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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Special Article

Rheumatoid Arthritis

Osteoarthritis

Cover image: The image on the cover (from Serling-Boyd et al, page 293) shows a signal abnormality in the L4–L5 disc space with associated end plate edema and cortical bone loss, suggestive of discitis and osteomyelitis.

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American College of Rheumatology
Empowering Rheumatology Professionals

CLINICOPATHOLOGIC CONFERENCE

An 80-Year-Old Man With Fevers, Altered Mental Status, and Joint Effusions

Naomi Serling-Boyd, Zachary Wallace, Jana Jarolimova, Sheila Arvikar, and Eli M. Miloslavsky

CASE PRESENTATION

Chief symptoms

An 80-year-old man presented with fevers, altered mental status, weakness, and pain in both legs.

History of present illness

An 80-year-old man with atrial fibrillation, hypertension, osteoarthritis status post bilateral total shoulder arthroplasty and right hip arthroplasty, a recent diagnosis of dementia, and monoclonal gammopathy of undetermined significance (MGUS) was admitted with fever, joint pain, and weakness. Prior to his first admission for these symptoms, he had been living independently at home with his wife and exercised multiple times weekly. Two months prior to the current hospitalization, he was admitted to another hospital (first admission) for acute functional decline with leg weakness that had developed over the course of approximately 2 weeks, altered mental status with episodes of confusion, and fever to 102.2°F. He noted shoulder and knee pain that was worse with movement. On physical examination, he was fully alert and oriented and was noted to have 4/5 strength with hip flexion, as well as 4/5 strength with shoulder abduction bilaterally. No spinal tenderness was noted on examination. He was able to ambulate with assistance. An evaluation for infections included blood cultures (negative after 5 days), a normal lumbar puncture result (1 nucleated cell per microliter, normal protein), normal urinalysis findings, chest radiography without any focal consolidation or other acute findings, and negative Lyme serologies. Serum procalcitonin was elevated at 0.29 ng/ml (normal range 0.00–0.08). Other laboratory values can be found in Table 1. Computed tomography (CT) of his chest, abdomen, and pelvis did not reveal any acute process or lymphadenopathy. Transthoracic echocardiogram (TTE) revealed dilated right and left atria, a left ventricular ejection fraction of 65%, and no evidence of vegetations. He was seen by the infectious disease service and started doxycycline treatment for a presumed tick-borne infection, resulting in mild improvement in his mental status. He was discharged with home health services, with plans to complete a 2-week course of doxycycline.

After completing the doxycycline course, he was readmitted (second admission) with fevers (to 102.5°F on admission) and recurrent altered mental status. He was noted to have an effusion of the left prosthetic shoulder joint. Orthopedic surgery service was consulted and aspirated his left shoulder, which showed 3,205 nucleated cells per microliter with 71% neutrophils, 21% lymphocytes, and 8% macrophages; fluid was negative for crystals, and joint fluid culture was negative. Additional evaluation included a normal creatine phosphokinase and rheumatoid factor (RF) finding, as well as negative results for anti–cyclic citrullinated peptide (CCP), anti–Jo-1, myositis panel, antinuclear antibody (ANA), anti–double-stranded DNA, anti-Ro, anti-La, anti-Sm, anti–U1 RNP, and Lyme antibody screen. He was treated with a 1-month course of doxycycline for a possible indolent prosthetic joint infection.

The patient was then readmitted (third admission) to the same hospital for altered mental status, joint pain, and fevers (to 101°F). He reported left hip pain as well as myalgias throughout his entire upper body without any reported morning stiffness. His temperature was 100.5°F on admission and he was hemodynamically stable. His erythrocyte sedimentation rate (ESR) was 45 mm/hour (normal range 0–13) and C-reactive protein (CRP) level was 99.8 mg/liter (normal range 0–8). Polymyalgia rheumatica (PMR) was considered, and he was started on prednisone 60 mg daily with significant improvement in his symptoms the following day. He received prednisone 60 mg daily for 2 days, followed by 40 mg daily for 2 days. His family reported that his symptoms started to worsen again while taking prednisone 40 mg daily. He

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Table 1. Laboratory evaluation results at each hospital admission*

Laboratory test	First admission	Second admission	Third admission	Current admission	Normal range
WBC, cells/mm^3	10.96	7.9	6.8	12.1	4.5–11
WBC differential, %					
Neutrophils	82.5	60.3	81.4	86.3	NS
Lymphocytes	10.7	21.9	8.4	6.4	NS
Monocytes	5	16.1	9.4	4.1	NS
Eosinophils	0	0.5	0	0.1	NS
Basophils	0.9	0.6	0.4	0.2	NS
Immature granulocytes	0.9	0.6	0.4	2.9	NS
Hemoglobin, gm/dl	14.8	13.2	12.5	12.8	13.5–17.5
Platelets, cells/mm^3	262	415	406	420	150–400
Creatinine, mg/dl	0.85	0.85	0.64	0.69	0.6–1.5
ESR, mm/hour	30	51	45	52	0–13
CRP, mg/liter	120.7	105.7	99.8	91.3	0–8
Uric acid, mg/dl	2.4	3.4	3.0	2.4	3.6–8.5
Synovial fluid WBC, cells/mm^3	NA	3,205 (LS)	NA	29,500 (RS), 7,433 (RK)	<200
Synovial fluid WBC differential, %					
Neutrophils	NA	71	NA	85 (shoulder), 68 (knee)	NS
Lymphocytes	NA	21	NA	11 (shoulder), 26 (knee)	NS
Monocytes	NA	0	NA	3 (shoulder), 6 (knee)	NS
Macrophages	NA	8	NA	1 (shoulder), 0 (knee)	NS
Synovial fluid crystals	NA	Negative (LS)	NA	Calcium pyrophosphate (RS and RK)	Negative

* WBC = white blood cell; NS = no specific reference range; NA = not applicable; LS = left shoulder; RS = right shoulder; RK = right knee.

was discharged with a dosage of prednisone 30 mg daily with a plan to decrease to 20 mg daily in 1 week. Three weeks later, while taking prednisone 20 mg daily, he presented to this hospital (current admission) with leg and shoulder pain, weakness, fever of 102°F, and worsening confusion and agitation. He endorsed weakness and pain in both legs and pointed to his right shoulder to indicate pain as well. His family reported new urinary and fecal incontinence as well as possible back pain.

Medical, social, and family history

The patient's past medical history was notable for atrial fibrillation, hypertension, dementia, and monoclonal gammopathy of undetermined significance. His surgical history included a sigmoid resection for perforated diverticulitis (13 years prior to presentation) as well as bilateral total shoulder arthroplasty (8 and 10 years prior to presentation) and a right hip arthroplasty (13 years prior to presentation), all performed for primary osteoarthritis. He had been seen by the hematology department for evaluation of MGUS and was not noted to have any evidence of end-organ damage. As part of this evaluation, he underwent a fat pad biopsy, which was negative for amyloidosis. He previously smoked for 20 years and quit almost 40 years prior to presentation. He also had a history of alcohol use disorder but had been abstinent for the past 2 years. He lived at home with his wife and had been previously independent. He denied any recent travel and denied having any pets or animal exposures. His family history was notable for heart disease and cancer in multiple relatives, as well as a niece with rheumatoid arthritis (RA).

Medications

At the time of this current admission, the patient's medications included prednisone, aspirin, atovaquone, lisinopril, omeprazole, quetiapine, thiamine, naproxen, polyethylene glycol, senna, calcium carbonate–vitamin D3, melatonin, and nystatin powder.

Review of systems

Further review of systems revealed a new oral ulcer on the patient's inner lip as well as recent-onset urinary incontinence without dysuria in the setting of recent confusion. The patient and his family denied that he had had any recent change in weight, headaches, visual changes, watery eyes, dry eyes, dry mouth, rhinorrhea, jaw claudication, chest pain, shortness of breath, acid reflux, nausea, vomiting, diarrhea, paresthesias, rashes, or Raynaud's phenomenon.

Physical examination

Physical examination revealed a blood pressure of 137/78 mm Hg, heart rate of 80 beats per minute, respiratory rate of 16 breaths per minute, temperature of 98°F, and oxygen saturation of 99% on room air. He was an elderly gentleman who was mildly confused, although pleasant and cooperative. His head and neck examination was notable for an aphthous oral ulcer on the inside edge of his front lip, as well as areas of white and yellow plaque on his inner cheeks and posterior oropharynx. He had poor dentition. His heart rate was irregularly irregular; there were no audible murmurs. The patient was breathing comfortably, and his lungs were

clear to auscultation. His musculoskeletal examination was notable for decreased right shoulder abduction to approximately 80 degrees, with warmth, tenderness, and a palpable glenohumeral effusion. He had bony hypertrophy of his metacarpophalangeal joints, as well as his proximal and distal interphalangeal joints. He had pain with internal rotation of his right hip, though no pain with range of motion of his left hip. His right knee had mild warmth and a small effusion appreciated. Range of motion of his knees was normal bilaterally. His other joints had no evidence of deformity, tenderness, warmth, erythema, or effusion. His neurologic examination was somewhat limited due to poor cooperation. He was alert and oriented to name, although did not know the year or location. He was conversant, yet intermittently agitated and speaking nonsensically. Gait was not assessed due to his pain and altered mental status. His strength was 4/5 with bilateral hip flexion and shoulder abduction, 4/5 with ankle flexion and extension, and hand grip was 5/5. He had no clonus, and reflexes were 2+ at the bilateral knees. Spinal tenderness was difficult to assess due to the patient's mental status. He was moaning at times, and it was unclear if this was due to pain. Examination of his skin was unremarkable; there were no sinus tracts, rashes, or other notable lesions.

Laboratory and radiographic evaluation

A complete blood count revealed an elevated white blood count at 12.1/mm^3 (normal 4.5–11), hemoglobin of 12.8 gm/dl (normal range 13.5–17.5), and elevated platelets of 420/mm^3 (normal range 150–400) (Table 1). His white blood count differential revealed 86.3% neutrophils, 6.4% lymphocytes, 4.1% monocytes, 0.1% eosinophils, 0.2% basophils, and 2.9% immature granulocytes. His metabolic panel was notable for normal renal function with a creatinine of 0.7 mg/dl (normal range 0.6–1.5). Serum calcium was 8.5 mg/dl (normal 8.5–10.5). Serum albumin was 2.2 gm/dl (normal range 3.3–5.0). Uric acid was 2.4 mg/dl (normal 3.6–8.5). ESR was elevated at 52 mm/hour (normal range 0–13), and CRP level was elevated at 91.3 mg/liter (normal range 0–8). IgG level was 1,637 mg/dl (normal range 614–1,295), IgA level was 518 mg/dl (normal range 69–309), and IgM level was 72 mg/dl (normal range 53–334), and serum protein electrophoresis revealed an abnormal 0.26 gm/dl IgG lambda M component band in the gamma region, as well as 2 IgG kappa M components of 0.19 gm/dl and 0.09 gm/dl in the gamma region. Serum kappa free light chains were mildly elevated at 35.3 mg/liter (normal range 3.3–19.4) and serum lambda free light chains were mildly elevated at 35.6 mg/liter (normal range 5.7–26.3), though the kappa-to-lambda ratio was normal at 0.99 (normal range 0.3–1.7). The urinalysis findings were negative, without evidence of blood or protein, and urine culture grew few (1,000 to <10,000) gram-negative rods. Blood cultures were initially negative. See Table 1 for laboratory values during this admission as well as prior admissions.

Radiographs of his shoulders revealed bilateral total shoulder prosthesis with high-grade subluxation of the glenoid component superiorly, likely a result of loosening, as well as severe degenerative changes of the glenoid bilaterally. Radiograph of his right knee showed severe medial tibiofemoral compartment predominant degenerative changes as well as chondrocalcinosis and trace joint effusion. CT findings of his chest were unremarkable.

The right knee arthrocentesis revealed 7,433 nucleated cells per microliter with 68% neutrophils, 26% lymphocytes, and 6% monocytes. Crystal analysis results were positive for calcium pyrophosphate crystals, some of which were intracellular. Gram stain and culture results were negative at 5 days. The right shoulder arthrocentesis revealed 29,500 total nucleated cells per microliter with 85% neutrophils, 11% lymphocytes, and 3% monocytes, as well as calcium pyrophosphate crystals, none of which were noted to be intracellular.

CASE SUMMARY

An 80-year-old man with a history of atrial fibrillation, hypertension, dementia, and monoclonal gammopathy of undetermined significance presented with an oligoarticular inflammatory arthritis as well as recent fevers and urinary and fecal incontinence in the setting of a prednisone taper prescribed for a diagnosis of PMR. Physical examination was notable for a confused man with diffuse pain as well as multiple joint effusions involving native and prosthetic joints. Laboratory evaluation revealed mild leukocytosis and thrombocytosis, elevated inflammatory markers, and hyponatremia. Synovial fluid from his right knee and right shoulder revealed inflammatory fluid with neutrophilic predominance and calcium pyrophosphate crystals, with a negative gram stain and culture at 5 days.

DIFFERENTIAL DIAGNOSIS

Fever with oligoarticular joint effusions involving prosthetic as well as native joints raised concern for infectious etiologies, although gram stain and culture findings from the patient's synovial fluid were negative after 5 days. We will focus on the differential diagnosis of oligoarticular arthritis in this patient.

Inflammatory arthritis. Seronegative spondyloarthritis as well as RA could be considerations in this patient. Five conditions (psoriatic arthritis, reactive arthritis, irritable bowel disease (IBD)–associated arthritis, ankylosing spondylitis, and undifferentiated spondyloarthropathy) comprise the seronegative spondyloarthropathies. Each of these conditions can present with peripheral arthritis, with psoriatic arthritis often presenting as an asymmetric oligoarthritis in 70% of patients, reactive arthritis often involving the large joints of the lower extremities, and enteropathic arthritis presenting either as an asymmetric oligoarticular arthritis or a symmetric polyarticular arthritis of the small joints (1).

However, our patient had no personal history or evidence of psoriasis on examination, no history of IBD, and no known preceding gastrointestinal or genitourinary infections. The patient did possibly endorse low back pain, although this was difficult to assess by history. Ankylosing spondylitis can involve the hips, shoulders, and sternoclavicular joints, among others, although it generally presents before age 40 years, and the patient did not endorse a longstanding history of back pain, making this less likely (1). Reactive arthritis would be considered less likely given the lack of an apparent preceding infection (although in many cases a preceding infection is not apparent), absence of ocular symptoms or pyuria, and the distribution of joints, which tends to favor the lower extremities, although can include the upper extremities. Reactive arthritis would remain a diagnosis of exclusion after evaluation of other etiologies in this case. Fever is rarely part of the presentation of spondyloarthropathy, although in cases with fever and seronegative spondyloarthropathy, Whipple's disease is one consideration to keep on the differential (2). RA can present at an older age; classically it presents as a symmetric polyarthritis of the smaller joints and involves the hands. However, it can present as an asymmetric oligoarticular arthritis or even as a PMR-like presentation. However, the predominance of large joints points away from RA (3). Additionally, RA rarely causes high fevers, and the patient's test results were negative for both RF and CCP, which makes RA less likely.

Systemic rheumatologic disease. Other systemic rheumatologic diseases such as lupus, vasculitis, myositis, adult-onset Still's disease (AOSD), or sarcoidosis can present with polyarthralgias or polyarticular arthritis. However, this patient had no evidence of extraarticular systemic disease. In this patient, an ANA test result was negative, which makes lupus less likely. The patient had a normal creatine kinase (CK) level and a negative myositis panel, which made myositis less likely, and his pain and weakness seemed to be more articular rather than muscular. He had no other cutaneous or other stigmata of vasculitis, and no rash to suggest AOSD. He had no hypercalcemia, hilar lymphadenopathy, erythema nodosum, or other findings to suggest sarcoidosis.

PMR. PMR presents with pain and stiffness of the shoulders and hips, generally in a symmetric distribution. Estimates of the prevalence of clinically detectable synovitis in patients with PMR vary widely, from almost none to more than two-thirds of patients (3). One study of PMR and temporal arteritis patients showed that of the patients who had peripheral arthritis, 34% had a monoarthritis, 62.3% had an oligoarthritis, and 3.8% had a polyarthritis at the time of diagnosis (4). Joint involvement during the disease course included most commonly the knee (55.6% of cases), metacarpophalangeal joints (46.3% of cases), and wrist (42.6% of cases) (4). In this study, no patients had hip or shoulder involvement by frank arthritis (4). Synovial fluid white cell differentials can be lymphocytic predominant; in one study, more than half of the synovial fluid analysis results showed a predominance of mononuclear cells (3). PMR can also be a source of fevers, with one study showing that PMR was responsible for 4 of 31 cases of fever of unknown origin in elderly patients and was responsible for several cases of fever lasting more than 3 months (5). Although this patient had a diagnosis of PMR, as supported by elevated inflammatory markers that improved with steroids, the oligoarticular nature of his joint effusions, the failure to respond to prednisone at 20 mg daily, and the involvement of both his shoulder and hip joints made it less likely that he had a peripheral arthritis associated with PMR.

Crystalline arthritis. While the patient had no prior history of either gout or pseudogout, the analyses of synovial fluid from his right knee and shoulder revealed calcium pyrophosphate crystals. Given this positive result of crystals from 2 joints, we considered the possibility that the entirety of his presentation was due to oligoarticular calcium pyrophosphate dihydrate crystal (CPPD) arthritis (i.e., pseudogout) since it can cause fevers (6). The most commonly involved joint in pseudogout is the knee, followed by the wrist, shoulder, and ankle (7). This patient's urinary and fecal incontinence raised concern for a process involving the spine as well. Although rare, pseudogout can affect the spine; one autopsy study of more than 1,000 spinal specimens from patients with CPPD arthritis showed that crystals can accumulate in a variety of locations in the vertebral column, including the intervertebral disks, median atlantoaxial articulations, intraspinal and extraspinal ligaments, and apophyseal and sacroiliac joints (8). Pseudogout has also been known to present with mass-like involvement of the spine that can be mistaken for tumors and has been reported as a cause of cauda equina syndrome (9). However, crystal-induced arthritis after arthroplasty is rare, with only several dozen cases reported. When it does occur, it is attributed to crystal deposition in the remaining synovial membrane or in the neosynovium that can develop around the prosthetic joint (10). Given the protracted course of this patient's presentation and the fact that his initial left shoulder aspiration was negative for crystals, we thought that pseudogout was an unlikely explanation for his entire illness, although we could not rule out a contribution of pseudogout to his clinical presentation.

Septic arthritis. There was a high concern for infection given fevers and oligoarticular inflammatory arthritis involving prosthetic joints. Risk factors for septic arthritis include older age, such that being age >80 years is associated with a 3.5-fold higher likelihood of septic arthritis in a patient presenting with arthritis (11). In addition, the presence of either a hip or knee prosthesis is associated with 3-fold higher likelihood of septic arthritis (11). Risk factors for infection after arthroplasty include obesity, malnutrition, diabetes mellitus, RA, smoking, alcohol, older age, bacterial colonization, and immunosuppression, among others (12). This patient had risk factors for septic arthritis, but we generally associate bacterial septic arthritis with a higher synovial white cell count.

Moreover, his synovial fluid cultures were negative, although these are positive in only about 60% of patients with nongonococcal septic arthritis of prosthetic joints; the gram stain is even less sensitive, with organisms seen in only half of cases (12). The patient had previously received a course of doxycycline, which could have further reduced the sensitivity of the gram stain and culture, although he had not been taking antibiotics during the time period immediately preceding his admission. It is relevant to note that joint infections caused by atypical or fastidious organisms, such as the *Mycoplasma* species, mycobacteria, or fungi can be even more difficult to diagnose based on synovial fluid cultures.

CLINICAL COURSE

Given the patient's fecal and urinary incontinence, magnetic resonance imaging (MRI) of the lumbar spine was performed and revealed T2 hyperintensity in the L4–L5 disc space with associated end plate edema, suggestive of discitis and/or osteomyelitis (Figure 1). MRI also demonstrated a multiloculated posterior epidural collection adjacent to the right L4–L5 facet joint that could have been reflective of an epidural abscess or a synovial cyst. An MRI of the pelvis revealed edema throughout the distal right psoas and iliacus muscles with a fluid collection that was concerning for abscess. MRI of the patient's brain showed some nonspecific chronic white matter disease and was negative for any acute lesions.

Six days after aspiration of the patient's right knee, the mycobacterial culture grew a rapidly growing nontuberculous mycobacterial species, eventually speciated to *Mycobacterium abscessus* complex. Aspirations from the right shoulder, right hip, and left shoulder also grew *M abscessus*, as did blood cultures (after 7 days) and a biopsy of the L4–L5 disk. A diagnosis of disseminated *M abscessus* infection was made. Explantation of the affected joints was thought to be too morbid given the number of joints involved, so the patient underwent arthroscopic lavage of his right shoulder and right knee. However, without joint explantation, curative treatment was thought to not be possible given the disseminated nature of the infection. He was initially treated with an empiric regimen of linezolid, imipenem, and azithromycin while awaiting sensitivities. This regimen was transitioned to tigecycline, imipenem, and azithromycin once final sensitivity data revealed that his strain

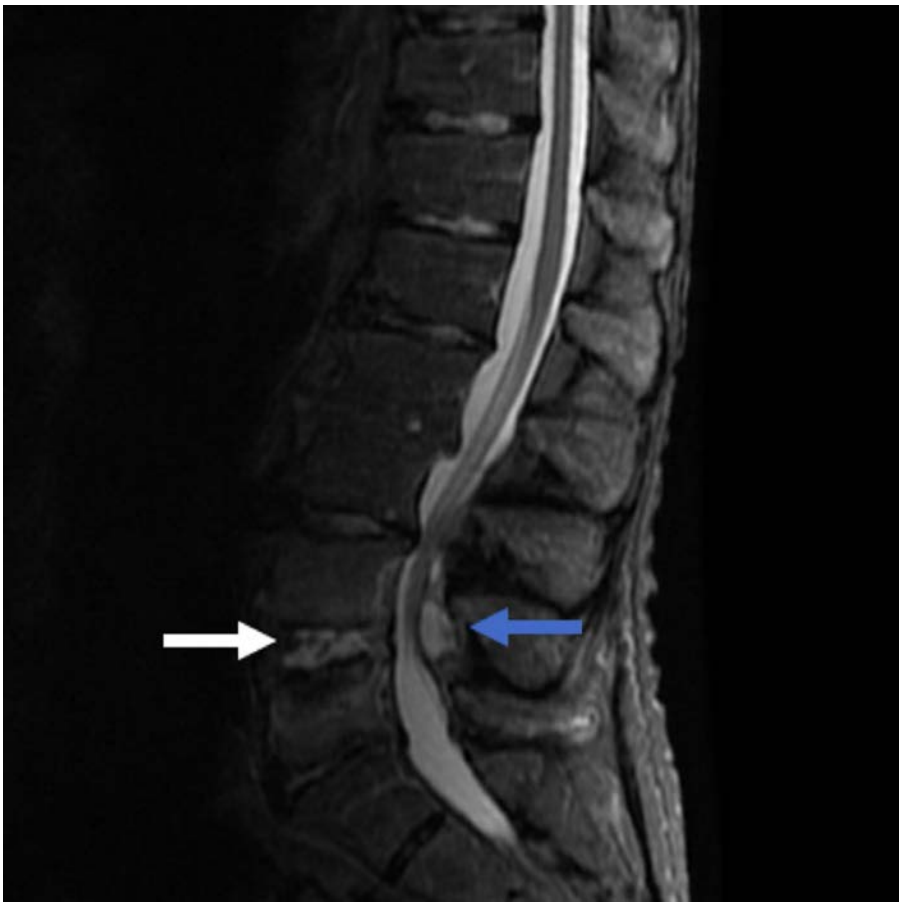

Figure 1. Magnetic resonance image of the lumbar spine. STIR imaging demonstrates signal abnormality in the L4–L5 disc space (white arrow) with associated end plate edema and cortical bone loss suggestive of discitis and osteomyelitis. The image also shows a multiloculated posterior epidural collection (blue arrow) adjacent to the right L4–L5 facet joint, concerning for an epidural abscess.

was sensitive to macrolides, with a plan for an indefinite duration of therapy given the disseminated nature of the infection. Prednisone was tapered off over 4 weeks. After discharge, the patient initially improved, with resolution of his fevers and improvement in his joint pain. However, he continued to have severe debility at home as well as subjective toxicity to oral and intravenous antibiotic therapy, thereby limiting his quality of life. Thus, approximately 3 months after hospital discharge the decision was made to discontinue antibiotics and transition him to hospice care.

DISCUSSION

Mycobacteria are a genus of *Actinobacteria* and include more than 190 different species. The Greek prefix myco means fungus and refers to the way in which they grow. They are often divided into *Mycobacterium tuberculosis* complex, mycobacteria causing leprosy, and nontuberculous mycobacteria (13). They are not identified on Gram stain and can be difficult to detect. Nontuberculous mycobacteria are ubiquitous in the environment, often present in water and food sources, and are notoriously difficult to treat (13,14). Ninety percent of nontuberculous mycobacterial infections involve the pulmonary system, and the remainder involve the lymph nodes, skin, soft tissue, bones, and less frequently the eye or nervous system (13). Septic arthritis, including prosthetic joint infections, due to mycobacteria has been described as well. In general, these infections occur more commonly in patients who are immunosuppressed, although there are reports of an increasing prevalence of cases in apparently immunocompetent patients as well (15). There is also increasing appreciation of the role of inherited and acquired defects in the host immune response, particularly the T helper cell type (Th1) pathway, in susceptibility to nontuberculous mycobacterial infection, especially among younger patients (16). One study of 31 cases of vertebral osteomyelitis caused by nontuberculous mycobacteria revealed that only 51.5% had some degree of underlying immunosuppression (17). Prior to his prednisone use, our patient did not have any known risk factors for mycobacterial infection.

M abscessus is a rapidly growing nontuberculous mycobacteria (RGM) (14). RGM are defined by growth in culture within 7 days, which is slower than most bacteria, though faster than slow growing mycobacteria or *M tuberculosis* (13). They exist ubiquitously in the environment with increasing incidence for unclear reasons, although it has been postulated that environmental factors could be contributing (18). The clinical disease spectrum ranges from skin and soft tissue infections to surgical wound infections, catheter-related sepsis, pulmonary infections, and prosthetic joint infections (14,19). There have been multiple cases of wound infections by *M abscessus* in patients who have received cosmetic surgery, particularly in Latin American countries (20). One case series refers to "lipotourists," where US or other residents travel abroad to undergo cosmetic surgery for fat removal; proposed reasons for infection include environmental contamination of the water systems, surgical instruments, medications, or antiseptic solutions (21). Regarding joint involvement, one study reported a cohort of patients with nontuberculous mycobacteria involving large joints, all of which were prosthetic, in contrast to infections involving small joints that occurred in the absence of prostheses (19). Infections are more likely to disseminate in immunocompromised patients, but dissemination has been reported in immunocompetent patients (14,15,18).

Septic arthritis from *M abscessus* results from direct inoculation or hematogenous dissemination. One study showed that the average synovial white blood cell count in patients with mycobacterial septic arthritis was approximately 30,000 nucleated cells/microliter (22). The synovial fluid count in this patient was remarkably low for septic arthritis, which likely contributed to the initial low suspicion for infection. His preceding treatment with doxycycline may have decreased synovial fluid cell counts and the sensitivity of culture.

Disseminated infection, as in this case, is associated with a high risk for morbidity and mortality. Disseminated infection is defined by involvement of more than 1 organ system, more than 2 groups of lymph nodes, or positive blood cultures (14). Moreover, immunosuppressive medications, such as the prednisone administered in this case, have also been associated with higher mortality (14).

Morbidity and mortality are particularly high *M abscessus* infections because treatment approaches are challenging, and as there is a lack of randomized controlled trial data, treatment is often based on expert opinion. Surgical treatment with resection of the prosthesis is often required along with prolonged courses of multi-drug antimycobacterial therapy for curative treatment (23). Regarding medical therapy, RGM are associated with inducible macrolide resistance as well as multiple intrinsic and extrinsic drug-resistance mechanisms. As such, susceptibility testing and use of multiple concurrent antibiotics are always required. It is recommended that RGM be tested for susceptibility to amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline, imipenem, linezolid, moxifloxacin, trimethoprim-sulfamethoxazole, and tobramycin (13).

Further complicating this patient's management was the involvement of prosthetic joints. In general, prosthetic joint infections (PJI) are estimated to complicate approximately 1% of primary hip and knee arthroplasties (23). In addition to immunosuppression, as in this case, other risk factors for PJI include obesity, diabetes mellitus, and RA (23). The most common clinical manifestations include pain (the most common symptom), joint swelling or effusion, fever, drainage, or the presence of a sinus tract (which in some criteria is considered to be definitive evidence of prosthetic joint infection) (23). Loosening of the components of the prosthesis or periprosthetic lucency on imaging can be suggestive of infection as well (23). Synovial fluid aspiration is critical in any suspected case of PJI; however, cell counts are generally much

lower than in native joint infection. The sensitivity of a synovial fluid leukocyte count of >1,700 cells/microliter or a differential of >65% neutrophils was considered to be 94% and 97%, respectively (24). The most common organisms include *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, *Streptococcus* species, aerobic gram-negative bacilli, and less commonly *Enterococcus* species, anaerobic bacteria, or polymicrobial (23). Nontuberculous mycobacteria are an extremely rare cause of PJI; these are only described in small case series and reports, and *M abscessus* is an even more rare cause (23). In general, PJI often require a combination of medical therapy (e.g., antibiotics) and revision surgery, but this approach is best determined in consultation with orthopedic surgeons as well as infectious disease specialists (24). There are no specific management recommendations for *Mycobacterial* prosthetic joint infections.

It is likely that the entirety of this patient's presentation was due to *M abscessus*. While a crystalline arthritis was considered as a potential cause of his presentation, especially before synovial fluid cultures grew RGM, it was thought to be an unlikely explanation for the entirety of his presentation. We cannot rule out the possibility that pseudogout contributed to some of his pain and swelling.

Multiple studies have evaluated the frequency of concomitant crystal arthritis and septic arthritis. Studies have found rates ranging from 1.5 to 5% of patients with crystalline arthritis who also have concomitant infection (25,26). One study found that the mean synovial white blood count in patients with concomitant crystalline and septic arthritis was 113,000 (95% confidence interval 72,700–153,200), although much lower values have been reported as well (25). Multiple mechanisms have been postulated regarding why this coexistence occurs. It has been suggested that crystalline arthritis may predispose patients to joint-space infection. In another report by Gordon et al, septic arthritis preceded the appearance of calcium pyrophosphate crystals in the joint fluid, suggesting that infection leads to shedding of crystals from the cartilage and synovium into the joint space. Subsequently, in a rat model, they demonstrated release of crystals after injection of pyogenic bacteria (27). Although infrequent, if infection is suspected, this suspicion should not be eliminated by the discovery of crystals in the joint fluid.

Ultimately, it is unclear whether this patient initially had a single joint affected by RGM and prednisone subsequently led to dissemination of the infection, or whether it had begun to disseminate prior to the initiation of prednisone. This case highlights the need for high clinical suspicion of infection in patients with prosthetic joints, even in the setting of a positive crystal analysis and awareness of mycobacteria as potential pathogens.

FINAL DIAGNOSIS

Oligoarticular mycobacterial septic arthritis with disseminated *M abscessus* infection with concomitant crystalline arthritis.

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. Serling-Boyd 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. Serling-Boyd.

Acquisition of data. Serling-Boyd, Wallace, Jarolimova, Arvikar, Miloslavsky.

Analysis and interpretation of data. Serling-Boyd, Wallace, Jarolimova, Arvikar, Miloslavsky.

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Changes in Alcohol Use and Associations With Disease Activity, Health Status, and Mortality in Rheumatoid Arthritis

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Objective. Better disease activity and quality of life have been observed among patients with rheumatoid arthritis (RA) who drink alcohol. This association might be explained by reverse causality. We undertook this study to identify predictors of change in alcohol use and to evaluate independent associations between alcohol use and RA activity and mortality.

Methods. Participants in Forward, The National Databank for Rheumatic Diseases, were asked about alcohol use (any versus none), and disease activity was collected through the Patient Activity Scale–II (PAS-II) on semiannual surveys. We identified factors associated with changes in alcohol use and determined associations between alcohol use and disease activity and mortality using linear and logistic regression models, Cox proportional hazards models, and marginal structural models.

Results. A total of 121,280 observations were studied among 16,762 unique participants. Discontinuation and initiation of alcohol were common among drinkers and abstainers (8.2% and 9.2% of observations, respectively). Greater discontinuation and less initiation were observed with greater disease activity, older age, female sex, non-white race, obesity, greater comorbidity, low quality of life, low educational level, low income, and work disability. While alcohol users had lower PAS-II (β = –0.15 [95% confidence interval (95% CI) –0.18, –0.11], $P < 0.001$) and a lower mortality (odds ratio 0.87 [95% CI 0.76, 0.98], $P = 0.03$) in traditional models, associations were not seen in marginal structural models.

Conclusion. Higher disease activity, disability, comorbidity, and poor quality of life contribute to reductions in alcohol use. Active use and changes in use were not associated with disease activity or mortality when adjusting for confounding, suggesting no clear benefit of alcohol consumption in RA.

INTRODUCTION

There is interest in identifying dietary and behavioral exposures that may contribute to the activity and severity of rheumatoid arthritis (RA). For example, several previous studies have demonstrated that moderate use of alcohol is associated with lower disease activity, superior quality of life, and better functional status (1–7). Furthermore, in the general population, moderate alcohol consumption has been associated with reduced cardiovascular mortality (8,9). Thus, providers may be tempted to encourage moderate alcohol consumption among patients with RA.

While alcohol use has been associated with lower RA disease activity and superior function in RA in cross-sectional studies, studies evaluating other, more long-term outcomes have been inconsistent. Some studies have found a reduced risk of radiographic damage and its progression among alcohol users,

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SIGNIFICANCE & INNOVATIONS

- Patients with higher rheumatoid arthritis (RA) disease activity are more likely to discontinue the use of alcohol and less likely to initiate use.
- Patients with greater comorbidity, disability, and poor physical and mental quality of life are less likely to use alcohol over time.
- Active alcohol use and recent changes in use were not found to be associated with disease activity or death when considering some of the reasons contributing to the behavior.
- This study refutes prior evidence suggesting a beneficial effect of alcohol in patients with RA.

while others have found the opposite (5–7). A recent study also found that alcohol users were less likely to reach clinical remission (10).

A challenge for epidemiologic studies in this area is that alcohol use is not static over the lifetime, and its use has been associated with changes in health status and quality of life in other populations (11,12). Poor and worsening health status, RA disease activity and severity, comorbidity, and quality of life may all result in reductions in use of alcohol and result in bias in epidemiologic studies due to reverse causality, although this has never been studied (13). In RA, the use of potentially hepatotoxic agents at higher doses may further influence these behaviors. If severely affected individuals are more likely to discontinue alcohol use over time, studies that consider alcohol use at a fixed point in time, perhaps at enrollment in a disease registry, are likely to identify a protective association of alcohol use when one, in fact, does not exist.

We evaluated the longitudinal associations between patient-reported disease activity, disability, comorbidity, and quality of life on initiation and discontinuation of alcohol use over time in a large registry of patients with RA and determined if changes in alcohol use were independently associated with subsequent changes in disease activity and mortality. Finally, we aimed to assess the risk of adverse outcomes from current alcohol use using statistical methods that more effectively account for time-varying confounding.

MATERIALS AND METHODS

Study setting. Patients were active participants in Forward, The National Databank for Rheumatic Diseases, between 1999 and 2016. Forward is a patient-based, multi-disease, multipurpose rheumatic disease registry and cohort study with patients enrolled from community-based rheumatology practices across the US and followed-up semiannually with detailed questionnaires (14). Key patient data are validated regularly using medical records. The registry has been described in detail elsewhere (14,15). The study is approved by the Via Christi Hospitals Wichita Institutional Review Board (IRB00001674). All participants provided signed informed consent.

Assessment of alcohol use in follow-up. Participants in the registry are regularly asked about alcohol use. Between 2002 and 2007, patients were asked, "Do you regularly drink alcoholic beverages?" This question was modified, and participants between 2007 and 2017 were asked, "How often do you drink alcohol?" Those who reported use of alcohol were subsequently asked to provide the average number of drinks per day. Participants were considered to have discontinued alcohol use if they answered "never" to either question but reported any amount of use on the prior survey. Participants were considered to have initiated use if they reported any consumption but reported no use on the prior survey.

We performed additional sensitivity analyses limiting our definition to moderate use only (observations with greater than moderate use were excluded). Moderate alcohol use was defined as ≤1 drink per day for women and ≤2 drinks per day for men among those who reported use (16).

Disease activity assessments. Disease activity was assessed using the Patient Activity Scale–II (PAS-II), a self-reported assessment of function, pain, and overall health, which is collected on each questionnaire (17,18). Low, moderate, and high disease activity were defined as described previously (17). A clinically important change for PAS-II has not been defined. We defined an important change in disease activity as a change of >1 unit (0.5 × SD) (19). This is comparable to the minimum clinically important change (3.6 of 30 units) defined for the Routine Assessment of Patient Index Data (20).

Other assessments. Comorbidity burden was calculated using the Rheumatic Disease Comorbidity Index, a validated quantitative measure of comorbid illness (21). Patient assessment of mental and physical quality of life was derived from the physical and mental component summary scores of the Short Form 36 health survey (22). Other potential confounding factors were assessed, including demographics, smoking, work disability, RA disease duration, depression, heart disorders, lung diseases, psychiatric disease, gastrointestinal disorders (liver disease, ulcer), educational level (≥16 years), household income, marital status, and calendar date of the observation. Vital status was determined from the National Death Index and alternative family member contact.

Statistical analysis. *Predictors of changes in alcohol use*. In this analysis, the outcomes of interest were the report of cessation of drinking at the subsequent survey among observations where active drinking was reported. We also evaluated the report of initiation of drinking among abstainers. Multiple observations over time in a single participant were permitted to be included in

Table 1. Baseline characteristics (first nonmissing data) of participants who never reported alcohol use through follow-up, never reported abstaining from alcohol, and those who sometimes reported drinking alcohol*

	Never drank alcohol (n = 6,706)	Never abstained from alcohol (n = 6,703)	Sometimes drank alcohol (n = 3,353)	*P*
Age, mean ± SD years	60.2 ± 13.1	56.5 ± 13.5	57.6 ± 13.3	<0.001
Male sex	1,141 (17)	1,544 (23)	615 (18)	<0.001
White race	6,252 (93)	6,398 (95)	3,092 (92)	<0.001
BMI, mean ± SD kg/m^2	29.2 ± 7.4	27.8 ± 6.2	28.9 ± 7.1	<0.001
Disease duration, median (IQR) years	11.8 (5.5–22.3)	10.6 (4.8–20.3)	10.3 (5.1–20.1)	<0.001
Smoking	360 (5)	375 (6)	227 (7)	0.01
PAS-II, mean ± SD	4.1 ± 2.2	3.14 ± 2.0	3.50 ± 2.1	<0.001
Methotrexate	3,415 (53)	3,083 (49)	1,770 (54)	<0.001
Prednisone, no./total no. (%)	2,210/6,450 (34)	1,855/6,354 (29)	1,051/3,268 (32)	<0.001
Biologics, no./total no. (%)	2,097/6,450 (33)	2,373/6,354 (37)	1,107/3,268 (34)	<0.001
Mental QoL, mean ± SD	47.4 ± 12.3	49.0 ± 11.3	48.9 ± 11.5	<0.001
Physical QoL, mean ± SD	33.9 ± 10.7	39.3 ± 10.8	36.7 ± 10.7	<0.001
Unemployed due to disability	1,335 (20)	649 (10)	478 (14)	<0.001
Education >16 years	1,732 (26)	2,742 (41)	1,201 (36)	<0.001
Mean income, median (IQR) US dollars	35,000 (15,000–65,000)	55,000 (35,000–95,000)	45,000 (25,000–75,000)	<0.001

* Values are the number (%) unless indicated otherwise. BMI = body mass index; IQR = interquartile range; PAS-II = Patient Activity Scale–II; QoL = quality of life.

these analyses, and exposure was permitted to vary over time. We assessed associations between disease activity, health status, and subsequent changes in alcohol use by the time of the next survey. Population-averaged logistic regression models incorporating generalized estimating equations (GEEs) with robust estimators were utilized to assess factors associated with the probability of any alcohol use at the time of the next questionnaire among observations where drinking was reported. Similar analyses were performed among abstainers. Partially adjusted models included demographics, body mass index (BMI), PAS-II scores, and RA therapies (methotrexate, prednisone, and biologics). Fully adjusted models considered further variables, such as smoking, disease duration, comorbidity, quality of life, education level, income, health satisfaction, marital status, and disability. Backward selection of variables with $P < 0.2$ was performed on fully adjusted models to generate final reduced models shown in the tables.

Associations between changes in alcohol use and disease activity and mortality. Multivariable logistic regression models incorporating GEEs were used to determine if reporting of discontinuation or initiation of alcohol since the prior survey was associated with a significant worsening or improvement in disease activity at the time of the subsequent survey. A schema for the study design is shown in Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23847/abstract. Extended Cox proportional hazards models were also used to assess associations between discontinuation of alcohol among those reporting use on the prior survey and subsequent mortality (separate analyses evaluated the risk of initiation of alcohol use among abstainers). These analyses were adjusted for factors that were identified in the aforementioned selection process to be associated with alcohol discontinuation or initiation.

Associations of active drinking with disease activity and mortality. Exposures often vary over time in observational studies, and this variation may be related to important changes in health. Standard approaches for adjustment of confounding may be biased when time-dependent confounders exist that are affected by a previous exposure. Marginal structural models offer an approach that can allow for improved adjustment for this type of confounding. We compared a marginal structural model approach to a more traditional multivariable modeling approach using GEEs.

We used marginal structural models to evaluate associations between active drinking and PAS-II over time as well as the risk of mortality. These models use stabilized inverse probability weighting to balance the probability of being exposed to alcohol across drinkers and abstainers. Variables included in the models for propensity scores for drinking status and later censoring included all variables noted above, including current values, values from the prior visit, values from the first nonmissing observation, as described previously (23). Time, in months, from the first study observation was also adjusted for using cubic splines. For analyses evaluating the relationship of alcohol use with disease activity, we excluded PAS-II, physical, and mental quality of life from models used to generate propensity scores because these variables capture constructs similar to the disease activity outcome. A complete list of variables included in propensity scores is provided in Supplementary Tables 1 and 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23847/abstract. Standardized differences were visualized prior to and after application of the inverse probability weights (Supplementary Figure 2). In all analyses, registry observations that were missing data for alcohol use (primarily, visits occurring prior to initiation of the alcohol use questions introduced in 2002; 34%) were not eligible for inclusion. Analyses were performed using Stata, version 14.2.

Table 2. Adjusted associations between disease activity and other factors and discontinuation of alcohol among active drinkers*

	Odds of discontinuation among active drinkers (n = 7,817; obv. = 51,073)		Odds of initiation among abstainers (n = 7,768; obv. = 48,413)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, years				
<50 (reference)				
50–60	1.01 (0.90, 1.12)	0.90	0.85 (0.77, 0.94)	0.002
60–70	1.04 (0.93, 1.16)	0.13	0.76 (0.68, 0.85)	<0.001
70–80	1.12 (0.98, 1.27)	0.002	0.66 (0.58, 0.74)	<0.001
>80	1.27 (1.08, 1.51)	0.005	0.72 (0.60, 0.85)	<0.001
Male sex	0.72 (0.64, 0.81)	<0.001	1.18 (1.04, 1.34)	0.01
White race	0.73 (0.62, 0.87)	<0.001	1.10 (0.92, 1.31)	0.30
BMI				
Low	1.03 (0.71, 1.50)	0.86	0.94 (0.64, 1.36)	0.73
Normal (reference)				
Overweight	1.04 (0.93, 1.17)	0.47	0.99 (0.88, 1.11)	0.84
Obese	1.37 (1.22, 1.54)	<0.001	1.05 (0.94, 1.18)	0.38
Methotrexate	1.05 (0.97, 1.13)	0.21	0.90 (0.84, 0.97)	0.004
Prednisone	1.06 (0.98, 1.14)	0.16	0.95 (0.88, 1.02)	0.16
Any biologic	0.94 (0.87, 1.01)	0.08	1.06 (0.99, 1.14)	0.12
PAS-II				
Remission (reference)				
Low	1.07 (1.00, 1.15)	0.06	0.97 (0.91, 1.04)	0.43
Moderate to high	1.22 (0.90, 1.66)	0.19	0.95 (0.77, 1.18)	0.66
Work disability	1.18 (1.06, 1.32)	0.003	0.91 (0.83, 1.00)	0.001
RDCI	1.02 (1.00, 1.04)	0.02	–	–
Liver disease	1.23 (0.99, 1.53)	0.07	–	–
Heart disease	–	–	0.90 (0.81, 0.99)	0.06
Diabetes mellitus	–	–	0.83 (0.74, 0.93)	0.002
SF-36 PCS	0.99 (0.98, 0.99)	<0.001	1.01 (1.01, 1.01)	<0.001
SF-36 MCS	0.99 (0.99, 1.00)	0.001	–	–
Education ≥16 years	0.84 (0.76, 0.93)	0.001	1.19 (1.07, 1.31)	0.001
Income, US dollars	–	–		
0–25,000 (reference)				
35,000–55,000	0.84 (0.77, 0.92)	<0.001	1.16 (1.08, 1.26)	<0.001
65,000–150,000	0.72 (0.65, 0.79)	<0.001	1.37 (1.24, 1.51)	<0.001

* Also tested but not associated and not included in the final models: odds of discontinuation (disease duration, smoking, marital status, depression, psychiatric disease, malignancy, heart disorders, lung disease, and gastrointestinal disorders); odds of initiation (disease duration, smoking, marital status, health satisfaction, depression, psychiatric disease, malignancy, lung disease, liver disease, and gastrointestinal disorders). obv. = observations; OR = odds ratio; 95% CI = 95% confidence interval; BMI = body mass index; PAS-II = Patient Activity Scale–II; RDCI = Rheumatic Disease Comorbidity Index; SF-36 PCS = Short Form 36 physical component summary; SF-36 MCS = Short Form 36 mental component summary.

RESULTS

In 121,280 observations among 16,762 unique patients, at least some alcohol use was reported at 63,524 observations (52%). Among these, 9,327 reported more than moderate use (15%). The characteristics of participants that never used alcohol, never abstained from alcohol, or sometimes used alcohol in follow-up are shown in Table 1.

Discontinuation of alcohol use among active drinkers. Discontinuation of alcohol was common among drinkers (4,285 events in 52,345 eligible observations; 8.2%). Figure 1 shows the predicted time-to-discontinuation of alcohol use by disease activity category adjusting for age, sex, race, and BMI. High disease activity was associated with a substantially shorter time to discontinuation of alcohol use (hazard ratio [HR] 2.40 [95% confidence interval (95% CI) 1.81, 3.17], $P < 0.001$). Greater PAS-II scores were associated with a greater likelihood of discontinuing alcohol use by the next survey after adjusting for age, sex, race, BMI, and RA therapies. Compared to participants with low PAS-II scores, those with a moderate or high PAS-II score had a substantially higher odds of alcohol discontinuation (odds ratio [OR] 1.36 [95% CI 1.27, 1.44], $P < 0.001$ and OR 1.85 [95% CI 1.37, 2.51], $P < 0.001$, respectively). Fully-adjusted models including comorbidity, work disability, and physical and mental quality of life completely attenuated this association (Table 2). The most important confounders were mental and physical quality of life, suggesting that the effect of

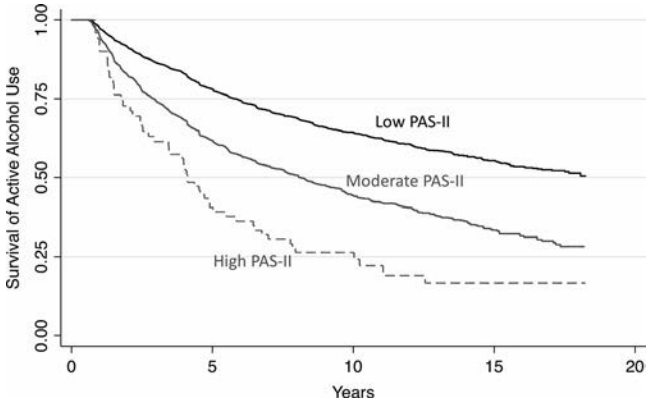

Figure 1. Predicted time-to-discontinuation of alcohol use among individuals who remain in different disease activity groups over long-term follow-up, adjusting for age, sex, race, body mass index, and rheumatoid arthritis therapies. Patient Activity Scale–II (PAS-II) is evaluated as time varying; participants can contribute follow-up time to multiple disease activity categories over time.

disease activity on behavior is almost entirely explained by its association with quality of life.

Factors that were independently associated with greater odds of discontinuing alcohol use included older age, obesity, greater comorbidity, and work disability. Factors associated with lower odds of discontinuing alcohol use included male sex, white race, greater physical and mental quality of life, higher education level, and greater household income (Table 2). Sensitivity analyses limited to moderate alcohol use only were similar to the primary analyses and are shown in Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23847/abstract.

Initiation of alcohol use among abstainers. Initiation of alcohol use was common among abstainers (4,258 events in 46,364 eligible observations; 9.2%) and was less likely to occur among those with moderate or high PAS-II scores compared to those with low PAS-II scores (OR 0.83 [95% CI 0.79, 0.88], $P < 0.001$ and OR 0.74 [95% CI 0.61, 0.89], $P = 0.002$, respectively) after adjusting for age, sex, race, BMI, and RA treatments. As with discontinuation of alcohol, the association between disease activity and alcohol initiation was fully attenuated and not significant in adjusted models that included disability, physical quality of life, education level, and household income (OR 0.95 [95% CI 0.77, 1.18], $P = 0.66$) (Table 2). The most important confounders were work disability and physical quality of life. Older age, work disability, and use of methotrexate were each associated with a lower odds of initiating alcohol use, while male sex, superior physical quality of life, higher education level, and greater household income were each associated with a greater odds of initiating use (Table 2). Sensitivity analyses limited to moderate use only were similar to the primary analyses (see Supplementary Table 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23847/abstract).

Associations between changes in alcohol use, disease activity, and mortality. An increase in disease activity was observed in 7,909 of 45,753 observations among previous drinkers (17.3%). Reporting of discontinuation of alcohol in the prior interval (compared to continued drinking) was not associated with worsening of disease activity in adjusted models (Table 3). In survival analyses, 615 deaths occurred among 8,114 subjects who had ever used alcohol. Discontinuation of alcohol was associated with a greater subsequent risk of death in models adjusting for age, sex, race, BMI, disease duration, and smoking status (HR 1.58 [95% CI 1.25, 2.00], $P < 0.001$) (data not shown). However, the association with mortality was attenuated and not significant in fully adjusted models (Table 3).

A subsequent improvement in disease activity occurred in 7,321 of 43,600 observations (16.8%) among previous abstainers. Initiation of alcohol in the prior interval was not associated with an improvement in disease activity in fully adjusted models (Table 3). There were 993 deaths among 8,129 eligible subjects

Table 3. Associations between recent discontinuation and initiation of alcohol use in the prior period (versus no change in behavior) and the risk of a change (>0.5 SD) in disease activity over the subsequent interval or the risk of subsequent death*

	Increase in PAS-II† (n = 6,768; obv. = 45,753)		Risk of death‡ (n = 7,808; person years = 29,251)		Decrease in PAS-II† (n = 6,855; obv. = 43,600)		Risk of death‡ (n = 7,708, person years = 27,799)	
	OR (95% CI)	*P*	HR (95% CI)	*P*	OR (95% CI)	*P*	HR (95% CI)	*P*
Stopped drinking (vs. kept drinking)	0.97 (0.89, 1.07)	0.56	1.11 (0.85, 1.45)	0.44				
Began drinking (vs. kept abstaining)					0.98 (0.88, 1.08)	0.65	0.84 (0.62, 1.16)	0.30

* PAS-II = Patient Activity Scale–II; obv. = observations; OR = odds ratio; 95% CI = 95% confidence interval; HR = hazard ratio.
† PAS-II analyses fully adjusted for age, sex, race, enrollment body mass index (BMI) category, smoking, disease duration, PAS-II, methotrexate, prednisone, biologic therapy, work disability, Rheumatic Disease Comorbidity Index (RDCI), liver disease, Short Form 36 physical component summary (SF-36 PCS), Short Form 36 mental component summary (SF-36 MCS), household income, marital status, education level, health satisfaction, and calendar date.
‡ Mortality analyses fully adjusted for age, sex, race, enrollment BMI category, smoking, disease duration, PAS-II, methotrexate, prednisone, biologic therapy, work disability, RDCI, diabetes mellitus, heart disorders, depression, high blood pressure, cancer, liver disease, psychiatric disease, SF-36 PCS, SF-36 MCS, household income, education level, marital status, health satisfaction, and calendar date.

who had ever abstained from alcohol. Initiation of alcohol was associated with a reduced subsequent risk of death in models adjusting for age, sex, race, BMI, disease duration, and smoking status (HR 0.72 [95% CI 0.54, 0.95], $P = 0.02$) (data not shown). However, the association was attenuated and not significant in adjusted models (Table 3).

Associations of active drinking with disease activity and mortality. The reported use of alcohol was associated with lower PAS-II scores in unadjusted models incorporating GEEs (β = –0.19 [95% CI –0.22, –0.15], $P < 0.001$) (Figure 2 and Supplementary Table 5, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23847/abstract). This was attenuated, although still significant, in multivariable models adjusting for a number of time-varying covariates (β = –0.15 [95% CI –0.18, –0.11], $P < 0.001$). A marginal structural modeling approach, aiming to balance the probability of being exposed to alcohol across drinkers and abstainers, demonstrated no significant difference in PAS-II scores among active drinkers (β = 0.002 [95% CI –0.094, 0.097], $P = 0.97$).

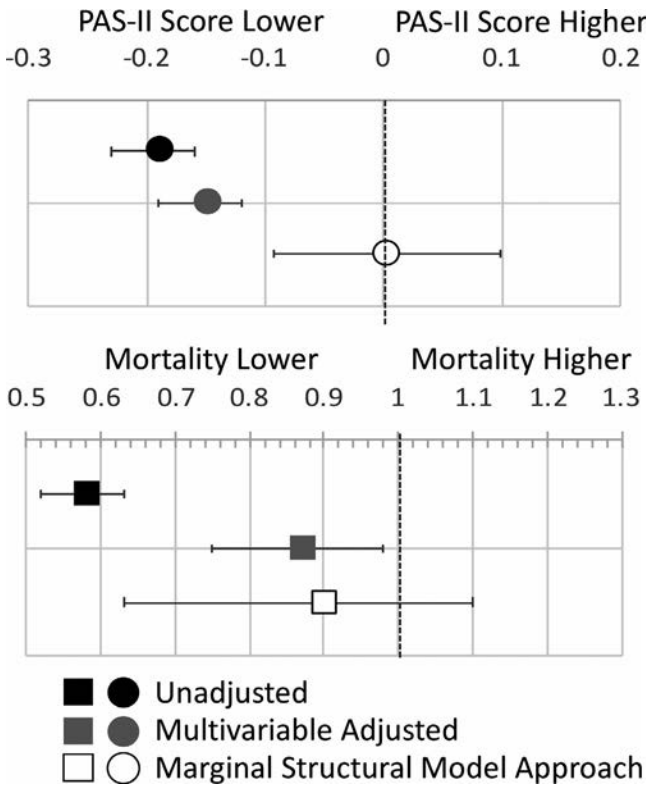

Figure 2. Association between alcohol use and disease activity (Patient Activity Scale–II [PAS-II], beta coefficient) and the risk of death (odds ratio) in unadjusted models (black), pooled linear and logistic regression using traditional multivariable modeling (with generalized estimating equations) (gray), and marginal structural models that consider the propensity for current alcohol use based on current and prior covariates (white).

In unadjusted pooled logistic regression models, active drinking was strongly associated with a lower risk of death (OR 0.58 [95% CI 0.53, 0.64], $P < 0.001$). In models adjusting for time-varying covariates, the association was attenuated but still significant (OR 0.87 [95% CI 0.76, 0.99], $P = 0.03$). A marginal structural modeling approach did not demonstrate significant differences in mortality among active drinkers (OR 0.90 [95% CI 0.70, 1.17], $P = 0.44$). Sensitivity analyses limited to moderate use were similar (see Supplementary Table 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23847/abstract).

DISCUSSION

To our knowledge, this is the first study to identify factors associated with initiation and discontinuation of alcohol use in patients with RA over long-term follow-up. Higher disease activity, older age, comorbidity, disability, and poor physical and mental quality of life were associated with greater discontinuation of use among drinkers and a lower likelihood of initiating use among abstainers. Overall, these observations suggest that patients with RA are substantially less likely to use alcohol when their disease activity is high and their health and quality of life are poor. This study also found that active drinking, recent discontinuation of drinking, and recent initiation of drinking were not associated with disease activity or death in this population when considering the reasons for the changes in behavior.

Participants who reported high disease activity were more likely to discontinue and less likely to initiate alcohol use. This is important since prior studies have suggested protective effects of alcohol use on disease activity (1–7). The current study suggests that many individuals who did not report drinking alcohol in these studies are likely to have discontinued (or to have never initiated) due to high disease activity and poor health. In other words, while it is true that alcohol use is associated with lower disease activity and better function, this association may be better explained by reverse causality as opposed to a biologically protective effect of drinking alcohol. This study emphasizes the importance of considering the potential for reverse causality when evaluating relationships between behaviors and RA disease activity in cross-sectional studies, particularly when the behaviors studied may be expected to change in association with poor health. The current study did not find an association between alcohol use and disease activity in marginal structural models that aim to balance confounding factors that vary with time. To our knowledge, this is the first longitudinal study to use this approach to deal with this problem in this context.

We also identified strong associations between discontinuation of alcohol use and greater subsequent mortality among active users. While this might suggest that discontinuation of alcohol has adverse implications for health in RA, multivariable models

suggest that these effects are largely dependent on current disease activity, disability, comorbidity, and quality of life. Similarly, initiating alcohol use appeared protective, but the effect was similarly confounded. This study is among the first to demonstrate relationships between discontinuation and initiation of alcohol use and long-term mortality in any population and supports the hypothesis that changes in this behavior might be related to mortality through noncausal mechanisms (24,25).

Studies in the general population have observed lower risks of frailty and death among those who drink alcohol (16,24,26). However, reduced risks of death were not observed among younger individuals who drink alcohol, suggesting that changes in this behavior over time occurring with illness and aging, as well as selection bias, may result in residual confounding in these cohort studies (25,27–30). Our results support the idea that bias, as opposed to a biologic benefit of alcohol, may represent the primary driver of these epidemiologic associations. This study did not have sufficient ability to rule out a small beneficial effect of alcohol use on the risks of death.

Overall, the findings in this study call into question prior evidence suggesting that moderate alcohol use provides a protective effect in patients with RA. However, the current study is limited in that it did not assess lifetime patterns of alcohol use prior to enrollment. As in any study using a self-reported exposure, there may be inaccuracies in the reporting of use, particularly among certain groups. Our study also did not explore the effect of alcohol across all different quantities of use; thus, we cannot rule out a benefit at all levels of use. Furthermore, the nature of the registry does not provide the opportunity to assess other outcomes, such as radiographic progression, serostatus, inflammatory markers, or other physician assessments. This study therefore cannot directly assess biologic relationships between the systemic inflammatory disease and alcohol use. However, it is likely that patient factors (pain, function, overall well-being) are most likely to influence and be influenced by patterns of alcohol consumption (30). Notably, it remains difficult to completely disentangle changes in use and changes in disease activity, even in this comprehensive longitudinal study, and residual confounding may be present. Finally, regional and cultural differences in behaviors surrounding the use of alcohol may affect the generalizability of some of these observations. Despite these limitations, this study suggests that patients should not expect that a decision to alter their intake of alcohol would have an important impact on their RA disease activity. This study also illustrates a problem common to observational studies that aim to study dietary or behavioral exposures that may vary in relationship to health status.

In conclusion, patient reporting of higher disease activity is associated with subsequent discontinuation of alcohol use and a lower likelihood of initiating use. These relationships are largely explained by comorbidity, disability, and poor physical and mental quality of life among those who report more active disease. In this study, active use and recent changes in alcohol use were not found to be associated with disease activity or death when considering confounding factors, suggesting no clear benefit of moderate alcohol consumption in RA.

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. Baker 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. Baker, Michaud.

Acquisition of data. Baker, Michaud.

Analysis and interpretation of data. Baker, England, Mikuls, Hsu, George, Pedro, Sayles, Michaud.

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Systematic Review of Recommendations on the Use of Disease-Modifying Antirheumatic Drugs in Patients With Rheumatoid Arthritis and Cancer

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Objective. To evaluate consensus recommendations regarding management of rheumatoid arthritis (RA) in patients with cancer.

Methods. We searched electronic databases, guideline registries, and relevant web sites for cancer-specific recommendations on RA management. Reviewers independently selected and appraised the recommendations according to the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. We identified similarities and discrepancies among recommendations.

Results. Of 4,077 unique citations, 39 recommendations were identified, of which half described their consensus process. Average scores for the AGREE II domains ranged from 33% to 87%. Cancer risk in RA was addressed in 79% of recommendations, with acknowledgement of increased overall cancer risk. Recommendations did not agree on the safety of using disease-modifying antirheumatic drugs (DMARDs) in RA patients with cancer, except for the contraindication of tumor necrosis factor inhibitors in patients at risk for lymphoma. Most recommendations agreed that RA treatment should be stopped and re-evaluated with a new diagnosis of cancer. Recommendations for patients with a history of cancer differed depending on the drug, cancer type, and time since cancer diagnosis. Few recommendations addressed all issues.

Conclusion. Recommendations for the treatment of RA in patients with cancer often fail to meet expected methodologic criteria. There was agreement on the need for caution when prescribing DMARDs to these patients. However, several areas continue to lack consensus, and given the paucity of evidence, there is an urgent need for research and expert opinion to guide and standardize the management of RA in patients with cancer.

INTRODUCTION

Patients with rheumatoid arthritis (RA) have a high prevalence of comorbidities, which are often suboptimally managed (1–4). Among them, a person diagnosed with RA is more likely than the general population to have a history of cancer (5,6). A meta-analysis reported that patients with RA have a 10% increase in the overall malignancy risk compared with the general population (7). Because both RA and cancer require aggressive and often long-term treatment, ensuring that the management of each condition does not interfere with the outcomes of the other is key. Tumor immunity plays a major role in controlling cancer progression, which is particularly important, because most drugs required for the treatment of RA are immunosuppressant.

Previous studies have reported on recommendations for the management of comorbidities in patients with RA, but the level of consensus regarding management of cancer has not been studied. The objective of this systematic review was to

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SIGNIFICANCE & INNOVATIONS

- Consensus regarding management of cancer has not been studied.
- We identified similarities, discrepancies, and gaps in knowledge in current clinical practice guidelines and consensus statements.
- Disagreements were generally related to the areas with lacking evidence.
- Agreement was observed in 5 areas related to risk management, screening, monitoring, and management in patients with rheumatoid arthritis newly diagnosed with cancer and for patients with a history of recent cancer (<5 years).

evaluate recommendations for the management of disease-modifying antirheumatic drugs (DMARDs) in patients with RA and cancer, and to identify similarities, discrepancies, and areas not covered.

MATERIALS AND METHODS

Eligibility criteria. Our report follows the 27-item checklist in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (8). Clinical practice recommendations derived from a consensus process regarding the use of DMARDs for the treatment of RA in the context of cancer and published after the year 2000 were considered for inclusion. When more than one version was produced by the same organization, we included the most updated one.

Information sources and search. We searched electronic databases (CINAHL, Cochrane, Embase [Ovid], Medline [Ovid], PubMed E-pubs, and Web of Science), guideline registries, and relevant organizational websites until June 2017. Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23865/abstract, lists the sources of grey literature. The search strategy was developed with an experienced health sciences librarian (GP). Keywords included "RA," "cancer," "recommendations," "guideline," and "consensus statement." No language limit was imposed (Medline strategy is shown in Supplementary Appendix A, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23865/abstract).

Study selection. EndNote (Clarivate Analytics) was used to store citations and eliminate duplicates. Two pairs of reviewers (IC and SRQ; NVZ and RS), blinded to author and journal, independently assessed eligibility based on title and abstract. Potentially eligible recommendations were retrieved as full-text articles, and only those mentioning cancer in the context of pharmaceutical management of RA were included. At all stages of the selection process, disagreements were resolved by consensus; if agreement could not be obtained, a third reviewer was consulted (MAL-O).

Data collection process. Two pairs of reviewers (NVZ and RS; MAL-O and ARKM) extracted data and assessed reporting quality. Disagreements were resolved by consensus; if agreement could not be obtained, a third reviewer was consulted (MES-A).

Data items. We extracted statements concerning management of cancer risk in patients with RA and DMARDs use in patients with a history of cancer, stratified by time since cancer diagnosis and type of cancer. DMARDs were classified as conventional synthetic and targeted synthetic (csDMARDs and tsDMARDs, respectively) or biologic (bDMARDs) (9). We noted consensus and evidence grading methods used, as well as the evidentiary basis of each recommendation.

Quality appraisal. Selected recommendations were evaluated according to the Appraisal of Guidelines for Research and Evaluation (AGREE) II reporting checklist (10). The instrument consists of 23 assessment criteria assigned to 6 domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence. Each domain is assessed on a 7-point scale and discussed between reviewers when the scores differ by >2 points. The final score per domain, expressed as a percentage, is calculated as

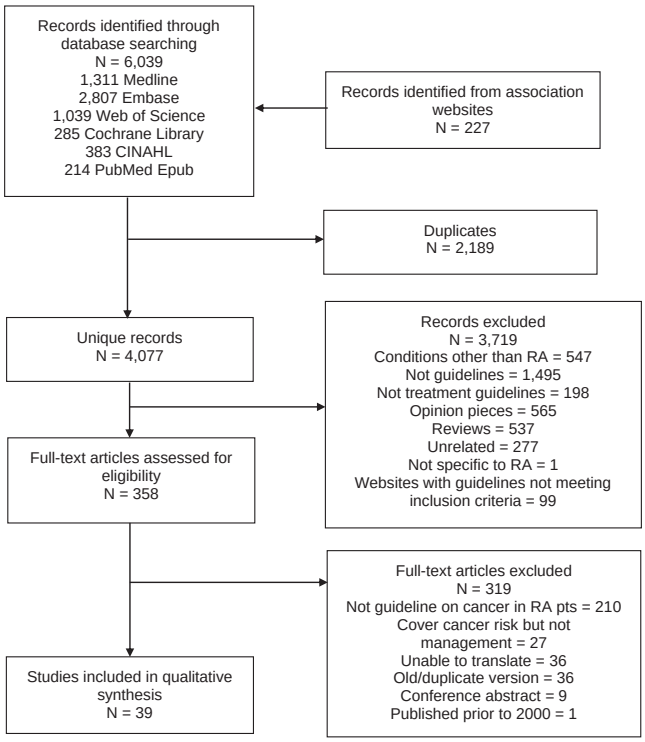

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram: study selection. RA = rheumatoid arthritis.

follows: (obtained score minus minimum possible score)/(maximum possible score minus minimum possible score). The results of the quality appraisal and data extraction were summarized in a narrative synthesis and tabulated.

RESULTS

Study selection. The initial search retrieved 6,266 records. Of the 4,077 nonduplicate records, 358 full-text articles were assessed for eligibility, resulting in 39 recommendations for analysis (Figure 1). We excluded 27 recommendations that mentioned a possible association between RA and/or DMARDs and cancer but did not provide management advice.

General characteristics of selected studies. Recommendations were from 14 countries, and 6 were international collaborations. Most recommendations were directed at rheumatologists. Just over half (21 of 39) reported funding sources, and 17 described their method for reaching consensus. In terms of topic, 11 recommendations focused on the management of RA in general, 3 specifically addressed the safety of tumor necrosis factor inhibitors (TNFi), and 2 addressed comorbidity management. Four recommendations discussed treatment with biologic agents, 5 concentrated on TNFi, and the remainder were agent-specific (Table 1).

Quality of reporting. Four recommendations (10%) scored above 60% in all AGREE II domains (5,6,11,12). The average overall score was 58.1%; recommendations received the highest scores for scope and purpose (87.8%) and lowest scores for applicability (34.2%). Results for each publication are shown in Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23865/abstract.

Management of cancer risk. Thirty-one recommendations (79%) mentioned cancer risk (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23865/abstract), citing increased risk among patients with RA, particularly for lymphoma, but also for lung cancer, melanoma, and nonmelanoma skin cancers (5,6,11–40). The risk of cancer associated with the use of specific DMARDs was noted as controversial and inconclusive. However, 19 recommendations attributed an increased risk for at least 1 type of cancer to at least 1 agent (5,6,11,12,14,15,17,19,24,25,28–30,32,33,37,38,40,41).

Cancer screening in general for patients with RA. Among the 14 recommendations (42%) discussing cancer screening (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23865/abstract), there was general agreement on the need for screening prior to RA therapy initiation, but disagreement on the comprehensiveness of screening (5,6,11,12,15,17,19,25,32–35,37,42). Of those that provided details, 6 recommended considering personal and family history of cancer and known risk factors for cancer when prescribing DMARDs (35). Most recommendations were based on expert opinion.

Cancer monitoring in patients with RA receiving DMARDs. Routine safety monitoring for signs and symptoms of cancer was mentioned in 14 recommendations (42%) (4,6,11,12,17,26,27,32–35,37,42,43); most referred to bDMARDs (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23865/abstract). The overall agreement was to watch for symptoms, but very few recommendations detailed which symptoms should be watched for, or which screening tests should be used or when. Skin cancer monitoring received special mention and was the only recommendation not based solely on expert opinion (11).

Management of RA in patients with cancer*. De novo cancer diagnosis during treatment for RA*. The 14 recommendations that discussed management of RA in patients with a new cancer diagnosis agreed, mostly based on expert opinion, that treatment should be reevaluated (see Supplementary Table 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23865/abstract) (6,11,17,26,28,30–35,37,38,42). Eleven recommendations unequivocally directed practitioners to discontinue bDMARD treatment. Only 5 recommendations offered more specific steps regarding, for example, tests to perform.

Finally, several recommendations mentioned the need to report the cancer to the country's surveillance system and inform the patient of the risk of worsened outcomes if continuing treatment. On completion of cancer treatment, cyclosporine, TNFi, and tocilizumab could be resumed on a case-by-case basis in consultation with the patient and treating oncologist/hematologist. The considerations for restarting rituximab were the same as those for patients with RA with a history of cancer.

Initiation of DMARD treatment for recent RA diagnosis in patients with cancer. Sixteen recommendations discussed initiating RA treatment in patients with active cancer (see Supplementary Table 5, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23865/abstract) (5,12,15,16,18,23,24,26,28,31,32,34–37,42). Owing to fears of increased infection rates and possible interactions with chemotherapy, it was agreed that DMARDs are contraindicated or should be avoided in patients with active cancer. Two recommendations advised caution with recommendations made on a case-by-case basis (5,28). Finally, one suggested that systemic therapy for malignancies might help control RA (5).

Fourteen recommendations discussed premalignant conditions (11,17–19,24,26,29,31–35,42,44): bDMARDs and cyclosporine were contraindicated or caution was advised (see Supplementary Table 6, available on the *Arthritis Care & Research*

Table 1. Characteristics of the recommendations included in our analysis*

Group, year (ref.)	Country/ region	Topic	Systematic review	Funding	Treatment algorithm
1. European League against Rheumatism, 2000 (39)	International	TNFi	No	Schering-Plough	No
2. National Institute for Clinical Excellence, 2002 (31)†	UK	Infliximab and etanercept	No	NHS	No
3. British Society for Rheumatology, 2005 (26)	UK	TNFi	Yes	NR	No
4. Hong Kong Society of Rheumatology, 2005 (29)	Hong Kong	TNFi	No	NR	No
5. Kalden, 2005 (47)	International	Leflunomide + bDMARDs	Yes	Sanofi-Aventis	No
6. Australian Rheumatology Association, 2006 (30)	Australia	TNFi	No	NR	No
7. Comité Mexicano del Consenso de Biológicos. Colegio Mexicano de Reumatología, 2006 (42)‡	Mexico	bDMARDs	Yes	Abbott, Bristol-Myers Squibb, Roche, Schering-Plow, Wyeth	No
8. Latin American Rheumatology Associations of the Pan-American League of Associations for Rheumatology and the Grupo Latinoamericano de Estudio de Artritis Reumatoide, 2006 (14)	Latin America	RA management	No	Abbot	Yes
9. de la Torre Aboki, 2007 (46)	Spain	Infliximab	Yes	Schering-Plough	No
10. Japan College of Rheumatology, 2007 (24)	Japan	Infliximab and etanercept	No	NR	No
11. Club Rhumatismes et Inflammation (a section of the French Society of Rheumatology), 2008 (35)	France	Rituximab	No	Katana Santé	No
12. Díaz-Jouanen, 2009 (17)	Mexico	Safety of TNFi	Yes	NR	No
13. Japan College of Rheumatology, 2009 (44)	Japan	Tocilizumab	No	NR	No
14. British Society for Rheumatology and British Health Professionals in Rheumatology, 2010 (11)	UK	Safety of TNFi	Yes	British Society for Rheumatology, British Health Professionals in Rheumatology	No
15. Club Rhumatismes et Inflammation, 2010 (34)	France	Tocilizumab	Yes	Raison de Santé	No
16. Mexican Social Security Institute, 2010 (15)	Mexico	RA management	No	NR	Yes
17. Buch, 2011 (13)	International	Rituximab	Yes	Hoffmann-La Roche	No
18. Club Rhumatismes et Inflammation, 2011 (32)	France	TNFi	No	Raison de Santé	No
19. Hong Kong Society of Rheumatology, 2011 (40)	Hong Kong	RA management	No	NR	No
20. Italian Society for Rheumatology, 2011 (19)	Italy	bDMARDs	Yes	NR	No
21. Rheumatology Service at Hospital Universitario La Paz, 2011 (27)	Spain	Rituximab	Yes	Roche Farma España	No
22. Spanish Society of Rheumatology, 2011 (12)§	Spain	RA management	Yes	NR	No
23. Canadian Rheumatology Association, 2012 (5)	Canada	Safety of TNFi	Yes	Canadian Institutes of Health Research Scoping Reviews, Research and Canadian Rheumatology Association	No
24. Club Rhumatismes et Inflammation, 2012 (33)	France	Abatacept	No	Raison De Santé, Katana Santé	No
25. Cyclosporine Clinic at the Mary Pack Arthritis Centre, 2012 (28)	Canada	Cyclosporine	Yes	NR	No
26. Brazilian Society of Rheumatology, 2013 (16, 41)	Brazil	RA management	Yes	NR	Yes
27. South African Rheumatism and Arthritis Association, 2013 (23)	South Africa	RA management	Yes	South African Rheumatism and Arthritis Association	Yes

(Continued)

Table 1. (*Cont'd*)

Group, year (ref.)	Country/ region	Topic	Systematic review	Funding	Treatment algorithm
28. Commission Pharmacotherapy of the German Society of Rheumatology, 2014 (20)	Germany	Abatacept	Yes	NR	No
29. Commission Pharmacotherapy of the German Society of Rheumatology, 2014 (36)	Germany	Rituximab	Yes	NR	No
30. European League Against Rheumatism (EULAR), 2014 (48)¶	Europe	RA management	Yes	EULAR	Yes
31. French Society of Rheumatology, 2014 (21)	France	RA management	Yes	NR	Yes
32. German Society of Rheumatology, 2014 (45)	Germany	RA management	Yes	German Society of Rheumatology, AbbVie, Chugai, Pfizer, Roche, Sanofi Aventis Deutschland, UCB	Yes
33. American College of Rheumatology (ACR), 2015 (38)	US	RA management	Yes	ACR	Yes
34. Asia Pacific League of Associations for Rheumatology, 2015 (25)	Asian Pacific	RA management	Yes	Asia Pacific League of Associations for Rheumatology	Yes
35. Canadian Dermatology-Rheumatology Comorbidity Initiative, 2015 (6)	Canada	Comorbidity management	Yes	AbbVie	No
36. Spanish Society of Rheumatology, 2015 (37)	Spain	Synthetic and bDMARDs DMARDs	Yes	NR	Yes
37. Rencontres d'experts en rhumatologie, 2016 (4)	France	Comorbidity management	Yes	AbbVie France	No
38. Portuguese Society of Rheumatology, 2017 (18)	Portugal	bDMARDs	Yes	NR	No
39. Portuguese Society of Rheumatology, 2017 (43)	Portugal	Methotrexate	Yes	NR	No

* TNFi = tumor necrosis factor inhibitors; NR = not reported; bDMARDs = biologic disease-modifying antirheumatic drugs; RA = rheumatoid arthritis.
† Updated versions do not include cancer recommendations.
‡ Noted as valid for only 2 years but no update found.
§ Valid only until 2016 but no update found.
¶ 2017 update published but does not include cancer recommendations other than to list malignancy as a contraindication (with no further treatment indication).

web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23865/abstract). The only possible exception was the use of rituximab in patients with in situ cancer (35).

Management of RA in patients with a history of cancer. Thirty-five recommendations (92%) included guidance regarding DMARD treatment in patients with past cancer, varying in terms of the type of cancer, time from cancer diagnosis or treatment, and the agents discussed (5,6,11–21,23–36,38–40,42,44–48) (see Supplementary Table 7, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23865/abstract, for a per-study summary).

Management of RA in patients with a history of unspecified cancer. Twenty-seven recommendations made general reference to a history of cancer (6,11,12,14–21,23,24,26,28–31,33,34,39,42,44–48). There was disagreement regarding the survivorship timeframe: 13 recommendations limited the restriction to 5 years or "recent" cancers (Table 2), and 7 applied it to cancers treated >5 years prior to the RA management decision (Table 3). Recommendations with the 10-year restriction were all published before 2007, and those with the 5-year restriction were published more recently.

Timeframe unspecified. Seven recommendations did not specify a timeframe (6,11,12,15,20,24,45) (Table 4). Cyclophosphamide was contraindicated, as were TNFi as a group, or etanercept and infliximab specifically. Regarding non-TNFi bDMARDs, rituximab could be used (45), but abatacept was contraindicated (20).

Unspecified cancer <5 years prior to RA. Thirteen recommendations referred to a "recent" history of cancer or one in the previous 5 years (16–19,21,23,28,34,39,44,46–48) (Table 3). Most recommendations agreed on limiting or contraindicating the drugs under discussion, such as cyclosporine, bDMARDs, and TNFi. However, rituximab could be used in patients with a history of cancer in the previous 5 years (21,48), and tocilizumab should be used with caution (34,44).

Table 2. Recommendations regarding history of cancer (survivorship) in the previous 5 years*

<5 years (includes "recent" and 1 year)	Solid tumor, no. (refs.)†	Hematologic, no. (refs.)‡	Skin cancer, no. (refs.)	Cancer not specified, no. (refs.)
csDMARDs§				
Total	–	–	–	1
Caution/can use¶	–	–	–	–
Not recommended	–	–	–	1 (28)
bDMARDs				
Total	–	–	1	2
Caution/can use¶	–	–	1 (30)	–
Not recommended#	–	–	–	2 (18,23)
TNFi**				
Total	4	2	–	6
Caution/can use¶	–	–	–	1 (17)
Not recommended#	4 (12,15,32,40)	2 (32,40)	–	5 (16,19,39,46,47)
non-TNFi bDMARDs††				
Total	3	3	2	4
Caution/can use¶	2 (18,35)	2 (21, 48)	2 (6,33)	4 (21,34,44,48)
Not recommended#	1 (33)	1 (33)	–	–

* csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; bDMARDs = biologic DMARDs; TNFi = tumor necrosis factor inhibitors; non-TNFi bDMARDs = non-TNFi biologic DMARDS.
† Includes melanoma.
‡ Includes lymphoma, non-Hodgkin's B cell lymphoma, Epstein-Barr virus–induced lymphoproliferative disease, lymphoproliferative disorder, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myelodysplastic syndrome, chronic myeloproliferative syndrome, monoclonal gammopathy of undetermined significance, solitary plasmacytoma, multiple myeloma, and blood cell count abnormalities.
§ Methotrexate, sulfasalazine, hydroxychloroquine, leflunomide cyclosporine, and cyclophosphamide.
¶ Includes wording from recommendations such as: "close monitoring is required," "can be prioritized," "can be considered as first line," "recommended," "good choice," "possible indication," "first line," "same as patients without history," "better than TNFi," "better than tofacitinib and bDMARD," "case-by-case consideration," "can be used in some cases," "consult with oncologist," "consult with dermatologist," "requires risk-benefit assessment," "inform patient of risk," and "limit."
# Includes wording such as "contraindicated," "not indicated," "not as first line," and "avoid."
** Includes recommendations that only addressed infliximab and etanercept as well as those that addressed the group as a whole.
†† Abatacept, rituximab, tocilizumab, and tofacitinib.

Unspecified cancer >5 years prior to RA. There were no recommendations regarding the prescription of csDMARDs in patients who had been diagnosed with cancer >5 years prior to RA (Table 2). Four recommendations continued to contraindicate bDMARDs as a group (14,30,42) or etanercept and infliximab for 10 years after cancer treatment (31). Other recommendations only advised caution in the prescription of TNFi for these patients (17,26,29).

Table 3. Recommendations regarding history of cancer (survivorship) >5 years previously*

>5 years (includes 5–10 years and >10 years)	Solid tumor, no. (refs.)†	Hematologic, no. (refs.)‡	Skin cancer, no. (refs.)	Cancer not specified, no. (refs.)
bDMARDs				
Total	1	–	–	3
Caution/can use§	1 (12)	–	–	–
Not recommended¶	–	–	–	3 (14,30,42)
TNFi#				
Total	2	–	–	4
Caution/can use§	2 (12,32)	–	–	3 (17,26,29)
Not recommended¶	–	–	–	1 (31)

* bDMARDs = biologic disease-modifying antirheumatic drugs; TNFi = tumor necrosis factor inhibitors.
† Includes melanoma.
‡ Includes lymphoma, non-Hodgkin's B cell lymphoma, Epstein-Barr virus–induced lymphoproliferative disease, lymphoproliferative disorder, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myelodysplastic syndrome, chronic myeloproliferative syndrome, monoclonal gammopathy of undetermined significance, solitary plasmacytoma, multiple myeloma, and blood cell count abnormalities.
§ Includes wording from recommendations such as: "close monitoring is required," "can be prioritized," "can be considered as first line," "recommended," "good choice," "possible indication," "first line," "same as patients without history," "better than TNFi," "better than tofacitinib and bDMARD," "case-by-case consideration," "can be used in some cases," "consult with oncologist," "consult with dermatologist," "requires risk-benefit assessment," "inform patient of risk," and "limit."
¶ Includes wording such as "contraindicated," "not indicated," "not as first line," and "avoid."
# Includes recommendations that only addressed infliximab and etanercept as well as those that addressed the group as a whole.

Table 4. Recommendations regarding history of cancer (survivorship) in the unspecified past*

Treatment and unspecified time	Solid tumor, no. (refs.)†	Hematologic, no. (refs.)‡	Skin cancer, no. (refs.)	Cancer not specified, no. (refs.)
csDMARDs§				
Total	2	3	3	2
Caution/can use¶	2 (5,38)	2 (5,38)#	3 (5,28,38)	–
Not recommended**	–	1 (5)††	–	2 (12,15)‡‡
bDMARDs				
Total	3	1	4	–
Caution/can use¶	3 (5,12,38)	–	4 (5,14,18,38)	–
Not recommended**	–	1 (12)	–	–
TNFi§§				
Total	1	4	3	3
Caution/can use¶	2 (32,38)	–	3 (31,32,46)	3 (6,11,24)
Not recommended**	–	4 (5,12,17,35)	–	–
non-TNFi bDMARDs¶¶				
Total	5	10	3	2
Caution/can use¶	4 (6,27,34,38)	9 (5,6,13,18,25,34–36,38)	2 (33,34)	2 (20,45)
Not recommended**	1 (38)##	1 (34)***	1 (38)##	–

* csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; bDMARDs = biologic DMARDs; TNFi = tumor necrosis factor inhibitors; non-TNFi bDMARDs = non-TNFi biologic DMARDS.
† Includes melanoma.
‡ Includes lymphoma, non-Hodgkin's B cell lymphoma, Epstein-Barr virus–induced lymphoproliferative disease, lymphoproliferative disorder, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myelodysplastic syndrome, chronic myeloproliferative syndrome, monoclonal gammopathy of undetermined significance, solitary plasmacytoma, multiple myeloma, and blood cell count abnormalities.
§ Methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, cyclosporine, and cyclophosphamide.
¶ Includes wording from recommendations such as: "close monitoring is required," "can be prioritized," "can be considered as first line," "recommended," "good choice," "possible indication," "first line," "same as patients without history," "better than TNFi," "better than tofacitinib and bDMARD," "case-by-case consideration," "can be used in some cases," "consult with oncologist," "consult with dermatologist," "requires risk-benefit assessment," "inform patient of risk," and "limit."
# Leflunomide, sulfasalazine, and hydroxychloroquine.
** Includes wording such as "contraindicated," "not indicated," "not as first line," and "avoid."
†† Methotrexate.
‡‡ Cyclophosphamide.
§§ Includes recommendations that only addressed infliximab and etanercept as well as those that addressed the group as a whole.
¶¶ Abatacept, rituximab, tocilizumab, and tofacitinib.
Tofacitinib.
*** Epstein-Barr virus–induced lymphoproliferative disease.

Management of RA in patients with a history of solid tumor or melanoma. Twelve recommendations referred to patients with a history of solid tumors (5,6,12,15,18,27,32–35,38,40). The timeframe was omitted in 60% of the recommendations and ranged from 1 to 10 years in the others.

Solid tumor with an unspecified timeframe. Seven of the recommendations referring to a history of solid tumor did not mention a timeframe (5,6,12,27,32,34,38) (Table 4). csDMARDs as a group, as well as leflunomide and methotrexate specifically, were allowed for these patients, while bDMARDs could be prescribed with caution or after consultation with a dermatologist or oncologist.

Solid tumor <5 years prior to RA. Seven recommendations addressed treatment options for patients diagnosed with a solid tumor in the previous 5 years (12,15,18,32,33,35,40) (Table 2). None addressed the use of csDMARDs. TNFi were contraindicated, and a guide to abatacept therapy and safety did not recommend its prescription. In contrast, rituximab could be considered on a case-by-case basis (18,35).

Solid tumor >5 years prior to RA. Two recommendations referred to solid tumors diagnosed >5 years previously to the RA diagnosis (12,32); neither addressed csDMARDs, but both suggested consultation with an oncologist before prescribing bDMARDs and TNFi (Table 3).

Management of RA in patients with a history of hematologic malignancies. Reference to hematologic malignancies was found in 16 recommendations (38.5%) (5,6,12,13,17,18,21,25,32–36,38,40,48). Most (14 of 16) did not stipulate a timeframe. Lymphoma was the most commonly discussed disease, followed by lymphoproliferative disorders in general. A footnote to Table 2 provides the full list of hematologic malignancies.

Two recommendations referred to csDMARDs, stating that they were a better choice than TNFi for these patients (38) but cautioning against leflunomide and not recommending methotrexate for patients with a history of lymphoma (5). One recommendation agreed on limiting or contraindicating the use of TNFi (12) in the treatment of patients with a history of lymphoproliferative disorders, lymphoma, and leukemia in

general, and B-cell lymphoma in particular. However, regarding non-TNFi bDMARDs, the consensus was that rituximab could be used, while abatacept and tocilizumab could be used with caution and were to be preferred to TNFi.

Management of RA in patients with a history of nonmelanoma skin cancer. Twelve recommendations agreed that DMARDs can be used in patients with a history of basal and squamous cell carcinomas (5,6,14,18,28,30–34,38,46). Most (10 of 12) did not state a timeframe. All agreed on the use of both csDMARDs and bDMARDs in these patients, but 1 did state that csDMARDs were preferable to biologics or to tofacitinib (38). In patients with a history of nonmelanoma skin cancer in the past 5 years, recommendations agreed that bDMARDs as a group, abatacept and rituximab specifically, can be used.

DISCUSSION

Following a systematic approach, we evaluated recommendations for the management of DMARDs in patients with RA and cancer. We identified similarities, discrepancies, and gaps in knowledge. Currently, 39 consensus recommendations cover at least 1 area related to cancer risk screening and/or monitoring or the management of patients with a current or past history of cancer. Most recommendations caution about an increased probability of cancer risk in patients with RA and a possible association between some DMARDs and specific cancers. Regarding screening, most recommendations were in favor of screening for age-prevalent cancer types prior to RA treatment initiation. For monitoring, the broad consensus was for ongoing monitoring of possible cancer symptoms during RA treatment. However, recommendations did not provide guidance on specific screening tests. For the management of patients with cancer, most agreed that DMARD treatment should be stopped and only resumed in consultation with a specialist in the case of de novo cancer. Similarly, it was not recommended to initiate RA treatment in patients with active cancer or premalignant conditions. Regarding a prior history of cancer, most recommendations advised caution when prescribing DMARDs, particularly when the cancer was treated within the past 5 years. Most cautioned against the prescription of TNFi for these patients, especially when the cancer in question was lymphoma or other hematologic malignancy. There were fewer restrictions on csDMARDs and non-TNFi biologics. Many recommendations considered rituximab as an adequate bDMARD choice.

We did not find consensus in terms of treatment of RA in patients at risk of cancer. In general, earlier recommendations were more conservative, contraindicating DMARDs, particularly bDMARDs, whereas more recent recommendations advised caution in prescribing, but not absolute contraindication. Cancer-specific advice (site, stage) in the included recommendations were vague, possibly reflecting the lack of evidence. This gap highlights the need of research in this area, to allow for personalized decision-making on the basis of cancer type and stage, as well as informing concurrent cancer therapies (e.g., immune checkpoint inhibitors). Updated recommendations of using recently-approved DMARDs in this context are also required.

To the best of our knowledge, this is the only systematic review of consensus recommendations for the treatment of RA in the context of cancer. Previous studies that compared recommendations for the management of RA have only assessed their methodologic quality and compliance with reporting standards (49–52). Our findings, together with those reported previously, indicate that quality, specific recommendations are needed for the treatment of RA in patients with multiple comorbidities. There are no recommendations that have resulted from the combined expertise of oncologists, radiotherapists, rheumatologists, and patients. Many recommendations were developed by rheumatologists with minimal input from other stakeholders, including patients, and the development process was often vague, if described at all, without external peer review. Few recommendations provided analysis of specific clinical scenarios that could be useful for individual patient management, and barriers and strategies for implementation were not considered.

Our study has limitations. Although its search strategy was designed to be as broad as possible, we were constrained to documents that could be translated with software. In addition, for 2 of the recommendations included in the analysis, recent versions did not provide cancer-specific information, so we used earlier versions that did. However, this omission could reflect a change in policy, such as a decision to base recommendations on more robust evidence. We also included 2 expired recommendations, i.e., with a future update planned that was not available at the time of this study. Finally, none of the included recommendations specifically addressed the use of combination therapy versus monotherapy (csDMARDs and/or bDMARDs).

In conclusion, the current consensus recommendations covering management of patients with RA and concomitant cancer agreed that there is an increased risk of cancer in patients with RA, particularly for lymphoma; cancer screening is recommended prior to initiation of bDMARDs; monitoring is recommended for signs and symptoms suggestive of cancer for patients on bDMARDs; clinicians should consider stopping DMARD treatment in RA patients newly diagnosed with cancer, and not initiate such treatment in cancer patients newly diagnosed with RA; and for patients with a history of cancer, particularly recent cancers (<5 years), caution is recommended when prescribing TNFis, and leflunomide or methotrexate in patients with lymphoma. Disagreements were generally related to the areas where evidence was lacking. Our findings suggest that additional research is needed on the effect of specific DMARDs on different types of cancer, at different stages, to provide personalized recommendations for patients with cancer and RA, considering

effects on recurrence and disease progression, quality of life, and patient preferences.

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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. Lopez-Olivo 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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Automated Text Message–Enhanced Monitoring Versus Routine Monitoring in Early Rheumatoid Arthritis: A Randomized Trial

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Objective. Frequent monitoring of patients with early rheumatoid arthritis (RA) is required for achieving good outcomes. This study was undertaken to investigate the influence of text message (SMS)–enhanced monitoring on early RA outcomes.

Methods. We randomized 166 patients with early, disease-modifying antirheumatic drug–naive RA to receive SMS-enhanced follow-up or routine care. All patients attended visits at 0, 3, and 6 months, and a follow-up visit at 12 months. Treatment was at the physicians' discretion. The intervention included 13 SMSs during weeks 0–24 with questions concerning medication problems (yes/no) and disease activity (patient global assessment [PtGA], scale 0–10). Patients were contacted if response SMSs indicated medication problems or PtGA exceeded predefined thresholds. Primary outcome was 6-month Boolean remission (no swollen or tender joints and normal C-reactive protein levels). Quality of life (QoL; measured by the Short Form 36 survey) and Disease Activity Score in 28 joints (DAS28) were assessed.

Results. Six and 12-month follow-up data were available for 162 and 157 patients, respectively. In the intervention group, 46% of the patients (38 of 82) reported medication problems and 49% (40 of 82) reported text message PtGAs above the alarm limit. Remission rates at 6 months ($P = 0.34$) were 51% in the intervention group and 42% in the control group. These rates were 57% and 43% at 12 months ($P = 0.17$) in the intervention and control groups, respectively. The respective mean ± SD DAS28 scores for the intervention and control groups were 1.92 ± 1.12 and 2.22 ± 1.11 at 6 months ($P = 0.09$); and 1.79 ± 0.91 and 2.08 ± 1.22 at 12 months ($P = 0.28$). No differences in QoL were observed.

Conclusion. The study did not meet the primary outcome despite a trend favoring the intervention group. This may be explained by the notably high overall remission rates.

INTRODUCTION

Achieving good outcomes in the treatment of early rheumatoid arthritis (RA) requires frequent monitoring and treatment targeted toward clinical remission. Current international recommendations suggest clinical assessments in active disease every 1–3 months (1). Some patients might benefit from even more frequent contacts with the rheumatology clinic. Implementation of the international

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SIGNIFICANCE & INNOVATIONS

- Automated text message monitoring is a feasible tool for remote assessment of disease activity and medication use in early rheumatoid arthritis (RA).
- Patients find text message monitoring easy to use and would recommend it to other patients with RA.
- In this study, remote monitoring did not influence early RA outcomes.

guidelines may be challenging, particularly in less affluent settings, possibly translating into worse outcomes. Therefore, barriers to more intensive monitoring should be overcome.

Poor medication adherence is another challenge in the treatment of early RA. Adherence to disease-modifying antirheumatic drugs (DMARDs) is on average 66% (2), but decreases over time (2,3). In early RA, nonadherence has been associated with worse outcomes during the first 6 months (3). However, improving medication adherence can be challenging (4,5).

Patient-reported outcomes have been shown to be as successful as clinical activity scores in distinguishing poor treatment responses (6). Use of patient-reported outcomes allows assessment at short intervals without a physician office visit. Thus, patient-reported outcomes could be used for early recognition of patients who do not achieve low disease activity, enabling prompt medication adjustment. Additionally, more frequent contact may increase patient confidence and promote medication adherence.

We have recently developed a simple and inexpensive automated monitoring system for patients with RA that is based on text message (SMS). This monitoring system aims at supporting successful initiation of DMARDs and improving drug adherence during the crucial first 6 months after the diagnosis of RA. In the current study, we assessed the effectiveness of 6-month SMS-enhanced follow-up compared to routine follow-up in early RA.

PATIENTS AND METHODS

Study design and selection of patients. We conducted an open, randomized trial comparing text message–enhanced monitoring to routine monitoring of early RA. We recruited 166 patients from 6 Finnish rheumatology centers from August 2013 through July 2015 and ceased randomization after reaching the minimum predefined sample size, due to slow recruitment. The patients were DMARD naive and fulfilled the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for RA (7). In addition, the participants were required to own a mobile phone and had to be able to send and receive text messages.

We randomized the patients 1:1 in blocks of 4 in each study center to receive text message–enhanced follow-up (intervention) or to receive routine follow-up (control). The 6-month intervention consisted of 13 SMSs at 1–2-week intervals during weeks 0–24. All patients were scheduled visits at 0, 3, and 6 months, after which the intervention ended. A follow-up visit after the intervention was scheduled at 12 months. Clinical assessments included a 46 swollen and tender joint count, patient's global assessment of RA disease activity within the previous 3 days (PtGA, 100-mm visual analogue scale [VAS]), patient's assessment of pain (VAS), patient's confidence in the treatment (VAS), physician's global assessment (VAS), and the Health Assessment Questionnaire (HAQ). Radiographs of the hands and feet were taken at baseline. Health-related quality of life was assessed using Short Form 36 (SF-36) questionnaire at 0, 6, and 12 months (8). Visits were scheduled at similar intervals as in routine clinical practice following treat-to-target guidelines and national recommendations (9,10). Treatment was not prespecified and was administered at the physician's discretion, following the Finnish Current Care guidelines (10). The protocol was approved by the ethics committee of South Karelia Central Hospital (400/13.02.02/2013) and the study was conducted according to the Declaration of Helsinki. We obtained written informed consent from all patients.

Showing Any Need For Reassessment (SandRA) software. The monitoring system used in the intervention group was an automated cloud-based software aiming at improvement of medication adherence and early identification of patients who respond poorly to treatment. Questions in the text messages concerned medication use and possible adverse effects at weeks 1 ("Have you started the prescribed medication?"), 2, 4, 8, 16, and 20 ("Have you had problems with your medication?"), and requested patient's assessment of disease activity at weeks 0, 6, 10, 12, 18, 22, and 24 ("What is the severity of your RA symptoms on a scale from 0 to 10, where 0 corresponds to no symptoms and 10 to as severe symptoms as you can imagine?"). Answers were given as a single letter (Y/N), or as a whole number (numbers 0–10). We used a simplified version of a PtGA using whole numbers, which has been validated previously (11). The software included a cutoff limit of scores of 4, 4, 3, and 2 for PtGA at 6-, 10-, 18-, and 22-week time points, respectively. Very low cutoff limits were chosen in order to detect possible problems early and to improve odds of reaching early strict remission. These limits were set based on data from 2 previous Finnish studies on early RA treatment strategy, in which patients with PtGAs above the cutoff limit had a low likelihood of achieving 6-month remission (12,13).

If patients' responses that suggested medication problems or insufficient reduction in disease activity, the system notified the treating clinic and sent the patient the following text message: "Your nurse will call you within 2 working days." The nurse called the patient, discussed the problem at hand, and consulted a physician if needed, as in routine clinical practice. If the problem could not be solved over the phone, the patient was called in for a visit before a scheduled appointment. If no problems were detected, the system responded "Have a nice day."

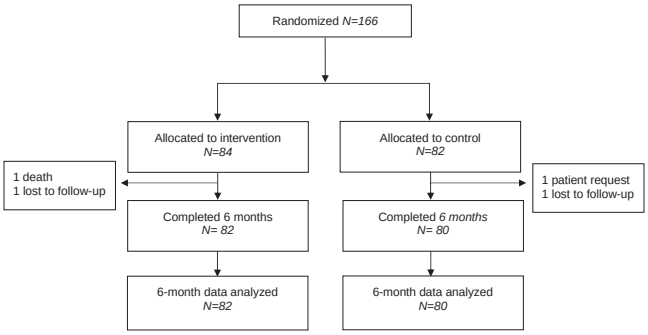

Figure 1. Flow of the study.

Participating rheumatology nurses received a short training of approximately 60 minutes in the use of the cloud-based SMS-monitoring system. The patients in the intervention group were given written and 30-minute oral instructions on performing the SMS monitoring. The patients were also able to practice its use during zero- and 3-month office visits. The patients in the control group did not receive text messages; in case of problems they left a callback request to their rheumatology nurse. After the intervention, the patients were asked to complete a short feedback questionnaire concerning the SMS monitoring (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23846/abstract). The nurses' actions were not documented in detail; only the number of additional nurses' and physicians' contacts was documented.

Outcomes. As primary outcome, we assessed strict Boolean remissions, defined as no tender or swollen joints (46 joint count) and normal C-reactive protein level, at 6 months.

Secondary outcomes were quality of life (SF-36) at 6 months, Boolean remissions at 12 months, patient confidence to the treatment (VAS) assessed at clinic visits at 0, 3, and 6 months, and use of health care resources during the 6-month intervention that was defined as the number of visits (physician or nurse office visits) and contacts (telephone contacts with physician or nurse) to the treating rheumatology clinic.

Statistical methods. We calculated the sample size based on remissions at 6 and 12 months in the combined patient cohorts from 2 earlier Finnish RA trials (12,13). We estimated that, with a power of 85% and at a significance level of 0.05, detecting a 25% difference in remission rates between the groups (30% versus 55%) would require 80–100 patients per group with an estimated dropout rate of 10%.

We analyzed the outcome measures by intent-to-treat. Statistical comparisons between the groups were performed by *t*-test, chi-square test, or Fisher's exact test, when appropriate. Repeated measures were analyzed using generalized estimating equations models with appropriate distribution and link function or analysis of covariance. In the case of violation of the assumptions (e.g., non-normality), a bootstrap-type method (10,000 replications) was used for estimating SE. The normality of variables was evaluated using the Shapiro-Wilk W test. In multivariable models, age, sex, years of education, and baseline disease activity (when appropriate) were used as covariates. Stata statistical software, version 14.1, was used for the analyses.

RESULTS

A total of 84 patients were allocated to the intervention group, and 82 patients to the control group. Follow-up data at 6 months were available for 162 patients (Figure 1), and for 157 patients at 12 months. Patients' baseline characteristics are shown in Table 1. Despite randomization, patients in the intervention group were somewhat younger (P = 0.021) and more educated (P = 0.026). The patients' baseline characteristics did not differ significantly between the 6 study centers.

Patient reviews (n = 80) of the system were positive. All patients (100%) would have recommended SMS monitoring for other RA patients, 94% found the monitoring messages technically easy to answer, and >80% felt secure and satisfied with their treatment. However, 25% of the patients found the self-assessment of disease activity using PtGA somewhat difficult or difficult.

Boolean remission rates at 6 months were 51% (95% confidence interval [95% CI] 40–62) and 42% (95% CI 32–53) in the intervention and control groups (P = 0.34), respectively. These rates were 57% (95% CI 45–68) and 43% (95% CI 32–55) at

Table 1. Baseline characteristics of the patients with follow-up data available at 6 months*

	Control group (n = 80)	Intervention group (n = 82)
Demographics		
Female, no. (%)	56 (70)	58 (71)
Age, years	59 ± 14	54 ± 13†
RF and/or anti-CCP positive, no. (%)	69 (86)	70 (85)
Years of education	11.3 ± 3.5	12.6 ± 3.6‡
Body mass index (kg/m^2)	27.5 ± 5.1	26.7 ± 5.2
Measures of disease activity		
DAS28	4.4 ± 1.3	4.1 ± 3.8
Erythrocyte sedimentation rate (mm/hr)	28 ± 18	24 ± 22
Serum C-reactive protein (mg/liter)	20 ± 22	16 ± 22
No. of swollen joints	6.5 ± 5.4	6.4 ± 5.1
No. of tender joints	9.0 ± 7.4	7.7 ± 7.0
Patient's global assessment (VAS)	46 ± 28	45 ± 28
Physician's global assessment (VAS)	41 ± 19	37 ± 20
Physical function (HAQ)	1.0 ± 0.7	0.9 ± 0.6
Erosions in hand or foot radiographs, no. (%)	14 (18)	17 (21)

* Values are the mean ± SD unless indicated otherwise. RF = rheumatoid factor; CCP = cyclic citrullinated protein antibody; DAS28 = Disease Activity Score in 28 joints; VAS = visual analog scale; HAQ = health assessment questionnaire.
† P = 0.021.
‡ P = 0.026.

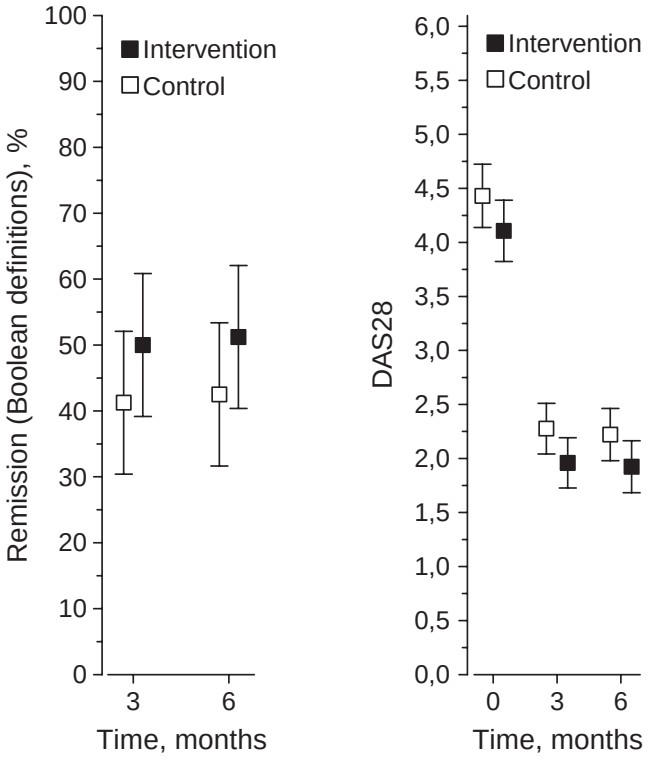

Figure 2. Boolean remission rates and Disease Activity Score in 28 joints (DAS28) during the follow-up in the intervention and control groups.

12 months (P = 0.17) (Figure 2). Similar DAS28 levels were achieved in both groups during the first 6 months, 2.18 (95% CI 1.86–2.56) in the intervention group, and 2.21 in the control group (95% CI 1.86–2.51, P = 0.18) (Figure 2). The corresponding DAS28 levels were 1.79 ± 0.91 and 2.08 ± 1.22 at 12 months (P = 0.28).

Quality of life at 6 months improved in both treatment groups. After adjustment for age, sex, and years of education, only improvement in SF-36 dimension of physical function was greater in the intervention group than in the control group (P = 0.042). Changes in physical (P = 0.076) and mental summary components (P = 0.81) did not differ between the randomization groups (see Supplementary Figure 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23846/abstract). We did not detect significant between-group differences in patient confidence to the treatment (P = 0.73).

Table 2. Use of csDMARDs during the 6-month intervention*

	Control group (n = 80)	Intervention group (n = 82)	*P*
Treatment with csDMARDs			
Methotrexate, peroral	51 (64)	56 (68)	0.54
Methotrexate, subcutaneous	25 (31)	23 (28)	0.66
Low-dose oral GCs	76 (95)	77 (94)	0.71
Hydroxychloroquine	68 (85)	76 (93)	0.12
Sulfasalazine	47 (59)	56 (68)	0.21
Leflunomide	0 (0)	1 (1)	0.34
Treatment strategy			
Monotherapy	10 (13)	6 (7)	0.27
Combination therapy	68 (87)	76 (93)	0.12
Two csDMARDs	28 (36)	30 (37)	
Three csDMARDs	40 (51)	46 (56)	

* Values are the number (%) unless indicated otherwise. csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; GCs = glucocorticoids.

Table 3. Adverse events during the 6-month intervention*

	Control group (n = 80)	Intervention group (n = 82)	*P*
Any adverse event	46 (57)	51 (62)	0.54
Respiratory	2 (2)	5 (6)	0.44
Gastrointestinal	29 (36)	35 (43)	0.40
Mucocutaneous	10 (12)	9 (11)	0.76
Urogenital	2 (2)	1 (1)	0.62
Central nervous system	3 (4)	4 (5)	0.72
Elevated liver enzymes	5 (6)	5 (6)	0.97
Cardiovascular	2 (2)	2 (2)	0.98
Psychological	2 (5)	5 (6)	0.44
Other	12 (15)	11 (13)	0.77
Serious adverse events			
Gastrointestinal	0 (0)	1 (1)	0.98
Cardiovascular	1 (1)	0 (0)	0.98

* Values are the number (%) unless indicated otherwise.

In most cases, a combination of conventional synthetic DMARDs (csDMARDs) was initiated for all patients at the baseline visit (Table 2). During the first 6 months, 89% of the patients used a combination of 2–3 conventional synthetic DMARDs. A total of 96% of these patients were prescribed methotrexate, and 94% oral low-dose glucocorticoids (GCs) (Table 2). The mean ± SD number of intraarticular GC injections was 2.5 ± 2.7 in the intervention group, and 3.0 ± 3.9 in the control group (P = 0.33). Only 3 patients required biologic DMARDs during the intervention. Adverse events, reported by 60% of the patients, were balanced between the randomization groups (Table 3).

During the intervention, the use of health care resources increased in the intervention group. The mean ± SD number of nurses' telephone contacts was 3.32 ± 2.93 in the intervention group and 2.0 ± 2.55 in the control group (P = 0.008). No differences were observed for other contact or visit types. The mean ± SD number of unscheduled nurses' visits was 0.56 ± 0.80 in the intervention group and 0.56 ± 0.65 in the control group (P = 0.56). In the intervention and control groups, the mean ± SD number of unscheduled physician visits was 0.13 ± 0.44 and 0.11 ± 0.39 (P = 0.86), and the mean ± SD number of physician telephone contacts was 0.56 ± 0.93 and 0.46 ± 0.75 (P = 0.65), respectively. Of the patients in the intervention group, 49% (40 of 82) reported PtGAs above the predefined alarm limits.

Mean PtGAs given in the intervention group at weeks 0, 6, 10, 12, 18, 22, and 24 were 5.3, 3.1, 2.5, 2.1, 1.9, 1.8, and 1.6, respectively. Of the PtGAs, 22% were above the alarm limit at week 6, and 16%, 17%, and 25% at weeks 10, 18, and 22, respectively

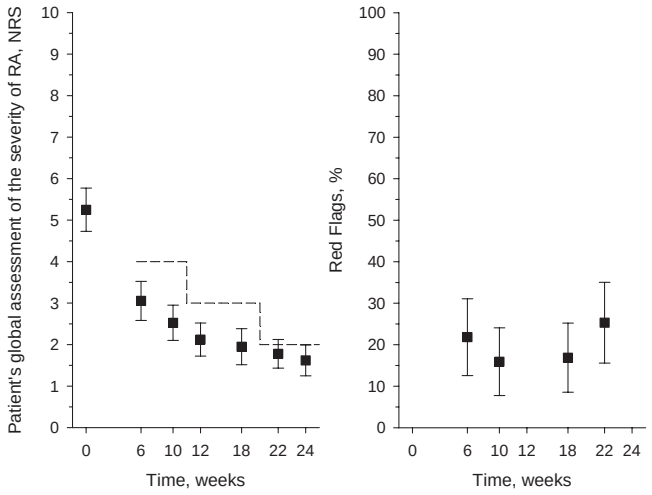

Figure 3. Change in text message patient global assessments (PtGAs) given as a whole number (numeric rating scale [NRS]) from 0 to 10 and alarms or "red flags" due to insufficient reduction in disease activity during the intervention. The broken line represents predefined PtGA alarm thresholds. Clinic visits were scheduled for weeks 0, 12, and 24. RA = rheumatoid arthritis.

(Figure 3). Medication problems were reported by 38 of 81 patients, and 4 of 81 reported not initiating the prescribed medication (one patient did not answer these questions).

DISCUSSION

In this study, we compared the impact of SMS-enhanced follow-up versus routine follow-up on early RA outcomes during the initial 6 months. The number of Boolean remissions at 6 and 12 months was higher in the intervention group than in the control group, but, despite 9% and 14% between-group differences at these time points, statistical significance was not reached. Overall, achieved remission rates were remarkably high; the mean DAS28 and its upper 95% CIs were below the DAS28 remission limit (DAS28 <2.6) at 6 and 12 months in both groups.

The fact that the vast majority of patients in both groups attained DAS28 remission may have rendered achievement of significant between-group differences difficult. Furthermore, the randomization was ceased soon after reaching the minimum sample size due to slow recruitment and a dropout rate that was lower than expected. If the randomization had continued to a sample size of 200, the trend in remission rates might have reached statistical significance. The high remission rate is likely attributable to the Finnish model of treating RA with a combination of 2–3 csDMARDs, low-dose oral prednisolone, and intraarticular GCs (10). Additionally, study centers have made efforts to optimize their rheumatology service; 4 of 6 centers routinely use a structured, electronic monitoring tool for clinical data collection and all aim at delivering prompt, multidisciplinary care to their patients. Patients with early RA in Finland are routinely scheduled visits at 0, 3, and 6 months in day-to-day clinical practice, as in the current study. Comparable outcomes have been reported from a Finnish early RA cohort, where 3 of 4 patients achieved a less stringent remission, the 3-variable DAS28 remission, at 1 year (14). The study design followed closely routine rheumatology clinical practice in Finland. However, the additional attention in the form of SMSs may have improved the remission rate in the intervention group. The number of additional visits in the intervention group remained very low, and was unlikely to influence the study outcome. The care of early RA is highly optimized and therefore difficult to improve. Patient groups whose care is less optimized might benefit more from similar interventions.

SMS-enhanced monitoring increased the use of health care resources. When the text messages indicated problems, the nurse contacted the patient, which increased the number of nurses' telephone contacts. The initiation of the SMS monitoring also required patient education. In contrast to our hypothesis, the nurses' increased workload did not translate into significantly improved clinical outcomes and did not reduce the number of contacts or visits in the intervention group. The nurses required only 60 minutes of training to use the cloud-based SMS-monitoring system. In addition to receiving a 30-minute training, the patients in the intervention group required only 1.3 additional 20-minute phone calls from a nurse compared to the control group, without any notable differences in physicians' or nurses' visits. Although the SandRA monitoring software is not currently commercially available, and its exact price is therefore unclear, the added burden resulting from SMS monitoring in early RA seems to be modest.

Most patients were very satisfied with the text message–based monitoring system. The patients felt that they were in good care and that the monitoring increased the safety of the treatment. Nevertheless, no differences were observed in reported adverse events or in QoL. The latter improved in intervention and control groups and between-group differences remained negligible.

We chose to use PtGA for assessment of disease activity due to its simplicity, as a more complex questionnaire that required a smartphone may not have been accessible to all patients with RA and may not have been as feasible to use. Nevertheless, one-fourth of the patients in the intervention group found remote self-assessment of disease activity using PtGA difficult, despite spoken and written instructions. Previous studies have shown that PtGA is a reliable measure on a group level that is sensitive to change and has a good test–retest reliability (15–17). However, individual-level factors like pain can influence PtGA significantly (6).

New technologies are used increasingly in health care. In some chronic diseases, such as diabetes mellitus and heart failure, remote monitoring improves treatment outcomes compared to conventional monitoring (18–20). To date, most remote monitoring studies on RA have focused on self-management (21,22) and only a handful of studies have utilized remote disease activity assessments. Compared to our study, 3 previous remote disease activity assessment studies have used different, significantly more complex approaches. A cross-sectional study by Nishiguchi et al

of 65 patients demonstrated that a smartphone application can be used for measuring RA disease activity (23). In this study, patients gave a disease activity assessment using the modified HAQ, self-assessed tender and swollen joint counts, and self-measured their gait using an accelerometer. The patients were also assessed by a rheumatologist. Using these measures, Nishiguchi et al developed a model for predicting DAS28 levels. Later, the same model was tested in 9 patients with RA, who assessed their disease activity daily for 3 months using a smartphone (24). In this study, self-assessed disease activity had a good correlation to the DAS28 at monthly clinic visits when the patient DAS28 score was low or moderate. In a third study, Espinoza et al used a very different approach and showed that hand grip strength was negatively correlated with disease activity using a smartphone-connected dynamometer (25). These studies tested the feasibility and accuracy of different remote disease activity assessments, but did not test the influence of remote disease activity assessments on RA outcomes.

To our knowledge, the current study is the first to assess the influence of text message–enhanced medication and disease activity assessments on treatment outcomes in RA. One previous study has evaluated the influence of web-based intensive monitoring to RA outcomes (26). Salaffi et al randomized 41 patients with early RA to receive intensive monitoring (including online assessments, additional visits, and treatment advice) or to receive usual care. Compared to usual care, intensive monitoring improved outcomes such as remission and physical function. In contrast to Salaffi et al, our intervention was aimed solely at detecting medication problems or insufficient reduction in disease activity, and treatment intensifications were entirely at the treating physician's discretion.

Our study population consisted of adult patients with early RA who were capable of using a simple mobile phone, making our results generalizable to most patients with RA. In Finland, 99% of the population used a mobile phone in 2017 (27), which reduces the possibility of selection bias in our study. However, worldwide mobile phone penetration is significantly lower, and would likely influence patient selection in less-resourced settings. The aim of the intervention was detection of treatment-related problems. The SMS-based system was chosen because at the time of the initiation of the study, all patients did not have a smartphone or daily access to the internet.

We conclude that, despite a favorable trend, text message–enhanced monitoring does not significantly improve remission rates in intensively treated early RA. However, this type of monitoring may be beneficial in less-resourced settings. Future studies are required in order to assess whether this simple and feasible monitoring method, which patients find easy to use, provides additional value.

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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. Kuusalo 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. Kuusalo, Sokka-Isler, Puolakka.
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Sex Differences in the Achievement of Remission and Low Disease Activity in Rheumatoid Arthritis

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Objective. In rheumatoid arthritis, whether women are less likely to achieve low disease activity is unclear. We evaluated sex differences in remission and low disease activity, comparing different clinical and imaging measures.

Methods. We used data from the Veterans Affairs Rheumatoid Arthritis (VARA) registry and from 2 clinical trials. Remission and low disease activity were defined using composite scores, individual items (tender joints, swollen joints, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP] level, and evaluator/patient global assessment), and magnetic resonance imaging (MRI). In the VARA registry, we assessed the likelihood of point remission at any time during follow-up using logistic regression, and time to sustained remission (2 consecutive visits) using Cox proportional hazards models. In the clinical trials, logistic regression models evaluated the likelihood of low clinical and MRI activity at 52 weeks.

Results. Among 2,463 patients in VARA, women (10.2%) were less likely to be in Disease Activity Score in 28 joints (DAS28)–ESR remission in follow-up (odds ratio [OR] 0.71 [95% confidence interval (95% CI) 0.55–0.91]; $P < 0.01$) and had a longer time to sustained DAS28-ESR remission. This difference was not observed for DAS28-CRP, Clinical Disease Activity Index, or Routine Assessment of Patient Index Data 3. Women were more likely to achieve favorable individual components except for an ESR <30 mm/hour (OR 0.72 [95% CI 0.57–0.90]; $P < 0.01$). Among 353 trial participants (83.7% women), women had reduced rates of DAS28-ESR remission (OR 0.39 [95% CI 0.21–0.72]; $P = 0.003$) but similar rates of low MRI synovitis and osteitis.

Conclusion. The comparison of remission rates between men and women varies based on the disease activity measure, with sex-specific differences in ESR resulting in reliably lower rates of remission among women. There were no differences in MRI measures.

INTRODUCTION

There are epidemiologic differences between men and women with rheumatoid arthritis (RA), with women having a higher prevalence, younger age at onset, and lower frequency of seropositivity (1–3). Women with RA are less likely than men to achieve clinical remission (2,4–6). However, these sex differences remain incompletely understood.

The American College of Rheumatology (ACR) encourages the use of a disease activity measure in patients with RA, and several composite measures of disease activity have been recommended for clinical use and endorsed as quality measures (7).

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SIGNIFICANCE & INNOVATIONS

- In this study of 2 large rheumatoid arthritis (RA) cohorts, women were consistently less likely to achieve low erythrocyte sedimentation rate (ESR) levels and Disease Activity Score in 28 joints (DAS28)–ESR remission.
- There were not consistent sex differences in remission or low disease activity for other composite RA disease activity measures.
- Achievement of low synovitis and osteitis scores on magnetic resonance imaging of the hand and wrist were similar between men and women.
- Sex-specific thresholds to define DAS28-ESR remission and low disease activity may be of value.

A recent nationwide survey of US rheumatologists found that the most used outcome measures (functional status and disease activity) in the care of RA patients are the Health Assessment Questionnaire (HAQ) or Multidimensional (MD)-HAQ (35.5%), the Routine Assessment of Patient Index Data 3 (RAPID3; 27.1%), the Clinical Disease Activity Index (CDAI; 17.5%), and the Disease Activity Score in 28 joints (DAS28; 15.7%) (8). While a number of disease activity measures are used, studies have shown that the rate of remission depends significantly on the criteria used (4,9–13).

Previous studies evaluated differences in component and composite measures of disease activity specifically in men and women with RA and suggested that remission rates for women are anywhere from 30% to 87% lower (10). Multiple studies using the Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis registry, a cross-sectional international registry study, showed that women were less likely to achieve remission defined by DAS28 with erythrocyte sedimentation rate (DAS28-ESR) as well by the CDAI and RAPID3 (14). A study in Finland found that women were less likely to be in DAS28-ESR remission at baseline, 2 years, and 5 years, but there was no difference between sexes when considering Boolean remission (4). In a study from the Corrona RA registry, a large prospective cohort study, women were less likely to achieve CDAI early sustained remission (5), but there was no difference in established remission or in early point remission. Another recent study showed that women were less likely to achieve remission when it was defined by DAS28-ESR, CDAI, and the Simple Disease Activity Index but found no difference in remission rates for Boolean criteria or RAPID3 (9). Overall, these studies suggest a more refractory phenotype among women, but the results lack consistency and vary based on the composite outcomes used and population studied.

Observed differences in remission rates between men and women may be the result of differences in the accuracy of disease activity measures in these 2 groups. For example, in other settings, the ESR is known to be higher in women (15). Laboratories using the Westergren method have reference ranges for ESR that vary by age and sex (16). While the ACR remission criteria define inactive ESR differently for female and male patients (17,18), the DAS28-ESR does not take into account this difference in ESR values between sexes (15,18). This difference of approach leads to higher DAS28-ESR values compared to the DAS28 with C-reactive protein (DAS28-CRP) in older women (19). CRP level can be also be falsely elevated in obese women with RA, a bias that is less apparent among men (20). Additionally, women have been shown to report higher pain scores compared to men in the general population, suggesting that subjective assessments may be influenced by differences in reporting (21,22). For these reasons, the lack of a direct measure of joint inflammation is a major limitation in prior studies. We are aware of no prior studies that have compared men and women in the achievement of low disease activity based on imaging criteria. Recently, a definition of low magnetic resonance imaging (MRI) activity has been proposed (23,24).

We aimed to compare the rates of remission and low disease activity between men and women using different composite and component measures, hypothesizing that sex differences in attainment of remission and low disease activity would vary depending on the measurement tool used. Furthermore, we hypothesized that achievement of low MRI activity would be similar between men and women.

MATERIALS AND METHODS

Study setting. *Veterans Affairs Rheumatoid Arthritis (VARA) registry study.* This is an analysis of a prospective cohort study of US veterans with RA using the VARA registry of patients enrolled between January 2003 and 2016. The VARA registry is a multicenter (12 active US sites) biorepository and longitudinal observational study of US veterans with RA. All participants satisfy the ACR classification criteria for RA and disease onset after age 18 years. Detailed clinical and laboratory data are collected at baseline and at subsequent rheumatology clinic visits. Eligible patients are systematically enrolled from participating rheumatology clinics, with RA patient characteristics that are reflective of the national VA population. Regulatory approval was obtained and studies were approved by the institutional review board at each individual site.

GO-BEFORE and GO-FORWARD clinical trials. The study population comes from secondary analysis of the GO-BEFORE (clinicaltrials.gov identifier NCT00361335) and GO-FORWARD (NCT00264550) randomized, multicenter, double-blind, placebo-controlled trials that evaluated the efficacy of tumor necrosis factor antagonist golimumab for the treatment of RA. Both studies compared golimumab in combination with methotrexate to methotrexate or golimumab monotherapy. Detailed methods and results of both studies have previously been published (25,26). The trials were conducted according to the Declaration of Helsinki. Secondary analysis of de-identified trial data was considered exempt by the Institutional Review Board at the University of Pennsylvania.

This analysis includes the subset of patients in both studies who had MRIs scored for synovitis, osteitis, and/or bone erosion at baseline and at 52 weeks of follow-up (the original follow-up duration for the trial). Patients ages ≥18 years who met ACR 1987 criteria for RA and had active disease were recruited into the MRI substudy at participating sites (27). Data collection through 52 weeks included blinded assessments of disease activity. MRI was performed at baseline and week 52. MRIs of the dominant wrist and second to fifth metacarpophalangeal joints were obtained using a 1.5T MRI with contrast enhancement, as previously described and scored by 2 independent blinded readers using the Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) scoring system (28).

Definitions of remission and low disease activity. We compared the achievement of remission and low disease activity between men and women as defined by several common composite scores: DAS28-ESR, DAS28-CRP, CDAI, and RAPID3. These disease activity scores were chosen based on a combination of composite indices, with and without acute phase reactants, patient-reported instruments, commonly used in clinical trials and recommended by the ACR/European League Against Rheumatism (EULAR) in 2011 for use in clinical practice (7). Remission and low disease activity were defined based on previously published thresholds for each composite score (29).

We also compared the achievement of individual low component measures, defined based on ACR/EULAR 2011 recommendations, Boolean criteria, and other prior published guidelines. Remission for component scores was defined as ESR <30 mm/hour, CRP level ≤1 mg/dl, swollen joint count in 28 joints (SJC28) ≤1, tender joint count in 28 joints (TJC28) ≤1, patient global assessment (PtGA; range 0–10) ≤1, evaluator global assessment (EvGA; range 0–10) ≤1, MD-HAQ score ≤0.5, and pain (visual analog scale; range 0–10) ≤1. Normal ESR was also defined separately based on previously described age- and sex-specific

Table 1. Baseline characteristics in men and women from the Veterans Affairs Rheumatoid Arthritis registry study*

	Men (n = 2,211)	Women (n = 252)	*P*
Age, mean ± SD years	71.3 ± 9.9	61.2 ± 12.7	<0.001
African American	307 (14)	83 (33)	<0.001
BMI, mean ± SD kg/m^2†	28.3 ± 5.4	30.1 ± 6.7	<0.001
Anti-CCP positive, no./total no. (%)	1,320/1,670 (79)	137/188 (73)	0.051
Disease duration, median (IQR) years‡	8.6 (2.5–18.4)	6.9 (2.6–14)	0.07
Chronic kidney disease	58 (3)	1 (0.4)	0.03
Diabetes mellitus	452 (20)	33 (13)	<0.01
Hypertension	1,191 (54)	95 (38)	<0.001
Osteoarthritis	375 (17)	31 (12)	0.06
Depression	177 (8)	17 (7)	0.81
Lung disease	355 (16)	10 (4)	<0.001
Tobacco use			
Current	589 (27)	41 (17)	<0.001
Former	1,217 (56)	84 (35)	–
Never	371 (17)	115 (48)	–
Biologic§	627 (28)	88 (35)	0.03
Anti-TNF i	577 (26)	79 (31)	0.07
Methotrexate	1,151 (52)	118 (47)	0.12
Prednisone	897 (41)	72 (29)	<0.001
Clinical composite and component measures, mean ± SD			
DAS28-ESR	3.9 ± 1.5	3.9 ± 1.4	0.92
DAS28-CRP	3.6 ± 1.4	3.4 ± 1.4	0.10
CDAI	16.4 ± 13.3	15.2 ± 13	0.30
RAPID3	12.3 ± 5.9	12.5 ± 6.2	0.63
ESR, mm/hour	26.4 ± 23.7	28.4 ± 22	0.25
CRP, mg/dl	1.6 ± 2.9	1.1 ± 1.6	0.048
Tender joint count, 28 joints	5.0 ± 6.7	4.4 ± 6.4	0.26
Swollen joint count, 28 joints	3.9 ± 5.3	3.1 ± 4.6	0.02
EvGA (range 0–10)	3.5 ± 2.3	2.9 ± 2.2	<0.01
PtGA (range 0–10)	4.0 ± 2.5	3.9 ± 2.7	0.48
Pain (VAS, range 0–10)	4.5 ± 2.8	4.5 ± 3.1	0.98
MD-HAQ (range 0–3)	0.9 ± 0.6	0.8 ± 0.7	0.02

* Values are the number (%) unless indicated otherwise. BMI = body mass index, anti-CCP = anti–cyclic citrullinated peptide; IQR = interquartile range; anti-TNF i = anti–tumor necrosis factor inhibitor; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CDAI = Clinical Disease Activity Index; RAPID3 = Routine Assessment of Patient Index Data 3; EvGA = evaluator global assessment; PtGA = patient global assessment; VAS = visual analog scale; MD-HAQ = Multidimensional Health Assessment Questionnaire.
† Men = 1,512, women =162.
‡ Men = 2,448, women = 246.
§ Anti-TNF i or rituximab or tocilizumab or abatacept.

Table 2. Odds of being in remission or low disease activity for women versus men in the Veterans Affairs Rheumatoid Arthritis registry study at any observation, adjusted for age, race, smoking, and disease duration*

	No./Total no.	Men LDA	Women LDA	aOR (95% CI)	*P*
Remission					
DAS28-ESR (<2.6)†	2,398/26,148	5,766/23,719 (24)	491/2,429 (20)	0.71 (0.55–0.91)	<0.01
DAS28-CRP (<2.6)	2,330/24,875	7,177/22,579 (32)	761/2,278 (33)	1.14 (0.91–1.42)	0.25
CDAI (≤2.8)	2,227/20,261	2,139/18,469 (12)	220/1,792 (12)	1.28 (0.96–1.71)	0.09
RAPID3 (≤3)	2,348/26,261	1,248/23,853 (5)	136/2,408 (6)	0.97 (0.67–1.39)	0.85
Low disease activity					
DAS28-ESR (≤3.2)†	2,398/26,148	9,851/23,719 (42)	933/2,429 (38)	0.87 (0.71–1.08)	0.21
DAS28-CRP (≤3.2)	2,330/24,875	11,132/22,597 (49)	1,165/2,278 (51)	1.19 (0.96–1.48)	0.12
CDAI (≤10)	2,227/20,261	8,656/18,469 (47)	848/1,792 (47)	1.36 (1.08–1.73)	0.01
RAPID3 (≤6)	2,348/26,261	3,808/23,853 (16)	398/2,408 (17)	1.04 (0.80–1.35)	0.76
Clinical components					
ESR (<30 mm/hour)†	2,442/26,714	16,273/24,222 (67)	1,607/2,492 (64)	0.72 (0.57–0.90)	<0.01
ESR (age- and sex-specific)	2,442/26,714	12,001/24,222 (50)	1,566/2,492 (63)	1.32 (1.05–1.64)	0.02
CRP (≤1.0 mg/dl)	2,366/25,196	14,489/22,863 (63)	1,639/2,333 (70)	1.26 (1.01–1.59)	0.04
Tender joint count, 28 joints (≤1)	2,475/28,991	13,788/26,266 (52)	1,405/2,725 (52)	1.07 (0.88–1.31)	0.48
Swollen joint count, 28 joints (≤1)	2,476/28,999	14,117/26,274 (54)	1,557/2,725 (57)	1.51 (1.22–1.88)	<0.001
EvGA (≤1; range 0–10)	2,238/20,363	4,933/18,552 (27)	539/1,811 (30)	1.54 (1.23–1.93)	<0.001
PtGA (≤1; range 0–10)	2,457/28,705	4,455/26,025 (17)	538/2,142 (20)	1.22 (0.95–1.56)	0.11
Pain (≤1; VAS, range 0–10)	2,469/28,867	4,646/26,163 (18)	436/2,704 (16)	0.87 (0.68–1.10)	0.24
MD-HAQ (≤0.5; range 0–3)	2,437/28,414	6,876/25,755 (27)	885/2,659 (33)	1.12 (0.87–1.44)	0.36

* Values are the number/total number (%) unless indicated otherwise. LDA = low disease activity; aOR = adjusted odds ratio; 95% CI = 95% confidence interval; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CDAI = Clinical Disease Activity Index; RAPID3 = Routine Assessment of Patient Index Data 3; EvGA = evaluator global assessment; PtGA = patient global assessment; VAS = visual analog scale; MD-HAQ = Multidimensional Health Assessment Questionnaire.
† A normal age- and sex-specific ESR was defined as ESR <30 mm/hour and <20 mm/hour for women and men age >50 years, respectively, and ESR <20 mm/hour and <15 mm/hour for women and men age <50 years, respectively.

thresholds (ESR <30 mm/hour and <20 mm/hour for women and men ages >50 years, respectively; ESR <20 mm/hour and <15 mm/hour for women and men ages <50 years, respectively) (16). Low MRI synovitis and low osteitis scores were defined as a RAMRIS score ≤3, based on recently defined thresholds (28).

Covariates. ESR and CRP level were extracted from the VARA registry data or medical record within 30 days of each study visit. Baseline demographics, disease duration, smoking status, and common comorbidities were extracted from the registry database. Enrollment weight and height were extracted from medical records (within 30 days) or registry data and were converted to body mass index (BMI; kg/m^2). Covariables of interest from the clinical trial data included demographics, treatment group, and the particular study (GO-BEFORE versus GO-FORWARD).

Statistical analysis. For analyses in the VARA registry data, the differences in characteristics at enrollment between men and women were assessed using *t*-tests of significance, rank sum tests, and chi-square tests. We evaluated achievement of remission or low disease activity in 2 ways: 1) point achievement among all participants over all observations, and 2) the time to sustained achievement (defined as 2 consecutive visits) among those not in remission at enrollment. Statistical methods included logistic models that incorporated generalized estimating equations with robust estimators to allow clustering on patient and multivariable Cox proportional hazards models. To avoid adjustment for factors that might be in the causal pathway, we built parsimonious multivariable models that included factors such as age, race, disease duration, and smoking status at enrollment. Cox proportional hazards models were further adjusted for differences in biologic and prednisone use at enrollment. Visits where the component or composite measure of interest was missing were not included in the analysis.

For analyses using clinical trial data, outcomes for clinical composite and component measures as well as MRI activity measures were evaluated at 52 weeks. The percent of men and women achieving low disease activity measures by 52 weeks was determined. Multivariable logistic regression models assessed the likelihood of achieving remission by 52 weeks among men and women, adjusting for age, race, study (GO-BEFORE versus GO-FORWARD), and treatment group.

RESULTS

Rates of remission and low disease activity in the VARA registry. The baseline characteristics of the VARA population are shown in Table 1. The median duration of follow-up was 2.6 years (interquartile range [IQR] 0.85–5.4) and the median number of visits was 21 (IQR 11–21). Missing data in follow-up varied for composite and component measures ranging from 1% to 30% of observations. The greatest missingness was observed for the EvGA score. At enrollment, women were younger, had a higher BMI, were more likely to

be African American, and were less likely to smoke or to have been diagnosed with chronic kidney disease, diabetes mellitus, hypertension, or chronic lung disease. Women were more likely to have been treated with biologics and less likely to have been treated with prednisone at enrollment. Women also had lower SJC28, CRP level, EvGA, and MD-HAQ score at baseline.

At any point in time, the adjusted odds of point remission for women were lower for DAS28-ESR (odds ratio [OR] 0.71 [95% confidence interval (95% CI) 0.55–0.91]; $P < 0.01$) (Table 2). Similarly, women were less likely to have an ESR <30 mm/hour (OR 0.72 [95% CI 0.57–0.90]; $P < 0.01$). However, in contrast, women were more likely to achieve a low ESR when using an age-, and sex-specific definition of low ESR (OR 1.32 [95% CI 1.05–1.64]; $P = 0.02$). In addition, among men and women who met strict criteria for Boolean remission, women were substantially less likely to be in DAS28-ESR remission (OR 0.42 [95% CI 0.25–0.69]; $P = 0.001$) or low disease activity (OR 0.28 [95% CI 0.088–0.88]; $P = 0.03$). Women were numerically but not significantly less likely to be in low disease activity based on the DAS28-ESR (Table 2). Adjusted rates of remission were not different for other composite scores. Women were also more likely to be in CDAI low disease activity (≤10) (OR 1.36 [95% CI 1.08–1.73]; $P = 0.01$) and were more likely to have a low SJC28, CRP level, and EvGA.

Table 3 shows that, among patients who were not in remission at enrollment, women were substantially less likely to reach DAS28-ESR sustained remission (hazard ratio [HR] 0.53 [95% CI 0.35–0.80]; $P < 0.01$). There was no difference in remission rates between men and women for the DAS28-CRP, CDAI, RAPID3, or achievement of sustained low disease activity (by any composite measure). Women were less likely to have achieved a sustained low ESR (<30 mm/hour) (HR 0.50 [95% CI 0.34–0.74]; $P = 0.001$). Women were more likely, however, to achieve low PtGA (≤1) (HR 1.49 [95% CI 1.02–2.18]; $P = 0.04$). There was no sex difference in the likelihood of achieving low values for other individual components.

Sex differences in remission rates in a clinical trial setting. The clinical trial population was distinct from the VARA registry population in that the participants were much younger, had a lower BMI, and were more likely to be female. Men (n = 58) and women (n = 295) were similar in terms of age, race, and BMI. Men and women had similar DAS28-CRP and CDAI at baseline, but women had higher DAS28-ESR and higher PtGA and TJC28 (Table 4). Women were less likely to achieve remission by 52 weeks when remission was defined by the DAS28-ESR (OR 0.39 [95% CI 0.21–0.72]; $P = 0.003$) (Figure 1 and Table 5). In multivariable models, women were also less likely to achieve CDAI remission (OR 0.50 [95% CI 0.26–0.94]; $P = 0.03$) (Table 5). However, there was not a significant difference in the achievement of remission between men and women for DAS28-CRP (OR 0.71 [95% CI 0.39–1.28]; $P = 0.26$).

Among component scores, women were less likely to reach a low PtGA score, less likely to reach a low ESR (<30 mm/hour), and less likely to reach a low TJC28 ($P = 0.056$) (Table 5). Women

Table 3. Achievement of sustained remission (2 consecutive visits) or low disease activity for women versus men, adjusted for age, race, smoking, and disease duration in the Veterans Affairs Rheumatoid Arthritis registry study*

	Men LDA	Women LDA	Sustained LDA/remission HR (95% CI)	*P*
Remission				
DAS28-ESR (<2.6)	340/1,391 (24)	27/147 (18)	0.53 (0.35–0.80)	<0.01
DAS28-CRP (<2.6)	379/1,170 (32)	43/111 (39)	1.15 (0.82–1.60)	0.42
CDAI (≤2.8)	118/1,078 (11)	16/117 (14)	1.26 (0.72–2.19)	0.43
RAPID3 (≤3)	110/1,759 (6)	13/184 (7)	1.05 (0.57–1.93)	0.87
Low disease activity				
DAS28-ESR (≤3.2)	397/915 (43)	37/93 (40)	0.73 (0.51–1.03)	0.08
DAS28-CRP (≤3.2)	426/915 (47)	41/93 (44)	0.94 (0.67–1.31)	0.70
CDAI (≤10)	275/705 (39)	26/76 (34)	0.77 (0.51–1.18)	0.23
RAPID3 (≤6)	215/1,517 (14)	21/159 (13)	0.78 (0.49–1.26)	0.31
Clinical components				
ESR (<30 mm/hour)	453/872 (52)	31/80 (39)	0.50 (0.34–0.74)	0.001
ESR (age- and sex-specific)	255/872 (29)	31/80 (39)	1.03 (0.67–1.57)	0.90
CRP (≤1.0 mg/dl)	268/578 (46)	33/54 (61)	1.21 (0.81–1.80)	0.36
Tender joint count, 28 joints (≤1)	585/1,114 (53)	55/112 (49)	0.93 (0.70–1.24)	0.61
Swollen joint count, 28 joints (≤1)	603/1,108 (54)	66/109 (61)	1.10 (0.84–1.43)	0.49
EvGA (≤1; range 0–10)	174/1,047 (17)	22/111 (20)	1.25 (0.78–2.01)	0.35
PtGA (≤1; range 0–10)	229/1,737 (13)	35/184 (19)	1.49 (1.02–2.18)	0.04
Pain (≤1; VAS, range 0–10)	329/1,658 (20)	32/177 (18)	0.93 (0.63–1.36)	0.70
MD-HAQ (≤0.5; range 0–3)	224/1,375 (16)	24/133 (18)	0.95 (0.61–1.48)	0.83

* Values are the number/total number (%) unless indicated otherwise. LDA = low disease activity; HR = hazard ratio; 95% CI = 95% confidence interval; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CDAI = Clinical Disease Activity Index; RAPID3 = Routine Assessment of Patient Index Data 3; EvGA = evaluator global assessment; PtGA= patient global assessment; VAS = visual analog scale; MD-HAQ = Multidimensional Health Assessment Questionnaire.

Table 4. Baseline characteristics from the combined study population from GO-BEFORE and GO-FORWARD*

	Men (n = 58)	Women (n = 295)	*P*
Age, mean ± SD years	51.3 ± 14.2	48.9 ± 10.9	0.14
White, no. (%)	36 (62)	181 (61)	0.92
BMI, mean ± SD kg/m^2	26.3 ± 5.5	26.2 ± 5.6	0.93
GO-BEFORE, %	55	56	0.86
Disease activity, mean ± SD			
DAS28-ESR	5.70 ± 1.36	6.13 ± 1.10	0.009
DAS28-CRP	5.26 ± 1.24	5.50 ± 1.02	0.11
CDAI	32 ± 15.2	35 ± 13.0	0.16
Clinical components			
ESR, mean ± SD mm/hour	40.2 ± 27.9	43.8 ± 27.8	0.37
CRP, mean ± SD mg/dl	2.21 ± 2.52	1.82 ± 2.38	0.26
Tender joint count, 28 joints	10 (5, 17)	12 (7, 19)	0.07
Swollen joint count, 28 joints	8 (5, 11)	8 (5, 12)	0.90
EvGA (range 0–10)	5.7 (4.3, 7)	6.2 (4.9, 7.4)	0.25
PtGA (range 0–10)	5.3 (2.9, 7.5)	6.5 (4.8, 7.9)	0.01

* Values are the median (interquartile range) unless indicated otherwise. BMI = body mass index; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CDAI = Clinical Disease Activity Index; EvGA = evaluator global assessment; PtGA = patient global assessment score.

were not less likely to reach a low ESR when using an age- and sex-specific threshold (OR 0.71 [95% CI 0.39–1.27]; P = 0.25). Men and women achieved a low CRP level, a low SJC28, and a low EvGA score with comparable frequency. Men and women also achieved low MRI synovitis scores and osteitis scores with similar frequency.

DISCUSSION

Our study shows that comparisons between men and women with RA in the rates of achievement of clinical remission and low disease activity vary substantially by the measure used to define remission. In particular, women were consistently less likely to achieve DAS28-ESR remission, while there was no consistent difference in remission rates or rates of low disease activity between men and women for the DAS28-CRP, CDAI, and RAPID3, or for MRI measurement of synovitis or osteitis.

Several prior studies showed that women are less likely to achieve remission when using the DAS28-ESR (1,2,9,14), but there are less consistent findings in studies examining the performance of CDAI and RAPID3 (5,9,14). Our study confirmed that women are less likely to reach remission when defined by the DAS28-ESR. However, while separate analysis of the component scores revealed that women were less likely achieve a low ESR, they were actually more likely to achieve a low ESR when "low" was defined using an age- and sex-specific definition (15,16). In addition, women were more likely to achieve CDAI low disease activity in the same population. These results suggest that in the absence of accounting for sex, there is significant bias related to the inclusion of this inflammatory marker in the composite measurement of disease activity.

While other RA populations have consistently shown that women are more likely to have higher disease activity and are less likely to achieve remission, the study of the VARA registry population suggested features of more severe disease in men. This finding was manifested by men having higher CRP levels, SJC28, and EvGA scores at enrollment and a lower likelihood of low values for these component assessments in follow-up. These differences probably stem from the distinct population studied here, namely the study of veterans. While this study population is distinct from prior studies, the lack of consistency with prior findings in this population is important. The inconsistency suggests that a biologic cause for sex differences in disease activity and response is less likely. Instead, differences between men and women are hypothesized to reflect differences in psychosocial, economic, and other nonbiologic factors that are likely to vary between populations studied.

An advance of this study over prior research is the inclusion of clinical trial data with a validated direct measure of joint inflammation, specifically MRI. While evaluation of this clinical trial population confirmed differences between men and women in remission rates for the DAS28-ESR, CDAI, ESR, and PtGA scores, there were no differences in the achievement of low MRI measures of joint inflammation. While by no means a definitive quantitation of the burden of disease, this additional evaluation that is provided by direct imaging assessment further suggests that previously noted sex differences may suffer from bias in clinical assessment as opposed to being a true biologic difference.

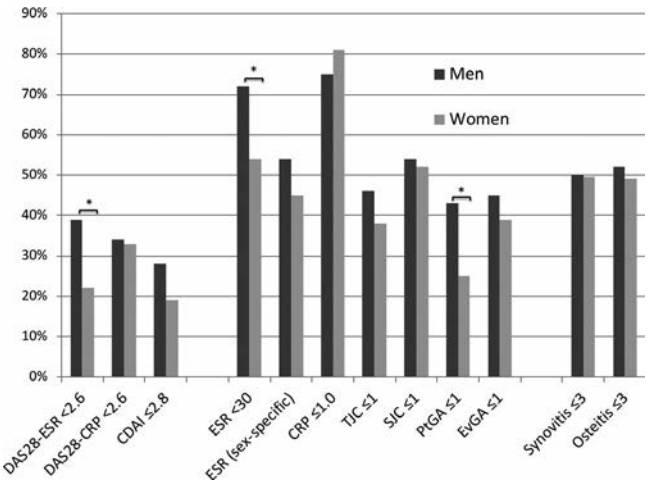

Figure 1. Percentage of men and women achieving low disease activity defined by different composite and component clinical measures as well as low magnetic resonance imaging synovitis and osteitis in the GO-BEFORE and GO-FORWARD studies. * = $P < 0.05$; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CDAI = Clinical Disease Activity Index; TJC = tender joint count; SJC = swollen joint count; PtGA = patient global assessment; EvGA = evaluator global assessment.

Table 5. Logistic regression evaluating the odds of women achieving remission or low disease activity at 52 weeks by different composite and component clinical and MRI measures of disease activity from GO-BEFORE and GO-FORWARD*

	Men LDA (n = 58)	Women LDA (n = 294)	Remission 52 weeks, OR for women (95% CI)†	*P*
Clinical composite scores				
DAS28-ESR (<2.6), no./total no. (%)	23/57 (40)	67/294 (23)	0.39 (0.21–0.72)	0.003
DAS28-CRP (<2.6)	24 (41)	103 (35)	0.71 (0.39–1.28)	0.26
CDAI (≤2.8)	19 (33)	61 (21)	0.50 (0.26–0.94)	0.03
Clinical components				
ESR (<30 mm/second), no./total no. (%)	42/57 (74)	162 (55)	0.40 (0.21–0.77)	0.006
ESR (age-, sex-specific), no./total no. (%)	31/57 (54)	134/294 (46)	0.71 (0.39–1.27)	0.25
CRP (≤1.0 mg/dl)	44 (76)	237 (80)	1.31 (0.66–2.60)	0.44
Tender joint count, 28 joints (≤1)	29 (50)	111 (38)	0.57 (0.32–1.01)	0.056
Swollen joint count, 28 joints (≤1)	31 (53)	159 (54)	0.96 (0.54–1.72)	0.90
EvGA ≤1 (range 0–10)	25 (43)	116 (39)	0.81 (0.45–1.45)	0.48
PtGA ≤1 (range 0–10)	27 (47)	77 (26)	0.37 (0.20–0.68)	0.001
MRI measures				
Synovitis (≤3)	29 (50)	146 (49)	0.93 (0.52–1.67)	0.82
Osteitis (≤3)	30 (52)	143 (49)	0.84 (0.45–1.57)	0.59

* Values are the number (%) unless indicated otherwise. Adjusted for age, white versus nonwhite race, study, and treatment group. LDA = low disease activity; OR = odds ratio; 95% CI = 95% confidence interval; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CDAI = Clinical Disease Activity Index; EvGA = evaluator global assessment; PtGA = patient global assessment; MRI = magnetic resonance imaging.
† Men = 58, women = 295.

There are several limitations to our study. This population of US veterans with RA does not necessarily represent the typical national RA population, which is generally >70% women (1). Results of this study in female veterans may not be fully generalizable to the population overall. The use of a VA population may also be considered a strength, since biologic differences between men and women should be robust across populations with different psychosocial or economic backgrounds. Furthermore, patients in the VA system have relatively more equal access to care, which mitigates biases related to these issues when assessing disease outcomes. A limitation of research evaluating different disease activity assessments is that a gold standard assessment of RA disease activity does not exist. While MRI was used here as an alternative method of quantifying joint disease, it may not capture all aspects of RA disease activity. MRI does, however, provide an objective measure of inflammatory joint disease, a defining feature of RA. The use of validated cutoff scores that identify an informative degree of inflammatory disease is another strength. Our study was also limited in the ability to evaluate the reasons for the observed sex differences in ESR, including differences in adiposity, hemoglobin levels, and other factors.

Other strengths of the study include the use of a large sample of well-characterized patients from 2 distinct RA populations with long-term follow-up. To our knowledge, this study is the first to comprehensively assess sex differences using a number of different composite and component measures of disease activity, the first to use age-and sex-specific thresholds for ESR, and the first to evaluate sex differences in the achievement of low MRI inflammation.

In conclusion, these data do not support systematic biologic differences between men and women with RA in clinical response. Furthermore, these data illustrate the fact that comparisons in disease activity between men and women with RA should not be performed using the DAS28-ESR, since rates of remission will vary based on expected differences in the inflammatory marker. In addition, studies that use the DAS28-ESR as a covariable should consider that the composite measure performs differently in men and women with RA, and there may be important sex interactions that may require stratified analyses. Finally, these observations have implications for clinicians adhering to a treat-to-target paradigm or assessing quality of care. Use of the DAS28-ESR may result in the overtreatment of women relative to men and may result in the inaccurate conclusion that poor quality of care is being provided to women. The future development of sex-specific definitions of clinical remission for RA using the DAS28-ESR and other composite indices may be of value.

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. J. Baker 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. Maynard, Mikuls, George, J. Baker.
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Cost-Effectiveness of Combination Disease-Modifying Antirheumatic Drugs Versus Tumor Necrosis Factor Inhibitors in Active Rheumatoid Arthritis: A Pragmatic, Randomized, Multicenter Trial

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Objective. To determine whether intensive combinations of conventional synthetic disease-modifying antirheumatic drugs (csDMARDS) achieve similar clinical benefits more cheaply than high-cost biologics such as tumor necrosis factor inhibitors (TNFi) in patients with active rheumatoid arthritis (RA) whose illness has failed to respond to methotrexate and another DMARD.

Methods. We used within-trial cost-effectiveness and cost-utility analyses from health and social care and 2 societal perspectives. Participants were recruited into an open-label, 12-month, pragmatic, randomized, multicenter, 2-arm, noninferiority trial in 24 rheumatology clinics in England and Wales. Costs were linked with the Health Assessment Questionnaire (HAQ; primary outcome) and quality-adjusted life years derived from 2 measures (Short-Form 36 health survey and EuroQol 5-domain 3-level instrument).

Results. In total, 205 participants were recruited, 104 in the csDMARD arm and 101 in the TNFi arm. Participants in the csDMARD arm with poor response at 6 months were offered TNFi; 46 participants (44%) switched. Relevant cost and outcome data were available for 93% of participants at 6-month follow-up and for 91–92% of participants at 12-month follow-up. The csDMARD arm had significantly lower total costs from all perspectives (6-month health and social care adjusted mean difference –£3,615 [95% confidence interval (95% CI) –4,104, –3,182]; 12-month health and social care adjusted mean difference –£1,930 [95% CI –2,599, –1,301]). The HAQ score showed benefit to the csDMARD arm at 12 months (–0.16 [95% CI –0.32, –0.01]); other outcomes/follow-ups showed no differences.

Conclusion. Starting treatment with csDMARDs, rather than TNFi, achieves similar outcomes at significantly lower costs. Patients with active RA and who meet the National Institute for Health and Care Excellence criteria for expensive biologics can be treated with combinations of intensive csDMARDs in a cost-effective manner.

INTRODUCTION

Rheumatoid arthritis (RA) is a common long-term inflammatory disorder affecting 0.5–1% of adults in industrialized countries (1), characterized by persistent joint inflammation. Consequences include erosive joint damage, systemic comorbidities like cardiovascular disease with consequent reductions in life expectancy (2), persistent disability and reduced quality of life (3), and high medical and societal costs (4).

Joint inflammation in RA is treated by methotrexate and other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). If methotrexate proves insufficient, more intensive treatments are used, including combinations of conventional DMARDs (5) (previously demonstrated as likely to be cost effective compared with DMARD monotherapy) (6), and biologic drugs like tumor necrosis factor inhibitors (TNFi). Both approaches are clinically effective. While biologics show promise of cost-effectiveness as part of a treatment escalation approach (7), they

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

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SIGNIFICANCE & INNOVATIONS

- Our results show that conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are a more cost-effective treatment approach for rheumatoid arthritis because the group of patients taking csDMARDs achieved similar outcomes compared with the tumor necrosis factor inhibitor group at significantly lower costs. This finding is important in the context of ongoing cost-effectiveness and affordability concerns regarding the use of biologics.
- High-quality cost-effectiveness evidence is vital to inform resource allocation decisions. These results are based on a robust, comprehensive, and prospective trial-based economic evaluation in the context of an evidence base thus far dominated by modeling studies.

are nevertheless substantially more expensive and carry ongoing cost-effectiveness (8) and affordability concerns; methodologic nuances also add to uncertainty over their cost-effectiveness (8).

In the Tumor Necrosis Factor Inhibitors Against Combination Intensive Therapy (TACIT) trial, we compared clinical and economic outcomes of 2 intensive treatment strategies in patients with active RA whose illness had failed to respond to methotrexate and another DMARD. One strategy was based on initial therapy with combinations of csDMARDs, using biologics only if patients failed to respond after 6 months. The other strategy was based on starting biologic therapy with TNFi. Clinical outcomes showed that starting with combinations of csDMARDs gave noninferior clinical outcomes to starting with TNFi (9). In this article we report the associated preplanned economic evaluation.

MATERIALS AND METHODS

Design and intervention. The TACIT trial was an open-label, 12-month, pragmatic, randomized, multicenter, 2-arm, noninferiority trial comparing 2 treatment strategies for RA patients, one strategy starting with csDMARDS and the other with TNFi (9). Recruitment started on April 1, 2007 and ended March 31, 2010. The University College London Hospital research ethics committee approved the trial (MREC reference 07/Q0505/57), and participants provided informed consent. We recruited from 24 rheumatology clinics in England and Wales. We included men and women ages >18 years with disease durations >12 months who met the 1987 criteria for classification of RA (10) and the National Institute for Health and Care Excellence (NICE) criteria for starting biologics in England and Wales (11) (subsequent to our trial, NICE recommended that biologics be used only if disease activity is severe and has not responded to intensive therapy with a combination of csDMARDs [12]).

We excluded those patients who were unable or unwilling to give informed consent, who had not had successful results with or had contraindications to all combinations of disease-modifying drugs (including possible pregnancy), had contraindications to TNFi, had serious intercurrent illness, or were taking high-dose corticosteroids (>10 mg prednisolone). Safety monitoring followed national guidance. Before randomization, all patients had received 2 disease-modifying drugs, 62 had received 3 disease-modifying drugs, 77 were taking combinations of 2 or more disease-modifying drugs, and 24 were taking prednisone (mean dose 4 mg/day; range 1–7 mg). A total of 162 patients were receiving methotrexate at baseline (132 oral, 30 subcutaneous); the average dose was 18 mg/week (range 5–25 mg). Clinical characteristics of the sample, including use of medications, are reported in related publications (9,13).

The sample size was based on testing the null hypothesis of a difference of >0.22 (minimal clinically important change) on the Health Assessment Questionnaire (HAQ) between the 2 treatments. With a 1-sided testing level of 5%, we needed a sample size of 176 to achieve 90% power. We recruited 214 patients to allow for nonreceipt of treatment or dropouts. After screening for eligibility, consenting patients were randomized in blocks of 4 with allocation stratified by region. MedSciNet generated the allocation sequence; trial staff had no prior knowledge of the allocation sequence.

Patients allocated to the TNFi arm were given a particular TNFi depending on patient preference and local circumstances. Methotrexate was also given to patients who were receiving TNFi to maximize efficacy and reduce formation of antichimeric antibodies where necessary. Patients intolerant to methotrexate took another DMARD. Patients being treated with TNFi had their TNFi stopped and another started for 3 reasons: poor response (disease activity score reduction <1.2) at 3 or 6 months, adverse events from medication, or patient choice. Patients in whom treatment with 2 TNFi failed and who were not able to start a third were offered a csDMARD.

Patients allocated to the csDMARD arm were given csDMARDs with proven efficacy over DMARD monotherapy. These included triple therapy with methotrexate (methotrexate/sulfasalazine/hydroxychloroquine), other methotrexate combinations (methotrexate/ciclosporin, methotrexate/leflunomide, and methotrexate/gold), and a sulfasalazine combination (sulfasalazine/leflunomide). Additional monthly steroids (intramuscular methylprednisolone acetate [120 mg] or equivalent) were used if needed. Treatment with csDMARDS was stopped for the same 3 reasons stated above for TNFi, but poor response was judged at 6 months only. Patients with poor response at 6 months were offered TNFi.

Resource-use data. Trial medication use (name, dose, frequency, and duration of use) was recorded prospectively on trial data collection forms by clinical and research staff over the entire study period. Other individual-level economic data were captured by self-report using an adapted client service receipt inventory (CSRI) (14) (Hurley et al [15] and Patel et al [16] had

Table 1. Characteristics of full sample and subsamples with costs and HAQ, EQ-5D-3L, and SF-36 data*

Characteristics	Full sample (n = 205)	Subsample: 6-month cost and HAQ/EQ-5D-3L/SF-36 data (n = 191)	Subsample: 12-month cost and EQ-5D-3L data (n = 186)	Subsample: 12-month cost and HAQ/SF-36 data (n = 188)
Sex, no. (%)				
Male	53 (26)	45 (24)	45 (24)	46 (25)
Female	152 (74)	146 (76)	141 (76)	142 (76)
Ethnicity, no. (%)				
White	181 (88)	168 (88)	162 (87)	164 (87)
Other	24 (12)	23 (12)	24 (13)	24 (13)
Region, no. (%)				
London and south	128 (62)	127 (67)	121 (65)	121 (64)
Midlands	16 (8)	13 (7)	11 (6)	13 (7)
North	61 (30)	51 (27)	54 (29)	54 (29)
Age, years	57.34 ± 11.97	57.11 ± 11.94	56.84 ± 12.08	56.91 ± 12.02
Duration of illness, years	8.20 ± 8.82	8.35 ± 8.98	8.25 ± 8.92	8.24 ± 8.88
HAQ, baseline	1.85 ± 0.63	1.86 ± 0.63	1.85 ± 0.64	1.85 ± 0.64
EQ-5D-3L–based utility, baseline	0.37 ± 0.31	0.37 ± 0.31	0.37 ± 0.31	–
SF-36–based utility, baseline	0.54 ± 0.11	0.54 ± 0.11	–	0.54 ± 0.11

* Values are the mean ± SD unless indicated otherwise. HAQ = Heath Assessment Questionnaire; EQ-5D-3L = EuroQol 5-domain 3-level instrument; SF-36 = Short Form 36 health survey.

similar applications), by interviewer-completed survey at baseline, and at 6 and 12 months postrandomization, covering the previous 3 months. This data collection covered sociodemographic data, use of all-cause community and secondary health and social care services and other medications, lost pay from illness-related time off work, and the receipt of social security benefits.

Cost estimation. Individual-level resource-use data, including trial medications, were multiplied by appropriate unit costs (see Supplementary Appendices A and B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23830/abstract) to calculate a cost per participant. Using a detailed approach, medication unit costs were converted into cost per mg based on the most cost-efficient pack size, choosing maintenance prices over initial treatment prices and generic prices over branded prices to obtain conservative estimates (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23830/abstract). Total costs were then computed at baseline, 6 months, and 12 months from 3 perspectives: a health and social care perspective; a societal perspective, additionally including participant lost pay due to work absence; and a second societal perspective, which further added social security benefits.

Trial medication costs were available for the full periods of 0–6 months and 7–12 months; all other costs represented data collection periods of 4–6 months and 10–12 months inclusive, so they were doubled to represent the first and second 6-month periods, respectively. All costs are reported in British pounds sterling at 2010/2011 prices and can be converted to US dollars or euros using the rates £1 = $1.42 or £1 = €1.28 (based on 2011 purchasing power parities that equalize the purchasing power of the currencies) (17). Discounting was unnecessary.

Outcomes. Cost-effectiveness analyses were based on the trial's primary outcome measure, the Health Assessment Questionnaire (HAQ) (18), with lower scores indicating better outcome. Cost-utility analyses were based on quality-adjusted life years (QALYs), estimated by applying appropriate general population utility weights (Brazier et al [19] and Dolan et al [20]) to individual health statement measurements, using both the Short-Form 36 (SF-36) health survey (21) and the EuroQol 5-domain 3-level instrument (EQ-5D-3L) (22) administered at baseline and at 6 and 12 months. QALY gains between baseline and 6 months and between 6 months and 12 months, were then calculated as the total area under the curve.

Statistical analysis. Costs and outcomes were compared at 6 and 12 months and are shown as mean ± SDs. Mean differences between trial arms and 95% confidence intervals (95% CIs) were obtained using nonparametric bootstrap regressions (1,000 repetitions). For cost comparisons, we included covariates for baseline cost from the same cost perspective, baseline HAQ score, duration of illness, age, sex, region (a stratification factor in the randomization process), and ethnicity. Outcome comparisons included covariates for baseline values of the same outcome plus baseline HAQ score, duration of illness, age, sex, region, and ethnicity.

An electronic data capture system (MedSciNet; http://medscinet.com) was programed to disallow individual-item nonresponse on the service use section of the CSRI. For nontrial medication and other societal impacts, we imputed missing values as necessary (see Supplementary Appendix C, available

on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23830/abstract).

We used available cases for each analysis. To explore the potential impact of excluding nonresponders, we examined sociodemographic and clinical characteristics of responders versus the full sample and, in a sensitivity analysis, we imputed missing 6- and 12-month total costs and outcomes using the multiple imputation command in Stata software, version 11.2 (23). Missing costs were imputed based on variables expected to predict total follow-up costs: baseline HAQ score, duration of illness, age, sex, region, ethnicity, trial arm, and equivalent baseline cost (and equivalent cost at 6 months for 12-month imputations). Imputations of follow-up HAQ scores were based on the baseline HAQ score, duration of illness, age, sex, region, ethnicity, and trial arm (and HAQ score at 6 months for 12-month imputations). Imputations of missing QALYs were based on the baseline HAQ score, duration of illness, age, sex, region, ethnicity, trial arm, and equivalent baseline utility score (and utility score at 6 months for 12-month imputations). Resulting full sample cost and outcome data were analyzed as per the main analyses.

Cost-effectiveness and cost-utility analyses. Accounting for the 3 cost perspectives and 3 outcomes, there were 9 possible cost-outcome combinations to consider in the economic evaluation. Incremental cost-effectiveness ratios were calculated only for combinations showing both significantly higher costs and better outcomes in either trial arm.

Uncertainty surrounding cost-effectiveness/cost-utility from a health and social care perspective was explored using cost-effectiveness acceptability curves based on the net-benefit approach (24) to present the probability that the csDMARD arm is cost-effective compared with the TNFi arm for a range of values (from £0 and £50,000) that a decision-maker would be willing to pay for an additional QALY or an additional point improvement in HAQ score. Data were analyzed using Stata software, version 11.2 (23).

Table 2. Resource use at 6- and 12-month follow-up for the previous 3 months*

		6 months		12 months	
Resource	Unit	TNFi (n = 97)	csDMARDs (n = 94)	TNFi (n = 93)	csDMARDs (n = 95)
General practitioner (GP)					
At surgery	Visit	55 (2 ± 1)	42 (2 ± 1)	58 (2 ± 2)	60 (2 ± 1)
At home	Visit	3 (2 ± 1)	2 (1 ± <1)	3 (1 ± 1)	4 (2 ± 1)
Phone call	Call	14 (1 ± 1)	9 (2 ± 1)	13 (1 ± 1)	16 (1 ± 1)
Repeat prescription request without GP contact	Prescription	70 (3 ± 1)	63 (3 ± 1)	61 (2 ± 1)	68 (3 ± 2)
Nurse					
At surgery	Visit	31 (3 ± 4)	31 (3 ± 3)	31 (2 ± 2)	24 (2 ± 1)
Phone call	Call	2 (1 ± <1)	2 (2 ± 1)	5 (2 ± 1)	2 (1 ± <1)
Physiotherapist					
At hospital	Therapy unit	4 (3 ± 1)	8 (4 ± 3)	7 (3 ± 2)	11 (5 ± 6)
At home	Visit	0	0	0	0
At GP surgery	Visit	1 (1 ± –)	2 (3 ± <1)	2 (3 ± 3)	1 (8 ± –)
Elsewhere	Visit	2 (2 ± 1)	0	1 (2 ± –)	1 (1 ± –)
Occupational therapist					
At hospital	Therapy unit	3 (1 ± 1)	4 (2 ± 1)	1 (1 ± –)	6 (2 ± 1)
At home	Visit	4 (1 ± <1)	2 (1 ± <1)	1 (1 ± –)	1 (1 ± –)
At GP surgery	Visit	0	0	0	0
Elsewhere	Visit	0	1 (1 ± –)	1 (3 ± –)	1 (1 ± –)
Hospital services					
Accident and emergency department	Visit	9 (1 ± <1)	4 (1 ± <1)	5 (1 ± 1)	10 (1 ± <1)
Hospital stay	Night	5 (7 ± 5)	4 (4 ± 5)	2 (11 ± 13)	5 (2 ± 1)
Outpatient	Appointment	58 (3 ± 1)	55 (3 ± 2)	55 (3 ± 2)	56 (2 ± 1)
Social services					
Meals on wheels	Meal	0	1 (60 ± –)	0	0
Home help	Visit	2 (46 ± 63)	1 (1 ± –)	3 (31 ± 51)	0 –
Social worker	Hour	3 (1 ± 1)	3 (1 ± 1)	2 (2 ± <1)	1 (1 ± –)
Social worker phone call	Contact	1 (3 ± –)	1 (2 ± –)	1 (1 ± –)	2 (2 ± 1)
Other health or social service	Service	3 (14 ± 11)	3 (31 ± 51)	2 (1 ± <1)	2 (19 ± 16)
Nontrial medication	NA	94 –	88 –	91 –	90 –

* Values are the number of users (mean ± SD). Means are for users only. Some means are not relevant because the number of users was 0 or 1. TNFi = tumor necrosis factor inhibitors; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; NA = not applicable.

RESULTS

Response rates. A total of 205 participants were recruited into the study, 101 into the TNFi arm and 104 into the csDMARD arm. Details of trial medications are reported in related publications (9,13). Response rates to CSRI and outcome questionnaires and completion of trial medication data were ≥90% for all components at baseline and at 6 and 12 months and across both trial arms. In all, 191 participants (93%) had both cost and outcome data at 6-month follow-up, and 186–188 participants (91–92%) had both cost and outcome data at 12-month follow-up. There were no notable differences in characteristics between the subsamples included in the available case analyses and the full sample (Table 1).

Resource use. Resource use (not tested statistically) was broadly comparable between groups (Table 2). General practitioner surgery visits, practice nurse surgery visits, repeat prescription requests, and hospital outpatient appointments were common in both groups at all time points, with other service use being relatively rare. The number of participants using nontrial concomitant medications was also similar in both groups at all time points.

Cost. Costs for both groups were equivalent at baseline (Table 3). Costs of social security benefits and lost income are small relative to health and social care costs. At 6- and 12-month follow-up, average values for cost categories remained equivalent between groups except for cost of trial medications, which was significantly lower in the csDMARD arm (6-month adjusted mean difference –£3,637 [95% CI –3,838, –3,420]; 12-month adjusted mean difference –£1,894 [95% CI –2,320, –1,427]). The additional trial medication cost in the TNFi group overshadowed all other cost categories in that arm. The increase in trial medication costs between 6 and 12 months in the csDMARD arm was due to a significant proportion of this group (n = 46 [44%]) switching to the more expensive TNFi at 6 months because of nonresponse to csDMARDs by 6 months. Switching in the reverse direction was uncommon (a total of 4 participants), so trial medication costs in the TNFi arm did not fall a great deal between 6 and 12 months.

Table 3. Summary costs at baseline and at 6 and 12 months*

Costs	TNFi (n = 101)	csDMARDs (n = 104)	Unadjusted mean difference (95% CI)†	Adjusted mean difference (95% CI)‡
Costs at baseline, previous 3 months§				
Health and social care, excluding trial medication	(101) 736 ± 1,082	(104) 601 ± 476	–131 (–379, 97)	–
Lost pay	(101) 60 ± 262	(104) 84 ± 440	24 (–66, 131)	–
Social security benefits	(101) 71 ± 76	(104) 63 ± 67	–9 (–29, 12)	–
Costs at 6 months, previous 3 months				
Health and social care, excluding trial medication§	(97) 536 ± 947	(94) 511 ± 705	–27 (–262, 202)	6 (–217, 206)
Lost pay§	(97) 71 ± 405	(94) 35 ± 310	–35 (–127, 67)	–35 (–115, 59)
Social security benefits§	(97) 77 ± 75	(94) 74 ± 77	–2 (–21, 21)	3 (–15, 19)
Trial medication costs¶	(97) 4,166 ± 1,012	(97) 510 ± 356	–3,660 (–3,855, –3,432)#	–3,637 (–3,838, –3,420)#
Costs at 12 months, previous 3 months				
Health and social care, excluding trial medication§	(95) 659 ± 1,699	(93) 583 ± 634	–74 (–486, 255)	–24 (–363, 230)
Lost pay§	(93) 19 ± 132	(95) 2 ± 18	–16 (–46, 2)	–17 (–42, 2)
Social security benefits§	(93) 85 ± 83	(95) 77 ± 84	–6 (–32, 16)	5 (–12, 23)
Trial medication¶	(96) 3,546 ± 1,631	(94) 1,547 ± 1,547	–1,988 (–2,458, –1,555)#	–1,894 (–2,320, –1,427)#
Total costs extrapolated to 6 months				
Costs at 6 months, previous 6 months				
Health and social care perspective, including trial medication	(97) 5,238 ± 2,093	(94) 1,538 ± 1,393	–3,703 (–4,175, 3,199)#	–3,615 (–4,104, 3,182)#
Societal perspective, including trial medication, excluding social security benefits	(97) 5,379 ± 2,236	(94) 1,607 ± 1,569	–3,774 (–4,298, –3,230)#	–3,683 (–4,198, –3,195)#
Societal perspective, including trial medication, including social security benefits	(97) 5,533 ± 2,241	(94) 1,755 ± 1,591	–3,778 (–4,303, –3,230)#	–3,684 (–4,199 to –3,194)#
Costs at 12 months, previous 6 months				
Health and social care, including trial medication	(93) 4,866 ± 3,147	(95) 2,718 ± 1,890	–2,129 (–2,941, –1,417)#	–1,930 (–2,599, –1,301)#
Societal perspective, including trial medication, excluding social security benefits	(93) 4,904 ± 3,218	(95) 2,722 ± 1,890	–2,162 (–2,977, –1,449)#	–1,974 (–2,648, –1,334)#
Societal perspective, including trial medication, including social security benefits	(93) 5,073 ± 3,208	(95) 2,876 ± 1,914	–2,175 (–2,991, –1,465)#	–1,977 (–2,644, –1,338)#

* Values are the (valid numbers) mean ± SD unless indicated otherwise. All costs are given in British pounds. TNFi = tumor necrosis factor inhibitors; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; 95% CI = 95% confidence interval.
† Comparisons include a covariate for region.
‡ Comparisons include covariates for equivalent baseline cost, baseline Health Assessment Questionnaire score, duration of illness, age, sex, region, and ethnicity.
§ 3-month costs.
¶ 6-month costs.
# Statistically significant.

Table 4. HAQ and QALY outcomes at baseline and at 6 and 12 months*

	TNFi	csDMARDs	Unadjusted mean difference (95% CI)†	Adjusted mean difference (95% CI)‡
Utilities and HAQ				
Baseline				
SF-36 utility	(101) 0.52 ± 0.11	(104) 0.56 ± 0.10	0.04 (0.01, 0.07)	–
EQ-5D-3L utility	(101) 0.35 ± 0.31	(104) 0.39 ± 0.31	0.04 (–0.04, 0.12)	–
HAQ	(101) 1.90 ± 0.67	(104) 1.80 ± 0.59	–0.10 (–0.28, 0.07)	–
6 months				
SF-36 utility	(97) 0.59 ± 0.13	(94) 0.62 ± 0.12	0.03 (–0.01, 0.06)	0.00 (–0.03, 0.03)
EQ-5D-3L utility	(97) 0.53 ± 0.30	(94) 0.56 ± 0.26	0.03 (–0.05, 0.10)	–0.01 (–0.08, 0.06)
HAQ	(97) 1.55 ± 0.83	(94) 1.52 ± 0.65	–0.03 (–0.22, 0.19)	0.07 (–0.08, 0.21)
12 months				
SF-36 utility	(94) 0.60 ± 0.14	(94) 0.64 ± 0.13	0.04 (0.01, 0.08)	0.03 (–0.00, 0.07)
EQ-5D-3L utility	(93) 0.50 ± 0.31	(94) 0.60 ± 0.28	0.10 (0.02, 0.19)	0.10 (0.02, 0.18)§
HAQ	(94) 1.60 ± 0.84	(95) 1.33 ± 0.77	–0.27 (–0.51, –0.04)	–0.16 (–0.32, –0.01)§
QALYs				
6 months				
SF-36 QALYs	(97) 0.28 ± 0.05	(94) 0.30 ± 0.05	0.02 (0.00, 0.03)	0.00 (–0.01, 0.01)
EQ-5D-3L QALYs	(97) 0.22 ± 0.14	(94) 0.24 ± 0.12	0.02 (–0.02, 0.05)	0.00 (–0.02, 0.02)
12 months				
SF-36 QALYs	(93) 0.30 ± 0.06	(87) 0.32 ± 0.05	0.02 (–0.00, 0.03)	0.01 (–0.00, 0.02)
EQ-5D-3L QALYs	(92) 0.26 ± 0.13	(88) 0.29 ± 0.11	0.03 (–0.01, 0.06)	0.02 (–0.01, 0.05)

* Values are the (number) mean ± SD unless indicated otherwise. HAQ = Heath Assessment Questionnaire; QALY = quality-adjusted life years; TNFi = tumor necrosis factor inhibitors; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; 95% CI = 95% confidence interval; SF-36 = Short Form 36 health survey; EQ-5D-3L = EuroQol 5-domain 3-level instrument.
† Comparisons include a covariate for region.
‡ Comparisons of HAQ include covariates for baseline HAQ, duration of illness, age, sex, region and ethnicity; comparisons of utilities and QALYs include covariates for appropriate baseline utility, baseline HAQ, duration of illness, age, sex, region, and ethnicity.
§ Statistically significant.

The csDMARD arm had significantly lower total costs from all perspectives at both follow-ups. The difference is greater at 6 months than at 12 months because of the greater trial medication cost differential before switching takes place. Costs from both societal perspectives are similar to those from a health and social care perspective because of the dominance of trial medication costs.

Comparison of outcomes. At baseline, the csDMARD arm had an advantage on utility scores estimated from the SF-36, but this advantage did not carry through in baseline-adjusted utility scores at either of the follow-ups or in the resulting QALY estimates (Table 4). The csDMARD arm did, however, show advantages in terms of the HAQ and EQ-5D-3L–based utility scores at 12 months, although the latter did not translate into QALY advantages.

Cost-effectiveness and cost-utility. Based on the HAQ score, the csDMARD arm dominated, with better outcomes and lower costs at 12 months from all 3 perspectives. All other cost-outcome combinations similarly suggested that the csDMARD strategy was preferable, given the fact that equivalent outcomes were achieved at a significantly lower cost. Cost-effectiveness acceptability curves showed high probabilities of cost-effectiveness for all examined cost-outcome combinations (Figure 1). Probabilities of cost-effectiveness at 6 months based on the HAQ were noticeably reduced after reaching thresholds greater than £10,000 per point improvement but were consistently high at 12 months. Sensitivity analyses based on imputed missing data produced the same conclusions.

DISCUSSION

We show that for patients with active RA whose illness has failed to respond to methotrexate and another DMARD, starting treatment with csDMARDs produces similar HAQ and QALY outcomes at 6 months compared with starting treatment with TNFi and is significantly cheaper (from all cost perspectives), largely due to the lower costs of csDMARD medications compared with TNFi. By 12 months, the csDMARD strategy has the advantage of statistically significant better HAQ outcomes (–0.16 [95% CI –0.32, –0.01]), although the cost difference is smaller due to the large proportion of patients (44%) switching from csDMARDs to TNFi. The HAQ score improvement is not clinically significant, so the clinically relevant conclusion is that the csDMARD strategy provides noninferior clinical outcomes to the TNFi strategy, but at significantly lower cost to the health and social care systems. Adverse events are fully described elsewhere (9), but we note that serious adverse events and withdrawals because of toxicity were equally common with csDMARDs and TNFi. The total number of adverse events (ranging from serious to minor), though higher with csDMARDs, was mainly due to 88 more adverse events related to

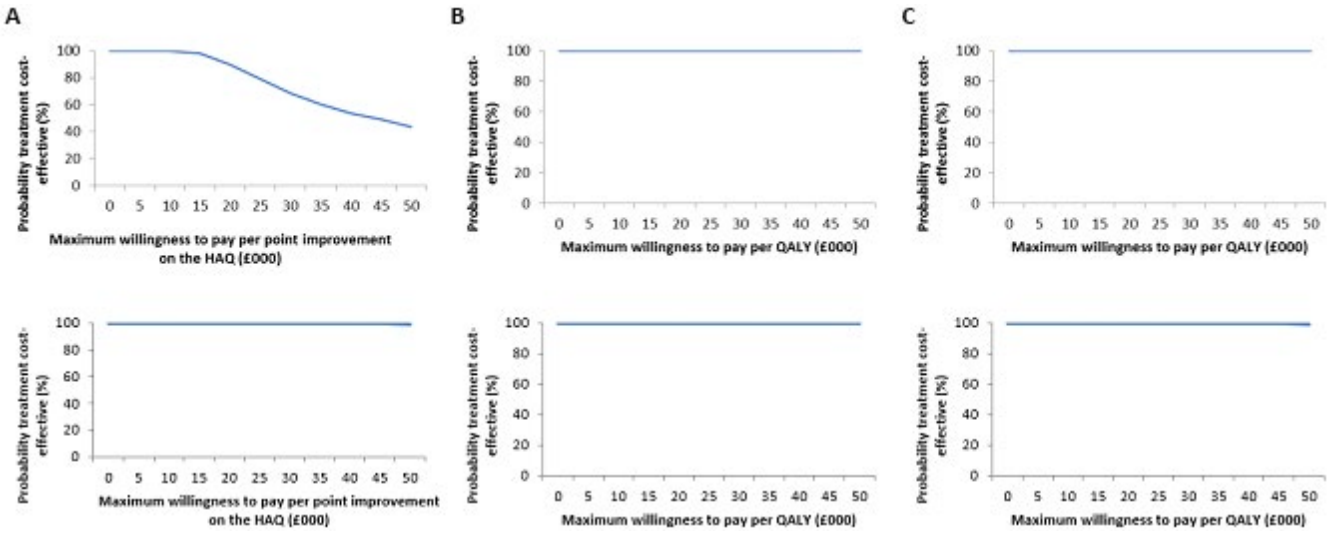

Figure 1. Cost-effectiveness acceptability curves at 6 (top row) and 12 months (bottom row) from a health and social care perspective for all outcomes. **A**, Health Assessment Questionnaire (HAQ); **B**, Short Form 36 (SF-36) health survey; and **C**, EuroQol 5-domain 3-level instrument (EQ-5D-3L). Coefficients of differences in net benefits between the trial arms were obtained through a series of bootstrapped linear regressions (1,000 repetitions) of group upon net benefit; we included covariates for baseline values of the same cost category, the same outcome, HAQ score, duration of illness, age, sex, region, and ethnicity.

the digestive system (148 versus 60) and 20 more adverse events related to the nervous system (61 versus 41).

This study was a comprehensive and prospective economic evaluation, embedded within a robustly designed and implemented clinical trial with high follow-up rates. Other trials of csDMARDs have lacked such broad perspectives (e.g., Wailoo et al [25]). The multicenter design and broad cost perspective necessitated some self-report, risking recall bias. We mitigated such risk by restricting recall periods to 3 months, but this restriction then necessitated data extrapolation to generate data for a 6-month period, which may not accurately reflect any variations in service use and other economic impacts across the measured and nonmeasured periods. Nevertheless, such biases are likely to be equivalent between arms and are minimal, given our finding that trial medication costs dominated total costs. These more influential medication data were available for the entire follow-up and were recorded prospectively by clinicians and the research team. Finally, we were unable to include informal care costs and only report 1-year outcomes because longer-term modeling was beyond the scope of this study.

There is now extensive evidence that intensive treatment strategies involving conventional DMARDs and, to an extent, glucocorticoids, are cost effective as well as beneficial in early RA (6,25,26). In early RA, economic analyses from all 3 published head-to-head trials comparing csDMARD combinations with TNFi with methotrexate show biologic strategies are not cost effective by conventional standards and that DMARDs are preferred (27,28). For example, the examination of infliximab (TNFi) by Eriksson et al (28) against conventional combination treatment reached similar conclusions of greater costs and lack of cost-effectiveness for the TNFi in a comparable trial-based economic evaluation covering 21 months. The only other head-to-head trial in established RA (Rheumatoid Arthritis Comparison of Active Therapies Trial [30]) similarly concludes that initiating biologics before triple therapy (combination csDMARDs) is not cost effective. Using modeling, Stevenson et al (31) argue that, in England, the cost-effectiveness of biologics for RA is questionable and will only be economically worthwhile in those with the worst prognoses.

The Bypass Surgery Versus Everolimus-Eluting Stent Implantation for Multivessel Coronary Artery Disease trial demonstrated that biologics might be cost-effective when accounting for lost productivity (29). The Dose Reduction Strategy of Subcutaneous TNF inhibitors trial concluded that optimizing TNFi dosing, titrating to the lowest dose, offers substantial cost savings without clinically significant QALY detriments (32). More commonly, modeling-based rather than trial-based studies have been used to justify the higher treatment cost of TNFi and other biologics by showing prevention of, or slowed, RA progression over longer time periods. For example, Stephens et al (33) examined combination adalimumab (TNFi) plus methotrexate (DMARD) versus methotrexate alone for patients with early aggressive RA in a 30-year simulation based on data from a short-term clinical trial (PREMIER), concluding cost savings and thus cost-effectiveness when accounting for irreversible radiographic damage and lost productivity costs.

However, recent reviews (34,35) highlight contradictory findings, methodologic nuances, and/or moderate-to-high cost-effectiveness ratios for biologics. For example, the systematic review (with quality assessment) of Joensuu et al (35) of 41 cost-utility analyses included 21 studies comparing biologics and csDMARDs in patients with insufficient response to csDMARDs.

While incremental cost-effectiveness ratios appeared unrelated to study quality, they naturally varied by specific study features (e.g., subgroup, specific medications, and comparators) or were contradictory. Against current cost-effectiveness thresholds, results broadly suggested that biologics lacked cost-effectiveness in treatment-naive patients and in patients with inadequate response to DMARDs. However, at higher thresholds of €50,000–100,000/QALYs, biologics might be cost-effective among csDMARD-resistant patients. Of note, all except 3 of the studies reviewed by Joensuu et al (35) were modeling studies (using multiple data sources, including trials and registries).

Modeling approaches are helpful when pursued with care (36,37) but can carry challenges and limitations. For example, Heather et al (38) found that only one-fifth of model-based economic evaluations of TNFi that they reviewed accounted for adverse drug event costs (and not always providing transparency on how such accounting was done), which may bias cost-effectiveness estimates for TNFi. Trials that assess a range of resource use inherently include such effects if the follow-up period is of sufficient duration, as is the case here. Further, Tosh and colleagues' review (39) of how RA treatment sequencing has been modeled suggested weaknesses in underlying evidence and in reporting of methods, again generating cost-effectiveness uncertainty. Treatment decisions for patients with RA can be complex, in practice and for modeling (40). Tran-Duy et al (40) used observational data to inform a simulation of long-term outcomes and cost-effectiveness of a Dutch clinical guideline–informed treatment strategy where both DMARDs and biologic response modifiers were available against a strategy without biologic response modifiers. They suggested that their flexible modeling approach could helpfully incorporate factors that determine disease progression, costs, and outcomes, although their simulated incremental cost-effectiveness ratios for the strategy, including biologic response modifiers, exceeded conventional thresholds for cost-effectiveness.

There is thus a mixed picture of cost-effectiveness for RA treatment. Models remain reliant on high-quality trial-based or observational evidence to underpin estimates of short-term treatment response; our high-quality trial can usefully inform such studies in the future. There remains uncertainty about the relative cost-effectiveness of different drugs within each class due to a paucity of head-to-head comparisons (41–43). Treatments also continue to evolve. Substantially cheaper biosimilars are now becoming available; these can drive down the costs of original drugs, and modeling studies in countries where biosimilars have been used suggest they will improve the cost-effectiveness of these treatments (44), though the way in which this cost reduction will impact the routine clinical use of biologics in RA is not yet fully known.

This economic evaluation suggests that for patients with established RA whose illness had failed to respond to methotrexate and another DMARD, beginning treatment with csDMARDs is a more cost-effective treatment approach, since such treatment provides equivalent outcomes to starting treatment with TNFi and either avoids or delays additional costs associated with the more expensive TNFi. This approach offers a pragmatic response to financial challenges presented by new and more expensive treatments.

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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. Patel 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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Systematic Review of Economic Evaluations of Cycling Versus Swapping Medications in Patients With Rheumatoid Arthritis After Failure to Respond to Tumor Necrosis Factor Inhibitors

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Objective. To systematically review the modeling approaches and quality of economic analyses comparing cycling tumor necrosis factor inhibitors (TNFi) to swapping to a therapy with a different mode of action in patients with rheumatoid arthritis whose initial TNFi failed.

Methods. We searched electronic databases, gray literature, and references of included publications until July 2017. Two reviewers independently screened citations. Reporting quality was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Data regarding modeling methodology were extracted.

Results. We included 7 articles comprising 19 comparisons. Three studies scored ≥16 of 24 on the CHEERS checklist. Most models used a lifetime horizon, took a payer perspective, employed a 6-month cycle length, and measured treatment efficacy in terms of the American College of Rheumatology improvement criteria. We noted possible sources of bias in terms of transparency and study sponsorship. In the cost-utility comparisons, the median incremental cost-effectiveness ratio was US $70,332 per quality-adjusted life-year for swapping versus cycling strategies. Rituximab was more effective and less expensive than TNFi in 7 of 11 comparisons. Abatacept (intravenous) compared to TNFi was less cost-effective than rituximab. Common influential parameters in sensitivity analyses were the rituximab dosing schedule, assumptions regarding disease progression, and the estimation of utilities.

Conclusion. Differences in the design, key assumptions, and model structure chosen had a major impact on the individual study conclusions. Despite the existence of multiple reporting standards, there continues to be a need for more uniformity in the methodology reported in economic evaluations of cycling versus swapping strategies after TNFi in patients with rheumatoid arthritis.

INTRODUCTION

Therapy with tumor necrosis factor inhibitors (TNFi) has greatly improved the management of disease in patients with rheumatoid arthritis (RA); however, substantial numbers of patients do not experience an adequate response to these drugs, necessitating a change in treatment regimen. The choice of a subsequent therapy is controversial for many reasons, among them doubts about efficacy, concerns about safety, and pervasive resource constraints; adalimumab and etanercept together accounted for over 5% of US pharmaceutical spending in 2013 (1).

Two basic approaches are used after TNFi failure: patients can switch either to another TNFi (cycling strategy) or to a drug with a new mechanism of action (swapping strategy). While systematic reviews of randomized controlled trials show that targeted drugs have similar effectiveness and safety profiles (2,3), evidence from a randomized controlled trial (4) and multiple observational studies (5–13) has supported a swapping strategy. Despite this

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SIGNIFICANCE & INNOVATIONS

- First study to review cost-effectiveness analyses comparing cycle versus swap strategies in rheumatoid arthritis patients who have failed their first tumor necrosis factor inhibitor.
- Reiterates the need for standardization and transparency in cost-effectiveness studies.
- Highlights the need of further studies evaluating cost-effectiveness with swapping choices other than rituximab or intravenous abatacept that better reflect current clinical practices.

evidence, physicians tend to cycle rather than swap (10,14–16), though this trend may be changing (14,17).

Results from economic evaluations comparing the cycling and swapping strategies have been inconclusive. Cycling appears to be the cheaper strategy (16,18,19), but cost-effectiveness analyses show that swapping has an incremental cost-effectiveness ratio (ICER) below willingness-to-pay thresholds and may, in some circumstances, be cost-saving (20,21). Our objective was to systematically review the modeling approaches and quality of economic evaluations comparing cycling versus swapping in patients with RA who have a failed response to TNFi therapy.

MATERIALS AND METHODS

Eligibility criteria. We followed the 27-item checklist of the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement to report our results (22). Our inclusion criteria included economic evaluations (cost-effectiveness, cost-utility, or cost-benefit analyses), publication before July 2017, comparison of TNFi (adalimumab, certolizumab, etanercept, golimumab, or infliximab) to non-TNFi biologics (abatacept, anakinra, rituximab, tocilizumab) or tofacitinib (oral small-molecule inhibitor), and studies consisting of patients with RA who had a failed response to TNFi. We excluded studies if the comparator group was a disease-modifying antirheumatic drug (DMARD), if the study was a conference abstract or poster presentation, or if model details were not provided.

Information sources. The search aimed to find published and unpublished studies and was developed with the assistance of a health sciences librarian experienced in developing strategies for systematic reviews. Searches were not limited by year or type of publication but were restricted to articles published in English. The databases searched were MEDLINE (Ovid), Embase (Ovid), Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, Database of Abstracts of Reviews of Effects, Health Technology Assessments, Web of Science, National Guideline Clearing House, National Institute for Health and Clinical Excellence, Agency for Healthcare Research and Quality, Turning Research Into Practice, Health Economic Evaluations Database, EconLit, National Health System Economic Evaluations Database, and Academy of Managed Care Pharmacy Abstracts. In addition, the reference lists of included articles were hand-searched. DistillerSR software (Evidence Partners) was used to store all citations for duplicate checking and screening.

Search. The initial keywords included "rheumatoid arthritis," the generic and brand names of the 10 drugs of interest, their mechanisms of action, "comparative effectiveness research," "costs," and "cost analysis." The detailed MEDLINE search strategy can be found in Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23859/abstract.

Study selection. Two reviewers (ARKM and MAL-O) performed eligibility assessments independently, blinded to author and journal. Disagreements at all stages were resolved through discussion. If agreement could not be reached, a third reviewer (SBC) made a final decision.

Data collection process. To systematically extract data, we developed a form based on the Guide to Community Preventive Services' standard abstraction document (23) and RA-specific guidelines (24,25). The form was pilot-tested on 5 randomly selected studies and refined accordingly. Data extraction was performed by 1 reviewer (ARKM) and crosschecked by another (MAL-O).

Data items. We extracted 1) general information such as title, authors, publication year, country, and study sponsor; 2) study characteristics: analytic technique, perspective of the study, funding source, and reporting quality; 3) modeling features: patients' characteristics, intervention characteristics, disease states (i.e., health states and pathways), cycle length, time horizon, parameters of effectiveness/safety, costs (drug and nondrug costs), and model outcomes (i.e., quality-adjusted life-year [QALY]) where 1 QALY is equivalent to 1 life-year spent in full health and/or cost per responder; 4) ICERs (i.e., the estimated difference in cost between the competing interventions divided by the difference in QALYs gained); and 5) assessment of uncertainty and model validation.

Quality appraisal. The selected studies were appraised for reporting quality using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (26), which consists of 24 items evaluating 6 aspects of an economic study. Items were assessed as true, false, or not applicable or partly true. Because many items consisted of >1 question, if a sub-item was not reported, the entire item was marked as partly true. The reporting quality of the studies was assessed as the total number of true ratings and expressed as a percentage.

Synthesis of results. Data were analyzed using narrative synthesis. Extracted data were tabulated from the studies. Quantitative meta-estimates were not calculated given the heterogenic nature of economic evaluations. However, we estimated the median and provide the maximum and minimum values as a reference. To facilitate comparability, all ICERs were adjusted to 2017 US dollars according to rules specified by the Community Guide (27): costs per QALY were first converted to US dollars using purchasing power parity rates as published by the World Bank (28) and then revised to 2017 values using the US Department of Labor's medical care consumer price index (base period 1982–1984) (29).

We considered an intervention cost-effective if the ICER fell below a threshold of $100,000 per QALY (30). A threshold of $50,000 per QALY has been used historically, but recently, thresholds of $100,000 to $300,000 per QALY gained are being considered more appropriate (30–32). Strategies that cost less and that are at least as effective as the comparator are dominating.

RESULTS

Study selection. After exclusion of duplicates, 5,221 citations were screened. The 7 included publications comprised 19 comparisons, because 4 articles examined more than 1 treatment strategy. Figure 1 shows the study selection flowchart.

Study characteristics. The 7 included studies represented 4 European countries and the US. There was 1 decision tree, 3 microsimulations, 2 discrete event simulations, and 1 trial-based study. Four studies were from the perspective of a third-party payer, 2 took a societal perspective, and the 7th did not report perspective. Six models were cost-utility analyses, and the last was a cost-effectiveness analysis. Five studies were sponsored by the pharmaceutical industry, all reporting favorable ICERs for their marketing strategy (Table 1).

Quality of reporting. While most studies reported their parameters as required by CHEERS (Figure 2), few justified their choices, as also recommended by the guideline; for example, most described the study perspective (5 studies), time horizon (6 studies), discount rate (5 studies), health outcomes (all studies), and choice of model (6 studies), but not all gave a reason for their choices. No study explained their selection of model. Characterization of uncertainty was another weak point; only 2 studies characterized population heterogeneity. The mean score (number of true answers on the 24-item checklist) was 15 (63.7%), with a range of 11–18.

Modeling features. *Patient characteristics*. Study cohorts were modeled on registries (33,34), clinical trials (35–37), or epidemiologic data (38,39). Cohorts modeled a population that was predominantly female (median 81%, range 67–81%), with a median age of 52 years (range 48–56 years), disease duration of 10.2 years (range 6.3–14.1 years), baseline Health Assessment Questionnaire disability index (HAQ DI) of 1.88 (range 1.4–1.9), and weight of 73.8 kg (range 70.0–77.7). No study reported all characteristics; 2 studies reported 4 (33,35), 3 studies did not report baseline HAQ DI, and 1 study did not report any patient characteristics at all (38).

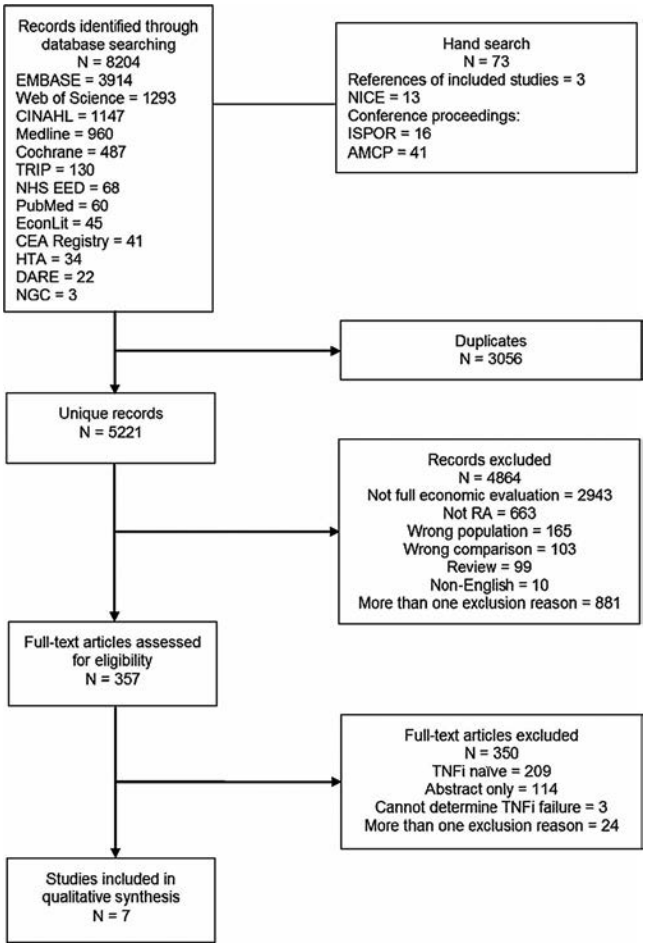

Figure 1. Flowchart illustrating the study screening and eligibility evaluation. This flowchart is modeled after the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (22). TRIP = Turning Research Into Practice; NHS EED = National Health Service Economic Evaluations Database; CEA = Cost-Effectiveness Analysis Registry; HTA = Health Technology Assessments; DARE = Database of Abstracts of Reviews of Effects; NGE = National Guideline Clearinghouse; NICE = National Institute for Health Care Excellence; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; AMCP = Academy of Managed Care Pharmacy; RA = rheumatoid arthritis; TNFi = tumor necrosis factor inhibitor.

Treatment strategies. Eleven of 19 comparisons evaluated rituximab versus TNFi, either as a class (33,35) or individually, with adalimumab being the most common comparator (34,36,37,39). Seven comparisons evaluated abatacept versus TNFi. In 1 study, tofacitinib was compared to adalimumab.

Table 1. Methods and modeling features of the included studies*

Study, year (ref.)	Country	Model type	Sponsor	Perspective	Horizon	Outcome	Comparisons
Claxton, 2016 (38)	US	Decision tree	Pfizer	Private payer	1 year	Cost/ responder	1
Hallinen, 2010 (39)	Finland	Microsimulation	Roche Oy	Society	Lifetime	QALY	6
Kielhorn, 2008 (37)	UK	Microsimulation	F. Hoffman-La Roche AG	Public payer	Lifetime	QALY	1
Lindgren, 2009 (33)	Sweden	DES	Roche AB	Society	Lifetime	QALY	1
Malottki, 2011 (34)	UK	DES	National Institute for Health and Clinical Excellence	Public payer	Not reported	QALY	6
Manders, 2015 (35)	Netherlands	Trial-based	Netherlands Organization for Health Research and Development	Not reported	1 year	QALY	2
Merkesdal, 2010 (36)	Germany	Microsimulation	Roche Pharma AG, Grenzach-Wyhlen, and F. Hoffmann-La Roche	Public payer	Lifetime	QALY	2

* QALY = quality-adjusted life-year; DES = discrete event simulation.

Health states and pathways. The 3 microsimulations and 2 discrete event simulations had at least 2 health states/events: "on treatment" and "death" (33,34,36,37,39). Patients on treatment could have varying degrees of response; those not responding moved to the next treatment in sequence or to palliative treatment. One study (33) allowed patients to be off treatment and another (36) had a separate state for palliative treatment. In all cases, costs and utilities were not allocated based on the disease state itself, but on the specific drug, cycle (first versus subsequent), and the associated HAQ DI score. In all cost-utility analyses, the HAQ DI score improved upon new treatment initiation and deteriorated over time, rebounding to its original value upon treatment discontinuation.

One study (35) was not a decision analysis model but was based on a pragmatic randomized controlled trial. In the decision tree study (38), patients experiencing an American College of Rheumatology 20% improvement criteria (ACR20) response (40) would continue treatment for the next 6 months before being reassessed. A total of 75% of those not responding or experiencing an adverse drug-related reaction would switch to the next treatment in sequence and the pattern would then be repeated. Discontinuation was either after a predetermined treatment time (36,37,39) or determined based on observational data (33,34). Only 1 study explicitly modeled probability of serious adverse events as a reason for discontinuation (38).

Cycle length. Cycle length represents the minimum amount of time an individual will spend in a health state before the possibility of transition to another. The length of the cycle needs to reflect the underlying disease process such that it can represent the frequency of clinical events and interventions. The 3 microsimulations and 1 decision tree used a 6-month cycle length. Of these, only 1 study stated that the cycle length was determined based on the effectiveness data (6-month clinical trials) (37).

Time horizon. Four of the 7 included studies used a lifetime horizon, and 1 is presumed to have done so (34). This finding is consistent with the International Society for Pharmacoeconomics and Outcomes Research best practices (41). One study (35) tracked outcomes over 1 year, and 1 study (38) used both 1- and 2-year frameworks. Shorter frameworks are preferred by the Outcome Measures in Rheumatology initiative (25), which

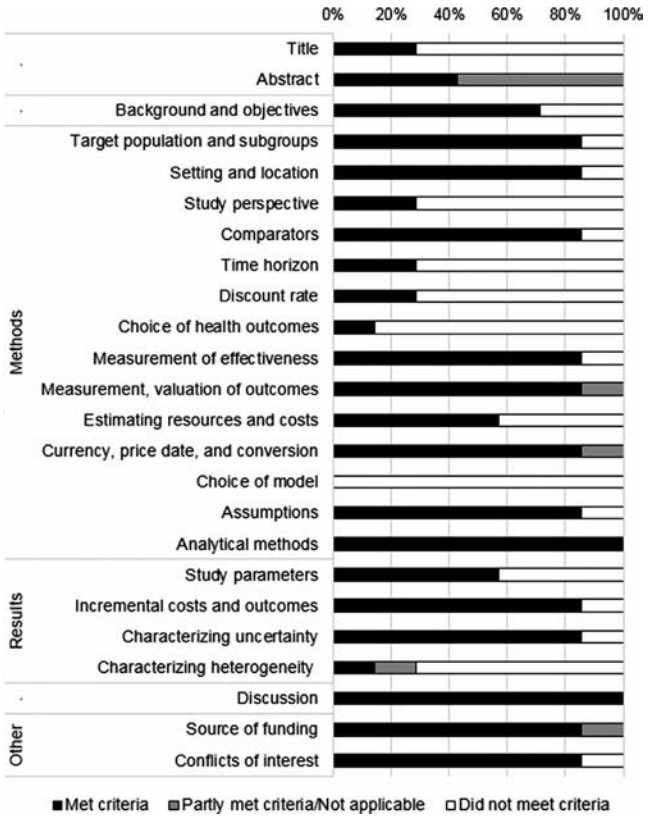

Figure 2. Results of Consolidated Health Economic Evaluation Reporting Standards quality of reporting checklist.

cautioned against extrapolating beyond the duration of the clinical trial, stating that efficacy estimates beyond 10 years are unlikely to be clinically acceptable.

Effectiveness and safety. ACR criteria were used by 4 studies to determine treatment efficacy (36–39). One study (38) only considered whether patients achieved at least an ACR20 response or not. One study (33) used HAQ DI scores only, and another (33) combined the HAQ DI with the Disease Activity Score in 28 joints. One study (35) used the EuroQol 5-domain questionnaire (EQ-5D), a standardized instrument for measurement of health-related quality of life (QoL) that can be converted to utilities. In 6 studies, the effectiveness measures were based on clinical trial data (34–39); however, 1 used registry data (33) (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23859/abstract).

Three studies mentioned adverse events: 1 explicitly excluded them from the model (33), 1 incorporated adverse event data from a meta-analysis into the model structure and detailed their costs (38), and the third reported using them in the sensitivity analysis without providing further detail (34). Six models considered treatment discontinuations (33,34,36–39), which are particularly important because they can affect the total treatment cost and thereby the overall cost-effectiveness of treatment.

Costs. Cost parameters were unevenly included across studies: in terms of direct medical costs, all studies included drug costs and at least 1 other component. Two studies each mentioned direct nonmedical costs (38,39) or indirect costs (33,36). Drug costs were sourced from national price lists, while other medical costs and expected resource use were derived from surveys, literature reviews, national fee schedules, and guidelines (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23859/abstract). Given the large disparity in reporting, we could not reconcile amounts for nondrug cost components.

Medication costs were recorded per dose in 5 studies, and 2 simply recorded annual costs (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23859/abstract). Regarding the latter, studies often differentiated the first and subsequent years/cycles to accommodate loading doses. Drug costs reported in the only study from the US were consistently twice those reported by studies from the European countries. Table 2 shows the per (subsequent) 6-month cycle costs of the 5 most commonly reported biologic drugs in the included studies. Rituximab and infliximab were consistently the least expensive drugs, whereas adalimumab and etanercept were the most expensive. One study did not report drug costs (33).

Costs other than those of targeted drugs were categorized into 22 different components (Table 3) and studies reported 1–10 of them (median: 8). The most commonly reported direct medical costs were laboratory tests and primary care visits (5 of 7 studies), followed by administration, monitoring, and radiology costs (4 studies each). However, in some studies, administration and monitoring were bundled with medication costs, increasing the difficulty of reconciling the study parameter outputs. Direct nonmedical costs, such as patient time costs and training and education costs, were only included in 1 model each (38,39). In general, costs were portrayed broadly; few studies noted the cost assigned per item, and fewer still described the derivation of that cost. Exacerbating the situation was the studies' use of disparate definitions of each of the components. For example, the radiology category might have included only radiographs in 1 study, but in another included computed tomography scans, magnetic resonance imaging, ultrasonography, and bone densitometry.

Model outcomes. QALYs were the model outcome in all cost-utility analyses. They are derived by multiplying the life-years gained from an intervention by the utility of those years. No study reported total life-years gained. Utilities were derived from the EQ-5D (35) or from regression formulae predicated on HAQ DI; the most common (36,37,39) was Bansback's equation (42). The outcome of the single cost-effectiveness analysis (38) was measured in terms of cost per responder.

ICERs. In the 18 cost-utility analyses, the median ICER was $70,332 per QALY for the swapping strategy, with a range of $24,770 to $239,104 per QALY. In 7 of the 11 comparisons between rituximab and TNFi, rituximab dominated TNFi, that is, rituximab was both more effective and less expensive than TNFi (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23859/abstract). The median ICER for the remaining 4 comparisons of rituximab and TNFi was $24,934 per QALY. The comparison of intravenous abatacept and TNFi yielded a higher median ICER of $86,334 per QALY. The abatacept ICERs fell into

Table 2. Distribution of drug costs per 6-month cycle in 2017 US dollars*

Value	Abatacept IV	Adalimumab	Etanercept	Infliximab	Rituximab
Mean	11,289	15,325	15,140	8,214	8,471
Median	10,050	11,513	10,986	7,335	7,216
Minimum	8,787	8,647	8,649	6,078	4,482
Maximum	16,268	26,260	25,786	12,107	16,471
SD	3,394	7,472	9,293	2,674	4,183
No. of studies	4	5	3	4	6

* Only includes drugs that were analyzed in at least 3 studies.

Table 3. Reported cost components in various studies*

Cost component	Claxton	Hallinen	Kielhorn	Lindgren†	Malottki	Manders	Merkesdal
Direct medical cost							
Drugs	✓	✓	✓	✓	✓	✓	✓
Administration	✓	–	✓	–	✓	–	✓
Monitoring	✓	–	✓	–	✓	–	✓
Primary care visits	✓	✓	✓	–	✓	–	✓
Rheumatologist visits	✓	✓	–	–	–	–	✓
Other specialist visits	–	–	–	–	–	–	–
Allied health	–	✓	–	–	✓	–	–
Phone consultation	–	✓	–	–	–	–	–
Outpatient	✓	–	–	–	✓	–	✓
Inpatient	–	✓	–	–	✓	–	✓
Home care	–	–	–	–	–	–	–
Palliative care	–	–	–	–	✓	–	–
Adverse events	✓	–	–	‡	§	–	–
Aids, devices, and home equipment	–	–	–	–	–	–	–
Non-bDMARD prescriptions	✓	–	–	–	–	–	–
Intraarticular injections	–	–	–	–	–	–	–
Joint replacement	–	–	–	–	✓	–	–
Radiology	✓	✓	–	–	✓	✓	–
Lab tests	✓	✓	✓	–	✓		✓
Direct nonmedical cost							
Training/education	✓	–	–	–	–	–	–
Patient travel	–	✓	–	–	–	–	–
Patient time	–	–	–	–	–	–	–
Indirect							
Productivity	–	–	–	✓	–	–	✓

* bDMARD = biologic disease-modifying antirheumatic drug.
† Included "direct and indirect costs" with no further details.
‡ Excluded: assumed similar in both arms.
§ Only included in sensitivity analysis.

2 distinct groups: 1 composed of 4 comparisons from 2 studies (34,35), with a median ICER of $73,961 per QALY (minimum $42,058 per QALY, maximum $86,334 per QALY), and the other comprising 3 comparisons from 1 study (39), with a median ICER of $223,850 per QALY (minimum $195,443 per QALY, maximum $223,850 per QALY). The source of this discrepancy could not be ascertained because the models differed in terms of their type, structure, assumptions, and variables. Table 4 shows the ICERs for the cost-utility analyses comparisons, including the adjustment rates for conversion to 2017 US dollars. In the single cost-effectiveness analysis comparison (38), swapping to tofacitinib was less costly and more effective compared with adalimumab, and in some scenarios it was a cost saving option in both the 1- and 2-year time horizons.

Assessment of uncertainty. Methodologic uncertainty, which pertains to the appropriateness of analytic decisions, was addressed by 6 studies (33,34,36–39); the most common items addressed (3 of 6 studies) were the HAQ DI–to-QoL equation, the rebound effect, allowing negative QoL (states worse than death), and the discount rate (adjustment for differential timing of events). Structural uncertainty, which pertains to the theory and assumptions underlying the model, was addressed by changing rituximab scheduling (33,34,37,39) and drug dosage assumptions (36). One study (34) addressed heterogeneity (first-order uncertainty), which accounts for variability among individuals, by running the model separately for different populations. Six models included sensitivity analyses to assess parameter (second-order) uncertainty (33,34,36–39), which focuses on the imprecision of data inputs: 6 performed 1-way sensitivity analyses, including 1 that also performed a 2-way analysis (38), and half performed probabilistic sensitivity analysis (33,34,36,37). One study included a 2-dimensional simulation that combined first- and second-order uncertainty (33). The rituximab dosing schedule (repeated treatments being given every 4–9 months) significantly affected results in 5 of the 6 studies evaluating the drug. Other influential parameters were assumptions regarding HAQ DI, such as progression, rebound effects, and the conversion-to-preference weights.

Validation. Internal and external consistency are important in determining model validity (43). Only 1 study (34) demonstrated the internal validity of the model by verifying its mathematical logic. No studies established the external validity of

Table 4. Incremental cost-effectiveness ratios (ICERs)*

Study (ref.)	Swap	Cycle	Original ICER	Currency, year	PPP†	MC inflation factor‡	Final ICER
Hallinen (39)	RTX	IFX	18,179	€, 2008	0.91	364.07	$26,021
Hallinen (39)	RTX	ADA	RTX dominant	€, 2008	0.91	364.07	RTX dominant
Hallinen (39)	RTX	ETN	RTX dominant	€, 2008	0.91	364.07	RTX dominant
Hallinen (39)	ABA	IFX	156,388	€, 2008	0.91	364.07	$223,850
Hallinen (39)	ABA	ADA	136,542	€, 2008	0.91	364.07	$195,443
Hallinen (39)	ABA	ETN	167,044	€, 2008	0.91	364.07	$239,104
Kielhorn (37)	RTX	ADA	11,601	£, 2004	0.69	310.10	$25,847
Lindgren (33)	RTX	TNFi	RTX dominant	€, 2008	0.91	364.07	RTX dominant
Malottki (34)	RTX	ADA	RTX dominant	£, 2008	0.70	364.07	RTX dominant
Malottki (34)	RTX	ETN	RTX dominant	£, 2008	0.70	364.07	RTX dominant
Malottki (34)	RTX	IFX	RTX dominant	£, 2008	0.70	364.07	RTX dominant
Malottki (34)	ABA	ADA	46,400	£, 2008	0.70	364.07	$86,334
Malottki (34)	ABA	ETN	37,800	£, 2008	0.70	364.07	$70,332
Malottki (34)	ABA	IFX	41,700	£, 2008	0.70	364.07	$77,589
Manders (35)	RTX	TNFi	RTX dominant	€, 2013	0.80	425.13	RTX dominant
Manders (35)§	ABA	TNFi	29,998	€, 2013	0.80	425.13	$8351
Merkesdal (36)¶	RTX	ADA	15,565	€, 2008	0.82	364.07	$24,770
Merkesdal (36)#	RTX	ADA	24,517	€, 2008	0.82	364.07	$39,017

* Final ICER is reported in 2017 US dollars. PPP = purchasing power parity; MC = medical care; RTX = rituximab; IFX = infliximab; ADA = adalimumab; ETN = etanercept; ABA = abatacept; TNFi = tumor necrosis factor inhibitor.
† Based on World Bank data.
‡ Based on US Bureau of Labor Statistics data (2017 inflation factor = 475.322).
§ Quality-adjusted life-year difference estimated from graph; time horizon is only 1 year, versus lifetime for all other comparisons.
¶ Including indirect (productivity) costs. Quality-adjusted life-year difference estimated from graph; time horizon is only 1 year, versus lifetime for all other comparisons.
# Direct costs only.

their models; no model was calibrated against independent data or tested for predictive validity. All model results appeared valid given the data presented (face validity), and 5 studies (34,36–39) reported that their results were consistent with previous models (cross-validity).

DISCUSSION

This systematic review included 7 studies that made 19 comparisons between TNFi and agents with other mechanisms of action. Adherence to the CHEERS reporting standard among these studies was moderate, with suboptimal reporting of clear, detailed explanation of modeling choices, methodology, and data sources. Despite the substantial uncertainty inherent in assumptions about disease progression under different treatment options, the included publications agreed that swapping to a non-TNFi targeted agent is a cost-effective alternative to cycling to another TNFi at the $100,000 per QALY threshold.

This consensus can, at least partly, be attributed to the largely homogenous structure and efficacy parameters of the included models. The efficacy estimates, while expressed differently, were derived from the same set of randomized clinical trials (see Supplementary Table 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23859/abstract). However, studies did not take into account safety data, because most models are based on results from individual trials comparing an experimental drug to a conventional synthetic DMARD and not on meta-analyses, and therefore there is a paucity of data comparing safety differences among the different treatments. The validity of the efficacy parameters would be enhanced had it been possible to base those parameters on meta-analyses rather than on single trials.

The relative ranking of drugs per study differed. While this ranking may reflect price differences across time and countries, it may also indicate sponsorship bias (44,45). More problematic are the large discrepancies and lack of transparency in both the reporting and the inclusion of other cost components, which further impedes understanding of differences in results. This opacity around cost estimates and the preponderance of studies funded by 1 pharmaceutical company leads to concerns regarding bias; in general, assessments performed by independent organizations have been found to result in less favorable ICERs than those funded by pharmaceutical companies (46).

The choice of comparator may be another source of bias: 11 of the 19 comparisons evaluated rituximab versus TNFi, which is interesting given that, at least in the US, 70% of patients who swap to an agent with other mechanisms of action switch to abatacept (19). Furthermore, although golimumab and certolizumab pegol have been on the market since 2009, only the latter was analyzed as an alternative to agents with other mechanisms of action (47); however, new non-TNFi drugs, tocilizumab (model excluded because the patients were TNFi-naive at entry to the model [48]) and tofacitinib, have been explicitly considered. A recent analysis reported nonbiologic triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine) to be cost-effective in comparison to etanercept when used as first-line therapy (49). However, no

publications have reported on this approach in patients who have already failed biologic therapy.

Whereas previous systematic reviews have looked at treatment options after the failure of the initial TNFi (21,34,50,51), the current study is the first to specifically compare the cycling and swapping strategies and the only one to comprehensively assess reporting quality and to investigate modeling differences. Our study was, however, limited by the inherent heterogeneity of the economic evaluations and the need to include only those that could be comparable. Furthermore, while we recognize that presenting model details in full is not always possible, we could only compare information explicitly reported in the articles, and this restriction may have resulted in more negative quality assessments than the actual models warrant. Also, only 1 study from the US met our eligibility criteria; therefore, the cost per QALY range reported may not entirely reflect US populations–based cost-utility studies.

Future research should determine the treatment sequences used in real-world clinical practice and the length of time patients continue taking each agent. More detailed analysis of the associated nondrug costs would be helpful, as would guidelines regarding the cost components to be included, along with standardization of efficacy estimate adjustments. Much of the uncertainty in the models could be attributed to a lack of knowledge regarding how commonly used disease activity, disability, and QoL measures change over time, in reaction to new treatment and with disease progression, as well as how these measures should be converted to utilities. Lastly, as noted, adverse events, a major issue of concern, had not been adequately assessed in the majority of these models owing to a lack of evidence on long-term safety. This concern is yet another fruitful area for investigation.

In conclusion, despite the findings showing that swapping to non-TNFi targeted agents is cost-effective at the $100,000 per QALY threshold, our study highlights the need for further studies evaluating cost-effectiveness with swapping choices other than rituximab or intravenous abatacept, to better reflect current clinical practices, of longer-term studies on the progression of RA, of RA costs over time, and for greater standardization and transparency in the reporting of economic evaluation studies.

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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. Lopez-Olivo 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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AMERICAN COLLEGE of RHEUMATOLOGY
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BRIEF REPORT

Live Zoster Vaccine in Patients With Rheumatoid Arthritis Treated With Tofacitinib With or Without Methotrexate, or Adalimumab With Methotrexate: A Post Hoc Analysis of Data From a Phase IIIb/IV Randomized Study

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Objective. To explore herpes zoster (HZ) rates and live zoster vaccine (LZV) safety in a subset of patients with rheumatoid arthritis who received LZV before tofacitinib ± methotrexate (MTX), or adalimumab (ADA) plus MTX in the ORAL Strategy.

Methods. ORAL Strategy was a 1-year, phase IIIb/IV, randomized, triple-dummy, active-comparator–controlled study. MTX-inadequate responder patients received tofacitinib 5 mg twice daily (BID), tofacitinib 5 mg BID plus MTX, or ADA 40 mg every other week plus MTX (1:1:1 randomization). Eligible patients age ≥50 years could opt to receive LZV 28 days before initiating study treatment. HZ incidence rates (IRs; patients with events per 100 patient-years) were calculated. Opportunistic HZ infections (multidermatomal/disseminated), serious HZ events, and LZV-related adverse events were monitored.

Results. In ORAL Strategy, 216 of 1,146 patients (18.8%) received LZV. Overall, 18 patients (1.6%) developed HZ (vaccinated: n = 3; nonvaccinated: n = 15). HZ IRs were 1.1 (95% confidence interval [95% CI] 0.3–2.9), 2.3 (95% CI 1.0–4.6), and 1.7 (95% CI 0.6–3.7) for tofacitinib monotherapy, tofacitinib plus MTX, and ADA plus MTX, respectively, and were generally similar between vaccinated and nonvaccinated patients. Three multidermatomal, 1 disseminated, and 2 serious HZ events occurred. No vaccinated patients had zoster-like lesions within 42 days of vaccination; 1 patient had vaccination-site erythema.

Conclusion. LZV was well tolerated, and HZ IRs were generally similar between treatment groups and vaccinated versus nonvaccinated patients. However, ORAL Strategy was not powered for comparisons between vaccinated and nonvaccinated patients because <20% of all patients were vaccinated. Furthermore, LZV has been shown to be effective only in ~50% of individuals.

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SIGNIFICANCE & INNOVATIONS

- Patients with rheumatoid arthritis (RA) are at greater risk of developing herpes zoster (HZ) than the general population, and this risk can be increased by some RA therapies, including tofacitinib.
- The American College of Rheumatology and European League Against Rheumatism recommend vaccination with live zoster vaccine (LZV) in patients with RA.
- However, there are limited prospective data to clearly define the effects of HZ vaccination and the effects of RA therapies on HZ vaccination efficacy.
- In the Oral Rheumatoid Arthritis Trial Strategy, LZV was generally well tolerated in patients who were vaccinated, and no patients developed zoster-like lesions within 42 days of vaccination.

INTRODUCTION

Herpes zoster (HZ) is a common and sometimes debilitating infection that most frequently affects elderly and/or immunocompromised individuals (1). Patients with rheumatoid arthritis (RA) have a 1.5–2-fold higher risk of developing HZ versus the general population (2). This risk may be further increased by RA therapies such as biologic disease-modifying antirheumatic drugs (bDMARDs) (3) and targeted synthetic DMARDs, such as Janus kinase inhibitors (4,5). The mechanism for this increase in risk is considered to be multifactorial and is currently not well understood (4).

As HZ can be prevented in many patients, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommend using live zoster vaccine (LZV) in patients with RA where appropriate, unless there are contraindications (6,7). However, LZV efficacy has been shown to be limited and to reduce with increasing age, with efficacy (assessed for up to 4.9 years) of only 51.3% reported in immunocompetent subjects age ≥60 years, versus 37.6% in those subjects age ≥70 years (8).

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Tofacitinib has been reported to increase HZ risk in patients with RA, and the risk is higher still in older patients, those receiving corticosteroids (4,9), and in certain Asian populations, particularly Japanese and Korean patients (9). In an analysis of data from phase II, phase III, and long-term extension (LTE) studies in patients with RA who received tofacitinib 5 or 10 mg twice daily (BID) without prior LZV (per protocol, some patients may have received LZV), the HZ incidence rate (IR) was 4.4 per 100 patient-years (95% confidence interval [95% CI] 3.8–4.9) globally and 9.2 per 100 patient-years (95% CI 7.5–11.4) in Japan/Korea (4). Analysis of phase I, phase II, phase III, and LTE study data showed that most HZ events in tofacitinib-treated patients with RA were not serious (per the investigator's assessment) and resolved with standard antiviral treatment (9). Increased HZ risk versus placebo has also been observed with another Janus kinase inhibitor, baricitinib, in an analysis of data pooled from phase I, phase II, phase III, and LTE studies. HZ rates with baricitinib were higher in Asia versus other geographic regions, and higher in Japan versus the rest of Asia (5).

Given that an increased HZ risk has been reported in patients with RA, considering whether this risk can be mitigated by vaccination is important. The ORAL Strategy was a 1-year, global phase IIIb/IV study evaluating the efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate (MTX), and adalimumab (ADA) with MTX (10). Although not protocol-mandated, eligible patients could receive LZV at the investigators' discretion before starting study treatment. In this post hoc analysis, we explore the rate of HZ events by treatment arm and LZV safety (in terms of vaccine-related adverse reactions, injection-site reactions, and development of zoster-like lesions), which were secondary objectives in ORAL Strategy.

PATIENTS AND METHODS

Study design. The full design of ORAL Strategy has been reported previously (10). Briefly, ORAL Strategy was a 1-year, phase IIIb/IV, double-blind, head-to-head, randomized, triple-dummy, active-comparator–controlled study (10). The study was conducted at 194 centers in 25 countries. All procedures were in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice and were approved by the institutional review board/ethics committee at each study center. All patients provided written informed consent. For data sharing information, see Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24010/abstract.

Patients. Eligible patients were age ≥18 years with active RA based on the ACR/EULAR criteria, despite receiving continuous MTX for ≥4 months and at 15–25 mg/week for ≥6 weeks before baseline. Concomitant oral corticosteroids (≤10 mg/day of prednisone or equivalent) were permitted. Patients were excluded if they currently had, or had a history of, recurrent (>1 episode) or disseminated (a single episode) HZ or disseminated herpes simplex.

Randomization and treatment. Between September 11, 2014 and December 28, 2015, patients were blindly randomized 1:1:1 to receive oral tofacitinib 5 mg BID monotherapy (tofacitinib monotherapy), oral tofacitinib 5 mg BID with MTX (tofacitinib plus MTX), or subcutaneous ADA 40 mg every other week with MTX (ADA plus MTX).

Live zoster vaccination procedure. In countries where LZV was available and allowed by local regulations, eligible consenting patients age ≥50 years could receive LZV at the investigators'

discretion, 28 days (± 1 week) before the initiation of study treatment. Full exclusion criteria are shown in Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24010/abstract.

Post hoc analysis of vaccination and HZ events. For all patients treated in ORAL Strategy and for those with HZ events, the proportion who were vaccinated was reported, together with demographics and baseline characteristics by treatment group and stratified by vaccination status. Baseline varicella zoster virus serology checks were not protocol-mandated. All HZ events were monitored, including potential opportunistic infection HZ events, which were evaluated by an external adjudication committee and defined in this study as events that were disseminated or multidermatomal (occurring in nonadjacent or >2 adjacent dermatomes). Serious HZ events were defined as those that were life-threatening, required parenteral antiviral treatment or hospitalization, or resulted in death, birth defect, or persistent/significant disability. LZV safety was assessed: zoster vaccine–related adverse events were reported, including injection-site reactions and development of zoster-like lesions.

Statistical analysis. Because self-reported vaccination status may not be reliable and was not verifiable, patients self-reporting previous vaccination were categorized as nonvaccinated. HZ events were summarized descriptively. HZ IRs (patients with events per 100 patient-years) and 95% CIs were calculated for each treatment group and for vaccinated versus nonvaccinated patients. Crude HZ IRs were also calculated for vaccinated and nonvaccinated patients stratified by age ≥50 years.

RESULTS

Live zoster vaccination. In ORAL Strategy, 1,146 patients received the study treatment (tofacitinib monotherapy, n = 384; tofacitinib plus MTX, n = 376; or ADA plus MTX, n = 386). Of these patients, 549 (47.9%) were eligible by age (≥50 years) to receive LZV, excluding those in Russia (n = 57) due to regulatory restrictions. Of all 1,146 patients, 216 (18.8%) received LZV prior to study treatment and 930 (81.2%) did not. Of the 549 patients eligible by age, 333 (60.7%) did not receive LZV due to institutional review board/investigator discretion and/or patient decision, other protocol exclusions, or lack of availability of frozen LZV in Canada, Israel, and

Table 1. Demographics and baseline characteristics of patients in ORAL Strategy by treatment group, stratified by LZV vaccination status*

	Tofacitinib 5 mg BID monotherapy (n = 384)		Tofacitinib 5 mg BID + MTX (n = 376)		ADA 40 mg Q2W + MTX (n = 386)	
	Vaccinated (n = 69)	Nonvaccinated (n = 315)	Vaccinated (n = 75)	Nonvaccinated (n = 301)	Vaccinated (n = 72)	Nonvaccinated (n = 314)
Age, years	58.7 ± 7.0	47.7 ± 12.3	58.2 ± 7.3	47.9 ± 13.7	60.5 ± 7.5	48.4 ± 13.4
Sex, no. (%)						
Male	11 (15.9)	54 (17.1)	16 (21.3)	49 (16.3)	15 (20.8)	51 (16.2)
Female	58 (84.1)	261 (82.9)	59 (78.7)	252 (83.7)	57 (79.2)	263 (83.8)
Geographic region, no. (%)						
North America†	15 (21.7)	47 (14.9)	25 (33.3)	46 (15.3)	28 (38.9)	45 (14.3)
Latin America	18 (26.1)	75 (23.8)	21 (28.0)	70 (23.3)	13 (18.1)	79 (25.2)
Europe	13 (18.8)	146 (46.3)	9 (12.0)	141 (46.8)	16 (22.2)	138 (43.9)
Asia	20 (29.0)	23 (7.3)	18 (24.0)	20 (6.6)	14 (19.4)	28 (8.9)
Australia/New Zealand	2 (2.9)	5 (1.6)	1 (1.3)	5 (1.7)	0 (0.0)	5 (1.6)
Rest of the world	1 (1.4)	19 (6.0)	1 (1.3)	19 (6.3)	1 (1.4)	19 (6.1)
TJC28 score	14.7 ± 7.1	15.5 ± 6.4	14.7 ± 7.0	15.8 ± 6.3	14.3 ± 7.4	15.3 ± 6.5
SJC28 score	11.1 ± 5.8	11.2 ± 5.5	10.3 ± 5.3	12.2 ± 5.8	10.8 ± 6.0	11.0 ± 5.2
CRP, mg/liter	16.1 ± 18.2	16.7 ± 19.5	17.4 ± 19.3	19.0 ± 22.5	16.4 ± 16.7	16.6 ± 22.2
ESR, mm/hour	48.2 ± 27.2	48.0 ± 26.1	51.0 ± 31.4	49.1 ± 26.8	43.9 ± 25.3	48.1 ± 25.6
CDAI score	36.8 ± 13.1	39.0 ± 12.4	36.3 ± 12.4	40.6 ± 12.7	36.5 ± 13.8	38.6 ± 12.7
DAS28 4 (ESR) score	6.4 ± 0.9	6.5 ± 0.9	6.3 ± 0.9	6.6 ± 0.9	6.2 ± 1.0	6.5 ± 1.0
Baseline corticosteroid use, no. (%)	41 (59.4)	187 (59.4)	44 (58.7)	171 (56.8)	45 (62.5)	178 (56.7)
Daily dose, mg	5.2 ± 2.8	7.6 ± 14.7	5.6 ± 2.6	6.3 ± 4.1	9.9 ± 32.1	6.5 ± 6.8
Weekly MTX dose, mg	16.2 ± 3.6	16.7 ± 3.4	16.0 ± 3.8	16.9 ± 3.6	17.1 ± 3.6	16.3 ± 3.7
Diabetes mellitus, no. (%)						
Yes	14 (20.3)	25 (7.9)	9 (12.0)	25 (8.3)	11 (15.3)	22 (7.0)
no	55 (79.7)	290 (92.1)	66 (88.0)	276 (91.7)	61 (84.7)	292 (93.0)
ALC, 10^3 cells/mm^3	1.7 ± 0.6	1.8 ± 0.6	1.9 ± 0.9	1.8 ± 0.7	1.8 ± 0.7	1.8 ± 0.6

* Values are the mean ± SD unless indicated otherwise. Data for patients age <50 and ≥50 years. LZV = live zoster vaccine; BID = twice daily; MTX = methotrexate; ADA = adalimumab; Q2W = every other week; TJC28 = tender joint count (28 joints); SJC28 = swollen joint count (28 joints); CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; CDAI = Clinical Disease Activity Index; DAS28 4 = Disease Activity Score in 28 joints using 4 variables; ALC = absolute lymphocyte count.
† US and Canada.

Table 2. Demographics and baseline characteristics of patients with HZ in ORAL Strategy by treatment group, stratified by vaccination status*

	Tofacitinib 5 mg BID monotherapy (n = 384; patients with HZ 4 [1.0%])		Tofacitinib 5 mg BID + MTX (n = 376; patients with HZ 8 [2.1%])		ADA 40 mg Q2W + MTX (n = 386; patients with HZ 6 [1.6%])	
	Vaccinated (n = 1)	Nonvaccinated (n = 3)	Vaccinated (n = 2)	Nonvaccinated (n = 6)	Vaccinated (n = 0)	Nonvaccinated (n = 6)
Age, years	75.0	40.7	58.0	58.8	–	52.2
Male/female, no.	0/1	0/3	1/1	0/6	–	2/4
Geographic region, no.†						
North America	0	1	1	3	–	2
Latin America	0	1	0	1	–	0
Eastern Europe	0	1	0	2	–	4
Western Europe	0	0	1	0	–	0
Asia	1	0	0	0	–	0
TJC28 score	17.0	17.0	8.0	12.0	–	17.3
SJC28 score	7.0	13.0	10.0	10.8	–	10.5
CRP, mg/liter	5.2	35.7	24.1	14.6	–	14.5
ESR, mm/hour	19.0	41.0	27.0	52.8	–	37.0
CDAI score	36.5	40.3	32.1	34.9	–	40.5
DAS28 4 (ESR) score	5.9	6.7	5.7	6.3	–	6.4
Baseline corticosteroid use, no.	1	3	1	4	–	3
Daily dose, mg	2.5	6.3	2.5	3.5	–	3.7
Weekly MTX dose, mg	0.0	0.0	22.5	17.1	–	16.3
Diabetes mellitus, no.						
Yes	1	0	0	0	–	2
No	0	3	2	6	–	4
Baseline ALC, 10^3 cells/mm^3	1.3	1.9	1.0	1.8	–	1.7

* Values are the mean unless indicated otherwise. HZ = herpes zoster; BID = twice daily; MTX = methotrexate; ADA = adalimumab; Q2W = every other week; TJC28 = tender joint count (28 joints); SJC28 = swollen joint count (28 joints); CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; CDAI = Clinical Disease Activity Index; DAS28 4 = Disease Activity Score in 28 joints using 4 variables; ALC = absolute lymphocyte count.
† USA (n = 7), Mexico (n = 2), Latvia (n = 1), Bulgaria (n = 1), Poland (n = 3), Russia (n = 1), Bosnia and Herzegovina (n = 1), UK (n = 1), and Taiwan (n = 1).

Thailand at the beginning of ORAL Strategy. Of the 216 patients who received LZV, 7 (3.2%) were age <50 years and were considered to be protocol deviations. Overall, 30 patients (2.6%) self-reported vaccination prior to the study and were categorized as nonvaccinated in this analysis since the vaccination was not verifiable.

Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24010/abstract, shows LZV use stratified by treatment group and country. Overall, the proportions of patients who received LZV were similar among patients receiving tofacitinib monotherapy (n = 69 of 384 [18.0%]), tofacitinib plus MTX (n = 75 of 376 [19.9%]), and ADA plus MTX (n = 72 of 386 [18.7%]). Demographics and baseline characteristics of patients in ORAL Strategy who received study treatment stratified by vaccination status are shown in Table 1 (all patients) and in Supplementary Table 2 (patients age ≥50 years), available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24010/abstract.

HZ events. Overall, 18 of the 1,146 patients (1.6%) who received the study treatment developed HZ. The demographics and baseline characteristics of these patients, stratified by vaccination status, are shown in Table 2. HZ events occurred in 3 of 216 vaccinated patients (1.4%) and 15 of 930 nonvaccinated patients (1.6%) (1 event per patient) and are summarized descriptively in Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24010/abstract. Notably, all patients receiving tofacitinib monotherapy who developed HZ received corticosteroids at baseline.

In vaccinated patients, 1 HZ event was adjudicated as an opportunistic infection (multidermatomal, tofacitinib monotherapy), and none were classified as serious (per the definition in Patients and Methods, above). No vaccinated patients had zoster-like lesions within 42 days of vaccination; 1 patient, treated with tofacitinib monotherapy, had vaccination-site erythema. In nonvaccinated patients, 3 HZ events were adjudicated as opportunistic infections (multidermatomal, tofacitinib monotherapy, n = 1; disseminated, ADA plus MTX, n = 1; multidermatomal, ADA plus MTX, n = 1), and 2 were classified as serious (tofacitinib plus MTX, n = 1; ADA plus MTX, n = 1). Of all HZ events: most (17 of 18 [94.4%]) were described by the investigator as mild or moderate in severity; all events resolved (72.2% treated with antiviral therapy); 1 case of varicella adjudicated as an opportunistic infection was included as

an HZ event (nonvaccinated, ADA plus MTX). Although strain testing was not performed systematically, in the 2 patients who were tested (vaccinated, tofacitinib monotherapy, n = 1; nonvaccinated, tofacitinib plus MTX, n = 1), wild type strains were reported.

Incidence of HZ. HZ IRs in ORAL Strategy were 1.1 (95% CI 0.3–2.9) for tofacitinib monotherapy, 2.3 (95% CI 1.0–4.6) for tofacitinib plus MTX, and 1.7 (95% CI 0.6–3.7) for ADA plus MTX. In vaccinated patients, HZ IRs were 1.5 (95% CI 0.0–8.3) for tofacitinib monotherapy, 3.0 (95% CI 0.4–10.8) for tofacitinib plus MTX, and 0 (95% CI 0.0–5.8) for ADA plus MTX. In nonvaccinated patients, HZ IRs were 1.0 (95% CI 0.2–3.0) for tofacitinib monotherapy, 2.2 (95% CI 0.8–4.7) for tofacitinib plus MTX, and 2.1 (95% CI 0.8–4.5) for ADA plus MTX (Figure 1A).

In patients age ≥50 years who were vaccinated, HZ IRs were 1.6 (95% CI 0.0–8.9) for tofacitinib monotherapy, 3.1 (95% CI 0.4–11.4) for tofacitinib plus MTX, and 0 (95% CI 0.0–5.8) for ADA plus MTX. In nonvaccinated patients, HZ IRs were 0.9 (95% CI 0.0–4.7) for tofacitinib monotherapy, 4.0 (95% CI 1.3–9.3) for tofacitinib plus MTX, and 2.4 (95% CI 0.5–7.1) for ADA plus MTX (Figure 1B).

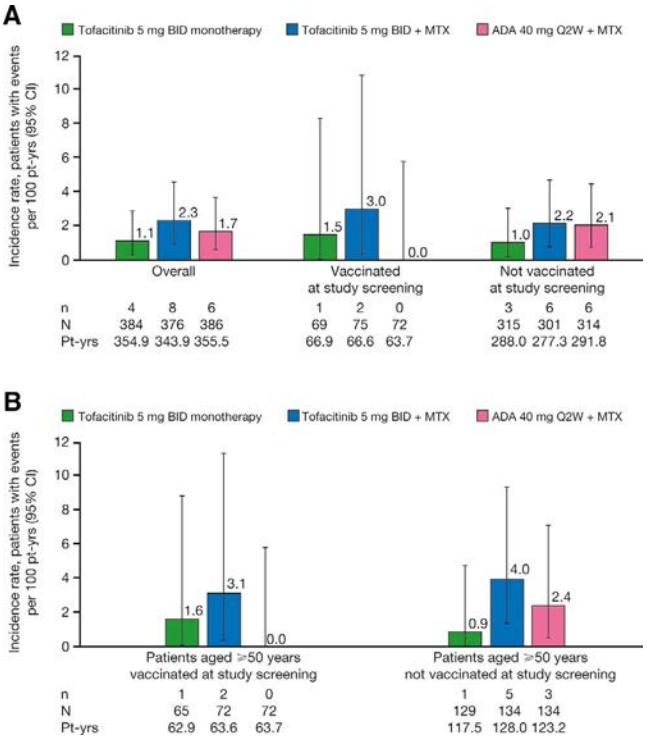

Figure 1. Incidence rates of herpes zoster (serious and nonserious) in the ORAL Strategy by treatment group, stratified by vaccination status, in **A**, all patients and **B**, patients age ≥50 years. BID = twice daily; MTX = methotrexate; ADA = adalimumab; Q2W = every other week; pt-yrs = patient-years; 95% CI = 95% confidence interval.

No HZ events were reported in the 7 patients age <50 years who were vaccinated (protocol deviations). HZ events occurred in 6 of 930 patients (0.6%) age <50 years who were nonvaccinated (per protocol): tofacitinib monotherapy, n = 2; tofacitinib plus MTX, n = 1; ADA plus MTX, n = 3.

DISCUSSION

In this post hoc exploratory analysis of data from the ORAL Strategy, we evaluated the effect of LZV in a subset of patients with RA who received the vaccine prior to treatment with tofacitinib monotherapy, tofacitinib plus MTX, or ADA plus MTX. HZ IRs were generally similar across treatment groups and between vaccinated and nonvaccinated patients, with wide and overlapping 95% CIs. ORAL Strategy was not designed/powered, however, for comparisons between vaccinated and nonvaccinated patients; vaccination was not protocol-mandated and <20% of patients received LZV. Moreover, a proportion of patients who self-reported HZ vaccination history were analyzed as nonvaccinated since the date/year of vaccination occurrence was not verifiable. Additionally, LZV administration was not randomized, in contrast with the randomization of study drugs in ORAL Strategy; confounding is therefore possible. ORAL Strategy was not conducted in Japan, where HZ risk in tofacitinib-treated patients with RA is increased versus other countries (4,9); therefore, this analysis may not give a full representation of LZV in tofacitinib-treated patients. The findings should also be interpreted in the context of the limited efficacy (~50%) that has been observed for LZV in immunocompetent subjects with up to 4.9 years of follow-up (8); in contrast, ORAL Strategy was limited to just 1 year of follow-up.

All patients receiving tofacitinib monotherapy who developed HZ were receiving corticosteroids at baseline. This result appears consistent with data from phase III studies in patients with RA receiving tofacitinib without prior LZV, in which HZ IRs were lowest with tofacitinib 5 mg BID without corticosteroids or conventional synthetic DMARDs (csDMARDs; 0.56 per 100 patient-years [95% CI 0.07–2.01]) and highest with tofacitinib 10 mg BID with corticosteroids and csDMARDs (5.44 per 100 patient-years [95% CI 3.72–7.68]) (9).

HZ IRs for the 3 treatment groups were generally similar in patients age ≥50 years, stratified by vaccination status. None of the 7 patients age <50 years who received LZV (considered protocol deviations) developed HZ, whereas 6 of 15 patients (40.0%) who did not receive LZV and developed HZ were age <50 years. Although this analysis was not designed/powered to detect the effect of age on LZV efficacy, in the general population (which, in 1 study, included immunosuppressed individuals and those with disorders previously associated with HZ, such as RA), the efficacy of LZV is reduced with increasing age (8,11). Meanwhile, HZ risk increases with age both in the general population (1) and in patients with RA (2), including those treated with tofacitinib (4,9).

Overall, evidence suggests that patients with RA should be vaccinated against HZ once eligible. Notably, EULAR guidelines recommend that vaccination against HZ should be considered only in patients who are less severely immunosuppressed (6); ACR recommends considering LZV before initiating RA therapies and while receiving csDMARD monotherapy or csDMARD combination therapy but not when receiving bDMARDs (7). A US National Institutes of Health trial (VERVE; NCT02538341) is assessing LZV use in patients with RA treated with biologic tumor necrosis factor inhibitor therapies; preliminary results from the pilot trial at 6 weeks showed no safety issues (12).

Given the limitations of LZV, interest has focused on newer vaccines that appear to offer improved efficacy. For example, a new adjuvanted HZ subunit vaccine (HZ/su) is indicated for use in adults age ≥50 years (13) and differs significantly from LZV. Since HZ/su is not a live vaccine, it is not contraindicated in those who are immunosuppressed due to disease or therapy. HZ/su efficacy has been reported to be 97.2% in immunocompetent subjects age ≥50 years and does not appear to decrease with advancing age: efficacy was 96.6%, 97.4%, and 97.9% in patients ages 50–59, 60–69, and ≥70 years, respectively (14). The reactogenicity of HZ/su should be noted: 81.5% and 66.1% of subjects were reported to experience injection-site reactions and systemic reactions, respectively (14), which may be attributable to the mode of action and/or strength of the adjuvant. The effect of HZ/su has not yet been evaluated in patients with RA.

In addition to evaluating the effect of LZV on HZ IRs in this post hoc analysis of ORAL Strategy, LZV safety was monitored: no vaccinated patients had zoster-like lesions in the 42 days following vaccination, and 1 patient had vaccination-site erythema. This result supports findings of a previous phase II trial in which patients age ≥50 years received LZV 2–3 weeks prior to initiating tofacitinib 5 mg BID or placebo with background MTX (15). LZV was well tolerated, but 1 patient who lacked pre-existing varicella zoster virus immunity developed cutaneous vaccine dissemination, which resolved with antiviral treatment and discontinuation of tofacitinib (15).

In this post hoc analysis of data from ORAL Strategy, HZ IRs were generally similar between treatment groups and between vaccinated and nonvaccinated patients, and safety findings were consistent with previous reports. These data suggest that LZV is well tolerated in patients with RA treated with tofacitinib with or without background MTX. However, due to the limitations of the analysis, definitive conclusions on vaccine efficacy cannot be drawn from these data. Further studies are necessary to fully compare LZV efficacy in patients with RA versus the general population and to identify potential modifiable factors, such as concomitant medications, to achieve maximal HZ prevention. Additionally, the efficacy and safety of the new HZ/su vaccine should be investigated in patients with RA.

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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 Takiya 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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I Would Never Take Preventive Medication! Perspectives and Information Needs of People Who Underwent Predictive Tests for Rheumatoid Arthritis

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Objective. Little is known about the experiences, values, and needs of people without arthritis who undergo predictive biomarker testing for the development of rheumatoid arthritis (RA). Our study aimed to explore the perspectives of these individuals and describe their information needs.

Methods. A qualitative, multicenter interview study with a thematic analysis was conducted in Austria, Germany and the UK. Individuals were interviewed who underwent predictive biomarker testing for RA and had a positive test result but no diagnosis of any inflammatory joint disease. Participants included patients with arthralgia and asymptomatic individuals. Information and education needs were developed from the qualitative codes and themes using the Arthritis Educational Needs Assessment Tool as a frame of reference.

Results. Thematic saturation was reached in 34 individuals (76% female, 24 [71%] with arthralgia, and 10 [29%] asymptomatic individuals). Thirty-seven codes were summarized into 4 themes: 1) decision-making around whether to undergo initial predictive testing, 2) willingness to consider further predictive tests, and/or 3) preventive interventions, including medication, and 4) varying reactions after receiving a positive test result. Individuals with arthralgia were more likely to be willing to take preventive action, undergo further testing, and experience psychological distress than asymptomatic individuals. All participants expressed the need for tailored, patient-understandable information.

Conclusion. Individuals at risk of RA are currently the subjects of research aimed at developing better predictive strategies and preventive approaches. Their perceptions and needs should be addressed to inform the future development of interventions combined with education.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease with an incompletely understood etiology. RA is characterized by polyarticular swelling leading to pain, stiffness, and loss of joint function, and the disease affects between 0.3% and 1% of the population (1). Delays in diagnosis and treatment are still common and are associated with worse outcomes, including irreversible joint destruction, disability, limitations in functioning, and reduced quality of life (2–5). Early identification of RA patients is thus essential to achieve an optimal clinical outcome (6) and has been the target of several research initiatives (7). Since RA is

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SIGNIFICANCE & INNOVATIONS

- To our knowledge, this study explored for the first time experiences of being tested, as well as information and support needs, of people with arthralgia and asymptomatic individuals who underwent predictive biomarker testing for rheumatoid arthritis (RA) and who had a positive test result.
- All individuals expressed the need for tailored, patient-understandable information on predictive testing. Most of them emphasized the advantage of knowing as early as possible that they were at risk for developing RA.
- Individuals with arthralgia were more likely to be willing to take preventive action, undergo further testing, and experience psychological distress than asymptomatic individuals.
- Because individuals at risk of RA are currently the subjects of research aimed at developing better predictive strategies and preventive approaches, their perceptions and needs should be addressed to inform the future development of interventions combined with education.

commonly preceded by a phase of immunologic abnormalities, including the presence of anti–citrullinated protein antibodies (ACPAs) and low-grade inflammation (8–12), future interventions might start even earlier by identifying and treating individuals who are at risk of developing RA (e.g., those with a first-degree relative with RA and patients with clinically suspect arthralgia or undifferentiated arthritis) before the development of clinically apparent polyarthritis (13,14). Therefore, researchers have explored predictive testing methods involving blood-based biomarkers and imaging (e.g., ultrasound and magnetic resonance imaging), as well as more invasive methods like synovial biopsies (6,8,15–20) in the time preceding RA.

Predictive and preventive approaches can lead to the early detection of certain diseases with benefits for the patients themselves, the health system and its payers, and for society as a whole (21,22). However, there is a risk of overtreatment of those receiving a false-positive test result (13). Although predictive tests have been carried out in a range of disease contexts, there is limited research on the perspectives of individuals who undergo such tests (23). Moreover, the tested individuals need to be informed by physicians and health professionals about the tests and their purpose, as well as about test results, potential risk factors, and preventive strategies relevant for the patient. Therefore, targeted, patient-centered information and communication strategies should be developed alongside the predictive tests to explain what it means to be at risk of RA and the potential benefits and risks of early intervention as well as preventive strategies. This approach may improve the self-efficacy and health literacy of individuals who are at risk of developing RA, raise awareness of future preventive interventions, reduce potential delays in help-seeking for early symptoms, and facilitate improved clinical outcomes. In recent years, a great number of putative predictive tests in the context of RA have been carried out in numerous cohort studies and as part of extended preventive medical check-ups (24,25). Nevertheless, little is known about the needs, values, and beliefs of individuals who undergo predictive testing for RA and are informed about a positive biomarker test result. In their recent work, Sparks et al (14,26) showed that individuals receiving personalized risk disclosure and education were more motivated to change their health behavior than individuals who received standard education about RA. However, the experiences of being tested, as well as the information and support needs of individuals who undergo predictive testing for RA, have not been described in detail yet.

The aims of this study were 1) to explore the perspectives of individuals who underwent predictive biomarker testing for RA and were informed about a positive test result regarding ACPA and/or rheumatoid factor, 2) to find similarities and differences in the views of individuals with arthralgia and asymptomatic individuals that might represent different levels of risk in the development of RA, and 3) to describe the information and education needs in both groups.

SUBJECTS AND METHODS

Design. A qualitative, multicenter interview study and thematic analysis were conducted, as part of the EuroTEAM (Towards Early diagnosis and biomarker validation in Arthritis Management) project (27). Information and education needs were developed from the codes and themes that emerged out of the qualitative analysis using the Arthritis Educational Needs Assessment Tool (ENAT) as a frame of reference (28–30).

Participants and sample size consideration. Individuals age ≥18 years attending rheumatology centers in Vienna (Austria), Erlangen (Germany), and Birmingham (UK) who had predictive biomarker tests for RA with a positive test result, but who had not received a diagnosis of any inflammatory joint disease, were eligible for the current study. Individuals were either referred for testing because of symptoms or had a predictive test for RA as part of an extended medical check-up. ACPA and rheumatoid factor were considered positive according to the reference values in each center. Participants included both individuals with arthralgia in ≥1 peripheral joint and asymptomatic individuals. All participants were contacted by phone, and appointments for conducting the interview at the participating center were made with those wishing to participate. Recruitment continued until thematic saturation was reached. Saturation was defined as no new qualitative codes coming up in at least 10 subsequent interviews (31,32). To determine the number of new codes in each interview, data analysis started soon after the first interview and proceeded in parallel with data collection (33).

The study was approved by the Ethics Committee of the Medical University of Vienna (EK number 2174/2013), the Ethics Committee of the University of Erlangen-Nuernberg (Re. No-87_14B), and the Humber Bridge National Research Ethics Committee of Birmingham (REC reference 13/YH/0329). Eligible individuals were informed about the purpose and procedures of the study and gave their oral and written informed consents.

Data collection. A semistructured one-to-one interview was conducted with each participant. Based on a review of the qualitative literature exploring public perceptions of predictive tests and experiences of being labeled as at risk for a chronic disease (34,35), the research team codeveloped an English interview guide together with biomarker experts and patient research partners (DS and MD). The initial structure of the interview schedule was revised and questions were modified as a result of feedback from both groups to ensure that the descriptions of predictive tests were accurate and understandable by a lay audience. The interview questions are shown in Table 1. Health professionals with experience in qualitative research data acquisition and/or experiences as principal investigators of qualitative studies performed the interviews: EM (female, MSc, background in occupational health and health science), MSM (female, PhD, occupational health and health science), RJS (female, PhD, psychology), GS (female, PhD, psychology), and AJH (male, MD, PhD, rheumatology). All interviews were audiorecorded, transcribed verbatim, and analyzed centrally in Vienna, Austria by EM with input from the local investigators from Erlangen and Birmingham and the patient research partners.

Data analysis. Qualitative data analysis followed a modified form of thematic analysis (36,37) and was facilitated by using QSR International's NVivo 10 qualitative data analysis software. The analysis comprised the following steps: first, the first author (EM) read through the transcripts to gain an overview of the collected data and to become familiar with the content. Second, the transcripts were divided into meaningful segments of data (defined as specific units of text, either a few words or a few sentences with a common meaning). In the third step, initial codes (descriptive or conceptual labels), such as "be shocked/be anxious," "get worried," and "stay calm" were assigned to these segments. Codes could refer to the main topic of a meaningful segment, but 1 segment could also contain more than 1 code. In the fourth step, the initial codes were grouped into associated higher-level themes. The codes "be shocked/be anxious," "get worried," and "stay calm" were grouped under the higher-level theme of varying reactions after receiving a positive test result. Thereafter, we compared the codes and themes between individuals with arthralgia and asymptomatic individuals for similarities and differences regarding the qualitative meaning of a concept and its quantitative frequencies using descriptive statistics. Information and education needs were developed based on the qualitative codes using the ENAT as a frame of reference (28–30).

Table 1. Interview questions for individuals who underwent biomarker testing for RA and had a positive test result but no diagnosis of any inflammatory joint disease*

Can you please tell me what you already know about RA? About which other issues would you like to be informed?
What do you think the causes of RA could be?
What do you think the risks factors for RA are?
Tell me about how serious you think RA is?
How would you know you had RA, for example, what symptoms would you expect?
What would be the impact of RA on your life?
Do you think you would be able to control RA yourself?
Do you think there are treatments available that would effectively treat RA?
Do you ever worry about the possibility of developing RA in the future?
What would you think if you were told that you could have a test that would tell you how likely you were to develop RA?
What sort of information should this test give you?
When do you think would be the right time to get this information?
How would you feel about a test telling you that you could develop RA in the future?
In what ways do you think it would be helpful to know your chances of developing RA?
What would your concerns be if you knew what your risk of developing RA was?
What kind of tests do you think people might be able to do to work out whether or not you might develop RA (tests that are available now and tests that might become available in the future)?
Various tests can currently be done, and various tests are currently being developed to predict the development of RA. What are your thoughts about: 1) Blood tests looking at biomarkers, molecules in the blood, 2) Blood tests looking at genes, 3) Tests involving scanning the joints with either an ultrasound or MRI, and 4) Tests involving taking tissue out of a joint (synovial biopsy) or elsewhere (e.g., lymph nodes)
What are your thoughts about taking medicines to reduce the risk of RA developing in the future?
What are your thoughts about changing your lifestyle (e.g. stop smoking, more exercise, change diet) to reduce the risk of developing RA in the future?

* For using the questions in Austria and Germany, the interview questions were translated from English into German and translated back to English, blinded for the original wording of the questions, by a member of the Austrian research team using a forward-backward approach (33). RA = rheumatoid arthritis; MRI = magnetic resonance imaging.

Rigor and accuracy of the qualitative data analysis. Several strategies were used to improve and verify the trustworthiness of the qualitative data: debriefing notes were recorded after each interview. All local investigators who conducted interviews, namely EM and MSM in Austria, AJH in Germany, and RJS and GS in the UK, checked the transcripts against the audiotapes for accuracy. After analyzing all interviews, the results were discussed with researchers of all centers and reviewed by patient research partners (DS and MD) and a senior researcher (TAS) who had not been involved in the analysis of the transcripts. Finally, the consolidated criteria for reporting qualitative research checklists (38) were used to ensure the high quality of reporting the study results (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23841/abstract).

Table 2. Demographic data of the participants*

Demographics	Asymptomatic (n = 10)	Symptomatic (n = 24)	Total
Participants	10 (29)	24 (71)	34 (100)
Women	7 (70)	19 (79)	26 (76)
Age, mean ± SD years	61.7 ± 9.6	48.6 ± 14.4	52.4 ± 14.4
Age, minimum/maximum years	51–81	18–76	18–81
Family history of RA	1 (10)	9 (37.5)	10 (29.4)
Did not smoke at the time of the interview	9 (90)	19 (79)	28 (82)

* Values are the number (%) unless indicated otherwise. RA = rheumatoid arthritis.

RESULTS

Participant characteristics. Thematic saturation was reached after including 34 individuals (76% female; 24 individuals [71%] with arthralgia and 10 asymptomatic individuals [29%]) (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23841/abstract). Of these individuals, 15 (44%) participated in Austria, 15 (44%) in Germany, and 4 (12%) in the UK (Table 2).

Codes and higher-level themes. We extracted 37 codes that were grouped under 4 higher-level themes, namely decision-making around whether to undergo initial predictive testing, willingness to consider further predictive tests and/or preventive interventions, including medication, and varying reactions after receiving a positive test result (Tables 3 and 4).

Similarities between individuals with arthralgia and asymptomatic individuals. Asymptomatic participants and individuals with arthralgia indicated that being told about their risk of developing RA had both positive aspects (knowing the risk; knowing whom to contact if symptoms progressed), as well as negative consequences (having to deal with the uncertainty associated with risk information). Regarding positive aspects, the majority of participants in this study (32 [94%]) were convinced that they benefited from knowing their risk status as early as possible. They felt this knowledge would enable them to react appropriately if RA-related symptoms developed or extended in the future. Furthermore, getting to know the people to approach in case of symptom onset or progression was described as positive:

> If I develop RA, I know that I will get the best possible care here. I know I'll get very quick access to care; and I know the people whom to approach; this will improve my outcome. (No. 13, female, age 40 years, arthralgia, UK)

> After the test I knew, if I develop it, I have to react quickly, so that something will be done. (No. 4, male, age 52 years, asymptomatic, Austria)

Regarding the negative experiences, some participants of our study reported that dealing with an imprecise risk without further information, such as information about when RA is likely to develop, had a negative impact for them and posed a substantial challenge. Two male participants described the feeling as follows:

> For me, the best would be to describe the risk in numbers and to know when the onset will be. How much will the disease impact my life? What can I do? How can I prevent the onset of the disease? And so on…just to say that it will come anytime is not enough for me. (No. 14, male, age 38 years, arthralgia, Germany)

> One would have to learn in what way that [test result] is significant. But you hear, you have 10% risk for something or 90% and the question is whether something can be done. (No. 4, male, age 52 years, asymptomatic, Austria)

Differences between individuals with arthralgia and asymptomatic individuals. Within all 4 higher-level themes, we found differences between individuals with arthralgia and asymptomatic individuals. Regarding the first higher-level theme of decision-making around whether to undergo initial predictive testing, people already suffering from pain or stiffness aimed to obtain assurance about causes for their symptoms and to receive confirmation that something was wrong with their body, whereas asymptomatic individuals were more likely to undergo predictive testing to contribute to research only.

Regarding the second higher-level theme of willingness to consider further predictive tests, individuals with arthralgia were more likely to agree to further predictive tests than asymptomatic individuals. Invasive methods such as synovial or lymph node biopsies were the areas with the largest difference between both groups: 12 individuals with arthralgia (50%) agreed to synovial biopsy compared to only 1 asymptomatic participant (10%).

> I would take it [synovial biopsy] and I would not mind but rather be interested in it. I am also not very sensitive to pain so it is no problem at all. (No. 21, female, age 76 years, arthralgia, Austria)

Regarding the third higher-level theme of willingness to consider preventive interventions, including medication, 9 individuals

Table 3. Qualitative coding scheme, corresponding information and education needs, and the related sections of the Arthritis Educational Needs Assessment Tool (ENAT)*

Higher-level themes and codes	Information and education needs of individuals who undergo predictive testing and have a positive test result	Related section of the ENAT
1. Decision-making around whether to undergo initial predictive testing Gain information about their own health Assurance about causes for symptoms Receive confirmation that something is wrong For research purposes only	Information on different reasons for undergoing predictive testing Reasons for repeating the biomarker testing: future options might include regular (annual) tests/assessments for research purposes, but also to improve future prediction; otherwise individuals should be advised to come once synovial swellings develop; telephone helplines might also be an option.	Predictive testing is so far not part of the ENAT Section related to support from other people
2. Willingness to consider further predictive tests Positive attitude toward the previous test Negative attitude toward the previous test Right time point, as early as possible Not the right time point Agree to biomarker test Refuse biomarker test Agree to genetic testing Refuse genetic testing Agree to ultrasound or MRI Agree to ultrasound or MRI only with symptoms Refuse ultrasound or MRI Agree to synovial biopsy Agree to synovial biopsy only with symptoms Refuse synovial biopsy	Information on evidence and availability of potential additional predictive test methods Additional information about advantages and potential side effects, as well as validity of the various tests (statement to what extent a test method is diagnostically conclusive)	Predictive testing is so far not part of the ENAT Section related to support from other people
3. Willingness to consider preventive interventions, including medication Agree to preventive medication Strictly reject preventive medication Fear of side effects Critical view on preventive medication More information needed to make a decision Modify one's life/changing lifestyle	Information about the lack of current availability of preventive medication for RA and potential future options	Section on treatments one may receive from health professionals (including medication)
4. Varying reactions after receiving a positive test result Be shocked/be anxious Be surprised Feel vindicated Feel weak and powerless Get worried Stay calm Reconsider one's life Ignore the positive test result Uncertainty due to lack of information Difficulties in talking about being at risk with others, including family and friends Criticism on unspecific test results Agree on monitoring See monitoring as critical	Knowledge about RA Probability of risk to develop RA based on the test results How and where to receive support to minimize psychological stress Information about healthy lifestyles in relation to the onset of RA When to see a rheumatologist based on symptoms Whom to contact when synovial joint swelling occurs Monitoring on a regular basis How to inform family members and significant others in easy words about being a person at risk of developing RA	Section related to disease processes of arthritis Section related to feelings Sections related to treatments one may do for oneself, movement and managing pain Sections related to treatments one may be receiving from health professionals and support from other people

* The ENAT was used as a frame of reference for identifying information and education needs. There were 4 higher-level themes and 37 codes.
MRI = magnetic resonance imaging; RA = rheumatoid arthritis.

with arthralgia (38%) agreed to take future preventive medication under certain conditions, if available, compared to none of the asymptomatic individuals. One participant with arthralgia described the circumstances and conditions under which he would be willing to take preventive medication as follows:

> Fundamentally [I would look at this] positively, whereby you have to consider the side effects. There is almost no medicine without any side effect. Nonetheless, when I envision future damage of the body, an early investigation is very useful. (No. 14, male, age 38 years, arthralgia, Germany)

Table 4. Additional quotes related to the 4 higher-level themes of the qualitative data analysis*

Themes and quotes	Corresponding codes
1: Decision-making around whether to undergo initial predictive testing	
That was during a preventive health check-up and I thought, it's good to do research in this field and it's definitely something useful and then I took part. (No. 3, female, age 67 years, asymptomatic, Austria)	For research purposes only
I thought, maybe this will help other people. Even if I am not affected, it might help somebody else. (No. 22, female, age 69 years, asymptomatic, Austria)	For research purposes only
Yes, I have pain in the joints regularly and that's why it was interesting to me to find out the results. I think it was just confirmation that my feeling wasn't just made up of thin air. (No. 24, female, age 47 years, arthralgia, Austria)	Assurance about causes for symptoms
You're never happy about a disease, but I consider clarification as important. Every person thinks about it differently but I always would like to have the facts because I can then adapt myself more easily. I find it much more reassuring than the lack of knowledge. (No. 19, female, age 49 years, arthralgia, Germany)	Assurance about causes for symptoms
2: Willingness to consider further predictive tests	
It's not one of my hobbies, that's not harmless, invasive, and probably painful. Extracting tissue is more substantial and I would only have that done if I really had problems. (No. 25, male, age 57 years, asymptomatic, Austria [about synovial biopsy])	Refuse synovial biopsy
I don't want that! It is going into too much detail, in my genes, I cannot imagine that I would like this at the moment. (No. 31, female, age 52 years, arthralgia, Germany [about genetic testing])	Refuse genetic testing
3: Willingness to consider preventive interventions, including medication	
I would not do that, simply from my point of view. I would try other possibilities first, as I've mentioned lifestyle. Not even a 100 percent chance of developing rheumatoid arthritis within the next 5 years would lead me to take prophylactic medicine. Then I'd have to put preventive pills, against everything, in my cereal bowl in the morning already instead of breakfast; no, I would never agree to take preventive medication. It's easy for me to say so, as I'm not in any pain. Maybe, if I will have any pain in 3 years, I would then think, if I only had taken preventive medication earlier! But you can't insure yourself against everything and you can't eat pills against everything! (No. 2, female, age 66 years, asymptomatic, Austria)	Strictly reject preventive medication
Only under the condition that a person would receive the necessary information to be able to decide whether to take a preventive medicine. (No. 26, female, age 43 years, arthralgia, UK)	More information needed to make a decision
4: Varying reactions after receiving a positive test result	
It's like looking into a crystal ball [of a fortune teller] and saying to you, "Oh, you could potentially get rheumatoid arthritis." And then, always, I have images of people in my mind who have deformities and disabilities. (No. 26, female, age 43 years, arthralgia, UK)	Uncertainty due to lack of information
I was quite shocked to find out that I had these cells [patient's interpretation after having been told they had a positive autoantibody test], to tell you the truth. How am I gonna, you know, carry on with work, you know, things like that and, you know, my future. (No. 11, male, age 50 years, arthralgia, UK).	Be shocked/be anxious
I know that I have those positive factors. That was a coincidence but it doesn't worry me at all. I cannot change it anyway. (No. 3, female, age 67 years, asymptomatic, Austria)	Stay calm
Well, changing lifestyle means changing diet, difficult, because changing your diet, abstaining from certain food that you like to eat, means reducing your quality of life. I personally don't agree with that, I'm definitely not going on a diet because of a disease I don't have at the moment! But I certainly would if I had any symptoms. (No. 25, male, age 57 years, asymptomatic, Austria)	Ignore the positive test result

* While themes 2 and 3 were strongly related to the interview questions, the first and last higher-level themes were brought up by the participants in addition to topics already raised by the researchers.

One asymptomatic participant who would refuse to take any future preventive medication said the following:

> I would only take medication if I am sick. In my opinion, chemicals and drugs always have side effects and you have to weigh the pros and cons, especially if you overdo it and take a whole cocktail of medicine, then you are experimenting without knowing the outcome. So, medication is for treating already existing disease, not for prevention. (No. 25, male, age 57 years, asymptomatic, Austria)

Regarding potential nonpharmacologic interventions, the majority of the individuals with arthralgia (20 of 24 [83%]) reported that they were willing to consider lifestyle changes to reduce their risk of developing RA, compared to only 2 of 10 (20%) of the asymptomatic participants.

Regarding the fourth higher-level theme of varying reactions after receiving a positive test result, asymptomatic individuals in our study described the fact that they had been able to stay calm (8 of 10 individuals [80%] compared to only 4 of 24 individuals [17%] with arthralgia). In contrast, 10 of 24 individuals with arthralgia (42%) reported anxiety and were shocked when they were told about the positive test result, compared to none of the asymptomatic individuals.

Furthermore, some individuals with arthralgia experienced difficulties in talking about being a person at risk and informing their families and friends. One woman talked about avoiding unnecessary burden for her loved ones:

> My last question when I left the clinic was how to tell people. So that was one of my concerns, the communication of it all and I didn't want to, even though I was feeling overwhelmed, I didn't particularly want other people to panic and then panic me. (No. 13, female, 40 years, arthralgia, UK)

We aimed to assess whether there were differences in views between participants with and without a positive family history of RA. Among asymptomatic participants, only 1 had a family history of RA. Despite the fact that her mother and grandmother had RA, this individual was not concerned about the positive test result and reported that she was unlikely to modify her lifestyle or take future preventive medication. In contrast, individuals with arthralgia and a positive family history of RA reported higher levels of anxiety when being informed about the positive test and said they would modify their life to a greater extent.

Information and education needs. All participants in both groups described the need for tailored, patient-understandable information to be delivered by health professionals together with the positive test result (middle column of Table 3). One participant expressed her experience in the following statement:

> It's important that they don't use these medical terms when explaining something, but try to explain it by using examples. For them, this is a standard vocabulary, but for me this is a foreign word. (No. 6, female, age 52 years, asymptomatic, Austria)

Furthermore, the majority of participants in this study missed having clear and precise statements concerning different possibilities to prevent the onset of the disease. In that sense, they were especially interested in whether and what they could do themselves to reduce the risk of RA development. As an example, one participant said:

> The one thing I would be curious about to find out would be what I can do to stay healthy. And there is not much I found out so far. Specific information would help a lot. (No. 15, female, age 52 years, arthralgia, Germany)

The qualitative codes and themes could be linked to all 7 sections of the ENAT, but predictive testing has not been part of the ENAT so far (last column of Table 3).

DISCUSSION

To our knowledge, this is the first study that provides insights about the experiences, values, and needs of people with arthralgia and asymptomatic individuals who underwent predictive testing for RA and had a positive test result. The results from the study show that predictive testing raises several ethical issues. All participants were informed about their risk of developing RA when receiving the test results. They also heard about RA-related symptoms that might occur in the future and whom to contact if such symptoms developed or if their current symptoms extended into the future. Nevertheless, and in accordance with the findings of Cornélis (39), participants in our study pointed out that they experienced a negative impact on their emotional well-being and that they were not well prepared for a possible positive test result. Participants with arthralgia in particular reported that they were frightened and worried. Although they had developed strategies to cope with this situation, they indicated that they would have preferred additional tailored information and support at the time when they were told that they had an elevated risk of developing RA. Clinicians should address the information and support needs identified in the current study by further developing effective, tailored education to support decision-making about whether to take a predictive test and to provide guidance and support for understanding and coping with test results (14,40).

Interestingly, insurance implications were only mentioned by 2 participants in this study; both were critical of the fact that preventive strategies were not paid for by their health insurance. Moreover, ethical issues, such as confidentiality of the given risk information, were not explicitly mentioned by any of the participants. Participants might have assumed that these tests fall under the legal requirements of data protection regarding health data and as such are strictly confidential. In contrast, some individuals with arthralgia had chosen not to talk about their risk for developing RA with their families and friends in order not to frighten them. These individuals decided to wait for tests with a higher degree of predictive accuracy before informing their loved ones. In 2 recent studies, researchers found that at-risk individuals had a strong preference for a predictive test that would rule future RA in or out with absolute certainty (23,41).

Despite the negative issues raised by the participants, only 2 regretted that they had been tested. However, arthralgia patients did not take an active decision to engage in predictive testing, but rather made a decision to seek medical help for their arthralgia, and the testing was a consequence of that decision. This knowledge might be of great importance when testing on a large scale and developing personalized, innovative preventive strategies in the next few years. Even if current evidence is limited to support both population-based screening programs and personalized individual predictive tests, the scenario may change significantly in the future (22,42). The desire to ensure that testing programs do not cause more harm than good has led to a considerable body of research on the psychosocial impact of predictive testing in adults for a range of conditions, including hereditary breast and ovarian cancer and Huntington's disease (43). In this sense, predictive testing for RA can also be seen as an important public health issue, with benefits for at-risk individuals themselves, clinicians, researchers, and the health system, if predictive testing were to be introduced into clinical practice and public health in a responsible manner combined with tailored information for all the persons concerned.

As the aim of our qualitative study was to explore a wide range of experiences, differences regarding the time between tests and the interviews were considered to be an advantage. Even if the time between being informed about the personal risk and being interviewed differed among the participants, the majority emphasized the advantage of knowing about their risk for developing RA. Being aware of their risk status would allow them to react appropriately and rapidly, if symptoms such as synovial joint swelling occurred. In accordance with the study results of Stack et al (23), exploring the perceptions of risk and predictive testing held by the first-degree relatives of patients with RA, some participants suggested that ongoing support by health professionals should be offered for those who have additional questions regarding their personal risk.

Another frequent topic was the question of effective preventive strategies that would be important to prevent the onset of RA. While some risk factors for RA related to lifestyle have already been identified (e.g., smoking), how most of the identified risk factors influence RA-related autoimmunity has not yet been fully clarified. Furthermore, risk factors may differ between individuals or groups of individuals and be influenced by sex and other personal and environmental factors (44). Participants in our study asked for activities that they could implement in daily life to reduce the risk of RA onset. Therefore, individuals need to be provided with more information about these present uncertainties. Individuals at risk need to know that still more data are needed before detailed environmental risk-factor modification and lifestyle changes, other than smoking cessation, can be recommended. Meanwhile, we could at least ensure that people at risk recognize the symptoms of disease development/progression and know where to go if such symptoms were to occur (4). European guidelines for the management of RA (45,46) highlight the importance of early treatment.

The strength of this study is that it represents a comprehensive exploration of the experiences, values, and needs of people who have undergone predictive testing for RA and had a positive test result by reaching data saturation in 3 centers/countries. However, 1 limitation of our study was the difficulty to recruit asymptomatic individuals with a positive test result. A selection bias might have occurred, since people who take part in an extended preventive health examination might be more interested in additional data about their own health than the average population. Furthermore, women were overrepresented in our study, because women were found to be more likely to sign up for health check-ups than men (47).

In conclusion, participants showed large differences in views about predictive testing in the context of RA risk and offered specific suggestions that should be incorporated into service design and delivery in the context of future predictive testing programs. These findings may also be relevant to prediction and prevention in the context of other diseases where multiple genetic risk factors interact with environmental risk factors to drive disease development.

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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. Stamm 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. Mosor, Stoffer-Marx, Steiner, Raza, Stack, Simons, Skingle, Dobrin, Schett, Englbrecht, Smolen, Kjeken, Stamm.
Acquisition of data. Mosor, Stoffer-Marx, Stack, Simons, Hueber, Stamm.
Analysis and interpretation of data. Mosor, Stack, Falahee, Skingle, Dobrin, Smolen, Stamm.

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Patient Perspectives on Smoking Cessation and Interventions in Rheumatology Clinics

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Objective. Although smoking is a risk factor for cardiovascular and rheumatic disease severity, only 10% of rheumatology visits document cessation counseling. After implementing a rheumatology clinic protocol that increased tobacco quitline referrals 20-fold, we undertook this study to examine patients' barriers and facilitators to smoking cessation based on prior rheumatology experiences, to solicit reactions to the new cessation protocol, and to identify patient-centered outcomes or signs of cessation progress following improved care.

Methods. We recruited 19 patients who smoke (12 with rheumatoid arthritis [RA] and 7 with systemic lupus erythematosus [SLE]) to participate in 1 of 3 semistructured focus groups. Transcripts of the focus group discussions were analyzed using thematic analysis to classify barriers, facilitators, and signs of cessation progress.

Results. Participant-reported barriers and facilitators to cessation involved psychological, health-related, and social and economic factors, as well as health care messaging and resources. Commonly discussed barriers included viewing smoking as a crutch amid rheumatic disease, rarely receiving cessation counseling in rheumatology clinics, and very limited awareness that smoking can worsen rheumatic diseases or reduce efficacy of some rheumatic disease medications. Participants endorsed our cessation protocol with rheumatology-specific education and accessible resources, such as a quitline. Beyond quitting, participants prioritized knowing why and how to quit as signs of progress outcomes.

Conclusion. Focus groups identified themes and categories of facilitators/barriers to smoking cessation at the levels of patient and health system. Two key outcomes of improving cessation care for patients with RA and SLE were knowing why and how to quit. Emphasizing rheumatologic health benefits and cessation resources is essential when designing and evaluating rheumatology smoking cessation interventions.

INTRODUCTION

Smoking is a leading risk factor for cardiovascular disease (CVD) incidence and rheumatic disease severity (1–3). Recognizing that rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) increase the risk of premature CVD (4,5), the European League Against Rheumatism and other experts recommend smoking cessation care for rheumatology patients (6–9). Despite smoking cessation treatment recommendations, only 10% of rheumatology visits with patients who smoke included documentation of cessation counseling or follow-up advice (10). In the US, where annual specialty visits nearly equal primary care visits (11), ~70% of RA visits occur in specialty clinics (12), and many patients identify their rheumatologist as their main doctor (13). Both the central role of rheumatology clinics and the increased risk of CVD among patients with rheumatologic disease highlight the critical need to address smoking during rheumatology clinic visits to reduce smoking-related morbidity and mortality. Although many forms of inflammatory arthritis, including ankylosing spondylitis and psoriatic arthritis, are also associated with an

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SIGNIFICANCE & INNOVATIONS

- Patients with rheumatoid arthritis and systemic lupus erythematosus reported that better understanding the negative effects of smoking on rheumatic disease and its treatment would motivate them to quit smoking.
- Patients who smoke requested point-of-care advice in rheumatology clinics on smoking cessation strategies and connections to cessation resources like tobacco quitlines, a free resource in all states.
- Emphasizing the rheumatology-specific why and the resource-specific how of smoking cessation is important when designing and evaluating smoking cessation interventions for use in rheumatology clinics.

increased risk of CVD, associations between smoking, CVD, RA, and SLE have been studied extensively and may be more profound (14). We therefore focused on RA and SLE, building upon our prior work with these populations (5,13).

In addition to increasing CVD risk, smoking predicts both higher RA and SLE disease activity and lower treatment responses (1). Patients with RA who smoke require more disease-modifying antirheumatic drugs (15) and are less likely to respond to methotrexate and tumor necrosis factor inhibitors than those who previously smoked or never smoked (16,17). Patients with SLE who have a history of smoking have higher disease activity (18) and higher chronic damage index scores (1) than those without a history of smoking. Likewise, data show that, among patients with SLE who smoke, cutaneous disease is more prevalent (19) and less treatable with hydroxychloroquine (20,21). Smoking is also associated with higher levels of RA- and SLE-associated inflammatory cytokines (22,23). Despite these links between smoking and rheumatic disease activity, smoking rates among patients with RA or SLE may be as high as 30%, significantly exceeding the national smoking rate of 15.1% (24–26).

As a leading modifiable risk factor for both CVD and rheumatic disease severity, smoking is a critical target to improve health in populations with RA and SLE. With this target in mind, we previously implemented a clinic protocol called Quit Connect that sought to connect patients from 3 academic rheumatology clinics to the state tobacco quitline for free coaching and 2 weeks of nicotine replacement. The protocol steps consisted of the following: 1) check: documenting smoking status and smokers' readiness to quit, 2) advise: counseling on the link between smoking and worsened rheumatic disease, and 3) connect: offering an electronic referral to the tobacco quitline. The Quit Connect protocol increased quitline referrals 20-fold, but not all who were ready to quit accepted or completed the referral process. Given the benefits of stakeholder engagement in tailoring effective interventions (27), we sought patient feedback on our approach. We organized focus groups to gather and incorporate the perspectives of patients with RA and SLE who smoke. The objectives of this study were to examine patients' barriers and facilitators to smoking cessation based on prior rheumatology experiences, to solicit reactions to the new cessation protocol, and to identify patient-centered outcomes or signs of cessation progress following improved care.

PATIENTS AND METHODS

Study sample. In 2016, using flyers and targeted letters, we recruited 19 adult patients (12 with RA and 7 with SLE) from 2 health systems to participate in 1 of 3 focus groups about smoking cessation. Inclusion criteria included having a diagnosis of RA or SLE, seeing a rheumatologist within 1 of the 2 health systems, and having a recent history of daily smoking. Initial criteria included being a current smoker or being a smoker who recently quit; the criteria were narrowed to only current smokers after the first focus group to maximize participation by current smokers. Recruitment of men (who are less likely to have RA or SLE) and patients from racial or ethnic minorities was prioritized to ensure a diverse representation of patients. To support inclusion of a predominantly Spanish-speaking patient, a family member served as an interpreter. All focus group participants received honoraria. Given that the third focus group did not raise any new issues, we concluded data gathering at that point (28).

The institutional review board certified this work as a quality improvement and program evaluation, granting a waiver of individual informed consent and permission to publish. Participants self-described their demographics during recruitment calls and provided verbal consent for audio recordings at the time of the focus groups.

Data collection. Two experienced focus group facilitators (AGB and JS) led 1-hour focus groups using a semistructured interview guide that addressed 3 main topics. Part 1 explored patients' experiences of barriers and facilitators within conversations, or lack thereof, about CVD risk and smoking cessation at their rheumatology clinics, specifically eliciting preferred versus nonpreferred aspects of cessation care. Part 2 elicited feedback on a short video demonstrating the new Quit Connect protocol, where the rheumatology nurse or medical assistant asked about the patient's readiness to quit and offers an electronic referral to the state tobacco quitline (video at https://vimeo.com/212653671). The final segment identified and prioritized patient-centered outcomes that might occur as a result of the protocol. To facilitate participants' understanding, we referred to these patient-centered outcomes as signs of progress toward smoking cessation. We investigated these patient-centered outcomes by providing a worksheet for participants to react to and rank potential outcomes based on importance and by facilitating an open discussion on other potential outcomes. The worksheet listed themes from common validated measures related to smoking cessation,

including Patient-Reported Outcomes Measurement Information System negative health expectancies (29), the US Adult Tobacco Use Survey (30), Processes of Change Questionnaire (31), Health Attitudes Survey (32), and other sources (33–38). At the first 2 focus groups, facilitators asked participants to rate each outcome on a 4-category scale from "not at all important" to "very important." Consistent with the dynamic nature of qualitative research, we asked participants at the third focus group to circle the 3 most important outcomes in order to overcome the ceiling effects observed in prior group evaluations.

Statistical analysis. Focus groups were audio recorded and transcribed verbatim. Given that the primary objective of the study was to describe participant perspectives, we first identified relevant text on smoking cessation, the new protocol, and patient-centered outcomes. Codes (meaning units labeled in text) were subsequently organized into categories, subcategories, and finally themes using the well-established thematic analytic techniques outlined in Braun and Clarke (39) to enable more comprehensive identification of salient patterns in patient preferences and experiences. Consistent with thematic analysis methods, 2 trained coders (AW and LB) reviewed and independently coded all data using NVivo software, version 11 (QSR International). Disagreements were rectified by a third reviewer (CMB) who also oversaw the coding scheme. The coding scheme was informed by prior qualitative work on cardiovascular prevention and clinic-based care delivery (13) from rheumatology patient and provider interviews and new codes based on current participant data. A detailed summary of the coding scheme is available in Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23858/abstract. Themes and categories were identified through collaborative review of the initial coding and examination of patterns across participant experiences and interrelationships between salient codes. Each theme was reviewed by all team members for consistency with collated categories and accompanying participant data to inform any needed refinements and ensure clarity and specificity in the definition of each theme (39). Consistent with the aims of this project, coders identified participant-reported facilitators and barriers, which were grouped as factors that contribute to quitting or not quitting, and themes to derive patient-centered outcomes regarding smoking cessation support.

Throughout the study, we applied established approaches to ensure rigor in qualitative analysis, including the use of multiple coders, triangulation between data sources, use of an interdisciplinary research team to review and inform analysis, and member checking (40). To conduct member checking, an approach well-supported in the medical literature (40), we shared results with focus group participants to allow them to review findings for accuracy.

Participant-rated, potential patient-centered outcomes from worksheets were analyzed using basic descriptive statistics. Weighted and ranked responses were combined using a point-based system to determine which outcomes were strongly, weakly, or not endorsed. These values were assigned based on the number of participants endorsing each outcome, the priority rankings in the final group, and triangulation with discussion transcripts.

RESULTS

Overall, 89% of focus group participants were female, consistent with the epidemiology of RA and SLE. Ages ranged 33–72 years, 58% were white and 42% African American, and 11% reported Hispanic ethnicity (Table 1). When discussing past experiences with smoking, cessation, and cessation treatment in rheumatology

Table 1. Characteristics of focus group participants*

	Focus group 1 (n = 6)	Focus group 2 (n = 5)	Focus group 3 (n = 8)	Total no. (%) (n = 19)
Age group, years				
18–39	1	0	1	2 (11)
40–49	1	2	1	4 (22)
50–59	2	1	5	8 (42)
≥60	2	2	1	5 (26)
Sex				
Female	6	5	6	17 (89)
Male	0	0	2	2 (11)
Race				
White	3	5	3	11 (58)
African American	3	0	5	8 (42)
Hispanic ethnicity	0	1	1	2 (11)
Condition				
RA	4	3	5	12 (63)
SLE	2	2	3	7 (37)

* Values are the number unless indicated otherwise. RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

clinics, participants reported personal and health system barriers and facilitators that were organized into 5 themes, each supported by several categories and subcategories (Tables 2 and 3).

Personal barriers and facilitators to smoking cessation. Participants identified psychological factors, health effects, and social and economic costs as either personal barriers or facilitators to smoking cessation (Table 2).

Theme 1: Psychological factors influence smoking and cessation. Common psychological barriers included the desire to maintain a sense of control, the use of smoking as a coping mechanism, and a history of addiction to tobacco and other substances. Many viewed smoking as "a crutch," "a comfort," and "the one thing I still have control over" while dealing with the burden of rheumatic disease, social and economic strain, and other stressors. Some participants reported that smoking helped them deal with family loss and trauma. Others referred to addiction as a barrier, mentioning withdrawal or psychological dependence concerns; one participant reported, "It's like taking away your friend." One participant expressed reluctance to try nicotine replacement therapy for fear of "giving up cigarettes to become addicted to another form of nicotine."

Theme 2: Visible health effects influence cessation desire. A commonly noted facilitator for cessation was the way in which visible negative health effects of smoking could provide motivation to quit. One participant reported, "In the last 3 months I could see and feel a difference in me, where I'm out of breath and wheezing… it's scaring me now." Another participant similarly identified negative health effects as a motivator to quit smoking, saying, "[I] don't know what's being caused by the lupus and what [are] side effects from this buffet of medications I take and if smoking is impacting that in any way…." One participant reported feeling motivated to quit when her primary care doctor said that doing so would allow her to go off her blood pressure medication.

Theme 3: Social and economic costs exist for both smoking and cessation. Other facilitators to cessation, although less commonly discussed, included the desire to minimize the costs of cigarettes, social stigma, and the smell of smoke. Several participants were motivated to cut down around family, and one was motivated to smoke less in winter to avoid the outdoors.

Table 2. Personal barriers and facilitators to smoking cessation*

Themes/categories	Barriers	Facilitators
Theme 1: psychological factors influence smoking and cessation		
Autonomy and control	"I've been through a lot… and I gave up a lot, and it's just like my last bastion."	"The times I've been successful in quitting was when I was pregnant, because I wasn't quitting for myself. It was different."
Coping and comfort	"What I find hard is every day, when you get up in pain, and you go to work, you have to put this persona on: I'm a happy person, life is good. And you get out there and you show the world that you're fine; you're not sick. And then that cigarette is the break that allows you to get through it."	"They say… forget that urge, find something else to distract you… Whatever you enjoy doing, do that… Like I play guitar so I just start playing the guitar and forget all about a cigarette."
Addiction	"Most of me really wants to quit smoking, but a pretty good-sized part of me is just like, 'Why'?! It's a horrible addiction."	"I *want* to not smoke at all, it is very important to me."
Theme 2: visible health effects influence cessation desire		
Burden of disease	"I've tried habit change, and I don't know how many scarves I've knitted and crocheted. I can't keep doing that [smoking], because I was getting so bad; my hands from my [RA] were hurting."	"I've been so sick. I'm on so many medications, so many things in my life would be so much easier and better [if I quit]."
Physical complications of smoking	"I think it's hard for me because one, I don't feel the effects of it, like I don't have shortness of breath, I don't get winded. I don't… it's just something that I do."	"I know I have to quit because I'm having shortness of breath, my heart is jumping all around inside my chest; it's scary, you know? It's scary."
Theme 3: social and economic costs exist for both smoking and cessation		
Convenience and cost	"All you see at [the store] is the $100 plus… for [nicotine replacement therapy brand]." "Well heck, my cigarettes are cheaper!"	"I'm outside [when I smoke]. So I tend to cut down a little in the winter. Seriously, I don't smoke [as much] because it's so stenchy."
Social pressure and stigma	"I've always smoked and everybody I know smokes; it's just a thing."	"My daughter has implemented a 'no smoking' [rule]. Her house is 'no smoking'. [She says] 'So mom, if you want to smoke you have to go outside'." "You're a leper."

* RA = rheumatoid arthritis.

Table 3. Perceived health system smoking cessation support in rheumatology clinics and responses to Quit Connect protocol*

Themes/categories	Barriers/nonpreferred	Facilitators/preferred
Theme 4: clinic's staff and provider approach and message matter		
Discussing smoking, quitting, and cutting back	"Every time I go to my appointment they do the questionnaire: 'You still smoking cigarettes'? 'Yes'. 'OK'. And that's it… [It feels] like they don't give a hoot!"	"I think it's scary to think of quitting. I think it's less scary to think of cutting back or making changes."
Patient relationship and familiarity	"But we're mostly talking to a nonsmoker… I mean I knew a few [doctors] that smoked, but for the most part, they're nonsmokers; they can't relate to us trying to quit."	"[My rheumatologist] is very supportive… She gives me [strategies] and just reminds me that I can do it." "I got to 2 cigarettes a day, and [my rheumatologist] was happier than I was."
Offering control and choice	"People forget that it's really your life, and it's really your decision, and there's no embarrassment or shame whether you [quit] or not… But I think sometimes doctors inadvertently feed into that with the tone they take."	"You have to feel like you can do something before you can start to do it. It's not helpful for [doctors] to just give you the directive of quitting smoking. It's helpful for them to help you feel like you have action steps… giving you tools and ideas."
Providing resources and tips for quitting	"Everybody just says 'quit, quit, quit'!… It just keeps feeling like they want to take something away without offering you any alternatives."	"It would be helpful if they suggested other things you could do… find out what you like to do, what habit you might be able to replace it with."
Theme 5: cessation resources and health risk education are valuable but lacking		
Quitline	"With the Quitline, you get somebody [new] every time you call. You have to explain it over and over and over and over again."	"I've used the Quitline, and I find it works very well… Most of those people are actually former smokers, and they'll tell you how long they stopped smoking for, and I find that very helpful."
Coverage for medications	"I requested from my primary doctor and my rheumatologist to put me on [medication], and they said that my health care doesn't cover that."	"The word's got to get out that your insurance covers [nicotine replacement therapy], because [I had] no idea."
Health information	"I know how bad it is…What I don't understand is *why* it's necessarily bad." "I knew [smoking] affected me, but I didn't know it changed the [RA/SLE] drugs."	"I didn't have any idea that it [smoking] changed how the [RA] medications work. Because the medications are super expensive, and there's always days when you wish it was working better, so if I'm inhibiting that [by smoking], then I need to take that into consideration."

* RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

However, costs for cessation products were a barrier to cessation as well.

Preferences for health system cessation support and feedback on cessation protocol. *Theme 4: Rheumatology clinic's staff approach and message matter*. Participants reflected on prior experiences with cessation support at rheumatology clinics and then viewed the Quit Connect protocol video to initiate discussion on preferred and nonpreferred approaches (Table 3). Several participants reported that rheumatologists and rheumatology staff often asked about smoking status, but few reported receiving counseling. Of those who had received counseling, most appreciated information on the rheumatology-specific negative health effects of smoking, which would, as one participant observed, "Put it on my mind and…give me something to think about." Some participants viewed omission of cessation support as a sign of not caring, as one participant noted, "Like they don't give a hoot," while others appreciated not being "harped on." However, participants agreed that rheumatology staff must find a balance between broaching the topic intentionally and providing a nonjudgmental space to discuss cessation-related challenges and goals.

Many reported that knowing more about the effects of smoking specifically on rheumatic disease and treatment would be a key motivator to quit. Most reported being previously unaware of the amplified health risk of smoking for people with RA and SLE. Few were aware of the physiological impact that smoking has on rheumatic diseases, and none had heard that smoking can reduce the efficacy of rheumatic disease medication. Participants also cautioned against vague health warnings from rheumatologists or staff. As one participant said, "I mean, we do all understand it's not good for us."

Several participants expressed that phrasing or language can be a barrier to useful conversations in clinics about smoking cessation. Participants endorsed the use of flexible terms like "cutting down" as opposed to strictly "quitting." One participant reported, "When somebody just says, 'You can never have this again', I wish they'd have some options." Another agreed that the word "quit" can feel overwhelming, whereas "cutting down" is more inviting and manageable. Some mentioned their nurse's or provider's inability to relate to tobacco addiction or to provide specific tips or resources at appointments. One participant reported, "Everybody just says, 'Quit, quit, quit!'," to which

another responded, "I hate when they say that because they don't give you a solution."

Some participants also provided examples of effective ways that providers have supported cessation among patients who smoke. One participant said, "It depends on how invested they are in you," explaining that her rheumatologist took the time to discuss day-to-day steps for smoking less and enthusiastically celebrated the goals she accomplished. Participants agreed that receiving sincere encouragement and discussing tangible strategies in clinics, especially with those who have personal smoking cessation experience, would greatly facilitate an attempt to quit.

Theme 5: Cessation resources and health risk education are valuable but lacking. Participants responded positively to the new Quit Connect protocol, affirming that assessing readiness to quit, discussing smoking risk in rheumatic diseases, and offering resources to quit were valuable practices in rheumatology clinics. Several had never heard of the quitline and did not know that it would send smokers free nicotine replacement for 2 weeks; most expressed that they would appreciate being offered a quitline referral at their rheumatology appointments. Many were unaware that most health insurance covers nicotine replacement. As one patient said, "The word's got to get out that your insurance covers [nicotine replacement therapy] because [I had] no idea." Participants felt that information on insurance coverage should be readily shared at appointments, supporting the use of the protocol talking points. One participant praised the Quit Connect protocol and details provided in the video vignette and then stated, "It's sad because nobody does that."

Patient-centered outcomes or signs of progress toward cessation. In our final segment, participants individually reviewed and then discussed a list of patient-centered outcomes of improved cessation care (what we referred to as signs of progress toward cessation) on the preestablished questionnaire list. Eight of 9 items were endorsed by participants to varying degrees as important aspects of their cessation journey (Table 4). Throughout the focus groups, nearly all participants rated cutting down or quitting smoking as an important outcome, and nearly all wanted to quit eventually. Participants also valued the ability to move at their own pace and set their own goals when working toward cessation. As one participant reported, "I'm not in control of much in my life because of pain, but I like to say that [smoking cessation] is something…I can make my own decision on." Several new signs of progress were discussed. For example, many described wanting to quit as a crucial sign of progress toward cessation. One participant stated that being able to successfully withstand a craving would be an important step in their journey. Others agreed and added that learning strategies or identifying alternative activities (e.g., chewing gum, drinking water) would be valuable outcomes.

Many emphasized the importance of receiving support from people who were familiar with their situation, either those who had personal experience with smoking, or those who lived with RA or SLE. Participants valued support from those who could relate across various contexts, such as clinical support (e.g., rheumatologists, nurses/medical assistants), public services (e.g., quitline staff), or support groups (e.g., others who smoke and/or have RA or SLE). Despite explaining during recruitment that a focus group was different from a support group, numerous participants avidly endorsed having more "groups like these, [where] everyone can relate to each other."

Beyond smoking cessation itself, the 2 new outcomes that participants reported as most valuable were knowing that smoking can exacerbate rheumatic diseases and reduce medication efficacy, and knowing how to find resources to make changes to smoking behavior. As one patient stated, "What I don't understand is why it's necessarily bad [i.e., smoking with RA/SLE]… I would like to know that." These overarching valued outcomes of knowing why to quit (specifically in RA or SLE) and how to quit (e.g., covered resources, day-to-day strategies for cravings) arose throughout all sections of the focus group discussions.

Table 4. Endorsed and suggested patient-centered outcomes or signs of progress*

Strongly endorsed by patients
Smoking less or quitting for good†
Knowing that smoking makes RA/SLE worse and makes medications not work as well
Knowing how to find resources that can help me change my smoking (quitline, medications, etc.)
Being able to set my own goals and pace when changing my smoking
Having someone [familiar, relatable†] I can talk to in my clinic about changing my smoking
Wanting to quit†
Knowing strategies to quit (alternatives to smoking, day-to-day distractions, etc.)†
Making it through a craving without smoking†
Moderately endorsed by patients
Knowing that RA/SLE add risk for heart disease or stroke
Feeling like I can make changes to my smoking
Making an attempt to change my smoking habits

* RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.
† Not a preestablished outcome; added by focus group participants.

DISCUSSION

We sought to examine experiences of barriers and facilitators to smoking cessation care in RA and SLE because of known connections between smoking and worsened rheumatologic and cardiovascular outcomes and gaps in cessation care (10). We found that barriers to cessation in the rheumatology clinic population are both similar to and different from those in the general population. We also found that despite health care aims to promote cessation, patients often received no cessation counseling, and they valued additional outcomes like knowing the health risks specific to rheumatic diseases and resources for taking steps toward cessation, such as a quitline. We can use the knowledge gained to better

design and implement smoking cessation interventions, such as our Quit Connect intervention, in rheumatology clinics.

Focus group participants with RA and SLE reported various psychological, health, social/economic facilitators and barriers to smoking cessation that are widely supported by previous research. A UK study on smoking cessation found that prospects of improved health and financial benefit were motivators to quit smoking but were often outweighed by the fear of losing a coping mechanism (41), which is consistent with ideas from our focus group participants. A 2015 Australian study (42) discussed barriers to cessation with 36 patients with RA who smoked. The patients identified not understanding the health risks of smoking with RA and isolation from other patients with RA as a barrier, and participants expressed interest in RA support groups, all of which were echoed by our participants. They also reported emotional attachment to smoking, echoing our own participants who compared quitting to "losing a good friend." Another study (43) of SLE patients found similar psychological barriers and lack of awareness of smoking's health impact on SLE and SLE treatment. Given the barriers and facilitators identified by our study and others, it is essential that efforts to promote cessation address the psychological factors, rheumatology-specific health-related factors, and social and economic factors that influence smoking behavior.

Our focus group participants responded positively to our new Quit Connect protocol. Although most participants reported never having explicit conversations about smoking with their rheumatologists or clinic staff, they thought such conversations would be highly beneficial. They agreed that assessing readiness to quit or cut back and discussing resources like a quitline and insurance coverage for cessation therapies were valuable. Most said they would appreciate being offered a referral to a quitline, and they considered our Quit Connect intervention to be an effective approach to connect them to quitline services.

Two nonrandomized studies reported positive benefits of RA-specific cessation efforts (44,45), but a randomized study showed no significant difference in quit rates when comparing tailored RA-specific to nontailored cessation care (46). This suggests that providing cessation treatment, even if it is not tailored to diagnosis, is a powerful intervention. Another study confirmed that a clinic protocol to refer patients with SLE to a general cessation clinic increased reported rates of quitting and cutting back (47). Future intervention research should evaluate approaches to engage patients at rheumatology clinics with point-of-care advice to connect them with existing cessation resources.

In addition to endorsing 8 of 9 measures of smoking cessation and reduction as valuable outcomes of improved cessation care, participants strongly endorsed steps before actually quitting as signs of progress. For example, participants stated that wanting to quit is a valuable outcome, which supports our protocol step assessing readiness to quit. Findings identified 2 key desired outcomes of smoking cessation support in rheumatology clinics: understanding the specific health risks of smoking in relation to rheumatic disease, and knowing tangible steps to take toward quitting. In other words, patients reported that knowing why and how to quit were key signs of progress. Knowing specific risks, including the fact that smoking can make RA and SLE worse or make medications not work as well, was endorsed by participants as a strong motivator to quit and therefore a valuable outcome. Likewise, participants requested specific advice and assistance on steps for how to cut back or quit. Therefore, emphasizing the why and the how of smoking cessation is essential when designing and evaluating outcomes of rheumatology smoking cessation interventions.

Reports from the few other qualitative studies on smoking in RA and SLE support our findings regarding the importance of knowing why and how to quit. In the Australian RA study (42) and the SLE study (43), a lack of health information prevented participants from understanding why it is important to quit, as we heard in our focus groups. A UK group (34) found that experiencing a known smoking-related disease was an effective motivator to quit and thus sought to raise awareness that RA is a smoking-related disease using campaign posters and national newspaper advertisements in Scotland. Following the campaign, they observed a 45% increased awareness of smoking's effect on RA treatment. They also reported a 14% increase in smokers who were considering quitting, supporting the notion that awareness of rheumatology-related health consequences can motivate cessation. Our participants felt that this information should be shared at appointments, supporting protocol talking points on how and why to quit.

Despite diverse participant engagement from 2 health systems, we acknowledge limitations. Although the third focus group did not raise any new issues, participation was voluntary, and self-selection among participants eager to talk about cessation may not reflect all perspectives. In the future, intervention development and evaluation research should engage patients who smoke from more diverse settings.

In conclusion, our focus group identified 5 themes, along with relevant categories and subcategories, of personal and health system barriers and facilitators to smoking cessation, as well as 2 key outcome signs of cessation progress in patients with RA and SLE. Emphasizing both the why (i.e., rheumatologic health benefits) and the how (i.e., cessation resources) is important when designing rheumatology smoking cessation interventions and evaluating outcomes. Our Quit Connect protocol that connects patients to a state quitline was well received, and future studies should evaluate this and other approaches in rheumatology clinics to support cessation.

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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. Bartels 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. Wattiaux, Bettendorf, Block, Gilmore-Bykovskyi, Ramly, Piper, Rosenthal, Sadusky, Cox, Chewning, Bartels.

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Analysis and interpretation of data. Wattiaux, Bettendorf, Block, Gilmore-Bykovskyi, Ramly, Cox, Chewning, Bartels.

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Men and Women's Occupational Activities and the Risk of Developing Osteoarthritis of the Knee, Hip, or Hands: A Systematic Review and Recommendations for Future Research

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Objective. To systematically review the evidence for an increased risk of osteoarthritis in the hip, knee, hand, wrist, finger, ankle, foot, shoulder, neck, and spine related to diverse occupational activities of men and women and to examine dose-response information related to the frequency, intensity, and duration of work exposures and the risk of osteoarthritis (OA).

Methods. Established guidelines for systematic reviews in occupational health and safety studies were followed. MEDLINE, Embase, CINAHL, and Cochrane Library were searched from inception to December 2017. Studies were reviewed for relevance, quality was appraised, and data were extracted and synthesized.

Results. Sixty-nine studies from 23 countries yielded strong and moderate evidence for lifting, cumulative physical loads, full-body vibration, and kneeling/squatting/bending as increasing the risks of developing OA in men and women. Strong and moderate evidence existed for no increased risk of OA related to sitting, standing, and walking (hip and knee OA), lifting and carrying (knee OA), climbing ladders (knee OA), driving (knee OA), and highly repetitive tasks (hand OA). Variability in dose-response data resulted in an inability to synthesize these data.

Conclusion. Evidence points to the potential for OA occupational recommendations and practice considerations to be developed for women and men. However, research attention is needed to overcome deficits in the measurement and recall of specific work activities so that recommendations and practice considerations can provide the specificity needed to be adopted in workplaces.

INTRODUCTION

Osteoarthritis (OA) ranks among the top 10 causes of disability world-wide and is associated with significant pain, stiffness, fatigue, and activity limitations (1–5). Although medical treatment often occurs in later stages of the disease, early intervention is increasingly recognized as a critical unmet need. One domain of importance for education and intervention is the workplace. To date, numerous studies have examined the relationship of physically demanding occupations like farming, mining, and floor laying, as well as work activities like kneeling, squatting, and heavy lifting to the onset of OA (6–16).

Also creating impetus for greater attention to the workplace is the aging of workforces and policy changes in many countries that push for longer employment trajectories (17–19). A longer work life increases the duration of exposure to work activities that may create risks for OA development. Older workers also may be at greater risk for workplace musculoskeletal injuries than younger workers (20), which can increase the likelihood of developing OA (21). As a result, workplace regulators and insurers are increasingly

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SIGNIFICANCE & INNOVATIONS

- A synthesis of 69 studies from 23 countries yielded strong and moderate evidence for lifting, cumulative physical loads, full-body vibration, and kneeling/squatting/bending as increasing the risks of developing osteoarthritis (OA) in men and women.
- Strong and moderate evidence existed for no increased risk of OA related to sitting, standing and walking (hip and knee OA), lifting and carrying (knee OA), climbing ladders (knee OA), driving (knee OA), and highly repetitive tasks (hand OA).
- Greater attention is needed to improve measures assessing employment activities and recall periods.
- A lack of consistency in dose-response information makes synthesizing data problematic and hinders practical recommendations.

seeking guidance, not only about specific types of work activities that may be problematic, but also about dose-response thresholds that can illuminate the frequency, intensity, and duration of job activities and their association with the development of OA. To date, few jurisdictions provide work disability compensation for job activities that may have resulted in OA disability (22). A focus on specific activity types (e.g., squatting), as opposed to broad occupational categories (e.g., farming) and dose-response information is needed by regulators to make informed decisions.

By going beyond occupational categories and identifying job activities and dose-response thresholds that may increase the risk for OA, we can inform occupational health and safety practices focused on earlier recognition of problematic work activities and the development of new strategies and interventions to prevent occupationally related OA. We can also identify subgroups of workers who may be particularly vulnerable to occupationally related OA. For example, some studies report sex (i.e., biologic) differences related to the development of OA in some joints (e.g., knees, hands), while others report gender effects (i.e., differences in social roles) related to the occupations of women and men that may signal differences in the likelihood of developing OA (23–26). However, assessing sex/gender differences in OA development has been hampered by less available data from women (27).

Several excellent reviews of the literature have examined occupational factors and OA (6–12,14–16,27). Most have focused on knees or hips, with less attention to other joints, differences between men and women, and dose-response data. The synthesized evidence has often been limited or moderate. To update and better target the available information, this systematic review focused on specific occupational activities and their relationship to OA of the hip, knee, hand, wrist, finger, ankle, foot, shoulder, neck, and spine. We synthesized study findings for men and women separately where possible and examined dose-response information to identify potential thresholds related to the frequency, intensity, and duration of work exposures and the associated risk of developing OA.

MATERIALS AND METHODS

Search strategy and relevance. We followed established guidelines for systematic reviews in occupational health and safety studies (28,29). Search terms were developed iteratively in consultation with a librarian, content area experts, and stakeholders. We searched MEDLINE, Embase, CINAHL, and Cochrane Library from inception to December 31, 2017. All English, peer-reviewed literature was included. The complete list of terms is shown in Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23855/abstract. References were managed using DistillerSR software (30), which enables screening, quality appraisal, and data extraction of study material.

Articles were included if the research was about OA and if OA was distinguishable from other conditions and diagnosed by a clinician (including self-report of a clinician diagnosis), if the research focused on paid employment activities and their potential impact on the development of OA, and if it was an original quantitative research study. In keeping with previous reviews on this topic, we included longitudinal, observational, cohort, cross-sectional case–control, and intervention studies. Where possible, we extracted data separately for men and women.

All authors participated in the review. Titles and abstracts were screened by a single reviewer after all reviewers came to a consensus on a set of titles and abstracts. Subsequently, the remaining full-text articles were screened using inclusion/exclusion criteria, with 2 authors independently reviewing each article and coming to a consensus. If a consensus could not be reached, a third author was consulted.

Quality appraisal. Relevant articles were appraised for their reported methodologic quality using 17 criteria, assessing the study design and objectives, sample/recruitment, study characteristics, outcomes, and analyses (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23855/abstract). Scores were calculated based on previous research that developed weighted criteria for each question (1 = somewhat important, 2 = important, and 3 = very important) (31). Studies scoring ≥85% in quality were ranked as high quality. Studies scoring between 50% and 84% were classified as medium quality and scores of <50% were deemed lower quality (31). Only medium- and high-quality studies were synthesized.

Data extraction and evidence synthesis. Standardized forms were used for data extraction. We documented sample sizes, the direction and significance of the relationship between work exposures and an OA diagnosis, and information about potential covariates. Data were sorted by the anatomical joint affected by OA. Evidence synthesis considered the quality, quantity, and consistency of findings (Table 1). A strong level of evidence

Table 1. Evidence synthesis algorithm*

Level of evidence	Minimum quality†	Minimum quantity	Consistency	Strength of message
Strong	H	3	3H agree; if ≥3 studies, ≥3/4 of the M + H agree	Recommendations
Moderate	M	2H or 2M + 1H	2H agree or 2M + 1H agree; if ≥3, ≥2/3 of the M + H agree	Practice considerations
Limited	M	1H or 2M or 1M + 1H	2 (M and/or H) agree; if ≥2, >1/2 of the M + H agree	Not enough evidence to make recommendations or practice considerations
Mixed	M	2	Findings are contradictory	Not enough evidence to make recommendations or practice considerations
Insufficient‡	–	–	–	Not enough evidence to make recommendations or practice considerations

* H = high; M = medium.
† High = score >85% in quality assessment; medium = score ranges from 50% to 84% in quality assessment.
‡ Medium quality studies that do not meet the above criteria.

reflects the potential for making recommendations and consists of a minimum of 3 high-quality studies that agree in their findings. A moderate level of evidence (a minimum of 2 high-quality studies or 2 medium-quality studies plus 1 high-quality study) points to possible practice considerations. For evidence scored lower than moderate, we lack evidence to guide policies or practices. This consideration does not mean that work exposures were not significantly associated with OA, only that evidence was insufficient to draw conclusions.

Due to the heterogeneity of outcome measures, study designs, and reported data, we did not calculate pooled effect estimates. If a study stratified the analyses by men and women separately and combined them, we only synthesized the stratified analyses. If a study did not stratify analyses by sex, the combined data were synthesized. There are no standardized criteria in the OA and work literature to evaluate dose-response levels. Hence, we extracted all dosage levels and reviewed the data for minimum thresholds where findings were associated with increased risks of OA versus no effect.

RESULTS

A total of 4,134 references were identified after removing duplicates (Figure 1). Relevance screening excluded 3,701 articles after title and abstract review and a further 321 articles upon full article review. Excluded studies often focused on OA's impact on work (e.g., absenteeism, productivity loss), the work of health care professionals managing OA, and the development of OA in working animals (e.g., dogs, horses). Quality appraisal was conducted on the resultant 112 articles, and data were synthesized from 69 unique studies appraised as medium quality (n = 30) or high quality (n = 39) in their reported methods.

Study characteristics are shown in Table 2. Research originated in 23 countries, with two-thirds of studies (65.2%) comprising samples of >500 respondents. Studies examined OA in knees (n = 41), hips (n = 28), wrists/hands/fingers (n = 14), spine (n = 6), shoulder (n = 5), ankles/feet/toes (n = 4), necks (n = 3), and elbows (n = 3). Study designs included retrospective cohorts (n = 10), prospective cohorts (n = 14), case–control studies (n = 22), and cross-sectional studies (n = 23). Samples were drawn from census, tax, or disability records (n = 38), surgical wait lists/hospital charts (n = 15), community advertising (n = 4), and occupational groups (e.g., dock workers) (n = 12).

Measurement of OA. Assessment of OA was rated as valid and reliable in 97% of the studies, with many studies using multiple methods to determine OA (e.g., radiographic evidence and clinical examination). OA was measured using radiographic

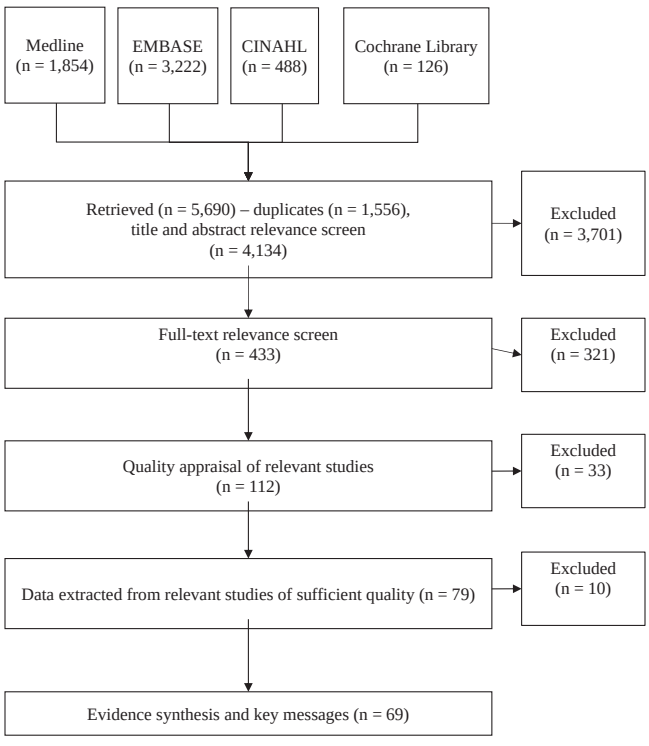

Figure 1. Summary of literature search.

Table 2. Summary of study characteristics*

First author, year (ref.)	Country	Study design (quality)	Sample type	Joints with OA	OA diagnosis	Industry	Work activities	Work history	Sample (no., % male, mean ± SD age [when given] years)
Allen, 2010 (32)	US	Cross-sectional (M)	Comm.	Hip, knee	Radiograph, other	Multiple	Walking, lifting, carrying, moving objects, sitting, standing, bending, twisting, reaching, kneeling, squatting, climbing, crawling, crouching, heavy work while standing	Work lifetime	Total: n = 2,729, 34.2%, 63.3
Amin, 2008 (33)	US	Retrospective cohort (M)	Clin.	Knee	ACR diagnostic criteria	Multiple	Squatting, kneeling, heavy lifting	Work lifetime	Occ. 1 (heavy lifting): n = 40, 100%, 69 ± 9; occ. 2 (squatting/ kneeling, heavy lifting): n = 47, 100%, 64 ± 9; occ. 3 (neither 1 or 2): n = 98, 100%, 70 ± 9
Andersen, 2012 (23)	Denmark	Retrospective cohort (M)	Pop.	Hip, knee	ICD codes	Multiple	Occ. type	Work lifetime	Total: n = 2,117,298, 48.0%, 38
Anderson, 1988 (34)	US	Cross-sectional (M)	Pop.	Knee	Radiograph	Multiple	Bending	Not described	Total: n = 315, 30%, age not reported
Apold, 2014 (35)	Norway	Prospective cohort (H)	Pop.	Knee	Other	Multiple	Sedentary, moderate, intermediate, or heavy work	>10 years	Total: n = 315,495, 48.7%, 58.8 ± 7.1
Armenis, 2011 (36)	Greece	Case–control (M)	Occ.	Ankle/foot/ toes	Radiograph, clinical exam	Sport	Soccer activities	>5–10 years	OA group: n = 170, sex not reported, 49.8 ± 7.4; non-OA group: n = 132, sex not provided, 50.7 ± 9.9
Badve, 2010 (37)	India	Cross-sectional (M)	Occ.	Neck	Clinical exam, other	Sales/service/ hospitality	Carrying loads on the head	>2–5 years	OA group: n = 107, 100%, 32.6; non-OA group: n = 107, 100%, 34.6
Bernard, 2010 (26)	US	Cross-sectional (H)	Comm.	Knee, wrists, hands, fingers, ankle, foot/ toes, neck	Radiograph	Unknown	Stair climbing, standing, walking, squatting, kneeling, jolting, lifting, carrying, jumping	Work lifetime	Total: n = 3,548, 30.9%, 63.4 ± 10.9
Bovenzi, 1980 (38)	Italy	Cross-sectional (H)	Occ.	Multiple	Radiograph, clinical exam	Construction	Vibration activities	Work lifetime	Occ. 1 (exposed to vibration): n = 169, 100%, 40.7; occ. 2 (not exposed to vibration): n = 60, 100%, 34.8

(Continued)

Table 2. (*Cont'd*)

First author, year (ref.)	Country	Study design (quality)	Sample type	Joints with OA	OA diagnosis	Industry	Work activities	Work history	Sample (no., % male, mean ± SD age [when given] years)
Bovenzi, 1987 (39)	Italy	Retrospective cohort (M)	Occ.	Multiple	Radiograph, clinical exam	Manufacturing	Occupational groups	Not described	OA group: n = 67, sex not reported, 39.6 ± 7.3; non-OA group: n = 46, sex not reported, 39.6 ± 7.2
Cleveland, 2013 (40)	US	Cross-sectional (M)	Comm.	Hip	Radiograph, clinical exam	Multiple	Kneeling, squatting, lifting, walking, sitting, standing, driving, climbing	Not described	Total: n = 3,087, 43.2%, 62.7 ± 9.9
Coggon, 2000 (41)	UK	Case–control (H)	Clin.	Knee	Radiograph	Multiple	Kneeling, squatting, lifting, walking, sitting, standing, driving, climbing	Work lifetime	OA group: n = 518, 40%, age not reported; non-OA group: n = 518, 40%, age not reported
Cooper, 1994 (42)	UK	Case–control (H)	Pop.	Knee	Radiograph, self-reported diagnosis	Multiple	Squatting, kneeling, climbing, lifting, walking, standing, sitting, driving	Work lifetime	OA group: n = 102, 29%, 72.7; non-OA group: n = 218, sex and age not reported
Cvijetic, 1999 (43)	Croatia	Cross-sectional (M)	Comm.	Hip	Radiograph	Multiple	Physical strain related to sitting, standing, walking, lifting	>10 years	Total: n = 590, 49.5%, 62.4 ± 10.3
Dahaghin, 2009 (44)	Iran	Case–control (H)	Pop.	Knee	ACR diagnostic criteria	Multiple	Standing, walking on flat ground, walking up/downhill, sitting on floor, sitting on chair, squatting, knee bending, cycling, climbing stairs, carrying loads	Work lifetime	OA group: n = 480, 30.2%, 57 ± 12; non-OA group: n = 490, 35.9%, 46.8 ± 15
D'Souza, 2008 (45)	US	Cross-sectional (M)	Pop.	Knee	Radiograph	Multiple	Sitting, standing, walking, running, carrying, lifting, kneeling, squatting, stooping, crawling, working in cramped spaces	>5–10 years	OA group: n = 314, 39.1%, 72.4; non-OA group: n = 966, 51.1%, 69.6
Ezzat, 2013 (13)	Canada	Cross-sectional (H)	Pop.	Knee	Radiograph, other	Multiple	Physical loads, knee bending, kneeling	Work lifetime	OA group: n = 109, 43.1%, 63.6 ± 9.6; non-OA group: n = 218, 53.8%, 55.9 ± 10.7
Felson, 1991 (46)	US	Prospective cohort (H)	Pop.	Knee	Radiograph	Multiple	Knee bending, physical demands	Not described	Total: n = 1,376, 41%, 73

(Continued)

Table 2. (*Cont'd*)

First author, year (ref.)	Country	Study design (quality)	Sample type	Joints with OA	OA diagnosis	Industry	Work activities	Work history	Sample (no., % male, mean ± SD age [when given] years)
Franklin, 2010 (47)	Iceland	Case–control (H)	Clin.	Hip, knee	Other	Multiple	Occupational groups	Work lifetime	OA group: n = 1,408, 40.9%, 74.25; non-OA group: n = 1,082, 45.3%, 70.5
Goekoop, 2011 (48)	Netherlands	Prospective cohort (M)	Pop.	Multiple	Radiograph	Unknown	Standing, walking, lifting, operating heavy machinery, bending, kneeling	Not described	OA group: n = 82, 32.9%, 90.4; non-OA group: n = 175, 23.4%, 90.6
Haara, 2003 (49)	Finland	Retrospective cohort (H)	Pop.	Wrists/hands/ fingers	Radiograph	Multiple	Lifting, carrying, awkward work postures (stooping, twisted), vibration equipment, repetitive movement, paced work	Work lifetime	Total: n = 3,595, 43%, age not reported
Haara, 2004 (50)	Finland	Prospective cohort (M)	Pop.	Wrists/hands/ fingers	Radiograph, clinical exam	Multiple	Lifting, carrying, vibration equipment, awkward work postures	Not described	Total: n = 7,217, sex and age not reported
Holte, 2000 (51)	Norway	Prospective cohort (H)	Pop.	Multiple	ICD codes	Unknown	Manual labor	>10 years	Total: n = 276,385, 39%, age not reported
Jacobsen, 2004 (52)	Denmark	Cross-sectional (H)	Pop.	Hip	Radiograph	Multiple	Sitting, standing, walking, daily lifting levels	Work lifetime	Total: n = 3,686, 38%, 61.5
Jacobsen, 2005 (53)	Denmark	Cross-sectional (M)	Pop.	Hip	Radiograph	Multiple	Lifting	Work lifetime	Total: n = 3,568, 62.5%, 61
Jacobsson, 1987 (54)	Sweden	Cross-sectional (M)	Clin.	Hip	Clinical exam, other	Multiple	Heavy labor, lifting, walking, standing, tractor driving, occupational groups	Work lifetime	OA group: n = 236, 100%, 78.8; non-OA group: n = 106, 100%, 77.8
Jarvholm, 2004 (55)	Sweden	Prospective cohort (M)	Pop.	Hip	ICD codes	Construction	Whole body vibration from heavy vehicles	>10 years	OA group: n = 5,643, 100%, age not reported; non-OA group: n = 64,225, 100%, age not reported
Jarvholm, 2008 (56)	Sweden	Prospective cohort (M)	Occ.	Multiple	ICD codes, other	Construction	Diverse construction occupations	Work lifetime	OA group: n = 204,731, 100%, age not reported; non-OA group: n = 9,136, sex and age not reported

(Continued)

Table 2. (*Cont'd*)

First author, year (ref.)	Country	Study design (quality)	Sample type	Joints with OA	OA diagnosis	Industry	Work activities	Work history	Sample (no., % male, mean ± SD age [when given] years)
Jensen, 2005 (57)	Denmark	Cross-sectional (H)	Occ.	Knee	Radiograph	Construction	Kneeling, squatting	>10 years	Occ. 1 (floor layers): n = 798, 100%, age not reported; occ. 2 (carpenters): n = 798, 100%, age not reported; occ. 3 (compositors): n = 500, 100%, age not reported
Jensen, 2012 (58)	Denmark	Cross-sectional (M)	Pop.	Knee	Radiograph, MRI	Multiple	Kneeling	Not described	Occ. 1 (floor layers): n = 92, 100%, 54.5 ± 7.2; occ. 2 (graphic designers): n = 49, 100%, 57.7 ± 5.6
Jones, 2002 (59)	Australia	Cross-sectional (H)	Admin.	Wrists/hands/ fingers	Radiograph, other	Multiple	High impact hand activities	>10 years	Total: n = 522, 33%, 53–57
Kaerlev, 2008 (60)	Denmark	Prospective cohort (M)	Pop.	Hip, knee	ICD codes	Fishing and seafaring	Fishing and seafaring activities	Work lifetime	Occ. 1 (fishermen): n = 4,410, 100%, 37.2 ± 9.8; occ. 2 (seamen non-officers): n = 4,845, 100%, 35.0 ± 11.1; occ. 3 (seamen officers): n = 4,774, 100%, 40.2 ± 10.0
Kaila-Kangas, 2011 (24)	Finland	Cross-sectional (H)	Pop.	Hip	Radiograph, clinical exam	Multiple	Lifting, carrying, pushing heavy loads	Work lifetime	OA group: n = 129, sex and age not reported; non-OA group: n = 6,427, sex and age not reported
Karkkainen, 2013 (61)	Finland	Prospective cohort (H)	Pop.	Multiple	ICD codes, other	Multiple	Sitting, standing, walking, lifting, carrying, heavy labor	>10 years	Total: n = 176, 50.8%, 41.8 ± 8.9
Klussman, 2010 (62)	Germany	Case–control (H)	Pop.	Knee	Radiograph, other	Multiple	Kneeling, squatting, sitting, standing, walking, climbing stairs, jumping, lifting, carrying	Work lifetime	OA group: n = 739, 41%, 58.5 ± 10.5; non-OA group: n = 571, 47%, 52.8 ± 12.3

(Continued)

Table 2. (*Cont'd*)

First author, year (ref.)	Country	Study design (quality)	Sample type	Joints with OA	OA diagnosis	Industry	Work activities	Work history	Sample (no., % male, mean ± SD age [when given] years)
Kujala, 1995 (63)	Finland	Retrospective cohort (H)	Pop.	Knee	Radiograph, clinical exam	Sport	Previous kneeling, squatting, heavy work	Work lifetime	Occ. 1 (Olympic long distance runners): n = 28, 100%, 59.7 ± 4.7; occ. 2 (Olympic soccer players): n = 31, 100%, 56.5 ± 5.1; occ. 3 (Olympic weight lifters): n = 29, 100%, 59.3 ± 5.3
Lindberg, 1984 (64)	Sweden	Retrospective cohort (M)	Pop.	Hip	Radiograph	Multiple	Heavy labor	Work lifetime	OA group: n = 332, 100%, 66 ± 5; non-OA group: n = 790, 100%, 64.4 ± 4
Manninen, 2002 (65)	Finland	Case–control (H)	Pop.	Knee	Other	Multiple	Walking, lifting, driving, standing, climbing, kneeling, squatting	Work lifetime	OA group: n = 281, 20%, 68.4 ± 5.5; non-OA group: n = 524, 27%, 67.1 ± 5.6
Martin, 2013 (66)	UK	Prospective cohort (H)	Pop.	Knee	ACR diagnostic criteria	Multiple	Kneeling, squatting, lifting, walking, climbing ladders or stairs, sitting	>10 years	Total: n = 302, 36.1%, 53
Mounach, 2008 (67)	Morocco	Case–control (M)	Clin.	Knee	Radiograph	Multiple	Standing, sitting, climbing stairs, kneeling, squatting, walking, heavy lifting	≥12 months to 2 years	OA group: n = 95, 27.4%, 59.7 ± 8.5; non-OA group: n = 95, 27.4%, 60.0 ± 8.5
Muraki, 2009 (68)	Japan	Prospective cohort (H)	Pop.	Knee, spine	Radiograph	Multiple	Sitting on a chair, kneeling, squatting, standing, walking, climbing, heavy lifting	Work lifetime	Total: n = 1,471, 36%, 68.4 ± 9.2
Muraki, 2011 (25)	Japan	Prospective cohort (H)	Pop.	Knee	Radiograph	Multiple	Sitting on a chair, kneeling, squatting, standing, walking, climbing, heavy lifting	Work lifetime	Total: n = 1,402, 36.5%, 68.2 ± 9.2
Nakamura, 1993 (69)	Japan	Cross-sectional (M)	Occ.	Wrists/hands/ fingers	Radiograph	Multiple	Cooking activities (e.g., food washing, chopping)	>10 years	Occ. 1 (elementary school cook): n = 260, sex not reported, 49.3; occ. 2 (preschool cook): n = 222, sex not reported, 47.2; occ. 3 (municipal employee): n = 298, sex not reported, 48.7

(Continued)

Table 2. (*Cont'd*)

First author, year (ref.)	Country	Study design (quality)	Sample type	Joints with OA	OA diagnosis	Industry	Work activities	Work history	Sample (no., % male, mean ± SD age [when given] years)
Olsen, 1994 (70)	Sweden	Case–control (H)	Pop.	Hip	Other	Multiple	Physical workload	Work lifetime	OA group: n = 233, 100%, age not reported; non-OA group: n = 322, 100%, age not reported
Ozturk, 2008 (71)	Turkey	Case–control (M)	Occ.	Spine	Radiograph	Multiple	Soccer activities	>10 years	Occ. (soccer players): n = 70, 100%, 45.6 ± 8.4; control group: n = 59, 100%, 46.0 ± 9.4
Ratzlaff, 2011 (72)	Canada	Prospective cohort (M)	Pop.	Hip	ACR diagnostic criteria, clinical exam, self-reported diagnosis	Multiple	Cumulative peak force index (lifetime physical load)	Work lifetime	Total: n = 2,918, sex and age not reported
Ratzlaff, 2012 (73)	Canada	Cross-sectional (M)	Pop.	Knee	ACR diagnostic criteria, clinical exam, self-reported diagnosis	Multiple	Cumulative peak force index (lifetime physical load)	Work lifetime	Total: n = 4,269, 37%, 60.0 ± 11.1
Roach, 1994 (74)	US	Case–control (H)	Clin.	Hip	Radiograph	Multiple	Light work standing, sitting, heavy work standing, kneeling, crouching, walking	Work lifetime	OA group: n = 99, 100%, 69.3; non-OA group: n = 233, 100%, 63.4
Rossignol, 2003 (75)	France	Cross-sectional (M)	Clin.	Multiple	Clinical exam	Multiple	Occupational groups	Not described	Total: n = 10,412, 33.8%, 66.2 ± 10.2
Rossignol, 2005 (76)	France	Cross-sectional (M)	Clin.	Multiple	Clinical exam	Multiple	Occupational groups	Work lifetime	Total: n = 2,834, 58%, 61.8 ± 9.3
Rubak, 2013 (77)	Denmark	Retrospective cohort (H)	Pop.	Hip	ICD codes	Multiple	Cumulative physical workload (lifting, vibration, standing, walking)	Work lifetime	Total: n = 1,910,493, 52.9%, 49.1 ± 10.5
Rubak, 2014 (78)	Denmark	Case–control (H)	Pop.	Hip	Other	Multiple	Lifting, standing, walking, sitting, kneeling, squatting, whole body vibration	Work lifetime	Total: n = 3,552, 51.5%, 64.9

(Continued)

Table 2. (*Cont'd*)

First author, year (ref.)	Country	Study design (quality)	Sample type	Joints with OA	OA diagnosis	Industry	Work activities	Work history	Sample (no., % male, mean ± SD age [when given] years)
Sahlstrom, 1997 (79)	Sweden	Case–control (M)	Clin.	Knee	Radiograph	Multiple	Light work (sitting, walking, carrying), medium (lifting and carrying, climbing stairs or ladders), heavy (light and medium plus jumping with and without carrying)	Work lifetime	OA group: n = 266, sex and age not reported; non-OA group: n = 463, sex and age not reported
Sairanen, 1981 (80)	Finland	Case–control (H)	Occ.	Multiple	Radiograph, clinical exam	Forestry	Tree felling activities	Work lifetime	OA group: n = 226, 100%, 42; non-OA group: n = 98, 100%, 42
Sandmark, 2000 (81)	Sweden	Case–control (H)	Pop.	Knee	Other	Multiple	Lifting, jumping, vibration, squatting, knee bending, kneeling, standing, sitting, climbing	Work lifetime	OA group: n = 625, 52%, age not provided; non-OA group: n = 548, 48.2%, age unknown
Seidler, 2001 (82)	Germany	Case–control (H)	Clin.	Spine	Radiograph	Multiple	Low, medium, high lifting and carrying, forward bending, whole body vibration	Work lifetime	OA group: n = 94, 100%, 48.4 ± 10.1; non-OA group (1): n = 107, 100%, 43.1 ± 10.3; non-OA group (2): n = 90, 100%, 39.7 ± 10.6
Seidler, 2012 (83)	Germany	Case–control (H)	Clin.	Knee	Radiograph	Multiple	Kneeling, squatting, lifting, carrying	Work lifetime	OA group: n = 295, 100%, age not reported; non-OA group: n = 327, 100%, age not reported
Seok, 2017 (84)	Korea	Cross-sectional (H)	Pop.	Knees/hips	Radiograph	Multiple	Occupational groups	Work lifetime	Total: n = 9,905, 45%, all participants age ≥50 years

(Continued)

Table 2. (*Cont'd*)

First author, year (ref.)	Country	Study design (quality)	Sample type	Joints with OA	OA diagnosis	Industry	Work activities	Work history	Sample (no., % male, mean ± SD age [when given] years)
Solovieva, 2006 (85)	Finland	Cross-sectional (M)	Occ.	Wrists/hands/ fingers	Radiograph	Health	Dentistry-related manual hand tasks	Work lifetime	Occ. 1 (dentists with variable tasks): n = 96, sex not reported, 52 ± 5.0; occ. 2 (dentists who perform restorative treatment 50% of time; perform prosthodontics 50% of time): n = 64, sex not reported, 54 ± 6.0; occ. 3 (dentists who perform restorative treatments): n = 64, sex not reported, 54 ± 6.0
Stenlund, 1992 (86)	Sweden	Cross-sectional (H)	Occ.	Shoulder	Radiograph	Construction	Vibration, lifting	Work lifetime	Occ. 1 (rock blasters): n = 55, sex not reported, 51.8 ± 11.6; occ. 2 (bricklayers): n = 54, sex not reported, 50.2 ± 11.4; occ. 3 (foremen): n = 98, sex not reported, 45.8 ± 10.2
Thelin, 1997 (87)	Sweden	Case–control (H)	Clin.	Hip	Radiograph	Multiple	Heavy physical work, machine work, occupational groups	Work lifetime	OA group: n = 216, 100%, age not reported; non-OA group: n = 479, 100%, age not reported
Toivanen, 2010 (21)	Finland	Prospective cohort (H)	Pop.	Knee	Radiograph, clinical exam	Multiple	Categories of light, sedentary work through to heavy manual work	Not described	Total: n = 823, 45%, 41.6 ± 8.3
Verrijdt, 2017 (88)	Belgium	Retrospective cohort (M)	Occ.	Thumb	Radiograph, clinical exam	Banknote processing	Hand activities related to banknote counting	Job role and production rate	Total: n = 195, 34%, 52.9
Vingard, 1991 (89)	Sweden	Retrospective cohort (H)	Pop.	Multiple	ICD codes	Multiple	High physical workload occupational groups	>10 years	OA group: n = 135,015, 54%, age not reported; non-OA group: n = 115,202, 46%, age not reported

(Continued)

Table 2. (*Cont'd*)

First author, year (ref.)	Country	Study design (quality)	Sample type	Joints with OA	OA diagnosis	Industry	Work activities	Work history	Sample (no., % male, mean ± SD age [when given] years)
Vingard, 1997 (90)	Sweden	Case–control (H)	Pop.	Hip	Other	Multiple	Sitting, standing, heavy lifting, jumping, twisting positions, stair climbing	Work lifetime	Total: n = 503, sex not reported, 63
Vrezas, 2010 (91)	Germany	Case–control (H)	Clin.	Knee	Radiograph	Multiple	Kneeling, squatting, lifting, carrying, vibration, posture	Work lifetime	OA group: n = 295, 100%, age not reported; non-OA group: n = 327, 100%, age not reported
Yoshimura, 2004 (92)	Japan	Case–control (H)	Admin. records	Knee	Radiograph, clinical exam	Multiple	Standing, sitting, climbing stairs, kneeling, squatting, driving, walking, heavy lifting	Work lifetime	OA group: n = 101, sex not reported, 73.3 ± 9.8; non-OA group: n = 101, sex not reported, 73.3 ± 9.8
Yoshimura, 2006 (93)	Japan	Case–control (H)	Pop.	Knee	Radiograph, clinical exam	Multiple	Standing, sitting, climbing stairs, kneeling, squatting, driving, walking, heavy lifting	Work lifetime	OA group: n = 37, 100%, 70.0 ± 6.6; non-OA group: n = 37, 100%, 70.1 ± 7.0
Zhang, 2013 (94)	China	Cross-sectional (M)	Pop.	Knee	Radiograph, ACR diagnostic criteria	Multiple	Underground work history	Not described	OA group: n = 983, 45.3%, age not reported; non-OA group: n = 6,143, 51.5%, age not reported

* (M) = medium quality; (H) = high quality; Admin. = administrative records; Comm. = community; Clin. = clinical; Occ. = occupational categories; Pop. = population; ACR = American College of Rheumatology; ICD = International Classification of Diseases; OA = osteoarthritis.

evidence in 65% of studies (n = 45; Kellgren/Lawrence grade 2 or greater), and in 24.6% of studies clinical examinations were used (n = 17) (95). Other methods of assessing OA were World Health Organization categories from the International Classification of Diseases, Eighth/Ninth/Tenth revisions (n = 8), American College of Rheumatology diagnostic criteria (n = 6), self-report of a clinician diagnosis (n = 4), and magnetic resonance imaging (n = 2).

Measurement of work. Three-quarters of studies included workers from multiple industries (n = 51), and the majority (85.5%; n = 59) asked about the duration of work activities. Overall, 70% of studies provided a reasonable description of work activities (n = 48). However, many studies classified duration as work "lifetime" (62%; n = 43), which lacked specificity (e.g., ≥10 years at a job activity). Moreover, a wide range of work activities were combined with other activities (e.g., kneeling/squatting/bending). As a result, only 55% of work history measures were appraised as reliable and valid.

Potential covariates. Nearly all studies included ≥1 covariate, commonly age, sex, body mass index (BMI), or smoking, and many studies included multiple covariates. Hip and knee studies often controlled for previous injury and other sport or physical leisure activities. Covariates were typically controlled for in statistical analyses, but no data were available for extraction.

Data extraction and synthesis. Data were synthesized for hips, knees, wrists/hands/fingers, and spines, and for studies that combined multiple joints. There were too few studies to synthesize findings for necks, ankles/feet/toes, shoulders, and elbows. Table 3 shows a summary of work activities associated with strong and moderate evidence for OA development in the knees and hips among men and women. Evidence was sometimes contradictory, depending on how an activity was measured. For example, when studies labeled their exposure as kneeling, squatting, and bending, there was strong evidence for a risk of developing knee OA in both men and women. Yet studies that examined kneeling separately found strong evidence for no increased risk of knee OA in both men and women. Squatting examined separately resulted in strong evidence for no increased risk of knee OA in men and a moderate level of evidence for no increased risk of knee OA in women. Overall, this finding meant that when we combined all studies that variously measured kneeling, squatting, or bending in some form, there was a moderate level of evidence for the development of knee OA among men only.

Lifting was associated with strong evidence of developing hip OA in both men and women, and vibration activities and cumulative physical workloads were associated with a moderate level of evidence for hip OA among men. Findings differed for knee OA, with lifting and carrying being associated with a moderate level of evidence for no increased risk of knee OA in women.

Table 3. Summary of strong and moderate evidence for work activities and risk of developing osteoarthritis (OA)*

Evidence level: work activities (references)	Men	Women
Strong evidence: increased risk of OA		
Lifting (24,32,40,43,48,52–54,61,77,78,90)	Hip	Hip
Kneeling, squatting, bending (13,25,32,33 41,42,44,45,48,57,62,63,65–68,81,83, 91–93)	Knee	Knee
Heavy physical demands (13,21,35,46,61,63,79,89)	–	Knee
Moderate evidence: increased risk of OA		
Vibration (38,55,77,78)	Hip	–
Cumulative physical load (70,72,77)	Hip	–
Kneeling, squatting, and/or knee bending (all studies combined) (13, 25, 32–34, 41, 42, 44, 45, 48, 57, 62, 63, 65–68, 81, 83, 91–93)	Knee	–
Strong evidence: no increased risk of OA		
Sitting, standing, walking (32,40,43,48,52,54,61,74,78,90,92)	Hip	–
Kneeling (13,25,32–34,41,42,44,45,48,57,62,63,65–68,81,83,91–93)	Knee	Knee
Squatting (13,25,32–34,41,42,44,45,48,57,62,63,65–68,81,83,91–93)	Knee	–
Climbing stairs/ladders (25,26,32,41,42,44,62,65,66,68,81,92)	–	Knee
Moderate evidence: no increased risk of OA		
Sitting, standing, walking (25,26,32,41,42,44,45,48,61,62, 65–68,81,92,93)	Knee	Knee
Squatting (25,32,33,41,42,44,45,57,62,63, 67,68,83)	–	Knee
Lifting, carrying (25,32,41,44,45,48,61,62,65–68,81,83,91–93)	–	Knee
Driving (65,92,93)	Knee	Knee

* References identify literature relevant to a category (e.g., lifting). The level of evidence is based on the totality of findings across relevant studies in that category and does not reflect the findings of an individual study.

Strong and moderate levels of evidence for no increased risk of knee or hip OA also were found for some work activities. There was strong evidence for no increased risk of hip OA in men related to sitting, standing, or walking activities, and moderate evidence for no increased risk of knee OA in men and women for these activities. There was also strong evidence for no increased risk of knee OA in women related to climbing stairs or ladders, and a moderate level of evidence for no increased risk of knee OA related to driving as an occupational activity in men or women.

For all other work activities, evidence was limited, mixed, or insufficient. Among men, this lack included insufficient evidence for jumping being associated with either hip or knee OA, lifting having a limited association with knee OA, and heavy physical demands yielding mixed evidence for knee OA. Among women there was insufficient evidence linking jumping and vibration activities to hip OA and mixed evidence for cumulative physical loads

and sitting, standing, and walking being associated with hip OA. There was also insufficient evidence linking jumping and cumulative physical load to knee OA.

Studies examining OA of the hand or spine, and studies that combined joints, mostly did not analyze data for men and women separately. In these studies men and women were combined and the evidence for highly repetitive hand tasks was moderate for no effect of these tasks on the development of wrist/hand/finger OA. Evidence was insufficient for work activities described as "jolting" of the hands. For men and women combined, evidence was mixed for lifting activities related to developing OA in the spine. Evidence was also mixed for physically demanding work related to developing OA in multiple joints. Evidence was insufficient in studies examining OA in multiple joints and work tasks related to sitting, standing, and lifting/carrying.

Dose-response data. To further illuminate the findings, particularly variable and contradictory evidence, we extracted dose-response information from the studies and examined them for thresholds that might link to an increased risk of OA (Table 4). Currently, there are no standardized dose-response criteria available to evaluate the relationship of work exposures to OA. This absence was reflected in the highly diverse and often unique criteria used across studies. Examples include dose levels related to frequency (e.g., daily), intensity (e.g., lifting >25 kg; number of stairs climbed), duration (e.g., >2 hours per day, 10 years or more), and total amount (e.g., lifetime kneeling >3,500 hours). In some cases, dose levels were combined (e.g., >80% of time in nonsitting positions AND frequent walking and lifting). In general, the data were too diverse and too few studies used similar dose-response exposure measures for any synthesis. However, measures of frequency were most common. Studies that used a measure of ≥1 hour/day spent at an activity across multiple years, or a minimum of 3,542 hours spent at an activity, were often linked to an increased risk of developing OA in the knee or hip, particularly related to kneeling, squatting, and bending. Studies that provided qualitative descriptors to assess dose levels (e.g., heavy lifting or a great deal of the time) often reported no significant effects. Table 4 summarizes examples of the doses used in studies for knees and hips related to different job activities.

DISCUSSION

This is the first systematic review to include a wide range of joints affected by OA. By also examining sex and extracting information on work exposures, we more comprehensively addressed the impact of specific occupational activities on the risk of developing OA and illuminated key gaps in research and measurement. Data synthesis yielded several work activities with strong or moderate evidence for the development of OA in hips and knees. However, the absence of clear dose-response information and contradictory findings limits the ability to provide workplaces and legislators with the specificity they need to implement recommendations and considerations. Moreover, there remains mixed or insufficient evidence related to work and OA of the hands, spine, and multiple joints, and too few studies exist to synthesize information on other joints affected by OA. Continued evidence is needed for these joints to refine measures and generate data.

Across men and women, strong or moderate evidence emerged for knee OA when combining kneeling, squatting, and bending activities. Yet there was no effect when squatting and kneeling were examined individually. This diversity in findings has been noted previously (7,14,27), and it highlights the need for attention to measurement, including whether compartmentalizing or differentiating among knee bending tasks accurately reflects real-world work conditions in the frequency and duration of knee bending, and whether knee bending occurs in conjunction with lifting heavy loads (7,16,27). Some jurisdictions are trying to address these issues and have identified minimum thresholds for frequency and duration of kneeling related to work compensation claims (22), but in the absence of detailed evidence, thresholds are set high.

In men, strong evidence emerged for hip OA risk related to lifting, and moderate evidence exists for cumulative physical loads and full-body vibration. This level of evidence is novel and warrants attention for worker awareness and prevention efforts. Previous research has speculated about loads and prolonged vibration in occupations like farming. By focusing on specific activities (e.g., driving a tractor), this review provides greater specificity of evidence and directions for moving forward. However, a lack of clarity related to dose-response levels linking full-body vibration to an increased risk for hip OA limits current practice recommendations. Many studies used vague descriptors (e.g., never versus ever; much tractor driving). Greater precision and specificity of measures is needed in future research.

Among women, fewer occupational activities reached levels for strong or moderate evidence, likely due to fewer available studies (9,11,27) and traditional differences in the types of occupations and levels of physical demands in the work undertaken by women compared to men. However, similar to men, there was strong evidence for an increased risk of hip OA in women related to lifting. This is the first systematic review to have examined lifting activities separately for women, and it underscores the need for greater attention to this aspect of work and its impact among women.

Of interest was strong and moderate evidence for a lack of association among several activities and increased risks of hip, knee, or hand OA. These included sitting, standing, and walking (hip and knee OA), lifting and carrying (knee OA), climbing ladders (knee OA), driving (knee OA), and highly repetitive tasks (hand OA). There are many reasons why studies yield null effects, suggesting caution in drawing conclusions. Moreover, although not a high priority in developing OA, activities like prolonged

Table 4. Summary of dose-response categories by joints and work activities

- Hips
  - Lifting
    - >20 kg at least 10 times/day: from 1–12 years, 13–24 years, >25 years
    - Heavy lifting (comparison not specified in 2 studies; 1 study compared high and medium versus low)
    - Tons lifted: high and medium versus low
    - No. of lifts >40 kg: high and medium number of lifts versus low
    - Ton years: 0 versus >0–9, 10–19, 20–115/86 (men: upper value of 115; women: upper value of 86)
    - Daily lifting equivalent: a) 50 lifts × 20 kg OR 20 lifts × 50 kg; b) 50–100 lifts × 20 kg OR 20–50 lifts × 50 kg; c) 200–500 lifts × 20 kg OR 100–250 lifts × 50 kg
  - Standing/sitting/walking
    - >80% of time sitting
    - >80% of time standing
    - Frequent walking, but low strain and light lifting up to 5 kg
    - Sitting: high versus low
    - Stairs climbed: high versus medium versus low
    - Standing years: 0, >0–9, 10–19, 20–29
  - Jumping
    - Number of jumps; low, medium, high
  - Vibration
    - Machine operator versus tractor in agriculture, forestry machine, dumper, etc.
    - Much tractor driving
    - Heavy equipment operation
    - Whole-body vibration (ever versus never)
  - Cumulative physical workload
    - Heavy work before age 16 years
    - >80% of work nonsitting, frequent walking, lifting heavy objects (with some analyses including years worked)
    - Cumulative physical workload (based on an industry exposure matrix with scores of 0–4, 5–14, 15–24, 25–34, 35–86)
    - Cumulative peak force index
- Knees
  - Sitting/standing/walking
    - Percent of day (e.g., 22–32%, 32–54%, >54%)
    - Time per day: ≥2 hours per day
    - Time per day: ≥3 hours per day
    - Time per day: floor and chair separately 1–2 hours/day, 2–3 hours/day, >3 hours/day
    - Unspecified intensity: medium and high
    - Lifetime hours: <16,032 hours, 16,032–33,119 hours, >33,119 hours
    - Likelihood of sitting: unlikely and highly likely versus somewhat likely
    - Distance: ≥3 km/day
    - Distance: ≥2 km/day
    - Distance: >2 miles/day for 1–9 years, 10–19 years, ≥20 years
    - Time: flat ground 1–2 hours, 2–3 hours, >3 hours plus up or downhill >30 minutes/day
  - Kneeling/squatting/bending
    - Percentage of day: 4–7%, 8–13%, >14% of workday
    - Time: ≥1 hour/day
    - Time: >30 minutes
    - Likelihood: unlikely and highly likely versus somewhat likely
    - Unspecified intensity: high exposure
    - Qualitative intensity: medium plus heavy bending
    - Qualitative intensity: sedentary or light, medium, heavy, very heavy
    - Amount: none, some, much
    - Qualitative intensity plus load: kneeling/squatting with heavy lifting
    - Lifetime/cumulative hours: <3,542, 3,542–8,934, 8,934–12,244, >12,244
    - Lifetime/cumulative hours: <4,757, >4,757, >4,757 with body mass index >24.92
    - Lifetime/cumulative hours: 0 to <870 hours, 870 to <4,757, 4,757 to <10,800, ≥10,800
    - Time per day: <2 hours/day, >2 hours/day, time/day plus duration: >1 hour/day plus: 1–9.9 years, 10–19.9 years, >20 years
  - Getting up from kneeling/squatting
    - Frequency: >30 times/day
    - Frequency plus duration: >30 times/day: 1–9.9 years; 10–19.9 years; >20 years
  - Lifting/carrying
    - Qualitative intensity: heavy lifting
    - Qualitative intensity: high exposure
    - Qualitative intensity: medium, high
    - Frequency: unlikely, somewhat likely, highly likely
    - Amount: weights >25 kg on an average day
    - Amount: 2–4 kg/day, >4 kg/day
    - Amount plus frequency: ≥10 kg at least once/week
    - Amount plus frequency (plus duration): ≥10 kg >10 times/week, ≥25 kg >10 times/week, ≥50 kg >10 times/week; all categories repeated with: 1–9.9 years, 10–19.9 years, ≥20 years
    - Percentage of day: 4–7% of day, 8–19% of day, >20% of day
    - Cumulative lifting by hours: 0 to <630 kg × hours, 630 to <5,120 kg × hours, 5,120 to <37,000 kg × hours, ≥37,000 kg × hours
    - Cumulative hours: <5,120, >5,120, >5,120 with body mass index ≥24.92
    - Cumulative weights: <1,088 tons/life, ≥1,088 tons/life
  - Climbing
    - Time/day: ≥1 hour/day
    - Episodes plus episodes with duration: >30 times/day, >30 times/day for 1–9.9 years, 10–19.9 years, ≥20 years
    - Qualitative intensity: medium; high
    - Qualitative intensity: high exposure
    - Amount, no. of flights: 3–5 stories, 5–10 stories, >10 stories
    - Amount, no. of flights: >10 flights/day
    - Amount, no. of stairs: ≥50 steps/day
  - Driving
    - Time/day: >4 hours/day
    - Qualitative intensity: medium, high level
  - Physically demanding
    - Qualitative intensity: sedentary, light, medium, heavy, very heavy
  - Jumping
    - No. of jumps
  - Cumulative physical loads
    - Cumulative occupational physical load: data in quintiles
    - Occupational cumulative peak force index: data in quintiles
- Hands
  - Total hours exposed
  - Banknotes/bank sheets counted manually or electromechanical (e.g., 15,000–25,000), stacking banknotes, preparation of packages

sedentary behavior are linked to morbidity and mortality for other health conditions (96).

Our quality appraisal identified several constraints and limitations to study designs and measurement. Most research used case–control or cross-sectional designs, with few longitudinal studies and no interventions. This methodology is likely, because of the prolonged time at a job that is needed before joint strain or damage would develop and lead to OA or become sympto-

matic. We can expect more longitudinal research in the future, given that many countries have established large, longitudinal OA cohorts. However, most cohorts have clinical treatment foci. In the current literature, we found that generally, the assessment of OA used valid and reliable methods, including standardized clinical and radiographic assessments. Many studies also controlled for a range of covariates (e.g., BMI, injuries, sports activities). Measures to assess employment activities and recall periods were problematic. Only approximately half of work exposures were rated as both valid and reliable, with exposures examining lower-extremity OA being of better quality than those for upper-extremity OA. For example, nearly two-thirds of studies asked participants to recollect their occupation or activity levels over their entire work history. There is a potential for recall bias across all methods of collecting work history, which is a limitation of most of the studies reviewed. Currently, we have little evidence for the validity of long-term recall assessments, which may be more appropriate for measuring occupation type (e.g., are you a farmer?) but less reliable for specific activities (e.g., do you engage in lifting activities?). Additional efforts are needed in research to help improve recall and work measurement, potentially through guided recall techniques, sensor technology, video assessment of work tasks, and longitudinal designs with repeated work activity measures that assess activities and the duration, frequency, and intensity of those activities.

A different bias that needs addressing in future research is a potential healthy worker effect. Specifically, some workers who develop joint problems (e.g., pain, stiffness) may give up their jobs prematurely. This phenomenon may result in a healthier or genetically different sample of workers who remain working in jobs that are thought to cause risks for OA than those who leave these occupations. This result can mask the impact of some work activities on OA in the population at large, leading to the conclusion either that some activities are not related to the development of OA or that damage occurs slowly and over a significantly longer period (97). This possibility highlights the complexity surrounding work and OA and the need for additional information about job tenure and work changes, as well as longitudinal data to assess work history and joint symptoms.

As noted, our extraction of data included dose-response information. These data highlighted a lack of consistency that made synthesizing data impossible. For example, lifting was measured in terms of differing levels of frequency, duration, intensity, lifetime composite levels, and combinations of doses. A similar difficulty arose for kneeling, squatting, and bending activities. Studies not only had differing dose-response data, but variously combined activities (e.g., kneeling alone; kneeling and squatting). Moreover, concerns about knee damage have started to change the nature of work in some occupations. Kneeling devices exist to help offset knee damage and a variety of practices have been put into place with recommendations and strategies to change knee activity patterns. To date, few studies ask about assistive devices or gadgets to ameliorate the impact of activities on OA. Additional research is needed with greater precision of dose-response information aimed at frequency, intensity, and duration of activities, as well as in gathering other relevant information like the use of assistive devices, work cessation, and job turnover related to specific job activities.

In conclusion, a synthesis of 69 studies from 23 countries yielded several work activities with strong and moderate evidence for increasing the risks of developing OA in men and women. These include lifting, cumulative physical loads, full-body vibration, and kneeling/squatting/bending combined. The levels of evidence point to the potential for recommendations and practice considerations to be developed and that those can be tailored for women and men. However, in going forward, additional attention is needed to overcome study deficits, particularly in the measurement and recall of work activities, so that recommendations and practice considerations can provide the specificity needed to be adopted in workplaces.

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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. Gignac 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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Association Between Weight Loss and Spontaneous Changes in Physical Inactivity in Overweight/Obese Individuals With Knee Osteoarthritis: An Eight-Week Prospective Cohort Study

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Objective. To describe spontaneous changes in time spent being physically inactive that is measured continuously by accelerometry during an 8-week weight-loss intervention in overweight/obese individuals with knee osteoarthritis (OA).

Methods. This study was designed as an observational cohort study including individuals from an OA outpatient clinic who were concomitantly overweight/obese and had symptomatic knee OA. Participants completed an 8-week dietary intervention that had been previously shown to induce substantial weight loss. The main outcome was accelerometer-based measurement of daily physical inactivity for 24 hours during the 8-week intervention period that was presented as change in the average daily time spent inactive (sitting, reclined, or sleeping) from 1 week prior to intervention to the last week of the intervention.

Results. A total of 124 participants completed the dietary intervention and had valid accelerometer recordings. The mean weight loss was 12.7 kg (95% confidence interval [95% CI] –13.2, –12.1; $P < 0.0001$) after 8 weeks, which corresponded to a decrease in body mass index of 4.3 kg/m^2 (95% CI –4.5, –4.2; $P < 0.0001$). Significant improvements in OA symptoms (assessed by the Knee Injury and Osteoarthritis Outcome Score [KOOS]) was found across all subscales; an improvement of 12.8 points (95% CI 10.6, 15.0; $P < 0.0001$) was observed for pain using the KOOS. No statistically significant change occurred in the average daily time spent inactive from baseline to follow-up (mean change 8.8 minutes/day [95% CI –12.1, 29.7]; $P = 0.41$).

Conclusion. Physical inactivity remains stable despite a clinically significant weight loss and improvements in knee OA symptoms. Change in inactivity does not seem to occur spontaneously, suggesting that focused efforts to reduce inactive behaviors are needed.

INTRODUCTION

Physical inactivity (lack of moderate-to-vigorous activity) is associated with increased risks of developing noncommunicable diseases such as heart disease, diabetes mellitus, and even premature death (1–3). Physical inactivity increases with age in all World Health Organization (WHO) regions (3) and thereby has a marked impact on the disease burden related to chronic diseases.

One of the contributors to physical inactivity in the aging population is osteoarthritis (OA) of the hip or knee (4). OA is characterized by pain during activity that results in reluctance to move (5). In fact, OA symptoms are negatively associated with physical activity (moderate-to-vigorous intensity) (6), and most adults with OA in both the US and Europe have a sedentary lifestyle (sitting or reclined most of the day) (7,8). Altogether, individuals with OA are very susceptible to development of chronic disease related to physical inactivity.

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

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SIGNIFICANCE & INNOVATIONS

- Physical inactivity remains stable during an 8-week intensive dietary intervention period despite a clinically significant weight loss and improvements in knee osteoarthritis symptoms.
- This indicates that changes in physical inactivity must be stimulated by other efforts (e.g., education, motivation, etc.) following a weight loss to reduce overall health risks associated with sedentary behavior and increase the chance of long-term weight-loss maintenance.

Obesity is also well-established as being associated with physical inactivity (9), and obesity is linked to the onset and progression of knee OA (10). Obesity and knee OA often share pathogenetic phenotypes. The onset or progression of one condition increases the risk of developing the other, and a vicious circle may be triggered (11). It is therefore not surprising that individuals with the combination of obesity and knee OA are generally very physically inactive and efforts should be made to reduce physical inactivity in this population.

Current treatment guidelines recommend weight loss as a primary treatment in concomitantly overweight/obese individuals who have knee OA (12–14). Weight loss interventions are well-documented and include beneficial effects on pain, physical functioning, and quality of life (QoL) (15–17). In an observational nonintervention cohort study, weight loss of >10 pounds (4.5 kilograms) during a 2-year period was associated with a minor reduction in time spent being sedentary (7 minutes/day), whereas a weight gain of >10 pounds was associated with more time spent being sedentary (25.8 minutes/day) (18). This suggests that a moderate change in weight (minimum 4.5 kilograms) is related to a change in time spent being sedentary after 2 years. As sedentary behavior is linked to being overweight/obese (19) and severity of knee OA symptoms (20), an assessment of whether an intensive weight-loss intervention aiming at a 10% weight loss and symptomatic improvements is associated with a spontaneous decrease in time spent physically inactive (sitting, reclined, or sleeping) is relevant.

The terms "physical inactivity," "physical activity," and "sedentary behavior" are used throughout the literature to describe participants' daily habits. In the present study, the term physical inactivity was used to describe time spent sitting, reclined, and sleeping during a 24-hour period. The term "physical activity" was used to describe time spent participating in moderate-to-vigorous activity during waking hours (10–15 hours), and the term "sedentary behavior" was used to describe time spent sitting or reclined during waking hours (10–15 hours).

The objective of this study was to explore if weight loss in overweight/obese individuals with knee OA was associated with a spontaneous change in physical inactivity during an 8-week intensive dietary intervention (IDI) period. We hypothesized that weight loss was associated with a spontaneous decrease in daily time spent being physically inactive.

PATIENTS AND METHODS

The present study was a prospective cohort study conducted from November 2016 to November 2017. Additionally, this study was a substudy of the randomized trial Effect of Liraglutide on Body Weight and Pain in Overweight or Obese Patients With Knee Osteoarthritis (ClinicalTrials.gov identifier: NCT02905864), in which participants underwent an 8-week IDI prior to a random allocation to either liraglutide or placebo. For the purpose of this substudy, we focused on the preallocation phase (before randomization to liraglutide or placebo) and took advantage of the initial 8-week IDI that was proven to induce a significant weight loss (21).

A detailed protocol was developed for this substudy (see Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23868/abstract) that was preregistered before commencement of any study-related activities. The protocol was approved by the local health research ethics committee (H-16019969), and all participants provided written informed consent.

Participants were recruited from the OA outpatient clinic by rheumatologists at the Parker Institute at the Copenhagen University Hospital Bispebjerg and Frederiksberg (HB and AO). The key inclusion criteria included a clinical diagnosis of knee OA according to the American College of Rheumatology (22), radiographic changes (Kellgren/Lawrence grades 1, 2, or 3), body mass index (BMI) ≥27 kg/m^2, and motivation for weight loss (judged subjectively by the aforementioned rheumatologists during an interview). The key exclusion criteria included planned knee surgery, previous or planned surgical treatment for obesity, and current medical or dietary obesity treatment. The rest of the inclusion and exclusion criteria have been recorded (Clinicaltrials.gov identifier: NCT02905864). In this study, participants with a BMI ≥30 kg/m^2 were considered obese and those with a BMI ≥27 kg/m^2 were considered overweight.

Weight-loss intervention. The IDI was comprised of a full meal-replacement diet for 8 weeks. The meal replacements consisted of soups, shakes, hot cereals, and bars (Cambridge Weight Plan UK), resulting in an energy intake of 800–1,000 kcal/day. Further, weekly educational group sessions (2 hours per session; 6–8 participants per group) that focused on healthy diet information and motivational support were provided. The program has been proven to result in a significant weight loss (>10% reduction in body weight) among overweight/obese knee OA patients (21). Two dietitians (with 11 and 14 years of experience) were responsible for the educational group sessions and supplied the participants with the meal-replacement products.

Body weight. The body weight of the participants was measured at baseline (1 week prior to the IDI) and at the end of the 8-week IDI by a study nurse using a decimal weighing scale (TANITA BW-800, Tanita Europe BV), with the participant fasting and wearing only underwear or light clothing. Further, body weight was measured at each weekly group session in the IDI period with the participant wearing normal clothing, but without shoes.

Physical inactivity measurements. Measurements of physical inactivity in daily life were obtained objectively by using a single-use miniature tri-axial accelerometer (dimensions 50 mm × 21 mm × 5 mm, weight 8 grams; SENS-MOTION activity measurement system, version 1.7.1). The accelerometer measured activity continuously at 12.5 Hz for 24 hours and had battery capacity for at least 20 weeks of continuous use. The accelerometer was placed within a small waterproof band-aid (soft cloth surgical tape on liner) (3M Medipore) and worn discreetly on the lateral side of the thigh. The accelerometer had an onboard memory and was connected to a dedicated smartphone application via Bluetooth, and the collected data were uploaded to a secured web-server for storage and subsequent analysis. To avoid loss of data (due to full memory), a connection to a smartphone with the dedicated application had to take place at least once weekly. The discreetly worn accelerometer did not interfere with the participant's daily habits (23). The accelerometer was also waterproof and therefore removal was not necessary during bathing, swimming, and showering.

The accelerometer was applied to the participants 1 week before commencement of the IDI, and participants were asked to wear it constantly until the follow-up visit at the end of the IDI (a total period of 9 weeks). During that period, the participants could change the band-aid if needed, and we have previously shown that replacing the accelerometer on the opposite thigh does not affect the measurements (23). An explanation of the purpose of the device was given to participants, and an instruction sheet and additional band-aids were provided.

The accelerometer has an inbuilt algorithm that categorizes data based on intensity thresholds and gravity vectors into inactivity (sitting, reclined, or sleeping), standing, walking, cycling, and other activities in 10-second epochs. The algorithm provides valid and reliable data on time spent physically inactive (sitting, reclined, or sleeping), standing, and movement (e.g., walking, running, cycling, and other activities) in patients with knee OA. We have previously investigated the agreement between actual observations and the algorithm, which showed that the algorithm

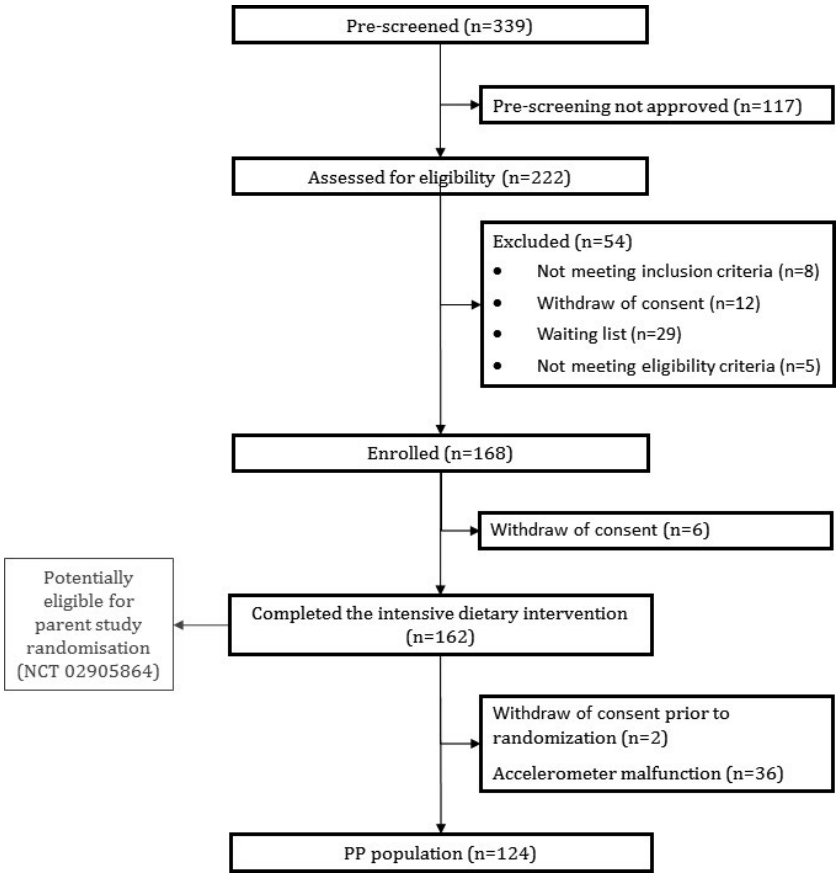

Figure 1. Flow chart of study participants. PP = per-protocol.

detected the actual time periods spent physically inactive a mean ± SD 99% ± 3% of the time and showed 95% ± 6% for standing and 97% ± 9% for movement. Day-to-day reliability for physical inactivity was mean ± SD 96% ± 8%, with 99% ± 1% for movement and 93% ± 7% for standing (23). Time spent (in minutes) in these categories was summed up for each day. In this study the main outcome was time spent physically inactive.

Knee OA symptoms. Knee OA symptoms were assessed by the Knee Injury and Osteoarthritis Outcome Score (KOOS), a patient-reported outcome questionnaire (24), 1 week prior to the IDI and right after the IDI period. The KOOS questionnaire was developed to assess patients' opinions about their knee problems and consists of 5 subscales: pain, other symptoms, function in daily living, function in sport and recreation (sport/rec), and knee-related QoL. Answers are given on 5-point Likert scales, with scores ranging 0–4. A normalized score is calculated (0–100) for each subscale, with 100 indicating no symptoms and 0 indicating extreme symptoms. KOOS has a high test–retest reliability and is regarded as a valid tool when assessing patients with knee OA (25,26). A change of 8–12 points is considered clinically relevant (27).

Statistical analyses. The analyses were performed on the per-protocol population that was defined as participants with baseline and 8-week follow-up data on body weight, as well as complete and valid accelerometer data from the initial week (the week prior to the IDI) and the last week of the IDI period, at the least. Data were deemed valid if a minimum of 24 consecutive hours of wear time in both the baseline period and the follow-up period was detected.

The main outcome of this study was change in average daily time spent physically inactive (minutes/day) from baseline (defined as the daily average during the 1 week prior to the IDI) to the 8-week follow-up (the daily average of the last week of the 8-week IDI). Similar averages were calculated for time spent standing and moving (see above), changes in body weight, and changes in knee OA symptoms as assessed by the KOOS questionnaire. The changes from baseline were analyzed using analysis of covariance, with adjustment for the baseline value. The analyses were repeated with further adjustment for age and sex.

The individual time-course patterns of body weight (weekly measurements) and physical activity (daily measurements) were plotted, and the linear trends in the time courses were analyzed by repeated-measures mixed linear models with time (day or week) as a fixed factor and participant as a random factor.

The main trial was powered to include at least 150 participants. Such a sample provided the current substudy with a power of 0.999 to detect a change in the average weekly time spent physically inactive of at least 30 minutes per day at a 2-sided significance level of 0.05.

We set the statistical significance at the conventional level of 0.05. All analyses were performed using commercially available statistical software (SAS, version 9.4).

RESULTS

A flow chart of the study participants is shown in Figure 1. A total of 168 participants were enrolled in the IDI and all had baseline assessments; 8 participants (5%) withdrew and 36 (21%) had accelerometer malfunction that resulted in invalid data either at baseline or at follow-up. Data loss was caused by batteries not being attached properly (25%), lack of connection between smartphone and device (30.6%), data not stored (30.6%), and accelerometer misplacements (13.9%). A total of 124 participants had valid accelerometer recordings throughout the observation period and thus constituted the per-protocol population. There were no statistically significant differences between the included and excluded participants (assessed by *t*-tests). Baseline characteristics of the participants are presented in Table 1.

The mean ± SD number of visits to the dietitian for the 124 participants was 7.4 ± 0.75 out of 8 possible visits, and the average weight loss was 12.7 kg (95% confidence interval [95% CI] –13.2, –12.1; $P < 0.0001$) corresponding to a decrease in BMI of 4.3 points (95% CI –4.5, –4.2; $P < 0.0001$).

Table 1. Baseline characteristics of the per-protocol population, intention to treat, and dropouts*

	PP (n = 124)	Excluded from analyses† (n = 44)	Intent-to-treat (n = 168)
Sex, no. (%)			
Female	78 (62.9)	31 (70.45)	109 (64.9)
Male	46 (37.1)	13 (29.55)	59 (35.1)
Age, years	59 ± 10.3	57 ± 11.0	59 ± 10.4
Body weight, kg	107.0 ± 19.4	103.2 ± 20.2	106.0 ± 19.6
Height, cm	170.8 ± 8.7	169.7 ± 9.7	170.5 ± 8.9
BMI, kg/m^2	36.6 ± 5.8	35.6 ± 4.8	36.3 ± 5.5
Physical activity measures, mins/day			
Inactivity‡	1,081.3 ± 115.7	1,075.7 ± 108.9	1,079.9 ± 113.6
Standing	111.1 ± 53.0	133.0 ± 68.5	116.9 ± 58.0
Movement§	228.8 ± 71.2	214.8 ± 89.1	225.1 ± 76.3
KOOS (scale 0–100)			
Function (ADL)	68.1 ± 18.5	66.4 ± 15.2	67.7 ± 17.6
Quality of life	43.4 ± 18.3	39.5 ± 16.2	42.3 ± 17.8
Pain	63.7 ± 17.2	63.7 ± 14.2	63.7 ± 16.5
Sport/ recreation	36.5 ± 25.3	31.3 ± 22.1	35.1 ± 24.5
Symptoms	67.7 ± 17.3	67.5 ± 16.9	67.6 ± 17.2

* Values are the mean ± SD unless indicated otherwise. PP = per-protocol; BMI = body mass index; KOOS = Knee Injury and Osteoarthritis Outcome Score; ADL = activities of daily living.
† Withdrew from the main trial (n = 8) and device malfunction (n = 36).
‡ The sum of time spent sitting or lying down.
§ The sum of time spent walking and other movements.

Table 2. Change from baseline to follow-up (8 weeks) in the per-protocol population (n = 124)*

Outcome	Mean change (95% CI)	*P*	Mean change, age- and sex-adjusted (95% CI)	*P*
Change in time spent, mins/day				
Physically inactive†	8.8 (–12.1, 29.7)	0.41	9.3 (–12.4, 31.1)	0.40
Standing	10.4 (3.2, 24.0)	0.13	9.4 (–4.8, 23.6)	0.19
Moving‡	–0.2 (–14.9, 14.5)	0.98	1.5 (–13.6, 16.5)	0.85
Body weight, kg	–12.7 (–13.2, –12.1)	<0.0001	–12.9 (–13.5, –12.4)	<0.0001
BMI, kg/m^2	–4.3 (–4.5, –4.2)	<0.0001	–4.4 (–4.6, –4.2)	<0.0001
Change in KOOS (scale 0–100)				
Quality of life	8.9 (6.5, 11.4)	<0.0001	8.6 (6.0, 11.2)	<0.0001
Pain	12.8 (10.6, 15.0)	<0.0001	13.0 (10.8, 15.3)	<0.0001
Sport/recreation	16.1 (12.6, 19.5)	<0.0001	15.8 (12.2, 19.4)	<0.0001
Symptoms	10.2 (7.9, 12.5)	<0.0001	10.1 (7.7, 12.5)	<0.0001
Function (ADL)	14.5 (12.6, 16.4)	<0.0001	14.6 (12.6, 16.5)	<0.0001

* 95% CI = 95% confidence interval; BMI = body mass index; KOOS = Knee Injury and Osteoarthritis Outcome Score; ADL = activities of daily living.
† The sum of time spent sitting or lying down.
‡ The sum of time spent walking and other movements.

No changes occurred in the average time (minutes/day) spent physically inactive from baseline to follow-up (mean difference 8.8 minutes [95% CI –12.1, 29.7]; *P* = 0.41). Likewise, no change occurred in the average time spent standing or moving (Table 2). There were statistically significant and clinically relevant improvements in the patient-reported knee OA symptoms following the weight-loss intervention. The age- and sex-adjusted analyses only changed the results slightly (Table 2).

The individual time-course patterns of the changes in body weight, time spent physically inactive, time spent standing, and time spent moving are presented in Figure 2. The figure demonstrates substantial day-to-day variability in each of the measurements; however, no trends toward systematic changes were detected, as illustrated by the linear regression fits.

DISCUSSION

Being overweight and obese is associated with the onset of knee OA and the progression and severity of symptoms, all of which are linked to a physically inactive behavior that is a serious threat to overall health. Weight loss could therefore prove beneficial in terms of a spontaneous decrease in time spent physically

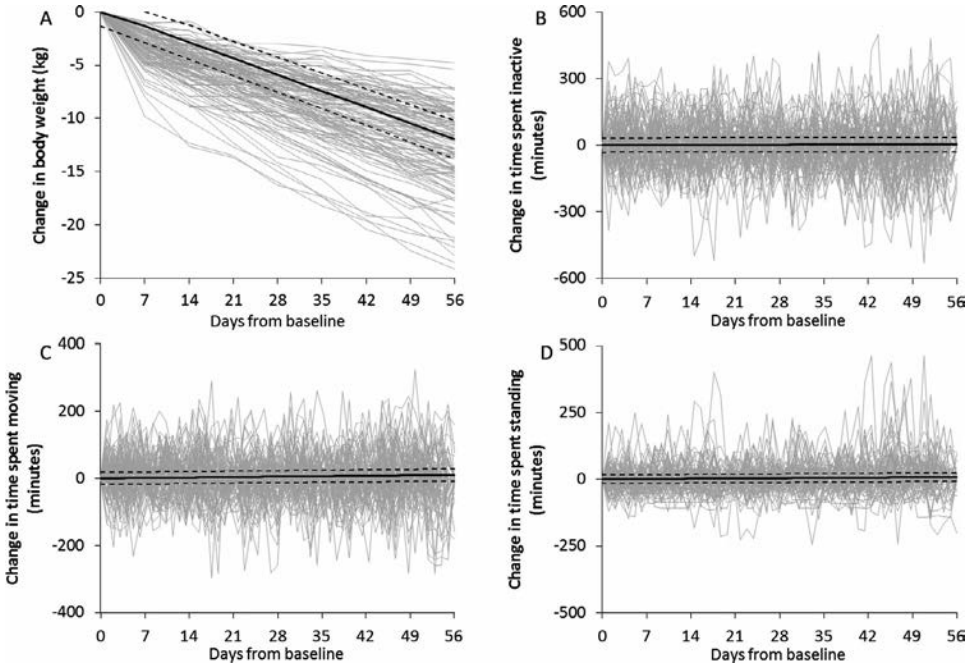

Figure 2. Individual trajectories for changes from baseline over the 8-week intensive dietary intervention in body weight measured weekly (kg/day) (**A**), daily time spent physically inactive (minutes/day) (**B**), daily time spent moving (minutes/day) (**C**), and daily time spent standing (minutes/day) (**D**).

inactive in a population of overweight/obese knee OA patients. However, our results show that despite a significant weight loss paralleled by clinically relevant symptomatic improvements, there were neither changes in time spent physically inactive nor were there signs of increased time spent moving.

The WHO recommends 30 minutes of physical activity 5 times weekly (28) but does not have any concrete recommendations about relevant reductions in physical inactivity. Accordingly, we powered our study for detection of a 30-minute reduction in daily time spent physically inactive as a best estimate of a clinically relevant change, but no such reduction was detected in the cohort. Indeed, our 95% CI respects this pragmatic margin and shows that weight loss does not lead to reduced time spent physically inactive. When looking at changes in daily time spent moving, the absence of change supports the fact that overweight/obese patients with knee OA maintain their daily habits despite a significant weight loss and reduction in symptoms. Therefore, our results show, very robustly, that changes in daily habits do not occur spontaneously in connection to weight loss among patients with knee OA.

The lack of change in time spent physically inactive may be related to the focus of the intervention. The participants volunteered for the study to achieve a weight loss with the purpose of reducing their symptoms, and not with the purpose of decreasing physical inactivity. However, as previous noninterventional studies have linked weight changes with changes in physical activity (18,29), we expected that a focused dietary intervention yielding a substantial weight loss would result in significant changes in physical inactivity. Our results suggest that an emphasis on changes in sedentary behavior is important in relation to weight-loss intervention in order to reduce health risk and increase the chances of a long-lasting weight loss (18,29).

Few studies have assessed accelerometer-based recordings of changes in physical activity following physical-activity interventions in OA populations, and the overall effect of the interventions shows little to no changes in physical activity level (30). Getting patients with knee OA to increase their overall physical activity level seems to be a challenge we have not yet successfully met. An 8-week intervention for patients with knee OA that combined several modalities (exercise and education-behavior change) showed an increase in the time spent exercising after 12 months (31); however, whether this extends to a change in daily time spent physically inactive is uncertain. Together with other studies (31,32), the findings of our study demonstrate that in order to change the daily habits of patients with knee OA, a specific focus on a decrease in physical inactivity is necessary.

To the best of our knowledge, this is the first study to report 9 weeks of 24-hour measurements of physical inactivity in patients with knee OA who participated in an IDI. Previous studies have typically measured physical activity for 10 hours per day for up to 7 days (33–35). We utilized a validated wearable sensor that enabled us to monitor physical inactivity continuously (24 hours per day) for 9 weeks without data loss (23), which exceeds the recommended 10 hours of wear time with a 90-minute nonwear threshold (36). Further, the 24-hour recording ensures capture of all activities performed, which gives a precise estimate of total time spent sitting or reclined. Thus, our estimates of time spent physically inactive most likely have better credibility than previous estimates.

The present study has some limitations. Due to the nature of the underlying main trial, we did not record physical inactivity after the 8-week IDI period. The low-calorie diet (800–1,000 kcal/day) can result in a feeling of low energy, which may have prevented a spontaneous decrease in physical inactivity during the intervention. However, we saw no such trends, and spontaneous changes after the IDI is unlikely. Further, it is likely that patients in this group, who have dealt with being overweight/obese and having knee OA for many years, have had a general low activity level for a long period of their lives (37,38), making it less likely that they spontaneously change behavior. Another limitation is the frequency of accelerometer malfunctions (in 21% of participants). However, the excluded participants were not different from the per-protocol population (Table 1), and the per-protocol population consisted of 124 participants, which provides strong statistical power to detect even minor changes in time spent physically inactive. It is unlikely that the results would have been different had there been fewer accelerometer malfunctions.

We observed a significant day-to-day variability in the individual physical inactivity levels. We are uncertain about the meaning of this observation, as daily observations over a prolonged period have not been published before. It is possible that this variability may be caused by the awareness of having daily habits measured (the Hawthorne effect) (39); however, this would be expected to result in reduced physically inactive behavior, at least in the initial phase, which we did not observe.

The generalizability of the results regarding time spent moving is limited, as we did not assess the intensity of the movements. It is possible that the types of movement changed with higher intensities, while the total time spent moving remained unchanged. However, we focused on time spent physically inactive as this is a risk factor for poor health outcomes independently of time and intensity of any movement (40–42). It is also important to notice that despite a substantial weight loss, the average participant would still be classified as obese after the 8-week period (mean BMI at follow-up ~32 kg/m^2). However, the combined weight loss and improvements in knee OA symptoms were hypothesized to induce a spontaneous decrease in physical inactivity despite patients still being overweight/obese. The findings in this study oppose that notion, and the hypothesis is rejected.

In conclusion, we found that time spent being physically inactive remained stable throughout an 8-week intensive dietary intervention among overweight/obese individuals with knee OA despite a substantial weight loss and clinically relevant changes in knee OA symptoms. This indicates that changes

in physical inactivity must be stimulated by other efforts (e.g., education on the importance of reducing time spent physically active, etc.) to reduce overall health risks associated with sedentary behavior and increase the chance of long-term weight-loss maintenance.

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. Bartholdy 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. Bartholdy, Christensen, Kristensen, Gudbergsen, Bliddal, Henriksen.

Acquisition of data. Bartholdy, Bliddal, Overgaard, Rasmussen.

Analysis and interpretation of data. Bartholdy, Henriksen.

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American Academy of Orthopedic Surgeons Appropriate Use Criteria for Hip Preservation Surgery: Variables That Drive Appropriateness for Surgery

Daniel L. Riddle[1] and Robert A. Perera[2]

Objective. Determining appropriate candidates for hip preservation surgery is challenging because criteria for judging appropriateness are not defined. The American Academy of Orthopaedic Surgeons (AAOS) recently published a hip preservation surgery appropriateness classification system using the RAND/University of California, Los Angeles approach. This study was undertaken to determin the extent and pattern of contribution of each of the variables used to predict the appropriateness of hip preservation surgery.

Methods. An AAOS-appointed multidisciplinary expert panel wrote 270 clinical vignettes incorporating all permutations of 5 indication variables derived from an evidence synthesis. A second independent panel of experts rated the appropriateness of each vignette during multiple Delphi surveys. We used logistic regression to determine the relative contribution of each variable to classification. We also used a classification-tree approach to determine which indication variables, in combination, contributed to the final classification.

Results. Odds ratios from the regression indicated that patient age and radiographic hip osteoarthritis (OA) evaluation were the main indications of appropriateness classification (e.g., the odds ratio for age <40 years was >999.99, with age >65 years as the referent group, for "appropriate/may be appropriate" as compared to "rarely appropriate" vignettes). Hip range of motion, risk for negative outcome, and function-limiting pain did not meaningfully contribute to the final classification.

Conclusion. The AAOS appropriateness classification system for hip preservation surgery is driven almost exclusively by age and radiographic hip OA evaluation. Additional research on appropriateness classification for hip preservation surgery is needed to identify important indication variables beyond age and radiographic hip findings.

INTRODUCTION

The American Academy of Orthopedic Surgeons (AAOS) has invested considerable effort toward the development of appropriate-use criteria (AUCs) for a variety of musculoskeletal conditions, including hip fracture and hip osteoarthritis (OA). These AUCs define patient-level characteristics that can be used to determine treatments and categorize decisions as "appropriate," "may be appropriate," or "rarely appropriate" for a given intervention. As part of this continued effort, AAOS developed the hip preservation surgery AUC, imbedded within the hip OA AUC in late 2017 (1).

The AAOS uses the RAND/University of California, Los Angeles (UCLA) appropriateness method to develop AUCs (2). The RAND/UCLA system uses Delphi-type consensus-based survey sessions that rely on identification of indication variables based on a comprehensive evidence synthesis. In the case of hip preservation surgery, AAOS used a recently developed evidence synthesis for hip OA (3). To develop AUCs, multiple Delphi-type surveys are conducted by multidisciplinary panels of clinical experts. The AAOS appoints 1 expert panel to identify indication variables from the evidence synthesis and to write brief clinical vignettes. A second, independent panel then rates each clinical vignette as appropriate, may be appropriate, or rarely appropriate for a given treatment, using defined methods. The AAOS then creates a no-cost publicly available app based on an algorithm that defines appropriateness ratings for all combinations of indication variables for a given treatment. The apps are designed to serve as simple-to-use decision aides for informing clinicians and the public about the extent of appropriateness of various orthopedic interventions.

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

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SIGNIFICANCE & INNOVATIONS

- The American Academy of Orthopedic Surgeons (AAOS) hip preservation appropriateness classification system is a first attempt to develop a surgical appropriateness classification for hip preservation surgery.
- The current study shows that while the AAOS system was defined using the clearly defined RAND/University of California, Los Angeles appropriateness approach, the outcome of the appropriateness classification system is not likely to positively impact hip preservation surgical decisions.
- Patient age and radiographic osteoarthritis severity variables dominated prediction of hip preservation appropriateness, and given the rudimentary nature of these variables for such a complex clinical syndrome, there appear to be substantial limitations associated with the AAOS hip preservation appropriateness system.
- There is strong need for an appropriateness classification system specifically devoted to individuals who fit a likely profile for optimal outcomes following hip preservation surgery.

Hip preservation surgery includes a constellation of procedures, the most common being arthroscopic procedures to address, most commonly, hip dysplasia and femoroacetabular impingement (FAI) (4). There has been substantial growth in the use of these procedures (5). Given the high prevalence of asymptomatic hip dysplasia/FAI findings (6) and substantial variation in symptoms and physical examination findings (7), the development of an AUC for hip preservation procedures is timely and important. Hip preservation surgery is an elective procedure with no clearly defined and agreed upon diagnostic criteria.

The first purpose of our study was to determine the extent of contribution of each of the 5 indication variables (i.e., age, function-limiting pain, hip radiographic evaluation, range-of-motion limitation, and the presence or absence of modifiable risk factors [e.g., obesity, mental health disorders, tobacco use, or uncontrolled diabetes mellitus]) for predicting the appropriateness of hip preservation surgery (1). Our second purpose was to determine the pattern of combinations of indication variables that associated with final classification. We hypothesized that hip preservation classification would be highly reliant on age and radiographic status, much like the knee replacement AUC developed by AAOS (8), and that function-limiting pain, range-of-motion limitation, and the presence of modifiable risk factors would contribute in only a minor or inconsequential way.

MATERIALS AND METHODS

We obtained the full report entitled "Appropriate Use Criteria for the Management of Osteoarthritis of the Hip" from the AAOS website (http://www.aaos.org) (1). The report summarized the results of the AAOS expert panels and provided complete versions of all vignettes (n = 270). The expert voting panel members who provided appropriateness ratings were 13 orthopedic surgeons, 1 physical therapist, 1 radiologist, and 1 rheumatologist. The panel members' clinical experience/expertise in treating patients who may be candidates for hip preservation surgery was not reported. Each vignette was scored as appropriate, may be appropriate, or rarely appropriate, using defined criteria during 3 modified Delphi rounds. Scoring by the expert voting panel was made on a 9-point scale with scores of 1–3 considered rarely appropriate, scores of 4–6 considered may be appropriate, and scores of 7–9 considered appropriate. Over the 3 Delphi rounds, all voting members used this scale to rate each vignette. Final ratings of appropriate were made when the median panel rating was between 7 and 9. When the median score for panel ratings was between 4 and 6, the final rating for a vignette was may be appropriate, and for median ratings between 1 and 3, the final rating was rarely appropriate. Additional scoring details can be found in the AAOS AUC full report (1).

We had no interaction with any member of the expert voting panel. Instead, we relied on the full AAOS report to extract all vignette data regarding hip preservation appropriateness ratings. Specifically, the investigators extracted data related to all indication variables (i.e., the term used to describe the variables chosen from published evidence to guide classifications of appropriateness) and the appropriateness ratings for each of the 270 vignettes scored in the final voting as appropriate, may be appropriate, or rarely appropriate. In the AAOS AUC for hip preservation surgery there were a total of 27 vignettes classified by the expert panel as appropriate for hip preservation surgery, 62 vignettes classified as may be appropriate, and 181 vignettes classified as rarely appropriate. Scores for each of the 5 indication variables for each vignette were analyzed as reported in the AAOS AUC document (Table 1). Three of the indication variables (i.e., age, hip motion, function-limiting pain) had trichotomous responses, 1 (i.e., modifiable risk factors) had dichotomous responses, and 1 (i.e., hip radiographic evaluation) had 5 response options. The variables were combined in the vignettes by AAOS using a factorial approach covering all permutations of the 5 prognostic variables ($[5^1 \times 3^3 \times 2^1] = 270$).

Data analysis. A logistic regression with the Firth correction was used to evaluate the association between indication variables and rarely appropriate versus a combined may be appropriate/appropriate category (9). Initially, multinomial regression was the intended model, but sparsity of cells necessitated combining the may be appropriate with appropriate categories. Combining the appropriate and may be appropriate categories is reasonable, given that both categories generally endorse a hip preservation procedure, while the rarely appropriate category does not. Even after collapsing these categories, some cells remained empty. This situation causes an issue of separation, where the response category can be perfectly categorized on the basis of a variable. To

Table 1. Characteristics of the 5 indication variables and appropriateness ratings for the AAOS hip preservation clinical vignettes (n = 270)*

Indication variable measurement scale	Values
Age	
Young (<40 years)	90 (33.3)
Middle-aged (40–65 years)	90 (33.3)
Elderly (>65 years)	90 (33.3)
Function-limiting pain	
Pain walking moderate/long distances (e.g., >0.25 mile)	90 (33.3)
Pain walking short distances (e.g., approximately 2 city blocks)	90 (33.3)
Pain at rest/night	90 (33.3)
Radiographic evaluation of the hip	
Minimal OA	54 (20)
Minimal OA with acetabular dysplasia	54 (20)
Minimal OA with FAI	54 (20)
Moderate OA	54 (20)
Severe OA	54 (20)
Hip range-of-motion limitation	
Minimal	90 (33.3)
Moderate	90 (33.3)
Severe	90 (33.3)
Presence or absence of risk factors for negative outcome	
Modifiable risk factors present	135 (50)
No modifiable risk factors present	135 (50)
Hip preservation classification	
Appropriate	27 (10.0)
May be appropriate	62 (23.0)
Rarely appropriate	181 (67.0)

* Values are the number (%). AAOS = American Academy of Orthopaedic Surgeons; OA = osteoarthritis; FAI = femoroacetabular impingement.

account for this separation, Firth's modified score procedure was used. This method works well under conditions of separation and small sample sizes and is preferred to unadjusted methods (10).

All indication variables were categorical and dummy coded. Because we studied the entire population of vignettes, *P* values and confidence intervals were not needed. Coefficients from the regression were used to assess the importance of each indication variable in determining appropriateness classification. Because all variables were categorical, coefficients for the different criteria are directly comparable. Additionally, because all permutations of variables were used in the vignettes, collinearity was not an issue. Nagelkerke's R^2 statistic was used to estimate explained variance. This statistic informs the degree to which the misspecified model, without all possible interaction terms, explains the outcome. Logistic analyses were completed using SAS software, version 9.4.

A classification-tree approach (exhaustive chi-square automatic interaction detection [CHAID]) determined the optimal combination of prognostic variables for predicting each appropriateness rating (11). The exhaustive CHAID was used to construct the tree to allow for the examination of all possible splits of polytomous indication variables (e.g., age, scored as young, middle-aged, and elderly). The analysis allowed for up to 5 levels of branching within the tree, with a minimum of 25 vignettes in a parent node (i.e., a major branch in the tree) and a minimum of 15 subjects in a terminal node (i.e., the end of a branch). The analysis systematically tested each of the 5 indication variables to determine which variable most strongly associated with appropriateness classification. Once the variable with the highest chi-square value was found, the tree branch was split and the process was repeated. Only variables that provided a statistically significant improvement in prediction compared to the more proximal branch, based on Bonferroni-corrected chi-square estimates with a *P* value less than 0.05, were included. The goal of the tree analysis was to find the purest terminal nodes (i.e., nodes that came closest to including only 1 type of classification) for each branch of the tree, while also considering parsimony. Cross validation, a step that involves testing the model on an independent data set, was not necessary because we studied the entire population of vignettes. Kappa values with linear weighting were used to judge the extent of agreement between the AAOS system classification and our classification tree findings. We used SPSS software, version 24, for all analyses.

RESULTS

Logistic regression findings. Two indication variables, age and radiographic evaluation, had the largest beta coefficients (Table 2). For example, with the elderly age group (age >65 years) set as the referent group, vignettes classified as young (<40

Table 2. Logistic regression analysis with Firth correction of hip preservation data from 270 vignettes with classification of appropriate ("rarely appropriate" as the reference category)*

AAOS indication variable and rating	β	Odds ratio
Intercept	–1.03	–
Function-limiting pain		
Moderate-to-long distances	0†	–
Short distances	1.08	2.9
Pain at rest or night	1.54	14.2
Range of motion minimal	0†	–
Limitation		
Moderate	1.68	5.3
Severe	2.65	14.2
Risk of negative outcome		
No modifiable risk factors	0†	–
Modifiable risk factors	0.33	1.4
Radiographic minimal OA	0†	–
Evaluation		
Minimal OA with autoinflammatory disease	8.20	>999.99
Minimal OA with FAI	10.36	>999.99
Moderate OA	–5.49	0.004
Severe OA	–5.49	0.004
Age		
Young (<40 years)	13.66	>999.99
Middle-aged (40–65 years)	8.18	>999.99
Elderly (>65 years)	0†	–

* AAOS = American Academy of Orthopaedic Surgeons; OA = osteoarthritis; FAI = femoroacetabular impingement.
† Parameter fixed to zero because of redundancy.

years) or middle-aged (40–65 years) had odds of being classified as appropriate/may be appropriate of >999.99 times larger relative to the rarely appropriate group. Similarly, the odds of being classified as appropriate/may be appropriate (relative to rarely appropriate) for minimal hip OA with FAI and minimal hip OA with acetabular dysplasia (with severe hip OA as the referent group) were also >999.99 times as compared to a vignette with minimal OA. Conversely, having vignettes with moderate or severe OA had odds that were 0.004 times smaller than those with minimal OA. Rather than interpreting the absolute magnitude of the odds ratio, considering their relative size compared to other variables in the model is more important. These results highlight the fact that the odds of being classified as appropriate/may be appropriate depend almost entirely on age and hip OA. Last, Nagelkerke's R^2 statistic for the model was 0.94, indicating excellent explanation despite model misclassification.

Decision-tree findings. The accuracy of the decision tree for correctly identifying AAOS hip preservation appropriateness classifications was 94.1% (66.7% for appropriate, 95.2% for may be appropriate, and 97.8% for rarely appropriate ratings). The extent of agreement between the decision tree and AAOS classifications was weighted $\kappa = 0.90$, indicating almost perfect agreement (12). The most powerful (i.e., most proximal in the tree) indication variable was hip radiographic evaluation and the next strongest was age (Figure 1). Risk factors for negative outcomes was the final variable that entered the tree (see terminal nodes 10 and 11).

The terminal nodes for each branch of the tree are labeled as nodes 3, 4, and 5 as well as 7 through 10 (Figure 1). Terminal nodes 3, 5, 7, and 10 are pure nodes, indicating there was no disagreement from the expert panel for these nodes. For the vignettes in node 10, a pure "appropriate" node, for example, the vignettes had minor hip OA with acetabular dysplasia or FAI, were age <40 years, and had no modifiable risk factors. In contrast, terminal node 4 is an example of a mixed terminal node, with most vignettes classified as may be appropriate for hip preservation surgery. These vignettes had minimal hip OA (without dysplasia or FAI) and were age <40 years.

DISCUSSION

Use of hip preservation surgery increased substantially in the past decade (5), which provides a strong stimulus to better understand factors that drive indications for surgery. Given the overall paucity of randomized trial evidence for hip preservation surgery (13), whether this rate of utilization is justified or whether these surgical procedures are underutilized or overutilized is unclear.

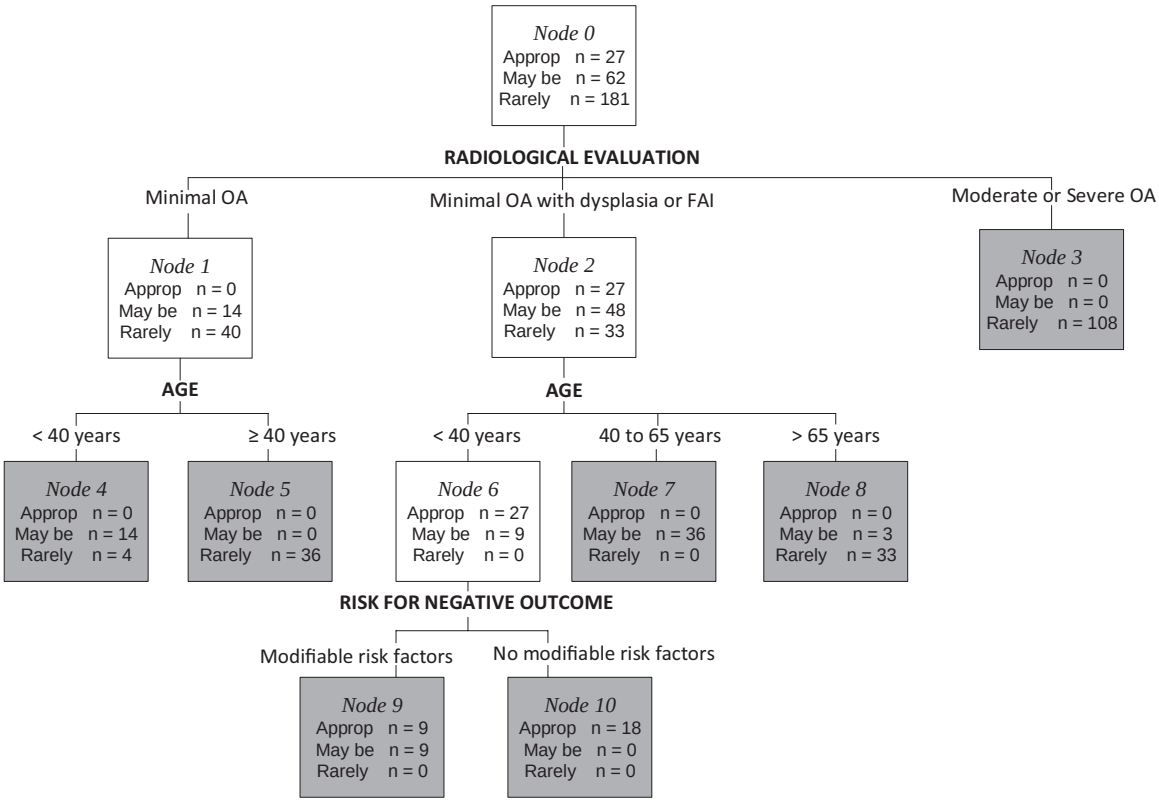

Figure 1. Classification tree for the entire sample (n = 270). The branches of the tree are labeled based on the key variables that discriminated among the classifications, and these are listed as Radiological Evaluation, Age, and Risk for Negative Outcome. The terminal nodes of each branch (nodes 3 to 5 and 7 to 10) indicate the final distributions of ratings of appropriate (Approp), may be appropriate (May be), and rarely appropriate (Rarely). Vignette sample sizes are reported in each box. OA = osteoarthritis; FAI = femoroacetabular impingement.

Two recently published randomized trials comparing arthroscopic surgery to physical therapy rehabilitation for patients with FAI reported inconsistent findings (14,15). Griffin et al (14) reported 1-year clinically important average improvements in hip-related quality of life in the arthroscopy group versus physical therapy, while Mansell et al (15) found no difference in 2-year hip pain, quality of life, or global ratings of change among the 2 treatment groups. The AAOS AUC system for hip preservation surgery has a strong potential to inform utilization, given that the RAND/UCLA approach to judging appropriateness has been endorsed for a variety of elective procedures (16), and recent evidence was used to derive indication variables for the AAOS hip preservation classification system.

The hip preservation AAOS appropriateness system relies almost exclusively on more traditional measures of hip radiographic assessment and age to drive classification. Function-limiting hip pain, the main driver of patient care seeking, and hip range of motion, which are 2 indication variables of relevance to individuals who are potential candidates for hip preservation surgery, did not contribute to prediction in either statistical model. Given the high rate of asymptomatic hip radiographic findings and the substantial variation in the symptoms of patients being considered for hip preservation surgery (6,7), we did not expect that neither function-limiting pain nor hip range of motion would play a role in classification. In our view, this finding is likely attributable either to a relative lack of prognostic evidence for these variables or to an overreliance by the expert panel on more traditional variables. Either way, the expert panel placed minimal emphasis on function-limiting pain when judging appropriateness, much like the AAOS knee arthroplasty appropriateness system (17). In our view, the literature lacks high-quality studies examining the effects of function-limiting pain and hip range of motion on outcomes. This apparent gap in the literature may explain why these specific factors were not weighted heavily by experts in hip preservation surgery and rehabilitation (18–20). These data make a case for more substantial prognostic studies of individuals undergoing hip preservation surgery.

An additional limitation of the AAOS hip preservation AUC was that the same vignettes designed for judging hip arthroplasty appropriateness were also used for rating hip preservation appropriateness. Given the substantial age and OA severity differences in indications for these 2 treatments, there were likely many vignettes that were clearly not applicable for the hip preservation AUC. For example, of the 270 vignettes written by the

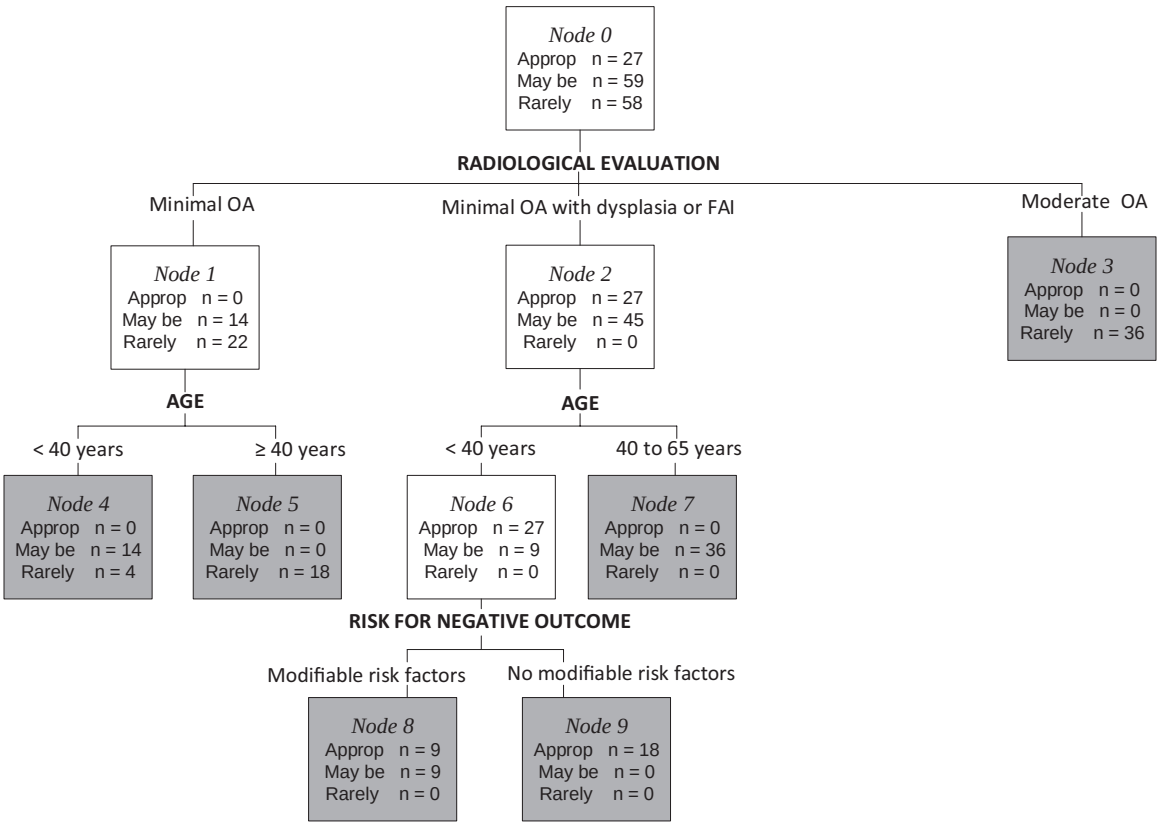

Figure 2. Classification-tree sensitivity analysis with vignettes classified as elderly or severe osteoarthritis (OA) excluded, leaving a total sample of 144. The branches of the tree are labeled based on the key variables that discriminated among the classifications, and these are listed as Radiological Evaluation, Age, and Risk for Negative Outcome. The terminal nodes of each branch (nodes 3 to 5 and 7 to 9) indicate the final distributions of ratings of appropriate (Approp), may be appropriate (May be), and rarely appropriate (Rarely). Vignette sample sizes are reported in each box. FAI = femoroacetabular impingement.

hip AUC writing panel, a third (n = 90 vignettes) were classified as elderly (i.e., age >65 years) and 20% had severe hip OA. These vignettes would probably be considered for hip preservation surgery. A multiuse strategy of writing 1 set of vignettes for both hip preservation and hip replacement AUC development likely led to a substantial reduction in the proportion of vignettes that would receive serious consideration for hip preservation surgery. In our view, this multiuse approach likely explains why only 27 of 270 vignettes (i.e., 10%) were rated as appropriate for hip preservation surgery.

In a post hoc sensitivity analysis, we repeated the regression tree analysis after excluding vignettes with age classified as elderly or with hip OA classified as severe. This repetition reduced the number of vignettes to 144 but also excluded vignettes almost certain to be classified by the expert panel as inappropriate for hip preservation surgery. Much like the tree for the full sample, age and radiographic evaluation still dominated, while risk for negative outcome played a minor role in the classification tree (Figure 2).

The most powerful indication variable of appropriateness in the full sample of vignettes was hip OA severity. When considering only hip OA severity, if the vignette indicated the candidate had minor hip OA without FAI or dysplasia, or moderate-to-severe hip OA, 148 of 162 vignettes were judged to be rarely appropriate for hip preservation surgery. All 27 vignettes that were classified as appropriate had minor hip OA with either FAI or dysplasia. Additionally, all 27 vignettes classified as appropriate were coded as age <40 years.

We found improvements in the hip preservation appropriateness system as compared to the AAOS-derived knee arthroplasty appropriateness system. For example, actual age ranges were provided for the vignettes in the hip system, which reduces uncertainty when using the system relative to the knee system, which did not include age ranges for the classification of age. Additionally, 3 nonsurgeons served on the hip preservation expert panel as compared to only 1 nonsurgeon in the knee arthroplasty appropriateness system.

Developers of the RAND/UCLA system recommend a diverse multidisciplinary panel of experts with knowledge in the area of interest in an effort to reduce bias risk associated with panels comprised entirely or almost entirely of specialists who conduct the surgery (2). Despite these improvements, there is almost complete reliance on traditional variables of age and OA severity and a lack of relevance for function-limiting pain severity and other patient-level symptom-based variables, which are key variables driving health care seeking.

In conclusion, we found that the AAOS hip preservation appropriateness classification system appears to be driven almost exclusively by hip OA severity and age and not by symptoms of importance to patients or by other more contemporary measures. The system, therefore, is likely to be substantially limited, given the heavy emphasis on traditional variables. The AAOS hip preservation appropriateness system and the corresponding app are freely available worldwide. Our data suggest that rheumatologists, orthopedic surgeons, other care providers, and most importantly, patients, are likely to derive minimal benefit from use of the AAOS system and app. Priority should be placed on development of an appropriateness system specifically devoted to hip preservation surgery.

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. Dr. Riddle 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. Riddle, Perera.
Acquisition of data. Riddle, Perera.
Analysis and interpretation of data. Riddle, Perera.

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Patient-Reported Outcomes One to Five Years After Anterior Cruciate Ligament Reconstruction: The Effect of Combined Injury and Associations With Osteoarthritis Features Defined on Magnetic Resonance Imaging

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Objective. Persistent symptoms and poor quality of life (QoL) are common following anterior cruciate ligament reconstruction (ACLR). We aimed to determine the influence of a combined ACL injury (i.e., concomitant meniscectomy and/or arthroscopic chondral defect at the time of ACLR and/or secondary injury/surgery to ACLR knee) and cartilage defects defined on magnetic resonance imaging (MRI), bone marrow lesions (BMLs), and meniscal lesions on patient-reported outcomes 1 to 5 years after ACLR.

Methods. A total of 80 participants (50 men; mean ± SD age 32 ± 14 years) completed the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the International Knee Documentation Committee (IKDC) questionnaires as well as a 3T MRI assessment at 1 and 5 years after ACLR. Median patient-reported outcome scores were compared between isolated and combined ACL injuries and with published normative values. Using multivariate regression, we evaluated the association between compartment-specific MRI cartilage, BMLs, and meniscal lesions and patient-reported outcomes at 1 and 5 years.

Results. Individuals with a combined injury had significantly worse scores in the KOOS subscale of function in sport and recreation (KOOS sport/rec) and in the IKDC questionnaire at 1 year, and worse scores in the KOOS subscales of pain (KOOS pain), symptoms (KOOS symptoms), and QoL (KOOS QoL) and in the IKDC questionnaire at 5 years compared to those with an isolated injury. Although no feature on MRI was associated with patient-reported outcomes cross-sectionally at 1 year, patellofemoral cartilage defects at 1 year were significantly associated with worse 5-year KOOS symptoms (β = –9.79, 95% confidence interval [95% CI] –16.67, –2.91), KOOS sport/rec (β = –7.94, 95% CI –15.27, –0.61), KOOS QoL (β = –8.29, 95% CI –15.28, –1.29), and IKDC (β = –4.79, 95% CI –9.34, –0.24) scores. Patellofemoral cartilage defects at 5 years were also significantly associated with worse 5-year KOOS symptoms (β = –6.86, 95% CI –13.49, –0.24) and KOOS QoL (β = –11.71, 95% CI –19.08, –4.33) scores.

Conclusion. Combined injury and patellofemoral cartilage defects shown on MRI are associated with poorer long-term outcomes. Clinicians should be vigilant and aware of individuals with these injuries, as such individuals may benefit from targeted interventions to improve QoL and optimize symptoms.

INTRODUCTION

Anterior cruciate ligament reconstruction (ACLR) is commonly performed following ACL injury in individuals seeking a return to preinjury sports participation. Patient-reported symptoms, function, and quality of life (QoL) typically improve during the first 6–12 months following ACLR but appear to plateau beyond this point (1–4). Although 65% of young people return to preinjury sports participation following ACLR (5), as many as 34% report unacceptable symptoms up to 2 years following surgery (6).

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SIGNIFICANCE & INNOVATIONS

- Individuals with a combined injury or patellofemoral cartilage defect on magnetic resonance imaging (MRI) had worse 5-year patient-reported outcomes and may benefit from additional education and targeted interventions.
- This study assists clinical interpretability of patient-reported outcomes: approximately one-half of all patients with a combined injury at 5 years after anterior cruciate ligament reconstruction do not achieve acceptable symptoms or quality of life.
- Meniscal lesions were the only tibiofemoral feature on MRI associated with worse patient-reported outcomes. Tibiofemoral bone marrow lesions were associated with better patient-reported outcomes. The long-term significance of these should be explored further in populations with anterior cruciate ligament injuries.

Persistent symptoms could induce negative lifestyle modifications (i.e., reduced physical activity, weight gain) (7), increasing the burden on health care systems in the longer term. Successfully identifying patients with persistent symptoms early following ACLR may allow for the development of targeted interventions.

A combined injury (i.e., ACL injury and meniscectomy and/or cartilage lesion assessed at the time of ACLR) might increase the risk of worse symptoms and QoL in the short to medium term (1–6 years) (1,3) and long term (15–20 years) (8). However, some studies report no or minimal association between combined injuries and patient-reported outcomes in the medium to long term (9–11). Previous studies (2,3,8,9) have utilized group-level data (i.e., in order to determine if a significant group mean effect exists between isolated and combined ACLR groups). This may not be relevant to patients and clinicians, who are most interested in their own individual effect in relation to treatment. The group-level approach does not describe the number of individuals who present with unacceptable outcomes and who may require and benefit from additional interventions. Identifying individuals with poor outcomes and enhancing clinical interpretability of patient-reported outcomes may be improved by comparing scores from each ACLR patient (as opposed to group means) to scores from other ACLR patients who report acceptable knee function.

Persistent symptoms following ACLR may be related to early deterioration of joint structure. Radiographic osteoarthritis (OA) occurs in 50–90% of knees 10–15 years after ACLR, but the relationship with patient-reported outcomes is unclear (12,13). In older populations with established knee OA, more specific imaging markers of disease observed on magnetic resonance imaging (MRI), such as bone marrow lesions (BMLs), inflammation, and cartilage defects, are associated with clinical outcomes (i.e., pain) (14–17). While early structural pathology identified on MRI may be preexisting or occur with injury, features of OA continue to deteriorate at an accelerated rate compared to primary OA between 1 and 5 years after ACLR (18). Yet, there is limited research on how these early features of OA affect patient-reported outcomes. Tibiofemoral cartilage lesions and BMLs have little association with knee symptoms cross-sectionally at 2 (19) and 12 years after ACLR (20). An important omission in previous research is the patellofemoral joint, which is a potential contributor to knee symptoms after ACLR (21). We recently identified patellofemoral cartilage defects at 1 year after ACLR as being associated with worse patient-reported outcomes at 3 years (22). Further cross-sectional and longitudinal evaluation of the relationship between OA features seen on MRI and patient-reported outcomes beyond 3 years is important to determine if imaging features of OA affect patient reported pain, function, or QoL.

The aims of the current study were to determine the influence of a combined injury on patient-reported outcomes measures from 1 to 5 years after ACLR and to compare these outcomes to known normative patient-reported outcome scores (in uninjured and ACLR patients). We also aimed to determine the association between patellofemoral and tibiofemoral cartilage defects, BMLs, meniscal lesions, and patient-reported outcomes at 1 and 5 years after ACLR.

MATERIALS AND METHODS

Study design and participants. All 112 consecutively recruited individuals who had completed patient-reported outcomes at 1 year after ACLR as part of our previous evaluation (23) (median age at surgery 27 years [range 18–51 years]) were eligible for the current prospective 5-year follow-up study. Baseline (1 year after ACLR) eligibility criteria, ACLR technique, and changes in cartilage, bone marrow, and meniscus between 1 and 5 years have been reported previously (18,23). Briefly, all patients underwent ACLR performed by 1 of 2 Melbourne-based orthopedic surgeons using a single-bundle hamstring-autograft. Baseline exclusion criteria included knee injury/symptoms prior to ACL injury, >5 years between ACL injury and reconstruction, and any secondary injury/surgery (between surgery and 1 year after ACLR). Secondary injury was defined as a new index or contralateral knee injury (ACL, meniscus, collateral ligament) or surgery. All

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participants were invited to participate in the 5-year post-ACLR follow-up, including 10 participants who sustained a secondary injury between 1 and 5 years given that this is a common occurrence and represents the wider ACLR population. A total of 81 (72%) participants completed the same patient-reported outcomes measures at the 5-year post-ACLR evaluation (Figure 1). Ethics approval was granted by La Trobe University Human Ethics Committee (HEC 15–100), and all participants signed informed consent.

Demographic, injury, and surgical factors. Data on participant age, sex, injury history, body mass index (BMI), and previous and current activity level (level 1 = pivoting/jumping sports up to level 4 = sedentary) (24) were obtained at 1 and 5 years. The combined injury group at 1 year consisted of individuals with ACL injury and concomitant meniscectomy or a significant cartilage defect (i.e., Outerbridge grade ≥2 [25]) at the time of ACLR (i.e., extracted from surgical notes). Those reporting to investigators a secondary injury/surgery to the index knee between the 1- and 5-year follow-ups were added to the combined injury group at 5 years. Defining a combined injury by the presence of a concomitant injury at time of ACLR and/or a secondary injury over time via this method is consistent with previous longitudinal cohort studies (8,11). Individuals without a combined injury were defined as having an isolated injury.

Patient-reported outcome measures. At 1 and 5 years, participants completed the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire and the International Knee Documentation Committee (IKDC) subjective knee evaluation with respect to their index knee condition during the previous week. The KOOS and IKDC questionnaires are used extensively for patients with ACL injuries with established reliability and validity (26). The following 4 subscales of the KOOS were assessed: pain (KOOS pain), symptoms (KOOS symptoms), function in sport and recreation (KOOS sport/rec), and knee-related QoL (KOOS QoL). The KOOS activities of daily living subscale was excluded due to the ceiling effects observed in young active populations (27). Patient-reported outcomes measures were completed either in person (pen and paper) or via the online portal PROmptus–Medical (DS PRIMA) with instructions matching the original paper version. The KOOS (intraclass correlation coefficient [ICC] >0.96) (28) and IKDC (ICC 0.79) (29) questionnaires have demonstrated test–retest reliability between paper and electronic formats.

Cartilage defects, BMLs, and meniscal lesions. Of the 112 participants completing patient-reported outcomes at 1 year, 111 completed MRI assessment at 1 year, and 80 (71%) at 5 years (Figure 1) with an identical MRI scanner and sequences as described previously (23). Briefly, with an Achieva 3T MRI system (Philips), sequences consisted of a 3-dimensional proton density–weighted volume isotropic turbo spin-echo acquisition technique acquired at 0.35 mm isotropically, a short-tau inversion recovery sequence, and an axial proton-density turbo spin-echo sequence. Cartilage defects, BMLs, and meniscal lesions were scored using the MRI OA Knee Score (MOAKS) by a musculoskeletal radiologist (AG) with 19 years of experience who established interrater and

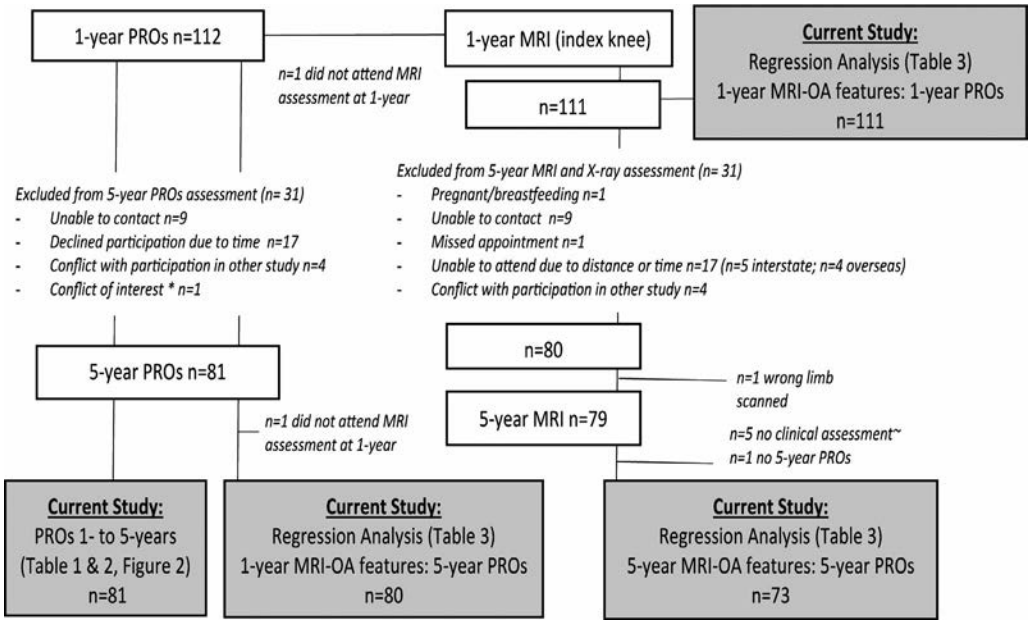

Figure 1. Flow chart of participant recruitment. Body mass index data from the clinical assessment were required for the regression analysis, which caused 6 patients to not be included in the analysis for the 5-year magnetic resonance imaging (MRI) assessment and the 5-year patient-reported outcomes (PROs) assessment. OA = osteoarthritis; * = the participant at 1 year was a member of the research team at 5 years; ~ = clinical assessment was also performed on a subset of the cohort at 1 and 5 years.

intrarater reliability in semiquantitative MRI assessment (κ = 0.61–0.80) (30). The 1- and 5-year images were read paired (i.e., using 1- and 5-year MRI scans side-by-side, the radiologist was not blinded to time points) and were blinded to clinical information. The MOAKS divides the knee into 14 articular subregions to score cartilage defects and BMLs. For the tibiofemoral compartment, cartilage defects and BMLs were graded in each of the following 10 subregions: central and posterior femur (medial and lateral) and anterior, central, and posterior tibia (medial and lateral). The following 4 subregions were used to grade cartilage defects and BMLs in the patellofemoral compartment: the patella (medial and lateral) and trochlea (medial and lateral). Meniscal lesions were defined as medial or lateral and divided into anterior, posterior, and central subregions. Cartilage defects and BMLs were graded as present or absent in the tibiofemoral and patellofemoral compartments if any corresponding subregions for that compartment had a lesion greater than or equal to grade 1 in size (i.e., any lesion >0% in size relative to each subregion surface area). Meniscal lesions were graded as present if in either tibiofemoral compartment subregion there was 1) a definite vertical, horizontal, or complex tear (definite = an area of abnormal signal that extends to the meniscal articular surface); 2) partial or progressive maceration (loss of morphologic substance of the meniscus); or 3) at least a grade-1 extrusion (i.e., >2 mm) (30). Details of the MRI sequences and MOAKS are presented in Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract.

Statistical analyses. Combined and isolated injury group medians and interquartile ranges (IQRs) for the KOOS and IKDC questionnaires were calculated at 1 and 5 years due to non-normally distributed data (assessed with Shapiro-Wilk's tests). For the KOOS and IKDC questionnaires, we visually compared and indicated if the ACLR median scores were at least a minimum detectable change (MDC) (i.e., ≥14 points) (26,31) below the normative median (32–34). Nonparametric analyses were used to account for the non-normal distribution of the KOOS and IKDC scores at 1 and 5 years. Mann-Whitney U tests compared patient-reported outcomes between the isolated and combined groups cross-sectionally at 1 and 5 years. The absolute change in patient-reported outcomes between 1 and 5 years was normally distributed and reported as mean ± SD, and parametric analyses (independent sample *t*-tests) compared the change in each group. In addition, each individual was classified as having an acceptable KOOS or IKDC score if it was greater than a predetermined cutoff (6,35). The KOOS cutoffs were determined from the Norwegian Knee Ligament Registry (n = 1,197) using the lower 95% confidence interval (95% CI) score for each subscale (KOOS pain 88 of 100; KOOS symptoms 83 of 100; KOOS sport/rec 73 of 100; KOOS QoL 73 of 100) for patients who perceived their knee function as acceptable 24 months after ACLR (6). The IKDC cutoff (75 of 100) was determined using the mean IKDC score (85 of 100) minus the SD (SD 10) for individuals who perceived their knee function as acceptable 3.5 years after ACLR (35). Fisher's exact test was used to compare the proportion of the isolated and combined groups defined as acceptable.

Multivariable linear regression was used to determine the cross-sectional relationship between the presence of cartilage lesions, BMLs, and meniscal lesions (dichotomous independent variables) in the patellofemoral and tibiofemoral compartments and patient-reported outcomes (continuous KOOS and IKDC scores) at 1 and 5 years. Regression was adjusted for age at the time of surgery, sex, BMI at 1 year, and combined injury due to their potential influence on patient-reported outcomes (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract). The relationship between cartilage lesions, BMLs, and meniscal lesions at 1 year with patient-reported outcomes at 5 years was also included, with additional adjustment for the baseline patient-reported outcome score. Stata, version 14.2 was used for statistical analyses. *P* values less than 0.05 were considered statistically significant.

RESULTS

Participant demographics. Demographic characteristics of the 81 participants included for patient-reported outcomes analysis at 1 and 5 years are presented in Table 1. There were no demographic, surgical, or baseline MRI-related differences between those who did (n = 81) and did not participate (n = 31) in the follow-up assessment at 5 years ($P \geq 0.05$) (see Supplementary Appendix C, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract). An exception was medial meniscal lesions, which were more prevalent in the participating group at baseline. Forty (49%) and 46 (57%) of the 81 participants were classified as having a combined injury at 1 and 5 years, respectively (i.e., 6 were added to the combined injury group at 5 years due to a secondary injury between 1 year and 5 years). Between 1 year and 5 years, 10 participants had experienced a secondary injury in the index knee (Table 1); however, 4 of these injuries were already classified as a combined injury at 1 year.

Patient-reported outcomes. At 1 year after ACLR, individuals in the combined injury group had significantly worse KOOS sport/rec and IKDC scores (median difference [IQR] 15 [4.6] and 5.0 [3.5], respectively; $P < 0.05$). At 5 years, all patient-reported outcomes (except KOOS sport/rec) were significantly worse in the combined injury group. The median differences (IQR) were as follows: KOOS pain 5.0 (2.5); KOOS symptoms 11.0 (4.2); KOOS QoL 13.0 (4.6); and IKDC 4.0 (3.2). KOOS and IKDC scores at

Table 1. Participant characteristics of combined and isolated injury groups at 1 and 5 years after ACLR*

	1 year (n = 81)		5 years (n = 81)	
	Combined (n = 40)	Isolated (n = 41)	Combined (n = 46)	Isolated (n = 35)
Age, median ± IQR years	31 ± 12†	25 ± 12	35 ± 14†	29 ± 13
Sex, male	26 (65)	24 (59)	31 (67)	19 (54)
BMI, median ± IQR kg/m^2‡	26.9 ± 5.4†	24.8 ± 3.0	27.5 ± 5.1†	24.7 ± 4.2
Preinjury activity level 1 sport§	28 (70)	28 (68)	34 (74)	22 (63)
Anteroposterior laxity between-knee difference, median ± IQR mm¶	1.1 ± 2.7	1.9 ± 2.1	NA	NA
Time of injury to surgery, median ± IQR weeks	19 ± 32†	12 ± 9	17 ± 26†	12 ± 9
Meniscectomy at time of ACLR#	32 (80)	0 (0)	32 (40)	0 (0)
Cartilage defect at time of ACLR**	16 (40)	0 (0)	16 (35)	0 (0)
New knee injuries (either knee)	0 (0)††	0 (0)††	13 (28)	3 (9)
ACLR knee‡‡	0 (0)††	0 (0)††	10 (22)	0 (0)
Contralateral knee§§	0 (0)††	0 (0)††	3 (7)	3 (9)
Returned to level 1 sport§	9 (23)	11 (27)	11 (24)	9 (26)

* Values are the number (%) unless indicated otherwise. Demographics for 111 participants from 1-year assessment were previously reported (23). Participants categorized as having a combined injury at 1 and 5 years if they had a significant cartilage defect/meniscectomy assessed at the time of anterior cruciate ligament reconstruction (ACLR). IQR = interquartile range; BMI = body mass index; NA = not assessed.
† Statistically significant ($P < 0.05$) difference between combined and isolated injury groups.
‡ N = 75 participating in BMI assessment at 5 years.
§ Level 1 sport = jumping, cutting, pivoting as per Sports Activity Classification based on Grindem et al (24).
¶ Assessed using the KT-1000 arthrometer (Mesmeric) at 30° of flexion with 30-pound load (45).
# Performed at the time of ACLR.
** Assessed arthroscopically at time of ACLR. Cartilage defect defined as in Outerbridge (25) grade ≥2 (i.e., at least a partial-thickness defect).
†† No new knee injuries were reported at 1 year because this was an exclusion criterion.
‡‡ 5-year new ACLR knee injuries/surgery: n = 10 (n = 3 ACLR revision, n = 6 meniscectomy, n = 1 lateral collateral ligament sprain).
§§ 5-year new contralateral knee injuries/surgery: n = 6 (combined injury group: n = 2 ACLR revision, n = 1 meniscectomy; isolated injury group: n = 1 ACLR, n = 1 meniscectomy, n = 1 lateral collateral ligament sprain).

1 and 5 years for both groups are presented in Figure 2. The entire cohort (n = 81) demonstrated significant ($P < 0.05$) improvement (i.e., fewer knee symptoms, better function, and QoL) between 1 and 5 years for all KOOS subscales (except KOOS symptoms) and the IKDC questionnaire. The mean ± SD changes for each of the subscales and the IKDC questionnaire were the following: KOOS pain 2.8 ± 9; KOOS symptoms 0.5 ± 16.1; KOOS sport/rec 6.0 ± 18.2; KOOS QoL 10.0 ± 18.9; and IKDC 4.7 ± 10.9. Improvement between 1 and 5 years did not differ between the combined and isolated groups ($P \geq 0.05$). At 5 years, the combined injury group median scores for the KOOS symptoms and KOOS QoL subscales were 14 and 25 points below age-matched normative values from uninjured young adults (34), which is greater than the recommended MDC (14–20 points) for individuals with an ACL injury (31) (see Supplementary Appendix D, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract, which presents patient-reported outcomes for all groups at 1 and 5 years and crude *P* values for between-group analyses).

The numbers of individuals above the acceptable cutoff for the KOOS subscales and the IKDC questionnaire are presented in Table 2. A significantly lower percentage of individuals with combined injury reported acceptable IKDC scores at 1 year and KOOS symptoms, KOOS pain, KOOS QoL, and IKDC scores at 5 years. These significant relationships persisted in the sensitivity analysis, which excluded the 10 participants with reinjury between 1 and 5 years (see Supplementary Appendix E, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract).

Association with OA features seen on MRI. There were no significant cross-sectional associations between cartilage defects, BMLs, or meniscal lesions and KOOS or IKDC scores at 1 year. The presence of a patellofemoral cartilage defect at 1 year was significantly associated with worse KOOS symptoms (β = –9.79, 95% CI –16.67, –2.91; $P = 0.006$), KOOS sport/rec (β = –7.94, 95% CI –15.27, –0.61; $P = 0.034$), KOOS QoL (β = –8.29, 95% CI –15.28, –1.29; $P = 0.021$), and IKDC (β = –4.79, 95% CI –9.34, –0.24; $P = 0.039$) scores at 5 years (Table 3). The presence of a meniscal lesion at 1 year was significantly associated with a worse KOOS symptoms score at 5 years (β = –8.47, 95% CI –16.54, –0.42; $P = 0.039$). Similarly, at 5 years, the presence of a patellofemoral cartilage defect or meniscal tear was associated with worse patient-reported outcomes, and tibiofemoral BMLs were associated with better patient-reported outcomes (Table 3). Regression analysis was also

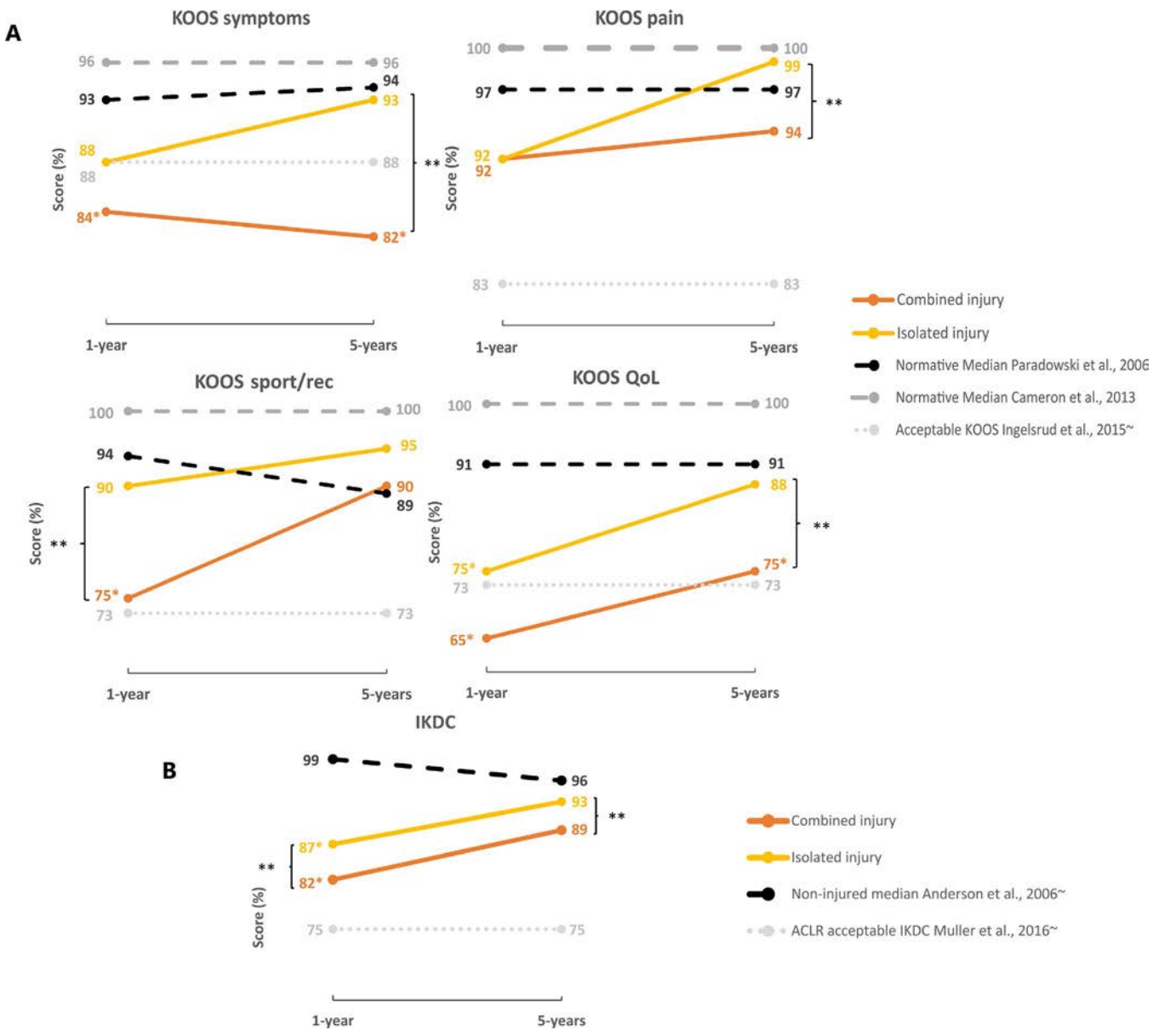

Figure 2. **A**, Comparison between isolated and combined anterior cruciate ligament reconstruction (ACLR) groups, uninjured and general population medians, and acceptable cutoff scores in ACLR patients for the Knee Osteoarthritis Outcome Score (KOOS) subscales. **B**, Comparison between isolated and combined ACLR groups, uninjured median values, and acceptable cutoff scores in ACLR patients for International Knee Documentation Committee (IKDC) scores. All values are presented as the median at 1 year and 5 years. Supplementary Appendix D (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract) presents interquartile range values and scores for the entire group (n = 81). At 1 year, n = 40 for the combined injury group and n = 41 for the isolated injury group. At 5 years, n = 46 for the combined injury group and n = 35 for the isolated injury group. QoL = quality of life; * = median value at 1 year or 5 years is greater than or equal to the minimal detectable change (26,31) below the general population (age-matched, uninjured) normative medians for the KOOS (32) and IKDC (34) questionnaires; ** = statistically significant difference ($P < 0.05$) between combined and isolated injury groups at 1 or 5 years; ~ = weighted average median values for KOOS and IKDC scores were calculated using respective data from healthy uninjured (no history of knee pain) participants (32), age- and sex-matched data in the general population (may have history of knee pain) (33,34), and acceptable cutoff scores in ACLR patients (6,35).

performed without adjustment for age at time of surgery, sex, BMI at 1 year, and presence of combined injury. The unadjusted analysis resulted in larger effect sizes and increased number of significant relationships (see Supplementary Appendix F, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract), suggesting that these factors somewhat influence patient-reported outcomes following ACLR. Sensitivity analyses excluding 10 participants with reinjury between 1 and 5 years resulted in similar effect sizes (but wider CIs), suggesting that the effect of reinjury on the relationship between

Table 2. Participants with acceptable KOOS and IKDC scores*

Outcome measure and group (acceptable cutoff score)†	1 year	5 years	Between-group difference, 1 year	Between-group difference, 5 years‡
KOOS pain (88)				
Whole group	63 (78)	66 (81)	0.601	0.010§
Isolated	33 (80)	33 (94)		
Combined	30 (75)	33 (72)		
KOOS symptoms (83)				
Whole group	47 (58)	47 (58)	0.180	0.042§
Isolated	27 (66)	25 (71)		
Combined	20 (50)	22 (48)		
KOOS sport/rec (73)				
Whole group	60 (75)	69 (85)	0.455	0.060
Isolated	32 (78)	33 (94)		
Combined	28 (70)	36 (78)		
KOOS QoL (73)				
Whole group	38 (47)	55 (68)	0.268	0.004§
Isolated	22 (54)	30 (86)		
Combined	16 (40)	25 (54)		
IKDC (75)				
Whole group	62 (77)	71 (88)	0.004§	0.004§
Isolated	37 (90)	35 (100)		
Combined	25 (63)	36 (78)		

* Values are the number (%) of participants in the group with a raw score above acceptable cutoffs using previously published data for anterior cruciate ligament reconstruction (ACLR) patients and the Knee Injury and Osteoarthritis Outcome Score (KOOS) (6) and International Knee Documentation Committee (IKDC) (35) questionnaires.
† N = 81 for whole group at 1 and 5 years. Participants were defined as having a combined injury at 1 and 5 years if they had a concomitant injury (significant cartilage defects/meniscectomy assessed at the time of surgery). At 5 years, individuals were added to the combined injury group if they had a new injury/surgery on the ACLR knee. All other participants were defined as having an isolated injury. At 1 year, n = 40 for the combined injury group and n = 41 for the isolated injury group. At 5 years, n = 46 for the combined injury group and n = 35 for the isolated injury group.
‡ Fisher's exact test was used to compare the proportions of the isolated and combined groups above the acceptable cutoff value.
§ Significant ($P < 0.05$).

lesions on MRI and patient-reported outcomes in this study was minimal (see Supplementary Appendix E, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract).

DISCUSSION

Despite improvement in KOOS and IKDC scores between 1 and 5 years following ACLR, individuals with a combined injury (i.e., concomitant meniscectomy and/or arthroscopic chondral defect at the time of ACLR and/or secondary injury/surgery to ACL knee) had worse patient-reported outcomes at 5 years after ACLR compared to those with an isolated injury. At 5 years, a lower proportion of individuals with combined injury met previously reported acceptable patient-reported outcome scores for ACLR patients (6) and presented with worse patient-reported outcome scores compared to healthy uninjured populations. In the second part of our analysis, MRI findings had minimal association with patient-reported outcomes at 1 and 5 years except for patellofemoral cartilage defects at 1 year, which were associated with worse KOOS symptoms, KOOS sport/rec, KOOS QoL, and IKDC scores at 5 years. Patellofemoral cartilage defects on MRI at 1 and 5 years were generally associated with worse KOOS and IKDC scores at 5 years. The only other MRI findings to be associated with patient-reported outcomes were meniscal lesions at 1 and 5 years (worse KOOS symptoms at 5 years) and tibiofemoral BMLs at 5 years (better KOOS sport/rec, KOOS QOL, and IKDC scores at 5 years).

At an entire group level, all patient-reported outcomes except KOOS symptoms improved from 1 to 5 years after ACLR. Although improvements did not exceed known clinically meaningful change scores for the KOOS (36) or IKDC (37) questionnaires, all KOOS subscales and IKDC entire group median scores at 5 years were near normative values (within MDC score) (26,31) when compared to the general population (33,34). While group-level scores for most KOOS subscales and IKDC questionnaire in the combined and isolated injury group at 5 years exceeded patient acceptable symptom state (PASS) cutoff values for ACLR populations (6,35) (Figure 2), our novel analysis (Table 3) identified many individuals within the group who did not achieve PASS values. Up to 42% (range 0–42%; average 22%) of all participants had not recovered to KOOS or IKDC PASS values at 5 years. Deficits were most evident for the KOOS symptoms and KOOS QoL subscales, in which 42% and 32% of participants (whole group) had not recovered to PASS values at 5 years, respectively. Entire group patient-reported

Table 3. Multivariable linear regression analysis of OA features shown on MRI (MRI-OA) associated with patient-reported outcomes at 1 and 5 years after ACLR*

MRI-OA features	With feature, %	KOOS symptoms	KOOS pain	KOOS sport/rec	KOOS QoL	IKDC
1-year/1-year PROs†						
PF any cartilage	45	−0.87 (−6.35, 4.62)	−0.37 (−4.18, 3.43)	2.69 (−3.77, 9.14)	5.34 (−2.20, 12.89)	−0.03 (−4.47, 4.52)
PF any BML	23	−1.73 (−7.78, 4.31)	−1.87 (−6.04, 2.30)	−6.39 (−13.39, 0.61)	−3.01 (−11.26, 5.24)	−1.02 (−5.96, 3.92)
TF any cartilage	48	2.81 (−2.33, 7.94)	1.25 (−2.32, 4.83)	−0.93 (−7.02, 5.16)	2.69 (−4.45, 9.85)	2.52 (−1.68, 6.74)
TF any BML	31	0.86 (−4.71, 6.44)	1.03 (−2.81, 4.90)	−0.26 (−6.81, 6.29)	−0.17 (−7.79, 7.45)	1.03 (−3.52, 5.58)
Meniscal lesion	72	−1.61 (−5.96, 9.17)	−1.06 (−6.66, 4.54)	−2.92 (−12.61 6.77)	1.42 (−9.74, 12.58)	−3.29 (−10.07, 3.48)
1-year/5-year PROs‡						
PF any cartilage	46	−9.79 (−16.67, −2.91)§	−2.88 (−6.62, 0.86)	−7.94 (−15.27, −0.61)§	−8.29 (−15.28, −1.29)§	−4.79 (−9.34, −0.24)§
PF any BML	26	−4.60 (−12.02, 2.81)	−1.28 (−6.44, 2.36)	−2.49 (−10.32, 5.34)	1.82 (−5.63, 9.27)	−1.62 (−6.39, 3.15)
TF any cartilage	47	−5.32 (−11.84, 1.20)	−1.26 (−4.73, 2.19)	0.47 (−6.39, 7.34)	1.95 (−4.67, 8.58)	0.24 (−4.09, 4.58)
TF any BML	30	0.12 (−6.89, 7.13)	1.97 (−1.67, 5.62)	3.46 (−3.79, 10.73)	−0.94 (−7.97, 6.09)	1.06 (−3.48, 5.61)
Meniscal lesion	79	−8.47 (−16.54, −0.42)§	−0.99 (−5.33, 3.34)	−0.44 (−8.21, 9.10)	−5.19 (−13.41, 3.04)	−3.74 (−9.07, 1.58)
5-year/5-year PROs†						
PF any cartilage	58	−6.86 (−13.49, −0.24)§	−2.49 (−6.78, 1.79)	−3.99 (−11.06, 3.07)	−11.71 (−19.08, −4.33)§	−3.86 (−9.08, 1.36)
PF any BML	22	−1.19 (−8.77, 6.40)	−0.74 (−5.96, 4.46)	2.12 (−10.03, 5.79)	−0.99 (−9.78, 7.80)	−4.36 (−10.16, 1.44)
TF any cartilage	56	−3.23 (−9.93, 3.45)	−0.16 (−4.10, 4.42)	1.53 (−5.48, 8.56)	6.83 (−0.78, 14.45)	4.23 (−0.89, 9.36)
TF any BML	27	3.26 (−4.23, 10.76)	4.19 (−0.47, 8.85)	9.32 (1.79, 16.86)§	11.84 (3.60, 20.07)§	6.89 (1.28, 12.49)§
Meniscal lesion	81	−9.12 (−17.41, −0.82)§	−1.81 (−7.23, 3.61)	−1.66 (−10.62, 7.29)	−3.74 (−13.64, 6.16)	−4.10 (−10.69, 2.49)

* Values are the beta coefficient (95% confidence interval). Cartilage, BMLs, and meniscal lesions were graded as present if greater than or equal to grade 1 in size as per the MRI-OA Knee Score. Meniscal lesions include any type of tear, maceration, or extrusion greater than or equal to grade 1 in either the medial or lateral tibiofemoral compartment. For 1-year MRI associations with 1-year patient-reported outcomes, n = 111; for 1-year MRI association with 5-year patient-reported outcomes, n = 80 (n = 1 patient with no MRI assessment at 1 year); for 5-year MRI associations with 5-year patient-reported outcomes, n = 73 (n = 2 patients with no MRI assessment at 5 years; n = 5 patients with no body mass index [covariate] assessment at 5 years). See Figure 1 for participant recruitment design. MRI = magnetic resonance imaging; OA = osteoarthritis; ACLR = anterior cruciate ligament reconstruction; KOOS = Knee Injury and Osteoarthritis Outcome Score; QoL = quality of life; IKDC = International Knee Documentation Committee; PROs = patient-reported outcomes; PF = patellofemoral; BML = bone marrow lesion; TF = tibiofemoral.
† Adjusted for age, sex, body mass index, and presence of a combined injury. Unadjusted results are reported in Supplementary Appendix F, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract.
‡ Adjusted for age, sex, body mass index, presence of a combined injury, and baseline KOOS and IKDC values. Unadjusted results are reported in Supplementary Appendix F.
§ Significant ($P < 0.05$).

outcome scores in ACLR cohorts should be interpreted with caution, as they may depict successful outcomes and do not necessarily represent the widespread disparity and considerably poor outcomes observed in some individuals.

Individuals with a combined injury demonstrate worse patient-reported outcomes at 1 year and a greater deficit at 5 years compared to those with an isolated ACLR and uninjured peers. KOOS symptoms and KOOS QoL subscales were particularly impaired in those with a combined injury at 5 years, being 14 and 25 points below normative values (32), respectively. The proportion of people with acceptable scores on all of the KOOS subscales and the IKDC questionnaire improved from 1 to 5 years in the combined injury group (1 year = 40–75% [average 60%], 5 years = 48–78% [average 66%]) and isolated injury group (1 year = 54–90% [average 73%], 5 years = 71–100% [average 89%]). This is consistent with previous reports that one-third of individuals have unacceptable symptoms 2 years after ACLR (6,10). The combined injury group had a higher proportion of people not achieving PASS values for KOOS pain, KOOS symptoms, KOOS QoL, and IKDC scores at 5 years. Specifically, the KOOS symptoms and KOOS QoL subscales in the combined injury group had the greatest proportion (52% and 46%, respectively) of individuals who had not recovered to PASS values. These results may assist clinical interpretation of patient-reported outcomes following ACLR. Clinicians can identify individuals with an acceptable outcome based on PASS scores (6) and provide education on realistic expectations of recovery for different patient groups. Clinicians should be cognizant that approximately one-half of patients with a combined injury may not achieve an acceptable outcome for symptoms or QoL 5 years after ACLR. Further research is needed to determine if targeted secondary prevention interventions can address current and potential future symptoms and functional and participation restrictions.

Our findings extend previous studies that describe worse patient-reported outcomes in the presence of a combined injury in the short term (injury to 1 year) (1,3) and long term (≥15 years) (8), confirming this relationship in the medium term. Interventions targeting symptoms and QoL should be a high priority for individuals with a combined ACL injury. This may include additional preoperative education and potentially ongoing intervention beyond 1 year after ACLR to enable the achievement of outcomes similar to those for patients with isolated injuries. The combined injury group

was significantly older and had a higher BMI at 1 year. Therefore, addressing potential negative lifestyle modifications, including physical inactivity (38) and weight gain (39), which could be associated with poorer QoL following ACLR (7,22), may be important. Such interventions are beneficial in older adults with established knee OA (40,41), but further high-quality trials are required to determine efficacy in younger individuals with posttraumatic knee OA following ACLR.

Overall, we found minimal cross-sectional associations between tibiofemoral or patellofemoral cartilage defects, BMLs, meniscal lesions, and patient-reported outcomes between 1 and 5 years after ACLR. These findings extend previous reports that there is no association between tibiofemoral radiographic OA and patient-reported outcomes in the longer term (12,13). However, consistent with our 3-year follow-up patient-reported outcome data (22), patellofemoral cartilage defects at 1 year were associated with worse KOOS symptoms, KOOS sport/rec, KOOS QoL, and IKDC scores at 5 years after ACLR. Additionally, patellofemoral cartilage defects at 5 years were cross-sectionally associated with worse KOOS symptoms and KOOS QoL scores. While clinicians should consider the patellofemoral compartment as a potential source of symptoms and driver of poorer function following hamstring-autograft ACLR (21,42), patient education should express that MRI findings are often unrelated to symptoms.

We recently reported that one-third of patients will have worsening BMLs between 1 and 5 years after ACLR (18). An interesting finding of the current analysis in the same cohort was that the presence of tibiofemoral BMLs was associated with better KOOS sport/rec, KOOS QoL, and IKDC scores at 5 years. This could indicate that BMLs reflect increased joint loading due to participation in sport, particularly in the presence of poor function (43). The future symptomatic consequences of BMLs following ACLR are unknown, but in individuals who were at risk of OA (i.e., older, higher BMI), worsening BMLs predicted subsequent knee symptoms, progression of OA features seen on MRI, and radiographic OA 4–7 years later (17,44). Further research is required to understand the long-term implications of BMLs on MRI in an ACLR population and measure the response of individual joint features and patient-reported outcomes to potential interventions.

Our follow-up rate of the original 1-year cohort was 72%, which may introduce some selection bias. However, there were no differences in baseline participant or surgical characteristics between those participating and those lost to follow-up (see Supplementary Appendix C, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract), and the current cohort had IKDC scores (1) and return-to-sport rates (5) that were similar to those of other larger ACLR cohorts at comparable follow-up time points. The combined injury group included 10 individuals who sustained a secondary injury between 1 and 5 years, which could influence results. Yet, sensitivity analyses excluding these 10 participants showed that the association between combined injury and patient-reported outcomes at 5 years and the relationship between cartilage, bone marrow, and meniscal lesions and patient-reported outcomes at 5 years were generally similar to the results from the whole cohort (see Supplementary Appendix E, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23854/abstract). Slightly smaller effect sizes with wider CIs were typically observed in this sensitivity analysis, which was likely due to the lower sample size and participants with a secondary injury reporting more symptoms at 5 years. Finally, regression findings should be interpreted cautiously; wide CIs observed in the regression analysis were likely driven by a wide range in scores and the multiple factors that may influence patient-reported outcomes.

In conclusion, individuals with a combined injury following ACLR may be an important subgroup requiring additional interventions when considering the likely worse outcomes compared to those of their peers with an isolated ACLR. Individuals with patellofemoral cartilage defects may also require more targeted interventions due to the association with worse symptoms, function, and QoL at 5 years after ACLR. Despite tibiofemoral BMLs being associated with fewer knee function and QoL impairments at 5 years, there seems to be a minimal relationship between other compartment-specific cartilage lesions, BMLs, and meniscal lesions identified on MRI and patient-reported symptoms, function, and QoL.

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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. Crossley 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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Association Between Symptom Duration and Patient-Reported Outcomes Before and After Hip Replacement Surgery

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Objective. Patients experience discomfort and compromised quality of life while waiting for hip replacement. Symptom duration may affect quality of life attained following surgery. We undertook this study to investigate the impact of symptom duration on patient-reported postsurgical outcomes from hip replacement surgery.

Methods. National observational data collected before and after hip replacement surgery in England between 2009 and 2016 were used to investigate determinants of symptom duration prior to surgery and the relationship between symptom duration and presurgical and postsurgical patient-reported outcomes. Multivariable linear regression models were used to estimate associations between patient-reported outcomes and symptom duration, controlling for a range of covariates.

Results. The sample included 209,192 patients; most (69%) experienced symptoms for 1–5 years. A few patients (14%) experienced symptoms for <1 year, for longer than 5 years (6–10 years [11%]), or for >10 years (5%). Symptom duration decreased overall over the studied time period and was shorter among patients who were male, older, and from areas of lesser deprivation. Patients with a symptom duration <1 year had better postsurgical pain and function outcomes (Oxford Hip Score [OHS] 0.875 [95% confidence interval (95% CI) 0.777, 0.973]) than those with 1–5 years symptom duration in an adjusted model. Conversely, those with symptom duration >5 years had increasingly poorer postsurgical outcomes (OHS –0.730 [95% CI –0.847, –0.613] for those with disease duration 6–10 years and OHS –1.112 [95% CI –1.278, –0.946] for those with disease duration >10 years).

Conclusion. Symptom duration prior to hip replacement has become more standardized in England over time. However, increasing duration remains a significant predictor of poorer outcomes after surgery.

INTRODUCTION

Hip replacement is one of the most commonly performed surgical procedures in the UK. There is increasing consensus and clear guidelines for a care pathway for people with osteoarthritis of the hip prior to referral to an orthopedic surgeon for total hip arthroplasty (THA). The recommended nonsurgical care pathway prior to THA typically involves stepped care, consisting of escalation of nonpharmacologic (e.g., education, lifestyle advice, and physical and occupational therapy) and pharmacologic intervention (analgesics and supplements, nonsteroidal antiinflammatory drugs, and intraarticular injections) (1–4). There is evidence of an underuse of nonsurgical treatments in primary care (5,6) as well as an absence of evidence for timing and prioritization of THA (1,5,7). Patients who have exhausted these options and are refractory to nonpharmacologic and pharmacologic interventions should then be considered for referral for THA. If at this point the specialist decides that surgery is an option, the procedure is then to be undertaken at the earliest available time.

Each stage in this process involves time and the potential for further delays. The total duration over which patients experience symptoms is a result of the willingness and ability of patients to initiate care and navigate through the health care system; shared decision-making at various stages between patients, clinicians, and surgeons; and the efficiency with which patients are processed through the health care system. The potential benefits of early THA surgery are still unclear. The presumed advantages of early THA surgery center on a window of opportunity to intervene before the

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SIGNIFICANCE & INNOVATIONS

- To the best of our knowledge, this is the first study to explore the impact of symptom duration on patient-reported postsurgical outcomes from hip replacement surgery using national, routinely collected data.
- More than two-thirds of patients undergoing total hip arthroplasty have a symptom duration of 1–5 years; longer symptom duration was positively associated with female sex, increasing income deprivation, and a black ethnic background.
- Symptom duration prior to hip replacement became more standardized in England between 2009 and 2016, with fewer people reporting very long or very short symptom duration over time.
- Postsurgical patient-reported pain and function (Oxford Hip Score) and health-related quality of life (the 3-level version of the EuroQol 5-domain index) outcomes were best for patients with 1-year symptom duration and worst for those with ≥6 years of symptom duration.

symptoms, pain, and impairment of physical functioning become too severe, which is supported by evidence that shows greater pain and increased impairment of preoperative physical functioning are predictive of poorer outcomes (8). However, as severity varies by individuals and because THA is an irreversible procedure, items that counter these potential benefits include evidence that the procedure is not always successful or beneficial for patients (9), concerns about the need for revision due to loosening and restricted lifespan of the hip prosthesis (10), and the diminished likelihood of success and patient satisfaction following such revision surgery (11,12). Consequently, the decision to refer and undergo surgery is often based on discussions between patients, referring clinicians, and surgeons (1).

There is considerable variation in the rates and timing of THA surgery, as well as the health status of patients undergoing surgery, within and between countries (7,13,14). Several factors are known to influence the decision to undergo surgery, including age, sex, socioeconomic status, patient willingness, and clinical decision-making (15–17). There is evidence that a longer formal waiting time between the surgeon's decision to operate and the surgery date is associated with poorer outcomes after surgery (18). There is also evidence that increased waiting time is independently associated with poorer postsurgical outcomes in other elective hip surgeries such as arthroscopy (19,20). Typically, however, symptom duration is a much longer period than waiting time. Waiting time only covers the period between a patient being deemed appropriate and ready for surgery and the date of surgery, whereas symptom duration includes the time periods when patients are not yet ready, as well as the waiting time when they are ready. The relationship between symptom duration and outcomes is unclear, and it is unknown whether variations in symptom duration reflect variation in the rates and timing of THA, or whether symptom duration has become more standardized with better evidence and more guidelines.

The present study used rich observational patient-reported data from 209,543 patients undergoing hip replacement in England between 2009 and 2016 to explore 1) the determinants of symptom duration, 2) trends in symptom duration over time, and 3) the relationship between symptom duration and presurgical and postsurgical health-related pain and function and health-related quality of life outcomes in patients who have undergone THA.

PATIENTS AND METHODS

Background to the Patient-Reported Outcome Measures (PROMs) Programme. Since 2009, all providers of elective surgery funded by the National Health Service (NHS) in England are required to distribute and collect PROMs before and after surgery for patients undergoing 4 high-volume elective procedures (groin hernia, THA, total knee arthroplasty, and varicose vein surgery). Patients undergoing THA are given a preoperative questionnaire before the date of surgery, usually at their last outpatient assessment or the date of the THA, and a subsequent postoperative questionnaire 6 months after the date of their surgery. The questionnaire includes the 3-level version of the EuroQol 5-domain index (EQ-5D-3L) (21) (a generic measure of health-related quality of life [HRQoL]), the Oxford Hip Score (OHS) (22) (a disease-specific measure of pain and functional disability), and a range of questions about the patient's living arrangements, symptoms and health status, previous surgeries, and perceptions of the intervention. Under the NHS PROMs Programme, it is mandatory for providers to offer patients the chance to complete the PROMs questionnaire, but participation by patients is voluntary. If patients fail to respond to either preoperative or postoperative questionnaires, 1 reminder is sent. Data from the PROMs questionnaire, from which all identifiable information is removed, can be linked to administrative data from Hospital Episode Statistics (HES), which contains detailed clinical and demographic information on all inpatient admissions funded by the English NHS.

Data. Data from the PROMs Programme in the English NHS (23) linked at patient level to the HES data for 7 financial years, from 2009–2010 to 2015–2016, were used.

Exposure (symptom duration) was captured by a question in the preoperative PROMs questionnaire that asks patients to report the length of their symptoms as a categorical variable encompassing 4 categories (<1 year, 1–5 years, 6–10 years, and >10 years). Patients' self-reported HRQoL (using the EQ-5D-3L) and functional ability and pain (using the OHS) were used as outcome measures. The EQ-5D-3L consists of 5 questions that capture pain/discomfort, ability to perform usual activities and self-care, mobility, and anxiety/depression on 3 levels of severity. Responses were converted to an index score of HRQoL (scaled between 1 [perfect health] and 0 [equivalent to death]) using preference weights (24). The OHS consists of 12 questions asking about function and pain related to hip

issues, each of which is scored from 0 to 4 indicating increasing severity. The scores for each question were summed to give a range of scores between 0 and 48, with higher scores indicating greater pain and functional disability.

A range of patient- and area-level covariates were controlled for in the analyses. Patient variables included sex, age (in 5-year bands from ages 51 to 90 years, and then all patients ages >90 years; patients ages <51 years were excluded), ethnicity (white, Asian, black, mixed, other, not stated), living alone, specific health conditions (high blood pressure, stroke, diseases of the nervous system, lung disease, and kidney disease), and Elixhauser comorbidities (which describes 31 comorbidities) (25). The area-level characteristics included whether the patient lived in a rural or urban area and area-level deprivation (Lower Layer Super Output Area [26], a region with an average of 1,500 individuals), which was captured using the income component of the Index of Multiple Deprivation (27).

All 5 of the health conditions (high blood pressure, stroke, diseases of the nervous system, lung disease, and kidney disease) that patients self-reported in the preoperative PROMs questionnaire were included. The 31 Elixhauser comorbidities were obtained using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, codes from linked HES data. This rich information on specific health conditions and Elixhauser comorbidities was used to control for sources of variation in preoperative and postoperative health scores.

Statistical analysis. Interval (28) and multinomial logit (29) regression analyses were used to estimate the factors associated with symptom duration. These factors included age, sex, ethnic group, living alone, and area income deprivation. Patients who experienced symptoms for 1 to 5 years were used as the reference category. All results reported were from adjusted models. Marginal effects for each observation were estimated to aid interpretation of the results.

Multivariable linear regression models were used to estimate the association between the 2 patient-reported outcome measures (EQ-5D-3L and OHS) and symptom duration, controlling for the same covariates. For each outcome measure, 3 models were estimated, including presurgery scores, postsurgery scores, and postsurgery scores controlling for presurgery scores. The latter analysis shows the association of symptom duration with the improvements in outcomes from surgery.

Changes in the distribution of symptom duration over time were also examined. The estimated differences in improvements in pain and function and in HRQoL by symptom duration were then used to calculate the overall effect of the change in the distribution of symptom duration on total gain from surgery.

As a sensitivity analysis, models on health gains from surgery were re-estimated on the sample of patients completing both the OHS and EQ-5D-3L (different numbers of respondents completed the OHS and EQ-5D-3L measures). In addition, analyses for both outcomes (OHS and EQ-5D-3L) were repeated after excluding the

Table 1. Descriptive statistics by symptom duration*

All years	<1 year	1–5 years	6–10 years	>10 years
Patients, no. (%)	29,894 (14)	145,131 (69)	22,787 (11)	11,380 (5)
Mean EQ-5D-3L score before surgery	0.342	0.362	0.361	0.345
Mean EQ-5D-3L score after surgery	0.810	0.793	0.774	0.756
Mean OHS before surgery	18.0	18.2	18.0	17.6
Mean OHS after surgery	39.9	39.3	38.6	38.1
Male sex	43	39	41	42
Age group, years				
51–55	3	6	8	11
56–60	6	9	13	15
61–65	12	16	19	19
66–70	18	21	22	21
71–75	22	20	18	17
76–80	22	16	12	11
81–85	12	9	6	5
86–90	4	3	2	2
>90	1	<1	<1	<1
Ethnic group				
White	89	90	89	89
Mixed	<1	<1	<1	<1
Asian	<1	<1	<1	<1
Black	<1	<1	<1	1
Other	<1	<1	<1	<1
Not stated	10	10	10	10
Rheumatoid arthritis	3	2	2	2
Rural area	29	28	28	28
Area income deprivation	11	12	12	12
Living alone	29	26	24	24

* Values are the percentage of patients unless indicated otherwise. EQ-5 D-3L = the 3-level version of the EuroQol 5-domain index; OHS = Oxford Hip Score.

first 2 years of data because the proportion of patients who completed PROMs questionnaires was smaller in the first 2 financial years than in later years (30).

Further sensitivity analyses that were conducted estimated models excluding patients who had rheumatoid arthritis (RA) as well as models that only included patients with RA. RA patients were excluded because they are a group who are likely to have a shorter duration of symptoms before THA, and in whom THA may be an indicator of failure of pharmacologic treatment for treatment of RA and poor prognosis (31).

RESULTS

Descriptive statistics. Between the 2009–2010 and 2015–2016 financial years, 320,474 patients underwent THA and completed a PROMS questionnaire that could be linked to the HES admission data. However, 47,183 patients did not complete both the preoperative and postoperative questionnaires, and a further 9,766 patients had missing data on ≥1 covariate and therefore could not be included in the analysis. Patients with congenital conditions (n = 2,892) and those who had a previous similar surgery (n = 31,495) were removed. Patients ages <50 years (n = 19,946) were also excluded from the analysis as the relationship between symptom duration and outcomes in younger age groups may be different because of decisions to delay surgery related to the limited lifespan of prostheses and/or number of possible revisions. Lastly, patients who had had a hip fracture (n = 429) were removed. The final data set consisted of 209,192 patients.

More than two-thirds (69%) of patients reported having experienced symptoms 1–5 years prior to THA, and 1 in 7 patients (14%) reported having symptoms for <1 year (Table 1). Approximately 5% of patients had experienced symptoms for >10 years. Older patients tended to have experienced symptoms for a shorter period of time and minority ethnic groups tended to have experienced symptoms for longer. There were only small differences in symptom duration across other characteristics, although the proportion of patients who lived alone was higher in those with symptom duration of <1 year (29%) than those with longer symptom duration (24–26%).

The proportions of patients with symptom durations of <1 year and >10 years declined over time (Figure 1). Conversely, the proportion of patients who reported having experienced symptoms between 1 and 10 years increased. The largest percentage point increase over time was observed in patients with symptom duration of 1–5 years (1%), while the largest percentage point reduction was for those with symptom duration of <1 year (<1%).

Determinants of symptom duration. Older patients reported experiencing shorter symptom duration (Table 2, models adjusted for patient- and area-level covariates). For example, patients ages ≥81 years experienced symptoms for an average of 1.3 years shorter timeframe than patients ages 51–55 years (95% CI –1.5, –1.2). Between the ages of 51–55 years until ages 71–75 years, symptom duration decreased with age, however, this trend was not sustained for ages ≥76 years. Men reported experiencing symptom duration on average 3 weeks shorter than women (–0.062, 95% CI –0.087 to –0.037); this finding was driven by patients who experienced symptoms for <1 year. Longer symptom duration was positively associated with income deprivation and a black ethnic background. On average, patients from a black ethnic background experienced symptoms 8 months longer (0.672 [95% CI 0.419, 0.926]) than white patients. A 10-percentage point higher level of income deprivation was associated with a 2-week longer symptom duration

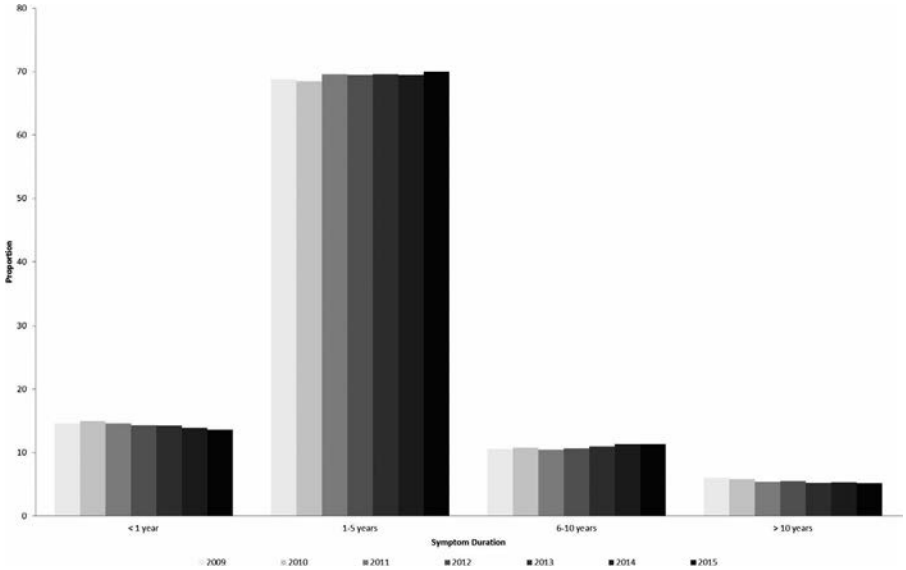

Figure 1. Bars show the change in the composition of symptom duration over time, with fewer patients reporting very short or very long symptom duration.

Table 2. Interval and multinomial logistic regressions of symptom duration (n = 209,192)*

		Multinomial logistic regression‡		
	Interval regression†	Symptoms <1 year	Symptoms 6–10 year	Symptoms >10 years
Male sex	−0.062 (−0.087, −0.037)	0.025 (0.022, 0.028)	−0.0003 (−0.003, 0.002)	0.001 (−0.001, 0.004)
Age ranges, years§				
56–60	−0.264 (−0.334, −0.193)	0.015 (0.009, 0.021)	−0.005 (−0.013, 0.003)	−0.021 (−0.027, −0.014)
61–65	−0.521 (−0.586, −0.456)	0.029 (0.023, 0.035)	−0.021 (−0.028, −0.013)	−0.037 (−0.043, −0.031)
66–70	−0.715 (−0.778, −0.652)	0.048 (0.042, 0.054)	−0.031 (−0.038, −0.023)	−0.047 (−0.052, −0.041)
71–75	−0.986 (−1.049, −0.923)	0.079 (0.073, 0.085)	−0.051 (−0.059, −0.044)	−0.057 (−0.062, −0.051)
76–80	−1.249 (−1.313, −1.185)	0.114 (0.108, 0.121)	−0.069 (−0.076, −0.061)	−0.066 (−0.072, −0.060)
81–85	−1.375 (−1.443, −1.306)	0.128 (0.120, 0.136)	−0.079 (−0.087, −0.071)	−0.071 (−0.077, −0.065)
86–90	−1.328 (−1.416, −1.240)	0.127 (0.115, 0.139)	−0.07 (−0.080, −0.061)	−0.07 (−0.077, −0.063)
>90	−1.343 (−1.521, −1.165)	0.125 (0.096, 0.154)	−0.079 (−0.098, −0.060)	−0.068 (−0.082, −0.054)
Ethnicity¶				
Mixed	0.276 (−0.159, 0.711)	0.036 (−0.018, 0.089)	0.002 (−0.038, 0.042)	0.033 (−0.001, 0.068)
Asian	−0.22 (−0.529, 0.089)	0.056 (0.012, 0.100)	−0.026 (−0.054, 0.002)	0.005 (−0.019, 0.028)
Black	0.672 (0.419, 0.926)	−0.036 (−0.061, −0.010)	0.042 (0.015, 0.068)	0.037 (0.017, 0.058)
Other	0.207 (−0.022, 0.437)	−0.024 (−0.050, 0.002)	−0.006 (−0.030, 0.018)	0.016 (−0.003,0.036)
Not stated	−0.017 (−0.056, 0.023)	0.006 (0.001, 0.011)	0.001 (−0.003, 0.006)	−0.000 (−0.004, 0.003)
Living alone	0.025 (−0.003, 0.052)	0.008 (0.004, 0.011)	0.003 (−0.000, 0.006)	0.004 (0.002, 0.006)
Rheumatoid arthritis	−0.206 (−0.309, −0.102)	0.027 (0.014, 0.039)	−0.004 (−0.017, 0.009)	−0.011 (−0.020, −0.001)
Area income deprivation	0.391 (0.248, 0.533)	−0.029 (−0.047, −0.010)	0.023 (0.008, 0.039)	0.021 (0.010, 0.033)
Rural area of residence	0.014 (−0.012, 0.040)	0.001 (−0.002, 0.005)	0.002 (−0.001, 0.005)	0.001 (−0.001, 0.004)

* Values are the marginal effect (95% confidence interval) unless indicated otherwise. Marginal effects are estimated at the mean; confidence intervals (CIs) are calculated using robust SEs. Model also includes Elixhauser comorbidities, health conditions (high blood pressure, stroke, nervous system, lung disease, and kidney disease), and dummy variables for each of the 60 months during the 5-year period.
† Values are the coefficient (95% CI).
‡ Base category is 1–5 years of symptoms.
§ Reference category is 51–55 years of age.
¶ Reference category is white ethnicity.

(0.391 [95% CI 0.248, 0.533]). Patients who lived alone were more likely to experience symptoms for <1 year and >10 years.

The relationship between symptom duration and patient-reported outcomes. Patients with a symptom duration of 1–5 years reported the highest presurgery OHS, and longer symptom duration was associated with lower postsurgery OHS after adjustment for patient- and area-level covariates (Table 3). Contingent upon presurgery scores, longer symptom duration was associated with lower postsurgery OHS. Patients who experienced symptoms for 6–10 years or >10 years reported lower improvements on the OHS (–0.730 [95% CI –0.847, –0.613]) and –1.112 (95% CI –1.278 to –0.946), respectively), compared to the mean improvement of 21.05 in the base

Table 3. Multivariable regression of OHS and EQ-5D-3L on symptom duration*

	OHS (n = 209,192)			EQ-5D-3L index (n = 192,255)		
	Presurgery	Postsurgery	After surgery, conditional on presurgery score	Presurgery	Postsurgery	After surgery, conditional on presurgery score
Symptom duration						
<1 year	−0.232 (−0.334, −0.130)	0.809 (0.708, 0.910)	0.875 (0.777, 0.973)	−0.02 (−0.024, −0.016)	0.019 (0.016, 0.022)	0.022 (0.019, 0.025)
1–5 years (ref.)	–	–	–	–	–	–
6–10 years	−0.27 (−0.377, −0.163)	−0.807 (−0.929, −0.685)	−0.73 (−0.847, −0.613)	0.003 (−0.007, 0.002)	−0.022 (−0.025, −0.018)	−0.02 (−0.023, −0.017)
>10 years	−0.675 (−0.826, −0.524)	−1.305 (−1.480, −1.129)	−1.112 (−1.278, −0.946)	−0.02 (−0.026, −0.014)	−0.039 (−0.044, −0.034)	−0.034 (−0.039, −0.029)

* Values are the coefficient (95% confidence interval). Models include the following covariates: 5-year age bands from ages 51 years to 90 years and older, male sex, ethnicity (white, mixed, Asian, black, other, and not stated), person living alone, rheumatoid arthritis marker, Elixhauser comorbidities, health conditions (high blood pressure, stroke, nervous system, lung disease, and kidney disease), Index of Multiple Deprivation income deprivation, and dummy variables for each of the 60 months during the 5-year period. OHS = Oxford Hip Score; EQ-5D-3L = the 3-level version of the EuroQol 5-domain index; ref. = reference.

Table 4. Multivariable regression of OHS and EQ-5D-3L on symptom duration*

	OHS postsurgery conditional on presurgery		EQ-5D-3L index postsurgery conditional on presurgery	
	All years	4/1/11 – 3/31/16	All years	4/1/11 – 3/31/16
Patients, no.	209,192	159,679	192,255	147,413
Symptom duration				
<1 year	0.875 (0.777, 0.973)	0.878 (0.766, 0.989)	0.022 (0.019, 0.025)	0.023 (0.020, 0.026)
1–5 years (ref.)	–	–	–	–
6–10 years	−0.73 (−0.847, −0.613)	−0.735 (−0.867, −0.603)	−0.02 (−0.023, −0.017)	−0.02 (−0.024, −0.016)
>10 years	−1.112 (−1.278, −0.946)	−1.103 (−1.295, −0.912)	−0.034 (−0.039, −0.029)	−0.035 (−0.040, −0.029)

* Values are the coefficient (95% confidence interval) unless indicated otherwise. Models include the following covariates: 5-year age bands from ages 51 years to 90 years and older, male sex, ethnicity (white, mixed, Asian, black, other, and not stated), person living alone, rheumatoid arthritis marker, Elixhauser comorbidities, health conditions (high blood pressure, stroke, nervous system, lung disease, and kidney disease), Index of Multiple Deprivation income deprivation, and dummy variables for each of the 60 months during the 5-year period. OHS = Oxford Hip Score; EQ-5D-3L = the 3-level version of the EuroQol 5-domain index; ref. = reference.

category of symptom duration of 1–5 years. Patients who experienced symptoms for <1 year reported an improvement in OHS that was 0.875 (95% CI 0.777, 0.973) points higher than those who reported 1–5 years symptom duration.

A similar pattern was observed for the EQ-5D-3L (Table 4). Presurgery EQ-5D-3L scores were highest for patients who reported experiencing symptoms for 1–5 years, and lower postoperative EQ-5D-3L scores were associated with increasing symptom duration. When we controlled for preoperative EQ-5D-3L scores, reporting a symptom duration of <1 year was associated with an increase in EQ-5D-3L score of 0.022 (95% CI 0.019, 0.025) following surgery, compared to patients who experienced symptoms for 1–5 years. In patients reporting a symptom duration of 6–10 years and >10 years, the increase in EQ-5D-3L score following surgery was 0.020 (95% CI –0.023, –0.017) and 0.034 (95% CI –0.039, –0.029) lower than patients experiencing symptoms for 1–5 years, respectively.

Sensitivity analysis. Results estimated from separate samples using all available EQ-5D-3L and OHS scores yielded similar results (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23838/abstract). Similarly, removing the first 2 years of data did not change the results for the EQ-5D-3L or the OHS; effect sizes were almost identical, and the 95% CIs were marginally wider (Table 5). Excluding patients with RA slightly attenuated the results using OHS but did not affect the results of the EQ-5D-3L analysis (Table 5).

The analysis that was restricted to patients with RA showed consistent but stronger associations between symptom duration and surgical outcomes compared to patients without RA (Table 5). In patients with RA, compared to people reporting symptom duration of 1–5 years, those reporting symptom duration <1 year had an additional improvement in OHS of 1.378 (95% CI 0.687, 2.069), while those reporting symptom duration of 6–10 years or >10 years had reductions in the improvement on OHS of –1.459 (95% CI –2.520, –0.398) and –2.611 (95% CI –4.076, –1.149), respectively.

Symptom duration over time. The composition of symptom duration changed over time, with fewer patients reporting very short or very long symptom duration (Figure 1). The proportion of patients receiving surgery who reported having either <1 year, or >10 years symptom duration was lower in 2015–2016 than in 2009–2010. These results suggest that in 2015–2016 there were 332 (–290.2 OHS units) fewer patients reporting symptom duration of <1 year, 215 (–157.07 OHS units) additional patients reporting symptom duration of 6–10 years, and 282 (313 OHS

Table 5. Multivariable regression of OHS and EQ-5D-3L on symptom duration with models excluding and consisting only of patients with RA*

	OHS postsurgery conditional on presurgery		EQ-5D-3L index postsurgery conditional on presurgery	
	Excluding RA patients (n = 204,970)	RA patients only (n = 4,222)	Excluding RA patients (n = 188,392)	RA patients only (n = 3,863)
Symptom duration				
<1 year	0.864 (0.765, 0.964)	1.378 (0.687, 2.069)	0.022 (0.019, 0.024)	0.044 (0.022, 0.066)
1–5 years (ref.)	–	–	–	–
6–10 years	−0.718 (−0.835, −0.601)	−1.459 (−2.520, −0.398)	−0.02 (−0.023, −0.017)	−0.024 (−0.056, 0.008)
>10 years	−1.087 (−1.255, −0.920)	−2.612 (−4.076, −1.149)	−0.034 (−0.038, −0.029)	−0.065 (−0.110, −0.019)

* Values are the coefficient (95% confidence interval). Models include the following covariates: 5-year age bands from ages 51 years to 90 years and older, male sex, ethnicity (white, mixed, Asian, black, other, and not stated), person living alone, rheumatoid arthritis (RA) marker, Elixhauser comorbidities, health conditions (high blood pressure, stroke, nervous system, lung disease, and kidney disease), Index of Multiple Deprivation income deprivation, and dummy variables for each of the 60 months during the 5-year period. OHS = Oxford Hip Score; EQ-5D-3L = the 3-level version of the EuroQol 5-domain index; ref. = reference.

units) fewer patients reporting symptom duration >10 years. This translates, within the 2015–2016 financial year, to a net reduction in overall improvement of 134 units in OHS (0.07% of the total gain during the period).

DISCUSSION

The present study used PROMs that were routinely collected presurgery and postsurgery in England in order to estimate the association of symptom duration with pain and function and health-related quality of life. Previous studies have focused on waiting times, but this study extends the presurgical period by focusing on the reported time from symptom duration to the date of surgery.

Our findings indicate that several patient characteristics, including age, sex, and ethnicity, are associated with symptom duration. This is consistent with findings of inequalities in the use of specific NHS services relative to need by people of lower socioeconomic status (32) and minority ethnic groups (33), including secondary care, preventive care, and treatments which include hip replacements (34). Furthermore, the rate of deterioration in health increases with age (35). With the exception of those reporting a symptom duration of <1 year, patients who reported longer duration of symptoms also reported poorer health prior to surgery. Finally, longer symptom duration was associated with poorer postsurgical patient-reported outcomes and smaller improvements in these outcomes from surgery, after controlling for presurgery scores.

Our findings suggest that discrepancies in health exist for patients reporting the extremes of symptom duration. Patients with symptoms <1 year and >10 years are likely to report poorer presurgical health outcomes than those reporting a symptom duration between 1 and 10 years. In addition, patients reporting symptoms for >10 years also experience smaller improvements from surgery. The difference in OHS was ~1 point, i.e., a 1-level improvement on 1 of the 12 questions. This improvement could, for example, be the difference between being able to walk "around the house" versus "not at all" "before the pain in your hip becomes severe," or being able to "put on a pair of socks, stockings or tights" with "little difficulty" instead of "moderate difficulty." The composition of patients with these extreme symptom durations appears to decrease over time; however, our results suggest that this change in symptom duration results in a net health loss representing 0.07% of the gains in OHS and 0.05% of the gains in EQ-5D-3L scores from surgery in 2015–2016.

Previous studies have focused on the length of the period between the decision to operate and the date of the operation. This study extends this work by showing how symptom duration (which typically encompasses a longer period than just waiting time) is associated with potential benefit from surgery and identifying patient characteristics associated with differences in symptom duration. To our knowledge, this is the first study to examine symptom duration in the context of THA outcomes. Our findings align with those in the study by Nikolova et al (18), which demonstrated that longer waiting times following the decision to operate were associated with poorer postsurgical outcomes for both THA and total knee arthroplasty. The findings of the present study are also similar to those demonstrated in the study by Fortin et al (8), who reported that poorer preoperative health resulted in poorer improvement from surgery. However, Nikolova and colleagues (18) reported that an additional week of elective waiting time for surgery resulted in larger reduction of postsurgical OHS (–0.0951) and EQ-5D-3L scores (–0.0620) than our findings. This suggests that the waiting time once a patient is deemed ready for surgery may play a more important role than the duration of symptoms.

One limitation of this study is the reliance on self-reported data on symptom duration. Patients may not be able to accurately remember how long they have experienced symptoms and were therefore asked to indicate the duration in 4 wide time bands. These broad bands of symptom duration would be likely, however, to reduce our ability to detect a significant impact of symptom duration on outcome, yet we were still able to detect an effect. More granular data would enable the impact of symptom duration and postsurgical outcomes to be explored in more detail. Issues with recall could also potentially introduce measurement error or recall bias. Random error in recalling the duration of symptoms by patients would make it more difficult to find a relationship. However, systematic recall bias, for example people with poorer presurgical health systematically reporting longer symptom duration, could have biased our results. More accurate measurement of the length of symptom duration would require linkage of PROMs data to administrative data from all general practices in England.

A further limitation is the amount of missing data because not all patients undergoing hip replacement responded to the PROMs questionnaires. Previously reported response rates suggest that 73% of patients complete the presurgical questionnaire and 86% complete presurgical and postsurgical questionnaires (36,37). Nonresponders to the presurgical questionnaire are more likely to be women from nonwhite ethnic backgrounds and areas of greater deprivation (36); those who complete the presurgery but not postsurgery questionnaires are more likely to be men, <64 years of age, from nonwhite ethnic backgrounds and areas of greater deprivation (37). The complete case analysis is presented as the main analysis, but the results remained stable in sensitivity analysis when the first 2 financial years of data that had lower response rates were omitted. A further aspect of missing data stems from patients who did not state their ethnicity. This means that complete data are not available on all patient characteristics; however, the distribution of patients who did not state their ethnicity was only 10% across all categories of reported symptom duration.

In conclusion, an increasing number of guidelines suggest alternatives to surgical care for patients who may need a THA with the aim to delay surgical intervention until all alternative care pathways have been exhausted. This increases the length of time over which patients experience symptoms and may ultimately

reduce the potential health gains from surgery and patient health for longer-term periods. This study found that patients who experienced longer symptom duration reported poorer health prior to surgery and lower health gains from surgery. Although the treatment pathway from symptom onset to THA is complex and causes of delays are multifactorial, interventions that minimize unnecessary delays to surgery that further extend symptom duration, such as inappropriate care or ineffective referral and triage processes, have the potential to improve patient outcomes.

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. Lau 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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US Adult Rheumatologists' Perspectives on the Transition Process for Young Adults With Rheumatic Conditions

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Objective. To assess the attitudes and common practices of adult rheumatologists in the US regarding health care transition (HCT) for young adults with rheumatic diseases.

Methods. An anonymous online survey was sent to US adult rheumatologist members of the American College of Rheumatology to collect demographic data and information on attitudes and common practices regarding the transition process.

Results. Of 4,064 contacted rheumatologists, 203 (5%) completed the survey. Almost half of respondents (45.1%) were never trained in transition practices, and 74.7% were not familiar with the American Academy of Pediatrics/American Academy of Family Physicians/American College of Physicians Consensus Statement About Transitions for Youth with Special Healthcare Needs. Only 56.2% felt comfortable caring for former pediatric patients. The vast majority of respondents (90.7%) did not have a multidisciplinary transition team, and 37% did not have a plan for transitioning pediatric patients into their practice. Most adult rheumatologists were unsatisfied with the current transition process (92.9%), due to insufficient resources, personnel (91.1%), and time in clinic (86.9%). They also were unsatisfied with referral data received concerning previous treatments (48.9%), hospitalization history (48%), disease activity index (45.1%), medical history summary (43.9%), comorbidities (36.4%), medication list (34.1%), and disease classification (32.6%). Three major barriers to HCT were lack of insurance reimbursement (33.7%), knowledge about community resources (30.8%), and lapses in care between primary provider and specialist (27.8%).

Conclusion. This survey identified substantial gaps in knowledge and resources regarding HCT for young adults with rheumatic diseases. These may be best addressed by further training, research, dedicated resources, adequate payment, and practice guidelines.

INTRODUCTION

The estimated number of children with arthritis in the US is 300,000 (1). Improved survival rates, currently at 99.7% at 10 years, allow the vast majority of youth with rheumatic conditions to survive into adulthood (2). Disease activity persists in 40–70% of pediatric rheumatology patients 10–28 years after diagnosis (3–5), and overall, half of patients with juvenile idiopathic arthritis (JIA) experience active inflammatory disease during adulthood (6), requiring ongoing immunosuppressive treatment (6,7). Persistent disease activity, functional disability, unemployment, and mood disturbances are important long-term sequelae of pediatric-onset rheumatic disease (7–12). Increasing patient survival, evidence of ongoing disease activity and organ damage in young adults with pediatric-onset rheumatic disease, and the negative long-term sequelae of pediatric-onset rheumatic disease on young adulthood highlight the need for an effective health care transition (HCT) process.

The Society of Adolescent Health and Medicine defines transition as "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health care systems" (13). In clinical practice, the HCT process should involve physician assessment of transition readiness, self-management education,

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SIGNIFICANCE & INNOVATIONS

- There is a paucity of literature regarding US adult subspecialty providers' perspectives on the health care transition (HCT) process, and this survey conducted in 2014, before the introduction of the Affordable Care Act, represents a first assessment of the perspectives and common practices of US adult rheumatologists in this regard.
- Almost half of the responders had never been specifically trained in transition practices and did not feel comfortable caring for patients with pediatric-onset rheumatic diseases.
- In total, 92.9% of adult rheumatologists surveyed were unsatisfied with the current transition process, citing insufficient resources, dedicated personnel, and time in clinic.
- Further training, research, dedicated resources, adequate payment, and practice guidelines for the HCT process are desired by US adult rheumatologists.

support for transfer to adult providers, and a designated transition coordinator and policy. A written transition policy should be developed with input from youth, families, and practice staff/providers, creating structure and mutual understanding of the process (14). This HCT policy should be dynamic and age-adjusted and should take into consideration medical as well as psychosocial and educational/vocational aspects of care (15).

These principles were integrated into a 2002 consensus policy by the American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), and the American College of Physicians (ACP)–American Society of Internal Medicine, which laid out 6 first steps for successful transitioning to adult-oriented health care (16). In 2011, these concepts were further reaffirmed and translated into practical operational guidance for care of all youth as they transition to adulthood in a second joint AAP/AAFP/ACP clinical report (17), which in turn provided the basis for the 6 core elements of HCT, definitions of the basic components of HCT, developed by Got Transition to support and assist providers and systems in improving the HCT process (18).

Studies examining the HCT in practice have found significant gaps in care for patients with pediatric-onset rheumatic diseases, similar to findings in other chronic childhood illnesses (19,20). Most recently, in response to these identified gaps in delivery of transition services for children with rheumatic illnesses, the European League Against Rheumatism and the Pediatric Rheumatology European Society released a first set of international standards for transitional care of young patients with juvenile-onset rheumatic illness (21).

Several models for the transition of care for young adults with chronic rheumatic diseases have been developed previously (22–24). Data derived from the experiences with these care models, as well as several recent reviews, emphasize the importance of an HCT process for pediatric rheumatology patients, because an unsuccessful transfer of care will probably lead to worse outcomes (15,24–26). While the attitudes of US pediatric rheumatologists toward the HCT process have been studied previously (27), in general, there is a paucity of literature regarding US adult subspecialty providers' perspective on the transition process.

The goal of this survey was to assess the perspectives and common practices of US adult rheumatologists regarding transition of care for young adults with pediatric-onset rheumatic diseases. To identify similarities and differences between US pediatric and adult rheumatologist perspectives on the HCT process, answers to questions shared between this current survey and a 2010 Childhood Arthritis and Rheumatology Research Alliance (CARRA) survey of pediatric rheumatologists' perspectives on HCT were compared.

Table 1. Characteristics of adult rheumatology survey responders*

Characteristic	Values
Position	
Adult rheumatologists	178 (87.6)
Adult and pediatric rheumatologists	11 (5.4)
Pediatric rheumatologists	–
Fellow	14 (6.9)
Other	–
Practice	
University-affiliated practice	92 (45.7)
Private practice	85 (42.9)
Government or military medical center	9 (4.48)
Others	15 (7.5)
Percentage of patients age <25 years seen per week	
0	6 (3)
1–5	98 (49.5)
6–10	55 (27.8)
>10	39 (19.7)
Proximity to pediatric rheumatology clinic	
Same facility	82 (41.6)
1–4 hours' drive	108 (54.8)
5 hours to 1-day drive	4 (2.0)
>1 day drive	–
Years in rheumatology practice	
<5	20 (10.15)
5–10	47 (23.9)
11–15	17 (8.6)
>15	113 (57.4)
Number of rheumatologists in practice	
1	39 (19.8)
2	23 (11.7)
3	11 (5.6)
4	22 (11.2)
≥5	102 (51.8)
Training regarding transition (all that apply)	
Workshops	7 (3.6)
Medical school	10 (5.1)
Education in institute	16 (8.2)
Residency	17 (8.7)
Practice	22 (11.3)
Meetings	34 (17.4)
Fellowship	69 (35.4)
Never	88 (45.1)

* Values are the number (%). Percentage was calculated from the total number of responders for each question.

MATERIALS AND METHODS

A survey of 28 questions was prepared by a group of adult (DZ, SPA, and PW) and pediatric rheumatologists (SPA, PC, PW, EvS, and EDM). The questions were based on a modified version of a 2010 CARRA survey of pediatric rheumatologists (27) and the AAP/ACP/AAFP 2002 and 2011 reports regarding HCT (16,17). The questionnaire aimed to characterize responders' practice and experience, to assess their knowledge and perspectives on the HCT process, and to describe how they welcomed young adults into their practice. The questionnaire also assessed outcome measures and resources felt to be important to the HCT process. One author (PW) conducted a pilot survey with rheumatologists for editing and clarification, after which, the final version was approved by all authors. The study was approved by human subjects review at Stanford University. Using Survey Monkey software, the online questionnaire was sent anonymously to 4,064 American College of Rheumatology (ACR) adult rheumatologist members practicing in the US and Canada in September 2014. The survey was advertised in the Rheumatology Morning Wire for 1 month and during the ACR Annual Meeting in November 2014. A reminder e-mail was sent to a group consisting of every tenth US adult rheumatologist in clinical practice listed in the ACR directory during November and December 2014.

Descriptive statistics were presented as absolute numbers and percentages. Responses to the current survey of adult rheumatologists were compared to pediatric rheumatologists' responses in the previous survey (27), using a chi-square test and Fisher's exact test, as appropriate. The same statistical approaches were used to compare the responses of adult rheumatologists according to several practice and experience characteristics. The Benjamini-Hochberg procedure for controlling the false discovery rate was used to adjust *P* value for multiple comparisons (28). Data were analyzed using SPSS statistical software, version 17.0.

RESULTS

Practice characteristics of responders. The questionnaire was completed by 214 individuals (5.3% of total providers queried). For the final analyses, we excluded 11 subjects, 9 non-US practitioners and 2 nonrheumatologists. The practice characteristics of the 203 responders included in this analysis are described in Table 1. The majority of responders (n = 178 [87.6%]) were adult rheumatologists. Approximately 7% were fellows and the rest were board certified in pediatric and adult rheumatology. Approximately half (n = 113 [57.6%]) were in practice for >15 years. Almost half (n = 98 [49.5%]) reported that approximately 1–5% of patients seen in their practices were young adults (age <25 years). The distribution between university-affiliated practices (n = 92) and private practices (n = 85) was almost equal (45.7% versus 42.9%). Only 115 survey respondents (54.9%) reported ever receiving

Table 2. Process for integration into adult practice*

Characteristics	Values
Existence of multidisciplinary transition service	18 (9.3)
Integration policy	
Written policy	2 (1)
Standard informal process	43 (22.4)
Developing a policy	10 (5.2)
Interested in developing a policy	38 (19.8)
No need for a policy	27 (14.1)
Did not think about it	71 (37)
Designated staff member coordinating the process	
Yes	25 (13.2)
Physician	27 (69.2)
Nurse	5 (12.8)
Nurse practitioner	4 (10.3)
Office manager	1 (2.6)
Social worker	–
Referrer (all that apply)	
Pediatric rheumatologist	153 (80.1)
Adult primary care	111 (58.1)
Patient or family	106 (55.5)
Pediatric primary care	83 (43.4)
Patients' age at integration, years	
14	7 (3.7)
15–17	32 (17)
18	68 (36.2)
19–20	40 (21.3)
≥21	29 (15.4)
Other	12 (6.4)
Average time lag between last pediatric rheumatology visit and first adult rheumatology appointment	
3–6 months	70 (40.7)
6–12 months	67 (39)
>12 months	18 (10.5)
Other	17 (9.9)
Knowledge gaps of young adults at first adult rheumatology visit	
Medication schedule	42 (23.7)
Medication names	47 (26.6)
Rheumatic diseases	57 (32.)
Purpose of medication	67 (37.9)
Medication side effects	90 (50.8)
Comorbidities	115 (65)
Physiotherapy recommendations	133 (75.1)
Vaccination recommendations	140 (79.1)
Satisfied with medical data provided at transfer	
Medical history summary	96 (55.2)
Family history	103 (59.2)
Disease classification	114 (65.5)
Disease activity index	86 (49.4)
Comorbidities	108 (62.1)
Hospitalization history	88 (50.6)
Previous treatments	88 (50.6)
Medication list	112 (64.4)
Vaccination history	71 (40.8)
Social history	100 (57.5)
Physiotherapy history	62 (35.6)
Dedicated time (sometimes/all the time) to discuss	
Welcome practice information	75 (42.6)
Use of tobacco, alcohol, or drugs	148 (84.1)
Sexuality, fertility, and contraception	156 (88.6)

(Continued)

Table 2. *(Cont'd)*

Characteristics	Values
Patient's knowledge of his/her health insurance status	106 (60.2)
Patient's educational and vocational plans	164 (93.2)
Satisfied with the current process	
In general	83 (49.4)
Resources and personnel	71 (42.3)
Time	74 (44)
Reimbursement	50 (29.8)
Outstanding needs	
Tools	133 (79.2)
Recommendation guidelines	141 (83.9)
Resources in use	
Open-ended discussions during visits	72 (78.3)
Telephone calls with teen	27 (55.1)
Written portable personal medical record	35 (50.7)
E-mail with teen	37 (49.3)
Online portable personal medical record	44 (43.6)
Hospital/health insurance portal	37 (43.5)
Written questions by teens	18 (26.1)
Written brochures, pamphlets	23 (22.3)
Face-to-face individual or group teaching session	16 (21.1)
Online brochures, pamphlets	17 (16.7)
Social networking media, e.g., Facebook with teen	5 (12.8)
Texting/SMS with teen	5 (11.4)
Online or electronic: CD, DVD	4 (6.3)
Written, home-based teaching session	1 (2)

* Values are the number (%). Percentage was calculated from the total number of responders for each question. SMS = short message service.

training regarding HCT of young adults with rheumatic diseases, mainly during fellowship (60%) and academic meetings (29.6%). The majority of respondents (96.4%) practiced in close proximity to pediatric rheumatology clinics.

Adult rheumatology HCT process activities. The integration of young adults into adult rheumatologists' care generally did not follow an organized protocol (Table 2). The vast majority of providers did not have a multidisciplinary transition team (90.7%), a written transition policy (99%), or a designated staff member to coordinate the HCT process (86.8%). Approximately 14% of respondents did not think that a special program was needed. Welcoming of young adults into the practice was coordinated by physicians (69.2%), nurses (12.8%), or nurse practitioners or office managers (2.6%). Patients were referred mostly by pediatric rheumatologists (80.1%) at the age of 18–20 years (57.5%). The average time lag between the last pediatric rheumatology visit and the first adult rheumatology appointment reported by most respondents was 3–6 months (40.7%) or 6–12 months (39%). In general, at initial visits, adult rheumatologists felt that young adult patients were knowledgeable regarding their disease (67.8%), medication names (73.4%), medication schedule (76.3%), and side effects (49.2%). The vast majority of young adults (79.1%) lacked knowledge with regards to vaccination recommendations.

When asked regarding their level of satisfaction (i.e., not satisfied, somewhat satisfied, satisfied, or completely satisfied) with data provided at transfer, adult rheumatologists indicated they were satisfied with the medical history summary (55.2%), disease classification (65.5%), comorbidities information (62.1%), medication list (64.4%), and hospitalization history (50.6%) provided. Only half the responders (49.4%) were satisfied with the current process of integrating young adults into their practices. The majority

Table 3. Adult rheumatologists' perspective on the health care transition process*

Characteristics	Values
Person leading the process	
Primary care	35 (18)
Patient	54 (27.7)
Adult rheumatologist	75 (38.5)
Pediatric rheumatologist	177 (90.8)
Age at transfer, years	
15–17	21 (10.8)
18–20	140 (71.8)
21–25	29 (14.9)
Not comfortable addressing	
Young adult care in general	18 (9.6)
Fertility and sexual health	25 (13.4)
Drug abuse	38 (20.3)
Psychological aspects	84 (45.2)
Health care insurance	35 (18.8)
Knowledge regarding the AAP consensus statement on health care transition for young adults with special health care needs	
Yes	5 (2.8)
Somewhat	40 (22.5)
No	133 (74.7)
Major barriers	
Lack of insurance reimbursement	57 (33.7)
Lack of knowledge about linkages to community resources	52 (30.8)
Lack of sufficient time of adult rheumatologist	50 (29.6)
Lapses between primary providers and specialists	47 (27.8)
Lack of available primary care physicians	39 (23.1)
Young adults' lack of knowledge about their own condition	36 (21.3)
Lack of pediatric staff time	36(21.3)
Lack of available adult rheumatologists	33 (19.5)
Recommended resources	
Online brochures, pamphlets	114 (89.8)
Online portable personal health record/medical record	116 (87.9)
Open-ended discussions during visits	108 (84.4)
Written brochures, pamphlets	111 (83.5)
Hospital/health insurance portal	85 (68)
Face-to-face individual or group teaching session	79 (62.2)
Written portable personal health record/medical record	77 (60.6)
Written questions by teens	75 (60.5)
E-mail with teen	74 (58.3)
Online or electronic: CD, DVD	69 (56.6)
Telephone calls with teen	51 (41.5)
Written, home-based teaching session	46 (37.7)
Texting/SMS with teen	33 (27.1)
Social networking media, e.g., Facebook with teen	22 (17.6)
Portable personal health record/medical record	91 (71)

* Values are the number (%). Percentage was calculated from the total number of responders for each question. AAP = American Academy of Pediatrics; SMS = short message service.

Table 4. Adult rheumatologists' perspective on knowledge gaps*

Gaps in addressing	Experience	Knowledge	Time	Supporting facilities
Young adult care	71 (71.7)	40 (40.4)	22 (22.2)	16 (16.1)
Fertility and sexual health	78 (73.6)	31 (29.3)	29 (27.4)	21 (19.8)
Drug abuse	97 (72.4)	47 (35.1)	43 (32.1)	37 (27.6)
Psychological aspects	114 (71.7)	84 (52.8)	39 (24.5)	35 (22)
Health care insurance	53 (48.6)	45 (41.3)	41 (37.6)	–

* Values are the number (%). Percentage was calculated from the total number of responders for each question.

felt that there is a need for standard recommendations or guidelines (83.9%) and tools (79.2%) to facilitate the process (Table 2) and 74.7% had never heard about the 2002 AAP/AAFP/ACP consensus statement (16) regarding the transition of care for youth with special health care needs.

Perspectives on the HCT process. With regard to perspectives on HCT processes (Table 3), most respondents (90.8%) thought that the pediatric rheumatologists should lead the transition process. Almost half (45.2%) did not feel comfortable addressing the psychological aspects of care for this age group and almost three-fourths (70%) lacked experience in addressing young adult care generally, especially issues regarding fertility and sexual health, drug abuse, and psychological issues (Table 4). The 3 most common barriers to a better HCT process included lack of insurance reimbursement (33.7%), lack of knowledge about accessing community resources (30.8%), and insufficient time in clinic (29.6%).

When compared to respondents in private practice, physicians in university-affiliated clinics more often reported lack of time (37% versus 15.3%; $P = 0.001$) and lack of support to address health care insurance difficulties (33.7% versus 10.6%; $P = 0.002$) as significant barriers to smooth HCT. University-based physicians were also more interested in an integration policy plan than private practitioners (34.8% versus 10%; $P = 0.0003$). They tended to integrate patients at an older age (>18 years) (52.8% versus 20.6%; $P = 0.0001$) and consider paper medical records less helpful (45.9% versus 74.1%; $P = 0.002$). Physicians who were board certified in both pediatric and adult rheumatology were significantly ($P = 0.0003$) more familiar with the 2002 AAP/AAFP/ACP consensus statement on HCT (81.8%) than fellows (27.3%) or adult rheumatologists (21.2%) and felt more comfortable addressing psychological aspects of young adult patients (81.8%, 30.8%, and 14.2%, respectively; $P < 0.001$). Experienced rheumatologists (time in practice >15 years) felt less comfortable addressing fertility and sexual health, drug abuse, and health care insurance issues compared to younger practitioners (time in practice ≤15 years) (42.1% versus 53.8% [$P = 0.041$], 25.2% versus 42.3% [$P = 0.03$], and 14.2% versus 28.6% [$P = 0.013$], respectively). When physicians who did not have a pediatric rheumatologist in their facility were compared to physicians who did, several differences in perspectives were noted. The former thought that patients' age at transfer of care should be <18 years (16.8% versus 1.3%; $P = 0.001$).

Adult rheumatologists specifically trained in the transition of young adults with chronic diseases, as compared to those who were not trained, felt more comfortable addressing young adult care in general (95.1% versus 84.6%; $P = 0.001$). In particular, they felt more prepared to address issues around fertility and sexual health (95.9% versus 75%; $P = 0.001$) and health insurance (93.2% versus 66.3%; $P < 0.0001$). Those specifically trained in the HCT process also reported less frequent lapses between primary providers and specialists as a barrier in the transition process (83.2% versus 95.9%; $P = 0.003$).

Comparison of pediatric and adult rheumatologists' perspectives. To compare the perspectives of pediatric and adult rheumatologists on issues related to transition of care, answers to questions shared between this current survey and a 2010 CARRA survey of pediatric providers' perspectives on HCT were compared (27). Both pediatric and adult rheumatologists shared similar perspectives regarding the major barriers to transition of care, the recommended resources for HCT, and the role of the pediatric rheumatologist in leading the HCT process. Less than half of both pediatric (42.6%) and adult rheumatologists (49.4%) were satisfied with the current HCT process in general, resources and personnel, time, and reimbursement. The vast majority (>80%) pointed out the need for a consistent approach to HCT that could result in transition guidelines (Tables 2 and 3). Different opinions were noted regarding age of transfer, with pediatric rheumatologists preferring an older age of transition ($P < 0.0001$). Pediatric rheumatologists were more knowledgeable regarding the AAP/AAFP/ACP 2002 consensus statement on HCT (8.3% versus 2.8%; $P = 0.0001$), used a multidisciplinary transition team more often, and were more likely to have a designated HCT policy (8.4% versus 1%; $P < 0.0001$). Pediatric rheumatologists designated less time in clinics to discuss use of tobacco, alcohol or drugs, sexuality, fertility and contraception, and patient's educational and vocational plans than adult rheumatologists (Table 2).

Outcome measures of successful transition. Similar numbers of respondents from the adult and pediatric surveys rated the following outcomes measures as very important: patients' survival (79.2% versus 75.9%), a maximum of 6 months

Table 5. Outcome measures identified as very important for successful transition to adult rheumatology care*

Measurements	Current survey: adult providers†	Pediatric rheumatologist survey‡	*P*§
Patient survival	152 (79.2)	104 (75.9)	NS
Treatment adherence	126 (67.7)	NA	NA
Adult rheumatologist visit within 6 months of final pediatric rheumatology visit	122 (62.9)	92 (66.2)	NS
Adult rheumatologist visit within 12 months of final pediatric rheumatology visit	114 (62.6)	60 (45.1)	<0.001
Patient functional status	107 (55.4)	NA	NA
Patient continues postsecondary education or employment	86 (44.3)	73 (53.6)	NS
Patient has health insurance coverage	77 (40.1)	79 (57.2)	0.002
Patient generic health-related quality-of-life measure	70 (36.7)	33 (24.4)	0.02
Patient-reported measure of satisfaction with transition process	60 (30.9)	61 (43.9)	0.015
Provider-reported measure of satisfaction with transition process	49 (25.3)	35 (25.2)	NS

* Values are the number (%) unless indicated otherwise. NS = not significant; NA = not applicable (data not collected in pediatric rheumatology survey).
† Percentage calculated from the total number of responders for each question.
‡ Chira et al (27).
§ Statistically significant difference $P < 0.025$.

between the appointments at the pediatric and adult rheumatologists' clinics (62.9% versus 66.2%), patient involvement in post-secondary education and/or employment (44.3% versus 53.6%), and provider-reported measure of satisfaction with the transition process (25.3% versus 25.2%). A larger number of pediatric rheumatologists felt that patients' insurance status (57.2% versus 40.1%) and patient-reported measure of satisfaction with the HCT process (43.9% versus 30.9%) were very important outcome measures. More adult rheumatologists voted for patient health-related quality-of-life measures (36.7% versus 24.4%) (Table 5).

DISCUSSION

To our knowledge, this study is the first assessment of US adult rheumatologists' perspectives on the HCT process of young adults with pediatric-onset rheumatic disease. According to results of this survey, few adult rheumatologists are familiar with HCT guidelines, with almost half of respondents reporting no training in the transition process and a lack of comfort in caring for patients with pediatric-onset rheumatic diseases. The vast majority of adult rheumatologists surveyed were unsatisfied with their current HCT process in general. Major concerns included a lack of formal transition process, resources, personnel/multidisciplinary teams, comprehensive referral data, sufficient time in clinic, insurance reimbursement for time spent providing transition services, and knowledge about community resources.

Our results, when viewed in the context of the 6 core elements of HCT (18), reveal areas for further work in improving the HCT process. Specifically, this survey highlighted major gaps in addressing 4 of 6 core elements (elements 1, 4, 5, and 6).

Element 1 calls for the development of a transition policy/statement. In our survey, 1% of adult rheumatologists had a written policy, although almost one-fourth reported having in place at least a standard informal transition process (22.4%). Almost 20% were interested in developing a policy; of note, 14.1% felt there was no need for a policy and more than one-third of respondents had not thought about an HCT policy.

The recommendations laid out in element 4 surround issues of transition planning. One specific aspect addressed in element 4 is determining the optimal timing of transfer in collaboration with youth, parents, and caregivers. The results of our survey reveal that adult and pediatric providers differ in their view of the optimal timing for transfer, with the majority of pediatric rheumatologists preferring an older age at transfer when compared to adult rheumatologists. Another component of element 4 recommends providing linkages to insurance resources, self-care management information, and culturally appropriate community supports to transitioning youth and their parents/caregivers. In our survey, almost one-third of adult rheumatologists described a lack of knowledge about linkages to community resources as a major barrier to the HCT process.

The focus of element 5 is the transfer from pediatric to adult care, which includes the provision of an adequate medical summary and an assessment of the patient's self-care knowledge upon arrival in adult care. In this survey, only approximately 50% of the adult rheumatologists were satisfied by the medical data provided at the time of transfer, and many reported significant gaps in transitioning young adults' knowledge of their health condition. Element 6 addresses transfer completion/ongoing care, including ongoing and collaborative partnerships between primary and subspecialty care providers. In our survey, a major

barrier to HCT identified by adult rheumatologists included lapses in communication between primary providers and specialists (27.8%), and in general a lack of available primary care physicians (23.1%).

Elements 5 and 6 recommend that pediatric rheumatologists provide care until the young adult is seen in an adult setting and that they communicate with the adult practice to confirm completion of transfer of care. In our survey, almost 40% of respondents reported an average lag time of 6–12 months between the last pediatric rheumatology visit and first adult rheumatology appointment, and for 10% of respondents, >1 year time lag was typical.

In this survey, US pediatric and adult rheumatologist perspectives on the HCT process were compared by looking at answers to questions shared between the current survey and a 2010 CARRA survey of pediatric rheumatologists (27). Both surveys highlighted a shared desire for specific transition-of-care guidelines: 84% of adult rheumatologists and 83% of pediatric rheumatologists. Assessing and comparing the perspectives of both pediatric and adult rheumatology providers can inform the design and implementation of more standardized approaches that address the needs of all participants during this vulnerable time for patients with chronic rheumatic disease.

The major barriers to an optimal transition process identified in our survey, consisting of time, funding, information on relevant resources, and lapses in care between providers, have previously been reported in other surveys conducted in different countries (27,29–31). Additional important barriers to an adequate HCT process identified in our survey and previous surveys were the availability of a transition coordinator (29) and adequate training of medical professionals in key areas of transition (30,32,33). The limited knowledge of the AAP/AAFP/ACP consensus statement regarding the transition of young adults with special health care needs among both adult rheumatologists in our survey and to a lesser degree in the CARRA survey of pediatric rheumatologists (27), highlights the need for further training and education in this area.

In this survey, outcome measures rated by physicians as most important were clinical parameters, such as patient survival, treatment adherence, patient functional status, and health-related quality of life. Notably, however, from the perspective of patients with JIA and their families, as described by Howland and Fisher (34), important outcomes include successful management of daily life, emotional and developmental factors, and independence. These same outcomes were rated as less important by both pediatric rheumatologists (27) and adult rheumatologists in our survey. Including patients' and families' perspectives in developing measures for a successful HCT process is necessary, and more research on the perspectives of patients with pediatric-onset rheumatic diseases and their families on the HCT process is needed. Apparently, the perspectives of patients and physicians, though different, are clearly related and complementary. These findings highlight the importance of joint efforts of patients and health care providers to define outcome measures.

While this survey addressed some important clinical outcomes, having a successful transition clearly does not mean that a patient will necessarily have a good outcome. Despite having a smooth transition to adult rheumatology care, a patient can continue to have poor treatment adherence, functional status, or health-related quality of life. The reverse can also be true, with patients having good outcomes despite having had a poor transition process. That being said, studies have shown having a structured HCT process significantly improves population health (adherence, quality of life, etc.), experience of care (satisfaction), and utilization and cost of care (shorter times from pediatric to adult care and less cost from ER use and hospitalizations) (35,36). Further research is needed to correlate health outcomes with the transition processes.

The survey was conducted in 2014 before the interim introduction of the Affordable Care Act, and it reflects the knowledge and practice at that time. An additional limitation of our study is sampling bias, because only 5% of adult rheumatologists who received the survey responded, despite several attempts at reminders. The majority of responses were from physicians in close proximity to pediatric rheumatology clinics, and 45.7% of the responders were university-affiliated rheumatologists. Thus, the survey results should be interpreted taking into consideration possible sources of bias. These could include, for example, perception of disease complexity, provider interest in completing the survey, provider time to complete the survey, provider expectations for data about referral, and the relationship with pediatric rheumatologists and referring physicians. The responders were likely to be those who are more interested and knowledgeable regarding transition, and thus not a true reflection of common practice. Overall, our results probably underestimate the barriers to an optimal transition process for young adults with rheumatic disease.

Based on our survey results, increased awareness of transition guidelines among practicing rheumatologists as well as knowledge regarding young adult care, with special emphasis on psychological aspects, are important points to be addressed during professional meetings as well as through online resources. In this regard it will be interesting in future surveys to study the influence of the Affordable Care Act and the specific toolkit developed by the ACR aimed to assist in the transition process.

The comparison of the current survey data to data from the 2010 CARRA survey of pediatric rheumatologists may have been influenced by the fact that the surveys were conducted 4 years apart, and in that time, practice characteristics of the 2 responding populations may have changed. Rheumatologists trained in both internal medicine and pediatrics were possibly counted twice, because they could have responded to both anonymous surveys. With the survey, a potential limitation is recall bias, with respondent answers regarding specific details like age of transfer, completeness of records received at transfer, etc., estimated based on individual provider recall. Last, we did not survey

patients, families, and other health care providers whose opinions are important for defining guidelines and recommendations.

In conclusion, this survey of rheumatologists caring for adults demonstrated substantial gaps in knowledge and resources to support the transition from pediatric to adult care for patients with pediatric-onset rheumatic diseases. Further evidence-based guidelines, research, dedicated resources for the HCT process, reimbursement for provider time, improved infrastructure for coordinated care, and adoption of innovative methods to track transition of care and measure outcomes can serve to address these gaps, thereby improving the quality of health care delivered to young adults as they enter adult-oriented care. Further research to definitively correlate the transition processes with improvements in health outcomes is also needed.

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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. Zisman 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. Zisman, Samad, Ardoin, Chira, White, Lavi, Mellins.

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BRIEF REPORT

Worse Quality of Life, Function, and Pain in Children With Enthesitis, Irrespective of Their Juvenile Arthritis Category

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Objective. To estimate the impact of enthesitis on patient-reported outcomes in children with juvenile idiopathic arthritis (JIA), irrespective of JIA category.

Methods. Children enrolled in the Research in Arthritis in Canadian Children Emphasizing Outcomes cohort were studied. Entheseal tenderness by physician examination in 33 defined locations, Juvenile Arthritis Quality of Life Questionnaire (JAQQ), Quality of My Life (QoML) Questionnaire, Childhood Health Assessment Questionnaire (C-HAQ), and a pain visual analog scale were completed at enrollment, every 6 months for 2 years, and then yearly up to 5 years. Analyses consisted of descriptive statistics, linear mixed models for longitudinal data, and analysis of covariance.

Results. Among 1,371 patients followed for a median of 35.3 months (interquartile range 22.1, 49.2), 214 (16%) had enthesitis, of whom 137 (64%) were classified as having enthesitis-related arthritis. After adjusting for JIA category and covariates, children with enthesitis reported higher JAQQ (mean raw score 2.71 versus 2.16, adjusted difference 0.41 points; 95% confidence interval [95% CI] 0.22, 0.59), higher C-HAQ (0.47 versus 0.31, adjusted difference 0.14 points; 95% CI 0.07, 0.22), higher pain (3.01 versus 1.68, adjusted difference 0.94 points; 95% CI 0.64, 1.25), and lower QoML (7.02 versus 8.23, adjusted difference –0.80 points; 95% CI –1.09, –0.51) scores than children without enthesitis. These differences persisted up to 5 years.

Conclusion. Children with enthesitis, regardless of JIA category, report worse patient-reported outcomes than those without enthesitis. Thus, enthesitis should be assessed in all children with JIA.

INTRODUCTION

Patient-reported outcomes are fundamental in guiding the care of children with rheumatic disease. Patient-reported outcomes, which are often surprisingly discordant with physician-measured outcomes, provide humbling but crucial feedback to the physician (1). Common patient-reported outcomes used in studies of children with juvenile idiopathic arthritis (JIA) include health-related quality of life measures, self-reported functional measures, and measures of pain (2,3).

As the biologic basis of JIA is being clarified, clinicians and researchers are realizing that the current International League of Associations for Rheumatology (ILAR) classification system for JIA may be inadequate (4). This is perhaps best illustrated when considering the juvenile spondyloarthritides (5). It has been suggested that enthesitis-related arthritis (ERA) is not a JIA category with unique characteristics, since some children with psoriatic JIA have similar characteristics, such as older age at diagnosis, axial involvement, and enthesitis. This suggests a common underlying biology between these 2 categories (6).

Enthesitis, inflammation of the attachment sites of tendon, ligament, or fascia into bone, is a feature that characterizes ERA. Children with ERA report more frequent pain, higher pain intensity,

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SIGNIFICANCE & INNOVATIONS

- In a large Canadian prospective cohort of children newly diagnosed with juvenile idiopathic arthritis (JIA), children with enthesitis reported worse patient-reported outcomes after adjusting for covariates and JIA category.
- Given its substantial effect on patient well-being, physicians should ascertain the presence of enthesitis and address its impact in all children with JIA.

and greater impairment of function compared to children with other categories of JIA (2,3).

Key limitations of previous studies of patient-reported outcomes in JIA include limited sample size and follow-up time for longitudinal cohorts (2) or use of cross-sectional data and a low prevalence of enthesitis (3). Further, according to current ILAR criteria (4), it is possible to have ERA without having enthesitis. In adults, enthesitis is known to negatively affect quality of life (7). Our study aimed to estimate the impact of enthesitis, irrespective of JIA category, on health-related quality of life, function, and pain in a multicenter prospective study of children with JIA.

PATIENTS AND METHODS

The general methods of the Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) study have been described previously (8). Briefly, children diagnosed with JIA at 16 Canadian centers from 2005 to 2010 were followed up for up to 5 years (8). JIA category was assigned by the rheumatologist based on information available at the 6-month visit and verified against ILAR criteria by the ReACCh-Out investigators (4). All children with >1 study visit were included in this analysis. Ethics approval from the University of Alberta was obtained.

The presence of entheseal tenderness at 33 sites shown on a homunculus was recorded for all enrolled children at all study visits. For this study, a child was said to have enthesitis if entheseal tenderness was recorded on >1 occasion or at >1 body site. The rationale for this definition is that if a patient was tender at a single site on a single occasion only, then this could be from any number of causes. However, if >1 site was involved or if tenderness persisted over time, then this was more likely to represent true enthesitis. This was the best available definition without the use of ultrasound, which would be impractical to use at every visit.

Instruments. We used 2 validated instruments to measure health-related quality of life (HRQoL): the Juvenile Arthritis Quality of Life Questionnaire (JAQQ) and the Quality of My Life (QoML) Questionnaire. The JAQQ is a JIA-specific questionnaire that includes 74 items in 4 domains: gross motor, fine motor, psychosocial, and systemic symptoms. Items are scored from 1 (no difficulty) to 7 (difficulty 100% of the time in the preceding 2 weeks). The mean of the 5 highest scoring items within a domain comprises each domain score, and the mean of the 4 domain scores comprises the total score (9). The minimum clinically important difference (MCID) has not yet been established for the JAQQ. The QoML questionnaire is not specific to JIA. It is a visual analog scale (VAS) with 2 scales from 0 (worst) to 10 (best). The first scale is for overall quality of life, and the second scale, the Health-Related Quality of My Life (HRQoML), is for HRQoL. The MCID for improvement for the HRQoML was found to be 11 mm in one study (10).

Functional ability was assessed with the Childhood Health Assessment Questionnaire (C-HAQ). This is a JIA-specific instrument that measures difficulty in daily living activities. Scores range from 0 (no difficulty) to 3 (unable to do some activities). Depending on the external standard used, the MCID for worsening of the C-HAQ is at most 0.125 (11). Average pain attributed to arthritis in the last week was assessed with a 10-cm VAS (0 = no pain and 10 = very severe pain) (11). The MCID for both improvement and worsening of the pain VAS was found to be 10 mm for children ages 8 to 15 years (12).

Parents completed the forms for children 9 years of age or younger. Older children typically completed their own questionnaires. Data from all completed questionnaires were entered into the analyses without differentiation between parent and child responders.

Statistical analyses. All statistical analyses were performed using Stata, version 13. The characteristics of children with enthesitis were compared to those of children without enthesitis using *t*-tests and chi-square analyses.

Mean patient-reported outcome scores were compared over time for those with and without enthesitis using linear mixed models for longitudinal data in order to account for repeated measures and variable timing of visits. Mean patient-reported outcome scores were adjusted for the following covariates: sex, age at JIA onset, JIA category, upper joint arthritis, lower joint arthritis, sacroiliac joint arthritis, polyarticular involvement, psoriasis, uveitis, antinuclear antibody positivity, and presence of HLA–B27. These covariates were felt to be most clinically relevant by our study team. Multicollinearity among variables was assessed, and none was observed (variance inflation factors were all <2 for all variables in the final models). Next, analysis of covariance was used to compare the last available patient-reported outcome scores in follow-up of those with and without enthesitis after adjusting for baseline values of the patient-reported outcome, the covariates listed above, and baseline medications.

RESULTS

The ReaCCh-Out study recruited a total of 1,497 children with JIA between 2005 and 2010. Of these, 5 were excluded

Table 1. Characteristics of children with JIA, with and without enthesitis*

Characteristic	Children with enthesitis	Children without enthesitis	*P*
No. of patients	214 (16)	1,157 (84)	–
Age at onset of JIA, mean ± SD years	10.8 ± 3.1†	7.5 ± 4.4†	<0.001
Male sex	121 (57)†	358 (31)†	<0.001
ANA positive‡	51 (24)†	549 (47)†	<0.001
HLA–B27 present§	69 (32)†	72 (6)†	<0.001
JIA category (at 6-month visit)			
ERA	137 (64)†	59 (5)†	<0.00001
Oligoarticular	12 (6)†	538 (47)†	<0.00001
Polyarticular RF negative	17 (8)†	250 (22)†	<0.00001
Polyarticular RF positive	4 (2)	50 (4)	0.09
Systemic	0	84 (7)	
Psoriatic	5 (2)¶	78 (7)¶	0.013
Undifferentiated	39 (18)†	98 (8)†	0.00001
Uveitis (ever)	21 (10)†	195 (17)†	0.009
Sacroiliitis (ever)	65 (30)†	41 (4)†	<0.001
Psoriasis (ever)	18 (8)	68 (6)	0.16
Polyarticular involvement (ever)	123 (57)†	475 (41)†	<0.001
Lower extremity involvement (ever)	174 (81)	933 (81)	0.82
Upper extremity involvement (ever)	118 (55)	592 (51)	0.29
Medication (at baseline)#			
Any treatment	147 (69)	828 (72)	0.39
Systemic steroids	18 (8)	93 (8)	0.85
NSAIDs	132 (62)	747 (65)	0.42
DMARDs	36 (17)	186 (16)	0.79
Biologics	2 (1)	3 (0.3)	0.13

* Values are no. (%) unless indicated otherwise. Adapted, with permission, from ref. 14. JIA = juvenile idiopathic arthritis; ANA = antinuclear antibody; ERA = enthesitis-related arthritis; RF = rheumatoid factor; NSAIDs = nonsteroidal antiinflammatory drugs; DMARDs = disease-modifying antirheumatic drugs.
† Significantly different at $P < 0.01$.
‡ ANA status unknown in 10.7% of the enthesitis group and 8.4% of the no enthesitis group.
§ HLA–B27 status unknown in 26.5% of the enthesitis group and 56.0% of the no enthesitis group.
¶ Significantly different at $P < 0.05$.
# Medications taken at the time of enrollment. Several more patients had taken previous medications (especially NSAIDs) that were stopped prior to enrollment.

due to unconfirmed JIA category and 86 were excluded because they only attended 1 visit. Of the remaining 1,406 children, 1,371 provided at least 1 patient-reported outcome during a median follow-up of 35.3 months (interquartile range 21.1, 49.1). Characteristics of these patients are shown in Table 1.

Enthesitis was detected in 214 children (16%). At enrollment, 116 (54%) had enthesitis; by 2 years, 204 (95%) had developed enthesitis. Children with enthesitis were older at the onset of JIA and more often male (Table 1). JIA category was ERA for 137 children (64%) and undifferentiated for 39 (18%). All JIA categories were represented, except for systemic JIA. Of note, as per ILAR criteria, it is possible to have ERA without ever having enthesitis. This was the case for 59 (30%) of 196 children with ERA.

HRQoL. The raw mean ± SD JAQQ score across all visits in children with enthesitis was 2.71 ± 1.33 compared to 2.16 ± 1.23 in those without enthesitis. The adjusted mean difference was 0.41 units higher (worse) (95% confidence interval [95% CI] 0.22, 0.59) in children with enthesitis ($P < 0.001$) (Table 2). The adjusted mean JAQQ score was 0.49 units higher (95% CI 0.33, 0.65) in those with enthesitis present at a given visit than in those with no enthesitis present ($P < 0.001$).

The last JAQQ score of those with enthesitis was, on average, 0.36 units higher (95% CI 0.12, 0.60) than those without enthesitis after adjusting for baseline JAQQ score (and other covariates) over the follow-up period ($P = 0.003$). For every additional affected enthesis site, the JAQQ score increased by a mean of 0.04 ($P = 0.001$). The mean JAQQ score tended to decrease over time in both groups, roughly in parallel to each other (Figure 1).

The raw mean ± SD HRQoML score across all visits in children with enthesitis was 7.02 ± 2.44 compared to 8.23 ± 2.10 in children without enthesitis. The adjusted mean HRQoML score of those with enthesitis was –0.80 units worse (95% CI –1.09, –0.51) than that of those without enthesitis ($P < 0.001$) (Table 2). The adjusted mean HRQoML score was –0.76 units worse (95% CI –1.15, –0.37) in those with enthesitis present at a given visit than in those with no enthesitis present ($P < 0.001$).

Table 2. Mean scores of patient-reported outcomes in children with and without enthesitis*

Patient-reported outcome	Patients with enthesitis	Patients without enthesitis	Mean difference	Adjusted mean difference (95% CI)
JAQQ score (1 = best, 7 = worst)†				
Across all visits	2.71 ± 1.33	2.16 ± 1.23	0.55	0.41 (0.22, 0.59)
First available	3.33 ± 1.35	2.80 ± 1.39	0.53	0.08 (–0.21, 0.37)
At last follow-up	2.41 ± 1.39	1.94 ± 1.12	0.47	0.36 (0.12, 0.60)
Enthesitis present at that visit (y/n)	2.96 ± 1.29	2.13 ± 1.21	0.83	0.49 (0.33, 0.65)
HRQoML score (0 = worst, 10 = best)‡				
Across all visits	7.02 ± 2.44	8.23 ± 2.10	–1.21	–0.80 (–1.09, –0.51)
First available	6.34 ± 2.60	7.51 ± 2.43	–1.17	–0.33 (–0.84, 0.19)
At last follow-up	7.25 ± 2.39	8.47 ± 1.91	–1.22	–0.76 (–1.15, –0.37)
Enthesitis present at that visit (y/n)	6.63 ± 2.33	8.25 ± 2.07	–1.62	–0.76 (–1.06, –0.45)
C-HAQ score (0 = best, 3 = worst)§				
Across all visits	0.47 ± 0.54	0.31 ± 0.49	0.16	0.14 (0.07, 0.22)
First available	0.67 ± 0.62	0.51 ± 0.59	0.16	0.13 (0.02, 0.25)
At last follow-up	0.39 ± 0.54	0.25 ± 0.43	0.14	0.07 (–0.004, 0.15)
Enthesitis present at that visit (y/n)	0.59 ± 0.54	0.34 ± 0.51	0.25	0.16 (0.10, 0.23)
Pain VAS score (0 = best, 10 = worst)¶				
Across all visits	3.01 ± 2.79	1.68 ± 2.34	1.33	0.94 (0.64, 1.25)
First available	4.19 ± 2.76	2.75 ± 2.71	1.44	0.31 (–0.28,0.90)
At last follow-up	2.67 ± 2.87	1.41 ± 2.17	1.26	0.70 (0.30, 1.11)
Enthesitis present at that visit (y/n)	4.00 ± 2.7	1.61 ± 2.31	2.39	1.57 (1.23, 1.92)

* Values are mean ± SD unless indicated otherwise. 95% CI = 95% confidence interval; JAQQ = Juvenile Arthritis Quality of Life Questionnaire; HRQoML = Health-Related Quality of My Life Questionnaire; C-HAQ = Childhood Health Assessment Questionnaire; VAS = visual analog scale.
† For JAQQ score, n = 183 for patients with enthesitis and n = 1,125 for patients without enthesitis.
‡ For HRQoL score, n = 212 for patients with enthesitis and n = 1,125 for patients without enthesitis.
§ For C-HAQ score, n = 213 for patients with enthesitis and n = 1,139 for patients without enthesitis.
¶ For pain VAS score, n = 212 for patients with enthesitis and n = 1,148 for patients without enthesitis.

The last HRQoML score of those with enthesitis was, on average, 0.76 units lower (95% CI –1.15, –0.37) than that of those without enthesitis after adjusting for baseline HRQoML score (and other covariates) over the follow-up period ($P < 0.001$). For every additional affected enthesis site, the HRQoML score decreased by a mean of 0.10 ($P < 0.001$). The mean HRQoML score tended to increase over time in both groups, roughly in parallel to each other. Scores for the enthesitis group remained lower than those of the no enthesitis group throughout the follow-up period (Figure 1).

Functional assessment. The raw mean ± SD C-HAQ score across all visits in children with enthesitis was 0.47 ± 0.54 compared to 0.31 ± 0.49 in children without enthesitis. The adjusted mean C-HAQ score of those with enthesitis was 0.14 units higher (worse) (95% CI 0.07, 0.22) than that of those without enthesitis ($P < 0.001$) (Table 2). The adjusted mean C-HAQ score was 0.16 units higher (95% CI 0.10, 0.23) in those with enthesitis present at a given visit than in those with no enthesitis present ($P < 0.001$).

The last C-HAQ score of those with enthesitis was, on average, 0.07 units higher (95% CI –0.004, 0.15) than that of those without enthesitis, after adjusting for baseline C-HAQ score (and other covariates) during the follow-up period ($P = 0.06$). For every additional affected enthesis site, the C-HAQ score increased by a mean of 0.015 ($P = 0.001$). The mean C-HAQ score tended to decrease over time until 36 months and then slightly increased for both groups. The mean C-HAQ scores for those with enthesitis were consistently higher than for those without enthesitis over the follow-up period (Figure 1).

Pain. The raw mean ± SD pain VAS score across all visits in children with enthesitis was 3.01 ± 2.79 compared to 1.68 ± 2.34 in children without enthesitis. The adjusted mean pain VAS score of those with enthesitis was 0.94 units higher (worse) (95% CI 0.64, 1.25) than that of those without enthesitis ($P < 0.001$) (Table 2). The adjusted mean pain VAS score was 1.57 units higher (95% CI 1.23, 1.92) in those with enthesitis present at a given visit than in those with no enthesitis present ($P < 0.001$).

The last pain VAS score of those with enthesitis was, on average, 0.70 units higher (95% CI 0.30, 1.11) than that of those without enthesitis after adjusting for baseline pain VAS score (and other covariates) throughout the follow-up period ($P = 0.001$). For every additional affected enthesis site, the pain VAS increased by a mean of 0.13 ($P < 0.001$). The mean pain VAS score tended to decrease throughout the follow-up period in both groups but was consistently higher in the group with enthesitis (Figure 1).

Missing data. The various patient-reported outcome measures (JAQQ, HRQoML, pain VAS, and C-HAQ) were missing in 21%, 23%, 20%, and 21% of the 7,125 main study visits, respectively. For baseline measures, the following were missing patient-reported outcomes: JAQQ 18%, HRQoML 7%, pain VAS 14%, and C-HAQ 19%. Linear mixed models were used in the analysis,

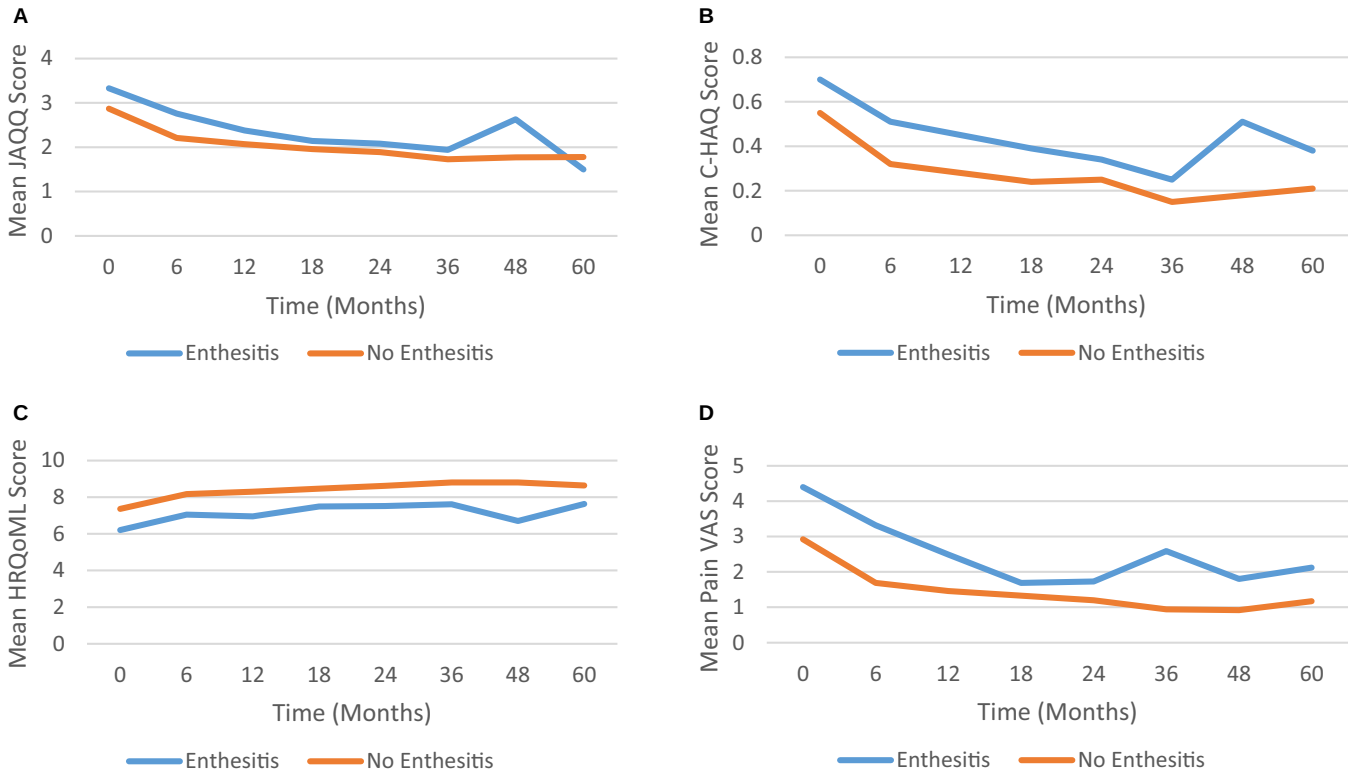

Figure 1. Mean scores over time in children with enthesitis versus without enthesitis. **A**, Juvenile Arthritis Quality of Life Questionnaire (JAQQ). **B**, Childhood Health Assessment Questionnaire (C-HAQ). **C**, Health-Related Quality of My Life (HRQoML) Questionnaire. **D**, Pain visual analog scale (VAS).

which maximized the use of the available data. Further, to assess if the data were missing at random, the characteristics of those missing the baseline JAQQ score were compared to those not missing the baseline JAQQ score. Few differences existed, with the exception of polyarticular involvement, which was higher in patients without a baseline JAQQ score (51% versus 42%; P = 0.01) (otherwise, data not shown).

DISCUSSION

Enthesitis was a frequent occurrence in this inception cohort of children with JIA and was seen in most JIA categories. Two-thirds of patients who developed enthesitis during follow-up were classified as having ERA. Children with enthesitis had worse HRQoL, poorer function, and worse pain throughout the course of follow-up than those without enthesitis after adjusting for JIA category and other covariates. Although statistically significant, the magnitude of the adjusted differences in scores was usually lower than the MCID for the score. The fact that all the patient-reported outcomes were worse in children with enthesitis, however, points to an important trend.

In a cross-sectional comparison among children with JIA, Weiss et al showed that children with ERA have higher pain intensity and poorer health status than children whose illness is in other JIA categories (3). These authors used similar measures as the current study, including the pain VAS and the C-HAQ, although the JAQQ was not part of that study. Our study assessed the impact of enthesitis (regardless of JIA category) on patient-reported outcomes.

In a single-center longitudinal study, Taxter et al compared patient-reported outcomes across JIA categories and showed that children with ERA and undifferentiated JIA had more pain, worse quality of life, and poorer function than children whose illness was in other categories (2). They used a numerical rating scale for pain assessment, the Pediatric Rheumatology Quality of Life scale for quality of life assessment, and the C-HAQ for functional assessment. In their models limited to ERA, female sex and tender enthesis count were significant predictors of decreased function (2).

Oen et al (13) examined patient-reported outcome trajectories in children from the ReACCh-Out cohort. They found that the odds of following an unfavorable JAQQ score trajectory were significantly increased for children with ERA. The same held true for HRQoML scores.

The main strengths of our study are the longitudinal structured assessment of entheseal tenderness across all Canadian pediatric rheumatology centers for a period of up to 5 years and the use of validated scales to assess patient-reported outcomes. We note 5 potential limitations. First, assessment of entheseal tenderness is subjective. However, this assessment is likely as accurate as it can be without the aid of diagnostic imaging, which would be time-consuming and impractical in a busy clinical set-

ting. It is also possible that despite instructions to assess enthesitis at 33 locations at each study visit, the rheumatologists devoted more attention to this in patients with ERA.

Second, patient- and parent-reported measures were analyzed together, regardless of who completed the questionnaires. Since young children may not fully understand some concepts that are being asked and may not be physically able to complete the forms, proxy assessments are unavoidable. However, for older children, there may be discrepancies between what they and their parents perceive.

Third, a significant proportion of children had no available HLA–B27 test results, which could have led to misclassification of disease for certain children. Fourth, the majority of children missed at least 1 patient-reported outcome assessment. However, we used linear mixed models, which may lessen the impact of missing data on our findings. Finally, patient-reported outcome values after 3 years of follow-up should be interpreted with caution due to the relatively low numbers of assessments at that time.

Patient-reported outcomes are a way that children and families tell physicians how they are doing and what matters most to them. This study shows that children with enthesitis, regardless of JIA category, report worse scores in multiple patient-reported outcomes than those without enthesitis. This has important implications. Because enthesitis impacts patient well-being, physicians should ascertain its presence in every child with JIA and address it if present. These are crucial steps, should we wish to heed what these children and families are telling us and hope to improve their pain, function, and quality of life.

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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. Rumsey 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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BRIEF REPORT

Association of Achieving Lupus Low Disease Activity State Fifty Percent of the Time With Both Reduced Damage Accrual and Mortality in Patients With Systemic Lupus Erythematosus

Chanakya Sharma,[1] Warren Raymond,[2] Gro Eilertsen,[3] and Johannes Nossent[4]

Objective. To assess the impact of achieving Lupus Low Disease Activity State ≥50% of the time (LLDAS-50) on damage accrual and mortality in an inception cohort of patients with systemic lupus erythematosus (SLE).

Methods. We used data from the Tromsø Lupus Cohort, a longitudinal population-based study of all patients with SLE in the 2 northernmost counties in Norway. LLDAS was defined as 1) a Systemic Lupus Erythematosus Disease Activity Index 2000 score of ≤4, with no activity in major organ systems, 2) no new features of lupus disease activity, 3) current therapy with prednisolone (or equivalent) dosage of ≤7.5 mg daily, and 4) well-tolerated standard maintenance dosages of immunosuppressive drugs.

Results. A total of 69 patients (33.5%) spent at least half of their follow-up time in LLDAS (thus, achieving LLDAS-50) and had significantly better survival and lower risk of developing severe damage over time, according to the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. After correcting for age and sex, LLDAS-50 was associated with a significant reduction in risk of having severe damage (hazard ratio [HR] 0.37 [95% confidence interval (95% CI) 0.19–0.73], $P < 0.01$), and also a reduction in mortality (HR 0.31 [95% CI 0.16–0.62], $P < 0.01$).

Conclusion. Our study validates the findings of the inception cohort by demonstrating that achievement of LLDAS-50 is associated with a significant reduction in severe damage and, for the first time, demonstrates a reduction in mortality.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune condition of unclear etiology with wide-ranging manifestations. Despite developments in the field, durable remission in SLE is rare; patients with SLE still face a 3-fold increase in mortality when compared to the general population (1). A major cause of morbidity is the cumulative damage, which is due to persistent inflammation, and its treatment (2). Higher levels of organ damage are seen with persistent high disease activity and have a profound impact on a patient's quality of life, causing significant levels of disability and unemployment. This increase has led to a push to develop a treatment strategy that results in minimizing disease activity with consequent reduction in organ damage.

Treat-to-target has been defined as "a therapeutic strategy aimed to treat patients to a goal which is capable of improving disease outcome" (3). The target is usually remission or low disease activity; however, rates of disease remission in SLE have been poor, regardless of the definition used (4). According to the international taskforce (Definitions of Remission In SLE), "the treatment target of SLE should be remission of systemic symptoms and organ manifestations or, where remission cannot be reached, the lowest possible disease activity, measured by a validated lupus activity index and/or by specific organ markers" (5). A definition of a Lupus Low Disease Activity State (LLDAS) has recently been introduced by The Asia Pacific Lupus Collaboration as a potential treatment target for patients with SLE. A patient is said to be in LLDAS when they meet the following criteria: 1) a Systemic Lupus

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SIGNIFICANCE & INNOVATIONS

- To our knowledge, this is the first study to demonstrate a reduction in mortality in patients with systemic lupus erythematosus who achieve a low disease activity state.
- This study also validates the findings of the inception cohort by showing reduced risk for severe damage for those patients meeting Lupus Low Disease Activity State ≥50% of the time.

Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of ≤4, with no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity; 2) no new features of lupus disease activity compared with the previous assessment; 3) Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) version of the SLEDAI physician global assessment of ≤1 (scale 0–3); 4) current prednisolone (or equivalent) dosage of ≤7.5 mg daily; and, 5) well-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents, excluding investigational drugs (6). The construct validity of this LLDAS definition has been tested against expert opinion and has been shown to have high overall agreement (7). The impact of achieving LLDAS was investigated with a prospectively collected data set. Those patients who spent the majority (>50%) of their time in LLDAS had reduced organ damage accrual and severity (according to the Systemic Lupus International Collaborating Clinics/American College of Rheumatology [ACR] Damage Index [SDI]), as compared to those who did not) (6). We assessed the validity of these findings in an inception cohort of white patients with SLE.

PATIENTS AND METHODS

The Tromsø Lupus Cohort is a longitudinal population-based study of all patients with SLE in the 2 northernmost counties in Norway. The inception cohort included patients who had been seen since 1990 and fulfilled at least 4 ACR criteria (1982 revision [8] and 1997 update [9]) for the classification of SLE (10). Patients with SLE were seen by attending physicians of the sole rheumatology service in the area who, as a rule, saw patients with quiescent disease twice annually, and patients with concerns and signs of complications were seen more frequently. Every hospital visit was registered in a database with the use of a template that recorded demographics, clinical findings, medication, and laboratory results. For each patient visit, disease activity was quantified using the SLEDAI-2K, while damage was scored using the SDI (11,12). Information was obtained from patients, hospital records, and general practitioners, and was verified before inclusion in the relevant scoring systems. Disease duration was the time interval from SLE research diagnosis (defined as fulfilling 4 ACR criteria) until last follow-up visit or time of death. The SDI scores were graded ordinally into 3 subgroups for every patient for each visit during follow-up, with scores of 0 indicating no damage, scores of 1–2 moderate damage, and scores ≥3 severe damage (10). LLDAS was defined as stated above (6). The original definition of LLDAS required patients to have a SELENA-SLEDAI physician's global assessment of ≤1 (scale 0–3); however, these data were not available for our cohort and, thus, it was not used in determining whether the patients were in LLDAS. Patients were excluded if they had <2 recorded visits.

We also evaluated the impact of 2 novel disease activity points, which were defined as those patients who spent ≥30% of their follow-up time in an LDAS (LLDAS-30) and those that spent ≥70% of their follow-up time in an LDAS (LLDAS-70).

Data are described as the frequency and percentage or as median and interquartile range (IQR). We applied Kaplan-Meier survival curves with Cox regression analysis to derive hazard ratios (HRs) and 95% confidence intervals (95% CIs) to quantify the association between LLDAS and time-dependent outcomes. All calculations were conducted using IBM SPSS Statistics, version 23. *P* values less than 0.05 were considered statistically significant.

RESULTS

The median age at diagnosis was 34 years, and the majority of patients were female (84%). The median follow-up time was 125 months (IQR 56–212 months), during which 3,646 visits were made by 206 patients for a median of 13 visits (IQR 7–24). Patients were most commonly treated with prednisolone and hydroxychloroquine (89% and 59%, respectively). Only 11 patients (3.4%) required either cyclophosphamide or rituximab. Arthritis and photosensitivity were the most common clinical manifestations of the ACR criteria (70% and 57%, respectively), and positive antinuclear antibody was the most common laboratory criterion (96%).

Table 1. Patient characteristics of the study cohort (n = 206)*

Characteristics	
Female, no. (%)	173 (84)
Age, years	34.5 (24.7–47)
No. of visits	13 (7–24)
Disease duration, months	127 (58–213.5)
SLEDAI, mean ± SD	2.75 ± 4.67
Cumulative SLEDAI per patient, mean	42.67
Baseline SLEDAI	7 (4–12)
Final SLEDAI	2 (0–8)
Baseline SDI	0 (0–0)
Final SDI	1 (0–3)
Death, no. (%)	46 (22)

* Values are the median (interquartile range) unless indicated otherwise. SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

At the last follow-up visit, most patients (58%) had a total SDI score of ≥1, with 28% having a final SDI score of ≥3 and 22% of the entire cohort having an increase in their SDI score by ≥3, from baseline (Table 1).

LLDAS of any duration was achieved by 74% of the cohort. The median time that patients spent in LLDAS was 34 months (IQR 0–61 months). A total of 69 patients (33.5%) spent at least half of their follow-up time in LLDAS (achieving LLDAS-50). These patients had significantly better survival and lower risk of developing severe disease (according to the SDI score) over time (Figures 1 and 2). After correcting for age and sex, LLDAS-50 was associated with a significant reduction in risk of having severe damage (HR 0.37 [95% CI 0.19–0.73], $P < 0.01$) and a reduction in mortality (HR 0.31 [95% CI 0.16–0.62], $P < 0.01$). In those patients who reached LLDAS-30 (n = 114) and LLDAS-70 (n = 38), there was similar protection against mortality, but achieving LLDAS-30 had no impact on severe damage. Further information on the LLDAS-30 and LLDAS-70 cohorts are shown in Supplementary Figures 1–3 and Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23867/abstract.

DISCUSSION

Due to the lack of a universally accepted definition of remission in SLE and the difficulty in achieving remission in studies, researchers have been trying to define alternate, more achievable targets, such as the LLDAS, to guide therapy in patients with SLE (6,13). An operational definition of LLDAS was provided by Franklyn et al, who analyzed the impact of achieving LLDAS in an inception cohort of 191 patients with SLE and noted that those patients who spent greater than 50% of their time in LLDAS had less organ damage than those that did not (6).

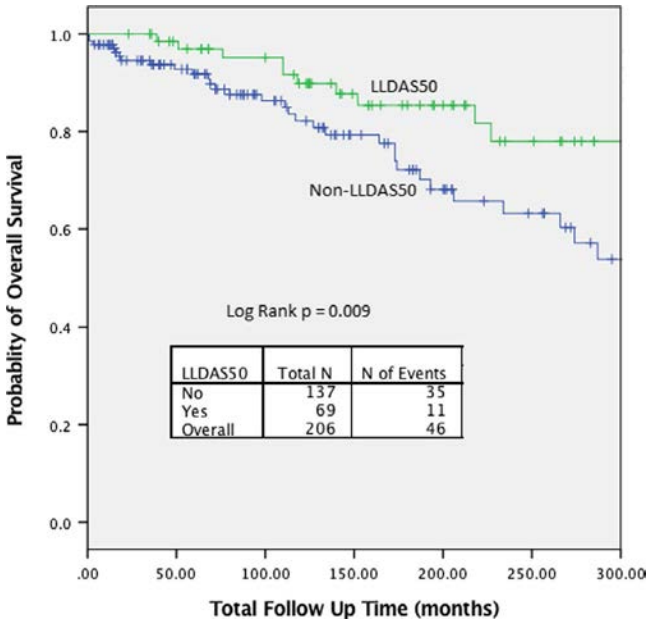

Figure 1. Survival analysis for patients who achieved Lupus Low Disease Activity State 50% of the time (LLDAS-50) compared to those who did not achieve LLDAS-50.

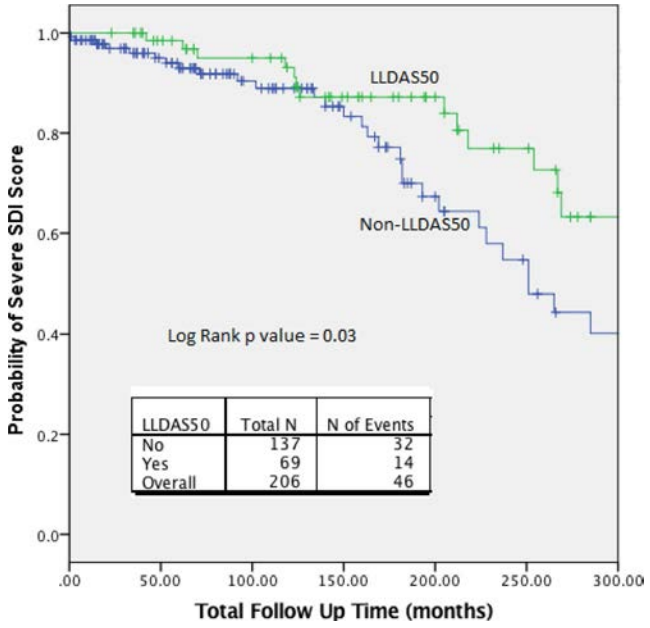

Figure 2. Survival analysis demonstrating the chance of remaining free of severe disease for patients who achieved Lupus Low Disease Activity State 50% of the time (LLDAS-50) compared to those who did not achieve LLDAS-50. SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

The current study demonstrates similar outcomes to the validation cohort with a notable reduction in risk of severe damage (HR 0.37 [95% CI 0.19–0.73], $P < 0.01$). In addition, we also noted a significant reduction in age- and sex- adjusted mortality risk (HR 0.31 [95% CI 0.16–0.62], $P < 0.01$) for those patients achieving LLDAS-50 compared to those who did not. We also analyzed the impact on damage and mortality for those patients who achieved LLDAS for 30% and 70% of their total follow-up duration. Our findings demonstrate that while achieving LLDAS-70 was also associated with a similar reduction in risk of severe damage (HR 0.38 [95% CI 0.16–0.93], $P < 0.05$) and mortality (HR 0.25 [95% CI 0.09–0.71], $P < 0.01$), even achieving LLDAS-30 resulted in a reduced risk of mortality (HR 0.36 [95% CI 0.20–0.65], $P < 0.05$) and a strong trend towards significance in reducing the risk of severe damage (HR 0.57 [95% CI 0.31–1.06], $P = 0.08$). The trend toward protection against damage accrual of the LLDAS-30 was similar to findings demonstrated in a study by Zen et al, which showed that a minimum of 2 years of LLDAS over a 7-year follow-up period (approximately equivalent to LLDAS-30) was required to demonstrate a decrease in damage progression (14).

Similar outcomes with regard to the impact on damage accrual have also been replicated in other studies. A study by Tsang et al, which evaluated the impact of achieving LLDAS-50

in a 183-patient cohort, also noted a significant reduction in damage accrual (odds ratio 0.52 [95% CI 0.28–0.99], $P = 0.046$) (15). Ugarte-Gil et al analyzed the impact of achieving LLDAS in the Latin American Lupus Cohort and also found that achieving LLDAS was associated with a lower risk of new damage (HR 0.66 [95% CI 0.48–0.93]) (16).

While the impact of LLDAS-50 on damage accrual has been demonstrated previously, to the best of our knowledge this is the first study to demonstrate an impact on mortality. The validation cohort did not observe any deaths; while the study by Ugarte-Gil et al did not show any significant impact on mortality, they conceded that this likely reflects their relatively short duration of follow-up (and consequently fewer events) (6,16). Only 1 death was reported in the cohort in the study by Zen et al, and therefore they were unable to evaluate the relationship between LLDAS-50 and mortality (14).

The fact that patients who spent 70% of their time in an LDAS (LLDAS-70) also had a reduction in their risk of severe damage and mortality is a logical extension of the findings of the above LLDAS-50 studies; however, the significant reduction in mortality associated with achieving at least LLDAS-30 is another very interesting finding. One must exercise caution in interpreting these results because there is likely to be a significant dilution of the effect due to inclusion of patients who achieved LLDAS-50 and LLDAS-70 in the LLDAS-30 cohort. This was shown by the fact that those patients who spent exactly 30% of their follow-up time (n = 5) in an LLDAS did not have a significant reduction in mortality.

This study has some limitations. We did not include a physician global assessment (which forms a part of the LLDAS criteria) as this information was not available at the time this inception cohort was started. However, previous studies have shown excellent correlation between the physician global assessment and SLEDAI, and the fact that our results echo those of previous studies does raise the interesting point as to whether a physician global assessment is required for the calculation of LLDAS (17). The study population was primarily white, a cohort known to have better outcomes in SLE. Another limitation is the timeframe of data collection (from 1990), as the definition of SLE and management concepts have changed significantly since 1990. Due to the retrospective observational nature of the present study, establishment of a causal relationship between disease parameters and outcomes is also difficult.

In conclusion, our study validates the findings of the inception cohort by demonstrating that achievement of LLDAS-50 is associated with a significant reduction in severe damage, but also demonstrates, for the first time, a reduction in mortality. Thus, LLDAS-50 is a practical and achievable surrogate target that is associated with reduced risk of severe damage, mortality, and higher quality of life for patients with SLE.

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. Sharma 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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Perspectives of Adult Rheumatologists Regarding Family Planning Counseling and Care: A Qualitative Study

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Objective. Little is known about whether and how rheumatologists provide family planning counseling and reproductive health care (FPCC) to reproductive-age women with rheumatic diseases. This qualitative study sought to assess rheumatologists' perspectives, attitudes, and practices regarding FPCC.

Methods. Semistructured interviews were conducted with a geographically diverse US sample of rheumatologists (n = 12). Interviews were transcribed verbatim, and a code book was inductively developed based on transcript content. Two coders applied the code book to all transcripts, and coding differences were adjudicated to full agreement. The finalized coding was used to conduct a thematic analysis.

Results. Six themes were identified across interviews. Rheumatologists said that they 1) feel responsible for providing some FPCC to patients, 2) experience tension between respecting patients' autonomy and their own anxieties about managing high-risk pregnancies, 3) view patient-initiated conversations as FPCC facilitators, and they regard lack of guidelines and the presence of competing clinical priorities as barriers to FPCC, 4) are reluctant to prescribe contraception, 5) desire greater access to resources to help guide FPCC, and 6) recognize the benefits of multidisciplinary collaboration with gynecologists.

Conclusion. Rheumatologists feel a sense of responsibility to provide some aspects of FPCC to reproductive-age female patients. However, their own apprehensions about managing complicated pregnancies may negatively influence how they advise patients about pregnancy planning or avoidance. Rheumatologists do not prescribe contraception but rarely refer patients to gynecologists for contraceptive care. Future work should focus on eliminating barriers and identifying solutions that support rheumatologists' efforts to provide high-quality FPCC to patients.

INTRODUCTION

Many women with rheumatic diseases are diagnosed during their reproductive years. Advances in diagnosis and treatment have enabled many of these women to live longer and healthier lives and therefore to consider the potential for pregnancy and childrearing (1). However, while healthy pregnancies are more achievable, the pregnancies of many women with rheumatic diseases are high-risk, because there may be a greater likelihood of adverse maternal and/or fetal outcomes, particularly among those women who have active rheumatic disease and/or who use fetotoxic antirheumatic drugs at the time of conception (2–6).

The American College of Rheumatology (ACR) and European League Against Rheumatism recommend that all reproductive-age female patients with rheumatic diseases receive family planning counseling and reproductive health care (FPCC) to optimize their pregnancy, maternal, fetal, and overall health outcomes (7,8). FPCC may help providers to clarify patients' reproductive goals, provide contraception and/or explore perspectives about abortion among women who wish to avoid pregnancy or childbearing, and provide preconception care for women who desire pregnancy, that is, optimizing their medical conditions, ensuring the compatibility of their medications with pregnancy, screening for additional risk factors (e.g., tobacco use), and providing folic acid or maternal vaccinations (9–11).

Rheumatologists' specific roles and responsibilities regarding FPCC remain undefined, although limited studies suggest that rheumatologists do not routinely engage in FPCC with

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SIGNIFICANCE & INNOVATIONS

- This study identifies specific barriers and facilitators to family planning counseling and reproductive health care (FPCC) that can inform interventions to initiate or improve FPCC for female patients.
- Rheumatologists' concerns and anxieties regarding managing complicated pregnancies may influence how they counsel patients.
- Rheumatologists require better guidelines and centralized resources to support female patients' family planning, pregnancy care, and medication management needs during preconception, pregnancy, and lactation.

reproductive-age female patients. For example, in several studies, young women with rheumatic diseases reported that they rarely received contraceptive counseling, even when starting an antirheumatic drug with fetotoxic potential (12,13). A survey including rheumatologists indicated that only 32–56% of these physicians had recently discussed family planning with female patients (14). However, no prior studies to our knowledge have explored rheumatologists' in-depth perspectives regarding FPCC for young, female patients. This qualitative study sought to explore rheumatologists' attitudes and practices related to FPCC and to highlight factors that they perceived as facilitators or barriers to the provision of FPCC for reproductive-age women.

MATERIALS AND METHODS

Study participant recruitment. This study was deemed exempt by the University of Pittsburgh Institutional Review Board. We used referral sampling to recruit adult rheumatologists to participate in this study. Referral sampling was used because of concern over the difficulty of finding rheumatologists willing to participate in an hour-long survey without adequate compensation for their time. Potential participants were ACR members who were identified through investigator networks. Participants were then asked to refer other rheumatologists who might provide unique perspectives to the study. The principal investigator (PI) sent up to 3 individual emails inviting referred rheumatologists to participate in the study. All interviews were completed between October 2017 and January of 2018. Participants were assured of complete confidentiality in their involvement in the study.

Interviews and data collection. Semistructured interviews were administered in-person or via telephone and explored rheumatologists' attitudes, beliefs, and practices regarding FPCC, barriers, and facilitators that affected their provision of FPCC, and information needs and preferences, related to reproductive-age female patients (see Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23872/abstract). Each rheumatologist reported demographic information about their number of years in practice, practice type (i.e., community versus academic), geographic location, sex, and race/ethnicity. Rheumatologists were also asked to estimate their proportion of reproductive-age female patients.

The PI (MBT) conducted all interviews, which were audio-recorded, anonymized, and transcribed verbatim. Interviews were conducted until thematic saturation was reached, i.e., the point at which no new themes were elicited; the interviewer perceived that this occurred after the tenth interview, based on the fact that she did not hear new information from interviews, suggesting that the final sample of 12 was sufficient for capturing a wide range of perspectives (15).

Data analysis. Transcripts were entered into ATLAS.ti software (Scientific Software Development) to facilitate coding. Our approach to coding and analysis was designed to involve considerable investigator triangulation through the use of multiple coders, and the review of coding and the resulting thematic analysis by multiple team members. Interview transcripts were reviewed by an experienced qualitative analyst (MH's research assistant), who generated a codebook using an inductive process known as editing, in which "the interpreter engages the text naively, without a [coding] template" (16). The codebook was reviewed by other members of the research team (MBT and MH) to ensure that the codes included barriers and facilitators to reproductive health care, and that code definitions were sufficiently clear. Involvement of several investigators involved in codebook development facilitated investigator triangulation; an additional benefit of an independent analyst developing the first draft was the potential reduction of bias in codebook development. Two coders then applied the finalized codebook to all transcripts and met to adjudicate any coding differences to full agreement. The primary coder (MH) reviewed the finalized coding to identify overarching themes and subthemes (15,17). Themes identified by the coder/analyst were discussed with the PI as a form of investigator triangulation. Quotations from the interviews were selected by the coders and the PI to illustrate major themes and subthemes.

RESULTS

Study participants. Of 16 rheumatologists who were approached, 12 completed interviews; 3 interviews were conducted in-person, and the remainder were conducted via telephone. Participant characteristics are shown in Table 1. Most participants (n = 7) had over 10 years of post-fellowship experience. Three rheumatologists worked for the US Veterans Affairs (VA) health care system, albeit in distinct geographic regions; otherwise, rheumatologists practiced in unique health care systems. VA rheumatologists had the fewest female patients overall and had not managed any pregnant patients in the past year.

Table 1. Participant characteristics*

Characteristic	Values
Years in practice, mean (range)	14.9 (1.5–42)
Region, no.	
West/Northwest	2
Midwest	2
East/Northeast	5
South/Southeast	3
Practice type, no.	
Community	6
Academic	6
Sex, no.	
Female	7
Male	5
Race/ethnicity, no. (%)	
African American	4 (33)
Asian	1 (8)
White	6 (50)
Latinx	1 (8)
Reproductive-age female, estimated total %	10–70
Pregnant patients treated in the past year, no.	
VA rheumatologists (n = 3)	0
Non-VA rheumatologists	4–16

* VA = Veterans Administration.

Themes. Six central themes were identified from the interviews. Rheumatologists said that they 1) feel responsible for providing some FPCC to patients, 2) experience tension between respecting patients' autonomy and their own anxieties about managing high-risk pregnancies, 3) view patient-initiated conversations as FPCC facilitators, and they regard lack of guidelines and the presence of competing clinical priorities as barriers to FPCC, 4) are reluctant to prescribe contraception, 5) desire greater access to resources to help guide FPCC, and 6) recognize the benefits of multidisciplinary collaboration with gynecologists.

Theme 1: rheumatologists feel responsible for providing limited FPCC to female patients. All rheumatologists expressed a sense of responsibility to provide some aspects of FPCC to female patients of reproductive age. When asked how they defined FPCC, rheumatologists' definitions unanimously centered on clarifying women's pregnancy intentions and timing, educating patients about the associations between their diseases and pregnancy, and optimizing women's health and antirheumatic drug regimens in anticipation of pregnancy. Several rheumatologists also mentioned that they would recommend folic acid supplementation to women contemplating pregnancy. As 1 participant stated, "We [rheumatologists] need to be involved because some of our medications can't be used in pregnancy, for obvious reasons. And then in terms of disease activity, if [patients are] under stress because [their] body is not doing well, then the success of the pregnancy is at risk as well. So you want to make sure that [their] disease is under control, that medications would be safe in pregnancy…to make sure you're giving [them] the best chance possible to have a successful pregnancy."

Rheumatologists' definitions of FPCC generally did not include contraception (Theme 4) or abortion care. When prompted to share whether they ever discussed abortion, most expressed discomfort with the topic, as described by 1 participant, "I would have a tough time discussing abortion with patients…I don't know that we are necessarily equipped to have that conversation, maybe it's all a comfort thing. I think that I'm most comfortable discussing medication with my patients."

Theme 2: rheumatologists experience a tension between respecting patients' autonomy and their own anxieties about managing pregnancies with a high risk of complications. Most rheumatologists expressed at least some degree of discomfort, fear, or anxiety about managing potentially high-risk pregnancies of women with rheumatic diseases. As 1 rheumatologist stated, "When you asked me about how many pregnant patients that I have had, despite the fact that I feel pretty comfortable discussing contraception, my heart did skip a beat. And I thought, you know, it's not one of the most pleasant things to deal with in my practice. And it's because of the fear. There is a fear that, what if something goes wrong? I think that we are all always concerned that anything could happen, something could go wrong."

Some rheumatologists volunteered the fact that fear and lack of confidence in managing complex pregnancies might, in turn, influence how they advised patients. For example, an outsized fear of complications might lead a rheumatologist to counsel a patient to avoid pregnancy altogether, even if her risk factors were not absolute contraindications to pregnancy. Several rheumatologists suggested that this "gloom and doom" approach might ultimately fracture the patient-provider relationship, as 1 participant said, "I think we probably overestimate the risks of medications and some diseases…and sometimes I think that we put pressure on patients to not want to get pregnant. I don't think it's on purpose, but I think it's probably just a side effect that sometimes happens. And then in that case, I don't think they want to talk to us about it."

Another rheumatologist described how feelings of fear and anxiety fractured the relationship with a newly pregnant patient, "I think I wasn't able to build up a very good physician-patient relationship, because I think that I got so scared that I kind of blurted out all the data for every single one of the drugs that we were talking about. I think that kind of scared her. She did not follow up very well…the pregnancy went well, but she never really did the follow-up as well as she should, and I felt it was because she wasn't trusting my judgment."

However, despite their apprehensions, rheumatologists generally respected patients' autonomy to pursue pregnancy. As 1 rheumatologist described it: "Sometimes I don't think it's a very good situation when they actually do want to get pregnant. I remember, I had a [patient] who was PL-7 [antibody positive] and she wanted to get pregnant. She was getting married and there

was no stopping the biological clock. I talked to a senior female faculty member. I was like, 'how do you approach?' And she said, 'you know if they want to get pregnant, they're going to, and you need to adjust.' I think you have to care for your patients…and part of their life is reproducing, usually."

Theme 3: facilitators of FPCC include patient-initiated conversations, whereas barriers to FPCC include lack of guidelines and the presence of competing clinical priorities. *Facilitators of FPCC*. Rheumatologists estimated that patients initiated family planning discussions 30–50% of the time, which the rheumatologists appreciated or even preferred. As 1 rheumatologist explained: "It's always helpful because with how busy we [rheumatologists] are, [FPCC] may slip and may not be mentioned on the first visit. I usually try to make an effort to always remember that, but if the patient mentions it, it's one extra reminder and prevents me from forgetting to talk about it." Some rheumatologists felt that a rheumatologist being female might also facilitate FPCC conversations, although no rheumatologists considered male sex to be a barrier to FPCC.

Barriers to FPCC. All rheumatologists mentioned that a lack of evidence-based resources to guide reproductive health care and medication prescribing was a barrier to providing FPCC. As 1 rheumatologist said, "The medication counseling, I find, is getting increasingly more difficult as things have shifted, with concerns with nonsteroidal drugs and pregnancy. You know, before the first couple of trimesters, it was thought to be okay. Now they've moved away from ABCDX [FDA pregnancy risk categories], and really made finding answers even more difficult. [I'm] trying to counsel the best I can, but I feel that it's very compromised at this point of time. There's a lot of interest in [medication risk]. Unfortunately, a lot of the interest, in my opinion, has made the waters even murkier when you're trying to explain things to a patient."

Most rheumatologists expressed the idea that competing priorities during clinic visits limited their ability to provide FPCC. As 1 rheumatologist stated, "[There is] pressure to see patients in the shortest amount of time. I focus on things that only I as a rheumatologist could focus on the disease process…there is a tendency to say, 'well, somebody else will talk to [patients] about contraception, somebody else will talk to them about family planning.'"

Other rheumatologists felt hesitant to initiate family planning discussions with patients who lacked clarity about their reproductive goals. As 1 provider mentioned, "I want the patient to be upfront with me. If you have a [family planning] conversation with a patient 14 times because every time she comes in she says, 'You know, I'm thinking about maybe getting pregnant here in another 5 or 6 months,' I'm thinking, should I think about stopping this or that [medication]? And then nothing happens, and she comes back in 6 months later and says the same things, and you have that same conversation all over again. You get fatigued by that."

Theme 4: rheumatologists are hesitant to prescribe contraception. While several participants reported that they required reproductive-age patients to use contraception if prescribed a fetotoxic antirheumatic drug, no rheumatologists in our sample prescribed contraception. Rheumatologists did not feel that they had sufficient knowledge about current contraceptive methods, and some felt unsure about the safety of estrogen-based contraception among women with some rheumatic diseases. All rheumatologists preferred for primary care physicians (PCPs) or gynecologists to prescribe contraception. As 1 rheumatologist said, "I think we need to ensure [patients] are on proper contraception if they're on teratogenic medications. I think that's a responsibility of the rheumatologist. The problem is, there are so many types of birth controls and the intricacies change all the time. And I'm not familiar with that. And we don't put in IUDs. I think we're responsible for making sure [patients are] on [contraception], but as a matter as well of primarily managing it? Maybe we should be, but right now I don't feel I have the training or the education to do that."

When asked whether they wanted to learn more about birth control methods so they could more confidently counsel patients or prescribe contraception, rheumatologists generally were not interested. As expressed by 1 rheumatologist, "I think we have enough to worry about and to know about without me starting to know all the nuances of the contraceptives, so I do not."

Theme 5: rheumatologists desire greater access to centralized resources to help guide reproductive decision-making. Some rheumatologists felt unclear about the most up-to-date recommendations in medication safety, which affected their confidence about whether they were providing the most accurate advice to patients. One rheumatologist said, "The truth is most rheumatologists don't want to have to deal with [pregnancy]. You know, just go have your baby, come back when you're done. Just because of the fear of the medications, the toxicity, the side effects, the intrapartum complications, the long-term risks to the baby and mother. So it's almost like [sigh], do we really have to have this discussion? I think it's just a matter of education…I think that's really needed." Rheumatologists consistently expressed the idea that they wanted access to consensus guidelines that gave them clear recommendations for managing diseases and antirheumatic drugs for women before, during, and after pregnancy, and through lactation.

Theme 6: rheumatologists recognize benefits of multidisciplinary collaboration with gynecologists. Most rheumatologists reported that they had an obstetrician-gynecologist with whom they had comanaged at least 1 patient, occasionally to identify a safe contraceptive method for a patient or to facilitate an infertility evaluation. As 1 rheumatologist described: "Rheumatology and OB-GYN [obstetrics/gynecology], it should be a collaboration. I don't think it's reasonable to expect family practitioners [to manage reproductive care] when they manage

so many diseases and so many medications." However, most rheumatologists did not formally refer patients to gynecologists or PCPs for reproductive health care, because most expected that reproductive-age patients already had providers to manage their contraception and other family planning needs. One rheumatologist explained, "I haven't had anyone that I have had to refer."

DISCUSSION

To our knowledge, this is the first qualitative study exploring attitudes, behaviors, and practices of rheumatologists regarding FPCC of women with rheumatic diseases. Rheumatologists felt compelled to provide some aspects of FPCC, which they generally defined as pregnancy focused, e.g., clarifying a patient's pregnancy intentions, managing medications in anticipation of and throughout pregnancy, and educating patients about how their antirheumatic drugs and disease activity could affect a pregnancy. Rheumatologists acknowledged that their own negative attitudes about managing complicated pregnancies could influence the family planning advice that they gave to patients. Lack of centralized guidelines augmented rheumatologists' anxieties about managing complex pregnancies and providing medication recommendations. While rheumatologists found gynecologists to be an important resource, they rarely referred patients for gynecologic care.

Rheumatologists infrequently addressed broader aspects of FPCC, such as contraception or abortion counseling, screening for nonrheumatic maternal risk factors (e.g., cigarette smoking), or promoting folic acid supplementation or maternal vaccination (9–11). Currently, no guidelines exist to clarify the FPCC topics for which rheumatologists should be responsible; thus, the content, quality, and even frequency of these conversations may vary substantially between rheumatologists. Whether the FPCC delivered by rheumatologists fulfills female patients' specific reproductive health needs is unclear, particularly for those patients who wish to avoid pregnancy or childbearing.

Future work should clarify the rheumatologist's specific roles and responsibilities with regard to FPCC. For now, a starting point could be the recommendation that all rheumatologists initiate FPCC with each of their reproductive-age female patients, to better ascertain their reproductive goals and/or referral needs. Specific open-ended phrasing that has been developed for the general population could help rheumatologists to initiate these conversations as part of routine office workflow (e.g., electronic medical records or intake forms): 1) PATH (Pregnancy Attitudes, Timing and How important is pregnancy prevention) questions (e.g., Do you think you might like to have [more] children at some point?"), or 2) One Key Question ("Would you like to become pregnant in the next year?") (10,18,19). In addition, trained rheumatology nurses have been found to enhance patient satisfaction and care for other aspects of rheumatologic care (20); they might potentially help to provide aspects of FPCC for patients, including facilitating appropriate referrals for reproductive health care.

Another key finding of our study was that rheumatologists were apprehensive about managing the high-risk pregnancies of women with rheumatic diseases, and several expressed the idea that this fear might lead rheumatologists to inadvertently discourage patients from pursuing pregnancy even when they lacked medical contraindications. Similar anxieties were expressed by US rheumatologists in a separate survey, in which 64% did not feel confident managing a moderate-risk systemic lupus erythematosus (SLE) pregnancy, and 70% felt "anxious" or "alarmed" when they had to manage a pregnant patient with SLE (21). Rheumatologists' apprehensions about pregnancy may come at the price of the patient-provider relationship, particularly if patients feel that their providers do not respect or support their reproductive goals (22).

An important message to providers and patients is that many women with rheumatic diseases have successful pregnancies and healthy babies (7,23–26) . Moreover, some women will choose to pursue pregnancy even if they face substantial health risks (27). Reproduction is an intimate, highly contextualized decision, and respecting women's autonomy about whether or when they would like to have children is an essential approach to patient-centered care. Providers who have open, honest, and judgment-free conversations with patients may be able to anticipate pregnancy among high-risk patients, mitigate health risks as much as possible in advance of pregnancy, and thereby optimize the chances that a woman is in the best health possible before she becomes pregnant (22,28). It is important that rheumatologists explore how their own attitudes about pregnancy management influence how they advise patients about their reproductive intentions and goals.

One of the primary reasons why rheumatologists expressed anxiety about managing the pregnancies of women with rheumatic diseases is because centralized guidelines are lacking that clarify how to manage peripartum disease flares or medications during pregnancy and lactation. Reproductive guidelines from the ACR are forthcoming in 2020, and other key resources are currently available to support FPCC (7,8,26,28–32). Future work should evaluate whether the existence of guidelines helps to reduce rheumatologists' anxieties about pregnancy, or whether additional resources are needed to support rheumatologists as they provide this care. This is potentially important work, because prior studies in medicine have suggested that it can take years for guidelines to change routine clinical practice (33,34).

Rheumatologists identified another barrier to FPCC as competing priorities during clinic visits. Ambiguous pregnancy intentions expressed by some patients seemed to complicate care plans, take up more clinic time, and frustrate some providers. However, one-third of all women have ambiguous, complex, and conflicted feelings about pregnancy, and there is no indication that women with rheumatic diseases are less conflicted than other women (35,36). Rather, prior work suggests that women with rheumatic diseases may be conflicted about pregnancy because of issues within the rheumatologists' expertise, such as

medication safety (37,38). Therefore, rheumatologists who invest the time to explore patients' ambiguities about pregnancy may ultimately provide women with the information they need to clarify their reproductive goals.

Rheumatologists in our study did not prescribe contraception for patients, although they routinely prescribed fetotoxic antirheumatic drugs to patients with reproductive potential; most lacked knowledge about current contraceptive methods and expected that the patient's gynecologist or PCP should be responsible for this aspect of care. However, only 25% of PCPs provide contraceptive care due to a lack of adequate training and skills, and some do not want to manage the gynecologic care of medically complex patients (39,40). While gynecologists in 1 study were significantly more likely to prescribe highly effective contraception to women with rheumatic diseases, only one-third of these patients saw a gynecologist over a 2-year period (41). Therefore, some patients may not have access to contraception or gynecologic care. Important practice modifications for rheumatologists may be to identify patients' unmet contraception needs, refer patients to gynecology when appropriate, and identify local rheumatologists to whom they can directly refer patients with urgent contraceptive needs (e.g., women with active rheumatic disease or fetotoxic medication use) (28,32).

Our study has several limitations. First, while participating rheumatologists had diverse backgrounds and we achieved thematic saturation, more themes may have arisen if the study sample were larger or included more male rheumatologists. Selection bias may also have affected some responses, as rheumatologists entered the study via referral sampling and might have been perceived to have more interest in FPCC than those who did not participate; however, we note that our final sample was diverse in practice characteristics and the number of female reproductive-age patients served annually. Finally, rheumatologists may have tailored their responses to be socially acceptable rather than to be truly reflective of their attitudes and practices, although we attempted to mitigate some of this risk by assuring confidentiality in their participation in the study.

In summary, this qualitative study underscores the fact that rheumatologists are dedicated to providing FPCC to patients and prefer to counsel on a limited range of topics related specifically to diseases, antirheumatic drugs, and pregnancy. Important barriers to FPCC included rheumatologists' anxieties about managing complicated pregnancies, competing priorities in the clinic, and a lack of knowledge about contraception options. Centralized guidelines and tools that help to support FPCC must be developed to improve care for this high-risk group of women. Finally, while we present only provider perspectives herein, future work must highlight the voices of women with rheumatic diseases, to identify their specific family planning care and counseling needs, preferences, and priorities.

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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. Birru Talabi 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. Birru Talabi, Clowse, Borrero.

Acquisition of data. Birru Talabi, Hamm.

Analysis and interpretation of data. Birru Talabi, Clowse, Blalock, Hamm.

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LETTERS

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Are thrombotic events in dermatomyositis related to the effect of antiphospholipid antibodies? Comment on the article by Moshtaghi-Svensson et al

To the Editor:

The high incidence of ischemic strokes among individuals with dermatomyositis was the subject of an intriguing article by Moshtaghi-Svensson et al (1), recently published in *Arthritis Care & Research*. The reported incidence of ischemic events is characteristic of antiphospholipid syndrome, a known association with connective tissue diseases (2,3). A possible explanation for ischemic events in dermatomyositis may be modulation of platelet and vascular function by antiphospholipid antibodies (4). Thus, assessment for the presence of antiphospholipid antibodies in dermatomyositis, especially in patients with ischemic events, seems worthwhile, with prophylactic action when present. Identification of antiphospholipid antibodies would be especially important for individuals with ischemic events, because the presence of antiphospholipid antibodies requires modification of standard intervention (5). The antibodies to test for would be IgG, IgM, and IgA antibodies to anticardiolipin, beta-2-glycoprotein I, and anti-phosphatidylserine/prothrombin (6).

If antiphospholipid antibodies are present, the use of aspirin or a cyclooxygenase 1–predominant nonsteroidal antiinflammatory drug (NSAID) might be considered. While use of low-dose aspirin for primary prevention of antiphospholipid complications has been controversial (7), there is an explanation for the confusion. It arises from the assumption that standard aspirin dosing (<100 mg/day) is a valid approach. There is significant variation in aspirin's clinical efficacy as an inhibitor of platelet function. A dose as high as 1,000 mg/day may be required, and even that may not be effective. Simply prescribing aspirin or an NSAID, without assessing efficacy as an inhibitor of platelet function and compliance, is inadequate. Platelet function testing (of response to epinephrine and collagen) is essential. Failure to produce response time prolongation (interference with platelet function) identifies inadequate efficacy (8). If anticoagulation intervention is alternatively chosen, the options are unfractionated heparin or high-dose warfarin (international normalized ratio 3.0–3.5) (5), recalling that the very convenient fractionated heparin has been ineffective in preventing further thrombotic events in individuals with antiphospholipid syndrome (9,10).

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Applications Invited for *Arthritis Care & Research* Editor-in-Chief (2021–2026 Term)

The American College of Rheumatology Committee on Journal Publications announces the search for the position of Editor, *Arthritis Care & Research*. The official term of the next *Arthritis Care & Research* editorship is July 1, 2021–June 30, 2026; however, some of the duties of the new Editor will begin during a transition period starting April 1, 2021. ACR/ARP members who are considering applying for this prestigious and rewarding position should submit a nonbinding letter of intent by May 4, 2020 to the Managing Editor, Maggie Parry, at mparry@rheumatology.org, and are also encouraged to contact the current Editor-in-Chief, Dr. Marian Hannan, to discuss details. Initial contact should be made via e-mail to Hannan@hsl.harvard.edu. Applications will be due by June 15, 2020 and will be reviewed during the summer of 2020. Application materials are available on the ACR web site at https://www.rheumatology.org/Portals/0/Files/ACandR-Editor-Application-Instructions.pdf.

ARP Announcements

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Call for Themed Submissions

Submissions Invited for Themed Issue of *Arthritis Care & Research*: Psychosocial Issues in Rheumatic Diseases.

Arthritis Care & Research is soliciting manuscripts for a Themed Issue addressing pertinent aspects of psychosocial issues as related to outcomes and concerns in the rheumatic diseases, as there is more than just a physical aspect to these disorders. Psychosocial issues may include all aspects related to living with a rheumatic disease, including the psychological, social, or economic influences that have an impact upon persons with rheumatic disease.

Manuscripts covering a broad range of topics related to the major theme are invited. For example, the effects and consequences of psychosocial factors in rheumatic diseases (rheumatoid arthritis, lupus, osteoarthritis, psoriatic arthritis, and others), psychosocial issues as linked with other symptoms and conditions such as pain, depression, anxiety, or disability among persons with rheumatic conditions, intervention studies addressing improvement in psychosocial measures, cost-benefit analyses as well as outcomes (such as physical limitations, severity of disease, family issues, drug interactions), and health behaviors. Chronic disease management strategies that address rheumatic diseases and psychosocial factors are also encouraged.

Submissions are encouraged from a range of disciplines relevant to psychosocial issues in the rheumatic diseases. We will consider both Original Research articles and Review articles.

The Themed Issue will include both themed and non-themed manuscripts; however, the bulk of the 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 non-themed issue of *Arthritis Care & Research*.

Please follow the formatting requirements found in our "For Authors" section at: http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658.

The deadline for submission is April 3, 2020. For further information, contact the editor of *Arthritis Care & Research*, Dr. Marian T. Hannan, (Hannan@hsl.harvard.edu).

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