel vasculitis, or extracranial GCA, in which limb claudication and constitutional symptoms predominate (3). The mainstay of treatment is high-dose glucocorticoids, gradually tapering over 1–2 years, which can be increased in response to signs of clinical relapse (4). The anti–interleukin-6 monoclonal antibody tocilizumab is now licensed for relapsing or refractory disease.

The physical manifestations of GCA as well as long-term glucocorticoid side effects (such as weight gain and proximal myopathy) may impact patients' ability to undertake physical activity, which is defined by the World Health Organization as any bodily movement produced by skeletal muscles that requires energy

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**SIGNIFICANCE & INNOVATIONS**

- Patients with giant cell arteritis (GCA) may benefit from increased physical activity through improving strength, stability, confidence, and cardiovascular and mental health.
- Patients with GCA report barriers to physical activity (symptoms of pain or stiffness, low confidence, and concern about risk of flare) and facilitators (encouragement from health care professionals and support groups, access to facilities, and personal goal setting).
- Further work is required to develop an acceptable and effective intervention to support increased physical activity in all patients with GCA.

expenditure (5). British Society of Rheumatology guidelines state that all patients with GCA should receive advice on physical activity along with other lifestyle guidance; however, since there are no published recommendations on physical activity in GCA, the advice is that "recommendations on physical activity in inflammatory arthritis and osteoarthritis may be tailored to individual patients with GCA" (4).

Maintaining physical activity has been shown to be beneficial in other inflammatory conditions, such as rheumatoid arthritis, inflammatory myopathies, and systemic lupus erythematosus (SLE) (6). There is a body of evidence to suggest that physical activity has antiinflammatory effects on a cellular level, for example by ameliorating the tumor necrosis factor response to inflammatory stimuli (7). Additionally, exercise training (one aspect of physical activity) has been demonstrated to improve fatigue, pain, strength, and aerobic capacity in several inflammatory conditions, including inflammatory arthritis (8), inflammatory myopathies (9), and SLE (10).

Moreover, physical activity is also a specific priority for GCA patients. Hellmann et al (11) devised Importance Rating Questionnaires exploring domains of quality of life affected by GCA, which were completed by 145 patients. Of the 20 items ranked highest in importance, 6 related to the ability to walk, or limb or muscle strength, demonstrating the importance of maintaining physical activity and independence.

On a population level, physical activity is integral to health. UK Department of Health guidelines recommend that adults (including older adults age ≥65 years) should be physically active daily and aim to accumulate 150 minutes of moderate intensity physical activity each week (12). Australian government guidelines for older adults are to "accumulate at least 30 minutes of moderate intensity physical activity on most, preferably all, days" (13). According to the World Health Organization, physical inactivity is the fourth leading risk factor for global mortality. In all, 6% of global deaths are estimated to be directly attributed to physical inactivity, and those who are inactive have a 20–30% increased risk of all-cause mortality (14). Aside from having risk factors for reduced levels of physical activity, patients with GCA also have an increased burden of cardiovascular disease (15); thus, physical activity has the potential to be protective via several mechanisms, including by maintaining a healthy body mass index. In addition, the psychological impact of GCA is increasingly recognized (16,17), and physical activity is known to have protective effects on mental health (18).

However, little is known about GCA patients' beliefs and views about physical activity. The aim of this study was therefore to gain new insights into patient perspectives of physical activity in GCA, including barriers, facilitators, and potential benefits, and to use these insights to explore what interventions may be of benefit to this cohort in the future.

## PATIENTS AND METHODS

This was a multinational study, using in-depth qualitative interviews with 36 patients from the UK (n = 25) and Australia (n = 11). This is a secondary analysis of data collected to explore health-related quality of life in people with GCA (16). The primary study was performed to provide underpinning data for the development of a patient-reported outcome measure. Themes relating to physical activity were noted as a topic of importance to patients and therefore this in-depth secondary analysis was undertaken.

The study had ethics approval obtained in the UK (South Central–Oxford B Research Ethics Committee; REC reference: 16/SC/0697, IRAS project ID: 217748) and Australia (Central Adelaide Local Health Network; HREC Ref: HREC/17/TQEH/275 and CALHN Ref: Q20170906). All participants provided informed consent and were selected using purposive sampling, including a range of disease phenotypes (such as visual loss and those with features of polymyalgia rheumatica or large-vessel vasculitis) from rheumatology and ophthalmology clinics in the UK and Australia. All participants had a definitive diagnosis from imaging or biopsy. A total of 48% of participants had self-reported active disease at the time of interview (16).

Braun and Clarke's approach to thematic analysis was followed for the primary and secondary analyses (19,20). Both the original and secondary analyses were undertaken from an inductive (coding and theme development were directed by the content of the data), semantic (coding and theme development reflected the explicit content of the data), and realist/essentialist (focused on reporting an assumed reality evident in the data) perspective.

For the primary study, semistructured interviews, performed by researchers experienced in qualitative methods, were recorded, transcribed verbatim, and analyzed. NVivo software, version 11, was used to manage and organize the data. For the secondary analysis, each interview was reanalyzed, and references to physical activity manually coded. A junior researcher with a clinical background in rheumatology (KA) performed the line-by-line coding. Codes were categorized, and overarching themes and subthemes were identified. An experienced methodologist with a

**Table 1.** Demographic details of primary study participants*

| Characteristic | UK (n = 25) | Australia (n = 11) | Total (n = 36) |
|---|---|---|---|
| Sex, male/female | 9 (36.0)/16 (64.0) | 4 (30.8)/7 (69.2) | 13 (36.1)/23 (63.9) |
| Age, years | | | |
| ≥70 | 20 (80.0) | 7 (63.6) | 27 (75.0) |
| Mean | 75 | 73 | 74 |
| Diagnostic test | | | |
| Biopsy | 21 (84.0) | 10 (90.9) | 31 (86.1) |
| USS | 5 (20.0) | 0 (0) | 5 (13.9) |
| CTA | 2 (8.0) | 0 (0) | 2 (5.6) |
| PET | 2 (8.0) | 1 (9.1) | 3 (8.3) |
| Time from diagnosis <1 year | 13 (52.0) | 6 (54.5) | 19 (52.8) |
| Disease active | 11 (44.0) | 6 (54.5) | 15 (48.4) |
| Flare <1 year | | | |
| Yes | 13 (52.0) | 5 (45.5) | 16 (51.6) |
| No | 10 (40.0) | 5 (45.5) | 13 (41.9) |
| Never | 2 (8.0) | 1 (9.1) | 2 (6.5) |
| Taking steroid-sparing agent | 2 (8.0) | 6 (54.5) | 7 (19.4) |
| Visual loss | 10 (40.0) | 3 (27.3) | 13 (36.1) |
| Polymyalgia rheumatica | 11 (44.0) | 5 (45.5) | 16 (44.4) |
| ESR ≥50 or CRP ≥10 | 24 (96.0) | 10 (90.9) | 34 (94.4) |

* Values are the number (%) unless indicated otherwise. CRP = C-reactive protein; CTA = computed tomography angiogram; ESR = erythrocyte sedimentation rate; PET = positron emission tomography; USS = ultrasound scan.

background in psychology (ED) and a clinical researcher (JCR) reviewed a subset of data and contributed to discussions. Differences in perspective and interpretation of the data were discussed within the team. An agreed framework of barriers and facilitators to physical activity was identified and all interview transcript data were reanalyzed to ensure consistent coding across the data set.

## RESULTS

A total of 36 patients were included. The majority (64%) were female, and the average age was 74 years. All had 1 or more positive diagnostic tests, including temporal artery biopsy, temporal artery ultrasound, computed tomography angiogram, or positron emission tomography scan. In all, 53% of participants were within their first year of diagnosis, and 36% had experienced visual loss from GCA. Further demographic details of the primary study participants can be seen in Table 1.

A 6-step process was used: familiarization with the data, coding, generating initial themes, reviewing those themes, defining and naming those themes, and then writing up. From this process, 2 overarching themes were identified: barriers to and facilitators of physical activity. Within each overarching theme, 4 subthemes were identified (Figure 1).

The 4 subthemes within the theme of barriers to physical activity were physical symptoms (including visual loss, fatigue, weakness, pain, and stiffness), perceptions of personal capability (including poor stamina, confidence, and mobility), negative perceptions around physical activity, and negative consequences (i.e., new physical symptoms following physical activity).

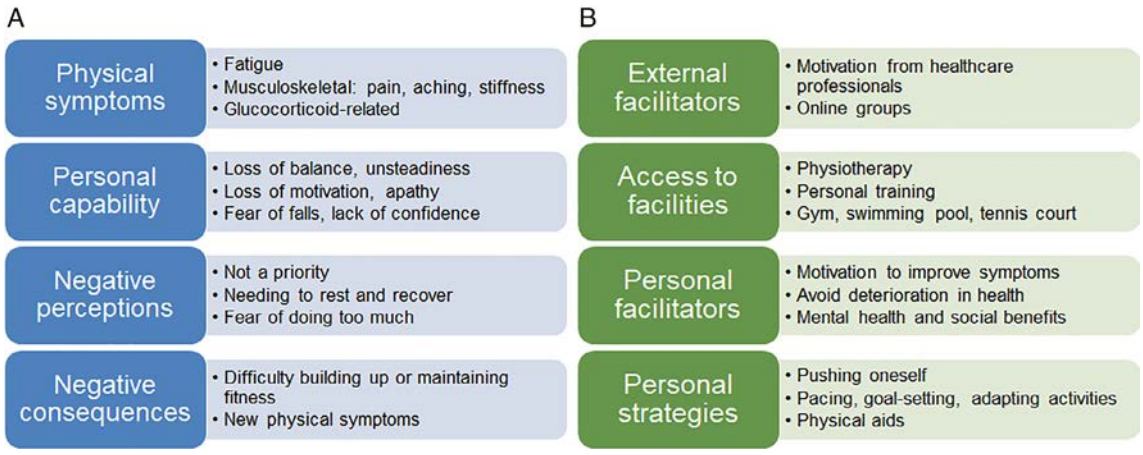


**Figure 1.** Barriers to (**A**) and facilitators of (**B**) physical activity, with examples of subthemes.

The facilitators of physical activity were also grouped into 4 subthemes: external facilitators (including motivation from health care professionals and support groups), access to appropriate facilities, personal strategies (including pacing and goal-setting) and personal facilitators (including internal motivation to improve symptoms and positive reinforcement from physical activity).

**Barriers.** Several participants reported difficulty knowing whether limitations in physical activity were related to GCA or related to advancing age ("I've got to realize that I am 83 and that confuses me…am I supposed to feel like this at 83, or is it this [GCA]?" female, age 83 years, Australia), but the majority described their limitations as being directly linked to their GCA or its treatment. Specific quotes in support of each subtheme are found in Table 2.

*Physical symptoms.* The barrier to physical activity most commonly described by participants was the presence of 1 or more physical symptoms. These were varied and related to multiple body systems, including musculoskeletal, cardiovascular, ocular, and respiratory, as well as various constitutional and medication-related problems.

By far the most common barrier reported by participants was fatigue, or lack of energy. Almost all participants referred to this barrier in some way, some mentioning it multiple times. Most referred to it as a primary problem, but others suggested causative factors, such as lack of sleep. Fatigue appeared to be a very significant factor for participants, and even those who described a range of other physical symptoms that limited their physical activity alluded to fatigue as being the biggest barrier. Fatigue or tiredness was referred to as "the main thing" (female, age 75 years, Australia), "the worst thing that I can say that's happened to me is this terrible tiredness I get" (female, age 83 years, Australia), and "the worst thing about the whole illness" (male, age 72 years, UK). Fatigue was described as being variable, sometimes relating to time of day, intensity of physical activity, and glucocorticoid dose, but also unpredictable.

Classical GCA/polymyalgia rheumatica symptoms were described as a barrier to physical activity. Unsurprisingly, visual symptoms impacted both the ability to stay active and confidence in keeping active. Musculoskeletal symptoms, including generalized pain, aching, and stiffness directly impacted physical activity for a number of participants. Limb weakness was also a feature, and sometimes this weakness was directly attributed to glucocorticoid use. Other glucocorticoid-related effects were described as barriers to physical activity, such as skin changes and weight gain. However, the negative physical effects of glucocorticoid treatment were balanced with the barriers to physical activity that came with disease flares. Participants also described other physical barriers to activity that were not classically associated with GCA, such as breathlessness, palpitations, dizziness or giddiness, and sensory symptoms in the feet and legs.

*Perceptions of personal capability.* Participants reported a lack or loss of some of the key physical and psychological attributes required to maintain physical activity. These included loss of balance, unsteadiness or clumsiness, loss of motivation or apathy, loss of stamina and needing to rest more, and loss of pace or speed. Falls and fear of falling also contributed, and participants reported a loss of confidence both related to falls as well as more broadly. Participants also referred to the increased support received from their partners, which reduced the motivation to remain active.

*Negative perceptions of physical activity.* Participants expressed wide-ranging negative perceptions and opinions of physical activity. Some felt it was not a priority compared with other facets of their life, too time consuming, or "a chore" (female, age 75 years, UK) or "a terrible effort" (female, age 64 years, UK).

Others were cautious around physical activity, for fear of "doing too much" (female, age 64 years, UK), and some reported giving up physical activities due to the perception that the body needs to rest or recover from GCA. Others said they had been told directly to avoid physical activity: "Just have a rest" (female, age 68 years, UK). Another reported barrier was embarrassment of glucocorticoid skin changes, for example at the swimming pool.

*Negative consequences.* A few participants described adverse effects from attempts to participate in or maintain physical activity, which negatively reinforced their opinions of it. Some described difficulties building up or maintaining fitness despite trying to keep active. Others described negative physical symptoms (including joint pain and excessive fatigue) following exercise.

**Facilitators.** Almost all participants also reported at least 1 thing that motivated or facilitated their physical activity. Specific quotes pertaining to each theme and subtheme are found in Table 3.

*External facilitators.* Some participants were motivated by others to undertake physical activity. For some, this motivation was theoretical; for example, 1 participant expressed a desire to undertake a structured support program akin to that provided to patients following myocardial infarction. Others were directly motivated by their health care provider such as a rheumatologist or physical therapist or reported the motivation that could be provided by online support groups.

*Access to facilities.* Some participants' engagement in physical activity was positively enabled by access to certain facilities. Examples cited included gyms, swimming pools, private hydrotherapy pools, tennis courts, a bowling green, personal trainers, Pilates and yoga classes, and physical therapy sessions.

*Personal facilitators.* Participants described internal motivators to undertake physical activity, and these were varied. Some felt that physical activity is simply fundamentally important and should be encouraged. Others reported a motivation to remain active because of a direct beneficial effect in reducing their GCA symptoms. Others felt a desire to maintain their general health, or to help avoid steroid side effects such as muscle atrophy, loss of bone density, or weight gain. There was also a perception of exercise improving or maintaining blood flow to the limbs. In

**Table 2.** Barrier themes and subthemes with supporting quotations*

| Theme and subtheme | Quotation and participant |
|---|---|
| Negative physical symptoms | |
| Fatigue, lack of energy, unpredictable nature of fatigue | "And so the sleep has been deprived, deprived of sleep. And that made everything such a battle." (Female, age 75 years, UK) |
| | "One day I'm fine and the next day I just can't do a thing. All I want to do is sleep all day." (Female, age 75 years, AU) |
| Visual symptoms | "I lost my vision almost completely. Couldn't drive. Couldn't do anything." (Female, age 62 years, AU) |
| Musculoskeletal pain and stiffness | "The characteristic muscle aching which was affecting me not going to the gym and walking, I just laid off the gym." (Male, age 77 years, UK) |
| | "When I got up to walk…my limbs, I couldn't." (Female, age 56 years, AU) |
| Weakness, weakness related to glucocorticoid use | "My legs…they just sort of give way. So I've got to be very careful what I do." (Female, age 75 years, AU) |
| | "It was the muscle deterioration from the prednisolone…that was causing the change in lifestyle because I'm quite an avid walker." (Female, age 80 years, AU) |
| Steroid-related effects | "I think I'll go cycling, but the danger is the skin…if I come off and lacerate myself." (Male, age 79 years, AU) |
| | "I think why the energy's gone is because I must've put a good stone on." (Female, age 73 years, UK) |
| Disease flare | "I had a terrible setback, I'd got right down to 10 milligrams and I seized up. I couldn't walk, I couldn't move." (Female, age 71 years, AU) |
| Cardiovascular, e.g., dizziness | "I go quite slow walking; I've got to be careful cause if I sort of look down and then look up, I go dizzy." (Female, age 83 years, UK) |
| Sensory | "I reckon I'll be cured once I can go for a run and my feet don't get numb." (Female, age 56 years, AU) |
| Constitutional symptoms | "Yeah so those symptoms, the night sweats and the feeling that of the flu-like symptoms and feeling that I wasn't able to walk out even to the shops." (Female, age 74 years, UK) |
| Physical capability | |
| Loss of balance; unsteadiness, clumsiness | "Very unstable, so even if I tried to play gold, I wouldn't be able to stand still to swing the club." (Female, age 86 years, UK) |
| Loss of motivation, apathy | "I've just got that can't-be-bothered feeling." (Female, age 83 years, AU) |
| Poor stamina, needing to rest more | "I used to go to keep fit. I don't go, I can't. There are women in that class, 93, and they can do more for an hour than I can do in 5 minutes; I can only do 5 minutes." (Female, age 75 years, UK) |
| | "When I played tennis I'd have to take a little stool out." (Female, age 56 years, AU) |
| Loss of pace or speed | "I can walk around the block…but I can't at any pace which…I thought I was leader of the pack." (Female, age 80 years, AU) |
| Fear of falls | "I don't walk far…I'm just frightened of falling again." (Female, age 86 years, UK) |
| Low confidence, anxiety | "It could be just confidence. I'm very much aware when I go down steps I hold handrails you know." (Female, age 78 years, UK) |
| Negative perceptions of exercise | |
| Not a priority compared with other aspects of life | "Not really being able to do anything much else except trying to keep my work going and my home life here." (Female, age 62 years, AU) |
| Not a priority in terms of time commitment | "I try to go swimming once a week if I got the time, you know, if I can fit it in." (Female, age 79 years, UK) |
| Fear or perception of doing too much | "I used to do Nordic walking and I haven't done any of that for over a year, because I just felt my body needs to recover." (Female, age 72 years, UK) |
| | "Just have a rest, people say just have a rest." (Female, age 68 years, UK) |
| Embarrassment | "But my scabby appearance is…I can't wander around in the swimming pool." (Male, age 79 years, AU) |
| Negative reinforcement | |
| Difficulty building up fitness | "I ride a stationary bike…I basically do the same distance every day. I don't improve on the distance. I feel that I can't push past that." (Female, age 62 years, AU) |
| | "I have noticed for going to the gym and doing things 5 days out of 7, my muscles are probably not as toned as they could be." (Female, age 56 years, AU) |
| New physical symptoms after exercise | "I got back at it a couple of weeks ago in there, and immediately damaged myself." (Male, age 79 years, AU) |
| | "Once a week I play bowls. That takes 3 hours. Ten-pin bowling this is. Last week, or this week just gone…last Tuesday, I really had to push through the last half a game, because I was extremely tired." (Female, age 83 years, AU) |

* AU = Australia; UK = United Kingdom.

addition, the mental health benefits were established as facilitators for several participants. The sociable nature of interacting with others while undertaking physical activity outdoors was also motivational. Finally, the positive reinforcement of seeing health and fitness improving with physical activity was also a facilitator and motivator for some participants.

*Personal strategies.* Participants described a range of different strategies used to facilitate physical activity. Some felt that

**Table 3.** Facilitator themes and subthemes with specific quotations*

| Overarching theme and subtheme | Quotation and participant |
|---|---|
| External facilitators | |
| Motivation from health care team | "He said…don't treat yourself as an invalid. He said just carry on life completely as normal…get on with your life and you know the exercise will do you good." (Male, age 74 years, UK) |
| | "My doctor said 'You must keep going because of the vascular side of things, you've gotta keep yourself moving.'" (Female, age 79 years, UK) |
| | "I started kind of exercising…because the doctor said that was, that's what I should do." (Female, age 68 years, UK) |
| Personal training | "I did have some help with a personal trainer." Female, age 62 years, AU) |
| Social media | "I have on the page tried to encourage people to exercise." (Female, age 56 years, AU) |
| Access to facilities | |
| Gym/swimming pool | "There's a new gym beside us, and a pool, so I do a session of about an hour in the gym, and then I go for a swim in the hydrotherapy pool. It's lovely and warm, and just relax." (Male, age 79 years, AU) |
| Physical therapy | "I'm having physio, for strengthening my legs, which is helping." (Female, age 82 years, UK) |
| Stretching/yoga/Pilates | "I do some stretching, floor exercises and some using a TheraBand and various exercises to help with my hips." (Female, age 62 years, AU) |
| Personal factors and motivation | |
| Belief that PA is important | "I believe that exercise is, and a good appetite, is the key to good health." (Male, age 74 years, UK) |
| | "I mean the one thing I think should be encouraged is exercise." (Female, age 56 years, AU) |
| To improve symptoms | "I actually feel if I'm tired and a little bit stiff before I go to the gym, once I leave the gym I'm fine. So exercise helps and I sleep better the days I exercise as well." (Female, age 80 years, UK) |
| To prevent muscle atrophy | "I'm trying to walk as far as I can every day, as much as I can, trying to push myself, cause I know that you can get the muscle wastage." (Female, age 64 years, UK) |
| To prevent osteoporosis | "I go to the gym and try and improve my bone density, or prevent any deterioration." (Male, age 79 years, AU) |
| To counteract steroid effects | "I do 20 to 25 minutes of exercises every morning…to try and deal a bit with weight gain with the use of prednisolone." (Female, age 62 years, AU) |
| For circulatory benefits | "I suppose if I keep up my exercises, more arteries and veins will develop that I should get enough blood flow to my feet." (Female, age 56 years, AU) |
| To improve mental health | "Cycling for me, a couple of hours or 3 hours, is stress relief as well as physical exercise." (Male, age 79 years, AU) |
| Finding PA sociable | "As I say, the walk, it's amazing, the number of old people that do walk around the [local area] on their own, but everybody says good morning or whatever, you know, it's lovely." (Female, age 83 years, UK) |
| Positive reinforcement | "Because I see improvement and because I've been able to still do it [play sport] I never really stopped doing anything." (Female, age 65 years, AU) |
| Personal strategies | |
| Pushing oneself | "You've got to push yourself as much as you can." (Female, age 75 years, AU) |
| Pacing oneself | "I'd limit myself, when I'm gardening I sort of put the timer on for 45 minutes and if I haven't finished it I just stop because I know I'm gonna be knackered." (Male, age 79 years, AU) |
| Modifying previous activities | "When I played tennis I'd have to take a little stool out…I just had to rest, then I could go again." (Female, age 56 years, AU) |
| Goal setting | "It's my ambition this summer to be able to walk to my…the post office and back." (Female, age 75 years, AU) |
| Use of aids, such as walking aids or good footwear | "I have it as a, sort of, prop." (Female, age 82 years, UK) |
| | "I'd been for a walk, and I always wear good sort of, reasonable good sort of padded, you know, good shoes." (Female, age 64 years, UK) |
| Maintaining good disease control | "I've felt so much better [on steroids]. It was lovely, you know, being able to sort of walk for hours." (Female, age 66 years, UK) |

* AU = Australia; PA = physical activity; UK = United Kingdom.

pushing themselves to continue with previous activities was helpful, but the majority described various modifications they had made to enable them to continue keeping active. For example, slowing down, pacing oneself, or reducing the duration or intensity of activity. Alternatively, some described modifying previously enjoyed activities to allow them to continue. Goal setting and gradually building up activity were also strategies reported by participants.

There were also some practical strategies that enabled physical activity for participants, such as wearing appropriate shoes, eating a high-protein diet, using walking aids (sometimes simply to provide reassurance and improve confidence), and maintaining good adherence to glucocorticoid treatment.

## DISCUSSION

This study aimed to examine perspectives on physical activity in a varied group of patients with GCA and has demonstrated both a wide range of barriers and facilitators of physical activity in a GCA population. Previous studies, including the primary analysis of these data that has led to the development of a disease-specific patient-reported outcome measure, have

explored the impact of GCA on patients' lives in a broader sense (16,17). The current study, however, specifically examined themes related to maintaining physical activity, which have not previously been described. A strength of this study is that it included a range of GCA patients with varying sex, ages, presenting features, and levels of disease activity, because of the purposive sampling method initially used. However, the study was limited to 2 English-speaking countries in which the guidelines and cultural attitudes to physical activity are broadly similar. While GCA does tend to affect Caucasians predominantly (21), further studies could examine other cultural influences on barriers and facilitators of physical activity in GCA. Additionally, the original interviews aimed to explore the full breadth of impact on health-related quality of life in GCA, so the focus of the interviews was not specifically physical activity, which may have limited the data available.

While there is a lack of research in physical activity in GCA patients, studies have been done examining attitudes around physical activity participation both in older adults in general and in other inflammatory conditions. One systematic review of 132 studies comprising almost 6,000 members of the general population age ≥60 years identified some very similar themes to this study, including physical limitations, competing priorities, and personal motivation, beliefs, and attitudes such as apathy toward physical activity (22). However, other (perhaps more practical) considerations emerged in the systematic review, such as access difficulties, including environmental barriers and affordability, as well as dependence on professional instruction. The findings of this review may suggest that acknowledging more general sociodemographic factors, including age, would be helpful in promoting physical activity to the GCA cohort and designing specific interventions tailored to these older adults.

Studies examining the attitudes of patients with inflammatory arthritis relating to physical activity have demonstrated similar themes to those that emerged in this study, with key barriers being physical symptoms such as pain and fatigue (23). A systematic review of literature around attitudes to physical activity in ankylosing spondylitis (24) has shown that patients are motivated by improvement in symptoms and general health, as seen in our data. Additionally, a 2016 study explored the views of people with rheumatoid arthritis regarding their physical activity support needs (25). Similar themes to those that emerged from this study included concerns around disease exacerbation and physical injury, and the positive influence of health care professionals in endorsing physical activity. The themes from the 2016 study reflect 2 of the key barriers and facilitators that emerged from our GCA research. However, the 2016 study also examined feasibility and acceptability of various physical activity programs, which may also be a helpful future step in designing interventions for GCA patients. Overall, the data from this work share similarities with other studies of physical activity in inflammatory conditions; therefore, interventions investigated in other conditions, such as educational or group-based interventions in rheumatoid arthritis (26,27), could therefore be considered as frameworks for interventions in GCA patients.

Any future GCA-specific intervention would need to be underpinned by an appropriate behavioral change framework, and in light of the many barriers and facilitators described in this study, consideration should be given to codesigning (28) such an intervention with GCA patients, to ensure that it is acceptable and effective. Dedicated strengthening regimens for preservation of muscle power in patients exposed to prolonged courses of glucocorticoids may be a key element.

British Society of Rheumatology guidelines specify, albeit briefly, the importance of promoting physical activity to patients with GCA (4). However, only a minority of participants in this cohort referred to advice or motivation offered by their health practitioner. However, when participants voluntarily discussed this advice, it was often quoted directly, perhaps suggesting the importance of the wording and phraseology used by clinicians. Lack of advice from clinicians may be related to lack of confidence or knowledge; studies have suggested that while rheumatologists are forthcoming in recommending physical activity, the majority do not advise on, or are not aware of, minimum physical activity recommendations (29,30). Wider education of the rheumatology multidisciplinary team in physical activity recommendations, and how to refer patients to resources and self-management programs, may be of benefit to patients with GCA. Furthermore, professional education may benefit from a more nuanced understanding of the patient perspective on barriers to physical activity, so that patient-centered discussions can take place.

Several dichotomies arose within this study. For example, some of the physical barriers reported by participants, such as fatigue and stiffness, were symptoms others said had improved by undertaking physical activity. In addition, some participants reported that they had been advised to keep active, while others had been told to prioritize rest. This conflicting advice may reflect the fact that there is no definitive guidance for GCA patients in maintaining physical activity, and there is conflicting advice within patient resources. For example, Polymyalgia Rheumatica and Giant Cell Arteritis UK advises GCA patients to reduce their usual activity by half following diagnosis (31), while Department of Health guidelines state that their recommendations apply regardless of "physical impairment." A unified evidence-based patient information leaflet or other educational material may therefore be helpful in providing advice and reassurance regarding maintaining physical activity. Thought should also be given to levels of literacy and cultural appropriateness of the information provided.

In summary, this study has demonstrated a wide range of barriers to and facilitators of physical activity in GCA patients, which are reflective of similar themes in studies exploring attitudes to physical activity in other inflammatory conditions and older adults in general. Further research is needed into how to address

barriers and promote facilitators to enable behavioral change in relation to increasing physical activity in GCA, for both patients and medical professionals.

## 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 submitted for publication. Dr. Austin 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.** Austin, Dures, Cramp, Guly, Hill, Hoon, Mackie, O'Brien, Watts, Robson.

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# Association of Pain Sensitization and Conditioned Pain Modulation to Pain Patterns in Knee Osteoarthritis

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**Objective.** To examine the cross-sectional association of ascending pain mechanisms, implicated in pain sensitization, and descending pain modulation with pain patterns and unpredictability of pain.

**Methods.** The Multicenter Osteoarthritis Study is a longitudinal cohort of older adults with or at risk of knee osteoarthritis. Peripheral and central ascending pain mechanisms were assessed using quantitative sensory tests, pressure pain thresholds using a handheld pressure algometer (knee/peripheral and wrist/central), and temporal summation using weighted probes (wrist/central). Descending modulation was assessed by conditioned pain modulation using pressure pain thresholds and a forearm ischemia test. Pain patterns were characterized based on responses to the Intermittent and Constant Osteoarthritis Pain questionnaire: 1) no intermittent or constant pain, 2) intermittent pain only, 3) constant pain only, and 4) combined constant and intermittent pain. A question regarding frequency assessed unpredictable pain. We assessed the association of quantitative sensory test measures to pain patterns using regression models with generalized estimating equations.

**Results.** There were 2,794 participants (mean age 63.9 years, body mass index 29.5 kg/m$^2$, and 57% female). Lower pain sensitization by wrist pressure pain threshold (odds ratio [OR] 0.80 [95% confidence interval (95% CI) 0.68, 0.93]) and adequate conditioned pain modulation (OR 1.45 [95% CI 1.10, 1.92]) were associated with having constant ± intermittent pain compared with intermittent pain only. Higher pain sensitization (by pressure pain thresholds and temporal summation) was associated with a higher likelihood of unpredictable pain.

**Conclusion.** Knee pain patterns appear to be related to peripheral ± central facilitated ascending pain mechanisms and descending modulatory mechanisms. These findings highlight the need for a broader approach to understanding pain mechanisms by symptomatic disease progression.

## INTRODUCTION

The nature and causes of knee pain in osteoarthritis (OA) are complex and poorly understood. The contribution of facilitated ascending pain mechanisms causing pain sensitization in that complexity is becoming apparent, evidenced by the role of pain sensitization in susceptibility to developing persistent pain (1) and association with joint inflammation (2). Altered nociceptive signaling that can impact the pain severity experienced is a complex process, comprising ascending facilitation of nociceptive signals and descending modulation that consists of facilitatory and inhibitory signals. Many questions about pain and its mechanisms in knee OA remain unanswered; for example, why is it that not everyone with knee OA progresses in severity or frequency of pain with worsening of disease? Qualitative work has suggested that with structural disease progression there is an evolution of pain whereby people experience intermittent activity-related pain in the earlier phases of the disease and constant pain as the disease progresses, and that the late stage is demarcated by constant pain overlaid by more severe, often unpredictable, intermittent pain (3). Sensitization in knee OA is known to be associated with intermittent pain that is more intense in severity, particularly when

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**SIGNIFICANCE & INNOVATIONS**

- In a cross-sectional analysis of a prospective cohort of people with or at risk of knee osteoarthritis, quantitative sensory tests (pressure pain thresholds, temporal summation, and conditioned pain modulation) were associated with knee pain patterns (intermittent pain, constant pain, or constant ± intermittent pain).
- These findings highlight the importance of understanding pain mechanisms more broadly by symptomatic disease progression.

evoked by movement or activity (4). However, the relation of alterations in pain signaling (ascending and/or descending) to the evolution of pain becoming constant in nature is not yet known.

Using the Intermittent and Constant Osteoarthritis Pain scale (ICOAP), developed in response to the aforementioned qualitative work, we have recently shown that the patterns of intermittent, constant, and constant ± intermittent pain are associated with the duration of disease, worsening pain severity, and radiographic OA, thus supporting the qualitative work on which the scale is based (5). In light of this evidence and our increasing understanding of altered pain signal processing, different pain mechanisms may underlie these qualitative pain patterns and the transitions from one to another. For example, early intermittent pain may be due to peripherally driven nociceptive input, while constant ± intermittent pain may represent peripheral and/or central sensitization or poor descending inhibitory modulation of pain.

Pain sensitization is measured indirectly using quantitative sensory testing (QST) such as pressure pain thresholds (PPTs) or temporal summation (TS). PPTs, when measured locally at the symptomatic knee for example, are thought to reflect primarily peripheral sensitization. Central sensitization is commonly measured using PPTs measured at an anatomical site remote from a symptomatic joint or using TS, implicating the central nervous system. Conditioned pain modulation (CPM) is another QST tool that measures the presence of endogenous descending pain inhibitory pathways using a "pain inhibits pain" premise (6). Therefore, the objectives of this study were to examine the association of pain sensitization (i.e., ascending facilitation) and descending pain modulation to ICOAP-defined pain patterns and the unpredictability of pain.

## PATIENTS AND METHODS

The Multicenter Osteoarthritis Study is a National Institutes of Health–funded longitudinal study of community dwelling adults. The study now comprises 2 cohorts. The original cohort was of adults between the ages of 50 and 79 years who had or were at risk of developing knee OA at baseline, and who were recruited from Birmingham, Alabama and Iowa City, Iowa from 2003 to 2005. Details of the original cohort have been published elsewhere (6). In 2016–2017 a second cohort was added consisting of adults ages 45–69 years at baseline from the same regions, having Kellgren/Lawrence grade ≤2, and either knee pain that is not reported as constant or severe, or having no knee pain. The study was approved by the institutional review boards at the University of Iowa, University of Alabama at Birmingham, University of California at San Francisco, and Boston University Medical Center (6). The current sample comprised participants who attended the 12th year (original cohort) and baseline (second cohort) visits (baseline for this study) since it was the first time that CPM (described below) was measured. The sample included the original cohort (n = 1,284) and the new cohort (n = 1,510).

**Sensitization measures.** Three commonly employed QST measures were used to determine sensitivity of the peripheral and central nervous systems to nociceptive input. PPTs were assessed by applying an algometer (1-$cm^2$ rubber tip, FDIX25; Wagner) at a rate of 0.5 kg/second on the center of the patellae bilaterally and distal radioulnar joint (control site; right side unless contraindicated). PPT was defined as the point at which participants indicated the pressure first changed to slight pain (7). The PPT at each anatomic site was calculated by averaging 3 trials. Those demonstrating lower PPTs represent those with a higher degree of pressure pain sensitivity. TS is a measure of central nervous system sensitivity and was assessed using a standard set of 7 weighted probes from 8 to 512 Nm (University of North Carolina at Chapel Hill).

Participants rated pain experienced by each probe being touched on the skin of the wrist until a pain rating of at least 4 of 10 was achieved. If that pain rating did not occur with any of the probes, then the highest weighted probe (#7) was used. The selected probe was applied at a rate of 1 Hz for 10 seconds (i.e., 10 touches). TS was calculated as the difference in pain ratings between the end and beginning of the trial (8). Greater increases in pain ratings indicated greater TS. CPM is a means of assessing the descending pain modulatory pathways, in which a test stimulus (PPT) is assessed prior to and after a painful conditioning stimulus, a forearm ischemia test. CPM was calculated as the ratio of final pain threshold and initial pain threshold (9). The presence of adequate CPM was defined as a CPM ratio >1, i.e., the postconditioning PPT was greater than the initial PPT. PPTs were assessed at the index knee described above (mean of 3 trials). Then a blood pressure cuff was applied to the contralateral arm and the cuff was inflated to 10 mm Hg above systolic pressure. The participant was then instructed to perform hand grip squeezes until pain of at least 4 of 10 occurred in the forearm. PPT at the index knee was then repeated, after which the cuff was deflated.

**ICOAP pain and pain patterns.** The ICOAP is an 11-item measure consisting of items for 2 subscales, intermittent and constant pain. Each respective subscale item assessed the pain severity ranging from none to extremely on a 5-point Likert scale, where higher scores are indicative of greater severity. The

constant pain subscale score ranges 0–20, whereas the intermittent pain subscale ranges 0–24. Each is then transformed to a score of 100. Initial psychometric testing of the scale demonstrated good validity and reliability (10). The ICOAP was obtained in a knee-specific manner, inquiring about symptom type and severity over the prior 7 days, following a previously validated method (5,11). ICOAP pain patterns were defined as follows: 1) no intermittent or constant pain, 2) intermittent pain only (of at least mild severity and with a frequency of at least sometimes), 3) constant pain only (of at least mild severity), and 4) a combination of constant and intermittent pain. We further qualified the occurrence of unpredictable pain using a question from the ICOAP that asks about pain that comes on without warning. Answers were dichotomized as unpredictable (i.e., "sometimes" or "often" responses versus "rarely" or "never" responses).

**Confounding variables.** Potential confounders included age, sex, body mass index (BMI), depressive symptoms, pain catastrophizing, study site, and race at the 144-month visit. BMI was calculated from measurements for weight and height taken by a trained research assistant. The Center for Epidemiologic Studies Depression Scale score of ≥16 was used to define the presence of depressive symptoms (12). Pain catastrophizing was measured using 1 item from the Coping Strategies Questionnaire, which has been shown to be valid and reliable (13). Race was categorized as Caucasian versus other. In a sensitivity analysis, we additionally adjusted for pain medication use, which included opioid use, though we recognize that pain medication use may be an intermediate in the causal pathway and not necessarily a true confounder.

**Statistical analysis.** We first evaluated the association of PPT, TS, and CPM (exposures) to the total ICOAP scale and the 2 subscale totals (constant and intermittent pain) (outcomes) using multivariable linear regression with generalized estimating equations (GEEs) to account for 2 knees within an individual. We then assessed the association of the measures of sensitization (exposures) to the prespecified ICOAP pain patterns (e.g., constant ± intermittent pain versus intermittent pain only) and the presence of unpredictable pain (outcomes) using logistic regression with GEEs. We hypothesized that evidence of pain sensitization would be associated with pain patterns indicative of later stages of the pain experience in OA, specifically constant pain with or without intermittent pain compared to intermittent pain only. To facilitate interpretation of comparative metrics, the effect estimates were computed per 1 SD unit of change for PPT and TS. All models were adjusted for age, sex, BMI, depressive symptoms, pain catastrophizing, clinic site, and race. As our main model was based on a minimum of "mild" severity of either intermittent or constant pain, we conducted a sensitivity analysis to assess the impact of having more severe pain. We therefore employed a model using at least "moderately" as the indicator of intermittent and constant pain intensity to assess the association of the measures of sensitization (exposures) to the prespecified ICOAP pain patterns (e.g., constant ± intermittent pain versus intermittent pain only) and the presence of unpredictable pain (outcomes) using logistic regression with GEEs. Last, we conducted a second sensitivity analysis that added pain medications as a potential confounder to the original model. All analyses were performed using SAS software, version 9.4.

## RESULTS

For the sample of n = 2,794 at 144 months (i.e., the baseline for this study), the mean ± SD age was 63.9 ± 10.6 years, 57% were female, and the mean ± SD BMI was 29.5 ± 5.7 kg/m$^2$. The mean ICOAP scores were 10.3, 2.2, and 6.6 for the intermittent and constant subscales and the total scale, respectively. The majority of knees (67%) had neither intermittent nor constant pain, 26% had intermittent pain only, and 7% had constant pain (3% with constant pain only, and 4% constant and intermittent). Unpredictable pain was experienced by 18% (Table 1).

**QSTs by ICOAP totals.** Greater pain sensitization (i.e., more pain sensitivity) as assessed by greater TS was associated with higher ICOAP intermittent subscale scores. Higher PPT values, indicative of less pain sensitization, at both the knee and the wrist were associated with lower intermittent, constant, and total ICOAP scores, with the largest coefficient seen with intermittent pain. Those with CPM (ratio >1) were more likely to have higher constant ICOAP scores compared to those without CPM (Table 2).

**QSTs by prespecified ICOAP pain patterns derived from qualitative data.** Higher PPTs locally and remotely (less pain sensitivity) were associated with lower odds of having constant ± intermittent compared with intermittent pain only. Similarly, higher PPTs were associated with a lower likelihood of having unpredictable pain occurring at least sometimes or very

**Table 1.** Participant characteristics (n = 2,794 [5,557 knees])*

| Characteristic | Value |
|---|---|
| Age, years | 63.9 ± 10.6 |
| Female, % | 57 |
| Body mass index, kg/m$^2$ | 29.5 ± 5.7 |
| Low back pain, % | 45 |
| Pain medications, % | 35 |
| ICOAP totals | |
| Intermittent pain subscale/24 × 100 | 10.3 ± 16.1 |
| Constant pain subscale/20 × 100 | 2.2 ± 10.0 |
| Total pain score/44 × 100 | 6.6 ± 11.1 |
| ICOAP pain patterns in knees, no. (%) | |
| No intermittent or constant pain | 3,728 (67) |
| Intermittent pain only | 1,474 (26) |
| Constant pain only | 157 (3) |
| Both constant and intermittent pain | 198 (4) |
| Unpredictable pain | 987 (18) |

* Values are the mean ± SD unless indicated otherwise. ICOAP = Intermittent and Constant Osteoarthritis Pain.

**Table 2.** Association of QSTs with ICOAP scale totals*

| | Intermittent score | Constant score | Total score |
|---|---|---|---|
| Temporal summation per SD unit increase | 0.53 (0.03, 1.04)† | –0.03 (–0.38, 0.31) | 0.28 (–0.08, 0.63) |
| PPT: patella per SD unit increase | –1.60 (–2.06, –1.14)† | –0.80 (–1.10, –0.51)† | –1.24 (–1.54, –0.93)† |
| PPT: wrist per SD unit increase | –1.44 (–1.92, –0.97)† | –0.64 (–0.92, –0.36)† | –1.08 (–1.40, –0.76)† |
| Presence of adequate CPM (ratio >1 vs. ≤1) | –0.74 (–1.73, 0.24) | 0.83 (0.25, 1.40)† | –0.03 (–0.69, 0.63) |

* Values are the ß estimated (95% confidence interval). Linear regression models were adjusted for age, sex, body mass index, race, pain catastrophizing, depressive symptoms, and site. CPM = conditioned pain modulation; ICOAP = Intermittent and Constant Osteoarthritis Pain; PPT = pressure pain threshold; QST = quantitative sensory test.
† Statistically significant.

often compared with rarely or never. The association of greater TS with having unpredictable pain was borderline significant. Greater TS (i.e., more pain sensitivity) was also associated with a higher likelihood of having unpredictable pain. The presence of adequate CPM, however, was associated with a greater likelihood of having constant ± intermittent compared with intermittent pain only (Table 3).

**Sensitivity analysis.** The sensitivity analysis, using a model where intermittent and constant pain severity was set at a minimum as "moderately," demonstrated a small increase in the association of the presence of adequate CPM (odds ratio [OR] 1.53 [95% confidence interval (95% CI) 1.07, 2.19]) with having constant ± intermittent pain compared with intermittent pain only, whereas PPT at the wrist was no longer significant (OR 0.83 [95% CI 0.67, 1.03]), though the effect estimate remained similar, likely reflecting loss of precision with fewer participants meeting this definition. All other values were unchanged (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24437/abstract).

The addition of pain medications as a confounder to our original model did not change the results in any meaningful way, with the exception of the association of TS with intermittent pain (OR 0.43 [95% CI –0.08, 0.93]) and with unpredictable pain (OR 1.07 [95% CI 0.99, 1.16]), both of which became nonsignificant.

## DISCUSSION

In light of the body of literature substantiating the role of sensitization in this population (4) and recent work validating ICOAP-identified pain patterns with disease duration, pain, and radiographic severity (5), we sought to evaluate whether these ICOAP-identified pain patterns were associated with different underlying pain mechanisms, as assessed by commonly used QST measures. We found that higher levels of sensitization were associated with 1) higher ICOAP intermittent (by PPT and TS) and constant subscale values (by PPT) and total scores (by PPT), and 2) a greater likelihood of constant ± intermittent pain compared with intermittent pain only (by PPT), and more frequent unpredictable pain (by PPT and TS). Interestingly and in contrast to our hypothesis, we found that the presence of adequate CPM, thought to be protective for the development of chronic pain (14), was also associated with higher ICOAP constant subscale scores and a higher likelihood of having constant ± intermittent pain versus intermittent pain only.

As per our initial hypotheses, we found a stronger association between PPTs and the ICOAP intermittent subscale than for the constant subscale; however, the clinical relevance of these differences is unknown. We have previously reported on the importance of PPT sensitivity to the development of persistent pain (1). These current findings provide new support for the role of PPT sensitivity in the development of constant pain (defined as pain that is there all the time) compared to intermittent pain (pain that comes and goes). However, these cross-sectional data suggest no difference in peripheral or central facilitatory input, as results were similar for PPTs tested at local (the knee) and remote (the wrist) sites, respectively, on ICOAP scores and risk of pain patterns. Conversely, TS, a phenomenon representative of windup in the central nervous system, produced a smaller increase in ICOAP pain scores (subscales and total) and this

**Table 3.** Association of QSTs with ICOAP pain patterns*

| | Constant ± intermittent vs. intermittent only | Without warning sometimes/often vs. rarely/never |
|---|---|---|
| Temporal summation per SD unit increase | 0.96 (0.84, 1.09) | 1.08 (1.00, 1.18)† |
| PPT: patella per SD unit increase | 0.80 (0.68, 0.93)† | 0.76 (0.70, 0.83)† |
| PPT: wrist per SD unit increase | 0.80 (0.66, 0.96)† | 0.82 (0.74, 0.90)† |
| Presence of adequate CPM (ratio >1 vs. ≤1) | 1.45 (1.10, 1.92)† | 0.96 (0.81, 1.13)† |

* Values are the adjusted odds ratio (95% confidence interval). Linear regression models were adjusted for age, sex, body mass index, race, pain catastrophizing, depressive symptoms, and site. CPM = conditioned pain modulation; ICOAP = Intermittent and Constant Osteoarthritis Pain; PPT = pressure pain threshold; QST = quantitative sensory test.
† Statistically significant.

increase was only significant for the intermittent subscale, though this association was no longer significant once adjusted for pain medications. The small increase in TS may also be in part due to the inherently smaller variance observed in TS compared to PPTs.

On the other hand, TS was not associated with a greater risk of having constant ± intermittent pain versus intermittent pain only, contrary to our hypothesis that TS may increase the likelihood of having constant pain. These findings suggest that TS may not drive pain patterns per se, but rather may contribute to the pain severity experienced. Of note, the association with increased intermittent pain severity complements previous work that shows TS is associated with knee pain severity (7). Collectively, these findings support the existing literature of clinical studies implicating the role of local peripheral nociceptive input as an important driver of pain in knee OA, at least initially, and contributing to the well-recognized intermittent, activity/weight-bearing related pain (15). Longitudinal analyses will be needed to confirm the strength of these relationships with intermittent and constant pain and to ascertain whether they may differ in their contribution from the peripheral or central nervous systems.

We found that those participants with greater ascending facilitation either peripherally (i.e., PPT at the knee) or centrally (i.e., PPT at the wrist) were more likely to have constant ± intermittent pain compared with intermittent pain only. This finding is in line with evidence supporting the association of greater facilitation, regardless of origin, with widespread pain that is often constant in nature (16).

Unexpectedly, we found that the presence of adequate CPM was associated with increases in the constant pain subscale total and with a greater likelihood of constant ± intermittent pain versus intermittent pain only. We had initially hypothesized that poor descending modulation would be associated with more constant pain. This finding is novel and is contrary to prior studies reporting reduced or absent CPM in those with higher sensitization in people with knee OA (17), as well as collective evidence in the pain literature suggesting that CPM is an important factor in determining whether pain becomes chronic or not (14). One potential reason for our findings is that, to our knowledge, we are the first to measure CPM in those with knee OA with pain defined as either intermittent or constant. For example, previous studies have sampled symptomatic people (18), with moderate or high pain severity (9), but the nature of their pain as being intermittent or constant has not been specified. Defining pain in this way and trying to understand its relation with measures of pain sensitivity and modulation, as well as progression of disease severity, may shed new light on our understanding of underlying pain mechanisms. Certainly, the pathways involved in pain sensitization are distinct from descending inhibition; thus our findings unsurprisingly differed somewhat between QST measures.

Other researchers have suggested that people may be either pain inhibitors or pain facilitators and have speculated that among the variability and range of CPM responses found in healthy volunteers, those in the lowest quartile may be vulnerable to the development of chronic pain (16). On the other hand, our current study was cross-sectional, so a possibility exists of reverse causation, in that individuals with chronic pain may be activating their descending inhibitory pathways as an appropriate response. That is, those with constant pain may have adequate CPM activated due to the presence of that constant pain. The results of our sensitivity analysis support this supposition, as the effect of having adequate CPM increased with increased severity of constant pain. Further longitudinal studies of endogenous modulation are needed in people with knee OA, specifically to address how endogenous modulation of pain may change with disease progression.

Finally, we found that higher ascending facilitation by PPT (locally or remotely) and TS were associated with more frequent unpredictable pain (however, this association was no longer significant when adjusted for pain medications) but not so for CPM. In keeping with our finding of greater association with constant pain, intermittent pain, regardless of severity (as per our sensitivity results), and whether predictable or unpredictable, may not be not sufficient to activate CPM. Unpredictable pain has been rarely studied in people with knee OA; however, a study of a similar but different concept, "movement-evoked" versus resting pain, has shown that pain associated with movement is related to greater sensitization (19). The difference is that movement-evoked pain is not necessarily unpredictable; in fact, pain commonly increases with activity acutely (20), and yet exercise may reduce sensitization acutely (21) and be an effective treatment for pain long-term (22). Given that the unpredictability of pain has been described as a feature of progressive disease and is one of the more bothersome aspects of OA pain, disentangling the concepts of pain, its unpredictability and triggers, as well as its relationship to movement and flares will be important in future work.

Limitations of this work include the fact that this is a cross-sectional analysis, thus restricting any inferences about causation or time progression per se. We were also unable to ascertain any information regarding triggers in regard to unpredictable pain, and this gap may be an important aspect to include to help clarify relationships in the future. In addition, we were unable to discern how long participants have had symptoms, nor account for the variable course of the disease, which may not uniformly progress as suggested by qualitative research. Strengths of our study include the examination of ICOAP-defined pain patterns with indicators of sensitization and endogenous pain modulation, with adjustment for known confounders, in addition to our use of standardized and validated questionnaires.

Taking a mechanistic approach to understanding pain in knee OA may provide the basis for a targeted and personalized approach to pain management, particularly when paired with validated clinical symptoms (23). We found that different pain sensitization–related mechanisms were associated with different pain patterns, particularly intermittent versus constant pain. These pain patterns can evolve over the course of OA and appear to be related to peripheral ± central-facilitated ascending pain

mechanisms and descending modulatory mechanisms. These findings highlight the need for a broader approach to understanding pain and its mechanisms that may differ by disease symptomology. Importantly, ascending pain facilitation appears to be associated with constant pain and unpredictable pain, and may therefore be an important mechanism in the transition from intermittent to persistent/constant pain.

## 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 submitted for publication. Dr. Carlesso 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.** Carlesso, Neogi.

**Acquisition of data.** Neogi.

**Analysis and interpretation of data.** Carlesso, Frey Law, Wang, Nevitt, Lewis, Neogi.

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# Challenges With Strengthening Exercises for Individuals With Knee Osteoarthritis and Comorbid Obesity: A Qualitative Study With Patients and Physical Therapists

Belinda J. Lawford, Kim L. Bennell, Kim Allison, Sarah Schwartz, and Rana S. Hinman

**Objective.** To explore challenges associated with implementing a home-based strengthening exercise program for individuals with knee osteoarthritis and comorbid obesity.

**Methods.** This is a qualitative study embedded within a randomized controlled trial comparing 2 home-based strengthening programs (weight-bearing functional exercise versus non–weight-bearing quadriceps strengthening exercise) for individuals with knee osteoarthritis and comorbid obesity. Patients in both exercise programs attended 5 consultations with a physical therapist and undertook a home-based exercise program for 12 weeks. After trial completion, semistructured individual telephone interviews were conducted with 22 patients and all 7 physical therapists who delivered trial interventions. Interviews were recorded, transcribed verbatim, and thematically analyzed using an inductive approach.

**Results.** Three themes arose: 1) psychological challenges (false assumptions about exercise; fear of pain; disliking exercise; mental effort of the weight-bearing functional program; underestimating capability); 2) physical challenges (complexity of the weight-bearing functional program; cuff weights and straight leg raise being problematic in non–weight-bearing quadriceps program; other health conditions); and 3) overcoming challenges (incentives to exercise; accountability; education and reassurance; tailoring the exercise program).

**Conclusion.** Patients and physical therapists experienced numerous psychological and physical challenges to exercise, including a fear of pain, having false assumptions about exercise, difficulties with exercise performance, application of cuff weights, and adverse impacts of other health conditions.

## INTRODUCTION

Knee osteoarthritis (OA) is a common and debilitating condition, placing an enormous burden on individuals and society (1). Obesity is a significant risk factor for the development of OA (2) and is a common comorbid condition, affecting ~25% of people with OA (3). It is associated with increased risk of disease progression, including greater structural damage and immobility (4,5). Individuals with OA who are obese are also more likely to have moderate-to-severe symptoms (6) and to undergo joint replacement surgery (7) compared to those with OA who are not obese. Given the increasing prevalence of both OA and obesity (8), it is imperative that OA management strategies consider the unique needs of this subgroup of people.

Exercise is a core recommended management strategy for all individuals with knee OA (9–11), including those with comorbid obesity. Benefits of exercise for knee OA are well established, including improvements in pain, physical function, and quality of life (12). Lower extremity muscle weakness is widespread in knee OA (13,14) and predicts severity of pain and physical dysfunction (15). Thus, muscle strengthening exercises, in particular, are advocated (10,11). Adherence to prescribed exercise programs is problematic in OA populations (16), and patients encounter a range of barriers to the uptake and maintenance of positive exercise behaviors (17). Individuals with OA and comorbid obesity likely encounter unique challenges to exercise participation. For example, there is evidence that those with OA who are obese

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**SIGNIFICANCE & INNOVATIONS**

- In individuals with knee osteoarthritis, being obese is associated with poorer outcomes and increased risk of disease progression. Strengthening exercises are recommended, yet little is known about the challenges that this cohort faces.
- Findings suggest that physical therapists should not be afraid to challenge patients with knee osteoarthritis and comorbid obesity physically and psychologically and that careful education and reassurance about the safety and benefits of strengthening exercises is essential.

experience increased fear of movement and pain catastrophizing compared to nonobese individuals with OA (18), which may lead to avoidance of physical activity, hinder adherence to prescribed exercise programs, and further contribute to functional decline and disease progression (19). There is also some existing evidence that people with OA who are obese may experience different barriers to different types of strengthening programs. For example, our recent randomized controlled trial (RCT) found higher rates of adverse events in individuals with OA and comorbid obesity who completed a non–weight-bearing exercise program (39% of 66 participants reported an adverse event), compared to a weight-bearing functional exercise program (23% of 62 participants) (20). However, it is not clear why this is or what barriers individuals with OA who are obese face when engaging in such strengthening exercise programs. As such, investigating the challenges that those with OA who are obese face when participating in strengthening exercise programs is important.

The attitudes and beliefs of the clinicians involved in delivering and prescribing strengthening exercise to patients with knee OA and comorbid obesity can have a significant influence on patient behavior, including engagement with exercise. There is evidence that physical therapists demonstrate weight stigma (i.e., negatively stereotyping people perceived to be overweight as being lazy, having ill health, or lower intelligence) when providing care to patients who are overweight or obese (21–23). Weight stigma has been linked to poorer patient outcomes, including avoidance of health care appointments (24), reduced engagement in exercise (25), and more disordered eating (26). In addition, patients who perceive negative judgements from their physical therapist are less motivated to exercise (27). This further highlights the importance of exploring the challenges that individuals with OA who are obese, as well as their treating physical therapists, face when participating in and prescribing a strengthening exercise program.

Currently, little is known about the challenges of implementing strengthening exercise programs for those with knee OA and comorbid obesity, from either the patient or clinician perspective. Thus, the aim of this qualitative study was to explore the experiences and perceptions of patients and physical therapists who undertook or prescribed a strengthening exercise program for individuals with knee OA and comorbid obesity.

## SUBJECTS AND METHODS

**Design.** This study used a qualitative design based on an interpretivist paradigm to explore the perceptions and experiences of physical therapists who prescribed strengthening exercise for individuals with knee OA and comorbid obesity and of the patients who underwent those exercises. According to this paradigm, knowledge about a phenomenon is developed by gathering perceptions and interpretations of participants who experience it (28).

This qualitative study was nested within an RCT (Australian New Zealand Clinical Trials Registry ACTRN: 12617001013358) that compared the effectiveness of a non–weight-bearing quadriceps strengthening exercise (NWBE) program to a weight-bearing functional exercise (WBE) program in people with knee OA and comorbid obesity (29). The RCT found that both exercise programs improved primary outcomes of pain and function, but with a higher rate of mild adverse events with the NWBE program (20). The Consolidated Criteria for Reporting Qualitative Research checklist was used to ensure complete and transparent reporting of this study (30).

**Participants.** Participants who were enrolled in the overarching trial as patients, as well as the physical therapists who delivered the interventions, were recruited as key informants from our RCT. Selection criteria for patient enrolment into the RCT have been previously published (29). Briefly, eligible participants were ages ≥50 years, reported knee pain on most days and for at least the past 3 months, reported overall knee pain during the last week of ≥4 on an 11-point numerical rating scale, demonstrated tibiofemoral osteophytes on radiography, and were obese (body mass index [BMI] ≥30 kg/m$^2$). Participants were recruited from the community in Melbourne, Australia, via advertisements on social media, community locations, consumer organizations, radio and newspapers, and a previous volunteer database. Seven physical therapists with at least 5 years of musculoskeletal experience were recruited from various locations around Melbourne to deliver interventions for the RCT.

For this qualitative study, patients were consecutively invited to participate after completing their 12-week strengthening program for the trial. Purposive sampling was used to ensure a mix of interviewees with respect to sex, age, exercise program allocation, and exercise adherence. All interviews were conducted within 6 months of the patient having completed the intervention. The final sample was dictated by the principle of theoretical saturation, where no new themes or subthemes emerged from the data (31). All 7 physical therapists who were employed to deliver the trial intervention were invited to participate after they had

completed at least 80% of their consultations with study patients. All patients and physical therapists provided written informed consent, and the institutional ethics committee approved the study.

**Intervention.** The intervention has been published in detail (29). Briefly, 128 patients were randomly allocated to 1 of 2 exercise groups: NWBE and WBE. Both groups attended 5 individual physical therapy sessions over 12 weeks (approximately weeks 1, 2, 4, 7, and 10), where the physical therapist taught the exercise program and instructed patients to perform it on their own at home 4 times per week. Patients were provided with a logbook to record their exercise completions, a 1-page sheet providing information about OA, and a detailed exercise instruction booklet. During follow-up sessions, physical therapists progressed or modified the program (if appropriate) based on a brief reassessment. A number of behavior change techniques were incorporated into both exercise interventions based on behavior change techniques that are relevant for exercise (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24439/abstract) (32,33). Trial physical therapists delivered interventions in both groups and attended a 4-hour training session prior to trial commencement, supplemented by a detailed treatment manual.

The NWBE program (Table 1) focused on improving the strength of the quadriceps and involved exercises performed in a sitting or supine position (34). Patients were provided with an adjustable cuff weight (0.65–10 kg) to use for home exercises. The starting weight was the patient's 10-repetition maximum weight, as determined by the patient's level of effort, aiming for between 5 and 8 of 10 (hard to very hard) on the modified Borg Rating of Perceived Exertion scale for strength training (35). Progression of exercise involved increasing weight (0.5 kg at a time) when each exercise felt easier to complete and holding the end position of each exercise for longer (from 5 seconds to 10 seconds).

The WBE program (Table 1) incorporated neuromuscular exercises (34) that aimed to functionally strengthen the lower extremity muscles, improve trunk/lower extremity joint alignment, and improve quality of movement performance. Patients were provided with an adjustable step (10–15 cm in height), a foam mat, and elastic resistance bands to use. Progression of exercise was based on a combination of the patient's pain and rating of perceived exertion score for each exercise (at least 5 of 10 on the modified Borg Rating of Perceived Exertion scale [35]), as well as the physical therapist's own assessment of the quality of the exercise performance.

**Interviews.** A semistructured interview guide was utilized (Table 2). All individual interviews were conducted over the telephone by BJL, a postdoctoral researcher trained in qualitative methodologies who is not a clinician and who had no other involvement or contact with the patients or physical therapists or role in the overarching RCT. Interviews were audio recorded and transcribed verbatim by an external provider of transcription services. Pseudonyms were assigned to each patient and physical therapist for confidentiality purposes. All data were deidentified and stored in digital format on a password-protected university server.

**Table 1.** Exercise protocol and progression for non–weight-bearing and weight-bearing exercise programs*

| Exercise program |
|---|
| Non–weight-bearing exercise program† |
| Quadriceps over a roll (inner range knee extension) |
| Knee extension in sitting |
| Knee extension in sitting with a hold at 30° |
| Straight leg raise |
| Knee extension in sitting with TheraBand |
| Weight-bearing exercise program‡ |
| Forwards/backwards exercise |
| Level 1: Sliding |
| Level 2: Sliding with TheraBand |
| Level 3: Stepping |
| Level 4: Stepping with TheraBand |
| Sideways exercise |
| Level 1: Sliding |
| Level 2: Sliding with TheraBand |
| Level 3: Sliding with TheraBand and foam |
| Level 4: Sliding with TheraBand and foam and eyes closed |
| Hip muscle strengthening |
| Level 1: Wall push |
| Level 2: Wall push with deeper knee bending |
| Level 3: Crab walking with red TheraBand |
| Level 4: Crab walking with black TheraBand |
| Knee muscle strengthening |
| Level 1: Wall squats |
| Level 2: Wall squats with more weight on arthritis leg |
| Level 3: Chair stands |
| Level 4: Chair stands with more weight on arthritis leg |
| Step-ups |
| Level 1: Step-ups |
| Level 2: Step-ups with weight |
| Level 3: Forward touch downs |
| Level 4: Forward touch downs with weight |

* Progression of each exercise program type is listed in the footnotes.
† Weeks 1–2 (2 sets of 10 repetitions); weeks 3 onwards (3 sets of 10 repetitions; increase weights 0.5 kg at a time; progress from 5- to 10-second hold at end position of each exercise).
‡ Weeks 1, 2, and 3 (level 1); weeks 4, 5, and 6 (level 2); weeks 7, 8, and 9 (level 3); weeks 10, 11, and 12 (level 4).

**Data analysis.** Analysis was based on an inductive thematic approach (36). Data were analyzed iteratively as each interview was completed to ensure that data saturation was reached and to modify the interview schedule if necessary (no major modifications were required). Individual transcripts were read through by BJL soon after transcription, and then re-read and coded to identify topics and initial patterns of ideas emerging from the data. Codes were organized into categories and combined with similar or related ideas from across all participant data to form themes. Another researcher (KA, a physical therapist), who had no contact

**Table 2.** Physical therapist and patient interview guide*

| Physical therapists | Patients |
|---|---|
| What stands out most about your experiences prescribing an exercise program for people with OA who are overweight in the study? | What stands out most about your experience seeing the physiotherapist and undertaking the exercise program you were prescribed in the study? |
| When you volunteered for the study, what were you expecting? Was there anything surprising about the experience?† | When you volunteered for the study, what were you expecting? Was there anything surprising about the experience?† |
| How did your consultations with people in the trial compare to your usual clinical consultations for people with knee OA? Are your usual patients with knee OA of similar body size?† Did this impact your assessment/treatment approaches?† How were these people different?† Did they have any unique needs?† | What were the things you liked about the exercise program you received? Which exercises did you like best?† Why?† |
| As you know, there were 2 different exercise programs in this study: weight- bearing and non–weight-bearing. Did you encounter any challenges prescribing and progressing the WBE program for the participants? | Was there anything you didn't like about the exercise program you received? Any exercises you disliked?† Why?† |
| Did you encounter any challenges prescribing and progressing the NWBE program for the participants? | Was there anything challenging about undertaking the exercise program at home on your own? |
| In your experience with the trial, which exercise program do you think you were more successful at implementing with your participants? Did patients adhere better to one or not?† Did you find it easier to prescribe/progress one over the other?† Did you observe more benefits for the patients with one over the other?† | How would you describe your relationship with your physio? Did you feel like you could trust them and their advice?† Did they ask for your input when prescribing your exercise program?† |
| Overall, how would you describe the relationship you developed with your participants? How did this compare to relationships you normally have with patients in your clinical practice?† | How comfortable were you discussing your ability/inability to do your home exercises with your physio? Why/why not?† |
| How well did your participants attend their physiotherapy sessions and adhere to their prescribed home exercise program? What were the major barriers for these people?† | How comfortable were you performing the exercises in the clinic in front of the physiotherapist? Why/why not?† What made you comfortable/uncomfortable?† How could your discomfort have been overcome?† |
| Have your experiences in the trial changed anything about the way you prescribe exercise for patients with knee osteoarthritis who are overweight in your usual clinical setting? | How well did you stick to your exercise program at home? What made it easy/difficult to stick to the home program?† |
| Finally, can you summarise the 3 most important things you would want to share with other physios to help them engage people with knee OA who are overweight in exercise? | Will you continue with your home exercise program in the future? Why/why not?† |
| | What sorts of things do you think would help people like yourself stick to their exercise programs? Is there anything that physios or other health care clinicians could do to help?† |
| | Finally, can you summarise the 3 most important things you think help people like you have a positive experience doing exercise for their knee OA? |

* NWBE = non–weight-bearing quadriceps strengthening exercise program; OA = osteoarthritis; WBE = weight-bearing functional exercise program.
† Question was used as prompt if necessary.

with patients or physical therapists, independently reviewed and coded a subset of transcripts before meeting with BJL to compare and contrast findings. Thematic categories were then reviewed and revised by BJL and KA, divided into subthemes, and reviewed and discussed with the research team (37). To ensure credibility and confirmability of the data, another researcher (RSH) read all transcripts. Standard word processing software was used to organize qualitative data rather than qualitative analysis software.

## RESULTS

**Participant characteristics.** Interviews were undertaken with 22 patients (Table 3) and all 7 trial physical therapists (Table 4). Patients were typically female (59%), with a mean ± SD age of 63 ± 7 years and a mean ± SD BMI of 35.9 ± 5.0 kg/m$^2$. Physical therapists were mostly male (86%), worked in private practice (86%), and had a mean ± SD clinical experience of 14 ± 8 years. Three themes (and 4–5 subthemes per theme) were identified (Table 5) and are summarized in Figure 1.

**Theme 1 (psychological challenges).** *False assumptions about exercise.* Patients held false beliefs about the consequences of exercise for their knee OA, initially feeling skeptical about its effectiveness and believing that it would "wear out" their knees. They were thus surprised that strengthening exercises could help. Similarly, physical therapists found that patients were skeptical about the safety and benefits of strengthening exercises for their OA, making them initially difficult to work with to get buy-in and build rapport.

**Table 3.** Patient characteristics (n = 22)*

| Pseudonym | Age, years | Sex | BMI (kg/m$^2$) | Knee pain severity† | Change in knee pain at 12 weeks‡ | WOMAC score (pain)§ | WOMAC score (function)§ | No. of consultations with physical therapist | Employment status | Exercise group | Self-rated adherence to exercise program# |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Jane | 59 | F | 35.5 | 6 | 3 | 11 | 20 | 5 | Employed | WBE | 8 |
| Chris | 69 | M | 31.8 | 7 | 0 | 9 | 34 | 5 | Not employed | NWBE | 10 |
| Tamara | 61 | F | 33.4 | 5 | 4 | 8 | 25 | 5 | Employed | NWBE | 9 |
| Simone | 68 | F | 34.5 | 7 | 2 | 12 | 42 | 5 | Not employed | WBE | 9 |
| Anna | 64 | F | 32.8 | 7 | 1 | 6 | 29 | 5 | Employed | NWBE | 2 |
| Robyn | 60 | F | 30.3 | 6 | 0 | 12 | 32 | 5 | Employed | WBE | 10 |
| Linda | 68 | F | 42.6 | 6 | 2 | 4 | 17 | 5 | Not employed | NWBE | 7 |
| Annelise | 61 | F | 30.9 | 8 | 0 | 10 | 41 | 2 | Employed | NWBE | NA |
| Alan | 56 | M | 31.6 | 5 | 4 | 10 | 23 | 5 | Employed | WBE | 3 |
| Craig | 69 | M | 30.3 | 4 | 1 | 4 | 18 | 5 | Not employed | NWBE | 10 |
| David | 72 | M | 34.9 | 4 | 1 | 3 | 13 | 5 | Not employed | NWBE | 9 |
| Gabrielle | 64 | F | 40.9 | 6 | 4 | 9 | 35 | 5 | Not employed | NWBE | 10 |
| Hilary | 60 | F | 33.5 | 8 | 7 | 7 | 22 | 5 | Employed | NWBE | 9 |
| Henry | 58 | M | 31.0 | 4 | 2 | 3 | 12 | 3 | Employed | NWBE | 0 |
| Kaye | 53 | F | 38.1 | 8 | 5 | 8 | 33 | 5 | Employed | WBE | 10 |
| Gillian | 62 | F | 43.2 | 7 | 6 | 8 | 37 | 5 | Not employed | WBE | 10 |
| Ron | 79 | M | 40.0 | 7 | −1 | 4 | 20 | 5 | Not employed | NWBE | 7 |
| Karen | 52 | F | 41.8 | 7 | 6 | 13 | 47 | 5 | Employed | WBE | 10 |
| Rod | 59 | M | 32.9 | 7 | 4 | 8 | 36 | 5 | Employed | WBE | 7 |
| Roger | 64 | M | 39.7 | 7 | 5 | 7 | 24 | 5 | Not employed | NWBE | 10 |
| Peter | 74 | M | 32.0 | 4 | 3 | 7 | 21 | 5 | Employed | WBE | 7 |
| Judith | 62 | F | 47.2 | 5 | −1 | 8 | 31 | 5 | Not employed | WBE | 10 |
| Mean ± SD | 63 ± 7 | – | 35.9 ± 5.0 | 6 ± 1 | 3 ± 2 | 8 ± 3 | 28 ± 10 | 5 ± 1 | – | – | 8 ± 3 |

* BMI = body mass index; NA = not available (missing data); NWBE = non–weight-bearing exercise group; WBE = weight-bearing exercise group; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† Measured by 11-point numerical rating scale (0 = no pain, 10 = worst pain possible) prior to randomization for the trial.
‡ Calculated as baseline – 12 weeks; positive scores indicate improvement in pain over time, negative scores indicate worsening.
§ Measured by WOMAC prior to randomization for the trial, where pain scores range from 0 to 20, and physical function scores range from 0 to 68 (higher scores indicate worse pain and poorer function).
# Measured on 11-point Likert scale (0 = strongly disagree, 10 = strongly agree) for the statement, "I have been doing my exercises exactly as I was asked to by my physical therapist (number of sessions, exercises, and repetitions)."

**Table 4.** Physical therapist characteristics (n = 7)*

| Pseudonym | Sex | Work setting | Clinical experience, years | No. of patients total (across trial arms) |
|---|---|---|---|---|
| Simon | M | Private | 16 | 19 (9 NWBE, 10 WBE) |
| Mary | F | Private | 23 | 20 (11 NWBE, 9 WBE) |
| Alex | M | Private | 9 | 21 (12 NWBE, 9 WBE) |
| Aiden | M | Private | 27 | 13 (7 NWBE, 6 WBE) |
| Bob | M | Public | 5 | 16 (8 NWBE, 8 WBE) |
| William | M | Private | 6 | 18 (9 NWBE, 9 WBE) |
| Neil | M | Private | 13 | 21 (10 NWBE, 11 WBE) |
| Mean ± SD | – | – | 14 ± 8 | 18 ± 3 |

* NWBE = non–weight-bearing strengthening exercise group; WBE = weight-bearing exercise group.

*Fear of pain.* Patients were initially afraid to exercise and were apprehensive about aggravating pain or experiencing knee crepitus during movement. Being reassured about feeling pain by their physical therapist gave them confidence to engage in and continue their exercise program. Physical therapists also found that fear was a significant barrier in this cohort and that patients required a lot of encouragement and reassurance. Physical therapists were themselves apprehensive about aggravating pain in patients. However, their experiences in the study helped them push their patients through more pain than they would have previously.

*Disliking exercise.* Many patients did not like exercise, describing themselves as being lazy and finding exercises boring and a chore to complete. Patients thus experienced difficulties making exercise a priority and fitting it into their daily lives, and motivation waned after physical therapy consultations ended, which led to patients discontinuing their exercise program.

*Mental effort of WBE program.* Physical therapists felt that the mental effort required for the WBE program was challenging for patients. Rather than being purely physically taxing, the technicality of the exercises required a great deal of focus and concentration by patients. Implementing the rating of perceived exertion scale was difficult, as patients struggled to differentiate between cognitive and physical effort. Physical therapists believed that the NWBE program was generally easier for patients to follow and easier for them to prescribe.

*Underestimating capability.* Capability to exercise was underestimated. Patients were surprised that they could do as much as they did, and that they could progress their program at a faster rate than what was originally thought possible. Physical therapists also found that most patients tolerated a lot more than was expected and were pleasantly surprised by the amount of exercise that their patients could handle. Physical therapists reflected on the fact that they tended to avoid pushing patients in their usual clinical practice.

**Theme 2 (physical challenges).** *Complexity of WBE program.* A physical challenge was the complexity of the WBE program, which required more finesse, body awareness, and coordination than the NWBE program. Some exercises in the WBE program (e.g., wall push [Table 1; exercise number 3, level 1] and step downs [Table 1; exercise number 5, levels 3 and 4]) were difficult, as patients had trouble balancing and felt unsteady. Thus, it was easier for physical therapists to prescribe and progress the NWBE than the WBE program.

*Cuff weights problematic in NWBE program.* There were challenges associated with the cuff weights used to apply resistance in the NWBE program. When patients progressed to high levels of resistance, it was uncomfortable and cumbersome to apply the cuff weights. Many struggled to get down to put the cuff weights on because of abdominal bulk and often required assistance from a spouse or partner. Because of these difficulties, patients tended to use the same weight for all exercises rather than change to the specific weight prescribed for each. Similarly, the cumbersome nature of the cuff weights made it difficult for physical therapists to get adequate load onto their patients.

*Straight leg raise difficult in NWBE program.* Patients and physical therapists found the straight leg raise challenging in the NWBE program. This exercise triggered pain flares in the lower back, hip, or groin, and as such, physical therapists found it difficult to add resistance to progress the exercise. Some patients considered withdrawing from the study due to the difficulties with this exercise.

*Other health conditions.* Patients described a range of comorbid health problems that made exercise participation difficult (e.g., injuries from a fall, low back pain, depressive episodes, pneumonia, golfer's elbow, cancer, and groin injuries). Many also described incidents where their partner or family members were unwell and they had to act as a care giver, which limited time and motivation. Physical therapists themselves observed the significant impact other health problems had on their patients' ability to commit fully to their exercise program.

**Theme 3 (overcoming challenges).** *Incentives to exercise.* A major incentive for patients was noticing improvement in symptoms, which helped motivation to continue exercising. Physical therapists also noticed that when patients engaged in their exercise program and started seeing improvements, they were adherent and easy to work with.

**Table 5.** Themes, subthemes, and exemplary quotes relating to experiences of patients and physical therapists undertaking and prescribing weight-bearing functional exercise (WBE) and non–weight-bearing quadriceps strengthening exercise (NWBE)*

| | Patients | Physical therapists |
|---|---|---|
| Theme 1: Psychological challenges | | |
| False assumptions about exercise | Chris (NWBE): "The improvement it made…I suppose [I was surprised] that the type of exercise I did could make a difference, I wouldn't have thought the exercises I was doing would make any difference at all." Judith (WBE): "This study taught me that exercise can definitely help with mobility, with arthritis and I think a lot of people including myself were frightened of that, thinking 'Oh no, I'm going to hurt myself. Going to injure myself. Going to wear out my knees', you know – it was the opposite effect. The more you move, the better it feels, you know?" | Alex: "Often when people with OA come in they'll use terminology like, 'Oh, no I'm bone-on-bone' and things like that and they just, any sort of impact is going to worsen their symptoms. So I suppose providing some education to people, that strengthening exercises, weight-bearing exercises is not necessarily going to make it any worse and in a lot of cases, will make it better." William: "A lot of people were highly skeptical. Highly skeptical. And that was a big flag with a few – some people came in thinking this is a crock of [rubbish], this is not going to do anything, blah, blah, blah, and they were hard to work with. To get that buy in and that rapport, it was quite a challenge in those first couple of sessions." |
| Fear of pain | Karen (WBE): "I had been afraid to exercise because of the pain, and because of the study, I'm now aware that I can actually do something about it rather than just sit on the couch like I had been doing." Tamara (NWBE): "Just being told that it's okay to feel pain…I think it was finding that it needed to actually be uncomfortable, nobody had ever said that, they just said you need exercises and I'd sort of slightly cheat, I'd sort of do them but not really do them because I didn't know what it was meant to feel like." | William: "I think fear is quite a big thing in that group, particularly because we're asking them to do functional things like stairs and people are quite scared of pain…I think that the study forced me to push people through more pain than, perhaps, I would have previously, and I've learnt positively from that." Mary: "A lot of the patients I had would come in, and they were very fixated on their pain and the effects of the pain on their lifestyle…A lot of them just couldn't get past the pain in the knee…a barrier would definitely be beliefs and attitudes about pain and how much a patient would be prepared to push through a bit of pain." |
| Disliking exercise | Gillian (WBE): "I hate exercise. I have to say, I hate it. I'm one of these people that never go to the gym for exercise." Judith (WBE): "I'm a person if I start the gym, I go swimming and I do it a few times and I stop. I'm lazy, whatever." Robyn (WBE): "I mean, I'm a bit lazy, I don't really like exercise." | William: "These are also people that don't particularly like exercise. It hasn't been important to them, and they're fatigued, and they've got a low work capacity. They're not particularly fit, and exercise is something they don't always view positively." |
| Mental effort of WBE program | | Mary: "The [WBE] group would find those exercises more of a mental – mentally tiring. Focusing, concentrating, than actually getting an actual muscular exertion sense…for them it was not about the load on their muscles necessarily, it was about how much cognitive effort it was. Mental effort, for them to do the right alignment." Aiden: "The NWBE protocol was a lot easier for [patients] to follow [than the WBE]…just because it was less technical." |
| Underestimating capability | Judith (WBE): "[The physical therapist] had, I think, more faith in what I could achieve than what I did first and it was right. I could achieve it because I continued on and trusted him." Ron (NWBE): "I would say that this is a bloody hard exercise and he'd say, 'Well, just get on with it' sort of – I didn't resent what was going on, it was some parts were difficult." Linda (NWBE): "The physiotherapist challenged me to up the weight, like rather than just keep the same weight on all the time and do more repetitions it was, actually put greater weight on." | Alex: "[In private practice] we can tend to fall into a bit of a trap of maybe not pushing people…how much some of the participants could do probably surprised me – with both of the treatment protocols [we] were able to do some pretty tricky exercises and there wasn't an increase in their symptoms…initially I was anticipating that a lot of these people – being overweight and OA changes, they may not be able to handle a huge amount of exercise. But, as I said, I was pleasantly surprised with that." Aiden: "It was interesting to see that you could challenge particularly with the weighted work, that most of the knees tolerated a lot heavier loads that probably clinically in the past I probably would've put on people, in the physiotherapy setting." |

(Continued)

**Table 5.** (*Cont'd*)

| | Patients | Physical therapists |
|---|---|---|
| Theme 2: Physical challenges | | |
| Complexity of WBE program | Jane (WBE): "The only exercise I wasn't keen on was – because I could never balance myself very well – the step-up…I always felt that that particular exercise, for me, I probably never really did it correctly." Judith (WBE): "I couldn't do all of the step-downs, because of physical limitation with that, but I certainly tried to do most of them and with the physio, we varied them as much as I could so that I could, you know, get as much out of it as I could with my physical limitations." | Aiden: "The [WBE] protocol has a little bit more finesse and does require a person to have a little bit more, I don't know, body awareness to get it right…the NWBE one was easier to do just because it was less technical." Neil: "It's obviously really specific about technique with those [WBE] exercises…especially obviously these people are overweight so they haven't done a great deal of exercise or anything along those lines prior to this… [NWBE] was a lot easier to get because it's less reliant on technique, so it was a lot easier to get the patients to actually have an understanding of what they needed to." |
| Cuff weights problematic in NWBE program | Chris (NWBE): "The way that I had to attach the weights to my leg, it was just about impossible to do it by myself…if they were a lot easier to use I probably would've kept them up a bit more than what I did, but it was just very awkward." Henry (NWBE): "It's pretty difficult to manoeuvre when it's not properly strapped in around your ankle…that was probably the hardest part on me, was preparation…It was the reconfiguration of the equipment that weighed on my mind before I said, 'Oh, gee, I've got to go do that again. I'm going to blow about an hour'." | Mary: "The cuff weights were awkward – difficult to put on for patients, and me, at times. I found them awkward myself. Quite often, their abdominal bulk – because these are all bigger people – that their abdominal size meant it was hard for them to get down and put those ankle weights on." William: "The cuffs were really cumbersome…they're highly uncomfortable and really bite into their skin – and a lot of participants had trouble putting them on themselves due to poor mobility. They didn't have the hip and spinal flexion to be able to get down to put the cuffs on – and they couldn't climb on the floor because they couldn't get back up again." |
| Straight leg raise difficult in NWBE program | Craig (NWBE): "I liked them all except the straight leg lift; that was the hardest one and still is the hardest one of them all. Very demanding." Roger (NWBE): "The only one I had trouble with was the lightweight with the straight leg, lifting that up. I had a little bit of trouble – it was something to do with my lower back, where your spine goes down and separates towards your buttock." | Bob: "[The difficulty] would 100% be the straight leg raise…That was the one that I found had a lot of issues, whether it was flaring up hip or groin pain, or low back pain. It was also the one that was probably the most challenging to progress throughout the 5 sessions." Mary: "The straight-leg raise was an exercise that some patients did that with no weight the whole way through, because it's very long lever, long loaded exercise. So, for quite a lot of patients, we didn't add any weight at all, just because they would get too sore at the front of their hip or cause back pain…some patients we just didn't do it at all, because they hated it, and they were going to stop the study because of that one exercise." |
| Other health conditions | Annelise (NWBE): "I had a shoulder issue at some point and so I just went and saw about that, and I had bursitis of the hips." Robyn (WBE): "I get depression, so sometimes I just fall into a big hole and can't quite function very well. So, we just got through that." Gillian (WBE): "I was really sick for quite a long time and I ended up with pneumonia." Rod (WBE): "I've actually got quite unwell over the years. So, I ended up being in hospital and off work." | Alex: "There were a couple of people who withdrew from the study just due to other aspects of their life. They had things going a bit pear-shaped in their personal life. Another guy got like cancer and there were some understandable reasons why people withdrew." Simon: "I had a couple of people pull out for medical reasons – one cancer, and one's partner died, and that sort of thing…There was a few medical things where they sort of had to drop things and attend to other things." Mary: "One lady's mum had a stroke, so she went up to Queensland and she had to stay up there…another lady got sick, and she kept getting sick, so she couldn't get in." |
| Theme 3: Overcoming challenges | | |
| Incentives to exercise | Craig (NWBE): "Seeing some results early on I think, and then getting keen to do it…that was the main thing, that I got some improvement fairly quickly. Even now, the more I do the better it feels most times." Karen (WBE): "When | William: "To get that buy in and that rapport, it was quite a challenge in those first couple of sessions. But they actually started seeing improvement and their attitude changed and they were easy to work with after that." |

(Continued)

**Table 5.** (*Cont'd*)

| | Patients | Physical therapists |
|---|---|---|
| | I first started, I had to sort of talk myself into it but once I saw results, I was able to keep going very consistently." | |
| Accountability | Chris (NWBE): "If it wasn't for a programme that someone was going to use the results, well, I probably would've thrown the towel…some sort of motivation to do it is the biggest thing, which is probably having ongoing contact with a physio or something, maybe, cracking the whip sort of thing." Tamara (NWBE): "I could do it with someone's support – but as soon as the study ended, I just sort of dribbled off and I stopped doing it – I can't seem to self-motivate without that outside support." Judith (WBE): "I was surprised I was committed to it, but part of it was because I felt like I didn't want to let the program down." | William: "I think we had good rapport. I think I got on quite well. I certainly got some good feedback from a couple of patients…It's not just a clinical interaction. You're treating a person. You're not treating a problem. And I think that helps with compliance too." Mary: "I had a really nice rapport with the vast majority. Yes. There's a couple that probably – I had to work a bit harder with a couple of them to develop rapport, because they came in with – well I suppose negative attitudes – to whether this was going to help them…You have to work hard to win people over sometimes. Harder with some that are very set in their beliefs." |
| Education and reassurance | Karen (WBE): "The knowledge that exercise can help. I had no idea that actually exercise could help like that…that knowledge is the big one that really surprised me." Linda (NWBE): "I think reinforcement of the benefit [is important] because I think they probably have enough information now to say, well, if you do stick to it, if you do it the way you're supposed to do it, the number of times a week you're supposed to do it, you will see an improvement. But you can't if you go at it half-heartedly, then you get a half-hearted result." Alan (WBE): "I think if it was made clear at outset there was benefits, then I would've probably stuck to it or tried hard to stick to the programme more…I could see it helping but I think a statement at the start would've been helpful." | Bob: "Definitely some form of pain education or lots of reassurance. It was a bit tricky for people to exercise comfortably or out of apprehension – I think a lot of people were quite reluctant to go further into that exertion level. So you would need some form of guidance, reassurance." William: "If they could see why they were doing it, I think that helped the buy in as well…I said these exercises are purely trying to make you put a bit of weight through that leg and educating that it's okay and it's safe to do so…they definitely need to be encouraged and feel like that they can achieve the exercise." Simon: "I think once they got their head around the idea that if they push themselves it's going to help them and they expected a bit of pain – then they were fine. I found the people that were quite pain avoiders, they were the hard ones to get going. But that's just understanding those concepts of what pain is and that sort of stuff." |
| Tailoring the exercise program | | Mary: "The stiff knees tended to cope better and do better and feel better with the [NWBE group]. And the looser knees, more mobile knees, tended to do better with the [WBE] exercises…You've just got to find what's going to work for the patient." Aiden: "Overall, I think, if you have the right patients, the WBE one is fine and the [NWBE] one might be the person learning the exercises and there isn't that heavy grinding or clunking feeling when they loaded." |

* OA = osteoarthritis.

*Accountability.* A significant motivator for patients was the feeling of accountability to their physical therapist and to the study itself. Many did not want to let the study down by being nonadherent. Patients valued the encouragement that they received from their physical therapist, feeling as though they could do it with someone's support, but stopped exercising once their consultations with the therapist ended. Physical therapists commented on their strong therapeutic relationship with their patients.

*Education and reassurance.* Patients and physical therapists discussed the importance of pain education and reassurance about the safety and benefits of exercise, particularly at the beginning of the intervention. Physical therapists found that educating patients at the start of the trial helped address misconceptions about OA and that it was also important to provide a rationale for each exercise prescribed.

*Tailoring the exercise program.* Physical therapists believed tailoring the exercise programs to the individual patient would overcome some challenges. Ideally, therapists would have preferred to use a combination of exercises from both programs (rather than each program in isolation) based on individual patient presentation and physical capability. For example, some exercises in the WBE program were perceived to be better suited to

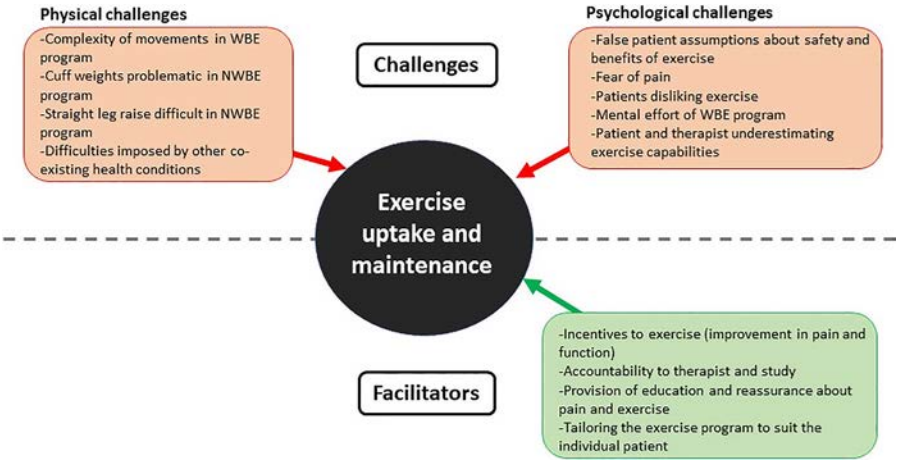


**Figure 1.** Challenges of strengthening exercises for individuals with knee osteoarthritis and comorbid obesity and strategies for overcoming them (facilitators). NWBE = non–weight-bearing strengthening exercise group; WBE = weight-bearing exercise group.

patients who were well coordinated and had better awareness of how their body moved, while exercises in the NWBE program were perceived to be better suited to patients who were just learning how to exercise and move their body.

## DISCUSSION

The aim of this study was to explore the challenges associated with implementing a home-based strengthening exercise program for individuals with knee OA and comorbid obesity. We found that patients and physical therapists experienced numerous psychological and physical challenges to exercise, including a fear of pain, having false assumptions about strengthening exercises, difficulties with exercise performance, application of cuff weights, and adverse impacts of other health conditions. Resisted straight leg raises were particularly problematic for this patient group.

To our knowledge, no previous studies have explored the challenges associated with strengthening exercise in the specific subgroup of individuals with knee OA and comorbid obesity. However, research about barriers to exercise (including strengthening, aerobic, and flexibility exercise) among broader samples of OA patients who were not specifically obese identified many barriers, including uncertainty about the benefits of exercise, beliefs about pain and limitations, lack of support, and lack of time and/or enjoyment with exercising are all challenges experienced (17). Facilitators included education about OA, feeling accountable to a research study, and improved pain with exercise participation. These broadly reflect our findings, suggesting that many challenges faced by individuals with knee OA and comorbid obesity are similar to those experienced by the broader population of individuals with knee OA. Challenges that were unique to our subgroup with comorbid obesity included strengthening exercises that required complex and coordinated body and lower extremity movements and application of exercise equipment (particularly cuff weights). This may be because obesity is associated with poorer physical function (including joint range of motion, balance, and coordination) (38,39), which, combined with their greater abdominal girth, means that many may experience greater difficulty performing complex technical exercises and may have more difficulty using exercise equipment that requires a greater range of motion to use or put on.

In individuals with obesity (not necessarily with OA), barriers to exercise include having other health issues, excess body fat, the perception of being too overweight, being self-consciousness, low mood, lack of enjoyment and motivation, and lack of knowledge (40). Compared to people of healthy weight, those with obesity are less likely to enjoy exercise (41), believe that they have a different physical response to exercise (e.g., lower tolerance for pain, increased symptoms of exertion such as a high heart rate or breathlessness, and safety concerns) (42), and feel more insecure and uncomfortable exercising (43), which contribute to fear and exercise avoidance. Collectively, these barriers broadly reflect our findings, where our patients tended to view themselves as being "lazy" non-exercisers and underestimated their physical capability for exercise, potentially indicating poor self-efficacy for exercise, which has previously been linked to participation in strengthening exercise (44). As our sample had chronic knee pain due to underlying OA, fear of aggravating knee pain was also a major challenge, often resulting in exercise avoidance. Interestingly, none of the patients we interviewed described feeling self-conscious about their weight nor specifically mentioned their weight as a barrier to strengthening exercises. It is not clear why this was, but given that patients had volunteered to participate in the RCT and also in the qualitative interview, they may have been more comfortable with their weight than others. Having other health conditions was identified as a barrier to exercise participation in our cohort, and further research is required to

explore this barrier in greater depth to better understand how it may affect adherence or motivation and how this particular barrier could be overcome.

Despite previous research showing that physical therapists may demonstrate weight stigma in clinical practice, we found little evidence of this among our cohort of physical therapists and patients. Other research in Australian physical therapy settings found that, when treating patients who are overweight or obese, therapists make assumptions about laziness or ill health (21) and perceive such patients as being difficult to treat (22). Similarly, other research showed that people with obesity tend to have less trust in their therapist and feel that they are being judged (23). In contrast, our patients felt comfortable with their physical therapist during consultations and trusted their therapists' advice. Our therapists felt that they had a good rapport with their patients and felt that, once rapport had been developed, they had good "buy-in" from their patients. Given the qualitative nature of our study with a small sample, this finding may be unique to our cohort of participants and may not necessarily reflect the perceptions of other people with OA who are obese, or other physical therapists, and thus further research may be necessary to explore weight stigma in this population.

Research has suggested that individuals with OA and comorbid obesity have reduced exercise tolerance due to higher baseline levels of pain and joint inflammation (5,45). As such, it has been recommended that strengthening exercise programs for this subgroup of patients be modified so as to reduce load on joints and reduce pain for patients (46,47), such as focusing on movements within nonpainful ranges of motion (46). Physical therapists can be reluctant to encourage patients to continue exercising with pain for fear of aggravating symptoms (48), a concern expressed by our cohort of therapists. However, we found that patients valued being challenged and pushed by their physical therapists to progress their strengthening exercise program. Similarly, physical therapists found that their experience in the RCT taught them that their patients could tolerate a lot more than they expected. A recent systematic review in chronic musculoskeletal pain found that painful exercise protocols (focusing on loading and resistance, where exercise was either purposely painful, or where pain was allowed or tolerated) lead to significantly greater improvements in pain compared to pain-free exercise protocols, at least in the short term (49). This, and our findings, suggest that therapists should not be afraid to challenge patients with knee OA and comorbid obesity when prescribing strengthening exercise. However, further research is required to determine the optimal exercise load to improve clinical symptoms of OA in this patient subgroup.

Our findings have a number of clinical implications relating to behavioral strategies for clinicians who prescribe strengthening exercises for individuals with knee OA and comorbid obesity. Findings suggest that clinicians may have a tendency not to push these patients hard enough and could challenge patients more (e.g., in the difficulty of exercises, the amount of resistance applied, or the dosage prescribed) in order to maximize the likelihood for clinical benefit. Verbal education before prescribing strengthening exercise may positively impact patient beliefs and expectations about consequences of exercise participation (including countering misconceptions that knee pain during exercise is dangerous), which may ultimately influence patient adherence to exercise, including reassurance that some knee pain with exercise is not dangerous, and that exercise is both safe and effective for people with knee OA and excess body weight. Recommendations for self-management of exercise-related pain is also important (50).

From a practical prescription perspective, our findings showed that a straight leg raise for quadriceps strengthening is particularly problematic for this patient group, even more so with increasing resistance applied. This exercise likely explains the higher rate of adverse events we observed in the NWBE group in the RCT (20). This patient subgroup also found it difficult to attach cuff weights to their leg for the NWBE program, suggesting that lower extremity cuff weights may be inappropriate. Clinicians should consider using alternative exercise equipment, such as resistance bands, or combine NWB exercises with WB exercises to utilize body weight for resistance. The complexity of the WBE program was also a barrier to participation, with physical therapists believing this program was more suited to patients who had good coordination and body awareness. This is supported by our physical therapists who found that the WBE and NWBE programs suited different participants and should be tailored and combined in a single program suited to individual capabilities.

From an implementation perspective, our findings highlight the importance of patient accountability via regular follow-up with the physical therapist, suggesting that increased follow-up, including booster sessions (51), over the longer term may be important. Therapists could also consider digital technology to promote a sense of accountability, such as the use of exercise apps and monitoring systems (52). Patient incentives to exercise were also important, particularly noticing improvements in symptoms. This suggests that physical therapists should consider including outcome-based measures (e.g., performance-based tests) to demonstrate improvement in pain or function over the course of treatment, which may improve patient motivation and adherence. Further research is required to investigate the challenges and solutions to long-term adherence to strengthening exercise in this population, as many of our patients had stopped exercising at the end of the 12-week RCT.

Strengths of our study include the broad sample of patients interviewed (e.g., male and female participants, employed and not employed, with varying levels of exercise adherence) and the fact that all trial therapists were interviewed. Another strength is the evaluation of a clearly described intervention and strengthening exercise protocol (29) that can be implemented and modified outside the research setting. Our study also had limitations. It

was nested in an RCT, and our sample was therefore constrained to the 7 therapists who delivered the intervention. Both patients and physical therapists volunteered to participate in the RCT and the qualitative study, and thus, perceptions may be biased, and experiences may not be transferable more broadly. We did not purposively sample for pain severity or for exercise experience, thus our sample may not have necessarily included a range of people with varying pain levels at baseline or those with a range of prior exercise experience. Finally, our patients and physical therapists were all based in Melbourne, Australia, and spoke English, so our findings may not be transferable to other populations of people in remote or rural areas or in other countries.

In conclusion, this study aimed to explore challenges associated with implementing a home-based strengthening exercise program for individuals with knee osteoarthritis and comorbid obesity. We found that patients and physical therapists experienced numerous psychological and physical challenges to exercise, including a fear of pain, having false assumptions about exercise, difficulties with exercise performance, application of cuff weights, and adverse impacts of other health conditions.

## 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 submitted for publication. Dr. Lawford 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.** Lawford, Bennell, Hinman.
**Acquisition of data.** Lawford, Schwartz.
**Analysis and interpretation of data.** Lawford, Allison, Hinman.

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# Quality Improvement Intervention to Reduce Thirty-Day Hospital Readmission Rates Among Patients With Systemic Lupus Erythematosus

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**Objective.** Systemic lupus erythematosus (SLE) has one of the highest 30-day hospital readmission rates among chronic diseases in the US. This quality improvement initiative developed and assessed the feasibility of a multidisciplinary postdischarge intervention to reduce 30-day readmission rates among SLE patients.

**Methods.** A retrospective study was performed using electronic health records of patients with SLE admitted to a university hospital prior to (nonintervention group) and after initiation of the study intervention (intervention group). The study population included patients with a diagnosis of SLE who were admitted to the hospital for any reason during an 8-month time period. The intervention involved sending a templated message at the time of discharge to the rheumatology clinic nurses, which prompted the nurses to call the patient to coordinate future visits and provide education. The primary outcome was the 30-day hospital readmission rate. Data were analyzed using a multivariate mixed binomial regression model.

**Results.** There were 59 hospitalizations in the nonintervention group and 73 hospitalizations in the intervention group during the 8-month study period. The 30-day readmission rate was 29% in the nonintervention group and 19% in the intervention group. The difference in readmission rates between the 2 groups was not statistically significant based on the multivariate model.

**Conclusion.** Our study demonstrates the feasibility of implementing a multidisciplinary postdischarge intervention to reduce readmission rates for patients with SLE in a large academic medical center. Further investigation is warranted to determine if this approach reduces the unacceptably high hospital readmission rates among SLE patients.

## INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic immune-mediated disease that often requires inpatient hospitalization. It is estimated that 20–25% of individuals with SLE are hospitalized each year, accounting for >140,000 hospitalizations annually in the US (1). Most of these hospitalizations have been found to be related to SLE disease activity, infection, thromboembolic disease, or an associated comorbidity (2,3). SLE hospitalizations are often serious and require considerable resources (4).

SLE has one of the highest 30-day hospital readmission rates among chronic diseases in the US, with 30-day readmission rates of 16.5–36% reported in the literature (3,5,6). The Agency for Healthcare Research and Quality published a report in 2010 based on data that included 14 million hospital discharges and found that SLE had the sixth highest 30-day readmission rate at 27.2%. This was higher than the readmission rate for other common chronic diseases such as congestive heart failure, chronic obstructive pulmonary disease, and diabetes mellitus (7). This represents a significant economic burden, with one study estimating the average cost of an SLE readmission at $14,409 in 2017 (4).

Prior studies on this topic have focused on identifying risk factors associated with primary hospitalization and readmission in SLE patients. One study utilized administrative data on 55,936 hospitalizations nationwide and found that 16.5% were readmitted within 30 days. Unlike many other chronic diseases, age was found to be inversely related to the risk of readmission. Readmitted SLE patients were more likely to be young, ethnically/racially diverse, have a public payor form of insurance, have multiorgan involvement secondary to SLE, and have other comorbid medical conditions (3,5). This is consistent with the large body of

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**SIGNIFICANCE & INNOVATIONS**

- It is feasible to implement a simple and low-cost postdischarge intervention to reduce 30-day hospital readmission rates among patients with systemic lupus erythematosus.
- While traditional discharge interventions focus on resources within the hospital, we utilized clinic-based resources to improve the inpatient to outpatient transition.

literature on disparities in SLE care, which reports worse outcomes in patients of ethnic and racial minorities, low socioeconomic status, and younger age (8–10).

There have been few studies focusing on interventions to reduce readmission rates among patients with SLE. Xie et al (11) published a single-center study performed at a university hospital in China examining the effects of a transitional-care model on readmission rates among SLE patients. The transitional-care model was a 12-week intervention performed by 2 nurses and included 4 in-person assessments as well as 4 telephone follow-up visits. During these follow-up assessments, a standardized list of 23 SLE-related health problems was addressed. Patients in the study were randomized to receive either the transitional-care model or usual care after hospital discharge. Compared with the usual-care group, the 30-day readmission rate for the transitional-care group was significantly lower (21.3% versus 4.7%, respectively; $P = 0.005$). The intervention group also had significantly greater improvement in their self-care score and quality of life score. The study did not report the time or cost involved in the intervention (11).

Multiple types of interventions have been implemented in other chronic diseases, such as chronic heart failure, to reduce hospital admissions. These are generally categorized as predischarge interventions (i.e., medication reconciliation and patient education), postdischarge interventions (i.e., follow-up phone call and home visits), and bridging interventions (i.e., transition coaches and inpatient and outpatient clinician continuity). A 2011 systematic review of 43 studies investigating interventions to reduce readmissions found that no single intervention alone was associated with a lower 30-day readmission risk. Generally, the more comprehensive, multifaceted interventions had greater success (12).

The aim of our quality improvement study was to reduce 30-day readmission rates among SLE patients by implementing a low-cost, multidisciplinary postdischarge intervention that utilizes a standardized communication template and a patient outreach telephone call. Specifically, our aim was to reduce the 30-day readmission rate among SLE patients at the University of Colorado Hospital from 29% to <20% over an 8-month time period.

## PATIENTS AND METHODS

**Data source and population.** Data were collected by abstracting information from the electronic medical record (EMR) (Epic) of the University of Colorado Hospital. We collected data over an 8-month period prior to our intervention (November 2017 through June 2018). The postintervention data consisted of hospital admissions over an 8-month period from November 2018 through June 2019. Patients were included if they were admitted to the hospital during this time, had a diagnosis of SLE on their problem list, and had a rheumatology consult ordered during their admission. Since our primary focus was hospital readmissions, patients were excluded if they died during the initial hospitalization. Patients were also excluded if post-hospitalization follow-up was arranged with a rheumatologist outside the University of Colorado system.

Our data analyst obtained these data by first searching the EMR for inpatient notes generated by the rheumatology service and then searching the inpatient encounters for a diagnosis name that included systemic lupus erythematosus in the list of diagnoses. We were then able to search for time to readmission, demographic characteristics, type of insurance, principal hospital diagnosis, and length of stay. All of the charts identified were manually reviewed by a rheumatology fellow to ensure that the diagnosis of SLE was confirmed by a board-certified rheumatologist.

**Intervention.** A postdischarge intervention was designed that involved the participation of a multidisciplinary team including the rheumatology fellows, faculty physicians, and the clinic registered nurses (RNs). We created a message template in the EMR that included information about medication changes made during the hospitalization, future infusions, future laboratory tests, and follow-up appointments (Figure 1). The fellows, faculty, and staff received an email with training on how to implement the intervention as well as reminder emails each month when a new fellow started on the consult service. The intervention was applied to patients who were admitted to the hospital, carried a diagnosis of SLE, and on whom the rheumatology inpatient service was consulted. The EMR message was sent by the rheumatology fellow to the clinic RNs when the patient was discharged from the hospital. The nurses then contacted the patient by telephone within 48 hours of hospital discharge to review the information and answer any questions. The nurses created a telephone encounter in the EMR with documentation of the phone conversation and the information reviewed. If a concern arose during the patient phone call that required physician advice, the nurses would consult with the on-call rheumatology fellow. The quality improvement team met quarterly with the clinic nurses to perform feedback and teaching on the intervention.

**Measures.** The primary outcome measure was all-cause readmission to the University of Colorado Hospital within 30 days of initial hospital discharge. We analyzed demographic characteristics including age, sex, race, and primary insurance. We also

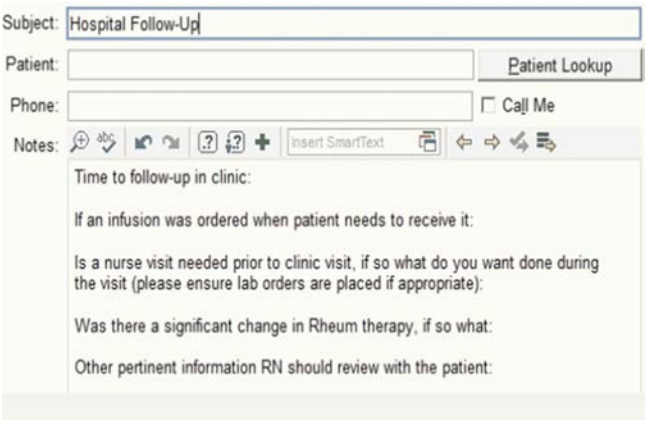


**Figure 1.** Postdischarge message template in the electronic medical record.

collected qualitative data on the information addressed and problems identified by the nurses during the outreach calls.

**Statistical analysis.** Data analysis consisted of a multivariate mixed binomial regression model. For this model, the outcome was readmission within 30 days, with predictor variables of intervention group assignment, sex, age, race, and insurance type. A mixed model was used to account for several instances where a patient had multiple encounters and to account for within-patient similarity. Data analyses were performed using SAS, version 9.4, and a significance threshold of 0.05 was used for all analyses.

## RESULTS

In the nonintervention cohort, there were 59 hospitalizations among 48 individuals with SLE who met the inclusion and exclusion criteria. Readmissions within 30 days occurred following 17 (29%) hospitalizations among 11 patients during this time period. In the intervention cohort, there were 73 hospitalizations among 56 individuals with SLE who met the inclusion and exclusion criteria. Readmissions within 30 days occurred following 14 (19%) hospitalizations among 10 patients. Demographic characteristics of the nonintervention and intervention cohorts are summarized in Table 1. Both groups had similar demographic characteristics, with the majority being female, non-White, and an average age of ~40 years.

Patient demographics for individuals readmitted within 30 days of primary hospitalization (17 in the nonintervention cohort, and 14 in the intervention cohort) were similar to the overall primary hospitalization group: predominantly female (85%), non-White (60%), with largely governmental forms of insurance (80%) and an average age of 40 years. The reasons for readmission in both groups are listed in Table 2. In the nonintervention group, the reason for readmission was SLE related in 53% of cases, followed by admissions for other medical issues (41%) and infection (6%). In the intervention group, 42% of patients were readmitted for infection, 29% for SLE-related causes, and 29% for other medical issues.

The odds of 30-day readmission according to the primary multivariate mixed binomial regression model are shown in Table 3. There was an 89% higher odds of readmission in the nonintervention group compared to the intervention group (odds ratio 1.89, $P = 0.128$), although this result was not statistically significant using a $P$ value cutoff of 0.05. The other variables examined (sex, age, race, and insurance type) were not statistically significant.

The nurses who performed the telephone calls recorded qualitative data obtained during the phone call. These data were not collected in a systematic fashion for every patient; hence, formal analysis was not possible, but a summary of the issues can be reviewed in Table 4.

**Table 1.** Demographic characteristics of the nonintervention and intervention groups*

| Characteristic | Overall population (n = 104) | Nonintervention group (n = 48) | Intervention group (n = 56) | *P* |
|---|---|---|---|---|
| Age, mean ± SD years | 41.45 ± 13.86 | 43.9 ± 13.76 | 39.36 ± 13.73 | 0.096 |
| Sex | | | | 0.3 |
| Female | 88 (84.6) | 43 (89.5) | 45 (80.4) | |
| Male | 16 (15.4) | 5 (10.4) | 11 (19.6) | |
| Race | | | | 0.97 |
| Black or African American | 26 (25) | 13 (27.1) | 13 (23.2) | |
| Self-identified Hispanic, regardless of race, no. (%) | 28 (26.9) | 13 (27.1) | 15 (26.8) | |
| Other | 7 (6.7) | 3 (6.3) | 4 (7.1) | |
| White | 43 (41.4) | 19 (39.5) | 24 (42.9) | |
| Insurance type | | | | 0.37 |
| Medicare or Medicaid | 63 (60.6) | 26 (54.1) | 37 (66.1) | |
| Private | 38 (36.5) | 20 (41.6) | 18 (32.1) | |
| Unknown | 3 (2.9) | 2 (4.2) | 1 (1.8) | |

* Values are the number (%) unless indicated otherwise. Demographic variables were compared between groups using a *t*-test for age and a chi-square test for sex, race, and primary insurance type.

**Table 2.** Reasons for 30-day readmission in the nonintervention and intervention groups*

| Reason for readmission | Nonintervention group (n = 17) | Intervention group (n = 14) |
|---|---|---|
| SLE related | 9 (53) | 4 (29) |
| Cytopenias | 6 (35) | 1 (7) |
| Lupus nephritis | 2 (12) | 0 |
| Serositis | 1 (6) | 1 (7) |
| Cerebritis | 0 | 1 (7) |
| Severe rash | 0 | 1 (7) |
| Infection | 1 (6)† | 6 (42)‡ |
| Other medical issue | 7 (41)§ | 4 (29)¶ |

* Values are the number (%). SLE = systemic lupus erythematosus.
† Endocarditis.
‡ Infections included urinary tract infection, septic arthritis, community-acquired pneumonia (n = 2), gastroenteritis, and skin and soft tissue infection.
§ Included cerebrovascular accident, gastrointestinal bleed (n = 2), pulmonary embolism, atrial fibrillation, cancer, and gastroparesis.
¶ Included opioid withdrawal, routine pregnancy, chronic heart failure exacerbation, and cancer.

## DISCUSSION

This quality improvement study examined the impact of a standardized communication template and a postdischarge telephone call on 30-day hospital readmission rates among adult patients with SLE. We reviewed 59 hospitalizations of 48 individuals with SLE who met our inclusion and exclusion criteria prior to initiating our intervention and found a 30-day readmission rate of 29%. After implementing our intervention, we collected data over the same 8-month time period of the following year to assess the results of our intervention. Our postintervention data included 73 hospitalizations of 56 individuals with SLE who were found to have a 30-day readmission rate of 19%. The results showed a trend toward a decrease in 30-day readmission rates in the intervention period. Although the results were not statistically significant, this intervention has the potential to result in significant cost savings and reduction in patient morbidity. Formal cost analysis was not carried out during this cycle of our quality improvement initiative, but we believe the cost of a 30-minute educational intervention (cost of nursing time) could lead to significant savings by reducing emergency room visits or hospital admissions. Given the low cost of our intervention, only a small number of emergency room or hospital admissions would need to be avoided to demonstrate cost-effectiveness. We intend to investigate this aspect further in future quality improvement cycles.

While there are prior studies describing the problem of high readmission rates among SLE patients and risk factors for readmission, this is one of the first studies to look at an intervention to reduce the number of hospital readmissions. The study by Xie et al (11) assessed a transitional-care intervention to improve readmission rates among SLE patients. This study found a significant reduction in readmissions of patients with SLE who received the transitional-care model. The authors did not conduct a cost analysis of their study. While there was likely overall cost savings with reduced hospital readmissions, the transitional-care model described in that study is a time and cost-intensive intervention. The model described by Xie et al (11) entails 4 in-person assessments and 4 phone calls per hospital discharge. In contrast, our model requires completion of a standardized template in the EMR and a single telephone call, and hence, may represent a more feasible intervention for clinics with limited resources.

Telephone outreach is an excellent method of providing additional support to patients, assessing clinical needs, reinforcing education about SLE, medications, and common complications such as drug side effects and infections, and allows for patients to ask pertinent questions to RN providers with expertise in the management of lupus. Our nurses identified several intervenable issues during the telephone encounters, including medication mistakes, concerns for infection, and logistical issues with infusions (Table 4). Telephone outreach also poses some challenges due to potential difficulty reaching the patient by phone and inability to physically examine the patient if they are reporting symptoms. Despite these challenges, telephone follow-up interventions have been shown to be successful at reducing hospital readmissions in other conditions such as congestive heart failure (13,14).

Our study has several limitations. First, our data are limited to a single, university-based hospital system. Therefore, the results may not be generalizable and should be reproduced with a larger study population and in additional health care settings. Second, our data were obtained over 2 separate years for the nonintervention and intervention group, so temporal changes in readmission could have influenced the readmission rates. Our study is based on limited data from the EMR at our hospital. These data do not capture readmissions to other hospitals, which could result in a falsely low readmission rate in our study. However, this would presumably affect the readmission rate of both the nonintervention and intervention groups equally. Finally, limited clinical information was obtained, and therefore, certain variables such as SLE disease activity measurements could not be assessed.

This study is timely and relevant given the increased attention to readmission rates over the past decade as a way to address cost and quality of care. The feasibility of the intervention make this an

**Table 3.** Odds of 30-day readmission using a multivariable mixed binomial regression model*

| Variable | Odds ratio | 95% CI | *P* |
|---|---|---|---|
| Group (pre vs. post) | 1.89 | 0.83–4.30 | 0.128 |
| Sex (male vs. female) | 1.64 | 0.58–4.62 | 0.346 |
| Age at admission | 0.98 | 0.95–1.01 | 0.192 |
| Race (White vs. all other races) | 0.99 | 0.46–2.17 | 0.987 |
| Insurance type (private vs. public) | 1.72 | 0.74–3.99 | 0.209 |

* 95% CI = 95% confidence interval.

**Table 4.** Critical information obtained during patient outreach calls and subsequent nurse interventions*

| Issues identified | Example | RN intervention |
|---|---|---|
| Incorrect amount of medication | Not enough prednisone tablets dispensed at discharge to complete taper | RN adjusted the orders and sent to the pharmacy |
| Patient misunderstanding of medication instructions | Patient took methotrexate daily rather than weekly; another patient took 8 tablets of dapsone daily instead of prednisone | RN instructed patient to come in for laboratory tests and education; contacted on-call physician |
| Medication sent to the wrong pharmacy, not in stock, or patient did not pick up at pharmacy | | RN sent to the correct pharmacy |
| Concern for infection | | RN asked about any concerning symptoms and encouraged the patient to seek care with PCP or urgent care |
| Patient needs infusion arranged | | RN coordinated infusion |
| Patient did not get follow-up laboratory tests due to misunderstanding of instructions | No cyclophosphamide nadir laboratory tests | RN provided education and reminder of laboratory tests |

* PCP = primary care provider; RN = registered nurse.

impactful study that should spark further research on this topic. Future directions may include examination of other risk factors that were not looked at in this study, such as geographic location, which may serve to identify the patients at highest risk for early readmission. To increase implementation of the intervention, we have discussed creating a discharge order set, which would include an automatic EMR message to the nurses. Additionally, future studies should explore alternative ways of communicating with our patients after discharge, such as the use of text messaging, messaging through the patient portal in the EMR, or telehealth. We also plan to include a cost analysis of the intervention in the future.

In conclusion, this is one of the first studies to describe a feasible and low-cost intervention to improve the unacceptably high hospital readmission rates among SLE patients. Future research in this area is needed to optimize the quality of care delivered, reduce cost, and improve health outcomes in this vulnerable population.

## 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 submitted for publication. Dr. Weinstein 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.** Bowers, Griffith, Kolfenbach, Pearson, Weinstein.

**Acquisition of data.** Bowers, Griffith, Weinstein.

**Analysis and interpretation of data.** Bowers, Griffith, Kolfenbach, Pearson, Hammes, Weinstein.

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# Identification of Distinct Disease Activity Trajectories in Methotrexate-Naive Patients With Rheumatoid Arthritis Receiving Tofacitinib Over Twenty-Four Months

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**Objective.** Tofacitinib is an oral JAK inhibitor for the treatment of rheumatoid arthritis (RA). To better understand tofacitinib treatment responses, we used group-based trajectory modeling to investigate distinct disease activity trajectories and associated baseline variables in patients with active RA.

**Methods.** This post hoc analysis used data from a phase III study of methotrexate-naive patients receiving tofacitinib 5 mg twice daily. Changes in the 4-variable Disease Activity Score in 28 joints, using the erythrocyte sedimentation rate (DAS28-ESR) from baseline to month 24 were used in group-based trajectory modeling to identify distinct disease activity trajectories. Patient and disease characteristics, changes in radiographic progression and patient-reported outcomes, and safety up to month 24 were compared among trajectory groups.

**Results.** From 346 methotrexate-naive patients, 5 disease trajectory groups, defined by DAS28-ESR scores, were identified, which progressed from high disease activity (HDA) to remission (group 1, n = 28), to low disease activity (LDA) rapidly (group 2, n = 107), to moderate disease activity (group 3, n = 98), to LDA gradually (group 4, n = 46), or remained in HDA (group 5, n = 67), at month 24. At baseline, groups 1 and 2 generally had lower disease activity and more favorable patient-reported outcomes, compared with other groups. Improvements in radiographic progression and patient-reported outcomes over 24 months were generally consistent with DAS28-ESR–predicted disease activity trajectories. Adverse event rates were generally comparable across groups.

**Conclusion.** Distinct phenotypic subgroups identified heterogeneity in patients with RA normally analyzed as a single population. Trajectory modeling may enable separation of clinically meaningful subsets of patients with RA, and may help optimize treatment outcomes.

## INTRODUCTION

Patients with rheumatoid arthritis (RA) exhibit wide variations in disease characteristics, sociodemographic factors, treatment adherence, and health status, which can affect response to treatment (1). Group-based trajectory modeling is one method to identify groups of patients according to their predicted response to treatment over time, which may be influenced by baseline

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**SIGNIFICANCE & INNOVATIONS**

- This group-based trajectory modeling analysis evaluated 346 methotrexate-naive patients in a phase III study. Five disease trajectory groups were identified in patients using the 4-variable Disease Activity Score in 28 joints, using the erythrocyte sedimentation rate. The groups comprised those who progressed from high disease activity (HDA) to remission, low disease activity (LDA) rapidly, moderate disease activity, LDA gradually, or remained in HDA, at month 24.
- Significant differences between trajectory groups in some baseline variables (e.g., sex, disease activity measures, and patient-reported outcomes) were observed.
- Improvements in patient-reported outcomes across trajectory groups over time were generally consistent with improvements in disease activity predicted by group-based trajectory modeling.
- These data demonstrate heterogeneity in patients who are normally analyzed as a single population; further exploration may help to better understand suboptimal treatment responses in rheumatoid arthritis.

characteristics (2–6). Understanding patient characteristics associated with distinct disease activity trajectories may make predicting responses to specific treatments possible at an early stage (2,3).

Tofacitinib is an oral JAK inhibitor for the treatment of RA. The efficacy and safety of tofacitinib 5 and 10 mg twice daily administered as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), mainly methotrexate (MTX), in patients with moderately to severely active RA, have been demonstrated in phase II (7–11), phase III (12–18), and phase IIIb/IV (19) studies of up to 24-months duration, and in long-term extension studies with up to 9.5 years of observation (20–22).

The 4-variable Disease Activity Score in 28 joints, using the erythrocyte sedimentation rate (DAS28-ESR) is a commonly used measure of disease activity status (e.g., remission or low/moderate/high disease activity [LDA/MDA/HDA, respectively]) (23,24). Previously, an analysis of data pooled from 3 phase III trials of patients with RA with a prior inadequate response to csDMARDs receiving tofacitinib 5 mg twice daily for up to 12 months identified distinct disease activity trajectories, characterized by baseline differences in DAS28-ESR and patient-reported outcomes (25).

ORAL Start was a 24-month phase III study of tofacitinib 5 and 10 mg twice daily in MTX-naive patients with active RA (18). This post hoc analysis of tofacitinib 5 mg twice daily data from ORAL Start aimed to identify distinct disease activity trajectories in MTX-naive patients with RA receiving tofacitinib, offering a characterization of baseline variables that could be used as early predictors of response.

## PATIENTS AND METHODS

**Study design.** ORAL Start was a 24-month, randomized, double-blind, phase III study completed in 2013 that compared efficacy and safety of tofacitinib 5 and 10 mg twice daily monotherapy with MTX monotherapy in patients with moderately to severely active RA who were MTX-naive or who had not received a therapeutic dose of MTX (18).

Full study details have been published previously (18). Eligible patients were age ≥18 years with a diagnosis of active RA, based on American College of Rheumatology 1987 revised criteria (26–28), had either an ESR of >28 mm/hour or a C-reactive protein level of >7 mg/liter, and had ≥3 distinct joint erosions detected on hand/wrist or foot radiographs, or were anti–cyclic citrullinated peptide or rheumatoid factor positive. At baseline, the duration of RA in patients was 2.7–3.4 years. In total, 6.9% of patients had received a nontherapeutic dose of MTX prior to study baseline; the most common non-MTX csDMARDs received by patients prior to study baseline were sulfasalazine and leflunomide (12.9% and 6.3% of patients, respectively). This post hoc analysis included data for patients receiving tofacitinib 5 mg twice daily who were MTX-naive at baseline.

**Trajectory analysis.** Trajectory groups are understood to be clusters of individuals following similar trajectories of disease response. As with previous analyses (3–5,25), DAS28-ESR scores at baseline and changes in DAS28-ESR over time were used to model predicted trajectories. Disease activity status was defined using DAS28-ESR scores as: HDA >5.1, MDA ≥3.2 to ≤5.1, LDA ≥2.6 to <3.2, and remission <2.6 (23,29).

**Outcomes.** Patient demographics, baseline disease characteristics and patient-reported outcome scores, changes in radiographic progression (total Sharp score, and erosion and joint space narrowing [JSN] scores, assessed at months 6, 12, and 24), patient-reported outcomes over time (assessed at months 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24), and adverse events (AEs) were compared across predicted disease activity trajectory groups.

Patient-reported outcomes included the Health Assessment Questionnaire disability index (HAQ DI) (30), the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) (31), the Short Form 36 health survey (SF-36; mental component summary [MCS] and physical component summary [PCS] scores and domain scores: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) (32,33), and and arthritis pain (visual analog scale [VAS] 0–100 mm) (34,35).

The proportions of patients reporting normative patient-reported outcome scores were also identified and compared; defined for HAQ DI as ≤0.25 (36) or <0.5 (functional remission) (37), and for FACIT-F as ≥40.1 (31), or more recently, ≥43.5 (38). SF-36 MCS and PCS and domain scores were assessed using

age- and sex-matched norms, as per the SF-36 scoring manual (32,33). Improvements in arthritis pain score of ≥30% and ≥50% from baseline were defined as moderate and substantial clinically important improvements, respectively (34,35). Safety end points were reported through month 24, including AEs, discontinuations due to AEs, and all-cause mortality.

**Statistical analysis.** For each disease activity trajectory group, predicted DAS28-ESR values and 95% confidence intervals over time, and the proportion (%) of patients within each group, were modeled. Group-based trajectory modeling (6) was applied to DAS28-ESR data to find distinct longitudinal subgroups of patients with similar disease activity changes through month 24. This is a special case of finite mixture models that seeks to classify patients into trajectories using a maximum-likelihood approach, based on the product of the conditional likelihoods for each individual being in the $j^{th}$ group, multiplied by the probability of membership in the $j^{th}$ group ($j$ = 1, 2, …, $k$, with $k$ being the number of groups specified).

The modeling algorithm only required a baseline value to allow initial assignment to a trajectory group. Each group was modeled by linear regression of DAS28-ESR versus time (months) added as polynomials (months, months$^2$, months$^3$, etc.), and $k$ and the degree of polynomial ($p$) were specified. For all $k$ = 1, 2, 3, 4, 5, and $p$ = 1, 2, 3, 4, 5, models were fit, and the Bayesian information criterion (BIC) of each result was calculated; the best BIC chosen from all possibilities was run. The algorithm jointly modeled all groups, using intercept values (month 0, i.e., baseline) as a start for assigning patients. The algorithm then became iterative: at the end of each linear regression, the posterior probability of a patient belonging to a particular group was calculated and patients were reassigned to the group with the highest probability.

This approach continued until no more increase in likelihood was reached, and the algorithm was then stopped. In cases where linear regression was replaced by a generalized linear model, e.g., Poisson or logistic regression, a censored normal distribution was used, where DAS28-ESR was censored to be on the interval 0–10 (6). Modeling was carried out using observed data, with no imputation for missing values (6).

Pair-wise comparisons of demographics and baseline characteristics were performed among predicted disease activity trajectory groups. Equality of mean values of continuous measures were assessed using $t$-tests, and equality of rates were assessed using chi-square tests. A 2-sided Bonferroni correction for multiple comparisons was applied; consequently, a $P$ value less than or equal to 0.005 indicated statistical significance ($P \leq 0.05$). Missing radiographic data were extrapolated linearly, and patient-reported outcomes were analyzed using a mixed-effects longitudinal model (39), as previously reported (18).

## RESULTS

**Predicted disease activity trajectory groups.** In total, 346 patients with HDA at baseline were included in the analysis. In the trajectory model, the majority of patients (98.8%) had at least 2 values (baseline value plus 1 additional observation post baseline), 84.7% had at least 7 values, and 71.4% had values from each observation. In total, 1.2% of patients in the analysis only had baseline values. In this case, the modeling algorithm placed the patient within the group with the y-intercept closest to the baseline value.

Trajectory modeling found 5 distinct groups of patients with similar predicted disease activity trajectories (Figure 1). Improvement in disease activity (based on DAS28-ESR change) was

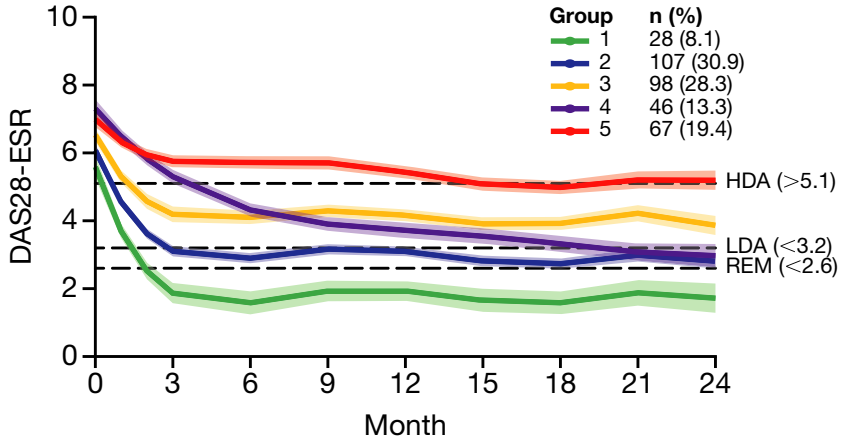


**Figure 1.** Predicted group trajectories based on the 4-variable Disease Activity Score in 28 joints, using the erythrocyte sedimentation rate (DAS28-ESR), with 95% confidence intervals (95% CIs) identified using group-based trajectory modeling in patients with active rheumatoid arthritis who were methotrexate-naive and receiving tofacitinib 5 mg twice daily over 24 months. Solid lines represent predicted values; shading indicates the 95% CI. Percentage reflects the proportion of patients in each group; modeling of trajectory groups was based on changes in DAS28-ESR scores over 24 months: high disease activity (HDA) >5.1, moderate disease activity ≥3.2 to ≤5.1, low disease activity (LDA) <3.2 to ≥2.6, and remission (REM) <2.6 (23).

**Table 1.** Patient demographics and baseline disease characteristics by predicted DAS28-ESR disease activity trajectory groups*

| | Group 1: HDA to remission (n = 28) | Group 2: HDA to LDA rapid (n = 107) | Group 3: HDA to MDA (n = 98) | Group 4: HDA to LDA gradual (n = 46) | Group 5: HDA to HDA (n = 67) |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Female, no. (%) | 11 (39.3)† | 81 (75.7)‡ | 84 (85.7)‡ | 36 (78.3)‡ | 54 (80.6)‡ |
| Age, years | 47.0 ± 16.4 | 52.1 ± 11.3 | 50.4 ± 12.6 | 49.9 ± 10.1 | 48.1 ± 12.6 |
| Body mass index, kg/m$^2$ | 25.2 ± 4.5 | 26.0 ± 4.8 | 27.2 ± 5.6 | 27.0 ± 5.8 | 25.7 ± 6.4 |
| Current smoker, no. (%) | 2 (7.1) | 23 (21.5) | 16 (16.3) | 8 (17.4) | 13 (19.4) |
| Geographic region, no. (%) | | | | | |
| US/Canada | 11 (39.3) | 36 (33.6) | 43 (43.9) | 20 (43.5) | 24 (35.8) |
| Europe | 11 (39.3)§ | 22 (20.6) | 15 (15.3) | 4 (8.7)‡ | 15 (22.4) |
| Latin America | 5 (17.9) | 24 (22.4) | 29 (29.6) | 9 (19.6) | 10 (14.9) |
| Rest of the world | 1 (3.6) | 25 (23.4) | 11 (11.2) | 13 (28.3) | 18 (26.9) |
| Race, no. (%) | | | | | |
| White | 24 (85.7)§ | 71 (66.4) | 64 (65.3) | 23 (50.0)‡ | 38 (56.7) |
| Other | 4 (14.3) | 36 (33.6) | 34 (34.7) | 23 (50.0) | 29 (43.3) |
| Baseline disease characteristics and activity measures | | | | | |
| Rheumatoid arthritis duration, years | 1.2 ± 1.9¶ | 3.2 ± 7.1 | 2.6 ± 4.4 | 2.6 ± 4.9 | 3.7 ± 5.1‡ |
| Day 1 steroid use, no. (%) | 10 (35.7) | 51 (47.7) | 39 (39.8)§ | 30 (65.2)# | 38 (56.7) |
| DAS28-ESR score | 5.7 ± 0.9** | 6.1 ± 0.8** | 6.7 ± 0.8†† | 7.5 ± 0.8‡‡ | 7.1 ± 0.8§§ |
| CDAI score | 31.2 ± 9.0** | 33.7 ± 11.1** | 39.6 ± 11.7†† | 50.6 ± 12.3¶¶ | 43.9 ± 10.5†† |
| ESR score | 33.1 ± 18.1† | 47.9 ± 23.4## | 57.8 ± 26.8‡ | 70.8 ± 30.0§§ | 64.2 ± 32.7§§ |
| CRP | 15.4 ± 16.3 | 20.3 ± 25.9 | 22.2 ± 22.0 | 25.5 ± 31.3 | 27.8 ± 35.4 |
| Patients with CRP score >7 mg/liter, no. (%) | 17 (60.7) | 62 (57.9) | 72 (73.5) | 35 (76.1) | 46 (68.7) |
| Total Sharp score | 5.9 ± 10.6*** | 18.7 ± 33.1‡ | 17.1 ± 41.6 | 16.4 ± 37.2 | 29.1 ± 45.2‡ |
| Erosion score | 3.3 ± 5.1*** | 9.0 ± 16.4‡ | 8.8 ± 23.1 | 8.0 ± 17.7 | 12.3 ± 19.1‡ |
| Joint space narrowing score | 2.6 ± 6.4*** | 9.7 ± 17.7‡ | 8.2 ± 19.6 | 8.4 ± 20.4 | 16.8 ± 27.4‡ |
| Tender joints | | | | | |
| 68 count | 19.3 ± 10.3††† | 21.1 ± 12.7††† | 25.2 ± 11.7§ | 34.9 ± 15.0‡‡ | 30.2 ± 14.3§§ |
| 28 count | 10.7 ± 4.7** | 12.6 ± 6.3** | 15.5 ± 6.2†† | 20.3 ± 6.0‡‡ | 17.8 ± 5.5§§ |
| Swollen joints | | | | | |
| 66 count | 12.8 ± 7.2§ | 13.6 ± 7.0††† | 15.9 ± 9.2§ | 24.5 ± 11.7¶¶ | 17.4 ± 7.9‡‡‡ |
| 28 count | 9.3 ± 3.5††† | 10.2 ± 4.7††† | 11.7 ± 5.6§ | 16.5 ± 6.1¶¶ | 12.5 ± 5.1†† |
| Physician global assessment (VAS 0–100) | 59.1 ± 15.3 | 58.1 ± 16.7††† | 62.3 ± 15.9 | 68.2 ± 13.4§§§ | 66.8 ± 16.5§§§ |
| Anti-CCP positive, no. (%) | 26 (92.9) | 93 (86.9) | 84 (85.7) | 35 (76.1) | 59 (88.1) |
| Rheumatoid factor positive, no. (%) | 23 (82.1) | 91 (85.0) | 78 (79.6) | 38 (82.6) | 56 (83.6) |
| Baseline patient-reported outcomes | | | | | |
| HAQ DI score | 1.2 ± 0.6** | 1.3 ± 0.6** | 1.7 ± 0.6§§ | 1.8 ± 0.7§§ | 1.7 ± 0.6§§ |
| FACIT-F total score | 33.1 ± 10.6††† | 32.5 ± 10.6** | 27.0 ± 9.7§§§ | 22.3 ± 11.3§§ | 25.3 ± 10.8§§ |
| SF-36 MCS score | 47.8 ± 12.0** | 44.8 ± 11.8** | 38.5 ± 10.5§§ | 33.7 ± 12.1§§ | 37.2 ± 11.8§§ |
| SF-36 PCS score | 35.8 ± 6.8¶¶¶ | 34.7 ± 8.1¶¶¶ | 31.5 ± 6.1§§ | 31.9 ± 8.3 | 30.8 ± 6.5§§ |
| Arthritis pain score (VAS 0–100) | 50.0 ± 25.4††† | 49.5 ± 26.0** | 62.3 ± 22.2§§§ | 71.1 ± 20.6§§ | 67.2 ± 18.0§§ |

(Continued)

**Table 1.** *(Cont'd)*

| | Group 1: HDA to remission (n = 28) | Group 2: HDA to LDA rapid (n = 107) | Group 3: HDA to MDA (n = 98) | Group 4: HDA to LDA gradual (n = 46) | Group 5: HDA to HDA (n = 67) |
|---|---|---|---|---|---|
| Patients with arthritis pain score >40, no. (%) | 17 (60.7)††† | 68 (63.6)** | 83 (84.7)§§§ | 43 (93.5)§§ | 63 (94.0)§§ |
| Patient global assessment (VAS 0–100) | 51.1 ± 27.9††† | 50.4 ± 26.8** | 64.4 ± 23.0§§§ | 69.7 ± 21.6§§ | 68.8 ± 18.2§§ |

* Values are the mean ± SD unless indicated otherwise. The number of patients assessed for each characteristic may be lower than the total number. Ranges based on the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR): high disease activity (HDA) >5.1, moderate disease activity (MDA) ≥3.2 to ≤5.1, low disease activity (LDA) <3.2 to ≥2.6, remission <2.6 (ref. 23). A 2-sided Bonferroni correction for multiple comparisons was applied; $P \leq 0.05$ indicated statistical significance. CCP = cyclic citrullinated peptide; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ DI = Health Assessment Questionnaire disability index; MCS = mental component summary; PCS = physical component summary; SF-36 = Short Form 36 health survey; VAS = visual analog scale.
† $P \leq 0.05$ versus group 2. $P \leq 0.05$ versus group 3. $P \leq 0.05$ versus group 4. $P \leq 0.05$ versus group 5.
‡ $P \leq 0.05$ versus group 1.
§ $P \leq 0.05$ versus group 4.
¶ $P \leq 0.05$ versus group 5.
# $P \leq 0.05$ versus group 3.
** $P \leq 0.05$ versus group 3. $P \leq 0.05$ versus group 4. $P \leq 0.05$ versus group 5.
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‡‡ $P \leq 0.05$ versus group 1. $P \leq 0.05$ versus group 2. $P \leq 0.05$ versus group 3.
§§ $P \leq 0.05$ versus group 1. $P \leq 0.05$ versus group 2.
¶¶ $P \leq 0.05$ versus group 1. $P \leq 0.05$ versus group 2. $P \leq 0.05$ versus group 3. $P \leq 0.05$ versus group 5.
## $P \leq 0.05$ versus group 1. $P \leq 0.05$ versus group 4. $P \leq 0.05$ versus group 5.
*** $P \leq 0.05$ versus group 2. $P \leq 0.05$ versus group 5.
††† $P \leq 0.05$ versus group 4. $P \leq 0.05$ versus group 5.
‡‡‡ $P \leq 0.05$ versus group 2. $P \leq 0.05$ versus group 4.
§§§ $P \leq 0.05$ versus group 2.
¶¶¶ $P \leq 0.05$ versus group 3. $P \leq 0.05$ versus group 5.

greatest during the first 3 months of treatment for group 1 (n = 28), group 2 (n = 107), and group 3 (n = 98), which improved from HDA into remission, LDA, and MDA, respectively, by month 3, and remained there through month 24. Group 4 (n = 46) showed continued gradual improvement through months 3–24 to LDA, while group 5 (n = 67) showed minimal improvement, with patients in HDA at baseline and month 24.

**Demographics and baseline characteristics of trajectory groups.** Baseline patient demographic information, disease characteristics, disease activity measures, and patient-reported outcomes by predicted disease activity trajectory group are shown in Table 1. Group 1 had a significantly lower proportion of female patients compared with all other groups. Age, body mass index (BMI), and geographic location were similar across trajectory groups, except group 1, which had a significantly higher proportion of patients from Europe, and patients of White race, compared with group 4. Group 1 also had the shortest duration of RA, which was significantly shorter, compared with group 5.

Groups 1 and 2 had significantly lower mean DAS28-ESR scores at baseline than groups 3–5. Group 4 had the highest mean DAS28-ESR score at baseline. Mean ESR level was significantly lower in group 1, compared with other groups, and mean tender joint count scores in 68 and 28 joints were significantly lower in groups 1 and 2, compared with groups 3 (tender joint count scores in 28 joints only), 4, and 5. Group 1 also had the lowest baseline total Sharp score, and erosion and JSN scores, which were significantly lower than in groups 2 and 5. Differences in baseline patient-reported outcomes among groups were generally consistent with differences seen in clinical measures.

**Changes in radiographic progression.** The total Sharp score increased over time in groups 3 and 5, and change from baseline was highest in group 5 at month 24, followed by group 3. Total Sharp score increased from baseline to month 12 in group 1, and between months 6 and 12 in group 2, with no further increases in total Sharp score in either group from months 12 to 24. There were minimal changes in total Sharp score through month 24 in group 4 (Figure 2A).

In group 5, the erosion score increased from baseline to month 24, while erosion scores in groups 1, 3, and 4 increased from baseline to month 6, with minimal further changes observed from months 6 to 24. In group 2, the erosion score fell from baseline to month 24. At month 24, the highest increase from baseline erosion score was observed in group 5, followed by group 1 (Figure 2B).

JSN scores increased up to month 24 in groups 3 and 5, and from baseline to months 6 and 12 in groups 1 and 2, respectively, with no or minimal subsequent changes to month 24. In group 4, the JSN score fell from baseline to month 12, and this response was maintained to month 24 (Figure 2C).

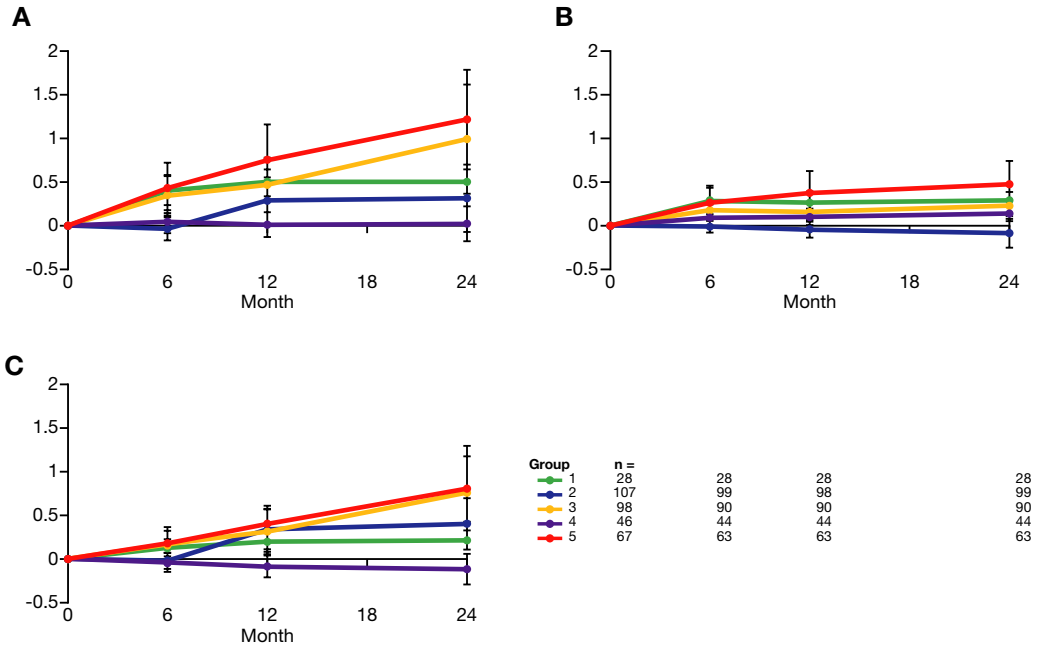


**Figure 2.** Mean change from baseline over time across the disease activity trajectory groups based on the 4-variable Disease Activity Score in 28 joints, using the erythrocyte sedimentation rate (DAS28-ESR). **A**, Total Sharp score, mean (SE); **B**, Erosion score, mean (SE); **C**, Joint space narrowing score, mean (SE). For **A**–**C**, the columns of group numbers in the legend correspond to the 0, 6-month, 12-month, and 24-month time points, respectively. Group 1: high disease activity (HDA) to remission; group 2: HDA to low disease activity (LDA) rapid; group 3: HDA to moderate disease activity (MDA); group 4: HDA to LDA gradual; group 5: HDA to HDA. HDA >5.1, MDA ≥3.2 to ≤5.1, LDA <3.2 to ≥2.6, remission <2.6 (23). Missing radiographic data were extrapolated linearly.

**Changes in patient-reported outcomes.** The mean changes from baseline in HAQ DI, FACIT-F total score, and SF-36 MCS and PCS scores at month 24 are shown in Table 2, and absolute scores from baseline to month 24 are shown in Figure 3. Group 4 had the largest numerical improvement in HAQ DI score at month 24, followed by group 1; improvements in HAQ DI score were similar in groups 2–5. The proportion of patients reporting normative HAQ DI scores was numerically highest in group 1 and lowest in groups 3 and 5 (Table 2). Proportions reporting HAQ DI functional remission were closely aligned with normative HAQ DI scores.

Group 4 had the largest numerical improvement in FACIT-F total score at month 24, followed by group 1. Improvements in

**Table 2.** Mean change in patient-reported outcome scores and proportion of patients reporting scores ≥ normative values at 24 months across DAS28-ESR disease activity trajectory groups*

| Patient-reported outcome | Group 1: HDA to remission (n = 28) | Group 2: HDA to LDA rapid (n = 107) | Group 3: HDA to MDA (n = 98) | Group 4: HDA to LDA gradual (n = 46) | Group 5: HDA to HDA (n = 67) |
|---|---|---|---|---|---|
| HAQ DI score, mean change ± SD | −1.1 ± 0.7 | −0.9 ± 0.8 | −0.8 ± 0.7 | −1.4 ± 0.8 | −0.8 ± 0.7 |
| Scores ≥ normative values (≤0.25) | 21/23 (91.3) | 54/81 (66.7) | 20/67 (29.9) | 19/37 (51.4) | 7/39 (17.9) |
| Functional remission (<0.5) | 21/23 (91.3) | 57/81 (70.4) | 21/67 (31.3) | 24/37 (64.9) | 9/39 (23.1) |
| FACIT-F total score, mean change ± SD | 10.0 ± 11.7 | 7.8 ± 11.3 | 8.6 ± 10.6 | 15.1 ± 12.3 | 8.1 ± 10.3 |
| Scores ≥ normative values (≥40.1) | 18/23 (78.3) | 46/81 (56.8) | 19/67 (38.4) | 13/37 (35.1) | 13/39 (33.3) |
| SF-36 MCS score, mean change ± SD | 3.1 ± 14.5 | 4.5 ± 13.1 | 5.6 ± 12.6 | 11.8 ± 13.0 | 8.0 ± 12.7 |
| Scores ≥ normative values† | 14/23 (60.9) | 46/81 (56.8) | 21/67 (31.3) | 13/37 (35.1) | 13/39 (33.3) |
| SF-36 PCS score, mean change ± SD | 15.2 ± 9.5 | 12.9 ± 9.8 | 10.9 ± 8.9 | 15.7 ± 10.2 | 8.6 ± 9.8 |
| Scores ≥ normative values† | 15/23 (65.2) | 44/81 (54.3) | 15/67 (22.4) | 18/37 (48.6) | 4/39 (10.3) |
| Arthritis pain (VAS 0–100), mean change ± SD | −35.0 ± 23.8 | −29.0 ± 31.5 | −33.1 ± 30.8 | −56.6 ± 24.5 | −32.5 ± 27.5 |

* Values are the number of patients included in the analysis/the number of patients evaluated at month 24 (%), unless indicated otherwise. Ranges are based on the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR): high disease activity (HDA) >5.1, moderate disease activity (MDA) ≥3.2 to ≤5.1, low disease activity (LDA) <3.2 to ≥2.6, remission <2.6 (ref. 23). Patient-reported outcomes were analyzed using a mixed-effects longitudinal model. FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ DI = Health Assessment Questionnaire disability index; MCS = mental component summary; PCS = physical component summary; SF-36 = Short Form 36 health survey; VAS = visual analog scale.
† SF-36 normative MCS and PCS scores were based on age- and sex-matched norm scores (ref. 32).

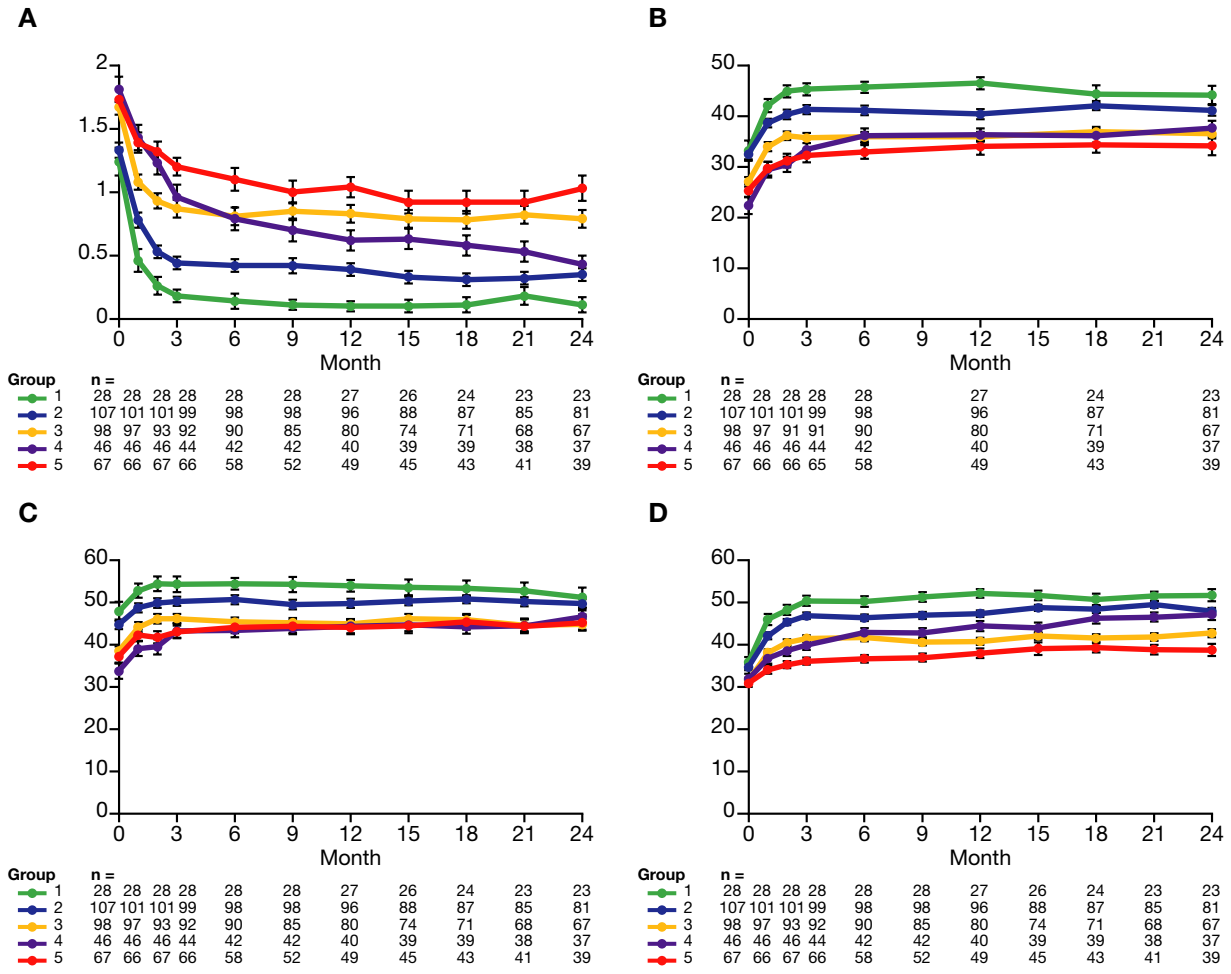


**Figure 3.** Mean absolute score over time in any disease activity trajectory group based on the 4-variable Disease Activity Score in 28 joints, using the erythrocyte sedimentation rate (DAS28-ESR). **A**, Health Assessment Questionnaire disability index score, mean (SE); **B**, Functional Assessment of Chronic Illness Therapy–Fatigue total score, mean (SE); **C**, Short Form 36 health survey (SF-36) mental component summary score, mean (SE); **D**, SF-36 physical component summary score, mean (SE). **A**–**D**, The first and fourth columns of group numbers in the legend correspond to the 0 and 3-month time points, respectively. Group 1: high disease activity (HDA) to remission; group 2: HDA to low disease activity (LDA) rapid; group 3: HDA to moderate disease activity (MDA); group 4: HDA to LDA gradual; group 5: HDA to HDA. HDA >5.1, MDA ≥3.2 to ≤5.1, LDA <3.2 to ≥2.6, remission <2.6 (23). Patient-reported outcomes were analyzed using a mixed-effects longitudinal model.

FACIT-F total score were generally similar in groups 2, 3, and 5. The proportions of patients reporting normative FACIT-F total scores were numerically highest in group 1 and lowest in groups 3 and 5 (Table 2).

Numerical improvements in SF-36 MCS and PCS scores were highest in group 4. Groups 1 and 2 had the smallest improvements in SF-36 MCS score, while groups 3 and 5 had the smallest improvements in SF-36 PCS score (Table 2). The proportions of patients reporting normative SF-36 MCS and PCS scores were numerically highest in groups 1 and 2, and lowest in groups 3 and 5. The proportions of patients reporting normative values in SF-36 domain scores were generally consistent with those reporting normative SF-36 MCS and PCS scores, with the exception of the bodily pain domain, where groups 1 and 4 had the highest proportions reporting normative scores (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24709/abstract).

At month 24, group 4 had the largest mean change in arthritis pain score (Table 2), and the proportions reporting ≥30%/≥50% improvements in arthritis pain score were highest in groups 1 and 4 and lowest in group 3 (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24709/abstract).

**AEs across trajectory groups.** Discontinuation rates were numerically lower in groups 1, 2, and 4, compared with groups 3 and 5 (Figure 4). Discontinuations due to AEs were lowest in groups 2 and 4 and highest in group 5 (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24709/abstract). There were 2 deaths (1 each in groups 2 and 3) (Figure 4).

| | Group 1 HDA to REM (n = 28) | Group 2 HDA to LDA rapid (n = 107) | Group 3 HDA to MDA (n = 98) | Group 4 HDA to LDA gradual (n = 46) | Group 5 HDA to HDA (n = 67) |
|---|---|---|---|---|---|
| Patients with discontinuations | 5 (17.9) | 24 (22.4) | 31 (31.6) | 9 (19.6) | 29 (43.3) |
| Deaths | 0 | 1 (0.9) | 1 (1.0) | 0 | 0 |
| Adverse events | | | | | |
| Blood and lymphatic system disorders | 2 (7.1) | 5 (4.7) | 5 (5.1) | 2 (4.4) | 7 (10.4) |
| Gastrointestinal disorders | 8 (28.6) | 30 (28.0) | 30 (30.6) | 9 (19.6) | 18 (26.9) |
| General disorders and administration site conditions | 3 (10.7) | 10 (9.4) | 9 (9.2) | 3 (6.5) | 9 (13.4) |
| Infections and infestations | 12 (42.9) | 48 (44.9) | 44 (44.9) | 14 (30.4) | 28 (41.8) |
| Injury, poisoning, and procedural complications | 3 (10.7) | 12 (11.2) | 9 (9.2) | 3 (6.5) | 3 (4.5) |
| Investigations | 5 (17.9) | 24 (22.4) | 18 (18.4) | 13 (28.3) | 16 (23.9) |
| Metabolism and nutrition disorders | 1 (3.6) | 5 (4.7) | 9 (9.2) | 5 (10.9) | 10 (14.9) |
| Musculoskeletal and connective tissue disorders | 6 (21.4) | 25 (23.4) | 15 (15.3) | 5 (10.9) | 21 (31.3) |
| Nervous system disorders | 5 (17.9) | 12 (11.2) | 13 (13.3) | 5 (10.9) | 12 (17.9) |
| Respiratory, thoracic, and mediastinal disorders | 4 (14.3) | 9 (8.4) | 3 (3.1) | 4 (8.7) | 9 (13.4) |
| Skin and subcutaneous tissue disorders | 3 (10.7) | 12 (11.2) | 10 (10.2) | 4 (8.7) | 7 (10.4) |
| Vascular disorders | 1 (3.6) | 7 (6.5) | 10 (10.2) | 10 (21.7) | 5 (7.5) |

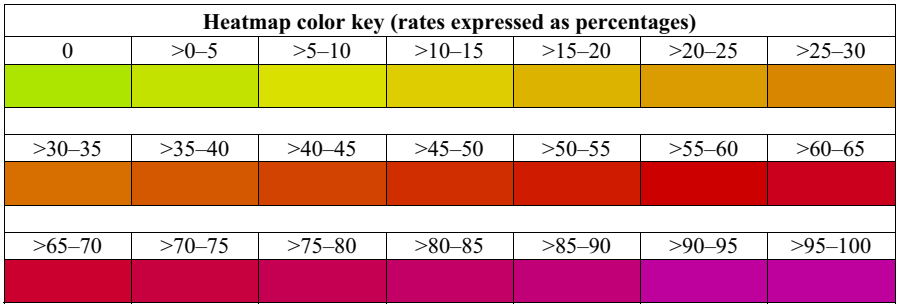


**Figure 4.** Heatmap of the incidence of adverse events (AEs) in any disease activity trajectory group based on the 4-variable Disease Activity Score in 28 joints, using the erythrocyte sedimentation rate. Values are the number (%), and data are presented for AEs by system organ class with an incidence of ≥10% in at least 1 trajectory group. High disease activity (HDA) >5.1, moderate disease activity (MDA) ≥3.2 to ≤5.1, low disease activity (LDA) <3.2 to ≥2.6, remission (REM) <2.6 (ref. 23).

Analysis of AEs indicated that incidences were generally comparable across groups (Figure 4). Group 4 had the numerically lowest proportion of patients with blood and lymphatic disorders, gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, musculoskeletal and connective tissue disorders, nervous system disorders, and skin and subcutaneous tissue disorders, compared with other groups. In contrast, rates of investigations and vascular disorders were highest in group 4. In group 5, a numerically higher proportion of patients experienced AEs in several system organ classes, compared with other groups, most notably musculoskeletal and connective tissue disorders.

Consistent with previous analyses, across all trajectory groups, the most common AEs were nasopharyngitis and upper respiratory tract infection, followed by nausea, headache, and hypertension (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24709/abstract).

## DISCUSSION

Identification of distinct latent trajectory groups among patients could inform treatment optimization and decision-making regarding subsequent lines of therapy. This post hoc analysis of data from ORAL Start is the first trajectory modeling analysis of MTX-naive patients with RA receiving tofacitinib. Based on the DAS28-ESR response to month 24, we identified 5 distinct predicted disease activity trajectories in patients receiving tofacitinib 5 mg twice daily. Groups 1–3 improved from HDA at baseline to remission, LDA, and MDA, respectively, over 3 months, and disease activity generally plateaued thereafter (i.e., improvements were maintained to month 24). Group 4 gradually improved from HDA to LDA over 24 months, while patients in group 5 remained in HDA at month 24.

There were significant differences in baseline characteristics between groups, including sex, disease activity measures, joint damage, and patient-reported outcomes. Group 1, which had the greatest improvement in disease activity at month 24 also had the lowest disease activity and most favorable radiographic and patient-reported outcome scores, as well as the shortest RA duration, at baseline. In contrast, group 5, which remained in HDA at month 24 had the longest RA duration at baseline and the highest total Sharp score. Significant differences in disease duration and radiographic evaluation at baseline were observed in group 1 versus group 5 only. Possibly other baseline characteristics, or interactions between characteristics not explored in the current model, may contribute to overall drug efficacy or influence the attainment of remission versus LDA.

At baseline, DAS28-ESR and Clinical Disease Activity Index (CDAI) scores were lowest in groups 1 and 2, followed by groups 3 and 5, and were highest in group 4. This finding suggests that baseline DAS28-ESR or CDAI scores may be predictive of short-term improvements in disease activity, such as those observed in groups 1, 2, and 3, which had the greatest improvement in disease activity during the first 3 months of treatment, but may be less predictive of the long-term improvements observed in group 4 over 24 months.

Improvements in patient-reported outcomes were generally consistent with predicted DAS28-ESR trajectories and plateaued after 3 months, suggesting that early patient-reported outcome data may be useful in informing treatment strategies. At month 24, the proportions of patients reporting HAQ DI scores ≥ normative values, and functional remission in HAQ DI, were generally consistent with predicted DAS28-ESR trajectories.

Discontinuations due to AEs were numerically higher in groups 3 and 5, compared with groups 1, 2, and 4, and group 5 had a relatively poorer safety profile compared with other groups. No consistent pattern could be identified between disease activity trajectories and incidence of AEs across groups, and careful monitoring of safety is required for all patients, irrespective of predicted disease trajectory.

While groups 4 and 5 had the highest baseline disease activity, radiographic scores, impaired quality of life, and fatigue (as assessed by DAS28-ESR, CDAI, swollen joint count in 66 joints, FACIT-F, arthritis pain score, and patient global assessment), the trajectories of these groups diverged over time. Group 5 also had greater radiographic progression over time, compared with group 4. Group 4 experienced generally greater improvements in patient-reported outcomes, notably at month 24, than group 5. In addition, similarities between groups 3 and 5 in outcome measures through month 24, and the differential disease activity trajectories observed in these patients, compared with those in group 4, merits further discussion. A higher proportion of patients in groups 3 and 5 were female, and group 3, followed by group 4, had the highest baseline BMI (associated with a poorer prognosis), and group 3 also had the highest proportion of patients from Latin America (which may have implications for socioeconomic factors that affect outcomes). Patients in group 5 had the highest mean total Sharp score at baseline, which may be indicative of previously undertreated disease. However, while a numerical difference in the proportion of female patients was observed in groups 3 and 5 versus group 4, no significant differences in baseline factors between groups 3–5 were identified.

At baseline, the mean total Sharp score and mean erosion and JSN scores were lowest in group 1 and highest in group 5, while groups 2, 3, and 4 were generally numerically similar. Only minimal changes in radiographic scores were observed through month 24, which were unlikely to be clinically relevant; with the exception of group 5, baseline total Sharp score and erosion and JSN scores were not predictive of disease activity at month 24.

Previously, distinct RA disease activity trajectories, characterized by baseline differences in disease activity and patient-reported outcomes, were identified over 12 months in patients receiving tofacitinib 5 mg twice daily who had an inadequate response to csDMARDs and were biologic DMARD (bDMARD)–naive (25). Similar to the current analysis, 5 disease activity trajectories were identified that improved from HDA to remission, LDA, and MDA (2 groups: based on rapid or gradual improvement), or remained in HDA at month 12; patients with higher disease activity at baseline were generally less likely to achieve improvements at month 12 (25). This result is consistent with the findings of the present analysis, where, with the exception of group 4, baseline disease activity was predictive of disease status at month 24.

Disease trajectories have also been identified in patients with RA receiving other treatments. An observational analysis in patients with early RA receiving combination csDMARDs identified 3 disease activity trajectories (good, moderate, and poor), demonstrating an association between persistence with initial csDMARD therapy and lower long-term disease activity (5). Furthermore, another analysis in patients with early RA in an observational cohort study found that baseline physician global assessment score was highest in those who improved from HDA to remission (equivalent to group 1 in the current analysis), and numerically lower in patients who improved from HDA to LDA or MDA (equivalent to groups 2 and 3, respectively), while patient global assessment scores were similar in all 3 groups (2). This finding contrasts with the results of the current analysis, where groups 1 and 2 generally had lower baseline disease activity, higher quality of life, lower fatigue, and numerically lower baseline physician global assessment and patient global assessment scores, compared with groups 3–5. These discrepancies may be due to differences in disease duration and severity between the populations evaluated in the previous and current analyses; only patients with ≤12 months of symptoms were included in the previous analysis, and the majority (51%) had MDA at baseline, whereas patients in the current analysis had a mean disease duration of 1.2–3.7 years, and all had HDA at baseline.

An analysis of patients with early RA following a treat-to-target strategy (using an escalating csDMARD to csDMARD + bDMARD treatment regimen) over 12 months, identified 3 response trajectories (fast response, slow response, and poor outcome); clinical outcomes and patient-reported outcomes over time were greatest in the fast response group (3). However, unlike the current analysis, the fast response group (82.6% of patients) were in MDA at baseline. Likewise, a pooled analysis of registry data for patients with established RA receiving abatacept identified 3 response trajectories (rapid, gradual, and inadequate). Time to discontinuation due to lack of efficacy was shorter in the group with the poorest response over time; however, again, the majority (91.7%) were in MDA at baseline (4).

It should be noted that trajectory groups identified by modeling should not be considered permanent, but instead

represent summaries of disease progression. Building on this analysis, future investigation into the heterogeneity of treatment responses could examine which clinical variables cluster together in similar-behaving trajectory groups. In particular, further exploration of clustering of disease and patient characteristics associated with more severe disease (e.g., longer disease duration, higher levels of initial structural damage, current smoking status, higher BMI, initial steroid use, greater pain sensitization) would be of potential interest.

A strength of this post hoc analysis was the use of data from a clinical trial, which enrolled a unique patient population for which tofacitinib is not indicated. Further validation of the model, through trajectory analysis of registry and/or real-world data, would strengthen the interpretation of any results. This was a descriptive analysis, which identified and characterized trajectory groups based on disease activity. The analysis was limited by small patient numbers in some trajectory groups. Also, a possible result of increasing the number of possible groups (*k*) is that a group containing a relatively large proportion of the analysis population could be spuriously separated into 2 new groups, containing the lower and higher proportions of the original population, without offering any new insight into the underlying trajectories. The algorithm may also return a group with no members; hence, user input is required to compare and interpret competing sets of trajectory results to select the best model.

In conclusion, this post hoc analysis identified phenotypic subgroups with distinct disease activity trajectories in MTX-naive patients treated with tofacitinib, reflecting heterogeneity in patients normally analyzed as a single group. More thorough exploration of the heterogeneity of any given patient population, in terms of a preplanned cluster analysis subsequent to the presentation of clinical trial outcomes, may help practitioners identify which patients are more likely to respond to treatment and provide a means of matching the right patient with the right treatment. Identification of distinct latent trajectory groups of patients enrolled in clinical trials could provide a better understanding of the characteristics of particular patient cohorts, give further insight into the impact of treatments under investigation, inform future trial development, and ultimately optimize outcomes. Future analyses to investigate potential effect modifiers that may predispose a patient to a specific response trajectory are warranted.

## 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 submitted for publication. Dr. Bykerk 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.** Bykerk, Lee, van Vollenhoven, Gruben, Fallon, Woolcott, Keystone.

**Acquisition of data.** Gruben.

**Analysis and interpretation of data.** Bykerk, Lee, van Vollenhoven, Gruben, Fallon, Woolcott, Keystone.

## ROLE OF THE STUDY SPONSOR

Pfizer Inc were involved in the study design and in data collection. All authors, including those employed by Pfizer Inc, had a role in data analysis, data interpretation, and writing the manuscript. Medical writing support, under the guidance of the authors, was provided by Anthony McCluskey, PhD, CMC Connect, McCann Health Medical Communications, and was funded by Pfizer Inc, New York, in accordance with Good Publication Practice (GPP3) guidelines (Ann Intern Med 2015;163:461–464). Publication of this article was not contingent upon approval by Pfizer Inc.

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# Enhancing Patient Understanding of Medication Risks and Benefits

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**Objective.** To evaluate the effectiveness of 2 interventions, including the DrugFactsBox format for presenting written medication information and the SMART (Strategic Memory Advanced Reasoning Training) program designed to enhance gist (i.e., "bottom-line" meaning) reasoning ability.

**Methods.** We used a 2 × 2 factorial research design. A total of 286 patients with rheumatoid arthritis were randomly assigned to 1 of 4 groups, including DrugFactsBox with the SMART program, DrugFactsBox without the SMART program, other consumer medication information (CMI) with the SMART program, and other CMI without the SMART program. Data were collected via telephone interviews and online questionnaires at 4 time points, including baseline and 6-week, 3-month, and 6-month time points following baseline. The primary outcome variable was informed decision-making, which was defined as making a value-consistent decision concerning use of disease-modifying antirheumatic drugs based on adequate knowledge.

**Results.** We found no main effects for the 2 interventions, either alone or in combination. However, there was a significant interaction between assignment to the SMART/no SMART groups and informed decision-making at baseline. Among participants in the SMART groups who did not meet the criteria for informed decision-making at baseline, 42.5% met the criteria at the 6-month follow-up, compared to 23.6% of participants in the no SMART groups (mean difference 18.9 [95% confidence interval 5.6, 32.2]; $P = 0.007$). This difference was driven by increased knowledge in the SMART groups. Among participants who met the criteria for informed decision-making at baseline, the difference between the SMART and no SMART groups was not statistically significant.

**Conclusion.** Participation in a theory-driven program to enhance gist reasoning may have a beneficial effect on informed decision-making among patients with inadequate knowledge concerning therapeutic options.

## INTRODUCTION

Guidelines for the management of rheumatoid arthritis (RA) endorse a treat-to-target strategy using disease-modifying antirheumatic drugs (DMARDs), with achieving clinical remission (or at least low disease activity) as the primary target (1). A major issue in implementing treat-to-target principles in practice, however, involves patient reluctance to escalate therapy when their symptoms are tolerable despite the presence of active disease (2–4). This reluctance is understandable, because the potential benefits associated with DMARDs may be accompanied by serious risks. Obtaining accurate, personally relevant information about these risks is challenging (5–8). Although the US Food and Drug Administration requires that patients receive a medication guide with most DMARDs, research suggests that many patients have difficulty understanding the information that the guides contain (9–13). This is likely due to both design issues (e.g., nonadherence to plain language guidelines) (14) and the prevalence of limited health literacy/numeracy skills among patients (15).

The present study was based on the premise that interventions designed to educate patients about the risks and benefits associated with different therapeutic options require a 2-pronged approach, including simplification of educational materials to convey the essential gist (i.e., "bottom-line" meaning) and assistance

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**SIGNIFICANCE & INNOVATIONS**

- Patients with rheumatoid arthritis (RA) are often reluctant to escalate therapy with disease-modifying antirheumatic drugs (DMARDs) due to concern about medication risks.
- Many RA patients have difficulty understanding the gist (i.e., "bottom-line" meaning) of currently available consumer medication information, including medication guides that the US Food and Drug Administration requires for most DMARDs.
- The Strategic Memory Advanced Reasoning Training (SMART) program is an innovative patient education program designed to enhance gist reasoning.
- Among patients with knowledge deficits, the SMART program may facilitate informed decision-making by helping them develop the skills needed to understand and use complex information concerning medication risks/benefits.

to patients in developing the health literacy/numeracy skills needed to process complex information (e.g., scientific uncertainty concerning medication risks/benefits) to derive that gist (16,17). Thus, we examined the effectiveness of 2 innovative communication strategies, including DrugFactsBoxes and the Strategic Memory Advanced Reasoning Training (SMART) program. DrugFactsBoxes were developed to enhance the usability of written consumer medication information (CMI), especially among individuals with limited health literacy/numeracy skills (18–20). The SMART program was developed to enhance patients' ability to understand and extract "bottom-line" meaning (gist) from complex information, which we view as an essential health literacy skill (21–27).

As shown in Figure 1, we hypothesized that both interventions would increase patient knowledge concerning medication risks/benefits and interest in obtaining additional information about illness self-management. By improving gist reasoning ability, we hypothesized that the SMART program would work synergistically with accessible information such as DrugFactsBoxes to enhance informed decision-making, which is defined as making value-consistent decisions concerning DMARD use based on adequate knowledge.

## PATIENTS AND METHODS

**Design.** We evaluated 2 educational interventions (DrugFactsBoxes and the SMART program) using a 2 × 2 factorial research design and adhering to Consolidated Standards of Reporting Trials (CONSORT) guidelines (28). Data were collected at the following 4 time points: baseline and 6 weeks, 3 months, and 6 months following baseline. At each time point, data were collected via a combination of telephone interviews and online questionnaires. Immediately after completion of the baseline interview, we used a 1:1:1:1 allocation sequence to randomly assign participants to 1 of 4 study groups, including DrugFactsBox with the SMART program, DrugFactsBox without the SMART program, other CMI with the SMART program, and other CMI without the SMART program. Participants and all staff involved with data collection were blinded to participants' group assignment. The study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill (UNC-CH) and is registered (ClinicalTrials.gov identifier: NCT02820038).

**Participants.** We recruited participants from the following resources: 1) 4 large academic rheumatology practices; 2) CreakyJoints, an online arthritis patient support community; 3) social media (e.g., Facebook, Twitter); 4) the Carolina Data Warehouse for Health, which includes patients treated at all inpatient and outpatient facilities at UNC-CH; and 5) Join the Conquest, a website administered by the UNC Translational and Clinical Sciences Institute that allows individuals in the general public to volunteer to participate in posted research studies. To be eligible to participate, individuals had to meet the following criteria: be ≥18 years of age, have physician-confirmed RA or be undergoing therapy with a DMARD approved for the treatment of RA, speak English, not have hearing or visual impairments that would prevent being able to complete data-collection procedures, have an email address and internet access, have moderate or high disease activity as evidenced by a score of >6 on the 0–30 Routine Assessment of Patient Index Data 3 (RAPID3) (29,30) scale, and not have any health problems that prevented changes in his/her RA medication regimen (e.g., ongoing serious infection). Participant recruitment began in September 2016 and ended in May

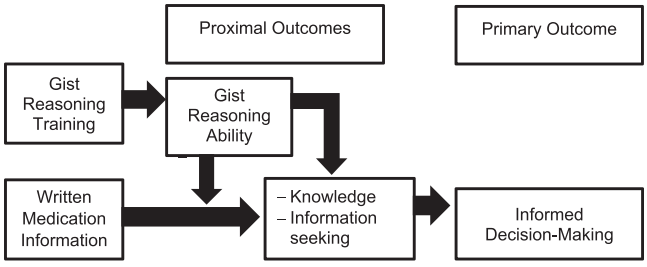


**Figure 1.** Conceptual framework for gist reasoning training and written medication information.

2018. Data collection was completed in December 2018. Participants received $125 for participating in the study: $25 after completing the baseline, 6-week, and 3-month data collection, and $50 after completing the 6-month data collection.

At rheumatology clinic sites, clinic staff or a research assistant identified potentially eligible patients and obtained verbal consent to administer a screening interview that assessed disease activity, age, email address, and access to the internet. They then contacted the patient's rheumatologist to obtain confirmation of diagnosis and presence/absence of health problems that would prevent changes in the patient's medication regimen. If the patient was eligible to participate in the study, written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization were obtained. The information collected via these screening procedures was then forwarded to staff in the central office at the UNC-CH to initiate data collection. For potential participants identified via other mechanisms, research staff at the UNC-CH administered the screening interview via telephone. If the patient appeared to be eligible to participate, he/she was mailed a consent form and HIPAA authorization to sign and return. When HIPAA authorization was obtained, staff contacted the patient's physician to obtain confirmation of diagnosis and presence/absence of health problems that would prevent medication regimen changes.

**Interventions.** The original DrugFactsBox format used a standardized 2-page summary that followed plain language guidelines and clinical best practices to convey relevant facts to individuals with limited literacy or numeracy skills (18–20). For the present study, we created a website that contained 16 DrugFactsBoxes for those medications most commonly used to treat RA in the US (i.e., abatacept, adalimumab, certolizumab, etanercept, golimumab, hydroxychloroquine, infliximab, leflunomide, methotrexate pill, methotrexate subcutaneous, prednisone, rituximab, sulfasalazine, tocilizumab infusion, tocilizumab subcutaneous, and tofacitinib). A pill bottle icon for each medication appeared on the website landing page. When an icon was clicked, an overview of the medication appeared. The overview included a section labeled "Bottom Line," which contained a narrative summary of potential medication benefits and harms, emphasizing the gist (31). The overview page also provided links to other pages within the website that contained additional information about the medication. These links were labeled trials, side effects, how to use, lifestyle changes, and interactions. The trials page provided quantitative information concerning potential medication benefits and harms, mirroring the original DrugFactsBox format. Participants in the other CMI groups were given access to a website that contained CMI for the same 16 medications. For medications that have an FDA-approved medication guide (i.e., all biologics and tofacitinib), a link to the guide was provided. For the remaining medications, the website provided a link to CMI developed by the American Society of Health-System Pharmacists' that are similar to the written information given to patients in the US when prescriptions are dispensed.

The SMART program is designed to enhance gist reasoning ability by training participants on the use of the following 3 metacognitive strategies: strategic attention (e.g., ignoring or eliminating distractions to facilitate single-minded focus on understanding the specific topic at hand), integrated reasoning (e.g., strengthening integrative mental capacity to synthesize information from multiple sources), and innovation (e.g., examining multiple perspectives and information sources to best understand the information available) (21–27). The program was delivered by research personnel at the Center for BrainHealth at the University of Texas at Dallas using an online video conferencing platform that permitted synchronous, audio and visual communication between trainers and participants. In most cases, the program was delivered in small groups with 3–4 participants. Initially, the program was delivered in four 90-minute sessions, spanning a 1-month period. However, because many participants had difficulty committing to sessions of this length, midway through the project, we reduced the length of each session to 1 hour in an effort to increase participant engagement.

**Measures.** Our primary outcome variable was informed decision-making regarding the use of DMARDs. Informed decision-making is typically conceptualized as making a value-consistent decision that is based on adequate knowledge (32–34). To use this approach, the online questionnaires included items asking participants to indicate the extent to which they agreed or disagreed with 10 value statements pertaining to the management of RA (e.g., "It is important to accept the risk of side effects now in order to improve my chances of being healthy in the future"), which were developed based on theory and empirically validated (35). Responses were recorded on a 4-point scale ranging from 1 (strongly agree) to 4 (strongly disagree). Responses were summed and transformed to a composite score ranging from –15 to 15, where positive numbers reflected values favoring aggressive treatment. Participants were classified as meeting the criteria for informed decision-making if they: 1) answered at least 85% of the knowledge items (described below) correctly, scored >0 on the values measure and were taking ≥1 DMARD or 2) answered 85% of the knowledge items correctly, scored ≤0 on the values measure, and were not taking a DMARD. All other individuals were classified as not meeting the criteria for informed decision-making.

Knowledge was assessed by 3 separate instruments administered via telephone interview, including an 8-item measure assessing knowledge concerning methotrexate (which is often first-line therapy for RA) (36), a 20-item measure assessing knowledge concerning biologic treatment options (35), and an 8-item measure assessing knowledge of RA and RA treatment options more generally (37). Correct answers were summed across all 3 measures and transformed to a 100-point scale, reflecting the percentage of questions answered correctly.

DMARD use was assessed via a checklist of 19 RA medications (abatacept, adalimumab, azathioprine, certolizumab pegol, cyclosporine, etanercept, golimumab, gold, hydroxycholoroquine, infliximab, leflunomide, methotrexate pill, methotrexate shot, minocycline, rituximab, sulfasalazine, tocilizumab infusion, tocilizumab shot, and tofacitinib) included in the online questionnaires. Participants were asked to check all of those medications that they were currently being treated with or to check an option labeled "none of the above."

Gist reasoning ability was assessed by the Test of Strategic Learning (TOSL). The TOSL was developed to systematically quantify participants' capacity to abstract gist meanings from complex input (26,38). The TOSL consists of nonmedical text passages varying in length (from 291 to 575 words) and complexity. At each time point, participants read one of the text passages presented via an online questionnaire. After reading the passage, participants clicked on a link to the next page of the questionnaire, which included a single item asking participants to summarize the original text, focusing on bottom-line meaning (i.e., "the moral of the story") rather than specific details. Participants had up to 5 minutes to complete this task and were not allowed to return to the page on which the passage appeared while writing the summary.

The next page of the questionnaire asked participants to take up to 3 minutes to list the lessons learned (i.e., take-home messages) from the text. A total of 4 different text passages were used. These were balanced across participants over the course of the study such that each participant viewed a different passage at each time point, with the order in which passages were viewed randomized across participants. Participants' responses were scored using a manualized, objective scoring system by a trained and experienced rater (MK) who was blinded to participants' group assignment and time of testing. Two separate scores, including complex abstraction and lesson quality, were derived from participants' responses. To assess interrater reliability prior to the initiation of coding, 2 raters scored 25 responses for each of the 4 text passages. The mean intraclass correlation coefficient for a single score was 0.74 for complex abstraction (range 0.43–0.94) and 0.95 for lesson quality (range 0.84–0.99), indicating good reliability.

Information seeking was assessed using behavioral measures. First, we created a website that provided easy access to information about RA, treatment options, and illness self-management. All participants were emailed a link to the website following the 6-week follow-up, regardless of their group assignment. We used Google analytics to track whether participants accessed the website. Second, after the 6-week follow-up, we also emailed all participants an invitation to participate (free of charge) in BetterChoices, BetterHealth, an online chronic illness self-management program, and tracked class enrollment. Finally, we assessed the following sociodemographic characteristics: age, sex (male, female), race (White, other), ethnicity (Hispanic, non-Hispanic), education (less than bachelor's degree, bachelor's degree or more), marital status (currently married, other), and difficulty affording RA medications (no trouble, a little trouble, a lot of trouble).

**Analyses.** Characteristics of study participants are presented using means and percentages, depending on the measurement properties of the variables. We used logistic regression to assess the effects of the 2 interventions on our primary outcome: informed decision-making at the 6-month follow-up. A separate regression model was performed at each follow-up time point (i.e., 6-week, 3-month, and 6-month). Each model controlled for informed decision-making at baseline (0 = did not meet criteria, 1 = met criteria) and indicator variables for each intervention indexing assignment to the SMART program (0 = no, 1 = yes) and the DrugFactsBox group (0 = no, 1 = yes). We also included three two-way interaction terms in each model. The first interaction term assessed whether the effects of the 2 interventions were dependent on one another. The other interaction terms assessed whether the effects of the interventions varied as a function of informed decision-making at baseline. Interaction terms that were not statistically significant ($P < 0.05$) were dropped from the models and the models were re-run to examine main effects.

When significant interactions were observed, we used stratified analyses to determine the nature of the interaction. Statistical significance was evaluated with alpha (2-tailed test) set at 0.05. Missing baseline data were imputed by substituting the mean or mode in the full sample for continuous variables and categorical variables, respectively. Missing follow-up data were imputed using multiple imputation methods, via PROC MI and PROC MIANALYZE in SAS. Because the pattern of missing data was not monotonic, we used the Markov chain Monte Carlo method. As recommended by Sullivan and colleagues (39), imputation procedures were carried out separately for each randomized group. In PROC MIANALYZE, we used the EDF option to specify the complete-data degrees of freedom for parameter estimates. Power analyses conducted a priori indicated that a sample of 300 would provide 80% power to detect a between-group difference of 25% in the percentage of participants meeting the criteria for informed decision-making (e.g., 35% versus 60%). This anticipated effect size is based on previous research (35) and corresponds to a moderate-sized effect (40). Power calculations were performed with alpha (2-tailed test) set at 0.05 and allowed for 15% attrition from baseline to final follow-up. All analyses were performed using SAS PC, version 9.4.

## RESULTS

A total of 634 patients were screened for eligibility (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24421/abstract). Of these, 309 met study eligibility criteria, provided written informed consent, completed the baseline interview, and were randomized to a group. However, 23 of the patients randomized

either withdrew from the study or were lost to follow-up before completing the baseline questionnaire. Therefore, only 286 (93%) of the 309 individuals who completed the baseline interview received the email giving them access to intervention materials. Characteristics of these study participants, assessed at baseline, are shown in Table 1.

**Informed decision-making.** None of the interaction terms in the logistic regression models predicting informed decision-making were statistically significant at the 6-week follow-up. However, there was a significant interaction between assignment to the SMART program and baseline informed decision-making at both the 3-month ($P = 0.05$) and 6-month ($P = 0.01$) follow-ups. To follow up on these interactions, we stratified the sample by whether participants were classified as meeting the criteria for informed decision-making at baseline. Of note is that the stratified analyses examined the main effects of each intervention (i.e., SMART/no SMART, DrugFactsBox/other CMI), because we found no statistically significant interactions between the interventions. Thus, with respect to the SMART program, data were pooled across participants regardless of whether they received DrugFactsBoxes or other CMI. As shown in Table 2, 42.5% of participants in the SMART group who did not meet the criteria for informed decision-making at baseline met the criteria at the 6-month follow-up, compared to 23.6% of participants in the no SMART group ($P = 0.007$). A similar difference was observed among these individuals at the 3-month follow-up. In contrast, among participants classified as meeting the criteria for informed decision-making at baseline, none of the differences between the SMART and no SMART groups were statistically significant. Finally, none of the interactions or main effects involving whether participants were assigned to receive DrugFactBoxes versus other CMI were statistically significant.

We used the complete case data (without imputed values for missing data) to identify the factors that caused participants to transition from not meeting the criteria for informed decision-making at baseline to meeting these criteria at the 6-month follow-up. A total of 45 participants (27 in the SMART group and 18 in the no SMART group) made this transition. Among these participants, 41 (23 in the SMART group, 18 in the no SMART group) exhibited knowledge gains that moved them above the 85% threshold required to meet the criteria for informed decision-making; 3 individuals who used a DMARD at baseline (all in the SMART group) had shifts in values that moved them above the threshold to be classified as valuing aggressive therapy; and 6 (3 in the SMART group, 3 in the no SMART group) began using a DMARD during the follow-up period, consistent with their values favoring aggressive therapy. All 45 participants who transitioned from not meeting the criteria for informed decision-making at baseline to meeting these criteria at the 6-month follow-up were being treated with at least 1 DMARD at the 6-month follow-up.

**Components of informed decision-making and other proximal outcomes.** Table 3 presents the results of analyses assessing differences between the SMART and no SMART groups with respect to the components of informed decision-making (i.e., knowledge, values, and DMARD use) and other proximal outcome variables. Compared to individuals in

**Table 1.** Baseline characteristics of study participants (n = 286)*

| Characteristic | Other CMI only (n = 78) | Other CMI w/ SMART (n = 77) | DrugFactsBox only (n = 65) | DrugFactsBox w/ SMART (n = 66) |
|---|---|---|---|---|
| Age, mean ± SD years | 55.5 ± 10.8 | 54.7 ± 11.8 | 56.2 ± 10.1 | 54.9 ± 14.7 |
| White race† | 76.3 (58) | 81.6 (62) | 73.4 (47) | 71.2 (47) |
| Married | 66.7 (52) | 52.0 (40) | 60.0 (39) | 65.2 (43) |
| Female sex | 89.7 (70) | 89.6 (69) | 92.3 (60) | 89.4 (59) |
| College graduate‡ | 52.0 (40) | 62.3(48) | 49.2 (32) | 57.6 (38) |
| Disease activity, mean ± SD | 4.6 ± 1.7 | 4.3 ± 1.6 | 4.8 ± 1.7 | 4.5 ± 1.7 |
| Reported having a lot of trouble affording medications | 16.7 (13) | 10.4 (8) | 13.9 (9) | 21.2 (14) |
| Met criteria for informed decision-making‡ | 37.7 (29) | 36.4 (28) | 38.5 (25) | 30.3 (20) |
| Not taking any DMARDs§ | 5.2 (4) | 10.7 (8) | 10.8 (7) | 9.1 (6) |
| Knowledge, mean ± SD | 77.1 ± 15.1 | 79.3 ± 14.3 | 77.2 ± 15.7 | 75.8 ± 17.2 |
| Values, mean ± SD | 5.0 ± 3.5 | 5.2 ± 4.2 | 5.7 ± 4.0 | 4.7 ± 3.5 |
| Gist reasoning ability¶ | | | | |
| Complex abstraction, mean ± SD | 2.0 ± 1.6 | 2.0 ± 1.5 | 2.0 ± 1.4 | 2.0 ± 1.5 |
| Lesson quality, mean ± SD | 1.0 ± 1.1 | 1.0 ± 1.2 | 1.0 ± 1.1 | 0.7 ± 1.0 |

* Values are the percent (number) unless indicated otherwise. For all variables, higher values reflect higher levels of the attribute measured. CMI = consumer medical information; DMARDs = disease-modifying antirheumatic drugs; SMART = Strategic Memory Advanced Reasoning Training.
† Due to missing data, the total number of study participants with the characteristic of White race was n = 282.
‡ Due to missing data, the total number of study participants with the characteristic of college graduate and who met criteria for informed decision-making was n = 285.
§ Due to missing data, the total number of study participants with the characteristic of not taking any DMARDs was n = 283.
¶ Due to missing data, the total number of study participants with scores for Test of Strategic Learning complex abstraction and lesson quality was n = 270.

**Table 2.** Effect of SMART program on informed decision-making at 6-week, 3-month, and 6-month follow-ups, stratified by informed decision-making at baseline*

| | 6-week follow-up | 3-month follow-up | 6-month follow-up |
|---|---|---|---|
| Did not meet criteria for informed decision-making at baseline (n = 184)† | | | |
| SMART program, % | 23.8 | 40.6 | 42.5 |
| No SMART program, % | 24.7 | 21.7 | 23.6 |
| Difference (95% CI) | −0.9 (−13.3, 11.5) | 18.9 (5.8, 32.0) | 18.9 (5.6, 32.2) |
| *P* | 0.89 | 0.006 | 0.007 |
| Met criteria for informed decision-making at baseline (n = 102)‡ | | | |
| SMART program, % | 77.1 | 75.4 | 63.0 |
| No SMART program, % | 80.0 | 83.3 | 78.2 |
| Difference (95% CI) | −2.8 (−18.8, 13.1) | −7.8 (−23.6, 7.9) | −15.2 (−32.7, 2.4) |
| *P* | 0.73 | 0.33 | 0.09 |

* Data in the Strategic Memory Advanced Reasoning Training (SMART) and no SMART program groups were pooled across participants regardless of whether they received DrugFactsBoxes or other consumer medication information. Percentages in the body of the table are averaged across 50 imputations used to estimate values for missing data at the follow-up assessments. 95% CI = 95% confidence interval.
† N = 95 for SMART program; n = 89 for no SMART program.
‡ N = 48 for SMART program; n = 54 for no SMART program.

the no SMART group, those in the SMART group exhibited greater knowledge at the 6-month follow-up and higher scores on the measure of complex abstraction at the 3-month follow-up. No other differences were statistically significant (no statistically significant differences between the DrugFactsBox and other CMI groups) (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24421/abstract).

**Engagement in intervention activities.** Table 4 shows information concerning the extent to which individuals actively engaged in intervention activities, stratified by the 4 study groups.

**Table 3.** Components of informed decision-making and proximal outcome variables by assignment to the SMART or no SMART program groups*

| | SMART program | | | |
|---|---|---|---|---|
| Outcome variable, by follow-up time period† | Yes | No | Difference (95% CI) | *P* |
| Not using any DMARDs, % (no.) | | | | |
| 6-week | 10.6 (15) | 7.8 (11) | 2.8 (−3.9, 9.5) | 0.42 |
| 3-month | 11.9 (17) | 7.7 (11) | 4.3 (−2.6, 11.2) | 0.22 |
| 6-month | 10.9 (16) | 7.7 (11) | 3.2 (−3.5, 9.9) | 0.35 |
| Knowledge | | | | |
| 6-week | 81.4 ± 0.8 | 80.6 ± 0.7 | 0.9 (−1.2, 2.9) | 0.42 |
| 3-month | 83.8 ± 0.8 | 81.8 ± 0.7 | 2.0 (−0.1, 4.1) | 0.06 |
| 6-month | 84.0 ± 0.7 | 81.7 ± 0.7 | 2.2 (0.3, 4.2) | 0.03 |
| Values | | | | |
| 6-week | 5.6 ± 0.3 | 5.3 ± 0.3 | 0.4 (−0.5, 1.2) | 0.39 |
| 3-month | 5.4 ± 0.4 | 6.0 ± 0.3 | −0.6 (−1.5. 0.4) | 0.24 |
| 6-month | 5.7 ± 0.3 | 5.9 ± 0.3 | −0.3 (−1.1, 0.6) | 0.55 |
| Gist reasoning ability | | | | |
| Complex abstraction | | | | |
| 6-week | 1.8 ± 0.2 | 1.8 ± 0.1 | 0.04 (−0.4, 0.5) | 0.87 |
| 3-month | 2.2 ± 0.2 | 1.7 ± 0.1 | 0.5 (0.1, 0.9) | 0.02 |
| 6-month | 1.8 ± 0.2 | 2.0 ± 0.1 | −0.10 (−0.5, 0.3) | 0.53 |
| Lesson quality | | | | |
| 6-week | 0.9 ± 0.1 | 0.9 ± 0.1 | 0.04 (−0.3, 0.4) | 0.79 |
| 3-month | 1.2 ± 0.1 | 0.9 ± 0.1 | 0.30 (−0.0, 0.6) | 0.08 |
| 6-month | 1.0 ± 0.2 | 1.1 ± 0.1 | −0.04 (−0.4, 0.3) | 0.86 |
| Information seeking, % (no.) | | | | |
| Viewed RA self-management website | 15.2 (22) | 22.3 (32) | −7.1 (−16.1, 1.9) | 0.14 |
| Participated in BetterChoices, BetterHealth | 15.2 (22) | 21.0 (30) | −5.9 (−14.8, 3.1) | 0.21 |

* Values are the adjusted mean ± SE, unless indicated otherwise. All mean values are adjusted for the baseline value of the dependent variable and group assignment. For use of disease-modifying antirheumatic drugs (DMARDs), raw percentages are shown. Frequencies and percentages are averaged across 50 imputations used to estimate values for missing data. The average frequencies are rounded to the nearest integer. 95% CI = 95% confidence interval; RA = rheumatoid arthritis; SMART = Strategic Memory Advanced Reasoning Training.

**Table 4.** Engagement in intervention activities*

| Variable | Other CMI only (n = 78) | Other CMI with SMART (n = 77) | DrugFactBox only (n = 65) | DrugFactBox with SMART (n = 66) | *P* |
|---|---|---|---|---|---|
| No. of SMART sessions attended, mean ± SD | NA | 1.60 ± 1.8 | NA | 1.41 ± 1.8 | 0.53 |
| Attended 1+ SMART sessions | NA | 48.1 (37) | NA | 40.9 (27) | 0.39 |
| Attended 3+ SMART sessions | NA | 41.6 (32) | NA | 34.9 (23) | 0.41 |
| No. of DrugFactsBox/other CMI pages viewed, mean ± SD | 1.63 ± 2.8 | 1.39 ± 4.1 | 2.63 ± 3.99 | 2.06 ± 4.0 | 0.22 |
| Viewed 1+ DrugFactsBox/other CMI pages | 38.5 (30) | 23.4 (18) | 53.9 (35) | 42.4 (28) | 0.003 |
| Viewed DrugFactsBox trials page | NA | NA | 21.5 (14) | 15.2 (10) | 0.34 |

* Values are the % (no.) unless indicated otherwise. CMI = consumer medication information; NA = not applicable; SMART = Strategic Memory Advanced Reasoning Training.

Overall, about half of the participants assigned to the SMART group completed at least 1 training session and about 40% of participants viewed at least 1 page on either the DrugFactsBox or other CMI website. Among those who had access to the DrugFactsBox website, 18.3% (n = 24) viewed at least 1 of the trials pages included on the website. These pages set DrugFactBoxes apart from other CMI in that they provide quantitative information concerning the probability of experiencing medication benefits and harms.

## DISCUSSION

Enhancing patients' ability to understand and use information about medication risks and benefits to make informed decisions concerning treatment alternatives remains an important goal. Although more than half of the participants in our sample were college graduates, nearly two-thirds (n = 184) did not meet the criteria for informed decision-making at baseline. In our full sample, neither of the interventions that were evaluated improved informed decision-making, either alone or in combination. However, although not hypothesized a priori, our analyses revealed a statistically significant interaction between the SMART program and informed decision-making at baseline. Specifically, the SMART program had a positive impact on informed decision-making in the subset of participants who did not meet the criteria for informed decision-making at baseline. This finding is consistent with previous research that has demonstrated benefits of the SMART program on performance on cognitive, neural, and functional measures immediately post-training and 3–6 months post-training (24,27,41–43).

The improvements in informed decision-making in this study were driven by increases in knowledge, which was the only component of informed decision-making that differed between the SMART and no SMART groups at the 6-month follow-up. This finding is noteworthy because the SMART program did not provide any content that would have increased patient knowledge concerning RA treatment options directly. Rather, the program is designed to enhance gist reasoning ability, which we view as an essential health literacy skill (24). We observed transient improvements in our measures of gist reasoning ability (i.e., complex abstraction and lesson quality) at the 3-month follow-up. Although these differences were not sustained at the 6-month follow-up, they may have been sufficient to facilitate uptake of medication information at earlier time points and facilitate decision-making.

The lack of any differences between the DrugFactsBox and other CMI group is surprising given that considerable research has demonstrated the superiority of the DrugFactsBox format compared to other types of CMI (18–20,44). Lack of participant engagement in intervention activities may have contributed to these null findings, as well as the null findings for the SMART program in the full sample. Less than 40% of study participants visited the DrugFactsBox/other CMI websites, and only about 50% of those who were randomized to SMART took part in any training sessions. Participant engagement with both interventions might have been higher if we had limited the study to patients who were actively contemplating a medication regimen change. These patients are more likely than others to be interested in obtaining information about treatment options and gaining the skills needed to better understand the information they obtain.

We focused on individuals with moderate-to-severe active RA because current guidelines call for a treat-to-target strategy, with remission or low disease activity being the primary target. Therefore, we expected most of our participants to be contemplating medication regimen changes to better control disease activity. However, the RAPID3 may overestimate RA disease activity in people who experience pain or functional impairment due to other health conditions (e.g., fibromyalgia, osteoarthritis). Thus, reliance on this measure likely resulted in some participants being inaccurately classified as candidates for escalation of DMARD therapy, which accounts for, at least in part, the lack of more active participant engagement with the interventions being evaluated. Participant engagement in the SMART program might also be enhanced by offering the program asynchronously, allowing participants greater flexibility when accessing program materials and completing required activities (45).

In conclusion, although we found no support for the study hypotheses in our full sample, our findings suggest that the SMART program may help support informed decision-making when targeted toward individuals with inadequate knowledge concerning

the risks/benefits associated with different treatment options. This conclusion is consistent with prior research investigating gist-based interventions (46); however, because our findings emerged from unplanned, subsample analyses, more research is needed to assess the replicability and generalizability of our findings and evaluate other approaches to enhance patients' health literacy/numeracy skills. More research is also needed to evaluate the effectiveness of DrugFactsBoxes in real-world settings, incorporating procedures to enhance utilization and focusing on patients actively contemplating either initiating DMARD therapy for the first time or making a medication regimen change.

## 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 submitted for publication. Dr. Blalock 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.** Blalock, Solow, Reyna, Keebler, Carpenter, O'Neill, Chapman.

**Acquisition of data.** Blalock, Solow, Keebler, Hunt, Hickey, Curtis, Chapman.

**Analysis and interpretation of data.** Blalock, Solow, Reyna, Keebler, Carpenter, Hunt, Hickey, O'Neill, Curtis, Chapman.

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# Measurement of Minimal Disease Activity in Psoriatic Arthritis Using the Patient-Reported Outcomes Measurement Information System–Physical Function or the Health Assessment Questionnaire Disability Index

Erin Chew,[1] Jamie Perin,[2] Thomas Grader-Beck,[3] and Ana-Maria Orbai[3]

**Objective.** To assess the interchangeability of the Health Assessment Questionnaire disability index (HAQ DI) with the Patient-Reported Outcomes Measurement Information System–Physical Function (PROMIS-PF) in the calculation of minimal disease activity (MDA) in psoriatic arthritis (PsA).

**Methods.** Comprehensive PsA disease activity was collected concomitantly with the HAQ DI and the PROMIS-PF measures in a PsA cohort. The PROMIS-PF–based MDA definitions were built using the existing cross-walk between the scores: HAQ DI ≤0.5 equivalent to a PROMIS-PF T score of ≥41.3. We assessed agreement between MDA (MDA HAQ DI) and the PROMIS-PF MDA definitions (MDA PROMIS-PF short form 4a and MDA PROMIS-PF bank) at each visit and longitudinally (MDA state changes between consecutive visits) through the kappa statistic. The predictive value of the MDA PROMIS-PF for the MDA HAQ DI was assessed using receiver operator characteristic (ROC) curve analysis.

**Results.** A total of 100 participants contributed 352 observations with up to 5 visits. The mean ± SD age was 52 ± 12 years, 60% were female, and 43% were in MDA at baseline. The kappa statistic for the PROMIS-PF–based MDA reflected excellent agreement with the HAQ DI MDA: $\kappa = 0.94$ (95% confidence interval [95% CI] 0.90–0.97) for MDA PROMIS-PF bank, and $\kappa = 0.90$ (95% CI 0.80–0.95) for MDA PROMIS-PF4a. Higher longitudinal agreement was seen between the MDA HAQ DI and the MDA PROMIS-PF bank versus the MDA PROMIS-PF4a between consecutive visits: κ values ranged between 0.81 and 0.94 versus a range between 0.72 and 0.84, respectively. The area under the ROC curve for predicting the MDA HAQ DI was 0.97 for the MDA PROMIS-PF bank and 0.95 for the MDA PROMIS-PF4a.

**Conclusion.** Excellent agreement was seen between the HAQ DI and the PROMIS-based MDA definitions both cross-sectionally and longitudinally. The PROMIS-PF bank and PROMIS-PF4a are accurate replacements for the HAQ DI in calculating MDA state in PsA.

## INTRODUCTION

Psoriatic arthritis (PsA) is an autoimmune disease that affects up to 1% of the US population and approximately 1 of 3 people living with the skin disease psoriasis. PsA is heterogeneous in pathophysiology, affecting the joints, entheses, digits, spine, skin, and skin appendages. Its impact on quality of life is equally broad and manifests with symptoms of pain, fatigue, and depression/anxiety, as well as decreased physical function and social participation, disability, and work loss (1,2).

The PsA treat-to-target state was established through consensus among international experts (3) and was provisionally endorsed by the American College of Rheumatology and the National Psoriasis Foundation (4). Minimal disease activity (MDA) is a PsA treat-to-target state defined by meeting prespecified criteria for disease activity across PsA pathophysiologic manifestations (swollen and tender joints, enthesitis, psoriasis) and patient-reported outcomes (physical function, pain, and patient global assessment of psoriatic disease) (5). The original MDA criteria capture patient-reported physical function

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**SIGNIFICANCE & INNOVATIONS**

- This study demonstrated excellent cross-sectional and longitudinal agreement between the Health Assessment Questionnaire disability index (HAQ DI) and Patient-Reported Outcomes Measurement Information System (PROMIS)–based minimal disease activity (MDA) definitions in psoriatic arthritis (PsA).
- The PROMIS–Physical Function short form 4a or computer adaptive test can adequately replace the HAQ DI for the purpose of defining MDA and treat-to-target determination in PsA.
- PROMIS–Physical Function has the advantage of assessing physical function on an extended spectrum of ability and can concomitantly be used for MDA calculation in PsA.

through the Health Assessment Questionnaire disability index (HAQ DI) (6).

The Patient-Reported Outcomes Measurement Information System (PROMIS) (7) is a library of patient-reported outcome instruments developed using state-of-the art psychometric science and normed to the general US population (a T score of 50 represents the US population mean and the SD is 10 points) (8). PROMIS measures are increasingly available in medical records and can be incorporated into routine care (8). Through the PROsetta Stone project (9), walkways have been developed between PROMIS scores and commonly used legacy instruments, such as linking PROMIS–Physical Function (PF) scores with HAQ DI scores (10). Specifically, for assessing physical function, adapting patient-reported outcomes to include activities that reflect therapeutic advances in rheumatology is increasingly relevant (11). PROMIS measures have been developed using qualitative research as the basis of item content and item formulation for each questionnaire/item bank, and assessments are focused on each individual's physical function ability, not merely on the lack of disability and/or frequency of tasks performed (12). From this perspective, the PROMIS-PF items cover the basic activities of daily living (walking, dressing) and also complex activities (dancing, jogging, taking part in sports, and strenuous activities). Items are formulated in the present tense using simple syntax for clarity and comprehension, and each item has 4 or 5 response options instead of 3, as is the case with the HAQ DI, to reduce floor and ceiling effects and provide greater discrimination (12).

Thus, while physical function has been assessed for a long time using the HAQ DI, transitioning to more current population-normed instruments such as the PROMIS-PF is of interest (10). Schalet et al conducted a single-group design study using a large standardization sample centered on the 2000 US census and linked legacy physical function patient-reported outcome to the PROMIS-PF scale. Thus, there now exists a common reporting metric that can support transition from legacy instruments to PROMIS-PF scales.

In our study, we sought to determine whether the PROMIS-PF can replace the HAQ DI as a measure of physical function to accurately classify the MDA treat-to-target state in PsA. The objective was to compare agreement between the routine HAQ DI–based MDA definition and the PROMIS-PF–based MDA definitions in a PsA cohort where we conducted longitudinal PsA-specific disease status assessments.

## PATIENTS AND METHODS

**Johns Hopkins Psoriatic Arthritis Cohort.** The Johns Hopkins Psoriatic Arthritis cohort is approved by The Johns Hopkins Institutional Review Board (00063222). All study subjects signed written informed consent prior to participating in the study. Research visits were conducted every 3–6 months in conjunction with guideline-based rheumatologic care for PsA.

Adult patients with rheumatologist-diagnosed PsA were eligible to participate if they met the Classification Criteria for Psoriatic Arthritis (13). At each visit, PsA-specific measures included tender joint count (0–68), swollen joint count (0–66) (14), enthesitis count using the Leeds Enthesitis Index (0–6) (15), active tender dactylitis count (0–20), percent body surface area affected by active psoriasis (0–100%), pain numeric rating scale (NRS) (0–10), patient global psoriatic disease NRS (0–10), patient global PsA NRS (0–10), and the HAQ DI (0–3).

In addition, we collected PROMIS-PF measures, including the PROMIS bank, version 1.2, Physical Function, and the PROMIS short form, version 2.0, Physical Function form 4a (collected as part of the PROMIS Profile-29, version 1.0) (8). Participants completed all questionnaires in the clinic room, prior to the rheumatology visit with the physician, through self-report and without assistance.

**Measures.** *HAQ DI.* The HAQ DI is a legacy physical function patient-reported outcome developed by the Stanford Arthritis Center for Rheumatoid Arthritis (6). It has been used in every PsA randomized controlled trial as part of the American College of Rheumatology response criteria and is also included in the MDA definition. The HAQ DI consists of 20 questions in 8 categories (dressing and grooming, hygiene, arising, reach, eating, grip, walking, outside activities). Each item has 4 response options, ranging from No difficulty to Unable to do, corresponding to scores from 0 to 3 (6). Lower HAQ DI scores mean better function. The minimally important difference, or the smallest improvement considered to be clinically important in PsA, is defined by a longitudinal improvement in HAQ DI score of 0.35 points (16). The PsA MDA criterion for the HAQ DI is met by a score of ≤0.5 (5). The HAQ DI was administered on paper clinical research forms concomitantly with the pain and patient global NRS.

*PROMIS instruments.* The PROMIS instruments were developed using item response theory by the National Institutes of Health (NIH) (7). PROMIS scores are normed to the US population and expressed as T scores with a mean of 50 (representing the US population mean for the measure as the reference) and an SD

of 10. Higher PROMIS-PF scores mean better function. The PROMIS-PF measures can be administered either as fixed-content short forms or as a computer adaptive test (CAT) that selects items from the entire Physical Function item bank (PROMIS-PF bank). For CAT administration, items from the PROMIS-PF bank are dynamically selected based on a patient's prior response to precisely capture each patient's functional status (17,18). The equivalent PROMIS-PF T score for a HAQ DI score of ≤0.5 has been defined as ≥41.3 (10). Participants completed the fixed PROMIS-PF short form 4a, which includes PROMIS items PFA11, PFA21, PFA23, and PFA53 (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24433/abstract). They also completed the PROMIS bank, version 1.2, Physical Function, administered on a tablet through the assessment center platform (www.assessmentcenter.net) using CAT and limited to 8 items maximum, followed by the PROMIS-PF4a. The short form was programmed without repetition with the CAT. English language versions, developed for adult participants, were used in the study. Scoring was performed automatically through the assessment center platform, and results were downloaded. Reporting of study results is being done in accordance with the recently published "Reporting checklist for ASCQ-Me, Neuro-QoL, NIH Toolbox Emotion, and PROMIS Measures" (19).

*Treat-to-target states.* The MDA criteria are listed in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24433/abstract. If 5 of the 7 criteria are met (tender joint count [0–68] ≤1, swollen joint count [0–66] ≤1, enthesitis [0–6] ≤1, pain NRS [0–10] ≤1.5, patient global assessment psoriatic disease [0–10] ≤2, HAQ DI [0–3] ≤0.5, and body surface area affected by psoriasis [0–100] ≤3%), then PsA disease activity corresponds to the MDA state and the treat-to-target objective has been achieved. We also examined the very low disease activity (VLDA) state, defined as all 7 MDA criteria being met (5). In addition, we calculated the clinical Disease Activity in Psoriatic Arthritis (cDAPSA) score, defined as the sum of the tender (0–68) and swollen (0–66) joint counts, pain NRS (0–10), and patient global PsA NRS (0–10). Disease activity thresholds for cDAPSA were defined as remission (≤4), low (>4 to ≤13), moderate (>13 to ≤27), and high disease activity (>27) (20). A cDAPSA score of ≤13 is considered as an alternate treat-to-target state to MDA (3).

**Statistical analysis.** Descriptive analyses for PsA disease characteristics, disease activity, and demographic characteristics were calculated. The established crosswalk tables between the HAQ DI criterion (HAQ DI ≤0.5) and the PROMIS-PF corresponding cutoffs (T score ≥41.3) (10) were used to build PROMIS-based MDA definitions. For each patient, we assessed MDA using the usual method, with the HAQ DI score of ≤0.5 criterion (HAQ DI MDA) and alternate MDA definitions using the PROMIS-PF score of ≥41.3 as a replacement for the HAQ DI criterion, with all other MDA criteria except PF/HAQ DI being kept constant (PROMIS-PF4a MDA and PROMIS-PF CAT MDA).

To measure agreement between the original HAQ DI MDA definition with the PROMIS MDA definitions (MDA state met, MDA state not met), we used the kappa statistic with the following interpretation: ≤0.2 = slight, 0.2 to ≤0.4 = fair, 0.4 to ≤0.6 = moderate, 0.6 to ≤0.8 = substantial, and >0.8 = excellent agreement (21). We calculated the kappa statistic at each visit, globally across all visits, and longitudinally for state changes in MDA between consecutive visits. We used bootstrapping of individual patients, with 2,000 repetitions to calculate bias-corrected 95% confidence intervals (95% CIs) for the kappa statistic (22). Additionally, we conducted sensitivity analyses by estimating kappa values in subgroups, including sex, age, pain level, patient global assessment, treat-to-target state, and levels of physical function and disability. To further assess the validity of PROMIS-based MDA definitions, we calculated the agreement of all MDA definitions with the alternative definition of treat-to-target state using the cDAPSA cutoff of ≤13 (20). Where the number of available observations was <50, the kappa statistic was not calculated.

We calculated the sensitivity and specificity of PROMIS-MDA for the HAQ DI–based MDA by assessing the area under the curve from logistic regression, modeled to predict the HAQ DI MDA using each PROMIS MDA definition by visit and globally across all visits. In an exploratory analysis, we built a receiver operator characteristic (ROC) curve to compare different thresholds of the PROMIS scores to identify which cutoff best approximates patients with a HAQ DI score of <0.5. Using each measured value of the PROMIS score as a cutoff, we plotted the true positive rate (sensitivity) against the false positive rate (1 – specificity) (23). To define the most favorable cutoff among this PsA cohort, we calculated a Youden index (sensitivity + specificity – 1) for each cutoff of the PROMIS score, and chose the cutoff with the highest value (24).

To assess longitudinal construct validity of PROMIS-based MDA definitions, we calculated agreement of change in PROMIS MDA with change in HAQ DI MDA. To accomplish this assessment, each participant was evaluated for longitudinal change in their MDA status at consecutive visits. MDA state change was determined between consecutive visits for each MDA definition (MDA HAQ DI change, MDA PROMIS-PF4a change, and MDA PROMIS-PF CAT change). Participants were categorized as either improved if they transitioned from non-MDA to MDA at consecutive visits; worsened if they transitioned from MDA to non-MDA; or unchanged if their MDA category remained stable across consecutive visits. For all analyses specified above, when the number of observations was sufficient, we also assessed the kappa statistic between HAQ DI VLDA and PROMIS-PF VLDA definitions for static and change states.

## RESULTS

**Participant characteristics.** A total of 100 patients contributed 352 total observations with up to 5 visits. The mean ± SD age was 52 ± 12 years at cohort enrollment, 60% were female, 92% were White, 4% African American, and 4% Asian. The majority of participants were working full time (56%), while 15% were retired and 14% were on disability. Among participants, 93% had at least 2 consecutive visits, 84% had ≥3, 71% had ≥4, and 4% had 5. The average time intervals between consecutive visits were 18.4, 12.1, 13.3, and 17.2 weeks, respectively. Participants completed a mean ± SD number of PROMIS-PF bank items as follows: 4.39 ± 1.07 at baseline, 4.39 ± 1.09 at the second visit, 4.37 ± 1.04 at the third visit, and 4.35 ± 0.99 at the fourth visit.

At baseline, the mean ± SD number of tender (of 68) and swollen (of 66) joint counts was 3.23 ± 4.87 and 3.08 ± 3.74, respectively. Seven percent of participants had enthesitis, and 3% had active dactylitis. The mean ± SD pain NRS was 3.61 ± 2.87, patient global psoriatic disease 3.77 ± 3.18, HAQ DI score 0.71 ± 0.76, PROMIS-PF4a T score 43.03 ± 9.39, and PROMIS-PF CAT T score 43.76 ± 10.29. At baseline, 43% met HAQ DI–based MDA/PROMIS-PF4a–based MDA/PROMIS-PF CAT–based MDA, and 53% met cDAPSA (≤13). The majority (56%) were treated with biologics alone or in combination with disease-modifying antirheumatic drugs (DMARDs), and 25% were treated with DMARDs alone (Table 1). At baseline, 25% of participants had a HAQ DI score of zero (floor effect), and at subsequent visits, percentages ranged from 23% to 30%, with a HAQ DI score of zero (Table 1). This floor effect did not occur with the PROMIS-PF scores. In addition, the PROMIS-PF CAT scores were approximately normally distributed in the PsA population (see Supplementary Figure 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24433/abstract). Missing data on all variables used are summarized in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24433/abstract.

**Agreement among MDA/VLDA definitions.** The kappa statistic for HAQ DI– and PROMIS-PF–based MDA definitions reflected excellent agreement (κ >0.8) consistently at each visit: the kappa value ranged between 0.83 and 0.93 for the PROMIS-PF4a–based MDA, and between 0.91 and 0.98 for PROMIS-PF CAT–based MDA (Table 2). Kappa values for VLDA were consistent with MDA and ranged between 0.81 and 0.88 for the PROMIS-PF4a–based VLDA and between 0.76 and 0.91 for PROMIS-PF CAT–based VLDA (Table 2).

Agreement between physical function equivalence thresholds for HAQ DI and PROMIS-PF reflected substantial agreement (κ > 0.6) at each visit and overall, across visits: κ = 0.73 (95% CI 0.65–0.80) for PROMIS-PF4a and κ = 0.75 (95% CI 0.67–0.81) for PROMIS-PF CAT (see Supplementary Table 2, available on

**Table 1.** Summary statistics of the psoriatic arthritis cohort at each visit*

| Measures | Visit 1 (n = 100) | Visit 2 (n = 93) | Visit 3 (n = 84) | Visit 4 (n = 71) |
|---|---|---|---|---|
| Tender joint count (0–68) | 3.23 ± 4.87 | 3.97 ± 5.92 | 3.94 ± 4.95 | 5.66 ± 7.98 |
| Swollen joint count (0–66) | 3.08 ± 3.74 | 3.09 ± 3.78 | 3.65 ± 3.69 | 4.14 ± 5.16 |
| Enthesitis, no. (%) | 7 (7) | 7 (7.53) | 8 (9.52) | 12 (16.90) |
| Dactylitis, no. (%) | 3 (3) | 5 (5.38) | 4 (4.76) | 2 (2.82) |
| Psoriasis BSA (0–100) | 2.23 ± 4.73 | 3.07 ± 9.35 | 4.77 ± 12.03 | 3.03 ± 6.25 |
| Percent BSA ≥10, no. (%) | 5 (5) | 5 (5.38) | 10 (11.90) | 6 (8.45) |
| Pain NRS (0–10) | 3.61 ± 2.87 | 3.45 ± 2.89 | 3.73 ± 3.13 | 3.48 ± 2.93 |
| Patient global psoriatic disease NRS (0–10) | 3.77 ± 3.18 | 3.29 ± 2.99 | 3.34 ± 2.99 | 3.53 ± 2.98 |
| Patient global psoriatic arthritis NRS (0–10) | 3.79 ± 3.02 | 3.33 ± 2.87 | 3.31 ± 2.95 | 3.57 ± 2.98 |
| PROMIS-PF4a (0–100), T score | 43.03 ± 9.39 | 44.15 ± 9.74 | 43.70 ± 9.86 | 45.15 ± 9.71 |
| PROMIS-PF CAT (0–100), T score | 43.76 ± 10.29 | 45.02 ± 9.97 | 44.49 ± 10.23 | 44.85 ± 9.46 |
| HAQ DI (0–3) | 0.71 ± 0.76 | 0.61 ± 0.70 | 0.68 ± 0.73 | 0.64 ± 0.73 |
| HAQ DI = 0, no. (%) | 25 (25) | 30 (32.26) | 25 (29.76) | 23 (32.39) |
| MDA HAQ DI, no. (%) | 43 (43) | 47 (57.32) | 33 (45.21) | 28 (48.28) |
| MDA PROMIS-PF4a, no. (%) | 43 (43) | 43 (51.81) | 31 (42.47) | 28 (46.67) |
| MDA PROMIS-PF CAT, no. (%) | 43 (43) | 46 (54.76) | 33 (44.59) | 31 (51.67) |
| VLDA HAQ DI, no. (%) | 9 (9) | 11 (11.83) | 10 (11.90) | 9 (12.68) |
| VLDA PROMIS-PF4a, no. (%) | 9 (9) | 11 (11.83) | 10 (11.90) | 9 (12.68) |
| VLDA PROMIS-PF CAT, no. (%) | 10 (10) | 12 (12.90) | 10 (11.90) | 9 (12.68) |
| cDAPSA treat-to-target state, no. (%) | 53 (53) | 54 (63.53) | 45 (55.56) | 34 (54.29) |
| Biologics alone or in DMARD combination, no. (%) | 56 (56) | 58 (62.37) | 58 (69.05) | 52 (73.34) |
| DMARD alone, no. (%) | 25 (25) | 25 (26.88) | 17 (20.24) | 15 (21.13) |

* Values are the mean ± SD unless indicated otherwise. Minimal disease activity (MDA) Patient-Reported Outcomes Measurement Information System short form, version 2.0, Physical Function 4a (PROMIS-PF4a) includes the PROMIS-PF4a T score of ≥ 41.3 criterion. The MDA PROMIS bank, version 1.2, Physical Function computer adaptive test (PROMIS-PF CAT) includes the PROMIS-PF CAT T score of ≥41.3 criterion. The MDA Heath Assessment Questionnaire disability index (HAQ DI) includes the HAQ DI score of ≤0.5 criterion. BSA = body surface area affected by psoriasis; cDAPSA = clinical Disease Activity Psoriatic Arthritis; DMARD = disease-modifying antirheumatic drug; NRS = numeric rating scale; VLDA = very low disease activity (VLDA variables similarly defined to MDA variables).

**Table 2.** Agreement between the HAQ DI–based MDA/VLDA and the PROMIS-PF–based MDA/VLDA definitions at each visit*

| Agreement | Visit 1 | Visit 2 | Visit 3 | Visit 4 |
|---|---|---|---|---|
| MDA HAQ DI and MDA PROMIS-PF4a | | | | |
| Kappa (95% CI) | 0.91 (0.80–0.98) | 0.93 (0.82–1.00) | 0.92 (0.80–1.00) | 0.83 (0.66–0.96) |
| No. | 86 | 81 | 72 | 58 |
| MDA HAQ DI and MDA PROMIS-PF CAT | | | | |
| Kappa (95% CI) | 0.91 (0.81–0.98) | 0.98 (0.90–1.00) | 0.94 (0.84–1.00) | 0.93 (0.82–1.00) |
| No. | 86 | 82 | 73 | 58 |
| VLDA HAQ DI and MDA PROMIS-PF4a | | | | |
| Kappa (95% CI) | 0.82 (0.72–0.91) | 0.88 (0.78–0.95) | 0.85 (0.75–0.93) | 0.81 (0.68–0.92) |
| No. | 80 | 69 | 68 | 55 |
| VLDA HAQ DI and VLDA PROMIS-PF CAT | | | | |
| Kappa (95% CI) | 0.76 (0.65–0.86) | 0.88 (0.79–0.95) | 0.91 (0.83–0.98) | 0.87 (0.77–0.96) |
| No. | 80 | 70 | 68 | 55 |

* Bias-corrected 95% confidence interval (95% CI) was calculated using bootstrapping with 2,000 repetitions of individual patients. The minimal disease activity (MDA) Patient-Reported Outcomes Measurement Information System short form, version 2.0, Physical Function 4a (PROMIS-PF4a) includes the PROMIS-PF4a T score of ≥41.3 criterion. The MDA PROMIS bank, version 1.2, Physical Function computer adaptive test (PROMIS-PF CAT) includes the PROMIS-PF CAT T score of ≥41.3 criterion. The very low disease activity (VLDA) PROMIS-PF4a includes the PROMIS-PF4a T score of ≥41.3 criterion. The VLDA PROMIS-PF CAT includes the PROMIS-PF CAT T score of ≥41.3 criterion. The MDA Heath Assessment Questionnaire disability index (HAQ DI) and the VLDA HAQ DI both include the HAQ DI score of ≤0.5 criterion.

the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24433/abstract).

**Sensitivity analyses in subgroups.** Agreement between the MDA HAQ DI and the MDA PROMIS-PF CAT was generally greater than that between MDA HAQ DI and MDA PROMIS-PF4a among subgroups of male and female, age ≤51 and age >51 years, high and low pain as defined by pain NRS median, high and low global psoriatic disease as defined by the patient global psoriatic disease NRS median, and treat-to-target state subgroups using cDAPSA (≤13/>13) (see Supplementary Figure 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24433/abstract).

**Table 3.** Agreement between the HAQ DI–based MDA and the PROMIS-PF–based MDA in subgroups defined by physical function ability across all visits*

| | HAQ DI MDA | | HAQ DI VLDA | |
|---|---|---|---|---|
| Agreement in subgroups | PROMIS-PF4a MDA | PROMIS-PF CAT MDA | PROMIS-PF4a VLDA | PROMIS-PF CAT VLDA |
| HAQ DI ≤0.5 (less/no disability) | | | | |
| Kappa (95% CI) | 0.86 (0.77–0.93) | 0.94 (0.88–0.99) | 0.84 (0.78–0.90) | 0.93 (0.88–0.97) |
| No. | 184 | 186 | 159 | 160 |
| HAQ DI >0.5 (more disability) | | | | |
| Kappa (95% CI) | 0.76 (0.53–0.95) | 0.76 (0.53–0.95) | 0.80 (0.71–0.88) | 0.70 (0.60–0.79) |
| No. | 116 | 116 | 116 | 116 |
| PROMIS-PF4a T score ≥ 41.3 (better physical function ability) | | | | |
| Kappa (95% CI) | 0.93 (0.85–0.98) | 0.93 (0.85–0.98) | 0.86 (0.79–0.91) | 0.86 (0.79–0.91) |
| No. | 182 | 182 | 157 | 157 |
| PROMIS-PF4a T score < 41.3 (worse physical function ability) | | | | |
| Kappa (95% CI) | 0.55 (0.31–0.78) | 0.86 (0.70–0.97) | 0.78 (0.70–0.86) | 0.81 (0.72–0.88) |
| No. | 118 | 120 | 118 | 118 |
| PROMIS-PF CAT T score ≥ 41.3 (better physical function ability) | | | | |
| Kappa (95% CI) | 0.87 (0.79–0.94) | 0.94 (0.88–0.99) | 0.80 (0.73–0.87) | 0.81 (0.74–0.87) |
| No. | 203 | 205 | 177 | 178 |
| PROMIS-PF CAT T score < 41.3 (less physical function ability) | | | | |
| Kappa (95% CI) | 0.65 (0.17–0.92) | 0.65 (0.17–0.92) | 0.88 (0.80–0.95) | 0.88 (0.79–0.94) |
| No. | 98 | 98 | 98 | 98 |

* Bias-corrected 95% confidence intervals (95% CIs) for the kappa statistic were calculated using bootstrapping with 2,000 repetitions of individual patients. The minimal disease activity (MDA) Heath Assessment Questionnaire disability index (HAQ DI) and the very low disease activity (VLDA) HAQ DI both include the HAQ DI ≤0.5 criterion. The MDA Patient-Reported Outcomes Measurement Information System short form, version 2.0, Physical Function 4a (PROMIS-PF4a) includes the PROMIS-PF4a T score of ≥41.3 criterion. The MDA PROMIS bank, version 1.2, Physical Function computer adaptive test (PROMIS-PF CAT) includes the PROMIS-PF CAT T score of ≥41.3 criterion. The VLDA PROMIS-PF4a includes the PROMIS-PF4a T score of ≥41.3 criterion. The VLDA PROMIS-PF CAT includes the PROMIS-PF CAT T score of ≥41.3 criterion.

**Table 4.** Agreement between MDA definitions and clinical Disease Activity in Psoriatic Arthritis (cDAPSA) treat-to-target state (≤13) across all visits*

| Agreement | MDA PROMIS-PF4a | MDA PROMIS-PF CAT | cDAPSA treat-to-target (≤13) |
|---|---|---|---|
| MDA HAQ DI | | | |
| Kappa (95% CI) | 0.90 (0.84–0.95) | 0.94 (0.90–0.97) | 0.70 (0.62–0.77) |
| No. | 301 | 303 | 299 |
| MDA PROMIS-PF4a | | | |
| Kappa (95% CI) | – | 0.96 (0.93–0.99) | 0.67 (0.59–0.75) |
| No. | – | 307 | 303 |
| MDA PROMIS-PF CAT | | | |
| Kappa (95% CI) | – | – | 0.71 (0.63–0.78) |
| No. | – | – | 305 |

* Bias-corrected 95% confidence intervals (95% CIs) for the kappa statistic were calculated using bootstrapping with 2,000 repetitions of individual patients. The minimal disease activity (MDA) Heath Assessment Questionnaire disability index (HAQ DI) includes the HAQ DI score of ≤0.5 criterion. The MDA Patient-Reported Outcomes Measurement Information System short form, version 2.0, Physical Function 4a (PROMIS-PF4a) includes the PROMIS-PF4a T score of ≥41.3 criterion. The MDA PROMIS bank, version 1.2, Physical Function computer adaptive test (PROMIS-PF CAT) includes the PROMIS-PF CAT T score of ≥41.3 criterion.

Agreement between MDA HAQ DI and MDA PROMIS-PF CAT reflected excellent agreement in sex groups: $\kappa = 0.93$ (95% CI 0.86–0.98) for female patients and $\kappa = 0.95$ (95% CI 0.87–1.00) for male patients. Agreement was slightly higher between MDA HAQ DI and MDA PROMIS-PF4a in female patients: $\kappa = 0.91$ (95% CI 0.84–0.96) compared to male patients: $\kappa = 0.86$ (95% CI 0.77–0.95). Agreement was higher between MDA HAQ DI and both PROMIS-PF MDA states in patients who were younger than the median age of 51 years: $\kappa = 0.91$ (95% CI 0.84–0.97) for MDA PROMIS-PF4a and $\kappa = 0.96$ (95% CI 0.91–1.00) for MDA PROMIS-PF CAT, compared to those ages >51 years: $\kappa = 0.89$ (95% CI 0.80–0.96) for MDA PROMIS-PF4a and $\kappa = 0.92$ (95% CI 0.84–0.97) for MDA PROMIS-PF CAT. There was higher agreement between MDA HAQ DI and both PROMIS-PF MDA states in participants with lower pain: $\kappa = 0.82$ (95% CI 0.68–0.93) for MDA PROMIS-PF4a and $\kappa = 0.90$ (95% CI 0.79–0.98) for MDA PROMIS-PF CAT compared to higher pain: $\kappa = 0.76$ (95% CI 0.55–0.91) for MDA PROMIS-PF4a and $\kappa = 0.84$ (95% CI 0.66–0.96) for MDA PROMIS-PF CAT (see Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24433/abstract).

Taking physical function as the grouping criterion, agreement between MDA HAQ DI and PROMIS MDA was higher in those with HAQ DI scores of ≤0.5: $\kappa = 0.86$ (95% CI 0.77–0.93) for MDA PROMIS-PF4a and $\kappa = 0.94$ (95% CI 0.88–0.99) for MDA PROMIS-PF CAT, compared to those with worse HAQ DI scores of >0.5: $\kappa = 0.76$ (95% CI 0.53–0.95) for MDA PROMIS-PF4a and $\kappa = 0.76$ (95% CI 0.53–0.95) for MDA PROMIS-PF CAT. Analysis using grouping defined by T scores for physical function (≥41.3 versus <41.3) yielded similar results (Table 3). Findings for agreement between VLDA definitions were consistent with the findings for MDA except when physical function ability was grouped by PROMIS-PF CAT scores: agreement was slightly higher in the subgroups with a PROMIS-PF CAT T score of <41.3 versus ≥41.3, although in the excellent range for all subgroups (Table 3).

**Validity of PROMIS MDA using cDAPSA treat-to-target states and area under the curve.** We calculated agreement between clinical cDAPSA treat-to-target state (cDAPSA ≤13) with each of the MDA definitions and found substantial agreement for each. As seen in Table 4, $\kappa = 0.70$ (95% CI 0.62–0.77), $\kappa = 0.67$ (95% CI 0.59–0.75), and $\kappa = 0.71$ (95% CI 0.63–0.78) for MDA HAQ DI, MDA PROMIS-PF4a, and MDA PROMIS-PF CAT, respectively. Figure 1 represents agreement among the 3 MDA definitions with cDAPSA treat-to-target using Venn diagrams and reflects almost overlapping agreement among the MDA definitions with the cDAPSA, while confirming cDAPSA as a more generous treat-to-target classification compared to any of the MDA definitions (Figure 1).

VLDA agreement with cDAPSA remission (cDAPSA ≤4) was substantial, with $\kappa = 0.65$ (95% CI 0.52–0.76), $\kappa = 0.68$ (95% CI 0.59–0.79), and $\kappa = 0.68$ (95% CI 0.56–0.78) for MDA HAQ DI, MDA PROMIS-PF4a, and MDA PROMIS-PF CAT, respectively (see Supplementary Table 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24433/abstract). Areas under the ROC curve to predict HAQ DI–based MDA using MDA PROMIS-PF4a or MDA PROMIS-PF CAT across all visits were 0.95 and 0.97, respectively. These calculations were consistent at each visit (see Supplementary Figure 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24433/abstract).

The best cutoffs of the PROMIS-PF T scores to represent whether the HAQ DI score is <0.5 in this PsA cohort were based on the Youden index and are presented in comparison with the performance of the external cutoff, as exploratory analyses. For the PROMIS-PF4a, the best cutoff in the PsA data set was represented by a T score of 39.8, which had a sensitivity of 81.6%, a specificity of 95.4%, and a corresponding Youden index value of 0.770. Comparatively, the external cutoff determined by Schalet et al (10), a T score of 41.3, had a sensitivity of 85.8%, a specificity of 87.3%, and a corresponding Youden index value of 0.731, for representing a HAQ DI score of <0.5 in the cohort (see Supplementary Figure 4, available on the *Arthritis Care & Research* website at http://

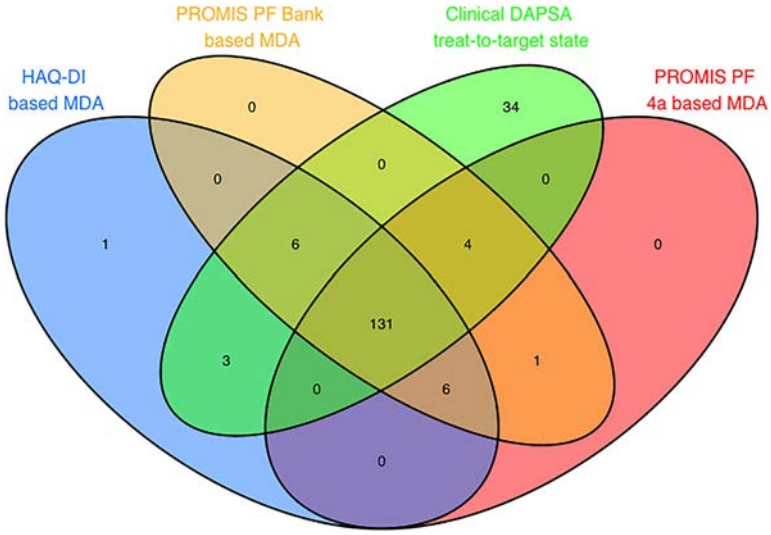


**Figure 1.** Classification overlap between the 4 proposed definitions of treat-to-target: minimal disease activity (MDA) Heath Assessment Questionnaire disability index (HAQ-DI), MDA Patient Reported Outcomes Measurement Information System short form, version 2.0, Physical Function form 4a (PROMIS PF), MDA PROMIS bank, version 1.2, Physical Function CAT, and clinical Disease Activity Psoriatic Arthritis (DAPSA) treat-to-target. Numbers represent available observations across all visits where participants were classified as having met 1 of the treatment targets. Diagram is not represented to scale.

onlinelibrary.wiley.com/doi/10.1002/acr.24433/abstract). For the PROMIS-PF CAT, the best cutoff was a T score of 40.2, which had a sensitivity of 77.3%, a specificity of 97%, and a corresponding Youden index value of 0.742. Comparatively the cutoff represented by a T score of 41.3 had a sensitivity of 79.4%, a specificity of 92.4%, and a corresponding Youden index value of 0.719, for representing a HAQ DI score of <0.5 in the cohort (see Supplementary Figure 5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24433/abstract).

**Longitudinal validity of PROMIS-based MDA definitions.** The kappa value between MDA HAQ DI change and MDA PROMIS-PF4a change was $\kappa = 0.75$ (95% CI 0.47–0.95), $\kappa = 0.84$ (95% CI 0.58–1.00), and $\kappa = 0.72$ (95% CI 0.37–0.94) across consecutive visits 1–2, 2–3, and 3–4, respectively. The kappa value between the MDA HAQ DI change and the MDA PROMIS-PF CAT change was $\kappa = 0.81$ (95% CI 0.49–1.00), $\kappa = 0.94$ (95% CI 0.75–1.00), and $\kappa = 0.84$ (95% CI 0.48–1.00) across consecutive visits,

**Table 5.** Longitudinal agreement between the HAQ DI–based MDA state change and the corresponding PROMIS-PF4a–based MDA state change*

| Agreement | Visit 1–2 | Visit 2–3 | Visit 3–4 |
|---|---|---|---|
| MDA HAQ DI with MDA PROMIS-PF4a | | | |
| Kappa (95% CI) | 0.75 (0.47–0.95) | 0.84 (0.58–1.00) | 0.72 (0.37–0.94) |
| No. | 71 | 67 | 51 |
| MDA HAQ DI with MDA PROMIS-PF CAT | | | |
| Kappa (95% CI) | 0.81 (0.49–1.00) | 0.94 (0.75–1.00) | 0.84 (0.48–1.00) |
| No. | 72 | 68 | 52 |
| VLDA HAQ DI with VLDA PROMIS-PF4a | | | |
| Kappa (95% CI) | 0.75 (0.44–0.95) | 0.84 (0.51–1.00) | – |
| No. | 59 | 57 | 47 |
| VLDA HAQ DI with VLDA PROMIS-PF CAT | | | |
| Kappa (95% CI) | 0.82 (0.55–1.00) | 0.92 (0.64–1.00) | – |
| No. | 60 | 58 | 47 |

* Minimal disease activity (MDA) or very low disease activity (VLDA) state changes were defined as transitions in corresponding MDA or VLDA state between consecutive visits, for example visit 1–2 represents agreement between transitions in MDA (or VLDA) Heath Assessment Questionnaire disability index (HAQ DI) state from visit 1 to visit 2 with transitions in each MDA (or VLDA) Patient-Reported Outcomes Measurement Information System short form, version 2.0, Physical Function 4a (PROMIS-PF4a) state from visit 1 to visit 2. Bias-corrected 95% confidence intervals (95% CIs) for the kappa statistic were calculated using bootstrapping with 2,000 repetitions of individual patients. When sample size was <50, kappa value and 95% CI were not calculated. The MDA HAQ DI and the VLDA HAQ DI both include the HAQ DI ≤0.5 criterion. The MDA PROMIS-PF4a includes the PROMIS-PF4a T score of ≥41.3 criterion. The MDA PROMIS bank, version 1.2, Physical Function computer adaptive test (PROMIS-PF CAT) includes the PROMIS-PF CAT T score of ≥41.3 criterion. The VLDA PROMIS-PF4a includes the PROMIS-PF4a T score of ≥41.3 criterion. The VLDA PROMIS-PF CAT includes the PROMIS-PF CAT T score of ≥41.3 criterion.

respectively (Table 5). Agreement between transitions was similarly in the substantial-to-excellent range for VLDA definitions (Table 5).

## DISCUSSION

Measuring patient outcomes efficiently and accurately is crucial to evaluating therapies and monitoring disease progression in PsA. Patients who are receiving newer biologic agents are now functioning above average. Early detection of deterioration in clinical status in those with high levels of physical function is essential to providing optimal clinical care. Because the HAQ DI focuses on assessing degree of disability, it performs well in disabled populations but not as well in those with average or above average physical function (25). Thus, those classified as having no disability and at treat-to-target as defined by the HAQ DI MDA criteria may have an overestimated measure of physical functioning. Similarly, deterioration or improvement within the range of no disability may not be captured. Compared to the HAQ DI, the PROMIS-PF item bank is expanded to include items assessing higher levels of physical functioning (i.e., strenuous and vigorous exercise such as running and weight lifting). Thus, the PROMIS scales are designed to focus on ability and are more sensitive than the legacy HAQ DI in detecting clinical improvement or deterioration on newer therapies (17,26,27). The PROMIS instruments are also designed to be less taxing on patients and offer higher precision in assessing physical function than the legacy HAQ DI, with fewer questions (17,26), especially with CAT administration.

Our study is the first to compare agreement of the PROMIS and the HAQ DI MDA definitions in a PsA cohort, based on the equivalency of a HAQ DI score of 0.5 to a PROMIS-PF T score of 41.3 (10). Our findings suggest that the PROMIS is an accurate replacement for the HAQ DI, given substantial to excellent agreement between the PROMIS and the HAQ DI–based MDA definitions, in cross-sectional as well as longitudinal analyses.

In our cohort, agreement was always higher between the HAQ DI and the PROMIS-PF CAT–based MDA states than between the HAQ DI and the PROMIS-PF4a–based MDA states, which may be explained by higher precision and reduced ceiling and floor effects with the use of CAT. On average, $\kappa = 0.90$, indicating near perfect agreement between the HAQ DI–based MDA and both PROMIS-based MDA states in this guideline-based treated PsA population. Furthermore, the area under the curve for predicting the HAQ DI–based MDA using either PROMIS definition was consistently >0.90 at each visit, supporting excellent accuracy for both PROMIS-based MDA definitions. Agreement of MDA definitions with the cDAPSA treat-to-target state was substantial and in the ranges observed in other studies (28).

Substantial agreement ($\kappa$ >0.6) was observed between HAQ DI and PROMIS scores at the equivalence cutoff used, compared to excellent agreement ($\kappa$ >0.8) between HAQ DI and PROMIS-based MDA states. At baseline, agreement between the HAQ DI and each PROMIS-PF–based MDA definition remained high despite lower agreement between the HAQ DI and each PROMIS score. Since the physical function score was the only changing variable in calculation of the HAQ DI versus the PROMIS-PF–based MDA state, perfect agreement of raw physical function scores may not be necessary for high MDA state agreement. However, at lower states of physical functioning, MDA agreement dropped from excellent (at high physical function level) to moderate-substantial, reflecting the fact that differences in the physical function score were more likely to change the MDA status in this group, likely because other MDA criteria were not met.

Excellent agreement between HAQ DI and PROMIS-based MDA states was maintained within subgroups of sex, age, and pain levels. Agreement was overall higher between the MDA HAQ DI and the MDA PROMIS-PF CAT than the MDA PROMIS-PF4a; agreement was also generally higher in men versus women, in participants above or below age 51 years, lower versus higher pain/patient global assessment, those at treat-to-target state versus not, lower HAQ DI scores, and higher PROMIS scores. In sum, agreement between the HAQ DI and the PROMIS-PF4a–based MDA was highest in those doing well on multiple MDA criteria. The observed differences in agreement between the MDA HAQ DI with the PROMIS-PF4a definitions among people doing well versus people doing not so well, attenuated significantly with the use of the PROMIS-PF CAT–based MDA. These findings were also observed for VLDA.

We provided an additional anchor for the treat-to-target state, cDAPSA low disease activity, for greater generalizability of our results to other cohorts. We confirmed that cDAPSA treat-to-target was easier to achieve than MDA. For all MDA definitions, whether the PROMIS or the HAQ DI were used as measures for physical function, agreement with cDAPSA treat-to-target was substantial and similar between definitions.

Our study also provides comparative performance results for the external standard cutoff, a T score of 41.3 (10), and the best cutoff determined through an exploratory analysis in the PsA cohort. The best T score cutoff was numerically very close to the external cutoff for both PROMIS instruments. The external cutoff had slightly higher sensitivity (an increase by 4% for PROMIS-PF4a, and 2% for PROMIS-PF CAT) that came with a trade-off in specificity of 8% for the PROMIS-PF4a, and 5% for the PROMIS-PF CAT in this PsA data set. However, cutoffs used in the data set in which they were derived would bias toward higher agreement than using other standard measures. The analysis was conservative in using the external cutoff for agreement and supports the validity of this external cutoff in the PsA population.

Finally, there was substantial to excellent longitudinal agreement between the HAQ DI and the PROMIS-PF–based MDA states over time. However, as we may expect, the PROMIS-PF CAT was more sensitive to MDA change as exhibited by higher

kappa values compared to PROMIS-PF4a. These findings remained consistent when we examined VLDA definitions.

Our study findings may encourage clinicians who administer the HAQ DI–based measures to switch to the PROMIS-PF. Additionally, institutions that collect the PROMIS-PF need not recollect the HAQ DI for the purposes of calculating MDA and treat-to-target determination. Given the interchangeability of the PROMIS and the HAQ DI in determining MDA, the use of the PROMIS-PF offers the advantage of capturing a broader range of physical functioning more efficiently. The PROMIS-PF CAT measures disability just as well as the HAQ DI, because the item bank still contains questions focused on limited functioning (i.e., opening jars) without requiring completion of an extensive questionnaire. Further, the PROMIS-PF CAT is able to measure maximum functional capacity for each patient regardless of whether they meet MDA, as higher scores correlate with greater performance status.

The characteristics of our guideline-based treatment cohort may limit generalizability to other cohorts, because most patient were White, slightly more than half were treated with biologic DMARDs, and approximately 50% were at treatment targets. As discussed by Schalet et al, validity of the crosswalk table may be sensitive to population differences and weaker at extreme ends of the physical function continuum (10). Consistent with this observation, we observed a drop from excellent agreement when physical function was good, to moderate and substantial agreement in participants with low physical function ability. Finally, a limitation to crosswalk tables is that they are based on summed raw scores and can only be used when there are no missing values. However, the HAQ DI has similar limitations and cannot be computed unless at least 1 item in a category score has been completed. Strengths of our study are the collection of the HAQ DI, the PROMIS-PF4a, and the PROMIS-PF CAT concomitantly at each study visit, in addition to comprehensive PsA-specific phenotype and disease activity data. We performed analyses by visit that showed stability of our findings longitudinally and by subgroups of interest (sex, treat-to-target, and physical function ability). Results were consistent when we triangulated methods of agreement (kappa) with prediction (ROC analysis).

In conclusion, we demonstrated interchangeability of the HAQ DI threshold of ≤0.5 with a PROMIS-PF threshold of ≥41.3 in the calculation of PsA MDA and VLDA, which provides supportive data toward the validity of this cross-walk between the HAQ DI and the PROMIS-PF scores in the PsA population. Results from our study demonstrate agreement between legacy HAQ DI and PROMIS-based MDA definitions statistically, longitudinally, and within demographics, disease activity, functioning, and symptom subgroups. Thus, the PROMIS-PF can replace the HAQ DI in calculating MDA state in PsA, and cohorts switching from the HAQ DI to the PROMIS-PF can convert scores longitudinally on the physical function scale of their choice.

## 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 submitted for publication. Dr. Orbai 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.** Chew, Perin, Orbai.

**Acquisition of data.** Orbai.

**Analysis and interpretation of data.** Chew, Perin, Grader-Beck, Orbai.

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American College of Rheumatology
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## LETTERS

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### All-cause mortality and allopurinol use: comment on the article by Hay et al

*To the Editor*:

A systematic review and meta-analysis conducted by Hay et al, recently published in *Arthritis Care & Research* (1), reported that there was no significant association between allopurinol use and all-cause mortality in patients with gout (adjusted hazard ratio 0.8 [95% confidence interval 0.60–1.05]). This meta-analysis is technically sound and the data support the conclusions, and various interesting points are discussed.

First, the most life-threatening adverse reaction related to allopurinol use is allopurinol hypersensitivity, which can manifest as a series of cutaneous reactions and systemic reactions (2). Approximately 99% of patients with allopurinol hypersensitivity are associated with the HLA–B*5801 allele, with Asian ancestry particularly accounting for the majority (3). Second, the estimated death rate related to allopurinol hypersensitivity was approximately 14% (3). Given the high death rate related to allopurinol hypersensitivity, HLA–B*5801 screening seems to be worthwhile in preventing allopurinol hypersensitivity among patients of Asian ancestry who are indicated for allopurinol treatment (4). Third, when explaining the results of the study by Hay et al in plain language, the probability of dying from any cause is similar between the allopurinol use group and the nonuse group in patients with gout. Although the all-cause death rate did not reach statistical significance in the study by Hay et al, the death rate of allopurinol hypersensitivity is high, and it cannot be ignored (3). Whether patients really do not need to worry about the risk of death associated with allopurinol use should be explained cautiously. Finally, I agree with the conclusion of Hay et al that the number of included studies was small in their study, so further studies are needed to clarify this issue.

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### Reply

*To the Editor*:

We thank Dr. Lai for the interest in our study. While we did not show a statistically significant link between the use of allopurinol and mortality in people with gout, we agree that allopurinol hypersensitivity syndrome (AHS) is the most serious side-effect of allopurinol, particularly in populations with South East Asian ancestry, leading to the recommendation to screen people of South East Asian descent for the HLA–B*5801 allele prior to starting treatment with allopurinol (1,2).

While AHS can be fatal, its incidence is low. One study reported an incidence of AHS in a large South East Asian sample of 4.68 per 1,000 new users of allopurinol and a related mortality of 0.39 per 1,000 new users (3).

Investigation of the mortality risk from AHS was outside the purview of our study, which aimed to compare all-cause and cardiovascular mortality between allopurinol users and nonusers, but we agree that AHS is an important consideration for all clinicians managing gout, of which all patients starting allopurinol should be made aware.

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## Clinically effective concentration and risk of hydroxychloroquine retinopathy in systemic lupus erythematosus: walking on a thin line. Comment on the article by Garg et al

*To the Editor*:

We read with great interest the study by Garg et al recently published in *Arthritis Care & Research* (1). A threshold of 750 ng/ml hydroxychloroquine (HCQ) blood levels as a target is very helpful for clinicians. However, we have a hard time envisioning the use of this threshold due to a recent recommendation by the American Academy of Ophthalmology, the American College of Rheumatology (2), and the European Alliance of Associations for Rheumatology (3) to stay below 5 milligram per kilogram per day of HCQ. Even though the correlation between the dose per day and blood levels is poor, to envision achieving both objectives is difficult. Thus, recent literature (4) has established that to remain in the lowest tertile of retinopathy risk (1.2% of patients with retinopathy are in this tertile), patients must have a mean serum concentration below 741 ng/ml. This is hardly compatible with the threshold of efficacy established by Garg et al (above 750 ng/ml). Can the authors explain how they envision achieving both a daily intake below 5 mg/kg to prevent retinopathy and achieving drug levels above 750 ng/ml to have the best therapeutic efficacy?

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## Reply

*To the Editor*:

We thank Dr. Bitoun and colleagues for their interest and comments regarding our meta-analysis on HCQ levels. Bitoun et al raised an important question about the threshold of HCQ blood levels for clinical efficacy compared to the thresholds that predict the risk of retinal toxicity in lupus.

The first point to discuss is that the mentioned studies are difficult to compare since they did not have the same objective (efficacy in lupus versus retinal toxicity) nor the same design. The first study, by Petri et al, reported means and maximums of multiple HCQ blood levels obtained at serial visits of 537 patients (1), whereas our meta-analysis was based on 1 value per patient. We reported that HCQ levels ≥750 ng/ml offered a clinically meaningful threshold predicting 58% lower risk of active lupus. Even though our study was not specifically designed to define a threshold for retinal toxicity, these values remain below the maximum HCQ level tertile (0–1,182 ng/ml; Petri et al) that predicted the least retinal toxicity at 1.2% (1).

Moreover, Petri et al did not control for cumulative exposure time or other known factors that could contribute to higher toxicity despite similar HCQ levels. A recently published French case–control study did not find an association between HCQ blood levels and retinal toxicity risk across 23 cases with retinal toxicity and 547 controls without retinal toxicity, but that study did confirm the association of cumulative exposure, duration of intake, and creatinine clearance (2,3).

Other studies have also suggested that higher HCQ level thresholds have clinical benefits. For example, Petri et al highlighted the fact that the risk of thrombotic events significantly decreased by 69% in patients with mean HCQ levels above 1,068 ng/ml compared to those with levels below 648 ng/ml (risk ratio 0.31, $P = 0.024$) (4).

The next question that Dr. Bitoun raised was about achieving both a daily intake <5 mg/kg to prevent retinopathy and achieving drug levels above 750 ng/ml to have the best therapeutic efficacy. We agree that HCQ blood levels and HCQ daily dose are not well correlated and that comparing data from studies using different methods to examine safety is very difficult (1,5).

In addition, as previously published, we would like to emphasize that the 5 mg/kg threshold has been defined in terms of rare retinal toxicity, not efficacy (6). Further, this dose is confusing, since this threshold was based on pharmacy refill information, which often represents actual HCQ intake rather than the prescribed

dose. Melles et al estimated that in their population, this cutoff of 5 mg/kg corresponded to a dose of approximately 6 mg/kg real weight actually prescribed (because of nonadherence) (5). In other populations, the disparity between the prescribed and actual drug dosage is known to be much larger, especially in young patients with SLE (7). We can then hypothesize that many patients with HCQ blood levels above 750 ng/ml do not collect (or take) >5 mg/kg/day of HCQ dose.

We conclude that probably the most important thing about HCQ blood levels is that they are especially helpful to detect severe nonadherence, and that more studies are required to clarify correlations between HCQ blood levels and HCQ doses. Future research is then needed to investigate optimal ranges balancing the benefits of protection from the common outcome of flare and the rare, potentially serious event of retinal toxicity.

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# ARP Announcements

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**Submissions are invited for the AC&R 2023 Themed Issue: Health Disparities and Health Equity in the Rheumatic Diseases**

*Arthritis Care & Research* is soliciting manuscripts for a Themed Issue addressing health disparities and health equity, as related to outcomes and issues in the rheumatic diseases. This theme issue is part of an initiative across the American College of Rheumatology journals to better address these important issues in our field. Manuscripts may focus on health disparities or health equity related to race and ethnicity, sex and gender, socioeconomic status, sexual orientation, or other characteristics. Exploration of health disparities among understudied patient groups, as well as the intersection of multiple patient characteristics, are encouraged.

Manuscripts covering a broad range of topics related to the major theme are invited. Examples include observational studies that elucidate factors underlying disparities in health care quality or access; intervention studies that address health disparities; studies of differential impacts of treatments or behavioral interventions; studies describing mechanisms underlying disparities in key outcomes in rheumatic diseases (e.g., pain, function). Manuscripts addressing research related to disparities in rheumatology training and work force are also of interest. Both Original Research and Review articles will be considered.

The 2023 Themed Issue will include regular submissions as well, but a certain number of pages will be reserved for manuscripts accepted in response to this solicitation. All manuscripts will be peer reviewed. The Editor will select papers for publication in the Themed Issue based on reviewer ratings and the balance of subject matter. It is possible that manuscripts submitted for the themed issue may be accepted for publication in a regular issue of *Arthritis Care & Research*, rather than the themed issue.

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