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

Special Themed Articles: Rheumatology Registries, Big Data, and the Rheumatic Diseases

Rheumatoid Arthritis

Cover image: The figure on the cover (from Yun et al, Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24083/abstract) shows a partial study design using the RISE registry of ≥1 rheumatology visit with a valid rheumatoid arthritis disease activity measure, ≥1 previous visit with same disease activity measure, and ≥1 RISE follow-up visit with the disease activity measurement.

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American College of Rheumatology
Empowering Rheumatology Professionals

2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee

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Objective. To develop an evidence-based guideline for the comprehensive management of osteoarthritis (OA) as a collaboration between the American College of Rheumatology (ACR) and the Arthritis Foundation, updating the 2012 ACR recommendations for the management of hand, hip, and knee OA.

Methods. We identified clinically relevant population, intervention, comparator, outcomes questions and critical outcomes in OA. A Literature Review Team performed a systematic literature review to summarize evidence supporting the benefits and harms of available educational, behavioral, psychosocial, physical, mind-body, and pharmacologic therapies for OA. Grading of Recommendations Assessment, Development and Evaluation methodology was used to rate the quality of the evidence. A Voting Panel, including rheumatologists, an internist, physical and occupational therapists, and patients, achieved consensus on the recommendations.

Results. Based on the available evidence, either strong or conditional recommendations were made for or against the approaches evaluated. Strong recommendations were made for exercise, weight loss in patients with knee and/or hip OA who are overweight or obese, self-efficacy and self-management programs, tai chi, cane use, hand orthoses for first carpometacarpal (CMC) joint OA, tibiofemoral bracing for tibiofemoral knee OA, topical nonsteroidal antiinflammatory drugs (NSAIDs) for knee OA, oral NSAIDs, and intraarticular glucocorticoid injections for knee OA. Conditional recommendations were made for balance exercises, yoga, cognitive behavioral therapy, kinesiotaping for first CMC OA, orthoses for hand joints other than the first CMC joint, patellofemoral bracing for patellofemoral knee OA, acupuncture, thermal modalities, radiofrequency ablation for knee OA, topical NSAIDs, intraarticular steroid injections and chondroitin sulfate for hand OA, topical capsaicin for knee OA, acetaminophen, duloxetine, and tramadol.

Conclusion. This guideline provides direction for clinicians and patients making treatment decisions for the management of OA. Clinicians and patients should engage in shared decision-making that accounts for patients' values, preferences, and comorbidities. These recommendations should not be used to limit or deny access to therapies.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, affecting an estimated 302 million people worldwide (1–5), and is a leading cause of disability among older adults. The knees, hips, and hands are the most commonly affected appendicular joints. OA is characterized by pathology involving the whole joint, including cartilage degradation, bone remodeling, osteophyte formation, and synovial inflammation, leading to pain, stiffness, swelling, and loss of normal joint function.

As OA spans decades of a patient's life, patients with OA are likely to be treated with a number of different pharmaceutical and nonpharmaceutical interventions, often in combination. This report provides recommendations to guide patients and clinicians in choosing among the available treatments. Certain principles of management apply to all patients with OA (see Comprehensive Management of OA below and Figure 1). Some recommendations are specific to a particular joint (e.g., hip, knee, patellofemoral joint, first carpometacarpal joint [CMC]) or particular patient populations (e.g., those with erosive OA).

METHODS

This guideline, from the American College of Rheumatology (ACR) and the Arthritis Foundation (AF), follows the ACR guideline development process (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of the available evidence and to develop the recommendations (6). ACR policy guided management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Osteoarthritis). A full description of the methods is presented in Supplementary Appendix 1 (on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract).

Briefly, this work involved 5 teams: 1) a Core Leadership Team that supervised and coordinated the project and drafted the clinical/population, intervention, comparator, outcomes (PICO) questions that served as the basis for the evidence report and manuscript; 2) a Literature Review Team that completed the literature screening and data abstraction and produced the Evidence Report (Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract); 3) an Expert Panel that had input into scoping and clinical/PICO question development; 4) a Patient Panel; and 5) an interprofessional Voting Panel that included rheumatologists, an internist, physical and occupational therapists, and patients (Supplementary Appendix 3, http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract).

This guideline included an initial literature review limited to English-language publications from inception of the databases to October 15, 2017, with updated searches conducted on August 1, 2018 and relevant papers included. Studies published after August 1, 2018 were not evaluated for this guideline. Supplementary Appendix 4 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract) shows search terms used and databases reviewed, and Supplementary Appendix 5 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract) highlights the study selection process. The guideline evidence base results from our own systematic review of randomized

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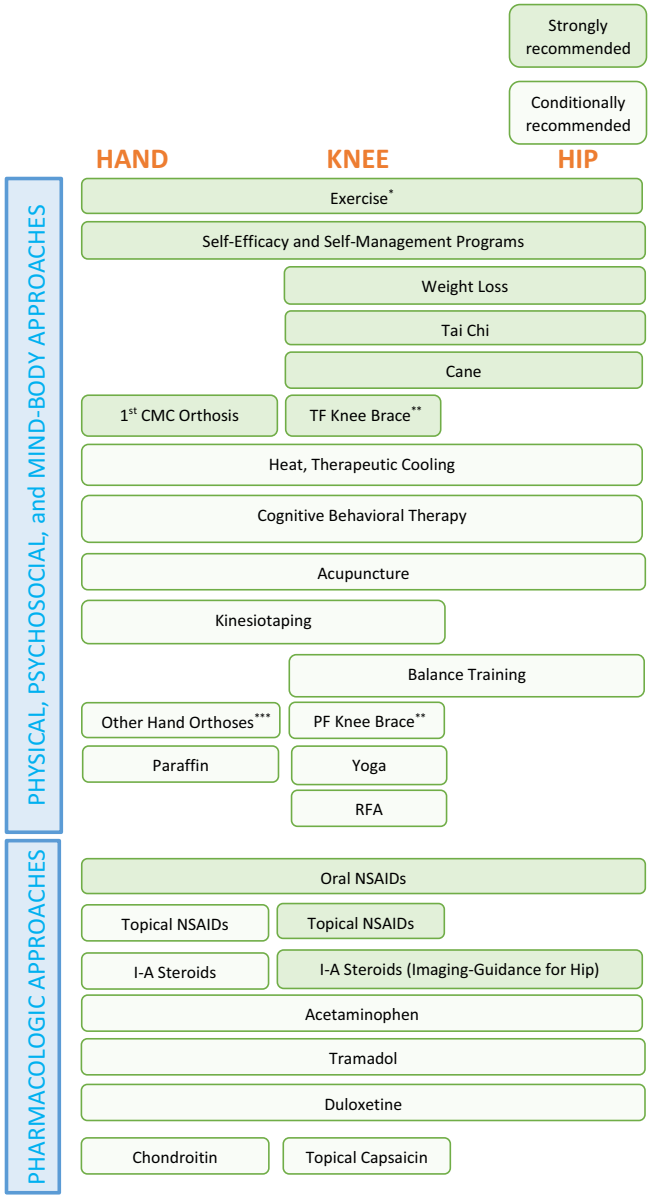

Figure 1. Recommended therapies for the management of osteoarthritis (OA). Strongly and conditionally recommended approaches to management of hand, knee, and/or hip OA are shown. No hierarchy within categories is implied in the figure, with the recognition that the various options may be used (and reused) at various times during the course of a particular patient's disease. * = Exercise for knee and hip OA could include walking, strengthening, neuromuscular training, and aquatic exercise, with no hierarchy of one over another. Exercise is associated with better outcomes when supervised. ** = Knee brace recommendations: tibiofemoral (TF) brace for TF OA (strongly recommended), patellofemoral (PF) brace for PF OA (conditionally recommended). *** = Hand orthosis recommendations: first carpometacarpal (CMC) joint neoprene or rigid orthoses for first CMC joint OA (strongly recommended), orthoses for joints of the hand other than the first CMC joint (conditionally recommended). RFA = radiofrequency ablation; NSAIDs = nonsteroidal antiinflammatory drugs; IA = intraarticular.

controlled trials (RCTs), rather than focusing on systematic reviews and meta-analyses published by others, as was done for the 2012 ACR recommendations for the use of nonpharmacologic and pharmacologic therapies in hand, hip, and knee OA (7). Systematic reviews of observational studies published by others were included if, in the opinion of the Voting Panel, they added critical information for the formulation of a recommendation: for example, related to adverse effects that may not be seen in shorter-duration RCTs. Subsequent updates of this guideline will consider studies included here and new RCTs published since completion of the literature review for the current publication.

Although RCTs are considered the gold standard for evaluation, a number of limitations of RCTs proved particularly important in the formulation of the final recommendations: possible publication bias (favoring publication of positive results), inadequate blinding, and inadequate provision of active comparators and appropriate sham alternatives. Further, short-duration RCTs cannot provide adequate prognostic information when applied to a complex disease such as OA, in which pathophysiologic processes are slowly progressive over decades.

We focused on management options that are available in the US and, for pharmacologic therapies, we additionally focused on agents that are available in pharmaceutical-grade formulations, thus eliminating most nutraceuticals. We limited our review to the English-language literature. We reviewed www.clinicaltrials.gov to identify phase 2 and 3 trials that may be far enough along to be US Food and Drug Administration (FDA)–approved and available by the time this guideline was published.

A hierarchy of outcome measures assessing pain and function in OA was developed based on the published literature (8,9). This hierarchy is detailed in Supplementary Appendix 1 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract).

Using GRADE, a recommendation can be either in favor of or against the proposed intervention and either strong or conditional (10,11). The strength of the recommendation is based on a 70% consensus among the Voting Panel members. Much of the evidence proved indirect (did not specifically address the PICO question as written) and of low-to-moderate quality (12,13). The Voting Panel made *strong recommendations* when it inferred compelling evidence of efficacy and that benefits clearly outweighed harms and burdens. Thus, a strong recommendation means that the Voting Panel was confident that the desirable effects of following the recommendation outweigh potential undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion of patients would not want to follow the recommendation.

The Voting Panel made *conditional recommendations* when the quality of the evidence proved low or very low and/

or the balance of benefits versus harms and burdens was sufficiently close that shared decision-making between the patient and the clinician would be particularly important. Conditional recommendations are those for which the majority of informed patients would choose to follow the recommended course of action, but some would not (14,15). Thus, conditional recommendations are particularly value- and preference-sensitive and always warrant a full shared decision-making approach involving a complete and clear explication of benefits, harms, and burdens in language and in a context that patients understand (16). Where recommendations are made regarding a particular approach, details and references regarding that approach can be found in the Evidence Report (Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract).

RESULTS/RECOMMENDATIONS

Comprehensive management of OA

A comprehensive plan for the management of OA in an individual patient may include educational, behavioral, psychosocial, and physical interventions, as well as topical, oral, and intraarticular medications. Recommendations assume appropriate application of physical, psychological, and/or pharmacologic therapies by an appropriate provider. Goals of management and principles for implementing those goals have broad applicability across patients. However, for some patients at some time points, a single physical, psychosocial, mind-body, or pharmacologic intervention may be adequate to control symptoms; for others, multiple interventions may be used in sequence or in combination. Which interventions and the order in which interventions are used will vary among patients. An overview of a general approach to management of OA is outlined in Figure 1 for recommended options, but no specific hierarchy of one option over another is implied other than on the basis of strength of the recommendation. Figure 2 summarizes the approaches that were not recommended.

Treatment decisions should take the personal beliefs and preferences of the patient, as well as the patient's medical status, into consideration. This guideline applies to patients with OA with no specific contraindications to the recommended therapies. However, each patient should be assessed for the presence of medical conditions, such as hypertension, cardiovascular disease, heart failure, gastrointestinal bleeding risk, chronic kidney disease, or other comorbidities, that might have an impact on their risk of side effects from certain pharmacologic agents, as well as injuries, disease severity, surgical history, and access to and availability of services (transportation, distance, ability to take time off work, cost, insurance coverage) that might have an impact on the choice of physical, psychological, and mind-body approaches. It is assumed that such an assessment

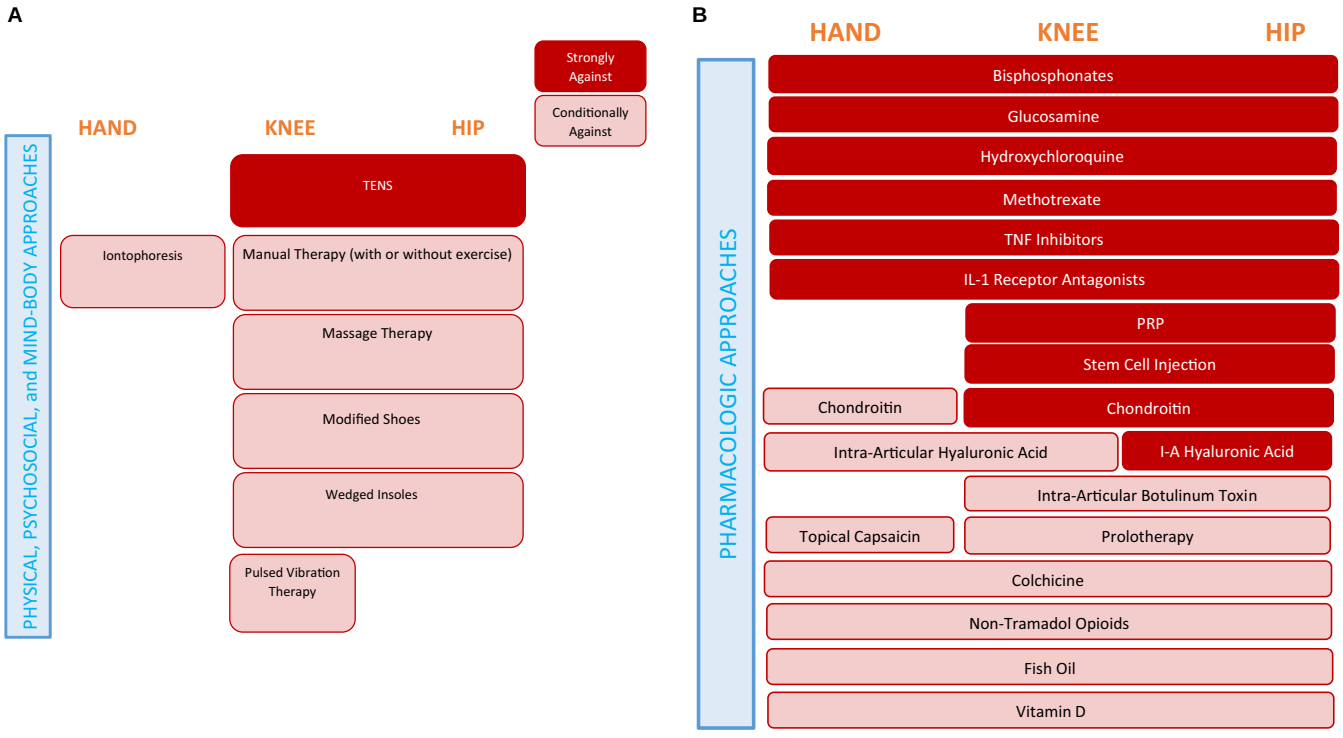

Figure 2. Therapies recommended *against* (physical, psychosocial, and mind-body approaches [**A**] and pharmacologic approaches [**B**]) in the management of hand, knee, and/or hip osteoarthritis. No hierarchy within categories is implied in the figure. TENS = transcutaneous electrical nerve stimulation; TNF = tumor necrosis factor; IL-1 = interleukin-1; PRP = platelet-rich plasma; IA = intraarticular.

will be performed prior to finalization of an individual treatment plan. When choosing among pharmacologic therapies, management should begin with treatments with the least systemic exposure or toxicity.

Patients may experience a variety of additional symptoms as a result of the pain and functional limitations arising from OA and/or comorbidities. These include mood disorders, such as depression and anxiety, altered sleep, chronic widespread pain, and impaired coping skills. The Patient Panel noted that the broader impact of OA on these comorbidities is of particular importance when choosing among treatment options and best addressed by a multimodal treatment plan, rather than one that is limited to the prescription of a single medication. Measures aimed at improving mood, reducing stress, addressing insomnia, managing weight, and enhancing fitness may improve the patient's overall well-being and OA treatment success. Indeed, interventions that have proven beneficial in the management of chronic pain may prove useful in OA (17) even when data specific to patients with OA are limited.

Unless otherwise specified, recommendations regarding physical, psychosocial, and mind-body approaches assume that the patient will be adding the intervention to usual care. For the purposes of this guideline, usual care includes the use of maximally recommended or safely tolerated doses of over-the counter oral nonsteroidal antiinflammatory drugs (NSAIDs) and/or acetaminophen, as has generally been explicitly permitted in clinical trials of nonpharmacologic interventions.

Physical, psychosocial, and mind-body approaches (Table 1)

During the GRADE analysis, clinical trials involving physical modalities and mind-body approaches were often designated as yielding low-quality evidence because blinding with regard to the active treatment was not always possible. This contributed to a preponderance of conditional recommendations for physical modalities and mind-body approaches. The delivery of instruction by physical and occupational therapists is helpful, and often essential, for the appropriate initiation and maintenance of exercise as a part of OA management. In addition to exercise, physical and occupational therapists often incorporate self-efficacy and self-management training, thermal therapies, and instruction in use of and fitting of splints and braces in their practices. Most patients with OA are likely to experience benefit from referral to physical therapy and/or occupational therapy at various times during the course of their disease.

Exercise is strongly recommended for patients with knee, hip, and/or hand OA.

Though exercise is strongly recommended for all OA patients, there is considerably more evidence for the use of exercise in the treatment of knee and hip OA than for hand OA, and the variety of exercise options studied is far greater. While patients and providers seek recommendations on the "best" exercise and the ideal dosage (duration, intensity, and frequency), current evidence

Table 1. Recommendations for physical, psychosocial, and mind-body approaches for the management of osteoarthritis of the hand, knee, and hip

Intervention	Joint		
	Hand	Knee	Hip
Exercise			
Balance training			
Weight loss			
Self-efficacy and self-management programs			
Tai chi			
Yoga			
Cognitive behavioral therapy			
Cane			
Tibiofemoral knee braces		(Tibiofemoral)	
Patellofemoral braces		(Patellofemoral)	
Kinesiotaping	(First carpometacarpal)		
Hand orthosis	(First carpometacarpal)		
Hand orthosis	(Other joints)		
Modified shoes			
Lateral and medial wedged insoles			
Acupuncture			
Thermal interventions			
Paraffin			
Radiofrequency ablation			
Massage therapy			
Manual therapy with/without exercise			
Iontophoresis	(First carpometacarpal)		
Pulsed vibration therapy			
Transcutaneous electrical nerve stimulation			

Strongly recommended
Conditionally recommended
Strongly recommended against
Conditionally recommended against
No recommendation

is insufficient to recommend specific exercise prescriptions. Broad recommendations suggesting one form of exercise over another are based largely on expert opinion. A substantial body of literature (see Evidence Report, Supplementary Appendix 2 [http://onlinelibrary.wiley.com/doi/10.1002/acr.24131/abstract]) supports a wide range of appropriate exercise options and suggests that the vast majority of OA patients can participate in, and benefit from with regard to pain and function, some form of exercise. Exercise recommendations to patients should focus on the patient's preferences and access, both of which may be important barriers to participation. If a patient does not find a certain form of exercise acceptable or cannot afford to participate or arrange transportation to participate, he or she is not likely to get any benefit from the suggestion to pursue that exercise.

In the majority of studies that assessed the role of aerobic exercise in the management of OA, walking was the most common form of exercise evaluated, either on a treadmill or as supervised, community-based, indoor fitness walking. Other studies used supervised group cycling on stationary bicycles. Strengthening exercises have included the use of isokinetic weight machines, resistance exercise training with and without props such as elastic bands, and isometric exercise. Neuromuscular training has been developed to address muscle weakness, reduced sensorimotor control, and functional instability specifically seen with knee OA, with a series of dynamic maneuvers of increased complexity. Aquatic exercise often encompasses aspects of aerobic fitness exercises and exercises for enhancing joint range of motion, in a low-impact environment.

A specific hierarchy of these various forms of exercise could not be discerned from the literature. Patient participants on the Patient and Voting Panels raised the concern that patients who are in pain might be hesitant to participate in exercise. There is no uniformly accepted level of pain at which a patient should or should not exercise, and a common-sense approach of shared decision-making between the treating clinician and the patient regarding when to initiate an exercise program is advisable. However, clinical trials of exercise for OA include patients with pain and functional limitations due to OA, and improvements in OA-specific outcomes have been demonstrated; thus, results are likely to be generalizable to most patients with pain due to OA.

Although there is currently insufficient evidence to recommend one form of exercise over another, patients will likely benefit from advice that is as specific as possible, rather than simple encouragement to exercise. Given the wide range of evidence-based exercise interventions shown to effectively improve pain and function in OA, all patients should be encouraged to consider some form of exercise as a central part of their treatment plan. Individual preferences, access, and affordability are likely to play a role in what works best for an individual patient. Overall, exercise programs are more effective if supervised, often by physical therapists and sometimes in a class setting, rather than when performed by the individual at home. They also tend to be more effective when combined with self-efficacy and self-management interventions or weight loss programs.

Few studies have employed monitoring devices or pre- and postintervention assessment of cardiovascular or musculoskeletal fitness, so targets using these devices or assessments are not available. Future research is essential to establish specific exercise guidelines that will direct the patient and provider toward more individualized exercise prescriptions.

Balance exercises are conditionally recommended for patients with knee and/or hip OA.

Balance exercises include those that improve the ability to control and stabilize body position (American Physical Therapy Association: http://www.apta.org/BalanceFalls/). Although one might expect balance exercises to help reduce the risk of falls in patients with OA, RCTs to date have not addressed this outcome in this population, and the low quality of evidence addressing the use of balance exercises necessitates only a conditional recommendation for balance exercises.

Weight loss is strongly recommended for patients with knee and/or hip OA who are overweight or obese.

A dose-response has been noted with regard to the amount of weight loss that will result in symptom or functional improvement in patients with OA (18). A loss of ≥5% of body weight can be associated with changes in clinical and mechanistic outcomes. Furthermore, clinically important benefits continue to increase with weight loss of 5–10%, 10–20%, and >20% of body weight. The efficacy of weight loss for OA symptom management is enhanced by use of a concomitant exercise program.

Self-efficacy and self-management programs are strongly recommended for patients with knee, hip, and/or hand OA.

Although effect sizes are generally small, the benefits of participation in self-efficacy and self-management programs are consistent across studies, and risks are minimal. These programs use a multidisciplinary group–based format combining sessions on skill-building (goal-setting, problem-solving, positive thinking), education about the disease and about medication effects and side effects, joint protection measures, and fitness and exercise goals and approaches. Health educators, National Commission for Certification Services–certified fitness instructors, nurses, physical therapists, occupational therapists, physicians, and patient peers may lead the sessions, which can be held in person or online. In the studies reviewed, sessions generally occurred 3 times weekly, but varied from 2 to 6 times weekly.

Tai chi is strongly recommended for patients with knee and/or hip OA.

Tai chi is a traditional Chinese mind-body practice that combines meditation with slow, gentle, graceful movements, deep diaphragmatic breathing, and relaxation. The efficacy of tai chi may

reflect the holistic impact of this mind-body practice on strength, balance, and fall prevention, as well as on depression and self-efficacy.

Yoga is conditionally recommended for patients with knee OA.

Yoga is a mind-body practice with origins in ancient Indian philosophy and typically combines physical postures, breathing techniques, and meditation or relaxation (National Center for Complementary and Integrative Health [NCCIH]: https://nccih.nih.gov/health/yoga). Though far less well studied than tai chi, yoga may be helpful in OA through a similar blend of physical and psychosocial factors. Due to lack of data, no recommendation can be made regarding use of yoga to help manage symptoms of hip OA. Other mind-body practices could not be assessed due to insufficient evidence, as well as a lack of standard definitions of certain interventions (hypnosis, qi gong).

Cognitive behavioral therapy (CBT) is conditionally recommended for patients with knee, hip, and/or hand OA.

There is a well-established body of literature (19,20) supporting the use of CBT in chronic pain conditions, and CBT may have relevance for the management of OA. Trials have demonstrated improvement in pain, health-related quality of life, negative mood, fatigue, functional capacity, and disability in conditions other than OA. In OA, limited evidence suggests that CBT may reduce pain (21). Further research is needed to establish whether or not benefits in OA are related to alteration in mood, sleep, coping, or other factors that may co-occur with, result from, or be a part of the experience of OA (22).

Cane use is strongly recommended for patients with knee and/or hip OA in whom disease in 1 or more joints is causing a sufficiently large impact on ambulation, joint stability, or pain to warrant use of an assistive device.

Tibiofemoral knee braces are strongly recommended for patients with knee OA in whom disease in 1 or both knees is causing a sufficiently large impact on ambulation, joint stability, or pain to warrant use of an assistive device, and who are able to tolerate the associated inconvenience and burden associated with bracing.

Patellofemoral braces are conditionally recommended for patients with patellofemoral knee OA in whom disease in 1 or both knees is causing a sufficiently large impact on ambulation, joint stability, or pain to warrant use of an assistive device.

The recommendation is conditional due to the variability in results across published trials and the difficulty some patients will have in tolerating the inconvenience and burden of these braces. Optimal management with knee bracing is likely to require that clinicians are familiar with the various types of braces and where they are available and have expertise in fitting the braces. Patient Voting Panel members strongly emphasized the importance of coordination of care between primary care providers, specialists, and providers of braces.

Kinesiotaping is conditionally recommended for patients with knee and/or first CMC joint OA.

Kinesiotaping permits range of motion of the joint to which it is applied, in contrast to a brace, which maintains the joint in a fixed position. Published studies have examined various products and methods of application, and blinding with regard to use is not possible, thereby limiting the quality of the evidence.

Hand orthoses are strongly recommended for patients with first CMC joint OA.

Hand orthoses are conditionally recommended for patients with OA in other joints of the hand.

A variety of mechanical supports are available, including digital orthoses, ring splints, and rigid or neoprene orthoses, some of which are intended for specifically affected joints (e.g., first CMC joint, individual digits, wrist) and some of which support the entire hand. In addition, gloves may offer benefit by providing warmth and compression to the joints of the hand. Data are insufficient to recommend one type of orthosis over another for use in the hand. Patients considering these interventions will likely benefit from evaluation by an occupational therapist.

Modified shoes are conditionally recommended *against* in patients with knee and/or hip OA.

Modifications to shoes can be intended to alter the biomechanics of the lower extremities and the gait. While optimal footwear is likely to be of considerable importance for those with knee and/or hip OA, the available studies do not define the best type of footwear to improve specific outcomes for knee or hip OA.

Lateral and medial wedged insoles are conditionally recommended *against* in patients with knee and/or hip OA.

The currently available literature does not demonstrate clear efficacy of lateral or medial wedged insoles.

Acupuncture is conditionally recommended for patients with knee, hip, and/or hand OA.

Although a large number of trials have addressed the use of acupuncture for OA, its efficacy remains a subject of controversy. Issues related to the use of appropriate blinding, the validity of sham controls, sample size, effect size, and prior expectations have arisen with regard to this literature. Variability in the results of RCTs and meta-analyses is likely driven, in part, by differences in the type of controls and the intensity of the control

interventions used. In addition, the benefits of acupuncture result from the large contextual effect plus small differences in outcomes between "true" and "sham" acupuncture. The latter is of the same magnitude as the effect of full-dose acetaminophen versus placebo. The greatest number of positive trials with the largest effect sizes have been carried out in knee OA. Positive trials and meta-analyses have also been published in a variety of other painful conditions and have indicated that acupuncture is effective for analgesia. While the "true" magnitude of effect is difficult to discern, the risk of harm is minor, resulting in the Voting Panel providing a conditional recommendation.

Thermal interventions (locally applied heat or cold) are conditionally recommended for patients with knee, hip, and/or hand OA.

The method of delivery of thermal interventions varies considerably in published reports, including moist heat, diathermy (electrically delivered heat), ultrasound, and hot and cold packs. Studies using diathermy or ultrasound were more likely to be sham controlled than those using other heat delivery modalities. The heterogeneity of modalities and short duration of benefit for these interventions led to the conditional recommendation.

Paraffin, an additional method of heat therapy for the hands, is conditionally recommended for patients with hand OA.

Radiofrequency ablation is conditionally recommended for patients with knee OA.

A number of studies have demonstrated potential analgesic benefits with various ablation techniques but, because of the heterogeneity of techniques and controls used and lack of long-term safety data, this recommendation is conditional.

Massage therapy is conditionally recommended *against* in patients with knee and/or hip OA.

Massage therapy encompasses a number of techniques aimed at affecting muscle and other soft tissue (NCCIH: https://nccih.nih.gov/health/massage/massageintroduction.htm#hed2). Studies addressing massage have suffered from high risk of bias, have included small numbers of patients, and have not demonstrated benefit for OA-specific outcomes. Patient participants on the Patient and Voting Panels noted that some studies have shown positive outcomes and minimal risk and felt strongly that massage therapy was beneficial for symptom management (23). However, based on the available evidence regarding OA specifically, a conditional recommendation against the use of massage for reduction of OA symptoms is made, though the Voting Panel acknowledged that massage may have other benefits.

Manual therapy with exercise is conditionally recommended *against* over exercise alone in patients with knee and/or hip OA.

Manual therapy techniques may include manual lymphatic drainage, manual traction, massage, mobilization/manipulation, and passive range of motion and are always used in conjunction with exercise (http://guidetoptpractice.apta.org/content/1/SEC38.extract). A limited number of studies have addressed manual therapy added to exercise versus exercise alone in hip and knee OA. Although manual therapy can be of benefit for certain conditions, such as chronic low back pain, limited data in OA show little additional benefit over exercise alone for managing OA symptoms.

Iontophoresis is conditionally recommended *against* in patients with first CMC joint OA.

There are no published RCTs evaluating iontophoresis for OA in any anatomic location.

Pulsed vibration therapy is conditionally recommended *against* in patients with knee OA.

Few trials have addressed pulsed vibration therapy, and in the absence of adequate data, we conditionally recommend against its use.

Transcutaneous electrical stimulation (TENS) is strongly recommended *against* in patients with knee and/or hip OA.

Studies examining the use of TENS have been of low quality with small size and variable controls, making comparisons across trials difficult. Studies have demonstrated a lack of benefit for knee OA.

Pharmacologic management (Table 2)

RCTs of pharmacologic agents may be subject to a variety of limitations, including generalizability of their findings across patients. Publication bias may reduce the likelihood that negative trials will become part of the published literature. Statistically significant findings may represent benefits so small that they are not clinically important to patients. We have highlighted these considerations where relevant.

Topical NSAIDs are strongly recommended for patients with knee OA and conditionally recommended for patients with hand OA.

In keeping with the principle that medications with the least systemic exposure (i.e., local therapy) are preferable, topical NSAIDs should be considered prior to use of oral NSAIDs (24). Practical considerations (e.g., frequent hand washing) and the lack of direct evidence of efficacy in the hand lead to a conditional recommendation for use of topical NSAIDs in hand OA. In hip OA, the depth of the joint beneath the skin surface suggests that topical NSAIDs are unlikely to

Table 2. Recommendations for the pharmacologic management of osteoarthritis of the hand, knee, and hip

Intervention	Joint		
	Hand	Knee	Hip
Topical nonsteroidal antiinflammatory drugs			
Topical capsaicin			
Oral nonsteroidal antiinflammatory drugs			
Intraarticular glucocorticoid injection			
Ultrasound-guided intraarticular glucocorticoid injection			
Intraarticular glucocorticoid injection compared to other injections			
Acetaminophen			
Duloxetine			
Tramadol			
Non-tramadol opioids			
Colchicine			
Fish oil			
Vitamin D			
Bisphosphonates			
Glucosamine			
Chondroitin sulfate			
Hydroxychloroquine			
Methotrexate			
Intraarticular hyaluronic acid injection	(First carpometacarpal)		
Intraarticular botulinum toxin			
Prolotherapy			
Platelet-rich plasma			
Stem cell injection			
Biologics (tumor necrosis factor inhibitors, interleukin-1 receptor antagonists)			

Strongly recommended
Conditionally recommended
Strongly recommended against
Conditionally recommended against
No recommendation

confer benefit, and thus, the Voting Panel did not examine use in hip OA.

Topical capsaicin is conditionally recommended for patients with knee OA and conditionally recommended *against* in patients with hand OA.

Topical capsaicin is conditionally recommended for treatment of knee OA due to small effect sizes and wide confidence intervals in the available literature. We conditionally recommend against the use of topical capsaicin in hand OA because of a lack of direct evidence to support use, as well as a potentially increased risk of contamination of the eye with use of topical capsaicin to treat hand OA. In hip OA, the depth of the joint beneath the skin surface suggests that topical capsaicin is unlikely to have a meaningful effect, and thus, the Voting Panel did not examine use of topical capsaicin in hip OA. Insufficient data exists to make recommendations about the use of topical lidocaine preparations in OA.

Oral NSAIDs are strongly recommended for patients with knee, hip, and/or hand OA.

Oral NSAIDs remain the mainstay of the pharmacologic management of OA, and their use is strongly recommended. A large number of trials have established their short-term efficacy. Oral NSAIDs are the initial oral medication of choice in the treatment of OA, regardless of anatomic location, and are recommended over all other available oral medications.

While this guideline did not address the relative merits of different NSAIDs, there is evidence suggesting that certain agents may have more favorable side effect profiles than others (25–27). Clinical considerations aimed at risk mitigation for the safe use of NSAIDs, such as appropriate patient selection, regular monitoring for the development of potential adverse gastrointestinal, cardiovascular, and renal side effects and potential drug interactions, were not specifically included in the GRADE process for the formulation of recommendations. Doses should be as low as possible, and NSAID treatment should be continued for as short a time as possible.

Intraarticular glucocorticoid injections are strongly recommended for patients with knee and/or hip OA and conditionally recommended for patients with hand OA.

Trials of intraarticular glucocorticoid injections have demonstrated short-term efficacy in knee OA. Intraarticular glucocorticoid injection is conditionally, rather than strongly, recommended for hand OA given the lack of evidence specific to this anatomic location. There are insufficient data to judge the choice of short-acting over long-acting preparations or the use of low rather than high doses. A recent report (28) raised the possibility that specific steroid preparations or a certain frequency of steroid injections may contribute to cartilage loss, but the Voting Panel was uncertain of the clinical significance of this finding, particularly since

change in cartilage thickness was not associated with a worsening in pain, functioning, or other radiographic features.

Ultrasound guidance for intraarticular glucocorticoid injection is strongly recommended for injection into hip joints.

When available, ultrasound guidance for steroid injection may help ensure accurate drug delivery into the joint, but is not required for knee and hand joints. However, imaging guidance for injection into hip joints is strongly recommended.

Intraarticular glucocorticoid injections versus other injections are conditionally recommended for patients with knee, hip, and/or hand OA.

In OA generally, intraarticular glucocorticoid injection is conditionally recommended over other forms of intraarticular injection, including hyaluronic acid preparations. Head-to-head comparisons are few, but the evidence for efficacy of glucocorticoid injections is of considerably higher quality than that for other agents.

Acetaminophen is conditionally recommended for patients with knee, hip, and/or hand OA.

In clinical trials, the effect sizes for acetaminophen are very small, suggesting that few of those treated experience important benefit, and meta-analysis has suggested that use of acetaminophen as monotherapy may be ineffective (29). Longer-term treatment is no better than treatment with placebo for most individuals. Members of the Patient Panel noted that, for most individuals, acetaminophen is ineffective. For those with limited pharmacologic options due to intolerance of or contraindications to the use of NSAIDs, acetaminophen may be appropriate for short-term and episodic use. Regular monitoring for hepatotoxicity is required for patients who receive acetaminophen on a regular basis, particularly at the recommended maximum dosage of 3 gm daily in divided doses.

Duloxetine is conditionally recommended for patients with knee, hip, and/or hand OA.

While studied primarily in the knee, the effects of duloxetine may plausibly be expected to be similar for OA of the hip or hand. While a variety of centrally acting agents (e.g., pregabalin, gabapentin, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants) have been used in the management of chronic pain, only duloxetine has adequate evidence on which to base recommendations for use in OA. However, in considering all the ways in which OA may be affecting an individual patient, shared decision-making between the physician and patient may include consideration of any of these agents. Considering the utility of these agents in pain management generally, their use may be an appropriate target of future investigations specific to OA. Evidence suggests that duloxetine has efficacy in the treatment of OA when used alone or in combination with NSAIDs; however, there are issues regarding tolerability and side effects. No recommendations were made for the other centrally acting agents due to lack of direct studies of relevance in OA.

Tramadol is conditionally recommended for patients with knee, hip, and/or OA.

Recent work has highlighted the very modest level of beneficial effects in the long-term (3 months to 1 year) management of non-cancer pain with opioids (30). Nonetheless, there are circumstances in which tramadol or other opioids may be appropriate in the treatment of OA, including when patients may have contraindications to NSAIDs, find other therapies ineffective, or have no available surgical options. Patient Panel input demonstrated a high level of understanding concerning addiction potential, but also included an appreciation for the role of these agents when other pharmacologic and physical options have been ineffective. However, RCT evidence addressing the use of tramadol and other opioids for periods longer than 1 year is not available. Clinical trials have demonstrated some symptomatic efficacy, though concerns regarding potential adverse effects remain. If an opioid is being considered, tramadol is conditionally recommended over non-tramadol opioids.

Non-tramadol opioids are conditionally recommended *against* in patients with knee, hand, and/or hip OA with the recognition that they may be used under certain circumstances, particularly when alternatives have been exhausted.

As noted above, evidence suggests very modest benefits of long-term opioid therapy and a high risk of toxicity and dependence. Use of the lowest possible doses for the shortest possible length of time is prudent, particularly since a recent systematic review and meta-analysis suggests that less pain relief occurs during longer trials in the treatment of non-cancer chronic pain (30).

Colchicine is conditionally recommended *against* in patients with knee, hip, and/or hand OA.

Two very small studies have suggested analgesic benefit of colchicine in OA, but the quality of the data was low. In addition, potential adverse effects, as well as drug interactions, may occur with use of colchicine.

Fish oil is conditionally recommended *against* in patients with knee, hip, and/or hand OA.

Fish oil is the most commonly used dietary supplement in the US (31). Despite its popularity, only 1 published trial has addressed its potential role in OA. This study failed to show efficacy of a higher dose of fish oil over a lower dose.

Vitamin D is conditionally recommended *against* in patients with knee, hip, and/or hand OA.

A number of trials in OA demonstrated small effect sizes with vitamin D treatment, while others have shown no benefit and pooling data across studies yielded null results. In addition, limited

and questionable health benefits from vitamin D supplementation have been suggested in other contexts (32,33).

Bisphosphonates are strongly recommended *against* in patients with knee, hip, and/or hand OA.

Though a single small study of an oral bisphosphonate suggested a potential analgesic benefit in OA, the preponderance of data shows no improvement in pain or functional outcomes.

Glucosamine is strongly recommended *against* in patients with knee, hip, and/or hand OA.

Pharmaceutical-grade preparations of glucosamine are available and have been studied in multiple trials. However, discrepancies in efficacy reported in studies that were industry sponsored as opposed to publicly funded have raised serious concerns about publication bias (34,35). In addition, there is a lack of a clear biologic understanding of how efficacy would vary with the type of salt studied. The data that were deemed to have the lowest risk of bias fail to show any important benefits over placebo. These recommendations represent a change from the prior conditional recommendation against the use of glucosamine. The weight of the evidence indicates a lack of efficacy and large placebo effects. Nonetheless, glucosamine remains among the most commonly used dietary supplements in the US (31), and clinicians should be aware that many patients perceive that glucosamine is efficacious. Patients also often perceive that different glucosamine formulas are associated with different degrees of efficacy and seek advice on brands and manufacturers. The potential toxicity of glucosamine is low, though some patients exposed to glucosamine may show elevations in serum glucose levels (36).

Chondroitin sulfate is strongly recommended *against* in patients with knee and/or hip OA as are combination products that include glucosamine and chondroitin sulfate, but is conditionally recommended for patients with hand OA.

A single trial suggested analgesic efficacy of chondroitin sulfate, without evidence of harm, in hand OA.

Hydroxychloroquine is strongly recommended *against* in patients with knee, hip, and/or hand OA.

Well-designed RCTs of hydroxychloroquine, conducted in the subset of patients with erosive hand OA, have demonstrated no efficacy.

Methotrexate is strongly recommended *against* in patients with knee, hip, and/or hand OA.

Well-designed RCTs of methotrexate, conducted in the subset of patients with erosive hand OA, have demonstrated no efficacy.

Intraarticular hyaluronic acid injections are conditionally recommended *against* in patients with knee and/or first CMC joint OA and strongly recommended *against* in patients with hip OA.

In prior systematic reviews, apparent benefits of hyaluronic acid injections in OA have been reported. These reviews have not, however, taken into account the risk of bias of the individual primary studies. Our review showed that benefit was restricted to the studies with higher risk of bias: when limited to trials with low risk of bias, meta-analysis has shown that the effect size of hyaluronic acid injections compared to saline injections approaches zero (37). The finding that best evidence fails to establish a benefit, and that harm may be associated with these injections, motivated the recommendation against use of this treatment.

Many providers want the option of using hyaluronic acid injections when glucocorticoid injections or other interventions fail to adequately control local joint symptoms. In clinical practice, the choice to use hyaluronic acid injections in the knee OA patient who has had an inadequate response to nonpharmacologic therapies, topical and oral NSAIDs, and intraarticular steroids may be viewed more favorably than offering no intervention, particularly given the impact of the contextual effects of intraarticular hyaluronic acid injections (38). The conditional recommendation against is consistent with the use of hyaluronic acid injections, in the context of shared decision-making that recognizes the limited evidence of benefit of this treatment, when other alternatives have been exhausted or failed to provide satisfactory benefit. The conditional recommendation against is not intended to influence insurance coverage decisions.

In contrast, the evidence of lack of benefit is of higher quality with respect to hyaluronic acid injection in the hip. We therefore strongly recommend against hyaluronic acid injections in hip OA.

Intraarticular botulinum toxin injections are conditionally recommended *against* in patients with knee and/or hip OA.

The small number of trials of intraarticular botulinum toxin treatment in knee or hip OA suggest a lack of efficacy. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

Prolotherapy is conditionally recommended *against* in patients with knee and/or hip OA.

A limited number of trials involving a small number of participants have shown small effect sizes of prolotherapy in knee or hip OA. However, injection schedules, injection sites, and comparators have varied substantially between trials. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

Platelet-rich plasma treatment is strongly recommended *against* in patients with knee and/or hip OA.

In contrast to intraarticular therapies discussed above, there is concern regarding the heterogeneity and lack of standardization in available preparations of platelet-rich plasma, as well as techniques used, making it difficult to identify exactly what is being injected. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

Stem cell injections are strongly recommended *against* in patients with knee and/or hip OA.

There is concern regarding the heterogeneity and lack of standardization in available preparations of stem cell injections, as well as techniques used. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

Tumor necrosis factor inhibitors and interleukin-1 receptor antagonists are strongly recommended *against* in patients with knee, hip, and/or hand OA.

Tumor necrosis factor inhibitors and interleukin-1 receptor antagonists have been studied in trials using both subcutaneous and intraarticular routes of administration. Efficacy has not been demonstrated, including in erosive hand OA. Therefore, given their known risks of toxicity, we strongly recommended against their use for any form of OA.

Initial observations addressing the use of anti–nerve growth factor (anti-NGF) agents suggest that significant analgesic benefits may occur but that incompletely explained important safety issues may arise. A small subset of patients treated with these agents had rapid joint destruction leading to early joint replacement. The FDA temporarily halted clinical trials of anti-NGF as a result, but trials have since resumed, with ongoing collection of longer-term efficacy and safety data. As none of these agents were approved for use by the FDA and the longer-term data were not available at the time of the literature review and Voting Panel meeting, we are unable to make recommendations regarding the use of anti-NGF therapy.

DISCUSSION

These 2019 ACR/AF recommendations for the management of OA are based on the best available evidence of benefit, safety, and tolerability of physical, educational, behavioral, psychosocial, mind-body, and pharmacologic interventions, as well as the consensus judgment of clinical experts. The GRADE approach used provided a comprehensive, explicit, and transparent methodology for developing recommendations for OA management. The choice of any single or group of interventions may vary over the course of the disease or with patient and provider preferences, and is optimally arrived at through shared decision-making.

The Voting Panel made strong recommendations for patients to participate in a regular, ongoing exercise program. The literature provides support for choice from a broad menu of exercises for patients with OA. The effectiveness of an exercise program is enhanced when patient preferences and access to exercise programs are considered, as well as when they are supervised or coupled with self-efficacy, self-management, and weight loss programs. Strong recommendations were also made for weight loss in patients with knee and/or hip OA who are overweight or obese, self-efficacy and self-management programs, tai chi, cane use, first CMC joint orthoses, tibiofemoral bracing, topical NSAIDs for knee OA and oral NSAIDs for hand, knee, and/or hip OA, and intraarticular glucocorticoid injections for knee and/or hip OA. The Voting Panel made conditional recommendations for balance exercises, yoga, CBT, kinesiotaping, orthoses for hand joints other than the first CMC, patellofemoral bracing, acupuncture, thermal modalities, radiofrequency ablation, topical NSAIDs, intraarticular steroid injections and chondroitin sulfate for hand OA, topical capsaicin for knee OA, acetaminophen, duloxetine, and tramadol. The recommendations provide an array of options for a comprehensive approach for optimal management of OA encompassing the use of educational, physical, behavioral, psychosocial, mind-body, and pharmacologic interventions. The availability, accessibility, and affordability of some of these interventions vary, but in many communities the AF, as well as local hospitals and other health-related agencies, offer free self-efficacy and self-management programs.

For some patients with more limited disease in whom medication is required, topical NSAIDs represent an appropriate first choice. For others, particularly with hip OA or polyarticular involvement, oral NSAIDs are more appropriate. The appropriate use of other oral agents, particularly acetaminophen and opioids, will continue to evolve (39–41).

Despite the many options available, some patients may continue to experience inadequate symptom control; others will experience adverse effects from the available interventions. Clinicians treating patients in these circumstances should choose interventions with a low risk of harm, but both clinicians and patients may be dissatisfied with the options and unsure of how to choose among them. There are controversies in interpretation of the evidence, particularly with regard to the use of glucosamine and chondroitin, acupuncture, and intraarticular hyaluronic acid injections. Nonetheless, the process of updating treatment guidelines permits scrutiny of the state of the literature and identification of critical gaps in our knowledge about best practices. Further, it highlights the need for ongoing, appropriately funded, high-quality clinical research, as well as development of new treatment modalities, to address the human and economic impact of the most common form of arthritis.

No effective disease-modifying agents for OA have yet been identified though phase 2 and 3 trials are underway, and, for the time being, preventive strategies focus on weight management and injury prevention. Development of more effective therapies that

permit a sophisticated and individualized approach to the patient with OA await the outcome of future investigation. Important directions for research include gaining a more comprehensive understanding of the optimal types of exercises and the modifications that should be used based on disease location and severity, study of the intensity of exercise that would be optimal for a given individual (https://health.gov/paguidelines/second-edition/report.aspx), defining optimal footwear for patients with knee and hip OA and understanding the interaction between footwear and exercise, conducting rigorous RCTs for physical modality options in hand OA, assessing a broader array of outcomes, including fall prevention, assessing optimal use of oral, topical, and injectable agents alone and in combination, obtaining a better understanding of the role of integrative medicine, including massage, herbal products, medical marijuana, and additional mind-body interventions, and exploring agents with novel mechanisms of action for prevention and treatment.

In conclusion, optimal management requires a comprehensive, multimodal approach to treating patients with hand, hip, and/or knee OA offered in the context of shared decision-making with patients, to choose the safest and most effective treatment possible. A large research agenda remains to be addressed, with a need for more options with greater efficacy for the millions of people worldwide with osteoarthritis.

Addendum. Therapies that were approved after the original systematic literature review are not included in these recommendations.

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EDITORIAL

Reimagining Rheumatology: Big Data and the Future of Clinical Practice and Research

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In this issue of *Arthritis Care & Research*, we present another set of themed articles that are relevant to rheumatology clinical practice and research. Our themed issues are designed to spark interest and influence knowledge growth in rheumatology. The topic for this themed issue is the pertinent use of rheumatology registries, Big Data, and very large patient or administrative data sources to inform patient or individual aspects of key outcomes in the rheumatic diseases. Manuscripts representing a broad range of topics across the lifespan were considered, including treat-to-target, disease burden, costs, as well as other topics, using a wide variety of Big Data sources. Manuscripts submitted for the themed issues of *Arthritis Care & Research* undergo the same peer-review procedures as other scientific manuscripts in our journal, and therefore meet the same rigorous standards as articles in this or any other issue.

The call for articles for this theme issue on Big Data resulted in 76 submissions. From these papers, we are proud to publish 12 articles covering important topics and issues in the rheumatic diseases, including osteoarthritis, rheumatoid arthritis (RA), lupus, juvenile dermatomyositis, and patient care costs. The tremendous response and the wide array of topics addressed by registries, administrative data, and large patient data sources furthered our thoughts on using Big Data in rheumatology and the expected exponential growth in our utilization of these data to increase our understanding of rheumatic diseases. Big Data is an exciting resource that captures nuance and detail, highlighting the evidence in evidence-based medicine for many aspects of disease management that have not been fully appreciated by past study designs or data collection.

The volume of Big Data in health care is growing exponentially, outstripping data growth in other sectors and creating both new opportunities and significant challenges for medicine and research. Billions of dollars have been invested in health information technology (IT) infrastructure. Electronic health records (EHRs) have fundamentally changed the work of physicians and health systems. To be a rheumatologist today means spending as many or more hours interfacing with EHRs as with patients. These seismic shifts in medicine have been accompanied by promises of safer, better, and even more cost-efficient care, but to a large extent these promises remain unrealized. Yet, there is reason to be hopeful. Here we discuss the ways the field of rheumatology can harness Big Data to advance our specialty and improve health outcomes for people with rheumatic diseases.

What is Big Data? Big Data typically refers to databases or registries with high volume, rapid velocity, much variety, and high veracity. These 4 "Vs" characterize the vast amounts of data that can be aggregated from often disparate sources for analysis. The American College of Rheumatology's RISE (Rheumatology Informatics System for Effectiveness) Registry, a focus for one of the themed articles, is a great example of Big Data. With widespread participation, the RISE registry has aggregated EHR data generated by more than one-third of all US rheumatologists. Volume is the main characteristic of the Big Data in RISE, which now includes information on more than 2 million seen by rheumatologists and more than 20 million encounters. Velocity refers to the speed at which data flows. In the case of the RISE Registry, data are uploaded nightly, processed centrally, and are fed back to a web-based dashboard that displays quality measure performance on an ongoing basis. High-velocity data transfer and processing allows the RISE Registry to support practice improvement, quality reporting, and research. Variety is a key strength of the RISE Registry; the Registry's clinical data warehouse includes both structured data (e.g., vital signs, International Classification of Diseases [ICD], Tenth Revision codes, medications, and laboratory test results) and unstructured data (e.g., clinical notes that undergo text mining and natural language processing), and the Registry will soon be linked to outside data sources such as insurer claims. Finally, veracity refers to the validity or accuracy of the data. Like

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many Big Data sources, RISE Registry data are heterogenous given the varied provider documentation patterns and inherent differences in EHR products and their interoperability with sources of laboratory or radiology data. Preparing these data for quality reporting and for research takes significant effort and collaboration between the Registry's staff, data scientists, programmers, statisticians, and rheumatologists. As repositories like the RISE Registry grow, it is exciting to think about some of the ways that Big Data can shape the future of rheumatology. We outline a few of these ways below.

Generating real-world evidence. Big Data should play a central role in accelerating evidence generation. Despite fast-paced drug development for some rheumatic diseases, traditional research methods such as large (and very expensive) randomized trials have been unable to address many of the important research questions in our field. Large data networks like the RISE Registry can generate real-world evidence on not only drug effectiveness, but also on special populations such as the elderly, pregnant women, racial/ethnic minorities, or those with comorbidities, for which clinical trial results are scant. Big Data can provide important insights into practice patterns, as in the article by Curtis et al in this theme issue. There is also significant interest in using the RISE Registry to accelerate recruitment of patients with less common conditions or phenotypes into clinical trials, and the first demonstration project to test this concept is underway.

Phenotyping. Rheumatic diseases are often characterized by complex and often nuanced phenotypes. Our key cognitive skill as specialists is recognizing the patterns and subtleties of these phenotypes and using this information to guide management. To date, it has been challenging to harness this collective wisdom to advance our understanding of rheumatic diseases and their outcomes. In fact, most research studies still use crude disease phenotypes such as ICD codes or single-physician ascertainment based on classification criteria. However, computational methods that allow more granular phenotype extraction from EHRs are advancing rapidly. For example, in a recent study, we applied an artificial intelligence algorithm to recognize patterns of lupus and assign probabilities of disease (1). Work is ongoing to scale such algorithms in repositories like the RISE Registry to understand the full spectrum of phenotypes across a population, to track outcomes, and to conduct discovery research.

Prognostic modeling. Individual risk prediction in rheumatology has been notoriously difficult, and few predictive models have been well-established for rheumatic diseases. For the most part, rheumatologists rely on their longitudinal clinical experience to forecast the future and advise patients about therapy. However, Big Data has the potential to significantly accelerate predictive modeling. Given the high-dimensional and heterogeneous nature of EHR data, methods such as deep learning, a branch of artificial intelligence, have the potential to improve our ability to predict risk and therefore to prognosticate for our patients. For example, in a recent study, we used deep learning to successfully forecast RA outcomes across two health systems (2). Work is ongoing to further develop this work across the RISE Registry. Such algorithms create the foundation for developing more personalized prognostic models as well as treatment simulations that could potentially aid clinicians in both counseling patients and in making data-driven treatment decisions.

Precision medicine. Prognostic models that use large EHR data repositories are one way to bring the potential of precision medicine to the bedside. But such models would likely perform better if they also drew from "-omics" data. Significant resources are currently being invested in defining molecular phenotypes of disease through collaborations such as the National Institute of Arthritis and Musculoskeletal and Skin Diseases Accelerating Medicines Partnership, a topic addressed in a review article by Davison et al in this theme issue. Big Data arising from these innovative projects has the potential to inform more personalized diagnoses and treatment approaches in rheumatic diseases. Biologic and clinical Big Data can also inform precision medicine approaches to drug safety. Currently, there remains a significant disconnect between safety observed in trials and real-world experience in populations that are older, have more comorbidities, and are more diverse. Developing prognostic models that draw on clinical and biologic data to predict the risk of adverse events in real-world populations is a worthy goal. Big Data has also shown promising results in drug repurposing and in examining off-label use of drugs. These areas are critical in rheumatology given the high number of orphan diseases and the lack of adequate therapeutic options for many patients.

Population and public health. While Big Data has the potential to deliver precision medicine to individual patients, using these data is equally important to improve the health of populations. Such data will continue to play a critical role in disease surveillance and monitoring outcomes, as illustrated by articles in this theme issue that address disease burden as well as nationwide osteoarthritis implementation programs. A critical next step is to use Big Data to better target disease prevention and resource allocation in ways that improve health. The RISE Registry has taken an important step in this direction through its quality dashboard. The dashboard allows rheumatologists to identify gaps in evidence-based practice and to track improvement as they institute quality improvement initiatives.

Patient engagement. Rheumatic diseases are often chronic, and self-management strategies can help patients maintain their health. Many patients are interested in using devices and applications to record health items such as their symptoms, diet, exercise, and sleep. In some cases, Big Data from devices has helped identify potential health risks or helped patients with

arthritis understand how their pain responds to factors such as the weather. Connecting such personalized data from patients to other Big Data sources like EHRs or environmental data to more fully understand the impacts of disease and treatments will help patients with chronic disease management, while also helping physicians and researchers advance patient-centered care.

Two additional points are worth considering as we think about Big Data in rheumatology. First, the value of Big Data will be highly dependent on the specificity by which it is collected. For example, administrative data are plagued by faulty coding and EHR data by heavy duplication and nonstandardized collection of information. As a community, defining what meaningful data elements we want to collect, independent of billing requirements, and building robust and feasible systems to enable this collection will be important. In addition, we are now entering a period where data are plentiful, but the time and expertise to analyze it is limited. Therefore, a key factor to success in this new era will be collaboration to define priorities and prevent redundant efforts.

The articles in this theme issue highlight the diverse contributions of Big Data to advancing rheumatology, and much of this work already has important implications for clinical practice. It is exciting to think about the next levels of data integration for many of the research data sets presented, and the potential for such integrations to help us fully understand and treat our patients in all aspects in which their disease affects them. While there is much work to be done, we feel optimistic that Big Data will allow us to reimagine and improve the diagnosis and management of rheumatic diseases in the years to come.

AUTHOR CONTRIBUTIONS

Authors Yazdany and Hannan drafted the article or revised it critically for important intellectual content, and approved the final version to be published.

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RHEUMATOLOGY REGISTRIES, BIG DATA, AND THE RHEUMATIC DISEASES

Do Patients With Moderate or High Disease Activity Escalate Rheumatoid Arthritis Therapy According to Treat-to-Target Principles? Results From the Rheumatology Informatics System for Effectiveness Registry of the American College of Rheumatology

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Objective. Despite strong recommendations for routine measurement of rheumatoid arthritis (RA) disease activity and associated treatment changes to attain remission/low disease activity, the measurement tools that clinicians use to evaluate RA patients' disease activity and frequency of treatment change have not been well characterized. Therefore, we evaluated different measurement tools that physicians used to assess RA disease activity and associated RA treatment changes.

Methods. Using data from the Rheumatology Informatics System for Effectiveness (RISE) registry from January 2016 through June 2017, and using the following criteria: age ≥18 years, diagnosis of RA (International Classification of Diseases, Ninth and Tenth Revision, codes), ≥2 RISE visits, and ≥1 RA disease activity measure scored in 2016, we classified eligible patients' drug use at the index visit as monotherapy or combination therapy with conventional synthetic (cs) and biologic disease-modifying antirheumatic drugs (bDMARDs). Outcomes include change in treatment over 12 months. Mixed models identified factors associated with treatment change.

Results. Among 50,996 eligible patients, 27,274 had longitudinal data. The most commonly used measures were RAPID3 (78.9%) and the Clinical Disease Activity Index (CDAI) (34.2%). The frequency of treatment change during follow-up was relatively low (35.6–54.6%), even for patients with moderate/high disease activity according to RAPID3 or CDAI scores. Older patients (age ≥75 years; adjusted odds ratio [OR_{adj}] 0.63 [95% confidence interval (95% CI) 0.50–0.78]) and those already receiving combination therapy with csDMARDs (OR_{adj} 0.45 [95% CI 0.33–0.61]) or combination therapy with bDMARDs (OR_{adj} 0.30 [95% CI 0.24–0.38]) were less likely to change RA treatment even after multivariable adjustment.

Conclusion. Using the American College of Rheumatology's national RISE registry, one- to two-thirds of RA patients failed to change their treatment, even when experiencing moderate/high disease activity. Multimodal interventions directed at both patients and providers are needed to encourage shared decision-making, goal-directed care, and to overcome barriers to treatment escalation.

INTRODUCTION

Rheumatoid arthritis (RA), the most common autoimmune inflammatory arthritis in adults, has substantial impact on quality of life if the disease is not well controlled (1). To better control disease activity, both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have strongly recommended a treat-to-target approach, with the

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SIGNIFICANCE & INNOVATIONS

- Real-world data from the Rheumatology Informatics System for Effectiveness Registry, showed that the most used disease activity measure was RAPID3 (78.9%), followed by the Clinical Disease Activity Index (CDAI) (34.2%).
- One- to two-thirds of patients failed to modify rheumatoid arthritis (RA) treatment, even when they were in moderate/high disease activity as measured by either RAPID3 or the CDAI.
- Individuals receiving combination therapies with conventional synthetic disease-modifying antirheumatic drugs (DMARDs) or biologic DMARDs were less likely to change therapy, even after controlling for multiple other factors. Additionally, patients were less likely to change RA therapies when their disease activity was measured discordantly by RAPID3 and the CDAI.
- Interventions directed at both patients and providers are needed to overcome barriers to RA treatment change.

treatment goal of attaining sustained low disease activity or remission. Major components of a treat-to-target strategy include the routine measurement of disease activity and adjustment of drug therapy (i.e., treatment intensification) to reach the desired target. The ACR/EULAR have recommended that clinicians use one of several RA disease activity measures, including RAPID3, the Clinical Disease Activity Index (CDAI), the Disease Activity Score in 28-joint counts (DAS28) using the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, or others (2,3). In 2018–2019, the ACR Disease Activity Measures Working Group began the process of synthesizing the available evidence to update these recommendations (4). Some key areas of importance for these disease activity measures include sensitivity to change, feasibility for routine clinical use, and effective discrimination between remission, low, moderate, and high disease activity states (3).

Although such measures have been recommended by the ACR and EULAR for many years, the frequency with which these measures have been adopted by rheumatologists in real-world settings, and whether the rheumatologists who use them are adherent to treat-to-target guidelines (by way of intensifying treatment for RA patients experiencing moderate or high disease activity) is not clear. Based on a survey of approximately 500 US rheumatologists conducted in 2014, only approximately half the rheumatologists routinely and quantitatively measured RA disease, and of those, the RAPID3 was the most commonly used measurement tool (5). Depending on which measurement tool is being used for disease activity assessment, rheumatologists may be reluctant to modify RA treatment, as their confidence in the various tools available to assess active inflammatory disease might vary. For example, tools that contain more physician-derived elements (e.g., tender and swollen joint count, as in the CDAI and DAS28) may be felt to be more "objective" in the mind of clinicians. The patient's background RA treatment may also play a role in this decision-making process. For example, among patients who are already being treated with a biologic in combination with one or more conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) plus pain medications and glucocorticoids, an imperfect response to this treatment regimen might be satisfactory enough to continue without modification. Because there is some potential for at least short-term clinical worsening if the biologic was discontinued and another was started, both patients and clinicians may be reticent to switch treatments.

In light of the lack of evidence of how RA disease activity measurement tools are used, the current study used data from the ACR Rheumatology Informatics System for Effectiveness (RISE) Registry to address the following objectives: 1) identify which measurement tool(s) rheumatologists actually use to evaluate RA patients' disease activity; 2) describe RA medication use, treatment changes, and treatment response over time in relation to disease activity, background RA therapies, and other factors; and 3) assess how discordant disease activity measurement using different tools (e.g., CDAI versus RAPID3) impacts RA treatment changes.

MATERIALS AND METHODS

Study design and data source. RISE is a national electronic health record (EHR)–based registry, which passively collects data from EHRs of participating rheumatology practices, provides advanced measurement and data analytic capacities, and fulfills national quality reporting requirements. RISE captures all patient visits, and thus there is no potential for selection of certain patients as all patient visits and specific EHR data are available. We conducted this retrospective cohort analysis using RISE C data from January 2016 to June 2017. All RISE data were analyzed and reported in a de-identified fashion, and individual patient consent was not required. RISE data are collected for the purposes of clinical care, and research use is thus considered secondary. Therefore, all analyses should be considered as post hoc.

RA population. To be eligible for this analysis, patients were required to meet the following criteria: 1) age ≥18 years at the first RISE visit date; 2) rheumatologist-diagnosed RA according to ≥1 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (714.0, 714.2, and 714.81; and ICD-10-CM codes M05.*, M06.*, excluding M06.4); 3) ≥1 rheumatologist visit in 2016 with a valid RA disease activity measure; 4) ≥1 previous visit (index –1 visit) before the first visit with a valid disease activity measure (index visit) and 5) no prescription for >1 biologic on the same day. The second visit with a valid disease activity measure anchored the index date and the start of follow-up. RA disease activities were measured using RAPID3 (range 0–30), CDAI (range 0–76), DAS28-ESR (range 0–9.4), and DAS28-CRP (range 0–9.4), with values within the expected range of those measures, and were considered a valid disease

activity measure. To further evaluate disease activity and treatment changes, patients were required to have >1 RISE follow-up visit with the same disease activity measurement as used at the index visit. Follow-up time started at the index visit and ended through the last observed visit, up to June 30, 2017. A follow-up visit was defined as the first visit with a disease activity measurement occurring at 7–12 months after the index visit. If a follow-up visit was not available in the defined time period, the first visit with a disease activity measurement occurring in 3–6 months after the index date was identified as the follow-up visit. For a description of the study design, see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24083/abstract.

RA medication use. Based on prescription or administration of RA medications in the 16 weeks prior to the index visit date, we classified current RA drug use at the index visit date into 5 categories as follows: 1) monotherapy csDMARD use; 2) monotherapy biologic use; 3) combination csDMARD use defined as ≥2 csDMARDs, but no biologic use; 4) combination biologic use defined as biologic use in combination with ≥1 csDMARDs; and 5) no DMARD treatment (with or without nonsteroidal antiinflammatory drugs [NSAIDs] and glucocorticoids). Conventional synthetic DMARDs included methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine. The biologic DMARDs (bDMARDs) included adalimumab, etanercept, infliximab, certolizumab, golimumab, abatacept (subcutaneous [SQ] and intravenous [IV]), tocilizumab (SQ and IV), and rituximab. Tofacitinib, a targeted synthetic DMARD, was grouped with the bDMARDs due to the small number of patients (1.6%) who used tofacitinib during the study period. Acknowledging that clinicians might write a prescription that (with refills) might extend for up to 1 year, this 16-week window was used to maximize specificity for the classification of "current use."

Outcomes. The primary outcome was defined as any csDMARD or bDMARD treatment change between the index visit date and the main outcome visit during follow-up. Treatment change was a hierarchical categorical variable classified into the following mutually exclusive categories: 1) adding/switching a bDMARD, 2) adding/switching a csDMARD, or 3) no change. The composite of any b/csDMARD treatment change was used to characterize overall treatment switching.

The secondary outcome was disease activity change from the index date and main outcome visit. Disease activity change was measured as both a continuous and categorical variable. For categorical measures, disease activity change was classified as 1) a decrease from high/moderate disease activity at the index visit to low disease activity/remission at the main outcome visit; 2) increase from low disease activity/remission at the index visit to high/moderate disease activity at the main outcome visit, or 3) no category change.

Covariates. Based on clinical knowledge and subject matter expertise, we selected the potential factors that may be associated with patients' RA treatment change or intensification, including age, sex, race, health insurance, US region, body mass index (BMI), smoking status, types of disease activity measurement at the index visit, practice size, current RA medications, history of RA drug use, comorbidities, and concurrent non-RA medications measured on the index date or at any time prior to the index visit. Current RA medications use was measured at 16 weeks prior to the index date, including csDMARDs, tumor necrosis factor inhibitors (TNFi), and non-TNFi biologics. The history of RA drug use was measured with all available data before the 16 weeks prior to the index date, including the count of prior csDMARDs, TNFi, and non-TNFi biologics. Comorbidities included a diagnosis from data prior to the index date for depression, fibromyalgia, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, hyperlipidemia, and cancer. Concurrent non-RA medications use in the 16 weeks of data prior to the index visit included NSAIDs, narcotics, glucocorticoids, and antidepressants.

Statistical analysis. We conducted descriptive analyses to evaluate patients' demographic characteristics, medication use, and disease activity measurements at the index visit. Descriptive analyses were also used for comparison of the main independent variables: index visit RA treatment regimen (4 categories, grouped as monotherapy csDMARD, monotherapy bDMARDs, combination csDMARD, combination bDMARDs), stratified by moderate/high disease activity or low disease activity/remission as measured by RAPID3 or the CDAI at the index visit. The frequency of use of different types of disease activity measures in these patients at the index visit was also calculated for the subgroup of patients with moderate/high disease activity at the index visit who might be considered appropriate candidates for treatment intensification, and we evaluated treatment changes over time occurring through the 1-year follow-up. Similarly, we evaluated treatment changes for patients whose disease activity was measured discordantly by RAPID3 and the CDAI at the index visit (e.g., RAPID3 showed moderate/high disease activity and the CDAI showed low disease activity/remission) versus concordant (e.g., both measures showed moderate/high disease activity).

Due to the clustered nature of the data (patients nested within individual physician practice or within group practice), analyses using mixed models were conducted to examine the association between treatment intensification and other key factors (e.g., current RA treatment regimen, in the 4 categories described above), controlling for all potential confounders we measured (Table 1). All analyses were conducted in SAS, version 9.4. The University of Alabama at Birmingham Institutional Review Board for Human Use approved the study protocol.

Table 1. Demographics, medication use, and disease activity measurements of the eligible patients at the index visit*

Characteristic	Patients (n = 50,996)†
Median time of prior history, days (IQR)	897.0 (1,321.0)
Median time of follow-up (index date to last visit), days (IQR)	98.0 (182.0)
Age, mean ± SD years	62.4 ± 13.7
Age, years	
<50	8,576 (16.8)
50–64	18,391 (36.1)
≥65	24,029 (47.1)
Female sex	39,131 (76.7)
Race	
White	35,073 (68.8)
Black	4,222 (8.3)
Other	2,401 (4.7)
Missing	9,300 (18.2)
Health insurance (categories not mutually exclusive)	
Medicare	22,408 (52.8)
Medicaid	1,876 (4.4)
Commercial/other	39,935 (94.1)
Missing	8,544 (16.8)
US region	
Midwest	15,107 (29.6)
Northeast	2,658 (5.2)
South	29,010 (56.9)
West	3,276 (6.4)
Missing	945 (1.9)
Body mass index, kg/m^2	
<18.5	873 (1.7)
18.5–24.9	12,618 (24.7)
25.0–29.9	15,691 (30.8)
≥30.0	20,271 (39.8)
Missing	1,543 (3.0)
Smoking status	
Never	5,153 (10.1)
Current	1,313 (2.6)
Former	1,846 (3.6)
Missing	42,684 (83.7)
Seropositive for RA	
Either CCP or RF ever positive	11,840 (23.2)
CCP or RF negative	8,082 (15.8)
Both always missing	31,074 (60.9)
Comorbidities (all available data)	
Depression	2,806 (5.5)
Fibromyalgia	8,353 (16.4)
Diabetes mellitus	8,381 (16.4)
Chronic obstructive pulmonary disease	2,113 (4.1)
Coronary artery disease	1,325 (2.6)
Hyperlipidemia	4,690 (9.2)
Cancer	2,275 (4.5)
Concurrent medications	
Nonsteroidal antiinflammatory drugs	12,682 (24.9)
Narcotics	8,087 (15.9)
Glucocorticoids	12,879 (25.3)
Antidepressants	4,276 (8.4)
Practice site characteristics	
Solo	3,093 (6.1)
2–4	7,361 (14.4)
≥5	40,542 (79.5)
Treatment patterns (mutually exclusive)	
csDMARD monotherapy within 16 weeks prior to index date	12,945 (25.4)
Biologic monotherapy (i.e., no csDMARD) within 16 weeks prior to index date	8,276 (16.2)
csDMARD combination therapy within 16 weeks prior to index date	2,622 (5.1)
Biologic combination therapy within 16 weeks prior to index date	6,229 (12.2)
No RA medications within 16 weeks prior to index date, but had RA medications within 17–26 weeks	5,748 (11.3)
No RA medications within 26 weeks prior to index date, but had RA medications within 37–52 weeks	4,846 (9.5)
No RA medications within 52 weeks prior to index date, but had RA medications beyond the 52 weeks	6,131 (12.0)
Missing all RA medications (as of index date)	3,691 (7.2)
Missing all medications (as of index date)	508 (1.0)
csDMARDs, current use‡	
Methotrexate	14,786 (29.0)
Hydroxychloroquine	6,208 (12.2)
Leflunomide	2,766 (5.4)
Sulfasalazine	1,663 (3.3)
TNFi, current use‡	
Adalimumab	2,002 (3.9)
Etanercept	2,248 (4.4)
Infliximab	3,782 (7.4)
Certolizumab	804 (1.6)
Golimumab	959 (1.9)
Non-TNFi, current use‡	
Abatacept	2,269 (4.4)
Rituximab	1,325 (2.6)
Tocilizumab	757 (1.5)
Sarilumab	§
Tofacitinib, current use‡	802 (1.6)
No. of type of disease activity measurement (on the index date)	
1	43,350 (85.0)
2	7,246 (14.2)
>2	400 (0.8)

* Values are the number (%) unless indicated otherwise. Index visit is the second Rheumatology Informatics System for Effectiveness visit with a disease activity measurement. IQR = interquartile range; RA = rheumatoid arthritis; CCP = cyclic citrullinated peptide; RF = rheumatoid factor; csDMARD = conventional synthetic disease-modifying antirheumatic drug; TNFi = tumor necrosis factor inhibitor.
† Values measured on or prior to the index date, except as noted for medications.
‡ Current use is defined as any prescription or administration in the preceding 16 weeks (up to, but not including, the index date).
§ Not approved during study period (approval date May 2017).

RESULTS

Of the 457,950 patients included in 2016–2017 RISE data, we identified 154,436 patients (34%) who had at least 1 visit with a valid disease activity measure. After applying the inclusion and exclusion criteria, 50,996 adult RA patients had ≥1 previous visit

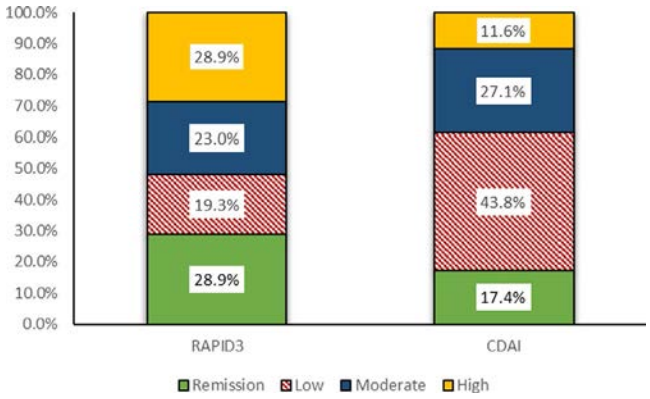

Figure 1. Percentages of disease activity at the index date as measured by RAPID3 (n = 40,256 patients) and the Clinical Disease Activity Index (CDAI; n = 17,430 patients).

before the first visit with a valid disease activity measure and were selected for the analysis. When the cohort was limited to patients who had ≥1 follow-up visit after the index visit, 27,274 patients were eligible for longitudinal analysis (see Supplementary Figure 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24083/abstract).

Of the 50,996 patients in the cohort, mean ± SD age at the index visit was 62.4 ± 13.7 years, and 76.7% were women (Table 1). Approximately 68.8% of patients were white, 8.3% were black, and 18.2% did not have race data available. Regarding insurance, 52.8% had Medicare coverage, and 4.4% had Medicaid coverage. More than 70% of these patients were overweight or obese (BMI ≥25 kg/m^2). Using data from the 16 weeks prior to the index visit, we found that 25.4% of patients were receiving csDMARD monotherapy, 16.2% were receiving biologic monotherapy, 5.1% were receiving csDMARD combination therapy, and 12.2% were taking both a biologic and a csDMARD (i.e., biologic combination therapy). A total of 24.9% of patients were taking NSAIDs, 15.9% narcotics, 25.3% oral glucocorticoids, and 8.4% were taking antidepressants. At the time of the data cut used for these analyses, the median follow-up time was 160 days for patients who had ≥1 follow-up visit after the index visit.

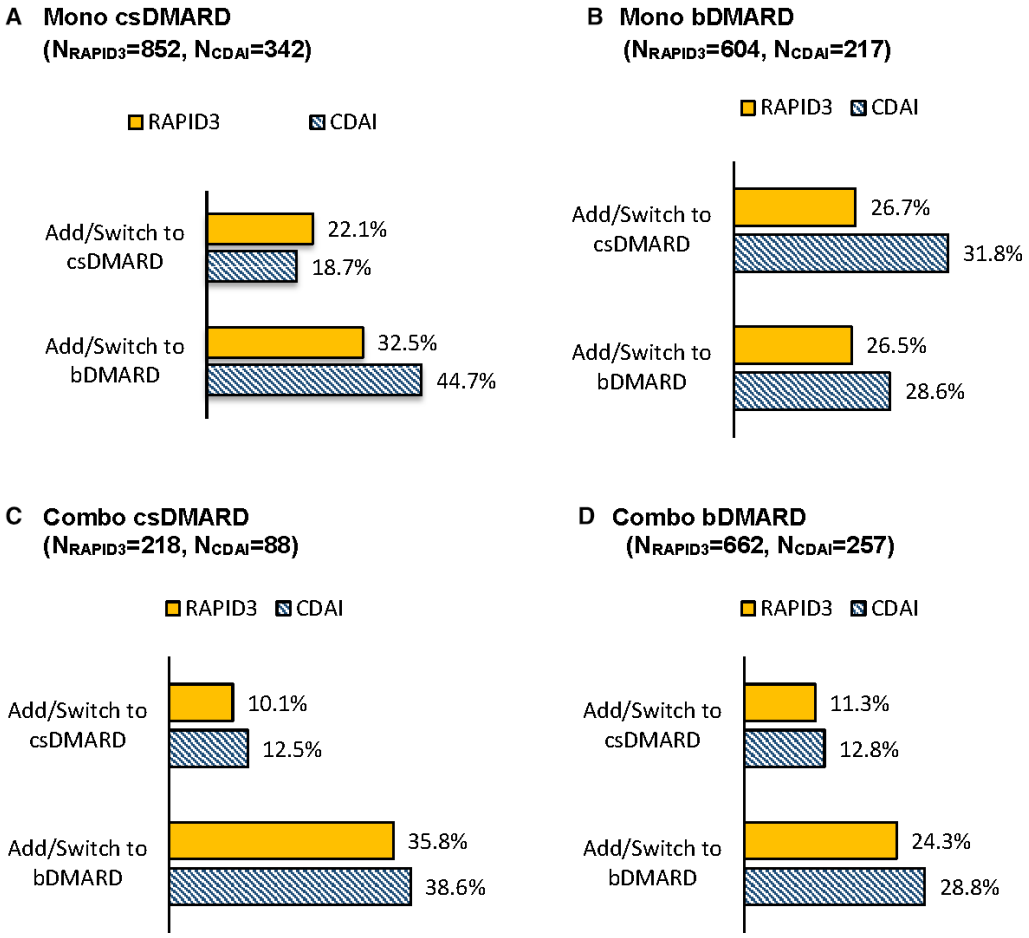

Figure 2. Percentages of treatment changes through 1 year (includes the index date up to and including follow-up visit 2) for patients with moderate/high disease activity (as measured by RAPID3 [n = 3,249] and the Clinical Disease Activity Index [CDAI; n = 1,146] at the index date and limited to patients who had a visit with a disease activity measurement occurring 7–12 months after the index visit). If patients initiated both biologic disease-modifying antirheumatic drugs (bDMARDs) and conventional synthetic (cs) DMARDs in the relevant time interval, they were counted only as biologic initiators, so that the drug exposure patterns are hierarchical and mutually exclusive.

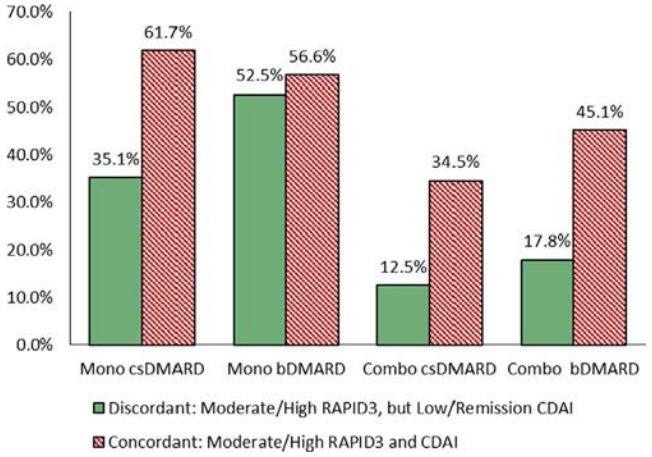

Figure 3. Percentages of any treatment change through year 1 (includes the index date up to and including follow-up visit 2) according to concordant (n = 402 patients) versus discordant (n = 156 patients) disease activity metrics. See Figure 2 for abbreviations.

According to disease activity measured on the index visit, 85.0% of the cohort were evaluated with only one type of RA disease activity measurement; 14.2% were evaluated with 2 different types of measurement instruments (mostly RAPID3 and CDAI), and 0.8% were evaluated with at least 3 measurement instruments (Table 1). Among these measurements, RAPID3 (78.9%) was the most common type, followed by CDAI (34.2%) and DAS28-ESR/CRP (2.5%) (data not shown). Among the patients with a RAPID3 measurement at the index visit, 28.9% were in disease remission, 19.3% had low disease activity, 23.0% had moderate disease activity, and 28.9% had high disease activity. Among patients with a CDAI measurement at the index visit, 17.4% were in disease remission, 43.8% had low disease activity, 27.1% had moderate disease activity, and 11.6% had high disease activity. In total, 48.2% of patients had low disease activity or remission according to RAPID3 measurement, and 61.2% had low disease activity or remission according to CDAI measurement (Figure 1).

Figure 2 shows treatment changes occurring through the 1-year follow-up among patients with moderate or high disease activity at the index visit. Among patients whose disease activity was measured by RAPID3 and who were taking monotherapy csDMARDs (Figure 2A), 54.6% of patients added/switched to csDMARDs (22.1%) or bDMARDs (32.5%) therapy during follow-up. For those taking monotherapy bDMARDs (Figure 2B), 53.2% added/switched to csDMARDs (26.7%) or bDMARDs (26.5%). For those taking combination csDMARDs (Figure 2C), 45.9% added/switched to csDMARDs (10.1%) or bDMARDs (35.8%), and for those taking combination bDMARDs (Figure 2D), 35.6% added/switched to csDMARDs (11.3%) or bDMARDs (24.3%). Among patients whose disease activity was measured by the CDAI, RA treatment change followed a similar pattern and was most frequent in those taking csDMARD monotherapy (63.4%), followed by biologic monotherapy (60.4%), then combination csDMARD therapy (51.1%) and combination biologic therapy (41.6%).

Restricting the cohort to patients with moderate/high disease activity as measured by RAPID3 or the CDAI and who had both measures available, 61.7% of patients taking monotherapy csDMARDs, 56.6% of patients taking monotherapy bDMARDs, 34.5% of patients taking combination csDMARDs, and 45.1% of patients taking combination bDMARDs at the index visit had a treatment change during follow-up. However, among patients with moderate/high disease activity as measured by RAPID3 but with low disease activity/remission as measured by the CDAI (i.e., the disease activity measures were discordant, 28% of total visits where both were measured), fewer patients had a change in their treatment (Figure 3) than when they were concordant (i.e., both measures showed moderate to high disease activity). This

Table 2. Change in RA disease activity over time among RA patients initiating new treatment at index visit*

Disease activity measure, index visit	Change in disease activity at follow-up visit†		
	No. (%)	Mean ± SD	Median (25%, 75% percentiles)
RAPID3 (range 0–30)			
High	1,150 (32.4)	−4.1 ± 6.4	−2.4 (−8.9, 0.3)
Moderate	834 (23.5)	−0.7 ± 5.1	−0.9 (−4.2, 2.0)
Low/remission	1,561 (44.0)	1.4 ± 4.0	0.2 (−0.7, 2.2)
CDAI (range 0–76)			
High	316 (21.3)	−13.3 ± 13.0	−13.0 (−22.5, −4.0)
Moderate	494 (33.3)	−2.6 ± 8.9	−3.0 (−8.5, 1.0)
Low/remission	673 (45.4)	1.2 ± 5.3	0.0 (−1.0, 2.0)

* Analysis conducted among patients with same disease activity measure as at index visit who initiated any biologic or conventional synthetic disease-modifying antirheumatic drug on the index date or within the following 2 weeks. The analysis excluded patients who were recent initiators (defined as patients who started a new therapy in the 16 weeks prior to the index visit) of any rheumatoid arthritis (RA) drug. CDAI = Clinical Disease Activity Index.
† Same disease activity measure used as at the index visit. If the second visit data were not available or were not from the same disease activity measurement as the index visit, then data from the first follow-up visit was used.

was particularly notable among patients taking either combination csDMARDs (12.5%) or combination bDMARDs (17.8%). There were too few visits to analyze where the RAPID3 score showed low disease activity/remission, but the CDAI score showed moderate/high disease activity.

Table 2 reports the change in RA disease activity over time among RA patients initiating a new treatment at the index visit or within the following 2 weeks. Among patients with high disease activity as measured by RAPID3 at the index visit, the median change in RAPID3 units between the index visit and main outcome visit was –2.4 units (mean change –4.1). For patients who started with moderate disease activity as measured by the RAPID3, the median change was –0.9 units (mean –0.7). The median change in the CDAI was –13.0 units (mean –13.3) for patients with high disease activity and –3.0 units (mean –2.6) for patients with moderate disease activity.

Table 3. Multivariable-adjusted mixed model for identifying the potential factors associated with treatment change (any new biologic/tofacitinib /csDMARD) between index visit and follow-up visit, restricted to patients who had moderate/high disease activity as measured by RAPID3 or the CDAI at the index visit*

	RAPID3 (n = 11,734)		CDAI (n = 3,807)	
	Crude OR (95% CI)	OR_{adj} (95% CI)	Crude OR (95% CI)	OR_{adj} (95% CI)
Current drug use†				
Monotherapy csDMARD	Reference	Reference	Reference	Reference
Monotherapy biologic	1.16 (1.02–1.31)‡	1.13 (0.97–1.32)	0.92 (0.75–1.13)	0.87 (0.67–1.12)
Combination csDMARD	0.63 (0.53–0.76)‡	0.44 (0.36–0.54)‡	0.56 (0.43–0.74)‡	0.45 (0.33–0.61)‡
Combination biologic	0.47 (0.41–0.53)‡	0.30 (0.26–0.36)‡	0.38 (0.31–0.47)‡	0.30 (0.24–0.38)‡
None	2.54 (2.27–2.83)‡	3.89 (3.43–4.43)‡	2.52 (2.08–3.05)‡	3.06 (2.44–3.84)‡
Recent initiator of any RA therapy in prior 16 weeks	1.08 (0.97–1.21)	1.74 (1.53–1.97)‡	0.76 (0.64–0.90)‡	1.12 (0.92–1.36)
Index visit RAPID3 measure				
Moderate disease activity	Reference	Reference	Reference	Reference
High disease activity	1.14 (1.05–1.23)‡	1.15 (1.05–1.25)‡	1.94 (1.67–2.24)‡	2.07 (1.76–2.44)‡
Age, years				
0 to <50	1.52 (1.34–1.72)‡	1.28 (1.10–1.49)‡	1.23 (1.00–1.52)	0.88 (0.67–1.15)
50 to 64	1.19 (1.08–1.31)‡	1.04 (0.92–1.17)	1.02 (0.87–1.20)	0.82 (0.66–1.01)
65 to <74	Reference	Reference	Reference	Reference
≥75	0.77 (0.68–0.86)‡	0.75 (0.66–0.85)‡	0.71 (0.58–0.87)‡	0.63 (0.50–0.78)‡
Male (female reference)	0.94 (0.86–1.04)	0.94 (0.84–1.04)	1.10 (0.93–1.31)	1.06 (0.87–1.28)
Race				
Black race (white reference)	1.02 (0.89–1.16)	1.01 (0.88–1.17)	1.00 (0.79–1.26)	1.03 (0.79–1.34)
Other race	1.10 (0.87–1.39)	1.04 (0.81–1.34)	1.36 (1.04–1.79)‡	1.22 (0.90–1.65)
Missing race	1.05 (0.93–1.20)	0.97 (0.84–1.12)	1.20 (0.97–1.48)	1.11 (0.88–1.42)
Health insurance (categories not mutually exclusive)				
Medicare				
Yes	0.69 (0.63–0.75)‡	0.82 (0.72–0.93)‡	0.66 (0.58–0.77)‡	0.65 (0.53–0.80)‡
No	Reference	Reference	Reference	Reference
Missing	1.15 (0.98–1.36)	1.27 (0.99–1.64)	0.84 (0.64–1.11)	0.81 (0.52–1.26)
Medicaid				
Yes	0.99 (0.84–1.17)	0.94 (0.77–1.13)	0.72 (0.54–0.97)‡	0.76 (0.54–1.07)
No	Reference	Reference	Reference	Reference
Missing	1.42 (1.21–1.66)‡		1.05 (0.80–1.36)	
Commercial/other				
Yes	1.22 (1.04–1.43)‡	1.18 (0.99–1.42)	1.29 (0.99–1.67)	1.24 (0.91–1.70)
No	Reference	Reference	Reference	Reference
Missing	1.70 (1.37–2.10)‡		1.34 (0.94–1.92)	
US region				
Midwest	Reference	Reference	Reference	Reference
Northeast	0.66 (0.36–1.22)	0.51 (0.24–1.08)	1.14 (0.61–2.14)	1.49 (0.72–3.07)
South	0.78 (0.58–1.06)	0.72 (0.51–1.02)	1.02 (0.66–1.57)	1.24 (0.76–2.03)
West	0.35 (0.16–0.77)‡	0.33 (0.13–0.87)‡	0.55 (0.26–1.15)	0.32 (0.15–0.71)‡
Missing	1.03 (0.49–2.14)	0.82 (0.35–1.96)	0.55 (0.20–1.49)	0.69 (0.22–2.18)
BMI, kgm^2				
<18.5	1.05 (0.77–1.44)	1.04 (0.74–1.45)	1.02 (0.60–1.74)	0.85 (0.47–1.52)
18.5–24.9	Reference	Reference	Reference	Reference
25.0–29.9	1.10 (0.98–1.23)	1.08 (0.96–1.22)	0.97 (0.80–1.17)	1.01 (0.82–1.23)
≥30.0	1.17 (1.05–1.29)‡	1.13 (1.01–1.27)‡	1.14 (0.96–1.36)	1.12 (0.92–1.36)
Missing	1.07 (0.80–1.43)	1.10 (0.80–1.51)	0.83 (0.47–1.47)	0.98 (0.52–1.85)

(Continued)

Table 3. *(Cont'd)*

	RAPID3 (n = 11,734)		CDAI (n = 3,807)	
	Crude OR (95% CI)	OR_{adj} (95% CI)	Crude OR (95% CI)	OR_{adj} (95% CI)
Seropositive for RA (time invariant)§				
Either CCP or RF ever positive	1.07 (0.95–1.20)	1.13 (0.99–1.28)	1.14 (0.92–1.40)	1.15 (0.91–1.44)
CCP or RF negative	Reference	Reference	Reference	Reference
Both always missing	0.87 (0.78–0.97)‡	0.93 (0.82–1.05)	0.97 (0.81–1.17)	1.06 (0.86–1.30)
Comorbidities, % (all available data)				
Depression	0.90 (0.77–1.05)	0.86 (0.72–1.01)	0.89 (0.67–1.19)	0.92 (0.67–1.27)
Fibromyalgia	0.98 (0.89–1.08)	0.90 (0.80–1.00)‡	0.99 (0.84–1.16)	0.99 (0.82–1.19)
Diabetes mellitus	0.90 (0.82–0.99)‡	0.95 (0.85–1.06)	0.89 (0.75–1.04)	0.88 (0.73–1.06)
Chronic obstructive pulmonary disease	0.88 (0.74–1.04)	0.91 (0.76–1.10)	1.00 (0.70–1.44)	1.12 (0.75–1.65)
Coronary artery disease	0.73 (0.58–0.92)‡	0.77 (0.60–0.98)‡	1.11 (0.71–1.75)	1.13 (0.68–1.85)
Hyperlipidemia	0.85 (0.73–0.98)‡	0.95 (0.81–1.11)	0.84 (0.66–1.09)	0.97 (0.74–1.29)
Cancer	1.04 (0.87–1.24)	1.09 (0.90–1.32)	0.93 (0.65–1.32)	0.88 (0.60–1.31)
Concurrent medications				
Nonsteroidal antiinflammatory drugs	1.05 (0.97–1.14)	1.11 (1.01–1.23)‡	0.98 (0.85–1.12)	1.06 (0.90–1.25)
Narcotics	0.95 (0.86–1.04)	0.93 (0.83–1.04)	0.83 (0.71–0.96)‡	0.84 (0.71–1.01)
Glucocorticoid use	1.26 (1.15–1.37)‡	1.46 (1.33–1.60)‡	1.07 (0.93–1.23)	1.20 (1.02–1.40)‡
Antidepressants	1.05 (0.93–1.18)	1.04 (0.90–1.19)	1.00 (0.83–1.20)	1.00 (0.81–1.23)
Number of clinicians in the practice				
1–2	Reference	Reference	Reference	Reference
3–7	1.10 (0.70–1.74)	0.91 (0.51–1.65)	1.25 (0.76–2.03)	1.27 (0.70–2.33)
8–11	0.81 (0.41–1.60)	0.75 (0.32–1.80)	0.99 (0.57–1.73)	0.88 (0.46–1.68)
≥12	1.12 (0.64–1.99)	1.10 (0.52–2.30)	1.07 (0.63–1.80)	1.02 (0.55–1.86)
Functional status assessment, no. (mean ± SD)				
Revised HAQ¶				
1: 0 to <0.5	0.87 (0.77–0.99)‡	0.90 (0.79–1.03)	0.90 (0.74–1.09)	0.93 (0.75–1.15)
2: 0.5 to <1.0	0.97 (0.86–1.10)	0.96 (0.84–1.10)	0.97 (0.82–1.15)	0.93 (0.77–1.11)
3: 1 to 3	Reference	Reference	Reference	Reference
Missing	1.07 (0.90–1.28)	1.00 (0.82–1.20)	0.93 (0.64–1.37)	0.80 (0.51–1.23)
History TNFi count (INF, GOL, CZP, ETA, ADA)				
0	Reference	Reference	Reference	Reference
1	0.97 (0.89–1.06)	1.43 (1.28–1.59)‡	0.83 (0.72–0.96)‡	1.23 (1.02–1.48)‡
2–5	1.15 (1.01–1.31)‡	1.52 (1.30–1.77)‡	0.94 (0.76–1.17)	1.38 (1.06–1.79)‡
History non-TNFi count (RTX, ABA, TCZ, TOF)				
0	Reference	Reference	Reference	Reference
1–4	0.92 (0.84–1.01)	1.15 (1.03–1.28)‡	0.78 (0.67–0.90)‡	0.99 (0.83–1.19)
History csDMARD count (HCQ, MTX, SSZ, LEF)				
0	Reference	Reference	Reference	Reference
1	0.93 (0.83–1.05)	1.81 (1.58–2.07)‡	0.53 (0.43–0.66)‡	1.11 (0.86–1.43)
2	1.07 (0.95–1.22)	2.61 (2.24–3.05)‡	0.55 (0.44–0.69)‡	1.48 (1.11–1.97)‡
3–4	1.26 (1.06–1.50)‡	3.02 (2.48–3.69)‡	0.52 (0.39–0.69)‡	1.26 (0.89–1.79)

* If the second visit data were not available or were not from the same disease activity measurement as the index visit, then we used the first follow-up visit data. Odds ratios (ORs) >1 indicate a greater likelihood to change treatments. CDAI = Clinical Disease Activity Index; 95% CI = 95% confidence interval; BMI = body mass index; INF = infliximab; GOL = golimumab; CZP = certolizumab pegol; ETA = etanercept; ADA = adalimumab; RTX = rituximab; ABA = abatacept; TCZ = tocilizumab; TOF = tofacitinib; HCQ = hydroxychloroquine; MTX = methotrexate; SSZ = sulfasalazine; LEF = leflunomide (see Table 1 for other definitions).
† Current use is defined as any prescription or administration in the preceding 16 weeks (up to, but not including, the index date).
‡ $P \leq 0.05$.
§ All laboratory data available, both before and after the index date, were used, given that rheumatoid arthritis serologies are not typically time varying.
¶ We combined all Health Assessment Questionnaire (HAQ) values in a hierarchical order due to the large number of missing values for each HAQ type. The full HAQ was the standard; however, if the full HAQ was not available, we took the value of HAQ II, followed by the Multidimensional HAQ and the modified HAQ.

Table 3 shows the results of mixed models for identifying the potential factors associated with treatment change. Among the patients who had moderate/high disease activity as measured by RAPID3 at the index visit (n = 11,734), being a recent initiator of an RA drug, high disease activity at the index visit, no current DMARD use, commercial insurance, obesity (BMI ≥30.0), NSAID use, glucocorticoid use, prior use of TNFi or non-TNFi, and use of csDMARDs were more likely to be associated with treatment change (Table 3). Current combination csDMARD use, current combination biologic use, older age, Medicare insurance, living in the West, concomitant fibromyalgia, and coronary artery disease were associated with a lower likelihood of treatment change.

Among the patients with moderate/high disease activity as measured by the CDAI at the index visit (n = 3,807), factors associated with treatment changes (shown in Table 3)

were similar to the RAPID3 analysis, although some were not significant. Significant factors associated with treatment change included recent initiation of a DMARD, history of TNFi use, and history of use of 3–4 csDMARDs. Considering the factors in common between the RAPID3 and CDAI analyses, older age, Medicare coverage, and those taking baseline combination therapy were less likely to change treatment. Patients receiving glucocorticoids and those with a greater number of past csDMARDs were more likely to change therapy.

DISCUSSION

In this real-world retrospective study using data from the ACR's RISE registry, the most commonly used disease activity measure was RAPID3 (78.9%) followed by the CDAI (34.2%). When assessed using RAPID3, approximately 50% of patients had disease activity that was well-controlled (low disease activity or remission), whereas 60% of patients had well-controlled disease activity when assessed using the CDAI. We found the overall rates of treatment change were relatively low (35.6–54.6%), even for patients with moderate/high disease activity as measured by either RAPID3 or the CDAI. Older individuals (age ≥75 years) and those already receiving combination therapies with csDMARDs or bDMARDs were less likely to change therapy, even after controlling for multiple other factors.

We found that among patients with disease activity measured by both RAPID3 and the CDAI, the results were discordant in 28% of patients. Several prior studies have studied the correlation and consistency between RAPID3 and the CDAI measurements among RA patients. Using data from 285 patients seen in usual care, Pincus et al reported the correlation between RAPID3 and the CDAI was 0.73 (6). Another study, conducted in a Korean RA population, found that RAPID3 scores were significantly correlated with the CDAI ($r = 0.75$) although the kappa agreement among the 4 disease categories was only 0.40–0.42, indicating low-to-moderate agreement. Neither of these 2 investigations examined how these differences might impact RA treatment changes for patients (7). In the second study, 86% of patients with moderate-to-high disease activity based on the CDAI had moderate-to-high disease activity as measured by RAPID3. In contrast, only 50% of patients with remission-to-low disease activity according to the CDAI had remission-to-low disease activity scores as measured by RAPID3 (7). For the purpose of comparing the efficacy of RAPID3 with the CDAI, a recent randomized study reported that RAPID3 and the CDAI measure different domains of treatment response, so that the CDAI classified more patients as treatment responders (8). These findings are consistent with the findings in our study showing that patients were less likely to change therapies when RAPID3 was discordant with the CDAI, which suggests that clinicians may have greater uncertainty regarding the extent of active inflammation as assessed by RAPID3, and therefore have less confidence in initiating treatment changes.

Importantly, we found several treatment factors associated with treatment change, with older age and Medicare coverage consistently associated with patients being less likely to change therapies. This association was observed even after adjusting for disease activity measures, comorbidities, and a variety of other clinical factors. Physicians may be less confident that therapies will have the same benefit in older patients given the dearth of RA trial data among older individuals. The potential for side effects that may or may not be related to RA therapies and other comorbidities may be additional concerns. Factors associated with treatment change have been examined in past studies (9). In contrast to some studies that showed African Americans were somewhat less likely to initiate bDMARD treatment compared to whites (10,11), we did not identify that race was associated with lack of treatment intensification or change. Our study also showed that being a recent initiator of an RA drug and having high disease activity at the index visit were positively associated with therapy change, which is compatible with physicians generally following treat-to-target guidelines. However, patients already taking combination therapy were much less likely to change treatments. While this could in part reflect channeling of patients with greater disease activity to receive combination therapy, it may also reflect reticence by the clinician to potentially stop a therapy (e.g., a biologic) in order to substitute another, thereby creating the potential for worsening disease activity or flare of RA.

Strengths of our study include the use of a large, real-world national data source with routinely captured data that are representative of community practices across the US. We also were able to show that RISE data were adequately able to demonstrate an expected and numerically reasonable improvement in disease activity for patients initiating a new RA therapy. Given the study design and the observational data source, we note several limitations. First, only 18 months of RISE data were available at the time of analysis; therefore, patient-specific follow-up time was relatively short, although still adequate to observe treatment changes in a 6–12-month period. Rheumatologists participating in RISE were practicing in predominantly community rheumatology practices, and results may not generalize to academic medical centers or other types of clinical settings (e.g., Veterans Administration clinics). Although RISE data reflect most of what might be available routinely in a rheumatologist's EHR, no specific data elements are required; therefore, our findings might be confounded by unmeasured or misclassified factors (e.g., high-deductible insurance plans that may have made it prohibitively expensive to intensify treatment using certain RA therapies). In addition, RISE medication data were based on prescriptions as written, not filled, so actual medication use could be overestimated. We also described current use based on medication use in the 16 weeks prior to the index visit. However, it is possible that patients could have been prescribed up to a year of treatment (e.g., a 1-month supply of a

medication with 11 refills), which would not have been classified as current use. However, given that this might have substantially misclassified current use, we intentionally looked only at 16 weeks to favor specificity of the current use definition. Moreover, the reasons why patients switched or failed to switch their treatment are not captured by RISE as structured data elements that could be analyzed. Several important factors such as smoking status and education were not consistently recorded in the registry, and thus were not included in the modeling results. We also acknowledge that we studied some but not all components relevant for treat-to-target, including treatment intensification and disease activity measurement, but these reflect only some of the necessary components of treat-to-target strategies. We did not study, for example, the process of setting a treatment target goal with the patient and associated shared decision-making (12), as these would have required analysis of the RISE unstructured data (i.e., free-text physician notes), which was beyond the scope of this project. We also did not study the outcomes between RA treatments, which is a potential topic for future comparative effectiveness research.

Compared to administrative insurance claims data derived from large health plans, RISE contains richer clinical data on information, including disease activity and functional status. Presently, RISE is the largest EHR-based rheumatology registry in the world and, given that it contains all patients treated within physicians' practices, is not subject to selection bias. RISE is relatively new, and the amount of longitudinal data is highly variable across practices. Thus, prior history before the start of follow-up may have misclassified some variables, depending on how long the clinician has been using their EHR system. Moreover, RISE captures medications as prescribed, so time on treatment may not be well recorded, and stop dates of medications are potentially inaccurate or missing. Finally, the physician practices that elected to join RISE to date are most likely early adopters and predominantly community practitioners. Thus, the proportion of patients with disease activity and disability measurements may not be generalizable to all US rheumatologists.

In conclusion, we found that one- to two-thirds of patients failed to modify RA treatment, even when they were experiencing moderate/high disease activity. Patients taking combination bDMARDs were less likely to switch, which may reflect patients' and rheumatologists' risk aversion to stop one biologic in order to start another. Multimodal treat-to-target interventions directed both at patients and providers are needed to encourage shared decision-making and goal-directed care, as well as to overcome barriers to RA treatment change.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Curtis 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. Yun, Chen, Xie, Boytsov, Curtis.
Acquisition of data. Yun, Curtis.
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ROLE OF THE STUDY SPONSOR

Eli Lilly and Company was involved in the study design, implementation of the analysis, and the writing of the manuscript but was not involved in the collection of data or execution of the analysis. This article is published with the approval of all coauthors from the University of Alabama at Birmingham (UAB) and Eli Lilly and Company, and the study protocol was prepared by UAB and Eli Lilly and Company. The data analysis was executed by UAB.

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Association of Seropositivity and Mortality in Rheumatoid Arthritis and the Impact of Treatment With Disease-Modifying Antirheumatic Drugs: Results From a Real-World Study

Evo Alemao,[1] Ying Bao,[1] Michael E. Weinblatt,[2] and Nancy Shadick[2]

Objective. Seropositivity for anti–citrullinated protein antibody (ACPA)/rheumatoid factor (RF) in rheumatoid arthritis (RA) is associated with increased overall mortality; however, the association between antibody titers and mortality is not well established. Investigating relationships between antibody titers and mortality may clarify their role in RA pathogenesis. This study was undertaken to evaluate the association of antibody titers with mortality and its modification by disease-modifying antirheumatic drugs (DMARDs).

Methods. Eligible patients with established RA were identified through administrative claims data linked to laboratory results (2005–2016). Patients were categorized by positivity status for ACPA, RF, or both. Patients were further divided into groups by autoantibody titers. DMARD-exposed patients were categorized into biologic DMARD (bDMARD) and conventional DMARD (cDMARD) subcohorts. Crude mortality rates/1,000 patient-years and Kaplan-Meier curves were compared between antibody categories. Adjusted Cox proportional hazards regression and sensitivity (propensity-matched patients) analyses were conducted.

Results. Overall, 53,849 and 79,926 patients had evaluable ACPA and RF status, respectively. For both autoantibodies, mortality rates were significantly higher in seropositive versus seronegative patients (risk increase of 48.0% and 44.0% in ACPA- and RF-positive patients, respectively; $P < 0.001$ each). Mortality rates were greatest in patients with higher versus lower autoantibody titers (ACPA hazard ratio [HR] 1.60 [95% confidence interval (95% CI]) 1.45–1.76]; RF HR 1.78 [95% CI 1.66–1.91]). In cDMARD-exposed patients, HRs were higher in seropositive versus seronegative cohorts; in bDMARD-exposed patients, there was no difference in mortality by serostatus.

Conclusion. Elevated ACPA/RF titers were independently associated with increased mortality among patients with RA and persisted in patients treated with cDMARDs but not with bDMARDs.

INTRODUCTION

The production of autoantibodies, particularly anti–citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF), is characteristic of rheumatoid arthritis (RA) (1). ACPA antibody titers, directed against posttranslationally modified citrullinated proteins and primarily of the immunoglobulin G isotype, are estimated to be present in 50–70% of patients with RA (1). Similarly, over 60% of patients with RA have detectable RF titers, primarily of the IgM isotype, which targets the Fc portion of IgG (1). Both autoantibodies can be present in the patient's serum in the absence of symptoms for up to 10 years before disease onset (2–6).

The presence of ACPA and/or RF is indicative of poor prognosis in RA (7), with ACPA being a stronger prognostic indicator for rapid disease progression (1,8). In patients with early RA

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SIGNIFICANCE & INNOVATIONS

- Seropositivity in rheumatoid arthritis (RA) has been associated with increased overall mortality, and although cause-specific mortality rates differ by autoantibodies, the association between antibody titers and mortality is not well established.
- In this retrospective study, elevated anti–citrullinated protein antibody (ACPA) and rheumatoid factor (RF) titers were independently associated with increased mortality among patients with established RA; importantly, the associations between ACPA/RF and mortality persisted in patients treated with conventional disease-modifying antirheumatic drugs (DMARDs) but not with biologic DMARDs.
- These findings warrant further investigation, particularly to confirm whether biologic DMARDs may have an impact on mortality in seropositive patients with RA.

with disease duration of <2 years, ACPA positivity is associated with a higher joint destruction rate (9). Moreover, double ACPA and RF seropositivity in RA is associated with a higher disease activity and, consequently, greater disability (10).

Both ACPA and RF are included in the 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) diagnostic criteria (11). Furthermore, EULAR treatment guidelines include ACPA and RF seropositivity as poor prognostic factors, indicating early, erosive RA that requires aggressive treatment (7,11,12). Nonetheless, the role of ACPA and RF in combination and at different concentrations in RA pathogenesis is not fully understood and thus the potential impact of these autoantibodies on prognosis remains unclear. Therefore, investigating the correlation between the presence and titer of these autoantibodies and disease outcomes, such as mortality, may help to elucidate the role of autoantibodies as diagnostic and prognostic markers for disease progression in RA.

RA is associated with reduced survival compared with the age- and/or sex-matched general population (13–15). Although the association between seropositivity and mortality in RA has been studied previously, findings have been inconsistent. The presence of autoantibodies has been shown to impact overall mortality (16,17), but the cause-specific mortality differs. Although some studies have found that autoantibody titers did not affect mortality (16), there is emerging evidence that titers could impact disease progression and joint destruction (18,19). Thus, the association between ACPA and RF status and their titers with mortality warrants further investigation. Moreover, while the impact of disease-modifying antirheumatic drugs (DMARDs) on ACPA (20) and RF in patients with RA has been studied (16,17,20–22), any subsequent effect on mortality is not known.

In this real-world study, the role of ACPA and RF seropositivity in predicting the risk of mortality, either independently or combined, was investigated. In addition, we studied the association between ACPA and RF titers and all-cause mortality and whether DMARDs impacted these associations.

PATIENTS AND METHODS

Study design, data sources, and patients. This was a retrospective study of patients with RA using data obtained from 2 US administrative claims databases linked to laboratory data. Patients were followed from the day after the analysis-specific index date until the occurrence of death, end of health plan enrollment, or end of the study period (June 30, 2016), whichever came first. The index date was defined as the first date of ACPA or RF test (or a DMARD prescription date for analysis evaluating DMARD exposures). Baseline was specified as a timeframe between 180 days before and 30 days after the index date.

Data were extracted from Optum Clinformatics Data Mart (OptumInsight, Inc.) and Humana (Humana, Inc.) administrative claims databases. Optum Clinformatics Data Mart contains health claims data from approximately 17 million patients. The Humana research database includes anonymized patient-level data from approximately 20 million demographically diverse current and former Humana members.

Patients were enrolled if they had a diagnosis code of RA (714.xx, International Classification of Diseases, Ninth Revision, Clinical Modification) (23) and at least 1 year of enrollment. The eligibility criteria included age ≥18 years, ≥3 months of enrollment before and after the index date (index date during January 1, 2005 to December 31, 2014 for Optum Clinformatics Data Mart and January 1, 2007 to December 31, 2014 for the Humana database). Patients were excluded from the analysis if they had diagnosis codes for autoimmune comorbidities of ankylosing spondylitis, Crohn's disease, systemic lupus erythematosus, psoriatic arthritis, or ulcerative colitis at or before the index date.

Data from Optum Clinformatics Data Mart and Humana databases were pooled in this study and several patient categories were evaluated based on test result availability (Figure 1). Patients who had the ACPA test first were grouped into ACPA seropositive (ACPA+)

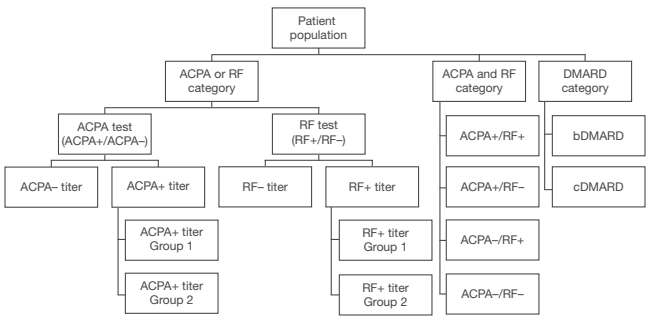

Figure 1. Analyzed patient population. ACPA = anti–citrullinated protein antibody; RF = rheumatoid factor; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug.

and seronegative (ACPA–) groups, and those who had the RF test first were divided into RF seropositive (RF+) and seronegative (RF–) groups. ACPA and RF seropositive patients were further categorized into 2 subgroups, each based on median ACPA or RF titer. Another categorization was based on the availability of both ACPA and RF tests, with patients forming 4 groups: ACPA and RF double-positive, ACPA positive/RF negative, ACPA negative/RF positive, or ACPA and RF double-negative. Finally, patients were categorized based on DMARD exposure: the biologic DMARD (bDMARD) group comprised patients ever treated with abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, or tocilizumab, and the conventional DMARD (cDMARD) group included patients who were exposed to ≥1 dose of a cDMARD (methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, minocycline, cyclosporine, or azathioprine) but were bDMARD-naive.

Outcomes and independent variables of interest. The main outcome of the study was all-cause mortality. The Optum Clinformatics Data Mart database was linked to the Social Security Administration Death Master File (24). Available mortality data were recorded by year and month, but for simplicity of calculation, the last day of the month was used to record the date of death in this analysis. Mortality data in the Humana database were available for Medicare (Medicare Advantage Prescription Drug Plan) patients only, from the Centers for Medicare and Medicaid Services, by month. The date of disenrollment was used as a proxy for date of death, with sensitivity analysis using the date of the last claim in the database.

Data on ACPA were collected using 2 commercially available tests. Both databases used Logical Observation Identifiers Names and Codes and had an internal laboratory test name specific to each laboratory vendor. ACPA and RF were defined according to titers measured by the diagnostic tests. ACPA positivity was defined as a level of >5 U/ml or ≥20 U/ml (depending on the testing kit) and RF positivity was defined as a level of ≥14 IU/ml. The ACPA mean ± SD titers (U/ml) by group and test kit were ACPA–, kit 1: 1.45 ± 1.13, kit 2: 7.72 ± 5.77; ACPA+ group 1, kit 1: 34.57 ± 26.44, kit 2: 84.96 ± 65.97; ACPA+ group 2, kit 1: 120.80 ± 101.20, kit 2: 253.20 ± 33.90. The RF mean ± SD levels (IU/ml) by group were RF–: 8.32 ± 2.37; RF+ group 1: 24.83 ± 9.44; RF+ group 2: 281.90 ± 387.00.

Statistical analysis. Data from the 2 databases were pooled for this analysis. The cumulative overall mortality rates were assessed per 1,000 patient-years. Adjusted analysis was conducted using a full Cox proportional hazards regression model, with all-cause mortality as the dependent variable and 23 covariates incorporated. Covariates included age, sex, region, number of physician office visits during the last 3 months, an indicator variable for 714.0x diagnosis, an indicator variable for RA diagnosis before ACPA or RF testing, past hospitalization, use of medications (steroids, nonsteroidal antiinflammatory drugs, salicylates), use of DMARDs (if applicable), and comorbidity conditions. A fully specified Cox proportional hazards regression model was used to evaluate the association between ACPA positivity and mortality, and RF positivity and mortality, independently. The model was redeployed using data from the combined ACPA and RF category to evaluate the association between mortality and a status of either ACPA or RF.

To further explore the association between mortality risk and ACPA and RF titer, the Cox regression model was used for all

Table 1. Baseline characteristics of eligible patients from 2 administrative claims databases*

	ACPA subcohort			RF subcohort		
	ACPA+ (n = 17,182)	ACPA− (n = 36,667)	Total (n = 53,849)	RF+ (n = 33,550)	RF− (n = 46,376)	Total (n = 79,926)
Age, mean ± SD years	62.8 ± 14.1	60.8 ± 15.6	61.4 ± 15.2	63.2 ± 14.7	60.8 ± 16.1	61.8 ± 15.6
Female	74.3	75.0	74.8	74.5	74.0	74.2
Previous DMARDs	86.8	58.0	67.2	71.4	47.2	57.4
Corticosteroid use	61.0	58.2	59.1	52.1	49.6	50.6
Two diagnoses	96.7	72.7	80.3	93.1	69.7	79.5
Previous hospitalization	26.0	28.5	27.7	26.7	27.3	27.1
Office visits, mean ± SD	4.6 ± 3.9	5.2 ± 4.3	5.0 ± 4.2	4.7 ± 4.0	5.1 ± 4.4	4.9 ± 4.3
Coronary artery disease	17.9	19.3	18.8	18.8	19.5	19.2
Heart failure	7.1	7.0	7.0	8.0	6.9	7.3
Hypertension	61.3	62.2	61.9	63.2	61.8	62.4
Diabetes mellitus	23.7	25.7	25.1	25.0	26.3	25.8
Asthma	11.3	13.6	12.9	11.9	13.2	12.7
Chronic kidney disease	9.9	12.2	11.5	10.9	11.4	11.2
Smoker (former or current)	15.7	12.5	13.5	14.9	11.7	13.0
NSAIDs	62.9	66.7	65.5	59.0	62.4	61.0
COPD	17.6	14.2	15.3	17.6	13.7	15.3

* Values are the percentage unless indicated otherwise. The anti–citrullinated protein antibody (ACPA) subcohort comprised patients with rheumatoid arthritis (RA) and an ACPA test result in the baseline period. The rheumatoid factor (RF) subcohort comprised patients with RA and an RF test result in the baseline period. DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal antiinflammatory drugs; COPD = chronic obstructive pulmonary disease.

Table 2. Mortality rates according to autoantibody status*

	Patients, no.	Deaths, no.	Patient-years	Mortality†	Adjusted HR‡
ACPA status					
ACPA–	36,667	1,798	126,451	14.2 (13.6–14.9)	1.00
ACPA+	17,182	1,276	57,719	22.1 (20.9–23.4)	1.48 (1.37–1.60)
ACPA+ group 1	8,321	606	29,518	20.5 (18.9–22.1)	1.38 (1.25–1.52)
ACPA+ group 2	8,861	670	28,201	23.8 (22.0–25.6)	1.60 (1.45–1.76)
Total	53,849	3,074	184,170	16.7 (16.1–17.3)	–
RF status					
RF–	46,376	2,522	179,247	14.1 (13.5–14.6)	1.00
RF+	33,550	2,688	118,583	22.7 (21.8–23.5)	1.44 (1.36–1.53)
RF+ group 1	16,758	1,098	60,393	18.2 (17.1–19.3)	1.18 (1.09–1.27)
RF+ group 2	16,792	1,590	58,190	27.3 (26.0–28.7)	1.78 (1.66–1.91)
Total	79,926	5,210	297,830	17.5 (17.0–18.0)	–

* The anti–citrullinated protein antibody (ACPA) subcohort comprised patients with rheumatoid arthritis (RA) and an ACPA test result in the baseline period. The rheumatoid factor (RF) subcohort comprised patients with RA and an RF test result in the baseline period. HR = hazard ratio.
† Incidence rate per 1,000 patient-years (95% confidence interval).
‡ HR per 1 unit increase in Z score or per 1 increase in SD (95% confidence interval).

prior applications using data from patients separated into 2 subgroups, each based on median ACPA or RF titer in the entire sample, and 2 groups in patients who were ACPA positive and RF positive, and Z scores were calculated. The grouping and calculation of Z scores were conducted separately for the 2 ACPA testing kits.

To assess the stability of the main findings and to balance the ACPA/RF positive and negative patient groups, 1:1 propensity-score matching within each separate database was used to construct Kaplan-Meier curves to investigate the difference in mortality over time between ACPA positivity/negativity and RF positivity/negativity scores. Propensity scores were calculated for ACPA positivity versus ACPA negativity and RF positivity versus RF negativity based on all covariates. In the analysis of patients exposed to DMARDs, a fully specified Cox proportional hazards regression model was used to investigate the effect of DMARD treatment on the association between mortality and ACPA or RF serostatus.

All analyses were performed using SAS software, version 9.4. All statistical tests were 2-tailed with *P* values less than or equal to 0.05 considered statistically significant. Results were expressed as the percentage of patients for categorical data and mean ± SD or median (interquartile range) for continuous data, unless specified otherwise.

RESULTS

A total of 133,775 patients with RA from both databases were included: 53,849 in the ACPA group and 79,926 patients in the RF group. Baseline characteristics were mostly balanced between the ACPA and the RF groups, with previous use of DMARDs, presence of 2 RA diagnoses, previous/current

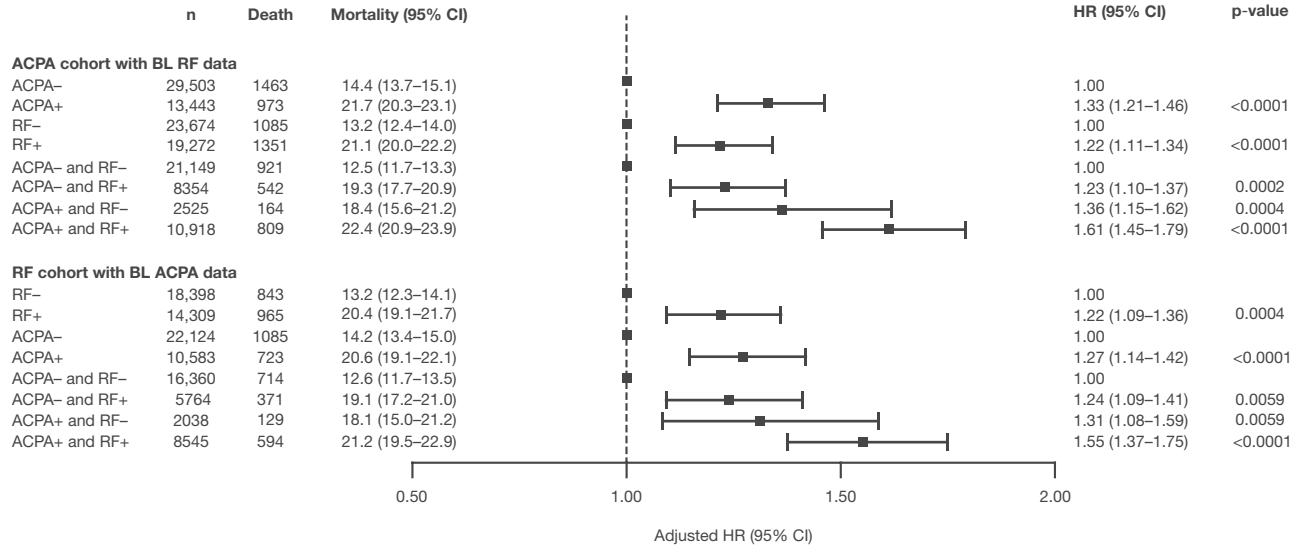

Figure 2. Association between anti–citrullinated protein antibody (ACPA) and rheumatoid factor (RF) and mortality in an analysis of data from patients with ACPA and/or RF seropositivity. 95% CI = 95% confidence interval; HR = hazard ratio; BL = baseline (the time period of within 180 days before and 30 days after the index date).

positive smoking status, and presence of chronic obstructive pulmonary disease significantly elevated in the seropositive versus seronegative patients ($P < 0.001$) (Table 1).

The ACPA patient category had 184,170 patient-years of follow-up; 5.7% of patients (3,074 of 53,849) died and the incidence rate for mortality was 16.7 per 1,000 patient-years (95% confidence interval [95% CI] 16.1–17.3). The RF patient category had 297,830 patient-years of follow-up; 6.5% of patients (5,210 of 79,926) died and the incidence rate for mortality was 17.5 per 1,000 patient-years (95% CI 17.0–18.0). ACPA and RF positivity were both associated with a significant increase in mortality risk ($P < 0.0001$ for both) (Table 2).

In the ACPA group with baseline RF data, ACPA positivity was associated with increased mortality compared with RF positivity (Figure 2). Mortality risk was the highest with double ACPA and RF positivity (ACPA and RF double-positive versus ACPA and RF double-negative group hazard ratio [HR] 1.61 [95% CI 1.45–1.79]). Single ACPA positivity was generally associated with a higher risk than single RF positivity (Figure 2). In the RF group with baseline ACPA data, the highest mortality risk was also observed in the ACPA and RF double-positive group (HR versus ACPA and RF double-negative group 1.55 [95% CI 1.37–1.75]), and a higher risk in RF-positive patients compared with RF-negative patients (HR versus RF-negative group 1.22 [95% CI 1.09–1.36]). All other combinations of the presence of ACPA and RF were associated with a significantly increased mortality risk compared with ACPA and/or RF seronegativity (Figure 2).

Mortality risk positively correlated with titers of ACPA and RF and was the highest in groups comprising patients with the highest titers for both ACPA (HR versus ACPA-negative group 1.60 [95% CI 1.45–1.76]) and RF (HR versus RF-negative group 1.78 [95% CI 1.66–1.91]). Findings were consistent when combining all groups, with adjusted HRs of 1.48 (95% CI 1.37–1.60) in ACPA-positive patients versus ACPA-negative patients and 1.44 (95% CI 1.36–1.53) in RF-positive patients versus RF-negative patients.

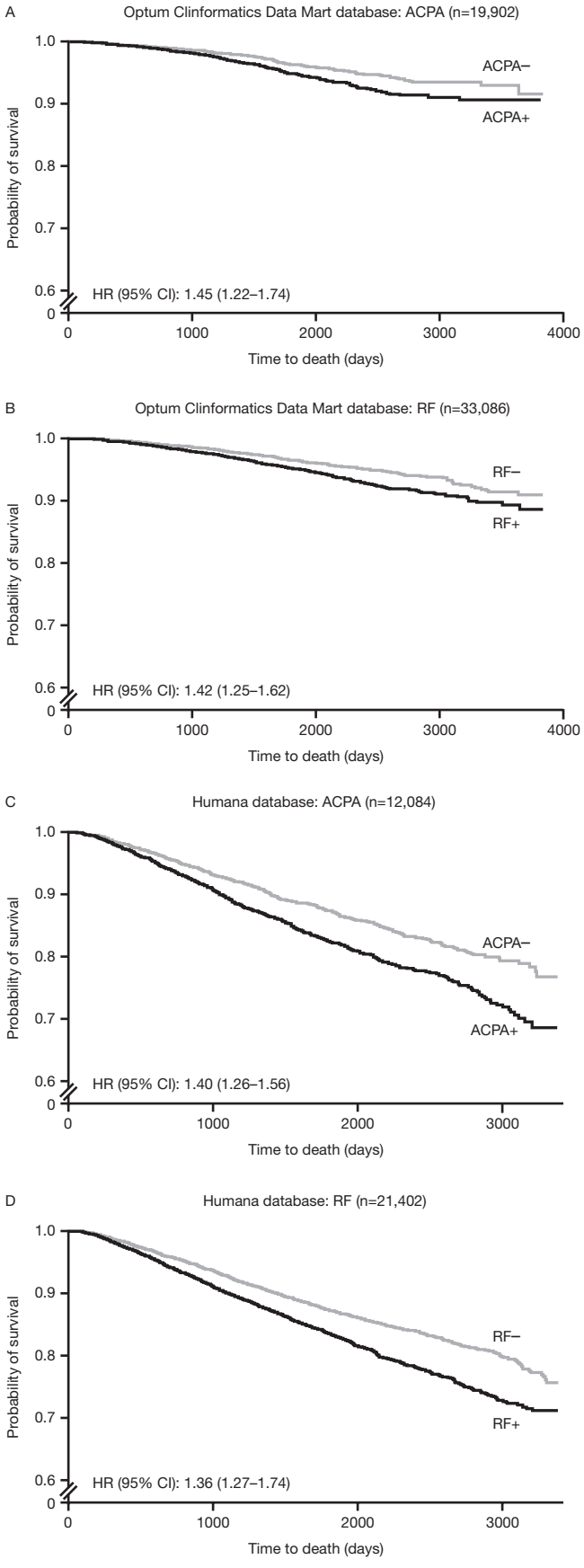

Figure 3. Kaplan-Meier curve for differences in mortality over time between anti–citrullinated protein antibody (ACPA) positivity/negativity (**A** and **C**) and rheumatoid factor (RF) positivity/negativity (**B** and **D**) scores (both databases) after 1:1 propensity-score matching. n = total numbers of patients for the 2 groups. The hazard ratio (HR) is from a Cox model with the ACPA or RF variable only. Propensity scores were calculated for ACPA positivity versus ACPA negativity and RF positivity versus RF negativity based on all covariates. Covariates included age, sex, region, number of physician office visits during the past 3 months, an indicator variable for 714.0x diagnosis, an indicator variable for RA diagnosis before ACPA or RF testing, past hospitalization, use of medications (steroids, nonsteroidal antiinflammatory drugs, salicylates), use of disease-modifying antirheumatic drugs (if applicable), and comorbidity conditions. 95% CI = 95% confidence interval.

Following propensity-score matching, survival curves comparing patients with available ACPA and RF serostatus from each database showed similar patterns of divergence (Figure 3). Single ACPA and RF negativity were associated with a higher survival rate in patients than ACPA and RF positivity. For ACPA-positive versus -negative patients, the HR was 1.45 (95% CI 1.22–1.74) for the Optum Clinformatics Data Mart database and 1.40 (95% CI 1.26–1.56) for the Humana database. For RF-positive versus -negative patients, the HR was 1.42 (95% CI 1.25–1.62) in the Optum Clinformatics Data Mart database and 1.36 (95% CI 1.27–1.47) in the Humana database.

ACPA and RF single-positive patients receiving cDMARDs had a statistically significant increase in mortality risk (ACPA HR 1.52 [95% CI 1.32–1.74]; RF HR 1.47 [95% CI 1.30–1.67]; both versus seronegative subcohorts). Patients with single ACPA or RF positivity receiving cDMARDs had, respectively, a 46% and 62% increased mortality risk versus patients with double ACPA and RF negativity (Figure 4). ACPA and RF single-positive patients receiving bDMARDs had no increase in mortality risk compared with ACPA- and RF-negative patients (ACPA HR 1.03 [95% CI 0.67–1.59]; RF HR 1.22 [95% CI 0.80–1.85]) (Figure 4). Further results from a sensitivity analysis performed to explore the potential for selection bias are available in Section 1 of Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24071/abstract.

DISCUSSION

This study investigated the association between ACPA and RF autoantibody titers and mortality in patients with RA, and the impact of treatment with DMARDs on this association. Both ACPA and RF single seropositivity and double seropositivity were associated with a decreased survival rate, which positively correlated with the ACPA and RF autoantibody titer. In DMARD-exposed patients, those with single ACPA or RF positivity receiving cDMARDs had a statistically significant increase in mortality risk versus double-negative ACPA and RF patients exposed to cDMARDs, whereas no increased mortality risk was observed in the bDMARD-exposed patients with single ACPA or RF positivity versus those with double ACPA and RF negativity.

In this study, ACPA and RF positivity were independently associated with a greater mortality risk than ACPA and RF negativity; this finding was seen consistently across 2 databases (data not shown). Despite ACPA being found to predict mortality independently of RF, when combined with RF the impact on mortality was greater, a finding consistent with a preceding report (25). Both ACPA and RF positivity were associated with increased all-cause mortality risk in patients with RA, while previously only RF positivity has been linked to increased overall mortality risk (26,27). However, these previous reports analyzed a markedly lower number of patients compared with the current study, and the patient population employed was exclusively from Europe (UK, The Netherlands, and Sweden).

Contrary to findings previously reported (25), higher titers of both autoantibodies were found to be associated with increased risk of mortality in our analysis. One possible explanation for this difference was that the study by Humphreys et al (25) limited their analysis to only patients with early inflammatory arthritis, whereas in our study, patients with established RA were included. Additionally, as outlined above, the sample size and geographical region differed from those of the present analysis.

We found that the associations between ACPA and RF with mortality seen in the overall patient population were also evident in patients treated with cDMARDs but not in those receiving bDMARDs. This is an interesting finding, particularly

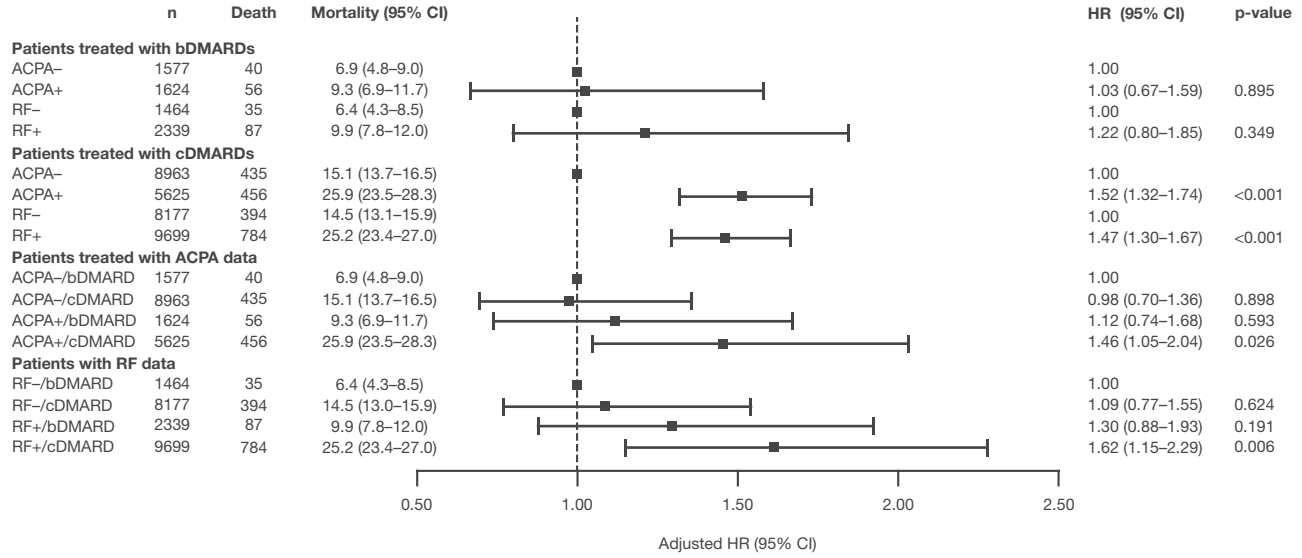

Figure 4. Association between anti–citrullinated protein antibody (ACPA) and rheumatoid factor (RF) and mortality among patients treated with biologic disease-modifying antirheumatic drugs (bDMARDs) and conventional DMARDs (cDMARDs) and with ACPA or RF seropositivity. 95% CI = 95% confidence interval; HR = hazard ratio.

for bDMARDs, because these are generally used later in the disease process when patients would be expected to have higher disease activity versus those treated with cDMARDs (7). Therefore, if mortality was driven by baseline disease, one would hypothesize that patients treated with bDMARDs would be at a higher risk of mortality versus those treated with cDMARDs. The effect-modifying role of bDMARDs observed in our analysis could possibly be due to the systemic antiinflammatory effects and disease-modifying aspect of these agents. There is some evidence to suggest that bDMARDs with different mechanisms of action may be effective in various populations based on patient serostatus (16,28,29); an effect of bDMARD therapy on seropositivity has also been shown (20,21). However, how these effects on ACPA and disease activity translate into differences in mortality risk is unknown. Overall, although an impact of treatment with bDMARDs on the association between ACPA and RF and mortality was suggested, additional direct studies are needed to explore this further.

The findings reported here may provide understanding of the impact of therapy on disease course and mortality in RA and may enable physicians to make informed treatment decisions. However, further investigations are warranted, particularly to fully confirm the notion that bDMARDs may have an impact on mortality in seropositive patients with RA.

This study has some important strengths. Retrospective data provide insights into the real-world management of patients with RA in the clinical setting, without the constraints and limitations of a randomized controlled trial. Furthermore, the large sample size from the 2 databases analyzed here has the potential to provide generalizable results. However, observational studies, by design, do have certain limitations: namely, the absence of randomization makes extrapolation of findings to a randomized controlled trial setting impossible. While the current study has the limitation of using administrative databases, it also has the advantage of controlling for measured confounding using a propensity score–based method. Additional analyses are warranted, including evaluation of the association of disease activity and mortality.

In conclusion, elevated ACPA and RF titers were independently associated with increased mortality among patients diagnosed with RA. The mortality risk was greater in patents with higher ACPA and RF titers. The association persisted in patients treated with cDMARDs but not in those treated with bDMARDs.

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. Alemao 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. Alemao, Weinblatt, Shadick.
Acquisition of data. Alemao, Shadick.
Analysis and interpretation of data. Alemao, Weinblatt, Bao, Shadick.

ROLE OF THE STUDY SPONSOR

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RHEUMATOLOGY REGISTRIES, BIG DATA, AND THE RHEUMATIC DISEASES

Recommendation Rates for Physical Therapy, Lifestyle Counseling, and Pain Medications for Managing Knee Osteoarthritis in Ambulatory Care Settings: A Cross-Sectional Analysis of the National Ambulatory Care Survey (2007–2015)

Samannaaz S. Khoja,[1] Gustavo J. Almeida,[2] and Janet K. Freburger[1]

Objective. To describe and compare triennial rates of physicians' recommendations for physical therapy (PT), lifestyle counseling, and pain medication for knee osteoarthritis (OA) and to identify patient, physician, and practice factors associated with each treatment recommendation.

Methods. We conducted a cross-sectional analysis examining data between 2007 and 2015 from the National Ambulatory Medical Care Survey. Visits to orthopedists and primary care physicians for knee OA were identified and assessed for the following: PT referral, lifestyle counseling, nonsteroidal antiinflammatory drug (NSAID) prescriptions, and narcotics prescriptions. Triennial rates for each treatment were calculated. We examined associations between patient (e.g., race, insurance), physician, and practice factors (e.g., ownership, location) and treatments prescribed using multivariate logistic regression that accounted for complex sampling design.

Results. A total of 2,297 physician visits related to knee OA (~67 [±4] million weighted visits) were identified. For visits to orthopedists, PT and lifestyle recommendation rates declined (158 to 88 of 1,000 visits and 184 to 86 of 1,000 visits, respectively), while NSAID and narcotics prescriptions increased (132 to 278 of 1,000 visits and 77 to 236 of 1,000 visits, respectively) over time ($P < 0.05$). For visits to primary care physicians, there were no significant changes in rates of PT, lifestyle counseling, and narcotics prescriptions over time, while NSAIDs prescriptions increased (221 to 498 of 1,000 visits; $P < 0.05$). Treatment recommendations were associated with nonclinical factors, including practice type, location, and type of provider.

Conclusion. In patients with knee OA, PT and lifestyle counseling seem underutilized, while pain medication prescriptions increased during the investigated timeframe. Variation in treatment choices were associated with nonclinical factors. Future research is necessary to examine ways to improve PT and lifestyle utilization and reduce variation in care for knee OA.

INTRODUCTION

Knee osteoarthritis (OA) is a major source of disability and health care burden in the US, with a prevalence that nearly doubled in recent years (from ~9 million in 2005 to 15 million in 2012) (1,2). The direct and indirect costs of knee OA are substantial, especially with the growth in knee arthroplasties (3). To streamline care and effectively manage knee OA, several health professional associations have released evidence-based clinical practice guidelines. Nonpharmacologic, nonsurgical approaches such as physical therapy (PT) and lifestyle modifications (exercise, self-management strategies, and weight reduction for overweight individuals) have been consistently recommended as first-line, evidence-based care in clinical practice guidelines since 1995 (4–9). These approaches are effective and can be safely applied to the majority of patients with knee OA (6). Management of knee OA

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SIGNIFICANCE & INNOVATIONS

- Although several clinical practice guidelines for managing knee osteoarthritis (OA) exist, adherence to guideline-based care in clinical practice is relatively understudied.
- Physical therapy (PT) and lifestyle modifications (exercise, weight management) are recommended at a relatively low rate during ambulatory care visits for a diagnosis of knee OA. Triennial rates decreased by nearly one-half for PT referrals and lifestyle recommendations during orthopedic visits, while triennial rates for PT referrals or lifestyle recommendation showed no significant changes during primary care visits.
- In contrast, prescriptions for nonsteroidal antiinflammatory drugs (guideline concordant) nearly doubled for orthopedic visits and primary care visits. Prescriptions for narcotics (guideline nonconcordant) increased 3-fold during orthopedic visits.
- Variation in physician treatments due to nonclinical factors such as type of provider and practice location indicates that there is room to improve delivery and quality of care.

through PT or lifestyle counseling may reduce overall health care utilization by minimizing the continuous need for pain medication (10,11) and delay the need for knee surgery and other invasive procedures (e.g., intraarticular injections) (11).

In the US, it is common practice for physicians to manage most patients' knee OA prior to referring them to physical therapists or other exercise and wellness specialists. Since PT and lifestyle-based approaches are not primarily physician-driven treatments, they may not be recommended as often as pharmacologic agents (e.g., nonsteroidal antiinflammatory drugs [NSAIDs] or narcotic analgesics) for controlling symptoms such as pain. While symptom control through medications such as NSAIDs is an evidence-based approach for managing knee OA, it is important to acknowledge that pain medications alone are not sufficient to reverse or mitigate disability caused by OA. Additionally, for some patients, PT and lifestyle modifications may be an important complement to or replacement for pain medication. Evidence regarding physician referral patterns to PT and lifestyle-based approaches is limited, and it is important to examine these referral patterns to inform future research to optimize guideline-based care for patients with knee OA.

The objectives of our study were to describe and compare ambulatory care physicians' referral rates for PT, lifestyle counseling, and prescription of pain medications in a population-based sample of ambulatory care visits for knee OA, and to identify patient, physician, and practice-level characteristics associated with the prescription of each of these treatments. Understanding factors associated with physicians' management of knee OA will help inform efforts to deliver high quality care (i.e., the right evidence-based treatment, at the right time, for the right patient) for all individuals with knee OA.

MATERIALS AND METHODS

Study design and data source. Several years of data from the National Ambulatory Medical Care Survey (NAMCS) database (2007–2015) were examined (12). The NAMCS is a national probability sample survey of non-federally employed, office-based physicians who are engaged in direct patient care. The survey is conducted on a yearly basis by the National Center for Health Statistics of the Centers for Disease Control and Prevention with the purpose of obtaining information on utilization of ambulatory medical care services in the US. Physicians are randomly assigned a 1-week data collection period during which census surveyors visit the practice and obtain information on a systematic random sample of visits. Surveyors use a standardized survey form that consists of information on patient demographics, such as age, sex, race, ethnicity, and insurance, as well as visit characteristics, such as major reason for visit, physician's diagnosis, and diagnostic and therapeutic services ordered or provided during the visit. Surveyors also interview the physicians and collect data on practice characteristics. Survey data were collected on paper forms until 2011, when laptops were adopted for data collection.

The basic sampling unit of NAMCS is the office visit. The NAMCS utilizes a multistage probability sampling design in which the first stage involves identifying primary sampling units (PSUs). A PSU consists of a county or a group of counties, towns, or cities that are stratified by socioeconomic and demographic variables and selected with a probability proportional to their size. The second stage of sampling involves selection of practicing physicians within each PSU. These physicians are then stratified into predefined specialty groups (e.g., internal medicine, orthopedic surgery, neurology, general surgery). The third stage of sampling consists of a selection of visits from the offices of the selected practicing physicians. From 2012 onwards, a 2-stage probability design was used, in which the first stage of sampling involved stratifying the physicians by their specialty, and the second stage involved selecting visits from these physicians' offices (13). Structured data sets are created for each year that the NAMCS is conducted. These data sets, along with the data dictionary and supporting documentations are publicly available through the Centers for Disease Prevention and Control website (12).

Cohort identification and variable selection. Records of visits associated with a diagnosis of knee OA using the International Classification of Diseases, Ninth Revision, codes 715.16, 715.36, and 715.96 were identified. We then assessed whether the physician prescribed PT, provided advice on exercise and/or weight reduction strategies, and/or prescribed pain medications during the visit. The NAMCS codifies drugs using Lexicon Plus classification (Cerner Multum), which is based on therapeutic class and drug ingredients (13). Pain medications were classified into NSAIDs (drug code 061), narcotic analgesics (drug codes 060 and 191), other, which included miscellaneous analgesic combinations, and salicylates (058, 059, 062, and 063).

Data on patient characteristics, such as age, sex, race, ethnicity, insurance type (e.g., private, Medicare, Medicaid, workers' compensation, no insurance), comorbidities (e.g., hypertension, diabetes mellitus, obesity), and major reason for visit (e.g., acute, chronic, surgical, or preventative) were extracted. Other extracted data included physician characteristics, such as specialty (e.g., orthopedist or medical specialties, such as internal medicine or family medicine, or other), whether the physician was the patient's primary provider, and whether the patient was seen by an advanced practice provider (i.e., nurse practitioner or physician assistant). Finally, the following information about the practice was extracted: location (census region, urban/rural), practice type (solo versus group practice), and ownership of practice (e.g., physician group, academic medical center, health maintenance organization/payer).

Statistical analysis. A final analytic data set was created using Stata, version 14.2. This data set included the necessary variables to respond to our questions, all of which were imported from the original NAMCS data files. Four dichotomous (yes/no)

Table 1. Knee OA visit characteristics from 2013–2015, stratified by physician treatment choices*

Variables	PT	Lifestyle	NSAIDs	Narcotics	Overall sample
Treatment recommendation rate	9.2	15.2	30.0	24.8	–
Age, mean ± SE years	63.5 ± 1.3	65.8 ± 1.9	60.0 ± 1.0	61.3 ± 1.0	64.2 ± 0.8
Female	70.3	81.6	69.1	67.4	64.0
Race					
White	70.9	83.5	76.9	79.1	82.8
African American	18.7	15.8	15.4	17	10.3
Other	10.4	0.7	7.7	3.9	6.9
Hispanic	4.5	16.2	9.3	10.8	11.1
Insurance					
Private	50.3	36.3	57.3	42.5	43.4
Medicare	32.5	45.5	26.9	39	39.5
Medicaid	5.1	2.6	7.4	8.9	4.3
Workers' compensation	5.9	1.4	3.4	3.5	3.4
Self/other	0.2	13.6	1.5	1.5	4.1
Missing	6.1	0.6	3.5	4.7	5.4
Major reason for visit					
Acute	11.7	12	23	12.2	18.6
Chronic	64	76.9	60	69	65.2
Surgical	19.3	4.6	11.4	12.0	10.2
Preventative	4.2	4.1	4.8	3.1	3.7
Missing	0.8	3.3	0.8	4.3	2.4
Pain medications†					
NSAIDs	46.3	34.3	–	44	29.8
Narcotics	44.5	27.9	37.2	–	25.3
Other medications	13.3	20.9	19.8	19	17.1
No pain medications	31.5	35.9	0.0	0.0	47.3
Physician specialty					
Family practice	4.6	9.2	19.4	14.1	12.5
Internal medicine	15.9	17	13.1	12.6	8.0
Orthopedic surgeon	61.2	36.9	55	50.9	60.7
Other	18.2	36.9	12.5	22.4	18.8
Patient's primary care physician	21	27	30.7	28.4	20.1
Region					
Northeast	32.1	18.2	21.2	20.9	27.5
Midwest	18.9	9.1	18.7	16.2	15.7
South	26.6	50.8	37	36	31.3
West	22.5	21.9	23.1	26.9	25.5
Rural area	3.4	2	3.8	5.9	5.0
Comorbidities					
Depression	5.4	5.1	7.5	10.4	6.7
Diabetes mellitus	32.5	22	23	18.7	20.1
Hyperlipidemia	28.9	26.1	22.8	19.6	19.4
Hypertension	45.7	40.4	47.3	42.8	42.7
Obesity	31.9	30.3	20.6	26	14.2
Osteoporosis	5.7	2.7	6.1	7.1	4.4
Other	31.2	33.3	17.3	29.2	21.5

* Values are percentages unless indicated otherwise. Weighted n = 2,440,879,610 visits. OA = osteoarthritis; PT = physical therapy; NSAIDs = nonsteroidal antiinflammatory drugs.
† Pain medications category adds up to >100% because patients reported taking >1 type of pain medication.

outcome variables were created: PT referral, lifestyle counseling (coded yes if advice on exercise and/or weight reduction counseling was provided), NSAIDs prescription, and narcotics prescription. We calculated the triennial prevalence rates of PT referrals, lifestyle recommendations, and pain medication prescriptions over 3-year intervals (2007–2009, 2010–2012, and 2013–2015) to increase the precision of the estimates. Since management of knee OA can differ by medical or surgical specialty, we opted to calculate triennial rates separately for orthopedic surgeons and primary care specialties. The prevalence rate calculations accounted for the complex sampling design and were adjusted for patient age, sex, race, ethnicity, insurance type, and major reason for visit to account for potential changes in these patient characteristics over time. Stata logit and margin commands were used to calculate adjusted triennial prevalence rates (14) and Stata regress commands were used to test linear trends over time.

Separate multivariate logistic regression analyses were conducted to identify factors associated with each of the following dependent variables: physician referral to PT, lifestyle counseling, NSAIDs prescription, and narcotics prescription. Regression models were further separated by physician specialty (i.e., orthopedic specialty and primary care specialty). Independent variables in each model included clinical characteristics (major reason for visit, comorbidities, number of medications), patient demographics (age, sex, race, ethnicity, insurance status), physician characteristics (MD or DO training, whether the physician was the patient's primary care provider, the physician's employment status, whether an advanced practice provider also saw the patient), and practice characteristics (type of practice [solo, group], location [urban, rural], and geographic region [Northeast, Midwest, South, West]). Prior to running the regression analyses, we also checked whether any statistical assumptions (e.g., multicollinearity) were violated. All analyses were conducted using the recommended weighting strategies and estimation procedures provided in the NAMCS data documentation (13).

RESULTS

We identified 2,297 visits related to knee OA, which approximated to 67 (±4) million weighted physician visits between 2007 and 2015 (~8 million visits/year). Among these visits, 44 (±3) million visits (66%) were to orthopedic surgeons and 14 (±1) million (21%) were to primary care physicians (PCPs), while the remainder were to other specialists. Table 1 presents visit characteristics stratified by physician treatment choices for the most recent 3 years (2013–2015). The sample largely consisted of visits by patients who were white, female, non-Hispanic, and ~64 years of age, and the most common reason for the visit was a chronic problem. Relative to the overall sample, visit characteristics differed by treatment choices. A greater proportion of visits by women involved prescriptions of PT and lifestyle counseling, and a greater proportion of visits by African American patients involved prescriptions of all 4 treatments. A higher proportion of visits for an acute problem involved prescriptions of NSAIDs, and a higher proportion of surgical visits involved prescriptions of PT. There were also differences by physician characteristics and region.

Trends in PT referral, lifestyle counseling, and medication use. Trends in physician recommendation of PT, lifestyle counseling, NSAIDs prescriptions, and narcotics prescriptions over time are depicted in Figure 1. There was a significant decline in triennial rates of PT referral by orthopedic specialists from 158 of 1,000 visits in 2007–2009 to 86 of 1,000 visits in 2013–2015 ($\beta = -0.012$, $P = 0.013$). A similar trend was seen for lifestyle counseling by orthopedic specialists, in which triennial rates decreased from 184 of 1,000 visits in 2007–2009 to 88 of 1,000 visits in 2013–2015 ($\beta = -0.020$, $P = 0.018$). Conversely, triennial rates of NSAIDs prescriptions increased significantly from 132 to 278 of 1,000 visits in 2013–2015 ($\beta = 0.019$, $P = 0.017$), and triennial rates of narcotics prescriptions increased

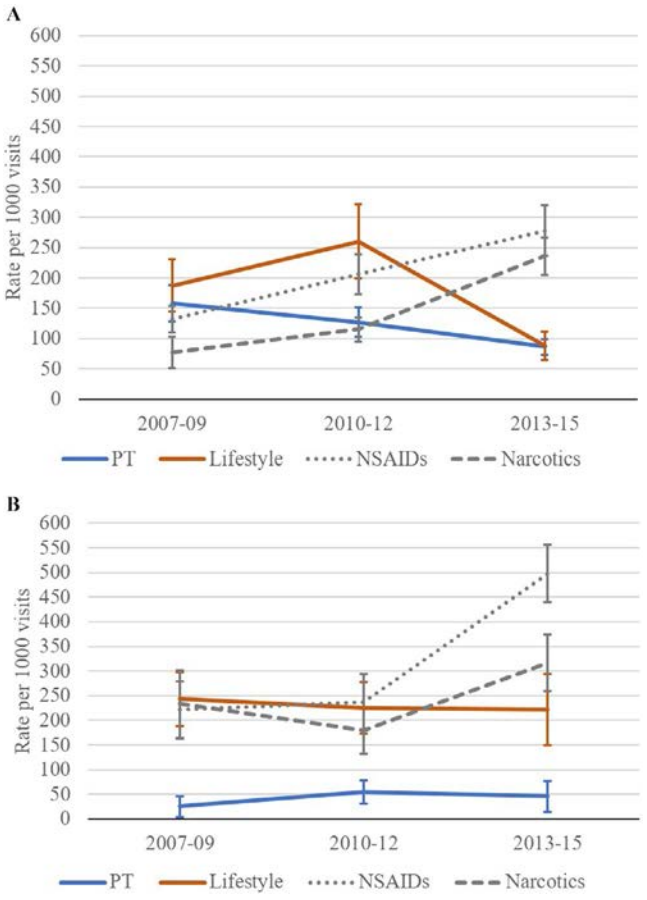

Figure 1. Adjusted triennial treatment rates during visits to orthopedic and primary care specialists for a knee osteoarthritis (OA) diagnosis. **A**, Treatments reported during visits to orthopedic specialists for knee OA. **B**, Treatments reported during visits to primary care specialists for knee OA. Rates are adjusted by age, sex, race, ethnicity, insurance type, and reason for visit. PT = physical therapy; NSAIDs = nonsteroidal antiinflammatory drugs.

Table 2. Associations between patient, physician, and practice characteristics and treatment choices for knee OA during visits to orthopedic specialists*

	PT	Lifestyle	NSAIDs	Narcotics
Demographics				
Age, years				
21–30	2.22 (0.17–28.53)	0.67 (0.04–10.72)	†	1.53 (0.20–11.75)
31–40	0.87 (0.17–4.48)	1.13 (0.25–5.08)	1.92 (0.52–7.05)	2.52 (0.52–12.09)
41–50	0.91 (0.27–3.11)	0.58 (0.18–1.88)	1.79 (0.77–4.14)	0.78 (0.26–2.33)
51–60	1.50 (0.57–3.91)	0.85 (0.33–2.18)	2.09 (0.99–4.39)	1.41 (0.60–3.29)
61–70	(0.84 (0.37–1.91)	0.96 (0.37–2.49)	1.44 (0.75–2.76)	1.25 (0.58–2.71)
>70 (reference)	1.00	1.00	1.00	1.00
Sex, female	1.24 (0.70–2.18)	1.02 (0.57–1.84)	1.12 (0.74–1.71)	1.01 (0.57–1.78)
Race, %				
White (reference)	1.00	1.00	1.00	1.00
African American	1.54 (0.50–4.69)	0.60 (0.21–1.69)	1.27 (0.61–2.64)	1.63 (0.69–3.86)
Other	4.07 (1.56–10.67)‡	0.67 (0.21–2.15)	0.80 (0.33–1.93)	1.21 (0.48–3.06)
Ethnicity, Hispanic	0.94 (0.36–2.46)	0.47 (0.18–1.21)	1.83 (0.87–3.84)	1.92 (0.84–4.38)
Insurance, %				
Private (reference)	1.00	1.00	1.00	1.00
Medicare	1.71 (0.67–4.37)	0.92 (0.45–1.90)	0.71 (0.42–1.21)	1.33 (0.73–2.42)
Medicaid	1.17 (0.40–3.40)	1.36 (0.33–5.56)	0.53 (0.14–1.94)	1.07 (0.28–4.11)
Workers' compensation	2.55 (0.32–20.57)	0.28 (0.05–1.41)	1.07 (0.41–2.83)	1.57 (0.38–6.58)
Other	1.15 (0.21–6.17)	1.21 (0.24–6.01)	0.54 (0.11–2.58)	0.62 (0.10–3.96)
Self/no charge	†	†	0.62 (0.02–17.23)	†
Insurance information missing	2.82 (0.64–12.40)	0.64 (0.13–2.99)	0.46 (0.19–1.08)	0.97 (0.21–4.59)
Clinical characteristics				
PT referral	NA	NA	1.04 (0.48–2.27)	1.47 (0.62–3.46)
Provided lifestyle counseling	NA	NA	1.36 (0.72–2.56)	1.01 (0.45–2.28)
Prescribed narcotics	1.68 (0.66–4.24)	1.10 (0.47–2.68)	NA	NA
Prescribed NSAIDs	1.23 (0.53–2.85)	1.42 (0.67–3.02)	NA	NA
Radiograph	1.23 (0.58–2.58)	1.41 (0.76–2.61)	1.31 (0.86–1.99)	0.81 (0.47–1.42)
Other imaging (CT/MRI)	1.59 (0.48–5.30)	1.76 (0.58–5.4)	0.91 (0.42–1.97)	1.78 (0.62–5.05)
Visit type				
Acute (reference)	1.00	1.00	1.00	1.00
Chronic	0.75 (0.32–1.77)	0.84 (0.43–1.63)	0.90 (0.52–1.55)	1.38 (0.70–2.72)
Surgical	4.59 (1.94–10.89)‡	0.86 (0.37–1.97)	0.49 (0.24–0.97)‡	3.12 (1.44–6.75)‡
Preventative	0.58 (0.04–9.44)	3.02 (0.15–61.56)	0.04 (0.00–0.67)‡	†
Missing	0.78 (0.08–8.13)	1.20 (0.17–8.65)	0.25 (0.06–1.10)	0.18 (0.02–1.59)
Physician characteristics				
Patient seen by primary care provider	0.53 (0.05–5.29)	1.83 (0.10–34.41)	1.65 (0.62–4.41)	2.62 (0.41–16.73)
Patient seen by advanced practice provider (RN, PA)	0.86 (0.36–2.06)	1.41 (0.39–5.11)	2.32 (1.15–4.66)‡	2.47 (1.06–5.72)‡
Doctor of osteopathy	1.92 (0.79–4.68)	1.38 (0.38–4.98)	1.45 (0.55–3.80)	1.39 (0.52–3.70)
Physician is full-time or part-time owner	1.23 (0.50–3.06)	0.90 (0.21–3.79)	0.58 (0.29–1.15)	0.98 (0.42–2.31)
Practice characteristics				
Solo practice	1.69 (0.90–3.19)	2.24 (0.90–5.59)	0.97 (0.48–1.94)	1.02 (0.53–1.95)
Clinic ownership				
Physician group (reference)	1.00	1.00	1.00	1.00
Academic/medical center	1.85 (0.54–6.37)	0.37 (0.04–3.04)	0.75 (0.27–2.06)	1.23 (0.38–3.92)
Corporate/HMO/insurance	1.05 (0.23–4.86)	0.58 (0.10–3.54)	0.92 (0.32–2.65)	0.49 (0.15–1.60)
Rural area	0.28 (0.10–0.80)‡	0.17 (0.03–0.96)‡	0.59 (0.29–1.23)	0.66 (0.26–1.66)
Region				
Northeast (reference)	1.00	1.00	1.00	1.00
Midwest	0.72 (0.36–1.43)	0.27 (0.09–0.86)‡	1.32 (0.53–3.30)	1.42 (0.56–3.63)
South	0.52 (0.22–1.21)	1.03 (0.39–2.73)	2.39 (1.01–5.66)‡	2.00 (0.94–4.23)
West	0.53 (0.22–1.27)	1.51 (0.54–4.20)	2.21 (0.90–5.44)	2.05 (0.90–4.66)

* Values are odds ratios (99% confidence intervals). All regression models were adjusted for comorbidities and year of data collection. Physical therapy (PT) and lifestyle models also accounted for the total number of medications reported at the visit. OA = osteoarthritis; NSAIDs = non-steroidal antiinflammatory drugs; NA = not applicable; CT = computed tomography; MRI = magnetic resonance imaging; RN = registered nurse; PA = physician assistant; HMO = health maintenance organization.
† Indicates missing data as the sample size was too small for estimation.
‡ Significant at α level of 0.01.

from 77 of 1,000 visits in 2007–2009 to 236 of 1,000 visits in 2013–2015 (β = 0.021, *P* = 0.001) (Figure 1A).

Triennial rates of PT referral by PCPs were low and showed no significant changes from 26 of 1,000 visits in 2007–2009 to 46 of 1,000 visits in 2013–2015 (β < 0.001, *P* = 0.988). Triennial rates of lifestyle counseling by PCPs were higher than PT referrals, and there were nonsignificant changes in triennial rates from 243 of 1,000 visits in 2007–2009 to 221 of 1,000 visits in 2013–2015 (β = 0.003, *P* = 0.837). Conversely, there was a significant increase in triennial rates of NSAIDs prescriptions from 221 of 1,000 visits in 2007–2009 to 498 of 1,000 visits in 2013–2015 (β = 0.039, *P* = 0.005) and a nonsignificant change in triennial rates of narcotics prescriptions from 233 of 1,000 visits in 2007–2009 to 316 of 1,000 visits in 2013–2015 (β = 0.016, *P* = 0.243) (Figure 1B).

Factors associated with orthopedic surgeon treatment recommendations. Few patient demographic characteristics were associated with orthopedic surgeons' treatment recommendations (Table 2). Of note, individuals of Hispanic ethnicity were more likely to be prescribed narcotics and NSAIDs. Individuals of nonwhite, non–African American race (relative to white race) were more likely to receive PT referrals. Regarding clinical characteristics, surgical-related visits were more likely to involve PT referrals and narcotics prescriptions and less likely to involve NSAIDs prescriptions. Preventative visits were also less likely to involve NSAIDs prescriptions. Regarding physician and practice characteristics, patients seen by advanced practice providers were more likely to receive NSAIDs and narcotics prescriptions. Visits to orthopedic surgeons in rural areas were less likely to involve PT referrals or lifestyle counseling.

Factors associated with PCP treatment recommendations. Demographics were mostly not associated with PCP treatment recommendations (Table 3). A few factors that approached significance and associated with higher likelihood of receiving narcotics included African American race and female sex. Visits covered by workers' compensation were less likely to receive NSAIDs prescriptions. Regarding clinical characteristics, visits with computed tomography or magnetic resonance imaging were more likely to include narcotics prescriptions. Regarding physician and practice characteristics, visits overseen by the patient's primary care provider were associated with a higher likelihood of NSAIDs prescriptions, while visits in an academic center were associated with a lower likelihood of lifestyle counselling.

DISCUSSION

This study provides an overview of physician recommendation rates for PT, lifestyle counseling, NSAIDs prescriptions, and narcotic prescriptions for knee OA using a nationally representative sample. Study findings suggest that adherence to guideline-based care for nonpharmacologic, nonsurgical treatments such as PT, exercise, or weight loss is low for knee OA and does not seem to be improving over time. In contrast, NSAIDs prescriptions increased by 30–50%, and narcotics prescriptions increased ~10–15% from the triennial period 2007–2009 to 2013–2015. The increase in narcotics prescriptions seems counterintuitive especially because of the increased awareness of the hazards of chronic use of narcotics (opioids) and because clinical practice guidelines for knee OA either have uncertain (6) or inconclusive (4) recommendations for opioid analgesics or recommend prescribing them very sparingly and in selective cases (e.g., if other treatments failed or patients cannot undergo replacement surgery) (7,15). The decrease in PT and lifestyle counseling is surprising because promoting physical activity interventions is a front-line approach for knee OA according to most clinical practice guidelines (4,6,7,15,16). The results of our study align with previous reports on OA that suggested an increase in trends of opioid prescriptions (17,18) and a low rate of lifestyle or PT interventions in clinical settings (19,20). The current evidence underscores the need for further investigation to explain why adherence to evidence-based practices is suboptimal and to investigate methods to effectively promote guideline-based care.

In order to understand physicians' choice of treatment options for knee OA, we examined the associations between patient, clinical, physician characteristics, and practice characteristics and the 4 treatment choices (i.e., PT, lifestyle counseling, NSAIDs prescriptions, or narcotics prescriptions). Associations were examined separately by specialty, i.e., orthopedic versus PCP. We found many nonclinical factors associated with the various treatment choices for knee OA.

In visits to orthopedic surgeons, the type of provider seen during the visit played a role in pain medication prescription. NSAIDs and narcotics prescriptions were more likely during visits overseen by an advanced practice provider. These associations may reflect how advanced practice providers manage knee OA. In visits to PCPs, advanced practice providers did not seem to influence the treatment choices; however, the associations between advance practice providers and NSAID and narcotics prescriptions approached significance (*P* < 0.05, but >0.01) and warrant further investigation. Although not observed in the current study, recent research has suggested that advanced practice providers tend to provide more health education counseling services than PCPs (21). As physicians are time- and resource-constrained, it is important to consider the role of nonphysician providers to ensure the delivery of guideline-based care that may not necessarily need direct supervision from a physician.

Orthopedic practice locations in rural areas were associated with a lower likelihood of PT referral or lifestyle counseling. While the lower likelihood of PT referral may be explained by PT supply (or lack thereof), the relationship between practice location and lifestyle counseling is less clear. Time and resource constraints and potentially high caseloads for orthopedic surgeons located in rural areas might explain why they are less likely to focus on nonphysician treatments such as PT or lifestyle counseling. We

Table 3. Associations between patient, physician, and practice characteristics and treatment choices for knee OA during visits to primary care physicians*

	PT	Lifestyle	NSAIDs	Narcotics
Demographics				
Age, years				
21–30	†	†	0.88 (0.07–11.62)	†
31–40	†	0.22 (0.01–8.63)	0.49 (0.03–6.96)	1.51 (0.07–34.89)
41–50	†	0.30 (0.01–7.30)	1.97 (0.30–12.85)	2.22 (0.17–29.02)
51–60	0.25 (0.01–12.7)	0.47 (0.07–3.25)	1.23 (0.27–5.72)	1.28 (0.28–5.88)
61–70	0.54 (0.01–66.4)	1.36 (0.31–6.10)	0.72 (0.22–2.34)	0.98 (0.27–3.53)
>70 (reference)	1.00	1.00	1.00	1.00
Sex, female	0.18 (0.01–13.53)	1.17 (0.29–4.68)	1.66 (0.55–5.00)	2.19 (0.80–5.99)
Race, %				
White (reference)	1.00	1.00	1.00	1.00
African American	†	1.56 (0.27–9.14)	1.33 (0.41–4.27)	3.03 (0.83–11.02)
Other	0.58 (0.02–20.94)	1.62 (0.15–17.02)	7.46 (0.96–57.90)	0.95 (0.02–48.28)
Ethnicity, Hispanic	1.03 (0.03–34.67)	0.78 (0.16–3.82)	0.78 (0.12–5.02)	1.77 (0.50–6.32)
Insurance, %				
Private (reference)	1.00	1.00	1.00	1.00
Medicare	0.49 (0.01–38.10)	0.30 (0.09–1.04)	0.34 (0.10–1.12)	0.39 (0.14–1.10)
Medicaid	†	1.30 (0.16–10.87)	0.40 (0.06–2.51)	0.58 (0.09–3.67)
Workers' compensation	†	†	0.05 (0.01–0.44)‡	†
Other	†	†	0.11 (0.01–2.73)	0.95 (0.01–141.57)
Self/no charge	†	4.62 (0.26–81.15)	3.62 (0.24–54.74)	0.97 (0.09–10.47)
Insurance information missing	3.12 (0.08–119.22)	0.19 (0.01–4.13)	0.11 (0.01–2.44)	1.26 (0.23–6.79)
Clinical characteristics				
PT referral	NA	NA	5.21 (0.69–38.91)	4.05 (0.76–21.60)
Lifestyle counseling	NA	NA	0.86 (0.24–3.08)	0.42 (0.11–1.62)
Prescribed narcotics	5.16 (0.33–80.83)	0.60 (0.12–2.96)	NA	NA
Prescribed NSAIDs	8.86 (0.70–250.53)	1.23 (0.37–4.09)	NA	NA
Radiograph	†	1.16 (0.26–5.26)	0.99 (0.21–4.51)	0.36 (0.10–1.24)
Other imaging (CT/MRI)	†	†	1.67 (0.11–25.86)	9.21 (1.55–54.61)
Visit type				
Acute (reference)	1.00	1.00	1.00	1.00
Chronic	1.92 (0.10–35.44)	1.94 (0.51–7.46)	0.73 (0.25–2.08)	2.08 (0.55–7.82)
Surgical	†	1.09 (0.04–26.51)	1.13 (0.11–11.97)	1.15 (0.09–14.83)
Preventative	†	2.04 (0.44–9.56)	1.33 (0.32–5.57)	0.99 (0.15–6.52)
Missing	†	2.31 (0.86–62.31)	0.06 (0.00–10.91)	1.19 (0.06–23.36)
Physician characteristics				
Patient seen by primary care provider	1.59 (0.05–46.09)	1.06 (0.14–7.87)	0.24 (0.08–0.72)‡	1.98 (0.25–15.56)
Patient seen by advanced practice provider (RN, PA)	0.01 (0.00–46.54)	1.18 (0.18–7.61)	5.27 (0.93–29.78)	0.26 (0.05–1.32)
Doctor of osteopathy	1.09 (0.05–22.24)	0.21 (0.03–1.49)	1.27 (0.44–3.67)	0.82 (0.16–4.24)
Physician is full or part-time owner	†	0.74 (0.19–2.84)	1.72 (0.45–6.65)	2.05 (0.46–9.13)
Practice characteristics				
Solo practice	0.05 (0.00–5.59)	2.56 (0.50–13.25)	1.65 (0.54–5.01)	0.93 (0.21–4.10)
Clinic ownership				
Physician group (reference)	1.00	1.00	1.00	1.00
Academic/medical center	†	0.10 (0.01–0.89)‡	4.63 (0.91–23.67)	0.72 (0.16–3.18)
Corporation/HMO/insurance	0.29 (0.01–7.44)	0.41 (0.08–2.22)	3.78 (0.87–16.50)	0.51 (0.14–1.86)
Rural area	†	0.32 (0.05–1.92)	1.44 (0.0.52–3.99)	2.31 (0.61–8.68)
Region				
Northeast (reference)	1.00	1.00	1.00	1.00
Midwest	0.15 (0.01–2.90)	3.86 (0.75–20.00)	1.58 (0.36–6.84)	1.47 (0.33–6.58)
South	0.93 (0.16–14.80)	1.64 (0.35–7.66)	1.58 (0.37–6.66)	2.94 (0.60–14.49)
West	0.71 (0.03–14.70)	2.21 (0.23–20.86)	1.67 (0.33–8.51)	3.17 (0.65–15.44)

* Values are odds ratios (99% confidence intervals). All models were adjusted for comorbidities and year of data collection. Physical therapy (PT) and lifestyle models also accounted for the total number of medications reported at the visit. OA = osteoarthritis; NSAIDs = nonsteroidal antiinflammatory drugs; NA = not applicable; CT = computed tomography; MRI = magnetic resonance imaging; RN = registered nurse; PA = physician assistant; HMO = health maintenance organization.
† Indicates missing data as the sample size was too small for estimation.
‡ Significant at α level of 0.01.

also observed variation in treatment choices by geographic region. For example, orthopedic visits in clinics in the southern region (compared to the Northeast) were associated with a higher likelihood of pain medication prescriptions. These findings are consistent with previous reports on health care access and delivery among different geographic regions in the US (22) and warrant further investigation to reduce these sources of variation in health care.

Variation in treatment choices was also associated with few patient demographic characteristics and insurance coverage. Nonwhite, non–African American patients who saw an orthopedic surgeon were more likely to receive a PT referral, and Hispanic patients seen by orthopedic surgeons were more likely to receive narcotics and NSAIDs prescriptions. We also noticed some associations that were approaching significance and may be worth investigating in future studies. Of note, African American and female patients who visited a PCP were more likely to have received a narcotics prescription, while orthopedic visits in a solo practice clinic were associated with a higher likelihood of PT and lifestyle recommendations.

The NAMCS survey is a rich source of health care utilization data collected using robust surveying methods. However, some limitations in the data need to be acknowledged. The basic unit is the visit and not the patient. There is a possibility that some patients may have received a PT referral or lifestyle counseling during a visit that was not part of the NAMCS data collection period. There are also limitations in distinguishing different drugs using the medication codes provided. For example, tramadol (a weak synthetic opioid) is part of guideline-based care, but the medication codes provided are not detailed enough to allow us to separate tramadol from stronger narcotic analgesics. The data do not provide an indicator for disease severity (except for the acute/chronic classification) or a measure of disability. Further, various contextual factors that could potentially influence referral behavior were not captured in the survey (e.g., provider years of experience, knowledge of OA guidelines, and whether referrals reflect a shared decision or solo decision by provider or patient). It is important to acknowledge that while we reported on rates of treatment recommendations, the ideal rates, particularly for PT and lifestyle counseling, for knee OA are unknown, and these treatments may not always be necessary (e.g., in cases of patients with mild symptoms or for those who are already active). Due to cross-sectional design and limitations in analysis (e.g., data did not fit exponential models and the presence of multiple comparisons), the study results are not causative and need to be confirmed by more focused, longitudinal investigations. However, it must be noted that our study findings highlight the importance of considering how nonclinical contextual factors may affect management of knee OA. Last, the NAMCS survey data are a probability sample from the US, and their generalizability to other countries with varying health systems and cultures may be limited.

In conclusion, PT and lifestyle counseling seem to be underutilized to manage knee OA, with no trends in improvement over time, while pain medication prescription significantly increased in this cohort. This contrasting trend suggests that knee OA is primarily managed from a perspective of symptom control and not from the perspective of improving physical function, fitness, and overall well-being. Even though PT and lifestyle interventions for knee OA have been included as part of guideline-based care as early as 1995 (9,23), the utilization of these recommendations as recently as 2013–2015 by physicians continues to remain low. If PT and lifestyle interventions were emphasized at a more optimal rate in clinical practice, reliance on pain medications (especially those that are not guideline concordant; i.e., narcotic analgesics) may be reduced. Treatment choices were also driven by nonclinical factors such as practice type, geography, and insurance coverage.

Future research to develop strategies to overcome barriers to patient care and to effectively implement guideline-based care for patients with knee OA is warranted. Cultural and contextual factors such as provider experience and years in practice, knowledge of guidelines, availability of resources, and patient values can be complex in how they affect the provider's treatment strategies. Therefore, future research using qualitative or mixed-methods designs that include provider and/or patient focus groups or surveys specifically designed to address such contextual barriers and facilitators to guideline-based care is needed.

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. Khoja 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. Khoja, Freburger.
Acquisition of data. Freburger.
Analysis and interpretation of data. Khoja, Almeida, Freburger.

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Disease Burden of Patients With Osteoarthritis: Results of a Cross-Sectional Survey Linked to Claims Data

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Objective. Osteoarthritis (OA) is a major reason for chronic pain, stiffness, and functional limitation. This study was undertaken to analyze factors associated with the burden of OA, taking the pattern of joint involvement into account.

Methods. From a random sample of 8,995 patients with OA (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, German Modification codes M15 [polyarticular], M16 [hip], or M17 [knee]) from a German statutory health insurance database, 3,564 patients completed a survey including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Patients with knee, hip, concomitant hip and knee, or polyarticular manifestation were compared concerning pain, stiffness, function, and impact on work and personal life. Data were linked to dispensation records. The association of age, sex, body mass index (BMI), symptom duration, and the World Health Organization–5 Well-Being Index (WHO-5) with WOMAC results was assessed in multiple linear regression models.

Results. Patients with knee (n = 1,448), hip (n = 959), hip and knee (n = 399), or polyarthritic (n = 758) OA were included. Concomitant hip and knee OA was accompanied by the highest WOMAC values (mean 44), frequent impairment of personal life (75%), and the highest use of analgesics (52% nonsteroidal antiinflammatory drugs, 22% opioids, and 37% others). In the regression analyses, BMI per 5 units and WHO-5 per 10% worsening were associated with an increase in WOMAC values of 4–5 points, irrespective of the joint manifestations.

Conclusion. Disease burden is high in patients with concomitant hip and knee OA and is connected with frequent prescription of analgesics. Involvement of several joints, BMI, and depressive symptoms need to be considered when using the WOMAC as an outcome instrument.

INTRODUCTION

Osteoarthritis (OA) is a major reason for chronic pain, joint stiffness, and functional limitation. In the majority of studies on the burden of OA, hip and knee OA are evaluated, while polyarthritic OA (POA) is less often considered. In the global burden of disease study, hip and knee OA were shown to be major contributors to global disability (1). So far, no disease-modifying drugs exist to provide causal OA therapy (2,3). Current treatment guidelines recommend information and education, weight loss for overweight patients, and physical therapy as the base of conservative treatment. Nonsteroidal antiinflammatory drugs (NSAIDs) are recommended for patients with persistent pain and (weak) opioids are considered the last option before total joint replacement (TJR) is indicated or if TJR is contraindicated (4). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a composite instrument for the measurement of pain, stiffness, and functional limitation (5). Medication use and the WOMAC are most relevant to evaluate disease burden in OA.

In the EUROHIP study, Huber et al (6) have shown that arthritis in other major joints strongly affects the outcome of hip surgery after 1 year. Because TJR is the most frequently examined outcome within OA, data on disease burden of prior OA stages without mandatory indication of surgery are less comprehensive. The Osteoar-

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SIGNIFICANCE & INNOVATIONS

- Disease burden of osteoarthritis (OA) has been investigated in a combined claims and survey data set in German patients with OA.
- Medication intake and disease burden was highest in patients with concomitant hip and knee OA.
- Bilaterally affected patients and patients with concomitant polyarthritic OA showed higher disease burden.
- More attention should be paid to physical treatment options.

thritis Initiative reported a lower health-related quality of life of patients with knee OA compared to that of the general population (7). To our knowledge, no data exist on the disease burden of unselected German patients with OA. The aim of this study was to compare the burden of OA in the knee, hip, and concomitant hip and knee and in the polyarthritic pattern. To evaluate disease burden, self-reported disease severity (using WOMAC) and the impact on personal and work life as well as dispensation records on analgesics and physical therapy were analyzed. We also compared hip and knee OA with or without concomitant POA, considering differences in age, sex, body mass index (BMI), and depressive symptoms.

MATERIALS AND METHODS

Study population. This study is part of the research project PROCLAIR (Linking Patient Reported Outcomes with Claims Data for Health Service Research in Rheumatology) (8). We used data from a German statutory health insurance fund (BARMER, with more than 9 million insured in 2018) to identify patients diagnosed with OA of the knee or hip or with POA (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, German Modification [ICD-10-GM] codes M15–17) in ≥2 quarters of the year 2014. A sample was drawn from the patients who were continuously insured in 2014 and 2015, stratified by age (30–39, 40–49, 50–59, 60–69, 70–79 years), sex, and diagnosis (M15: POA, M16: OA of the hip, M17: OA of the knee). The strata contained 330 patients, except for men with POA ages 30–39 years. In this stratum, all 164 patients were selected. The total sample size was 9,734. Data for analysis were obtained from 2 sources: survey and claims data.

Survey data. After the exclusion of patients who had changed their health insurance or were deceased, in 2016 a survey was sent by mail to 8,995 patients with 1 reminder. The survey contained information on joints with current pain (last 7 days) or chronic pain (3 months in the last 2 years), symptom duration, primary physician treating the OA, WOMAC results (5,9), the World Health Organization–5 Well-Being Index (WHO-5), the impact of OA on personal and work life, and sociodemographic variables. The WHO-5 is a measure for well-being on a scale of 0–10 (where 0 = worst outcome and 10 = best outcome) (10). It is also used to identify patients at risk of depression. Values ≤28 indicate moderate to severe depression, 29–50 mild depression, and >50 no depression (10). The WHO-5 is used in a wide range of fields and shows favorable properties to detect major depression (11). The WOMAC and its subscores for pain, stiffness, and physical function are given as a percentage score, with 100 representing the worst outcome.

Claims data. For patients who gave their written informed consent, the survey data were linked to the individual claims data. Prescriptions of analgesics were identified using Anatomical Therapeutic Chemical classification system codes, counting patients as users if they had ≥1 prescription of the corresponding drug in that year (12).

Assessment of nonresponse bias. We analyzed whether there was a systematic difference between responders and nonresponders to the survey by comparing age, sex, the number of medication prescriptions as an index of comorbidity, whether an orthopedic specialist was seen in the corresponding year, and whether opioids, NSAIDs, or physical therapy were prescribed.

Patient selection. Four analysis groups were defined: POA, hip OA, hip and knee OA, and knee OA. Patients who were drawn in the samples for hip, hip and knee, or knee OA could have a concomitant claims diagnosis of POA. Patients who reported current or

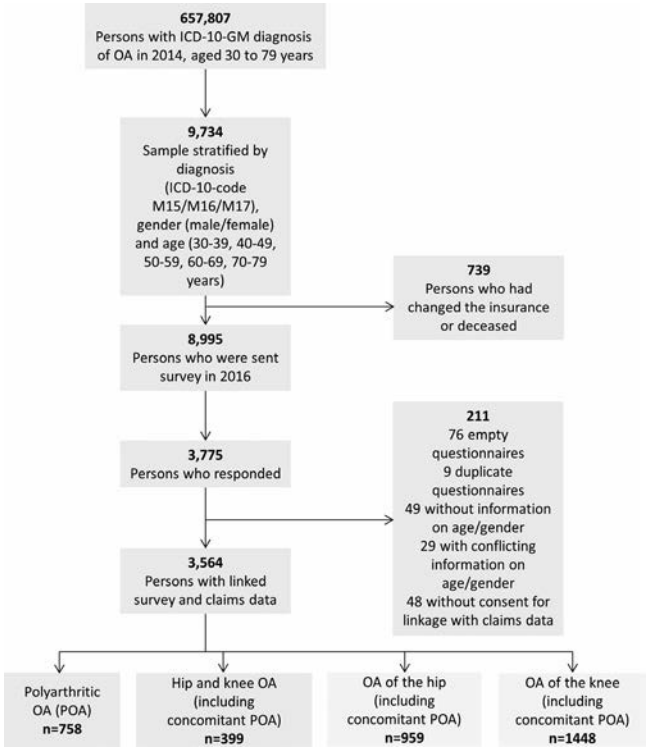

Figure 1. Flowchart showing the sampling process and survey response. ICD-10-GM = International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, German Modification; OA = osteoarthritis; POA = polyarthritic osteoarthritis.

chronic pain in the relevant joints (for POA every joint was relevant) were selected for a subgroup analysis. In the subgroup analysis, patients reporting pain in artificial joints only were excluded.

Statistical analysis. The results were weighted to match the distribution of all patients with OA in the claims data. This weighting ensures that the results are representative for all patients ages 30–79 years with POA, hip OA, hip and knee OA, and knee OA from the insurance population that was used. Subgroup analyses for the 4 analysis groups were performed with domain analyses, using procedures for complex survey samples in SAS/STAT software, version 9.4.

Values of the total WOMAC were compared for patients grouped by age, sex, BMI, WHO-5 groups, analgesics use, and unilateral or bilateral involvement of the joint. The association of WOMAC scores with age and sex, BMI, symptom duration, and the WHO-5 was assessed in multiple linear regression models. The models were adjusted for age and sex as confounders for the association of the other parameters with WOMAC scores. Multiple imputation, with 20 imputations for all variables used in the models, was performed using SAS software, version 9.4 with the fully conditional specification method, assuming data were missing at random.

Ethics approval. Ethics approval was obtained from the ethics committee of the Charité–Universitätsmedizin Berlin in March of 2015 (EA1/051/15). This research was conducted in agreement with the Declaration of Helsinki.

RESULTS

Description of the study sample. Of the 8,995 contacted patients, 3,775 sent back the survey (42%), and 3,564 gave their consent to link survey and claims data (Figure 1). The patients responding to the survey were older than those not responding (mean age 67.2 versus 65.8 years), and the percentage of women was comparable (70.5% versus 68.7%). Opioids were prescribed to 15.2% and 14.4%, respectively, of the patients, and the number of comorbidities was comparable. There were more pronounced differences in the prescriptions of NSAIDs (48% versus 37%), in physical therapy (53% versus 43%), and in the proportion of patients seeing an orthopedic specialist in the year of the study (58% versus 45%) between responders and nonresponders.

Patients with POA, OA of the hip, OA of the hip and knee, and OA of the knee. The analysis included 758 patients with POA, 959 with hip OA, 399 with hip and knee OA and 1,448 with knee OA. Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24058/abstract, provides data on the number of patients who did not report any current or chronic pain in the respective joints. A subgroup analysis including only the patients who reported symptoms is included in Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24058/abstract. Characteristics of the patients are shown in Table 1. The mean

Table 1. Patient characteristics and health-related quality of life*

Variable	Missing, no.	POA (n = 758)	Hip OA (n = 959)	Hip/knee OA (n = 399)	Knee OA (n = 1,448)
Age, mean years	0	66 (66, 67)	67 (66, 67)	69 (69, 70)	66 (65, 66)
30–39, %	0	0.5 (0.4, 0.7)	1.0 (0.8, 1.2)	0.3 (0.1, 0.4)	1.3 (1.1, 1.6)
40–49, %	0	4 (3, 5)	5 (4, 6)	2 (1, 3)	4 (3, 5)
50–59, %	0	20 (17, 23)	16 (14, 19)	10 (8, 13)	19 (17, 21)
60–69, %	0	31 (27, 36)	29 (26, 33)	27 (22, 32)	31 (28, 33)
70–79, %	0	44 (39, 49)	48 (44, 52)	60 (54, 65)	43 (40, 46)
Female	0	83 (82, 85)	63 (61, 66)	73 (69, 77)	68 (67, 68)
Symptom duration, mean years	471	14 (13, 16)	13 (12, 14)	15 (14, 17)	14 (13, 15)
BMI, mean kg/m²	91	27 (26, 27)	27 (27, 27)	29 (28, 29)	29 (29, 30)
WHO-5					
≤28	230	25 (20, 29)	21 (17, 24)	29 (24, 35)	23 (20, 26)
29–50	230	22 (18, 27)	21 (17, 24)	22 (17, 27)	23 (20, 26)
>50	230	53 (48, 58)	58 (54, 62)	48 (42, 55)	54 (50, 57)
WOMAC total, mean	685	38 (35, 40)	37 (35, 39)	44 (41, 46)	38 (37, 40)
WOMAC stiffness, mean	320	45 (42, 47)	41 (39, 43)	48 (45, 50)	42 (40, 44)
WOMAC pain, mean	496	39 (36, 41)	37 (35, 39)	43 (41, 46)	39 (37, 40)
WOMAC function, mean	321	35 (33, 37)	35 (33, 37)	43 (40, 46)	37 (35, 38)
Bilateral OA	1,765	–	54 (48, 60)	56 (49, 63)	60 (56, 64)
Concomitant RA†	0	17 (13, 21)	8 (6, 11)	9 (5, 13)	7 (5, 9)
Worsening symptoms in last 2 years	132	58 (53, 63)	54 (50, 58)	61 (55, 67)	54 (51, 57)
Impact on work life	358	49 (44, 54)	43 (39, 48)	50 (43, 56)	49 (46, 52)
Impact on personal life	117	67 (63, 72)	71 (67, 75)	75 (70, 81)	72 (69, 75)

* Values are percentages unless stated otherwise (95% confidence intervals for both means and percentages are in parentheses). POA = polyarthritic osteoarthritis; OA = osteoarthritis; BMI = body mass index; WHO-5 = World Health Organization–5 Well-Being Index; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; RA = rheumatoid arthritis.
† Claims data diagnosis of International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, German Modification code M05/M06.

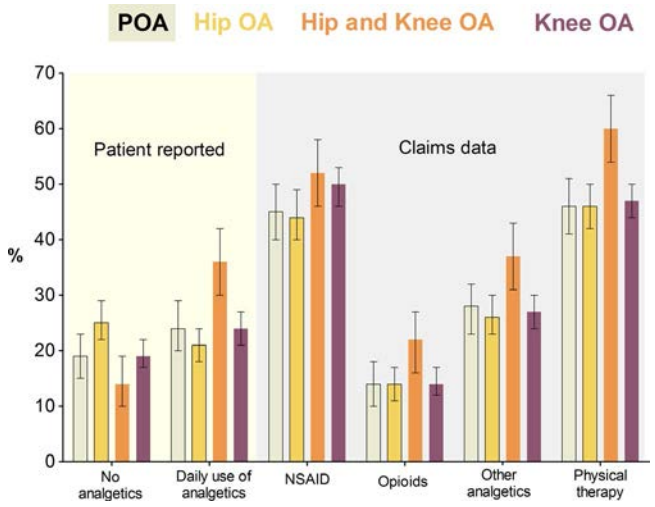

Figure 2. Patient-reported use and claims data prescriptions of analgesics and physical therapy. POA = polyarthritic osteoarthritis; OA = osteoarthritis; NSAID = nonsteroidal antirheumatic drug.

age in the 4 groups was 66–69 years. The proportion of women varied from 63% in hip OA to 83% in POA. The mean symptom duration varied between 13 and 15 years, the mean BMI was 27 kg/m² for POA and hip OA and 29 kg/m² for knee OA with or without hip OA. The frequency of obesity (BMI >30 kg/m²) was 25% in patients ages 70–79 years and between 34% and 38% in patients ages 30–69 years. Signs of at least mild depression (WHO-5 ≤50) were most frequently present in concomitant hip and knee OA patients (52%) compared to 42% to 47% in the other groups. There were no sex differences for depressive symptoms. Patients ages 40–49 and 50–59 years showed signs of moderate-to-severe depression most often (29% and 34% versus 19–26% in the other age groups).

WOMAC total mean values were highest in patients with OA of the hip and knee (mean 44), compared to 37 and 38 in the other groups. The WOMAC subcategories of stiffness, pain, and function were similarly distributed. More than half of the patients with hip and knee OA were affected bilaterally, and the WOMAC values in bilateral involvement were significantly higher when compared with unilateral involvement. In the POA group, 17% of patients also had a claims data diagnosis of rheumatoid arthritis (RA) compared to 8% in hip OA, 7% in knee OA, and 9% in hip and knee OA. Patients with hip and knee OA most frequently reported an impact on their personal life (75%). The proportion of patients who reported an impact on their work life did not differ much between the groups (43–50%).

Dispensation of analgesics was also highest in the group with concomitant hip and knee OA, with 36% of the patients reporting daily use of analgesics compared to 21–24% in the other groups,

Table 2. WOMAC values with 95% confidence intervals*

Variable	POA (n = 758)	Hip OA (n = 959)	Hip/knee OA (n = 399)	Knee OA (n = 1,448)
Age, years				
30–39	29 (25, 34)	32 (28, 36)	44 (33, 56)	28 (24, 32)
40–49	32 (28, 35)	35 (31, 39)	46 (39, 54)	36 (33, 39)
50–59	35 (32, 39)	41 (38, 44)	47 (42, 52)	42 (39, 45)
60–69	38 (34, 43)	36 (33, 40)	45 (40, 49)	36 (33, 39)
70–79	39 (35, 44)	36 (32, 40)	42 (39, 46)	39 (36, 42)
Sex				
Female	38 (35, 41)	37 (34, 40)	45 (41, 48)	40 (38, 42)
Male	35 (32, 38)	37 (34, 39)	41 (37, 44)	36 (34, 38)
BMI, kg/m²				
>30	40 (36, 44)	43 (39, 46)	47 (43, 51)	45 (43, 47)
≤30	37 (34, 40)	36 (33, 38)	42 (39, 46)	34 (32, 36)
WHO-5				
≤28	50 (46, 55)	54 (50, 57)	59 (55, 62)	54 (51, 57)
29–50	46 (43, 50)	41 (37, 44)	48 (44, 53)	44 (42, 47)
>50	28 (25, 31)	30 (28, 33)	32 (29, 35)	30 (28, 32)
Analgesics prescription†				
Opioid	54 (50, 59)	49 (45, 53)	54 (50, 58)	52 (49, 56)
No opioid	35 (32, 37)	35 (33, 37)	41 (38, 44)	36 (35, 38)
NSAID	42 (38, 45)	40 (37, 43)	47 (44, 50)	42 (40, 44)
No NSAID	34 (31, 38)	35 (32, 38)	39 (35, 43)	35 (33, 38)
Other analgesics	44 (40, 49)	45 (41, 49)	48 (44, 52)	46 (43, 49)
No other analgesics	35 (33, 38)	34 (32, 36)	41 (38, 44)	35 (34, 37)
Affected joints				
Bilateral OA	–	45 (42, 48)	51 (48, 54)	45 (43, 47)
Unilateral OA	–	38 (35, 42)	38 (33, 42)	36 (33, 38)
Total	38 (35, 40)	37 (35, 39)	44 (41, 46)	38 (37, 40)

* WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; POA = polyarthritic osteoarthritis; OA = osteoarthritis; BMI = body mass index; WHO-5 = World Health Organization–5 Well-Being Index; NSAID = nonsteroidal antiinflammatory drug.
† Values derived from claims data.

Table 3. Results of 4 separate multiple linear regression models and 95% confidence intervals with WOMAC score as the dependent variable*

Parameter	Reference	WOMAC dependent variable			
		POA	Hip OA	Hip and knee OA	Knee OA
Model 1:					
Age	Per 10 years	0.8 (−0.5, 2.1)	−0.4 (−2.1, 1.3)	2.6 (0.4, 4.8)	−1.7 (−4.2, 0.9)
Male	Female	−3.5 (−6.2, −0.8)	−1.0 (−4.5, 2.5)	−2.9 (−7.0, 1.3)	−3.9 (−8.9, 1.0)
Model 2: BMI, kg/m²†	Per 5 units	4.8 (3.6, 6.0)	4.0 (2.1, 5.9)	4.1 (1.9, 6.4)	3.7 (1.4, 6.1)
Model 3: symptom duration†	Per 10 years	3.4 (2.1, 4.6)	4.0 (2.6, 5.3)	2.2 (0.0, 4.4)	3.3 (1.6, 5.0)
Model 4: WHO-5 (range 0–100)†	Per 10% worsening	4.6 (4.1, 5.1)	4.5 (3.8, 5.1)	4.2 (3.3, 5.0)	4.8 (3.9, 5.7)

* WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; POA = polyarthritic osteoarthritis; OA = osteoarthritis; BMI = body mass index; WHO-5 = World Health Organization–5 Well-Being Index.
† Model adjusted for age and sex.

and 22% of patients with an opioid prescription in hip and knee OA, compared to 14% in the other groups (Figure 2). NSAIDs were prescribed for 45% of patients (with POA) to 52% (with hip and knee OA). Medication prescription rates did not differ substantially between the POA, hip OA, and knee OA groups. Patients who reported no use of analgesics had much lower prescription rates of physical therapy (22% in POA, 27% in hip OA, 48% in hip and knee OA, and 31% in knee OA). The mean WOMAC values of those patients ranged from 21 to 25.

Factors associated with the WOMAC. To identify particularly severely affected groups, the WOMAC was evaluated separately by age group, sex, symptom duration, BMI, WHO-5 category, use of opioids, NSAID, or other analgesics, and unilateral or bilateral involvement (Table 2). Older patients tended to have a higher WOMAC score, with the exception of concomitant hip and knee OA. In POA, hip and knee OA, and knee OA, women had slightly higher values. Overweight patients with a BMI >30 kg/m² had higher WOMAC values than patients with a BMI ≤30 kg/m². Patients who reported moderate-to-severe depressive symptoms (WHO-5 ≤28) had much higher WOMAC values in all OA groups than patients without depressive symptoms (54 versus 30 in hip OA, 54 versus 30 in knee OA). Across all groups, patients with pain medication prescriptions (opioids, NSAIDs, or other analgesics) had higher mean WOMAC values than patients without prescriptions. This difference was especially pronounced for opioid prescriptions (54 versus 35 in POA, 49 versus 35 in hip OA, 54 versus 41 in hip and knee OA, and 52 versus 36 in knee OA). Patients with bilateral involvement had higher WOMAC values than patients with unilateral disease (45 versus 38 in hip OA, 51 versus 38 in hip and knee OA, and 45 versus 36 in knee OA).

Multiple linear regression models. In multiple linear regression models, age was only associated with WOMAC scores for hip and knee OA (Table 3), while sex was only associated with WOMAC scores for POA. BMI was associated in all OA groups, with an increase of the WOMAC score of 4.8 (95% confidence interval [95% CI] 3.6, 6.0) for POA, 4.0 (95% CI 2.1, 5.9) for hip OA, 4.1 (95% CI 1.9, 6.4) for hip and knee OA, and 3.7 (95% CI 1.4, 6.1) for knee OA, per 5-unit increase of the BMI. Longer

Table 4. Differences between patients with unilateral and bilateral involvement*

Variable	Hip OA		Hip and knee OA		Knee OA	
	Bilateral (n = 289)	Unilateral (n = 670)	Bilateral (n = 178)	Unilateral (n = 221)	Bilateral (n = 597)	Unilateral (n = 851)
Age, mean years	64 (63, 66)	68 (67, 68)	67 (66, 69)	70 (69, 71)	64 (64, 65)	66 (66, 67)
Female	58 (51, 64)	65 (62, 68)	71 (64, 78)	74 (69, 79)	70 (67, 73)	66 (64, 69)
WHO-5						
≤28	31 (23, 38)	18 (14, 21)	37 (28, 46)	25 (17, 32)	28 (23, 32)	20 (16, 23)
29–50	25 (18, 32)	20 (15, 24)	21 (13, 28)	23 (16, 30)	26 (21, 31)	21 (18, 25)
>50	45 (37, 52)	63 (58, 68)	42 (33, 52)	52 (44, 60)	46 (41, 51)	59 (55, 63)
WOMAC total, mean	45 (42, 48)	34 (31, 36)	51 (48, 54)	39 (35, 42)	45 (43, 47)	33 (31, 36)
Daily intake of analgesics	30 (23, 37)	18 (14, 22)	46 (37, 56)	30 (23, 37)	28 (23, 32)	22 (18, 25)
NSAID prescription†	41 (34, 49)	45 (41, 50)	58 (48, 67)	49 (41, 57)	53 (48, 58)	47 (43, 51)
Opioid prescription†	22 (15, 29)	12 (9, 14)	25 (17, 34)	19 (13, 26)	15 (12, 19)	14 (11, 17)
Other analgesics prescription	32 (24, 39)	25 (20, 29)	30 (21, 39)	41 (34, 49)	30 (25, 35)	25 (21, 29)
Physical therapy prescription	48 (41, 56)	45 (41, 50)	61 (51, 70)	59 (52, 67)	49 (44, 54)	46 (42, 50)

* Values are percentages unless stated otherwise (95% confidence intervals for both means and percentages are in parentheses). For patients with hip and knee osteoarthritis (OA), both knees or both hips had to be symptomatic to be counted as affected bilaterally. WHO-5 = World Health Organization–5 Well-Being Index; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; NSAID = nonsteroidal antiinflammatory drug.
† Derived from claims data.

symptom duration was also associated with higher WOMAC values for all groups. A worsening of 10% in the WHO-5 was associated with higher WOMAC values, with coefficients ranging from 4.2 (95% CI 3.3, 5.0) for hip and knee OA to 4.8 (95% CI 3.9, 5.7) for knee OA.

Comparison of patients with unilateral or bilateral involvement of the hip or knee. Patients with unilateral hip OA, knee OA, or hip and knee OA were compared to those with bilateral OA on the respective joints (Table 4). Among the groups with bilateral involvement, patients were slightly younger. More patients in the bilaterally affected groups showed signs of moderate to severe depression (hip OA: 31% bilateral versus 18% unilateral; hip and knee: 37% bilateral versus 25% unilateral; knee OA: 28% bilateral versus 20% unilateral). There were more patients with daily intake of analgesics, opioids, and other analgesics in the bilateral groups. The difference in opioid prescription was especially high in hip OA; 22% in the bilateral group versus 12% in the unilateral group were prescribed opioids. The proportion of patients with a prescription of NSAIDs and physical therapy did not differ substantially.

Comparison of patients with and without concomitant POA. For the 3 groups of hip OA, hip and knee OA, and knee OA, the patients with an additional claims diagnosis of POA were compared to those without POA (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24058/abstract). Patients with POA were 1–5 years older, and there were more women in this group. Depressive symptoms were more prominent, and medication intake was higher in the groups with concomitant POA. Prescription rates of physical therapy were higher for patients with hip OA and POA than for patients with hip OA alone. For hip and knee and knee OA, these rates stayed roughly the same.

Subgroup analyses for patients with symptomatic OA. All analyses were repeated using only those patients who reported current (during the last 7 days) or chronic (for ≥3 months during the last 2 years) symptoms in the joints corresponding to the claims diagnosis. Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24058/abstract, shows how many patients remained in the analysis groups. Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24058/abstract, shows the characteristics of these patients. No substantial changes in the analyses occurred if patients without current or chronic symptoms were excluded. The overall WOMAC score somewhat increased, but the differences between the OA manifestations remained.

DISCUSSION

The disease burden of OA was investigated in a random sample of patients with OA from a statutory health insurance database. The unique combination of survey data with claims data in the PROCLAIR study allowed us to analyze patient-reported outcomes with the background knowledge of all prescribed medications and physical therapy.

The study has yielded several results. Self-reported outcomes on disease burden differed, depending on the joint manifestation. Patients with concomitant hip and knee OA, bilateral hip or knee OA, and patients with hip or knee OA in addition to concomitant POA reported the greatest impairment on all WOMAC subscales, as well as the greatest impact on work and personal life. Pain in joints other than the target joint has been reported to be associated with worse outcomes on pain and function, which is plausible (13). However, WOMAC values are frequently used preoperatively to evaluate a single knee or hip joint status, for example in the surgeons' recommendation for TJR (14,15). When cut points for treatment recommendations are discussed (16) or when WOMAC values are individually evaluated, our results show that all affected joints need to be considered.

The high disease burden in concomitant hip and knee OA is also reflected in a higher analgesics use. Dispensed prescriptions of analgesics in the claims data that were linked to patient-reported OA symptoms in the PROCLAIR study add to the knowledge on analgesics use in OA. Previous studies such as the Osteoarthritis Initiative have investigated self-reported analgesics use with the "brown bag" method (patients bring in all prescriptions) or performed telephone interviews (17). Overall use of NSAIDs and opioids in our claims records was higher compared to international data (18–20). Our data reveal a higher use of NSAIDs, opioids, and other analgesics in patients with concomitant hip and knee OA. We do not know the reason for opioid prescription, but for all OA groups, OA burden was highest for those with an opioid prescription, suggesting that patients most affected are prescribed opioids. In the context of current research on the comparative effectiveness of opioids and NSAIDs, the rate of opioid prescriptions will hopefully decline in the future. The findings of a systematic review and meta-analysis as well as the results of the SPACE pragmatic trial (21) suggest that NSAIDs offer similar levels of pain relief in OA (22) as opioids.

Up to 25% of the patients reported not using any analgesics. More than half of these patients stated that they did not want to take any medication, and the remainder stated that they did not need pain medication. Patient education might help to ensure that all patients who would likely benefit from medications have access to them.

Nonpharmacologic treatment for the management of OA is strongly recommended by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (4), and exercise education has been shown to be effective in hip and knee OA (23,24). However, deficits in the use of exercise, weight management, and other behavioral and rehabilitation strategies as well as the overuse of opioid analgesics have been recognized (25). Prescription rates of physical therapy

are quite low in this study (46–60%) and suggest that there is room for improvement concerning the use of physical therapy in the treatment of OA in Germany. Even lower prescription numbers have been reported from US claims data (20% physical therapy and <3% massage therapy) (26), but overall there are few data on the frequency of physical therapy in OA. A separate analysis in the PROCLAIR project also showed that only half of the patients with hip or knee OA were prescribed physical therapy in the year before joint replacement surgery (27).

Patients with POA had less pain medication and lower WOMAC values than patients with knee or hip OA. Nearly every fifth patient in this group also had a claims diagnosis of RA. This finding of a lower disease burden of POA or hand involvement caused by OA or RA is in accordance with the findings of Chua et al (28). They showed that OA patients had a similar burden as RA patients regarding pain as well as physical function, measured by the Health Assessment Questionnaire and by WOMAC in retrospectively reviewing several cohorts over time. However, WOMAC does not ask for specific impairment caused by finger or hand involvement.

Risk factors for disease burden in OA were described as personal risk factors (age, sex, obesity, genetics, diet) and joint-level risk factors by Palazzo et al (29). Of these factors, data on age, sex, and obesity were available in this study. While age was only associated with OA burden measured by the WOMAC for POA in this study, BMI as a measure for obesity was associated with higher WOMAC scores for all OA groups. Obesity is known as a modifiable risk factor for OA (30) and for functional limitation as well (31). Patients with knee OA show a significantly higher prevalence of obesity when compared with patients who have hip OA. Although a dose-response relationship between BMI and risk of hip OA exists (32), obesity is a more important risk factor for the development of knee OA (30,33). Higher levels of depressive symptoms according to WHO-5 were also associated with WOMAC scores in all groups. The association between depression and disease burden was also shown by Sharma et al (34) in a systematic literature review. Other reports indicate that comorbidity is also associated with pain and functional outcomes (35,36) and therefore needs to be accounted for.

The results of our study need to be viewed in the context of understanding that patients who sent back the survey were likely to be affected more severely than patients not responding (the prescription rate of NSAIDs and physical therapy was higher in responders). This nonresponse bias probably led to worse outcomes in the reported data. Approximately 30% of the patients reported no current or chronic symptoms. We did a subgroup analysis using only data from the patients who reported symptoms, and the results did not differ substantially. Given the fluctuating character of OA symptoms, this finding indicates that the claims diagnosis alone is useful to identify patients with OA.

This was a cross-sectional analysis. We therefore could not investigate any trends in time. Patients were selected based on 2 reported claims diagnoses of OA and in a subgroup analysis by patient-reported symptoms in the corresponding joints. A clinical diagnosis or radiographic grade of OA were not available. How patients with concomitant hip and knee OA are handled with respect to ICD-10 diagnoses is not clear. The description of the ICD-10-GM M15 code for POA is suitable for this group. Because there are substantial numbers of patients with concomitant diagnoses of hip and knee OA who have no POA diagnosis, coding these types of OA separately seems to be more common.

To our knowledge, this is the first study investigating disease burden of OA including unselected OA patients in Germany. The combination of claims and self-reported data ensured that there was no recall bias for medication or physical therapy and added patient-reported information to the comprehensive claims data.

The evaluation of disease burden in OA with instruments such as the WOMAC depends on the patterns of joint manifestation as well as on comorbid obesity and depressive symptoms. In OA management, the patients need to be viewed holistically, even if a single joint is the focus of care. The range of nonpharmacologic and medical therapeutic options should be used, paying greater attention to physical therapy options.

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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. Callhoff 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. Callhoff, Albrecht, Lange, Goronzy, Günther, Zink, Schmitt, Postler.

Acquisition of data. Callhoff, Albrecht, Redeker, Saam.

Analysis and interpretation of data. Callhoff, Albrecht, Redeker, Lange, Goronzy, Günther, Zink, Schmitt, Saam, Postler.

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RHEUMATOLOGY REGISTRIES, BIG DATA, AND THE RHEUMATIC DISEASES

Education, Home Exercise, and Supervised Exercise for People With Hip and Knee Osteoarthritis As Part of a Nationwide Implementation Program: Data From the Better Management of Patients With Osteoarthritis Registry

Andrea Dell'Isola,[1] Thérése Jönsson,[2] Jonas Ranstam,[1] Leif E. Dahlberg,[1] and Eva Ekvall Hansson[1]

Objective. To compare the effectiveness of education (ED) plus home exercise (HE) and ED plus supervised exercise (SE) according to information provided by the Better Management of Patients With Osteoarthritis (BOA) Registry, a nationally implemented rehabilitation program for patients with hip and knee osteoarthritis (OA). In addition, we investigated whether or not the effect of the treatments differed based on the joint affected by OA (hip versus knee).

Methods. We included 38,030 participants from the BOA Registry with knee or hip OA who were treated with either ED, HE, or SE. The effect of the 3 treatment options on the pain intensity reduction (range 0–10) immediately postintervention and at 12 months was estimated using a mixed-effects model adjusted for age, sex, body mass index, affected joint (hip or knee), pain at baseline, comorbidity, and level of education.

Results. The participants undergoing HE or SE experienced a greater pain reduction compared to participants who received ED, both after the treatment (group mean change for ED –0.91 [95% confidence interval (95% CI) –1.15, –0.68], for HE –1.06 [95% CI –1.10, –1.01], and for SE –1.12 [95% CI –1.15, –1.08]) and at 12 months (group mean change for ED –0.58 [95% CI –0.87, –0.30], for HE –0.82 [95% CI –0.87, –0.76], and for SE –0.82 [95% CI –0.86, –0.77]). Patients with knee OA who underwent HE or SE improved more compared to patients with hip OA at both follow-ups.

Conclusion. In primary care, HE and SE lead to similar reductions in pain intensity but are more effective than ED alone. In addition, people with knee OA benefit more from HE and SE than people with hip OA.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, affecting >40 million people across Europe, and it is the fastest growing cause of disability worldwide, driven by an increasingly older population and the growing incidence of obesity and sports-related injuries (1,2). Numerous randomized controlled trials (RCTs) have shown that education (ED) and exercise are effective in reducing pain in people with OA (3,4). However, their implementation in clinical practice is scarce, with only 36% of people with OA estimated to receive nonpharmacologic care according to guidelines (5). So far, few studies have analyzed the effectiveness of these nonpharmacologic interventions when delivered nationwide in clinical settings, with little evidence for the effect of home exercise (HE) when compared to supervised exercise (SE) (6). Understanding the effect that these modes of exercise delivery have on pain will help in the development of more effective programs targeting the rising burden of OA.

The Better Management of Patients With Osteoarthritis (BOA) Registry was initiated in Sweden in 2008 to offer evidence-based information and individually adapted exercise to all people with OA (7). As part of the BOA program, all participants receive ED, including information regarding OA pathogenesis and management. After receiving ED, participants have the option to undergo

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SIGNIFICANCE & INNOVATIONS

- Home exercise (HE) and education (ED) are as effective as ED and supervised exercise (SE) in reducing pain severity for people with hip or knee osteoarthritis (OA) when provided nationwide in a clinical context (primary care level).
- People with knee OA experienced clinically significant reduction in pain intensity up to 1 year after undergoing self-management intervention, including HE or SE, as opposed to people with hip OA.

a face-to-face session with a physical therapist (PT). During the session, an individually adapted exercise program is discussed, and detailed information on how to exercise independently is provided. In addition, participants are offered the option of carrying out their exercise program in a group under the supervision of a PT twice a week for 6–8 weeks.

The aim of this study was to compare the effectiveness of ED alone, HE therapy, and SE according to information provided the BOA Registry, a nationally implemented rehabilitation program for people with hip and knee OA. In addition, we investigated whether or not the treatments differ based on the joint affected by OA (hip versus knee).

MATERIALS AND METHODS

This was an observational, registry-based study. Data from the BOA Registry from 2008 to 2016 were used. People with knee or hip symptoms that resulted in contact with the health care system and a clinical diagnosis of OA by a PT or a medical doctor are eligible for the program. Clinical diagnosis is based on clinical history and examination as recommended by the National Board of Health and Welfare in Sweden (8). Radiographic evidence of OA is not required according to international guidelines and, therefore, is not part of the eligibility criteria (9). Enrollment in the program is voluntary, as is the choice of the treatment options provided. All the people taking part in BOA attend 2 mandatory, theory-based group sessions led by a trained PT. The first session focuses on the pathology and etiology of OA and recommended treatments according to international guidelines. The second session concerns the role of exercise in OA and focuses on the benefit of exercise, barriers to exercise, strategies to incorporate exercise into daily life, and self-management strategies to reduce pain and other OA symptoms (7). Between 1 and 3 weeks after receiving ED, all the participants are offered the option to take part in a noncompulsory, 1-on-1 session with a PT, who designs a personalized neuromuscular exercise program. The aim of the program is to increase muscle strength and improve the dynamic control of hip–knee–ankle alignment according to OA clinical guidelines and to the person's specific needs and goals (10,11). During this session, the participants are instructed on how to perform the program independently and how to manage pain during exercise using a tolerable pain model (12). In addition to the main exercise program, the participants learn 1 or 2 exercises to be incorporated in their everyday life and are encouraged to practice them a few minutes every day. Finally, participants can decide to perform their exercise program under the supervision of a PT in 12 group sessions for the duration of 1 hour. Further details on the BOA program can be found elsewhere (7).

Patients who participated in BOA received 1 of the following 3 treatment alternatives: ED alone; ED plus a face-to-face session with a PT in which a personalized exercise program is designed and tried out plus HE; or ED plus a face-to-face session with a PT in which a personalized exercise program is designed and tried out plus up to 12 group sessions of SE that were supervised by a PT. BOA participants answered validated and patient-relevant sociodemographic and outcome questionnaires after the interventions (2–5 months) and at 1 year (12–15 months) (13). A 3-month window for follow-ups was allowed for pragmatic reasons to ensure that all the participants were able to attend the follow-ups.

For the current analysis, we selected participants with knee or hip OA and outcomes available at baseline and at least 1 of the follow-ups (after treatment and at 12 months). In case more than 1 joint was reported as affected by OA, only the joint with the most severe symptoms was considered for the analysis. A reduction in the Numerical Rating Scale (NRS) measuring the average pain in the previous week on a scale from 0–10 (0 = no pain, 10 = maximum pain) was used to assess the effectiveness of the treatments. A relative reduction of 15% on the NRS was used to determine a minimum clinically important difference (MCID). This cutoff was previously validated against the patient global impression of change (PGIC) categories in a sample of people with OA and other chronic rheumatic conditions ($r = –0.823$ for Spearman's correlation coefficient between relative pain reduction and PGIC categories) and indicates participants who felt slightly better after the intervention (sensitivity 89.6%, specificity 80.1%) (14). We decided to use the relative change because it has been shown to be a more stable indicator of MCIDs when compared to absolute change, which is more influenced by the baseline values (15). This study was approved by the regional ethics review board in Gothenburg (1059–16).

Statistical analysis. A random coefficient model was fitted to the data, including a random intercept term and a fixed slope term for the participants and fixed intercept and slope terms for follow-up time (baseline, after treatment, and after 12 months), joint (hip or knee), and treatment (ED, HE, or SE). The covariance structure was set to first-order autoregressive. Treatment × time and joint × time interaction terms were assessed in 2 separate models to identify possible differences in pain reduction at follow-ups between participants undergoing the different treatments offered in BOA and participants with hip or knee OA. Potential confounders were selected based on theoretically driven direct pathways shared with the exposure (treatment) and the outcome (pain) (16).

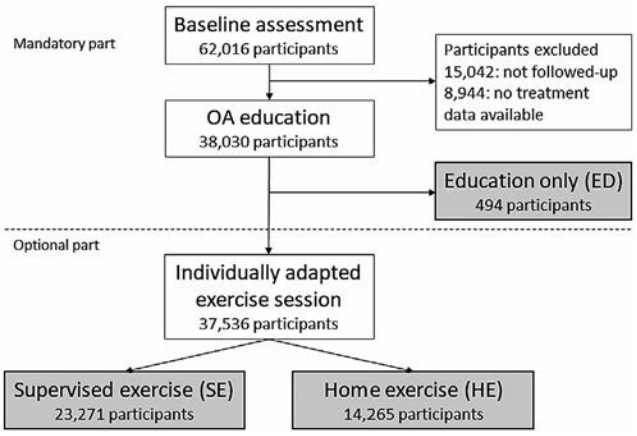

Figure 1. Study flowchart. The 3 shaded boxes represent the different treatment groups included in the Better Management of Patients With Osteoarthritis Registry and analyzed in the current study. OA = osteoarthritis.

The models included adjustments for differences in age, sex, body mass index, affected joint (hip or knee), pain at baseline, Charnley comorbidity score (where A = only the index joint is affected by OA; B = bilateral OA; and C = other factors/comorbidities influence the gait), and level of education (mandatory education, high school, or university or higher). Follow-up analysis comparing the 95% confidence interval (95% CI) of the estimated means was performed to evaluate the clinical significance of group differences. Results are presented as absolute values and percentages; negative values indicate reductions of pain intensity on the NRS from baseline to follow-up. Finally, we performed a sensitivity analysis including only participants who attended ≥10 supervised sessions (>80% of the provided sessions) in order to estimate the influence of treatment adherence on the outcome of SE. All the analyses were performed using SPSS Statistics, version 25.

RESULTS

Of the 62,016 people with knee or hip OA who participated in the BOA program between 2008 and 2016, a total of 15,042 were not followed up in the selected time span or were not yet followed up (Figure 1). For 8,944 participants, it was not possible to identify which treatment was received. Finally, a total of 38,030 BOA participants had knee or hip OA and outcomes available at baseline and at least 1 of the follow-ups (mean baseline pain 5.39 [95% CI 5.33, 5.44]) and were included in the study (Tables 1 and 2). The excluded participants had a level of NRS pain of mean ± SD 5.42 ± 1.99 and demographic characteristics similar to the participants included in the study (Table 1). Of the included participants, 11,981 had hip OA and 26,049 had knee OA. Of the 494 who received ED, 165 (33.4%) had hip OA and 329 (66.6%) had knee OA. Of the 14,265 participants who underwent HE, 4,624 (32.4%) had hip OA and 9,641 had knee OA (67.6%). Finally, of the 23,271 participants who underwent SE, a total of 7,192 (30.9%) had hip OA and 16,079 (69.1%) had knee OA. Among the participants who underwent SE, a total of 51.5% attended at least 10 of the 12 exercise sessions (51.5% knee OA, 50.9% hip OA).

Regardless of the treatment option selected, people who took part in BOA showed an overall reduction in pain intensity after the intervention (–1.03 [95% CI –1.11, –0.95]) and at 12 months (–0.74 [95% CI –0.84, –0.64]) (Table 3). However, the reduction was clinically significant only immediately after the treatment (–19% [95% CI –21, –18]) but not at 12 months (–14% [95% CI –17, –12]) (see Supplementary Table 1, available on the *Arthritis Care &*

Table 1. Participants' characteristics at baseline for different treatment groups*

Characteristic	Excluded participants (n = 23,986)	All participants (n = 38,030)	ED (n = 494)	HE (n = 14,265)	SE (23,271)
Age, mean ± SD years	65.6 ± 10.1	66.5 ± 9.2	66.1 ± 9.3	65.5 ± 9.7	67.0 ± 8.9
Sex†					
Women	15,917 (66.4)	26,323 (69.2)	290 (58.7)	9,306 (65.2)	16,727 (71.9)
Men	8,069 (33.6)	11,707 (30.8)	204 (41.3)	4,959 (34.8)	6,544 (28.1)
BMI, mean ± SD kg/m^2	28.3 ± 5.2	28.0 ± 4.8	28.6 ± 4.9	27.8 ± 4.9	28 ± 4.7
Education level					
Mandatory education	8,171 (34.1)	12,751 (33.7)	165 (33.7)	4,657 (32.8)	7,929 (34.2)
High school	9,251 (38.6)	14,099 (37.2)	198 (40.4)	5,485 (38.6)	8,416 (36.3)
University or higher	6,435 (26.8)	11,042 (29.1)	127 (25.9)	4,071 (28.6)	6,844 (29.5)
Charnley comorbidity score					
A‡	9,219 (38.4)	14,803 (38.9)	219 (44.3)	6,078 (42.6)	8,506 (36.6)
B§	3,767 (15.7)	6,419 (16.9)	90 (18.2)	2,355 (16.5)	3,974 (17.1)
C¶	11,000 (45.9)	16,808 (44.2)	185 (37.4)	5,832 (40.9)	10,791 (46.4)
Compliance with exercise therapy					
1 to 6 sessions	–	–	–	–	6,739 (29)
7 to 9 sessions	–	–	–	–	4,550 (19.6)
>10 sessions	–	–	–	–	11,982 (51.5)

* Values are no. (%) unless indicated otherwise. ED = education; HE = home exercise; SE = supervised exercise; BMI = body mass index.
† Percentage calculated within group.
‡ Only 1 joint involved.
§ Bilateral osteoarthritis.
¶ Factors/comorbidities other than osteoarthritis that may be an obstacle to locomotion.

Table 2. Mean pain estimates in the different treatment groups at baseline after treatment and at 12-month follow-up*

Joint treatment groups	Baseline	After treatment	12-month follow-up
Overall			
All participants (n = 38,030)	5.39 (5.32, 5.46)	4.36 (4.29, 4.43)	4.65 (4.58, 4.73)
ED (n = 494)	5.50 (5.30, 5.69)	4.58 (4.39, 4.77)	4.91 (4.69, 5.14)
HE (n = 14,265)	5.32 (5.29, 5.36)	4.26 (4.23, 4.30)	4.51 (4.47, 4.55)
SE (n = 23,271)	5.35 (5.32, 5.38)	4.23 (4.20, 4.27)	4.54 (4.50, 4.57)
Hip			
All participants (n = 11,981)	5.43 (5.37, 5.50)	4.59 (4.52, 4.65)	4.94 (4.87, 5.00)
ED (n = 165)	5.63 (5.30, 5.96)	4.79 (4.46, 5.12)	5.13 (4.74, 5.51)
HE (n = 4,624)	5.36 (5.29, 5.42)	4.54 (4.47, 4.60)	4.88 (4.80, 4.95)
SE (n = 7,192)	5.33 (5.28, 5.39)	4.47 (4.42, 4.52)	4.82 (4.76, 4.88)
Knee			
All participants (n = 26,049)	5.34 (5.28, 5.40)	4.13 (4.07, 4.19)	4.39 (4.33, 4.45)
ED (n = 329)	5.34 (5.11, 5.58)	4.39 (4.15, 4.63)	4.72 (4.45, 5.00)
HE (n = 9,641)	5.22 (5.18, 5.27)	4.05 (4.00, 4.09)	4.25 (4.20, 4.30)
SE (n = 16,079)	5.27 (5.23, 5.30)	4.04 (4.00, 4.07)	4.32 (4.28, 4.36)

* Values are estimated marginal means (95% confidence interval) adjusted for age, sex, body mass index, affected joint, pain at baseline, comorbidity, and level of education. ED = education; HE = home exercise; SE = supervised exercise.

Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24033/abstract). We found no clinical and statistical difference in pain at baseline between the treatment groups. Participants from all the 3 treatment groups improved after the intervention (ED –0.91 [95% CI –1.15, –0.68]; HE –1.06 [95% CI –1.10, –1.01]; SE –1.12 [95% CI –1.15, –1.08]) and at 12 months (ED –0.58 [95% CI –0.87, –0.30]; HE –0.82 [95% CI –0.87, –0.76]; SE –0.82 [95% CI –0.86, –0.77]) (Table 3). Participants who underwent ED improved less at both follow-ups when compared to participants who underwent HE and SE. Even though this difference was not clinically significant, only participants undergoing HE and SE had a reduction in the pain intensity that approached clinical significance at 12 months (pain reduction for both HE and SE –15% [95% CI –16, –14]) (see Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24033/abstract).

Both hip and knee OA participants showed a statistically significant improvement after the treatment and at the 12-month follow-up (see Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24033/abstract). However, only knee OA participants reached a clinically significant pain reduction at both follow-ups (after the treatment –23% [95% CI –23, –22]; 12 months –18 [95 CI –18, –17]). In a secondary analysis stratified by joint, we did not find any statistical and clinically significant difference in pain intensity in hip OA participants undergoing the different treatment options at either follow-up. In contrast, participants with knee OA undergoing HE or SE showed a statistically significantly lower level of pain at both follow-ups when compared to participants who underwent ED only. In addition, participants with knee OA undergoing HE or SE, but not the ones undergoing ED, showed a clinically significant reduction in the pain intensity

Table 3. Joint pain difference at baseline immediately after treatment and at 12 months after the BOA program, stratified by affected joint and treatment group*

	All participants	ED	HE	SE
Total sample†				
Baseline (ref.)	5.39 (5.32, 5.46)	5.50 (5.30, 5.69)	5.32 (5.29, 5.36)	5.35 (5.32, 5.38)
Difference at baseline				
After treatment	–1.03 (–1.11, –0.95)	–0.91 (–1.15, –0.68)	–1.06 (–1.10, –1.01)	–1.12 (–1.15, –1.08)
12-month follow-up	–0.74 (–0.84, –0.64)	–0.58 (–0.87, –0.30)	–0.82 (–0.87, –0.76)	–0.82 (–0.86, –0.77)
Hip OA‡				
Baseline (ref.)	5.43 (5.37, 5.50)	5.63 (5.30, 5.96)	5.36 (5.29, 5.42)	5.33 (5.28, 5.39)
Difference at baseline				
After treatment	–0.85 (–0.89, –0.80)	–0.84 (–1.25, –0.43)	–0.82 (–0.90, –0.74)	–0.86 (–0.92, –0.80)
12-month follow-up	–0.50 (–0.56, –0.44)	–0.50 (–1.00, –0.20)	–0.48 (–0.57, –0.38)	–0.51 (–0.59, –0.44)
Knee OA‡				
Baseline (ref.)	5.34 (5.28, 5.40)	5.34 (5.11, 5.58)	5.22 (5.18, 5.27)	5.27 (5.23, 5.30)
Difference at baseline				
After treatment	–1.21 (–1.24, –1.17)	–0.95 (–1.25, –0.66)	–1.18 (–1.23, –1.12)	–1.23 (–1.27, 1.19)
12-month follow-up	–0.95 (–0.99, –0.91)	–0.62 (–0.98, –0.26)	–0.97 (–1.03, –0.90)	–0.95 (–1.00, –0.90)

* Values are mean (95% confidence interval). BOA = Better Management of Patients With Osteoarthritis program; ED = education; HE = home exercise; SE = supervised exercise; ref. = reference; OA = osteoarthritis.
† Analysis adjusted for baseline pain, body mass index, age, sex, level of education, comorbidities, and affected joint.
‡ Analysis adjusted for baseline pain, body mass index, age, sex, level of education, and comorbidities.

after the treatment (HE and SE –23% [95% CI –24, –21]), which was maintained at 12 months (HE and SE –18% [95% CI –19, –17]) (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24033/abstract).

The results of the sensitivity analysis highlight a trend toward an increased effectiveness of SE over HE with the participants undertaking at least 10 SE sessions, but not the ones performing HE, experiencing a clinically significant pain reduction after the treatment (–1.18 [95% CI –1.22, –1.14]; –22% [95% CI –23, –21]) that was maintained at 12 months (–0.86 [95% CI –0.91, –0.81]; –16% [95 CI –17, –15]). Despite this, the difference between the 2 treatments was not statistically significant. The tendency toward a larger pain intensity reduction was observed also in the analysis stratified by joint; however, no change in the clinical or statistical significance of the results was observed when compared to the main analysis.

DISCUSSION

This is the first study to analyze the effectiveness of ED, HE, and SE in more than 30,000 participants who received intervention in primary care settings as part of a large pragmatic implementation program. Overall, people who took part in BOA experienced a reduction in the level of pain both after the intervention and at 1 year. However, participants who were treated with a personalized exercise program and received detailed information on how to exercise experienced a larger reduction of pain compared to participants who underwent ED alone, regardless of whether the exercises were supervised or unsupervised. In addition, knee OA participants benefited more from the program in showing clinically significant reductions of pain both after treatment and after 12 months when undergoing exercise (either HE or SE).

Even though the number of ED-based and exercise-based implementation programs is growing, few studies have been published that analyze the effectiveness of these interventions when provided in a pragmatic clinical context (6,17). A similar self-management program providing ED plus SE conducted in Denmark (GLA:D) showed greater, but comparable, pain reduction 12 months after intervention (pain reduction 12.0 mm on a visual analog scale of 0–100 mm; 95% CI 10.8, 13.2) (6). As suggested by the sensitivity analysis, this difference may be partially explained by the higher adherence reported in GLA:D, where more than 80% of the participants attended at least 10 of the 12 SE sessions.

The lower adherence observed in BOA may also explain the impossibility of identifying a difference in pain reduction in participants undergoing HE and SE in contrast with previous RCTs showing that SE is more effective in reducing pain in people with knee OA (18,19). In fact, exercise-based programs, including at least 12 supervised sessions, showed a larger effect size for pain compared to studies providing less than 12 sessions (3,20). However, even though the effect size for pain of supervised group-based exercise has been repeatedly shown to be larger than the one for HE, a recent Cochrane review showed that the effect sizes of the 2 modes of treatment delivery were not statistically or clinically different despite the slight superiority of SE (3,18,21). Our sensitivity analysis confirms these findings and shows a trend toward greater pain reduction in participants who attended at least 10 SE sessions when compared to participants who underwent HE.

It is important to notice that the magnitude of pain reduction at 12 months for BOA participants performing HE was significantly higher than the one reported in a previous RCT that compared HE and SE, where people with knee OA received a single session of ED before performing the HE program (19). A possible explanation for this difference may reside in patient preference for a specific treatment, which has been shown to have the potential to enhance the treatment outcome (22). The fact that BOA participants could choose to undertake the HE program rather than being assigned to that specific treatment option may have enhanced the treatment outcome (23). However, due to the lack of measurement of participant adherence to the HE program, it is not possible to comment on whether participants' preference may have increased compliance with HE. In addition, this effect should be present across all 3 treatment options. Finally, it must be considered that BOA participants may have sought additional care for their OA symptoms, which may have enhanced the effectiveness of the treatment. However, we were unable to account for this effect due to the lack of information regarding additional treatments received. Rather than a limitation, this can be considered an advantage of registry-based studies, which are able to assess the overall effect of an intervention (despite being unable to establish cause and effect links) while offering a more accurate estimation of the effect of a certain intervention when provided nationwide in a clinical context.

Even though the superiority of one mode of delivery over the other is unclear, the results from this study suggest that including the option to undertake an HE program as part of a self-management nonsurgical intervention is a valuable alternative for people who are unable or not willing to participate in SE and may lead to clinically significant pain reduction, especially in participants with knee OA. Ultimately, considering these results, the choice between HE and SE should be agreed upon with the participant and based on individual preference, with information regarding the effectiveness of the different modalities being part of the decision process (24). Alternative delivery modalities, such us web- or app-based interventions, should be explored and may serve as an important tool to further increase engagement with exercise, especially for people with limited access to services (25–27). Additionally, certain person- and disease-specific factors may be linked to a better response to a specific treatment modality. Several knee OA phenotypes based on different disease mechanisms have been suggested; however, evidence linking clinical

phenotype to nonpharmacologic treatment response is still scarce (28–31).

For this study, a reduction of 15% in the level of pain was considered clinically significant. This threshold has been previously validated against the PGIC measure and indicates participants who felt slightly better (14). According to the same study, a reduction of 33% in pain is required for people to feel much better. People with knee OA undergoing HE or SE in a clinical context, therefore, can be expected to feel slightly better immediately after and at 1 year following the intervention. On the other hand, people with hip OA or people undergoing only ED, despite improving, may not perceive their pain reduction as significant. However, it is important to consider that the benefit of exercise extends beyond its analgesic effect, and people with OA should be encouraged to remain active and take part in structured exercise programs when available (32). The lack of physical function measurements in the BOA Registry, therefore, may have led to an underestimation of the benefit of exercise.

The current study identified differences in treatment response depending on the joint affected by OA, with participants who had knee OA experiencing greater improvements, as shown in previous studies that investigated the effectiveness of ED and exercise-based interventions (3,4,6). In addition, a previous RCT could not identify benefit in pain reduction for people with hip OA undergoing SE and ED compared to people who received ED only, which supports our findings (33). Despite this, it is not yet clear why people with hip OA seem to benefit less from ED and exercise-based interventions. Differences in disease mechanisms and joint mechanics may play a role. Finally, it needs to be considered that the body of evidence used to develop guidelines and recommendations for exercise and ED in OA comes largely from studies on knee OA. Further studies focusing on the management of hip OA may provide the evidence necessary to develop more joint-specific interventions.

Analyzing the trend in pain reduction at the different follow-ups, it is possible to see a reduction in the benefit of the intervention over time, confirming the results of previous studies (34). One of the main factors believed to be responsible for the decline in long-term pain reduction is the decrease in compliance and adherence to treatment (35). Several barriers influencing exercise behavior have been identified, suggesting a complex interaction between internal and external factors, which may ultimately influence the effect of the intervention (35,36). Booster sessions have been suggested as an effective tool to mitigate the reduction in the long-term effects of exercise programs and should be considered as part of self-management programs for OA to further improve long-term effectiveness (34).

A few limitations need to be discussed. First, the clinical significance of the pain reduction shown in this cohort was based on a previously validated cutoff, but the use of different cutoffs may lead to different results. Interpretation of the clinical significance of the pain reduction suggested by this study requires caution. Second, this study used registry data collected in clinical practice where patients were not randomized and could choose a preferred treatment. Therefore, the results are likely to be influenced by the differences in treatment protocols and data collection that characterize clinical environments when compared to clinical trials. However, the inclusion of a large pragmatic sample from a nationwide implementation program increases the external validity of the study and supports the generalizability of the results. In addition, the presence of a group of participants who received minimal intervention (ED only) suggests that the additional benefit experienced by participants to HE and SE is likely due to the treatments rather than a physiologic fluctuation of pain or regression to the mean.

In conclusion, people with OA who underwent supervised or unsupervised exercise experienced greater pain reduction than people who received ED alone, with those who had knee OA experiencing a greater benefit. People who are not willing or cannot undergo an SE program may experience similar benefit from an HE program. However, assuming optimal adherence, SE may lead to better outcomes that extend beyond pain reduction.

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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. Dell'Isola 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. Dell'Isola, Jönsson, Ranstam, Dahlberg, Ekvall Hansson.

Analysis and interpretation of data. Dell'Isola, Jönsson, Ranstam.

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RHEUMATOLOGY REGISTRIES, BIG DATA, AND THE RHEUMATIC DISEASES

Impact of the Affordable Care Act Medicaid Expansion on Access to Care and Hospitalization Charges for Lupus Patients

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Objective. To examine the impact of the Affordable Care Act on preventable hospitalizations and associated charges for patients living with systemic lupus erythematosus, before and after Medicaid expansion.

Methods. A retrospective, quasi-experimental study, using an interrupted time series research design, was conducted to analyze data for 8 states from the Healthcare Cost and Utilization Project state inpatient databases. Lupus hospitalizations with a principal diagnosis of predetermined ambulatory-care sensitive (ACS) conditions were the unit of primary analysis. The primary outcome variable was access to care measured by preventable hospitalizations caused by an ACS condition.

Results. There were 204,150 lupus hospitalizations in the final analysis, with the majority (53.5%) of lupus hospitalizations in states that did not expand Medicaid. In unadjusted analysis, Medicaid expansion states had significantly lower odds of having preventable lupus hospitalizations (odds ratio [OR] 0.958); however, after adjusting for several covariates, Medicaid expansion states had increased odds of having preventable lupus hospitalizations (OR 1.302). Adjusted analysis showed that those individuals with increased age, public insurance (Medicare or Medicaid), no health insurance, rural residence, or low income had significantly higher odds of having a preventable lupus hospitalization. States that expanded Medicaid had $523 significantly more charges than states that did not expand Medicaid. Older age and rural residence were associated with significantly higher charges.

Conclusion. Our findings suggest that while Medicaid expansion increased health insurance coverage, it did not address other issues related to access to care that could reduce the number of preventable hospitalizations.

INTRODUCTION

Vulnerable populations, particularly individuals living with a chronic illness like systemic lupus erythematosus (SLE) or lupus, may face barriers gaining access to primary care services (1–3). SLE is a chronic illness with a varied spectrum of disease activity, damage, and flares unique to each individual living with the disease. Diagnosing SLE in a timely manner is often difficult because of complex clinical symptoms and disease manifestations that often mimic those of other serious health conditions (4,5). Approximately 322,000 individuals may have lupus in the US (6). Minorities and women carry the greatest burden of SLE, and African American women have a higher prevalence of SLE compared to white women (7–9). SLE is typically diagnosed in women during the childbearing stage of life, between puberty and menopause (8,10). Primary care providers have the ability to detect SLE and refer patients to specialty care. However, individuals living with SLE who do not have access to primary or specialty care may be at risk for delayed diagnosis and treatment of SLE, erroneous diagnoses, ineffective medication regimens, increased risk of complications and damage, and increased utilization of emergency health care services (11,12). Individuals living with chronic

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SIGNIFICANCE & INNOVATIONS

- While a handful of studies have investigated the impact of Medicaid expansion on health care access and utilization, no studies have examined the impact on hospitalization charges for lupus patient care.
- Medicaid expansion states had a higher likelihood of having preventable lupus hospitalizations when compared with nonexpansion states.
- Trends suggest that Medicaid expansion may be reducing hospitalization charges in those states with Medicaid expansion.
- Our findings suggest that while Medicaid expansion increased health insurance coverage, it did not address other barriers to care, which may include communication and trust, transportation, and socioeconomic status.

conditions must have adequate access to primary care and specialty care to reduce the burden of the disease on not only the patient but also the health care system.

The Patient Protection and Affordable Care Act of 2010, commonly referred to as the Affordable Care Act (ACA) or Obamacare, aimed to increase access to primary care, improve quality of care, and decrease health care costs. Under the ACA, Medicaid expansion across all 50 states sought to provide low-income individuals, particularly those individuals without children, better health coverage. However, some states chose not to expand Medicaid, which could have impacted access to primary care and patient outcomes, especially for those individuals living with chronic illnesses (13,14). The purpose of this study was to investigate whether Medicaid expansion, enacted by the ACA, improved access to care or lowered hospital charges for patients living with SLE.

SUBJECTS AND METHODS

Study design. The ACA's Medicaid expansion allowed for a retrospective, quasi-experimental study using an interrupted time series (ITS) research design to evaluate health policy. An ITS research design compares trends over time and examines differences in pre- and postintervention outcome measures. The design allows for some sort of change or intervention to separate time periods and compare the effect of the intervention; this technique is increasingly used in the evaluation of health care interventions such as health care policies and programs (15). The intervention, or "interruption," was the change in health policy, which was the implementation of Medicaid expansion under the ACA, effective January 1, 2014.

We compared 4 states that expanded Medicaid on January 1, 2014 with 4 states that did not expand Medicaid. We examined 8 quarterly preintervention time points over 2 years (January 1, 2012 to December 31, 2013) and 7 postintervention time points over 2 years (January 1, 2014 to September 30, 2015). In 2015, fourth-quarter hospital admissions, October through December, were not used due to the transition from International Classification of Diseases, Ninth Revision, (ICD-9) to Tenth Revision (ICD-10) codes.

Data sources. Data from the Agency for Health Research and Quality's Healthcare Cost and Utilization Project (HCUP) state inpatient database (SID) were used for analysis. SID provided administrative hospital data, patient demographics, ICD-9 diagnoses codes, total charges, length of stay, and expected payment source for all hospital inpatient stays in community hospitals, which included academic medical centers and tertiary care hospitals, in each state (16). We used 2012–2015 HCUP SID administrative data to measure access to primary care both before (2012–2013) and after (2014–2015) ACA Medicaid expansion. South Carolina 2015 data did not include costs. Data from HCUP SID were not linked to individual patient data, and the states were defined as the unit of analysis.

Study sample. The sample consisted of hospitalizations across 8 states. The states used in this analysis included 4 states that expanded Medicaid under the ACA on January 1, 2014: Arizona, Kentucky, New Jersey, and New York. These states were compared to 4 states that did not expand Medicaid under the ACA: Florida, Georgia, South Carolina, and Wisconsin. Inclusion criteria included the following characteristics: all payers, patients ages 20–64 years, all races, and all lupus hospitalizations.

Definition of Medicaid expansion. States that expanded Medicaid under the ACA increased their Medicaid income eligibility limits, which is measured by the Federal poverty level, to 138% of the Federal poverty level. However, on average, states that did not expand Medicaid chose to have lower Medicaid income eligibility limits (Figure 1) (17). States' Medicaid income eligibility for parents before and after Medicaid expansion are available in Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24080/abstract.

Definition of SLE cases. Lupus hospitalizations were defined as a hospitalization with an ICD-9 code of 710.0 for the discharge diagnosis. The ICD-9 code 710.0 was listed as the primary discharge diagnosis or in a subsequent discharge diagnosis field (e.g., Dx1, Dx2, Dx3, etc.). Within this cohort of lupus hospitalizations, preventable lupus hospitalizations were defined as a lupus hospitalization that had an ambulatory-care sensitive (ACS) condition (e.g., asthma, cellulitis, diabetes mellitus, etc.) as the primary discharge diagnosis. Appropriate dis-

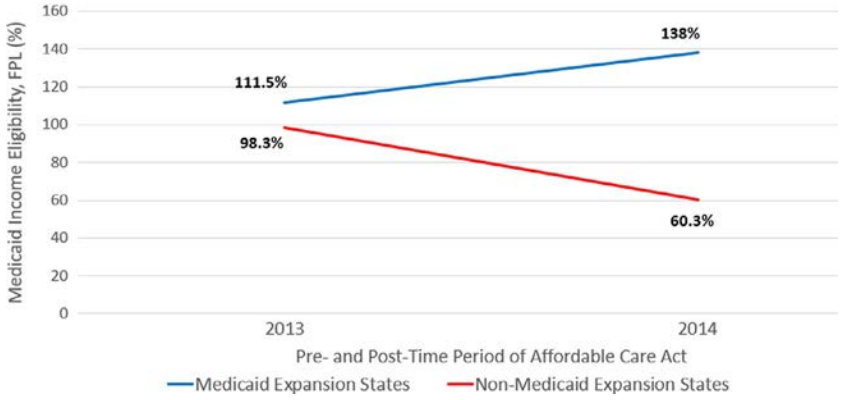

Figure 1. Mean Medicaid income eligibility for parents, by state Medicaid expansion status, 2013 versus 2014. This figure only includes data from states used in this analysis: Medicaid expansion states (Arizona, Kentucky, New Jersey, New York) and non-Medicaid expansion states (Florida, Georgia, South Carolina, Wisconsin). FPL = Federal poverty level.

charge diagnoses for lupus and ACS conditions were identified with ICD-9 codes.

Definition of preventable lupus hospitalization. Preventable hospitalizations were defined as a lupus hospitalization with an ACS condition as the principal discharge diagnosis. These specific hospitalizations were used to measure access to primary care. Theoretically, ACS conditions are illnesses or diagnoses that, with proper primary care, do not need hospitalizations if the disease is appropriately managed in the community setting (18). The use of ACS conditions is a validated method to measure access to primary care (19). Previous studies have used similar ACS conditions from a 1992 study on avoidable hospitalizations (20) and a 2010 SLE access to care study (11) for data analysis (Table 1).

Dependent variables. The primary dependent variable was the likelihood of a preventable hospitalization for adults hospitalized with lupus, ages 20–64 years, from January 2012 to September 2015, for selected states. Lupus hospitalizations with a principal diagnosis of a predetermined ACS condition were considered for analysis.

Table 1. Ambulatory-care sensitive (ACS) conditions and ICD-9 codes*

ACS conditions	Codes
Ruptured appendix	540.0, 540.1
Asthma	493
Cellulitis	681, 682
Congestive heart failure	428, 402.01, 402.11, 402.91
Diabetes mellitus	250.1, 250.2, 250.3, 251.0
Gangrene	785.4
Hypokalemia	276.8
Malignant hypertension	401.0, 402.0, 403.0, 404.0, 405.0, 437.2
Pneumonia	481, 482, 483, 485, 486
Pyelonephritis	590.0, 590.1, 590.8
Perforated or bleeding ulcer	531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.1, 533.2, 533.4, 533.5, 533.6

* ICD-9 = International Classification of Diseases, Ninth Revision.

The secondary dependent variable was diagnosis-related group (DRG) standardized charges, following the methodology of Cartmell et al (2018) (21). Based on the year of the discharge, the total charge was adjusted to a March 2019 dollar value using the US Department of Labor Bureau of Labor Statistics inflation calculator (22). Due to the varying profit margin inherent in hospital inpatient charges, we standardized charges based on the associated DRG, using the median charge for each DRG across all hospitals and states. To examine the association of Medicaid expansion with DRG standardized charges, we estimated a generalized linear model with gamma distribution and log link, based on the distribution of the charges.

Statistical analysis. Descriptive statistics compared differences in demographic variables between hospitalizations in states that expanded Medicaid and states that did not expand Medicaid. First, associations were tested between Medicaid expansion status (Medicaid expansion versus non-Medicaid expansion), patient demographics, and hospitalization type (preventable versus non-preventable) in bivariate logistic regression analyses. Chi-square tests were used to determine significance of associations between categorical variables. For continuous variables, 2-sample *t*-tests were conducted to test the equality of difference in means between the 2 cohorts.

A segmented regression analysis model was used to assess the impact Medicaid expansion had on the likelihood of having a preventable hospitalization. This segmented regression analysis (a form of ITS analysis) included a dummy variable specifying 2 segments: the time period before January 1, 2014 when the policy intervention was implemented, and the time period after January 1, 2014 (23). We included interaction of this dummy variable with time to define and test separate intercepts and slopes before and after the intervention. The unadjusted model accounted for change over time (quarterly data from January 1, 2012 to September 30,

2015), Medicaid expansion (time after January 1, 2014), and an interaction term between the 2 variables (time before and time after Medicaid expansion).

Covariates were entered into the model separately to determine the effect on the dependent outcome. After fitting the best model, results were provided for the adjusted model. Because states were chosen purposefully (not at random), to control for state to state variability, the model was used as a fixed effect, with Florida as the reference state, since Florida had the highest proportion of hospitalizations. We used SAS software, version 9.4, to complete all data analysis.

Ethics review. The Institutional Review Board at the Medical University of South Carolina deemed this research to not be human subject research (ID: Pro00037013) since we used de-identified public-use data. The appropriate individuals completed the HCUP data use agreement online training.

RESULTS

There were 204,150 lupus hospitalizations across the 8 states over 15 quarters, with approximately 53% of lupus hospitalizations occurring in the 4 states that did not expand Medicaid. States that did not expand Medicaid had significantly more lupus hospitalizations with the following characteristics: minority (52.50% versus 47.50%), male (52.73% versus 47.27%), rural residence (60.09% versus 39.91%), and preventable lupus hospitalizations (54.34% versus 45.66%) (Table 2). Both cohorts (Medicaid expansion states and non-Medicaid expansion states) saw more hospitalizations for patients ages 45–54 years and on Medicare (Table 2). Over time, states that did not expand Medicaid had a higher number of preventable lupus hospitalizations (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24080/abstract).

Preventable hospitalizations. From 2012 to 2015, the most prevalent ACS conditions were pneumonia, congestive heart failure, and cellulitis (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24080/abstract). The data illustrating all ACS conditions at each quarter are available in Supplementary Appendix 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24080/abstract. In the base model examining change over time, the probability of having a preventable lupus hospitalization was not significantly different over time (odds ratio [OR] 1.004 [95% confidence interval (95% CI) 0.996, 1.013]) (Table 3). After states' Medicaid expansion statuses were added to the base model, the cohort of Medicaid expansion states had significantly lower odds

Table 2. Demographic variables by Medicaid expansion status, 2012–2015, patients ages 20–64 years*

Demographic variables (n = 204,150)†	Non-Medicaid expansion states (n = 109,121)	Medicaid expansion states (n = 95,029)	*P*
Minority race	52,257 (52.50)	47,283 (47.50)	<0.0001
Male	12,029 (52.73)	10,783 (47.27)	0.0205
Age, years			<0.0001
20–34	19,229 (23.76)	16,800 (24.04)	–
35–44	18,002 (22.24)	14,960 (21.41)	–
45–54	22,789 (28.15)	19,422 (27.80)	–
55–64	20,924 (25.85)	18,693 (26.75)	–
Primary payer			<0.0001
Private insurance	23,829 (22.06)	25,862 (27.38)	–
Medicaid	20,884 (19.33)	21,432 (22.69)	–
Medicare	54,327 (50.28)	42,935 (45.45)	–
Uninsured	5,575 (5.16)	2,633 (2.79)	–
Other‡	3,426 (3.17)	1,604 (1.70)	–
Median household income§			<0.0001
Quartile 1 (<$42,000)	45,585 (43.53)	26,788 (29.39)	–
Quartile 2 (<$52,000)	31,068 (29.67)	18,447 (20.24)	–
Quartile 3 (<$68,000)	20,034 (19.13)	19,025 (20.87)	–
Quartile 4 ($68,000+)	8,032 (7.67)	26,895 (29.50)	–
Rural residence	3,252 (60.09)	2,160 (39.91)	<0.0001
Preventable hospitalizations¶	12,697 (54.34)	10,670 (45.66)	0.0039

* Values are the number (%) unless indicated otherwise. All *P* values were significant.
† Chi-square tests were conducted for categorical variables and *t*-tests were conducted for continuous variables. Each sample is all nonmissing data.
‡ Includes Worker's Compensation, Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), Civilian Health and Medical Program of the Uniformed Services (CHAMPVA), Title V, and other government programs.
§ Median household income quartiles changed each year from 2012 to 2015. See website for more information: https://www.hcup-us.ahrq.gov/db/vars/zipinc_qrtl/nisnote.jsp.
¶ Measure of access to care.

Table 3. Unadjusted model, with odds ratios for preventable lupus hospitalizations*

Characteristic	Value
Quarters (change over time)	1.004 (0.996, 1.013)
Medicaid expansion status	
Did not expand	Ref.
Did expand	0.958 (0.932, 0.985)†
Race/ethnicity	
White	Ref.
Nonwhite	0.998 (0.962, 1.016)
Sex	
Male	Ref.
Female	0.948 (0.908, 0.989)†
Age, years	
20–34	Ref.
35–44	1.256 (1.194, 1.321)†
45–54	1.405 (1.340, 1.473)†
55–64	1.444 (1.377, 1.514)†
Primary payer	
Private insurance	Ref.
Medicaid	1.197 (1.147, 1.249)†
Medicare	1.364 (1.316, 1.413)†
Uninsured	1.304 (1.213, 1.403)†
Other‡	0.999 (0.905, 1.103)
Median household income	
Quartile 1 (<$42,000)	1.121 (1.076, 1.167)†
Quartile 2 (<$52,000)	1.034 (0.990, 1.080)
Quartile 3 (<$68,000)	1.006 (0.960, 1.054)
Quartile 4 ($68,000+)	Ref.
Residence	
Urban	Ref.
Rural	1.287 (1.190, 1.391)†
State§	
Florida	Ref.
Georgia	1.173 (1.123, 1.226)†
South Carolina	1.160 (1.092, 1.233)†
Wisconsin	0.997 (0.928, 1.070)
Arizona	1.029 (0.975, 1.087)
Kentucky	1.124 (1.054, 1.199)†
New Jersey	1.169 (1.115, 1.227)†
New York	0.919 (0.884, 0.956)†

* Values are the odds ratio (95% confidence interval). Each covariate was entered in the base model separately. Ref. = reference (see Table 2 for other definitions).
† Significant.
‡ Includes Worker's Compensation, CHAMPUS, CHAMPVA, Title V, and other government programs.
§ The first 4 states listed did not expand Medicaid.

of having a preventable lupus hospitalization (OR 0.958 [95% CI 0.932, 0.985]). When the following covariates were added to the base model one at a time, they were associated with significantly increased odds of a preventable lupus hospitalization: increased age, public health insurance (Medicare or Medicaid), uninsured status, low income (<$42,000), and rural residence (Table 3). Race was the only covariate that was not statistically significant and was not considered in the final model.

In the final adjusted model, Medicaid expansion states had significantly higher odds of having preventable lupus hospitalizations (OR 1.302 [95% CI 1.119, 1.515]) (Table 4). A jackknife sensitivity analysis, where we removed each state one by one, showed Medicaid expansion states still had significantly higher odds of having preventable hospitalizations (OR 1.263 [95% CI 1.085, 1.471]) (see Supplementary Appendix 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24080/abstract). Individuals ages 55–64 years had 49% increased odds of a preventable lupus hospitalization compared to those ages 20–34 years. Those on Medicaid and the uninsured had 30% and 33% increased odds of having a preventable lupus hospitalization, respectively. Individuals in the lowest median household income quartile had a 1.14 times higher likelihood of a preventable lupus hospitalization compared to those in the highest median household income quartile. Additionally, being in Georgia (OR 1.171) or South Carolina (OR 1.114) (compared to Florida) was associated with a higher likelihood of having a preventable lupus hospitalization. Nevertheless, states that expanded Medicaid each had significantly lower odds of preventable lupus hospitalizations, when individually compared to Florida (Table 4).

Table 4. Adjusted model, with odds ratios for preventable lupus hospitalizations*

Characteristic	Value
Medicaid expansion status	
Did not expand	Ref.
Did expand	1.302 (1.119, 1.515)†
Sex	
Male	Ref.
Female	0.930 (0.882, 0.980)†
Age, years	
20–34	Ref.
35–44	1.273 (1.208, 1.341)†
45–54	1.430 (1.362, 1.501)†
55–64	1.488 (1.415, 1.564)†
Primary payer	
Private insurance	Ref.
Medicaid	1.298 (1.238, 1.361)†
Medicare	1.206 (1.156, 1.259)†
Uninsured	1.334 (1.235, 1.442)†
Other‡	0.962 (0.862, 1.074)
Median household income	
Quartile 1 (<$42,000)	1.138 (1.077, 1.202)†
Quartile 2 (<$52,000)	1.062 (1.002, 1.125)†
Quartile 3 (<$68,000)	1.000 (0.943, 1.061)
Quartile 4 ($68,000+)	Ref.
Residence	
Urban	Ref.
Rural	1.142 (1.032, 1.263)†
State§	
Florida	Ref.
Georgia	1.171 (1.111, 1.233)†
South Carolina	1.114 (1.027, 1.208)†
Arizona	0.793 (0.675, 0.932)†
Kentucky	0.788 (0.688, 0.929)†
New Jersey	0.960 (0.818, 1.128)
New York	0.679 (0.580, 0.796)†

* Values are the odds ratio (95% confidence interval). Each covariate was entered in the base model separately. Ref. = reference (see Table 2 for other definitions).
† Significant.
‡ Includes Worker's Compensation, CHAMPUS, CHAMPVA, Title V, and other government programs.
§ The first 4 states listed did not expand Medicaid.

Table 5. Adjusted model, DRG, and inflation-adjusted charges for preventable lupus hospitalizations*

Characteristic	Value
Medicaid expansion status	
Did not expand	Ref.
Did expand	523 (96, 950)†
Sex	
Male	Ref.
Female	–6,370 (–7,123, –5,616)†
Age, years	
20–34	Ref.
35–44	1,023 (453, 1,592)†
45–54	3,299 (2,737, 3,860)†
55–64	7,277 (6,652, 7,902)†
Primary payer	
Private insurance	Ref.
Medicaid	–3,105 (–3,669, –2,541)†
Medicare	1,361 (1,156, 1,259)†
Uninsured	–4,751 (–5,575, –3,928)†
Other‡	–511 (–1823, 799)
Median household income	
Quartile 1 (<$42,000)	–447 (–1,106, 210)
Quartile 2 (<$52,000)	–676 (–1,356, 3)
Quartile 3 (<$68,000)	–325 (–1,021, 371)
Quartile 4 ($68,000+)	Ref.
Residence	
Urban	Ref.
Rural	2,183 (807, 3,560)†
State§	
Florida	Ref.
Georgia	2,424 (1,579, 3,269)†
South Carolina	1,988 (1,129, 2,848)†
Wisconsin	3,017 (1,933, 4,100)†
Arizona	2,424 (1,579, 3,269)†
Kentucky	1,546 (563, 2,529)†
New Jersey	–1,032 (–1,791, –273)†
New York	376 (–227, 980)

* Values are the adjusted charge in dollars (95% confidence interval). Each covariate was entered in the base model separately. DRG = diagnosis-related group; Ref. = reference (see Table 2 for other definitions).
† Significant at $P < 0.05$.
‡ Includes Worker's Compensation, CHAMPUS, CHAMPVA, Title V, and other government programs.
§ The first 4 states listed did not expand Medicaid.

DRG standardized charges. States that expanded Medicaid had $523 significantly more DRG standardized charges than states that did not expand Medicaid. The following individual-level characteristics were associated with significantly higher DRG standardized charges in the adjusted model: ages 55–64 years ($7,277), ages 45–64 years ($3,299), and individuals from rural areas ($2,183) (Table 5). Female sex (–$6,370), the uninsured (–$4,751), and those on Medicaid (–$3,105) had significantly lower DRG standardized charges. When states were compared to Florida, which had the most preventable lupus hospitalizations, Wisconsin (non-Medicaid expansion state), Georgia (non-Medicaid expansion state), and Arizona (Medicaid expansion states) had significantly higher DRG standardized charges.

DISCUSSION

The probability of having a preventable lupus hospitalization did not change over time; however, once accounting for various covariates, including time, Medicaid expansion states had a higher likelihood of having preventable lupus hospitalizations when compared with nonexpansion states. In adjusted models, the following characteristics were associated with higher odds of a preventable lupus hospitalization: older age, public health insurance (Medicare and Medicaid), no insurance, low income, and rural residence. These findings are consistent with existing evidence that avoidable hospitalizations occur more often among older and poorer patients, suggesting that these patients have more difficulty accessing care (24).

According to Gillis et al (2007) (2), patients with SLE who have Medicaid, an insurance program for individuals with less income, may have limited access to care. In their study, they noted SLE patients with Medicaid were more likely to travel greater distances for specialized care and more likely to use general practitioners and emergency rooms more frequently than those with Medicare or other insurance. Thus, low-income individuals with SLE appear to have several issues related to access to quality care, including distance to quality care and limited specialized care in their local communities. Another study assessed the need for improved access to rheumatology care in Massachusetts. Feldman et al (2013) (3) surveyed community health center medical directors to determine the limitations in clinics and systems for patients with rheumatic diseases, including SLE. Alarmingly, the study showed that approximately 94% of respondents would not begin an immunosuppressive regimen for patients with SLE. This fact may have been due to their limited expertise in rheumatology or fear of prescribing erroneous medication or dosages. One of the key findings was the fact that many patients with SLE may not be put on the proper medications due to inexperience of local primary care physicians, which could negatively affect disease flares and disease progression.

In the current study, states that expanded Medicaid all had lower odds of having preventable lupus hospitalizations compared with Florida, which did not expand Medicaid. When states were combined into 1 cohort based on their Medicaid expansion status (e.g., expansion states), Medicaid expansion states' aggregated data showed higher odds of preventable lupus hospitalizations. However, when states were examined separately, all Medicaid expansion states had lower odds of having preventable lupus hospitalizations (compared to Florida), and the non-Medicaid expansion states, particularly South Carolina and Georgia, had increased odds of having preventable lupus hospitalizations compared to Florida. This finding may illustrate how well Medicaid expansion health care policy is faring for lupus patients in each individual state, or it could be measuring different state policies in the Medicaid expansion group. Ideally, Medicaid expansion increased the number of individuals eligible for health insurance for adults without children and more low-income adults. This

increase in coverage may have impacted access to care in Medicaid expansion states and may equate to lower odds of preventable lupus hospitalizations. Specifically, if individuals gain health insurance coverage and access to appropriate health care services, they have a better opportunity to work with their health care provider to treat, manage, and control various health conditions and should not be hospitalized for ACS conditions (e.g., asthma, diabetes mellitus, etc.) that can be treated in the ambulatory care setting (18). However, this fact does not explain why aggregate state data show Medicaid expansion states have higher odds of preventable lupus hospitalizations.

Aggregate state data for Medicaid expansion states may reflect other issues in accessing appropriate health care services. The Medicaid expansion cohort may have increased odds of preventable lupus hospitalizations due to issues and certain characteristics within the US health care system. For example, in Medicaid expansion states, adults may attain health care insurance (coverage) but may not get appropriate and timely primary care (access). A health insurance card does not lead to immediate access to health care (25). An insurance card does not create convenient office hours, does not guarantee transportation to a medical provider, and does not address the unique needs of each individual patient (25). Adults may face barriers with transportation, communication and trust, medication affordability, language/cultural barriers, and a host of other social determinants of health that cannot be measured in certain data sets (26).

Additionally, adults with hourly employment may not have the luxury to take time from work or may not have childcare, and the emergency department has some of the most convenient hours of operation compared to other providers in the ambulatory care setting. For example, many physician offices are closed on the weekends and close by 5 p.m. during the week. These barriers to health care access could influence the likelihood of being hospitalized for an ACS condition. Thus, while Medicaid expansion gave adults an insurance card (health care coverage), the policy did not address communication and trust between patient and provider (health care access). The policy did not create more convenient health care office hours. Last, the policy did not provide all adults with adequate or personal transportation to travel to physician appointments. As more individuals gain insurance under the ACA and find a usual source of care or primary care doctor, they may be less likely to have a preventable hospitalization. We may need more time to see individuals find and develop more trusting relationships with primary care providers before we see a significant decrease in the number of preventable hospitalizations (27).

With regard to DRG standardized charges, we observed higher charges in nonexpansion states (with the exception of Arizona, which was a Medicaid expansion state with higher charges), relative to Florida. These trends suggest that Medicaid expansion may be reducing charges in those states with Medicaid expansion. Variations in charges according to sociodemographic characteristics such as age and sex could be attributed to a number of factors. Older lupus patients may be sicker, which could lead to more charges. Individuals from rural areas tend to delay care, which could make them sicker and lead to more charges. Additionally, females are generally more proactive in their care, and thus may not present as being as sick as males (1,12).

This study had several limitations, including possible administrative errors with ICD-9 codes. There was also the inability to measure unobserved differences in populations across the different states, including the differences in Medicaid enrollment and marketing strategies and patient care-seeking behaviors. Lupus prevalence or severity was not accounted for in the analysis. Segmented regression analysis generally calls for 12 data points before and after the intervention, but this study had 8 time points before and 7 time points after the intervention. Finally, findings are limited to the population studied.

This study evaluated ACA Medicaid expansion and its impact on access to care for individuals living with lupus. Our findings emphasize the importance of addressing systemic problems with American health care delivery at multiple levels. Medicaid expansion has increased the rate of health insurance coverage in participating states, but subsequent gains do not appear to have been made in access to care. For SLE patients and other chronic disease–bearing populations, Medicaid coverage alone may not be sufficient to encourage effective use of health care services. Further policy initiatives, interventions, and operational changes will be needed to address access to care as well as associated patient-level factors to provide cost-effective chronic disease management.

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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. Williams 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. Brown, Faith, Williams.

Analysis and interpretation of data. Brown, Dismuke-Greer, Ramakrishnan, Faith, Williams.

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RHEUMATOLOGY REGISTRIES, BIG DATA, AND THE RHEUMATIC DISEASES

Hormonal Dependence and Cancer in Systemic Lupus Erythematosus

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Objective. To estimate the incidence and analyze any cancer-associated factors in patients with systemic lupus erythematosus (SLE), differentiating between hormone-sensitive (HS) and non-HS cancers.

Methods. This was a retrospective multicenter study of a patient cohort from the Systemic Lupus Erythematosus Registry of the Spanish Society of Rheumatology. Included were the first cancer post-SLE diagnosis, clinical and sociodemographic information, cumulative damage, severity, comorbidities, treatments, and refractoriness. Cancers were classified as HS (prostate, breast, endometrium, and ovarian) and non-HS (the remainder). The standardized incidence ratio (SIR) was calculated and logistic regression models were built.

Results. A total of 3,539 patients (90.4% women) were included, 154 of whom had cancer (91% female), and 44 had HS cancer (100% female). The cancer SIR was 1.37 (95% confidence interval [95% CI] 1.15–1.59), with higher values in women age <65 years (SIR 2.38 [95% CI 1.84–2.91]). The SIR in women with HS versus non-HS cancer was 1.02 (95% CI 0.13–1.91) and 1.93 (95% CI 0.98–2.89). In HS versus non-HS cancers, SLE diagnostic age (odds ratio [OR] 1.04 [$P = 0.002$] versus 1.04 [$P = 0.019$]), and period of disease evolution (OR 1.01 [$P < 0.001$] versus 1.00 [$P = 0.029$]) were associated with cancer. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (OR 1.27 [$P = 0.022$]) and angiotensin-converting enzyme (ACE) inhibitor prescriptions (OR 2.87 [$P = 0.048$]) were associated with non-HS cancers.

Conclusion. Cancer incidence in patients with SLE was higher than in the Spanish population, particularly among young women. This increase might be due to non-HS cancers, which would be associated with SLE involving greater cumulative damage where more ACE inhibitors are prescribed.

INTRODUCTION

Cancer is one of the most serious illnesses a person can have, because it affects both the physical and emotional state and can sometimes lead to death. Furthermore, when cancer is diagnosed in a patient with a chronic autoimmune disease such as systemic lupus erythematosus (SLE), with its associated cumulative damage and comorbidities, it presents challenges not only for that patient, but also for the doctors assessing and treating both illnesses. At present, there is insufficient knowl-

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SIGNIFICANCE & INNOVATIONS

- Cancer incidence rate in patients with systemic lupus erythematosus (SLE) is estimated to be higher with regard to the Spanish population.
- Cancer risk was higher in women ages <65 years and those with non–hormone-sensitive cancers.
- SLE diagnostic age and period of disease evolution were common factors associated with both hormone-sensitive and non–hormone-sensitive cancers.
- Angiotensin-converting enzyme inhibitor prescriptions and greater cumulative damage were also associated with non–hormone-sensitive cancers.

edge regarding the immune system alterations that occur in SLE, changes that may influence cancer onset and/or development (1). Several studies carried out in different countries, races, and ethnic groups show that the global cancer incidence in patients with SLE is higher than in the general population (2–7). In particular, the cancer standardized incidence ratio (SIR) is higher across virtually all anatomic locations (hematologic, lung, thyroid, hepatobiliary, vulva-vagina, cervix, and pancreas) (2,3,5,6,8,9). However, different studies have also highlighted a risk reduction in hormone-sensitive (HS) cancers such as breast, endometrial, and ovarian (2–4,10,11). The suggestion has been made that if the metabolism of estrogen or other predominantly female hormones was altered in SLE, that alteration could slow the progression of HS cancers. On the other hand, a nucleolytic lupus autoantibody, anti-5C6, might help prevent DNA repair mechanisms in breast, ovarian, and prostate cancers associated with BRCA2 mutations (12). Therefore, SLE autoantibodies may contribute to a decreased risk of certain HS cancers. Thus, in patients with SLE, there might exist some differences in the cancers in regard to hormonal dependence, although the exact mechanisms linking the immune and endocrine systems to cancer risk are unknown. For this reason, determining whether factors associated with HS cancer differ from those with non-HS cancer would be interesting. Most studies have focused on searching for factors associated with cancer onset in SLE and have grouped all cancer types, whereas other studies have explored factors related to the onset of hematologic, lung, and breast cancer. Yet, to date, no study has explored stratified cancers in relation to hormone-sensitivity. Thus, an analysis comparing HS and non-HS cancers within a multicenter cohort with a large number of patients might expand our understanding in this sense. The purpose of this study was to estimate the cancer incidence in patients with SLE and to analyze factors associated with its onset, differentiating between HS and non-HS cancers.

PATIENTS AND METHODS

Design, scope, and patients. We performed a retrospective observational, longitudinal study of a cohort of the Systemic Lupus Erythematosus Registry of the Spanish Society of Rheumatology (RELESSER). RELESSER includes patients ages >16 years with SLE (according to the revised American College of Rheumatology [ACR] criteria of 1997) (13) from 45 hospitals registered with the Spanish Society of Rheumatology hospital database. At least 80% of patients from each center were included, all of whom had had ≥1 appointment with a rheumatology department at some time since their initial disease diagnosis. Patients whose clinical history did not contain at least 50% of the information deemed essential were excluded. The design, variables, and general characteristics of the RELESSER registry have been published previously (14).

Data collection. Rheumatologists with experience in diagnosing and treating patients with SLE collected the data from each center and then uploaded it via an online software application designed ad hoc for the project. Data quality control was performed via professional online monitoring.

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

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Variables and operational definitions. The main study variable was the first cancer after SLE diagnosis. Endometrial, breast, ovarian, and prostate cancers were classified as HS and the remainder as non-HS. Patient follow-up was defined as the period between the date of SLE diagnosis and the date of the first cancer for those who had cancer, and the RELESSER data collection date (2010–2011) for patients who did not develop cancer. Patients for whom information was unavailable until the data collection date were censored to the date of their last appointment at the rheumatology clinic. Secondary variables included: sociodemographic; general symptoms; cancer location; accumulated SLE symptoms, defined according to ACR diagnostic criteria (13,15) and British Isles Lupus Assessment Group definitions (16); systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score (17,18); damage defined by the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) (19), excluding cancer; the degree of severity (Katz index) (20); comorbidities, hospitalizations, and causes of death; the Charlson comorbidity index, Deyo modified version (21); treatments for comorbidities and SLE control; and refractoriness, as defined for the registry (22).

Statistical analysis. A descriptive analysis was performed using absolute and relative frequencies of qualitative variables, and mean or median and dispersion measures (SD, interquartile range [IQR]) for quantitative variables. The accumulated incidence of cancers in patients included in RELESSER for 2011 was calculated. To estimate the cancer accumulated incidence in the general population, cancer cases in Spain for 2012 were compiled and measured against the overall population according to the 2011 Housing and Population Census (23,24). Both accumulated incidence measures were compared by calculating the SIR. The SIR calculation was made at the same time, differentiating between HS and non-HS cancers, and taking into account the number of cases per cancer type in Spain during 2014 (25). In addition, the prevalence of cancer globally and per anatomic location was estimated. The years between the diagnosis of SLE and the development of the first cancer were also calculated, as well as the mortality rate for each cancer type according to anatomic location. With a view to analyzing the association between cancer onset and the clinical characteristics of patients with SLE, a logistics regression model was built to analyze female patients, differ-

Table 1. Characteristics of patients with SLE, stratified by cancer incidence*

Variables	All (n = 3,539)	Cancer: yes (n = 154)	Cancer: no (n = 3,385)	*P*
Female sex	3,194 (90.4)	140 (90.9)	3,054 (90.4)	0.821
Age at first SLE criterion met, mean ± SD years	32.84 ± 14.4	38.35 ± 16.0	32.72 ± 14.3	<0.001
Age at SLE diagnosis, mean ± SD years	34.85 ± 14.5	40.37 ± 15.7	34.75 ± 14.5	<0.001
Age at last assessment, mean ± SD years	46.52 ± 14.8	57.74 ± 14.4	46.17 ± 14.6	<0.001
Race				
Caucasian	3,196 (93.0)	145 (96.7)	3,051 (92.8)	0.071
Others	241 (7.0)	5 (2.7)	236 (7.2)	
Period of disease evolution, mean ± SD months	142.86 ± 100.6	208.71 ± 103.0	140.1 ± 99.7	0.001
Follow-up in rheumatology, mean ± SD months	120 ± 87.6	170.1 ± 90.8	118.12 ± 86.9	<0.001
Sjögren's syndrome	503 (14.4)	31 (20.5)	472 (14.1)	0.029
SLEDAI, median (IQR)	2 (0–4)	1 (0–3)	2 (0–4)	0.026
Katz index, median (IQR)	2 (1–3)	3 (2–4)	2 (1–3)	0.001
Modified SDI, median (IQR)†	1 (0–2)	1 (0–3)	0 (0–1)	<0.001
Modified Charlson comorbidity index, median (IQR)†	2 (1–3)	3 (2–4)	1 (1–3)	<0.001
Antimalaria treatment, median (IQR) months	60 (24–120)	78 (27–136)	60 (24–110)	0.099
Smoking (past and current smokers)	1,656 (46.8)	76 (49.4)	1,580 (46.7)	0.515
Alcohol use	111 (3.482)	6 (4.4)	105 (3.4)	0.517
Statins	165 (5.1)	15 (10.7)	150 (4.9)	0.002
ACE inhibitors	313 (9.7)	20 (14.6)	293 (9.5)	0.05
Acetylsalicylic acid	1,061 (37.180)	55 (40.4)	1,006 (36.9)	0.408
Immunosuppressants	1,939 (57.2)	80 (53.3)	1,859 (57.4)	0.326
Immunosuppressant type				
Nonimmunosuppressants	2,133 (60.3)	98 (63.7)	2,035 (60.1)	0.668
Cyclophosphamide/mycophenolate/mycophenolic	973 (27.59	38 (24.7)	935 (27.6)	0.668
Methotrexate/leflunomide	433 (12.3)	18 (11.7)	415 (12.3)	0.668
Oral contraception	655 (26.89	25 (23.6)	630 (27.0)	0.437
Corticoids at maximum doses, occasionally	776 (27.4)	36 (27.1)	740 (27.4)	0.93
Hospitalization per activity	1,902 (54.6)	88 (57.9)	1,814 (54.5)	0.41
No. of hospitalizations per activity, median (IQR)	2 (1–3)	2 (1–3)	2 (1–4)	0.01
Refractoriness	873 (24.6)	39 (25.3)	834 (24.6)	0.847

* Values are the number (%) unless indicated otherwise. SLE = systemic lupus erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; IQR = interquartile range; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; ACE = angiotensin-converting enzyme.
† The score corresponding to cancer was excluded when calculating the index.

Table 2. Characteristics of women with SLE and cancer, stratified by hormone sensitivity*

Variables	Hormone-sensitive cancer: yes (n = 44)	Hormone-sensitive cancer: no (n = 96)	*P*
Age at first SLE criterion met, mean ± SD years	39.1 ± 15.6	37.65 ± 16.18	0.582
Age at SLE diagnosis, mean ± SD years	41.9 ± 14.4	39.58 ± 16.07	0.497
Age at last evaluation, mean ± SD years	57.9 ± 13.1	57.31 ± 15.29	0.901
Race			
Caucasian	44 (100)	87 (94.57)	0.107
Others	0 (0)	5 (5.43)	0.107
Period of disease evolution, mean ± SD months	198.8 ± 85.9	212.76 ± 112.33	0.352
Follow-up in rheumatology, mean ± SD months	175.66 ± 81.58	163.80 ± 94.78	0.493
Sjögren's syndrome	11 (26.2)	19 (20)	0.294
SLEDAI, median (IQR)	0 (0–2)	2 (0–4)	0.268
Katz index, median (IQR)	2 (2–3)	3 (2–4)	0.059
Modified SDI, median (IQR)†	1 (0–2)	1.5 (1–3.5)	0.011
Modified Charlson comorbidity index, median (IQR)†	2 (2–3)	3 (2–4.5)	0.034
Antimalaria treatment, median (IQR) months	84 (19–144)	74.5 (32–133.5)	0.715
Smoking (past and current smokers)	22 (60.0)	44 (45.83)	0.78
Alcohol	1 (2.9)	2 (2.27)	0.779
Statins	2 (5.4)	8 (8.89)	0.425
ACE inhibitors	4 (10.8)	11 (12.64)	0.735
Acetylsalicylic acid	15 (38.5)	33 (39.29)	0.836
Immunosuppressants	19 (46.3)	53 (55.79)	0.188
Type of immunosuppressant			
Nonimmunosuppressants	31 (70.5)	59 (61.46)	0.314
Cyclophosphamide/mycophenolate/mycophenolic	8 (18.2)	25 (26.04)	0.314
Methotrexate/leflunomide	5 (11.4)	12 (12.5)	0.314
Oral contraception	9 (32.1)	16 (23.19)	0.307
Corticoids at maximum doses, occasionally	6 (16.7)	24 (28.92)	0.163
Hospitalization per activity	21 (50.0)	57 (59.38)	0.382
No. of hospitalizations per activity, median (IQR)	2 (1–3)	2 (1–3)	0.257
Refractoriness	8 (18.2)	25 (26.04)	0.194

* Values are the number (%) unless indicated otherwise. See Table 1 for definitions.
† The score corresponding to cancer was excluded when calculating the index.

entiating between HS and non-HS cancer. The odds ratio (OR) was calculated for all independent variables together with their 95% confidence intervals (95% CIs). Inclusion of independent variables in a multivariant model was based on clinical judgment and on a *P* value less than 0.25 obtained in the bivariant analysis. The absence of multicolinearity among independent variables included was checked with the kappa correlation coefficients in the case of qualitative variables, and with Pearson's correlation for quantitative variables. In the final logistic regression model, the independent variables were adjusted by all the other model variables.

Ethical aspects. This project complied with principles of the Helsinki Declaration (26). The project also received the approval of the general Clinical Research Ethics Committee (Doctor Negrín University Hospital of Gran Canaria), as well as the approval of the Clinical Research Ethics Committee at each center where required.

Table 3. Accumulated incidence of cancer in RELESSER patients and general population according to the 2012 Cancer Registry of the National Institute of Statistics, stratified by age and sex*

	RELESSER†			General population‡		
Age	Men	Women	Total	Men	Women	Total
<65 years	3.54 (0.01–19.59)	4.9 (2.68–8.21)	4.78 (2.68–3.07)	2.35 (2.33–2.37)	2.06 (2.04–2.08)	2.21 (2.20–2.22)
≥65 years	14.10 (0.03–75.99)	15.98 (6.45–32.65)	15.71 (6.81–30.73)	23.72 (23.65–23.89)	10.27 (10.19–10.37)	16.03 (15.94–16.12)
Total	5.66 (0.68–20.3)	6.37 (3.95–9.73)	6.31 (4.00–9.45)	5.56 (5.53–5.59)	3.67 (3.64–3.69)	4.60 (4.58–4.62)

* Values are the accumulated incidence (95% confidence interval). RELESSER = Systemic Lupus Erythematosus Registry of the Spanish Society of Rheumatology.
† Accumulated incidence per 1,000 patients.
‡ Accumulated incidence per 1,000 inhabitants.

Table 4. Standardized incidence ratio of cancer (no. of cancer cases observed/no. of expected cancer cases), stratified by age and sex*

Age	Men	Women	Total
<65 years	1.51 (0.62–2.40)	2.38 (1.84–2.91)	2.16 (1.71–2.61)
≥65 years	0.59 (0.0–1.26)	1.55 (1.15–1.95)	0.98 (0.73–1.23)
Total	1.02 (0.49–1.56)	1.74 (1.45–1.55)	1.37 (1.15–1.59)

* Values are the standardized incidence ratio (95% confidence interval).

RESULTS

Patients. The total number of patients included in the analysis was 3,539 (90.4% women), with a mean age at diagnosis of 35 years and a mean period of disease evolution of 143 months (Table 1). The main characteristics of the registry patients have been published previously (14).

Patient characteristics according to cancer presence. The main characteristics of patients with a first cancer onset since SLE diagnosis compared to those without cancer are detailed in Table 1. The total number of patients with cancer was 154 (4.35%), 91% women, with a mean ± SD age at diagnosis of 40.37 ± 15.7 years. Age at diagnosis, the period of disease evolution, Sjögren's syndrome (SS) association, Katz index score, SDI and Charlson comorbidity index scores, and the prescription of statins were higher in patients with cancer. However, the SLEDAI score and number of hospitalizations due to SLE activity were higher in patients without cancer.

Patient characteristics per HS and non-HS cancers. Of the 154 patients with cancer, only 14 were men, and none of those cases were hormone dependent. Table 2 shows the HS and non-HS cancer characteristics in women. Both the SDI and Charlson indexes had higher values in patients with non-HS cancers.

Cancer incidence. The cancer accumulated incidence in patients with SLE was 6.31 cases per 1,000 patients (95% CI 4.00–9.45). After stratifying by age and sex, the group with the highest number of first cancers (16 cases per 1,000 patients [95% CI 6.45–32.65]) was women ages >64 years (Table 3). The cancer SIR was 1.37 (95% CI 1.15–1.59) and the group with the highest values was women ages <65 years, with 2.38 (95% CI 1.84–2.91) (Table 4). In women, the HS cancer SIR was 1.02 (95% CI 0.13–1.91), and for non-HS patients it was 1.93 (95% CI 0.98–2.89).

Cancer prevalence and distribution. As to the distribution of cancer according to anatomic location, breast and gynecologic cancer were the most frequently recorded (23.4% and 20.1%, respectively), followed by hematologic (75% non-Hodgkin's lymphoma and 25% Hodgkin's lymphoma) and skin (nonmelanoma), both 11.7%. These were followed by colorectal and thyroid cancer (both 5.2%), lung cancer (3.25%), and other locations (19.5%). After analyzing the subgroup of patients with SLE with associated SS, we found that the most frequent location was breast cancer at 29%, followed by gynecologic and hematologic cancers, both at 16.1%. Non-Hodgkin's lymphoma was the most common hematologic cancer (60%) in patients with SLE with associated SS.

Time frame for cancer onset. The median time frame until the onset of the first cancer was 10 years (IQR 5.75–17.00), which was significantly shorter in women (9.5 years [IQR 5.00–17.00]) than in men (12.5 years [IQR 8.75–17.50]), and in patients ages <45 years (8.0 years [IQR 5.00–16.00]) versus patients ages >45 years (10.9 years [IQR 7.00–18.60]).

Death due to cancer. Global mortality was 5.5% of patients, with cancer being the fourth leading cause of death, after SLE itself, cardiovascular disease, and infections. Death due to cancer in patients included in the study was 10.66%, with the most prevalent types being hematologic (19%) and breast (19%) cancers, followed by lung (14.3%) and colorectal (9.5%).

Factors associated with cancer onset in women. Tables 5 and 6 show the results obtained in the bivariant analysis of HS and non-HS cancers. Regarding the multivariant model, the variables with significant associations with HS cancer onset were SLE diagnostic age (OR 1.04 [95% CI 1.01–1.07], $P = 0.002$) and period of disease evolution (OR 1.01 [95% CI 1.00–1.01], $P < 0.001$). The multivariate model of non-HS cancers showed a significant association with SLE diagnostic age (OR 1.04 [95% CI 1.01–1.07], $P = 0.019$), evolution period (OR 1.00 [95% CI 1.00–1.01], $P = 0.029$), SDI (OR 1.27 [95% CI 1.04–1.57], $P = 0.022$), and prescription of angiotensin-converting enzyme (ACE) inhibitors (OR 2.87 [95% CI 1.01–8.14], $P = 0.048$) (Tables 5 and 6).

DISCUSSION

The results obtained in this national retrospective multicenter study showed that the cancer incidence in patients with SLE is higher than in the general population, with differences being more striking in women ages <65 years and in those with non-HS cancers. Furthermore, breast, gynecologic, and hematologic cancers were the most frequently recorded in patients with SLE and in those patients with associated SS. Onset of the first cancer post-SLE diagnosis occurred approximately 10 years later, with breast and hematologic cancers causing more deaths. Both SLE diagnostic age and the period of disease evolution were factors associated with HS and non-HS cancers. However, SDI score and ACE inhibitor prescriptions were solely associated with non-HS cancers.

The differences found among patients with and without cancer on the Katz and Charlson indexes, as well as among patients with a statin prescription, suggest that cancer patients have a

Table 5. Factors associated with hormone-sensitive cancers in women with systemic lupus erythematosus*

Variable	Bivariant OR (95% CI)	*P*	Multivariant OR (95% CI)	*P*
Age at first SLE criterion met, years	1.03 (1.01–1.05)	0.001	–	–
Age at SLE diagnosis, years	1.03 (1.01–1.05)	0.001	1.04 (1.01–1.07)	0.002
Age at last evaluation, years	1.05 (1.03–1.07)	<0.001	–	–
Race				
Caucasian (reference)	–	–	–	–
Others	–	–	–	–
Period of disease evolution, months	1.00 (1.00–1.01)	0.001	1.01 (1.00–1.01)	<0.001
Follow-up in rheumatology, months	1.01 (1.00–1.01)	<0.001	–	–
Sjögren's syndrome	1.94 (0.98–3.94)	0.057	1.60 (0.72–3.53)	0.246
SLEDAI	0.89 (0.78–1.01)	0.063	0.94 (0.82–1.08)	0.394
Katz index	0.96 (0.80–1.16)	0.707	–	–
Modified SDI†	1.11 (0.95–1.29)	0.188	–	–
Modified Charlson comorbidity index†	1.27 (1.10–1.46)	0.001	–	–
Antimalaria treatment time, months	1.00 (1.00–1.00)	0.818	–	–
Smoking (past and current smokers)	1.25 (0.69–2.26)	0.464	–	–
Alcohol	1.40 (0.19–10.36)	0.745	–	–
Statins	1.07 (0.26–4.50)	0.925	–	–
ACE inhibitors	1.22 (0.43–3.48)	0.706	–	–
Acetylsalicylic acid	1.10 (0.57–2.11)	0.772	–	–
Immunosuppressants	0.66 (0.36–1.23)	0.188	–	–
Type of immunosuppressant				
Nonimmunosuppressants (reference)	–	–	–	–
Cyclophosphamide/mycophenolate/mycophenolic	0.60 (0.27–1.30)	0.194	–	–
Methotrexate/leflunomide	0.78 (0.30–2.03)	0.618	–	–
Oral contraception	1.10 (0.50–2.45)	0.813	–	–
Corticoids at maximum dose, occasionally	0.55 (0.23–1.33)	0.186	0.74 (0.29–1.85)	0.516
Hospitalization per activity	0.89 (0.48–1.63)	0.699	–	–
No. of hospitalizations per activity	1.01 (0.86–1.19)	0.887	–	–
Refractoriness	0.72 (0.33–1.55)	0.394	–	–
Anti-DNA	0.69 (0.37–1.30)	0.249	0.88 (0.40–1.92)	0.75
No. of pregnancies	1.19 (1.01–1.39)	0.038	1.00 (0.80–1.25)	0.987
Menopause	12.1 (5.10–28.75)	<0.001	–	–

* OR = odds ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).
† The score corresponding to cancer was excluded when calculating the index.

more serious clinical state and greater risk of comorbidities. These variables had not been analyzed in previous studies, although the SDI had been, showing higher values in patients with cancer (27), results consistent with our own study. As to the number of hospitalizations per SLE activity, we noted a paradox, i.e., patients without cancer were hospitalized more frequently. This finding might be due to the effect of oncologic drugs on the activity and evolution of SLE.

On analyzing the differences between women with HS or non-HS cancers, our study revealed that the damage associated with SLE and comorbidity was higher only in patients with non-HS cancers. Notwithstanding such evidence, these results have yet to be replicated by other groups. Nonetheless, we consider this a relevant finding, since patients with non-HS cancers might require a more complex clinical and therapeutic approach.

Several studies in different countries, races, and ethnic groups have noted a global cancer increase, with an SIR between 1.14 and 3.6 (1). Likewise, those studies that stratified the SIR by sex and age found this increase particularly prevalent in women between ages 21 and 64 years (2,28). In our Spanish cohort, the results support previously published findings. Regarding HS breast, endometrial, and ovarian cancers, a very slight and not significant increase has been suggested (29,30); likewise, a significant drop in the SIR has been observed (2,3,6,10,11). This finding has led to the belief that a direct association cannot be established between SLE and the risk of HS cancers. Our study detected a very slight, albeit not significant, increase in the SIR in women with HS cancers. In non-HS cancers, the increase was higher, although it remained at the limit of statistical significance.

Regarding distribution by location, breast, gynecologic, and hematologic cancers (especially non-Hodgkin's lymphoma) were the most prevalent. These 3 cancers were also among the most frequent in other cohorts, which was true of studies carried out on different races or ethnic groups (2–4,28,30). In fact, this distribution was maintained in SLE and SS patients, with the hematologic tumor non-Hodgkin's lymphoma being the most frequently recorded, as is the case in patients with primary SS (28).

Focusing on the time frame relationship between SLE and cancer, our patients developed cancer following the SLE diagnosis within a median of 10 years (9 years in women ages <45 years). Other authors have tackled this time frame relationship via cancer risk stratification (SIR) pursuant to follow-up time. They

Table 6. Factors associated with non–hormone-sensitive cancer in women with systemic lupus erythematosus*

Variables	Bivariant OR (95% CI)	*P*	Multivariant OR (95% CI)	*P*
Age at first SLE criterion met, years	1.03 (1.01–1.04)	<0.001	–	–
Age at SLE diagnosis, years	1.02 (1.01–1.04)	<0.001	1.04 (1.01–1.07)	0.019
Age at last evaluation, years	1.05 (1.03–1.07)	<0.001	–	–
Race				
Caucasian (reference)	–	0.478	–	–
Others	0.72 (0.29–1.79)	–	–	–
Period of disease evolution, months	1.01 (1.00–1.01)	<0.001	1.01 (1.00–1.01)	0.029
Follow-up in rheumatology, months	1.01 (1.00–1.01)	<0.001	–	–
Sjögren's syndrome	1.39 (0.83–2.31)	0.213	0.95 (0.35–2.57)	0.246
SLEDAI	0.96 (0.90–1.02)	0.209	0.97 (0.86–1.09)	0.394
Katz index	1.16 (1.05–1.29)	0.005	–	–
Modified SDI†	1.32 (1.21–1.43)	<0.001	1.27 (1.04–1.57)	0.022
Modified Charlson comorbidity index†	1.43 (1.31–1.56)	<0.001	–	–
Antimalaria treatment time, months)	1.00 (1.00–1.00)	0.264	1.00 (1.00–1.00)	0.947
Smoking (past and current smokers)	1.06 (0.70–1.59)	0.791	–	–
Alcohol	1.10 (0.27–4.59)	0.893	–	–
Statins	1.83 (0.87–3.86)	0.112	0.33 (0.04–3.04)	0.329
ACE inhibitors‡	1.46 (0.77–2.78)	0.25	2.87 (1.01–8.14)	0.048
Acetylsalicylic acid	1.14 (0.73–1.78)	0.565	–	–
Immunosuppressants	0.96 (0.64–1.46)	0.864	–	–
Type of immunosuppressant				
Nonimmunosuppressants (reference)	–	–	–	–
Cyclophosphamide/mycophenolate/mycophenolic	0.98 (0.61–1.57)	0.929	–	–
Methotrexate/leflunomide	0.99 (0.53–1.86)	0.975	–	–
Oral contraception	0.70 (0.40–1.24)	0.221	1.20 (0.47–3.06)	0.704
Corticoids at maximum dose, occasionally	1.12 (0.69–1.82)	0.638	–	–
Hospitalization per activity	1.30 (0.86–1.96)	0.219	0.52 (0.22–1.26)	0.148
No. of hospitalizations per activity	1.10 (1.04–1.17)	0.001	–	–
Refractoriness	1.13 (0.71–1.80)	0.597	–	–

* OR = odds ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).
† The score corresponding to cancer was excluded when calculating the index.
‡ Cancer patients prescribed ACE inhibitors were more commonly hypertensive than those not prescribed these drugs (75% versus 41%; $P = 0.005$); furthermore, they were more frequently diagnosed with lupus nephritis (85% versus 18.8%; $P < 0.001$).

have found an increased global cancer risk between <1 year and >8 years from the time of SLE diagnosis, with a greater risk during the first year of follow-up (2,4,28).

Among the Spanish population, the cancers most frequently causing death in men are lung, colorectal, and prostate, while in women they are breast, colorectal, and lung (24,25). In our essentially female cohort, the same distribution held true, though hematologic cancers also met first-line inclusion. This finding is not surprising, given that chronic immune dysregulation due to SLE is associated with greater lymphoid proliferation, thus increasing the risk of hematologic tumors, specifically non-Hodgkin's lymphoma (31).

We are aware that the global standardized mortality rate for cancer in SLE has not increased (32). Patients with chronic diseases are subject to greater vigilance, which may favor early cancer diagnosis and improved prognosis. A suggestion has also been made that patients with SLE have a competitive premature mortality due to other causes, such as cardiovascular disease, infections, and lupus nephritis (32). Our results support this suggestion, since cancer was the fourth leading cause of death after SLE itself, cardiovascular disease, and infections.

SLE diagnostic age and period of disease evolution were associated with both HS and non-HS cancers. In other studies, age was associated with cancer in general, in particular with breast cancer and lymphomas (27,33,34). Bernatsky et al (27) have suggested that lupus duration confers a protective effect against cancer onset. This suggestion potentially contradicts our results, although their study had a different design, and SLE duration was established from the time the patient was included in the cohort, as opposed to the time of SLE diagnosis, as in our study. Accumulated SLE damage and ACE inhibitor prescriptions were solely associated with non-HS cancers. The SDI was found to be a possible factor associated with cancer (27); however, until now this association has not been known as an underlying factor in non-HS cancers. We have no information regarding ACE inhibitor prescriptions as a cancer-associated factor in SLE, since such information had not been included in previous analyses. In our cohort, those patients with cancer who had been prescribed ACE inhibitors suffered hypertension and lupus nephritis with greater frequency than those without ACE inhibitors. The role that ACE inhibitors might play in cancer risk is highly controversial, not only in SLE but in the general population as well. While some studies suggest they

may increase the risk of certain cancers, such as in the lung (35), others show a reduction or absence of such an association (36). We found no association between HS cancers and oral contraception, the number of pregnancies, or menopause, nor has this association been previously demonstrated with breast cancer (33).

Our results provide evidence that there are several factors exclusively associated with non-HS cancers. This interpretation would support the hypothesis that there are differences in cancer according to hormonal dependence. If these differences are confirmed by subsequent studies, the manner in which patients are assessed will also likely change. Preventative measures and/or cancer screening in patients with SLE based on the risk associated with hormonal dependence may be adopted.

Our study has several limitations. Its retrospective design might render the results somewhat less reliable. Nevertheless, the study remains an acceptable design for tackling infrequent events like cancer. The increased risk of non-HS cancers was on the threshold of significance, for although the total number of cancers was not depreciable when the SIRs of HS and non-HS cancers were separated, statistical power was nonetheless lost. The variables included in our model better explain the non-HS cancers, which leads us to believe that there are still other variables requiring identification and which are associated with HS cancers.

One of the strengths of this study is that it is the largest SLE multicenter cohort from Europe. In addition, we included variables not previously analyzed in other studies. Moreover, because the data were drawn from a clinical registry, as opposed to an administrative national health insurance database, we had more detailed information on the disease, allowing us to better adjust the models. Finally, the comparison between HS and non-HS cancers had not been explored before; thus, the study has greatly expanded upon information previously only hypothesized regarding the differences among these cancer types.

In conclusion, the cancer incidence in patients with SLE is higher than in the general Spanish population, particularly in young women. Above all, the incidence rate may be dependent on non-HS cancers. SLE age at diagnosis and period of disease evolution were common factors associated with both HS and non-HS cancers. However, non-HS cancers were also associated with ACE inhibitor prescriptions and greater accumulated damage. Further studies confirming our findings on the differences between HS and non-HS cancer are greatly warranted, as is a renewed search for factors that most clearly determine the risk of such cancers.

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. Cobo-Ibáñez 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. Cobo-Ibáñez, Urruticoechea-Arana, Rúa-Figueroa, Martín-Martínez.

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Analysis and interpretation of data. Cobo-Ibáñez, Rúa-Figueroa, Martín-Martínez.

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RHEUMATOLOGY REGISTRIES, BIG DATA, AND THE RHEUMATIC DISEASES

Time to Lupus Low Disease Activity State in the Hopkins Lupus Cohort: Role of African American Ethnicity

Hakan Babaoğlu,[1] Jessica Li,[2] Daniel Goldman,[2] Laurence S. Magder,[3] and Michelle Petri[2]

Objective. Lupus low disease activity state (LLDAS) is a potential treat-to-target goal in systemic lupus erythematosus (SLE). This study determined predictors of time to reach LLDAS in a longitudinal cohort.

Methods. Patients were grouped according to LLDAS status at cohort entry. Those who did not satisfy LLDAS at cohort entry were analyzed prospectively. The Kaplan-Meier approach was used to estimate the time to LLDAS. Cox regression was used to identify patient characteristics that were associated with time to LLDAS.

Results. The probability of LLDAS attainment within 1 year was 52% for Caucasians, 36% for African Americans, and 33% for SLE patients with renal involvement. The median time to LLDAS was 1.1 years. In multivariable models, African American ethnicity, baseline prednisone >10 mg daily, hypocomplementemia, baseline damage, and baseline renal activity remained significant predictors of longer time to attain LLDAS, while disease duration <1 year and cutaneous activity were associated with earlier attainment.

Conclusion. LLDAS is potentially attainable in the majority of SLE patients. The time to LLDAS was found to be longer in African American patients with SLE. Characteristics of African American patients with SLE, such as renal activity and hypocomplementemia, were also independent predictors of slower attainment of LLDAS. These findings point to the need to include African American patients with SLE in both clinical and pharmaceutical research.

INTRODUCTION

Control of both systemic lupus erythematosus (SLE) disease activity and corticosteroid use are important targets in the management of SLE. In the principles of treat-to-target recommendations for SLE, the main target state was remission, but where remission could not be reached, the lowest acceptable disease activity might be the target (1). Thus, Franklyn et al (2) developed and validated a less stringent targeted state than remission, the lupus low disease activity state (LLDAS). They found that SLE patients who were in LLDAS for more than half of the observation period had a lower risk of new damage (2). External validation of LLDAS included studies from Padova, Amsterdam, and Pisa, which reported up to 86.7% of SLE patients attained LLDAS at a single point of time, and confirmed that attainment of LLDAS lowered the risk of new damage (3–5). The previous analysis of our cohort found that, if >50% of the follow-up time satisfied LLDAS, there was a 50% reduction in later organ damage (6). Furthermore, LLDAS has now been found to be a meaningful and discriminative end point in both primary and post hoc analyses of several SLE randomized clinical trials (7–9).

Baseline characteristics that predicted the likelihood of attaining LLDAS were evaluated in several studies. Younger age, discoid rash, disease duration ≤1 year, elevated anti–double-stranded DNA (anti-dsDNA) (10), renal disease, and hypocomplementemia (10,11) were found to be negative independent predictors of attaining LLDAS. Cumulative prednisone dose, physician global disease assessment (PhGA) score of >1 (3), a higher Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, and joint and skin (3,4) involvement were found to be negative predictors of sustained LLDAS.

The presentation and course of SLE is affected by ethnicity. African American patients with SLE are known to experience more severe SLE, more chronic disease activity

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

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SIGNIFICANCE & INNOVATIONS

- The achievability of lupus low disease activity state (LLDAS) in both African Americans and Caucasian patients was demonstrated, supporting the validity of LLDAS in multiple ethnicities.
- African American patients with systemic lupus erythematosus (SLE) were found to take longer to achieve LLDAS.
- These findings point to the need to include African American patients with SLE in both clinical and pharmaceutical research, because we cannot generalize from studies from Europe and Asia.

pattern (12–14), and worse survival (15–18). African Americans require a longer time to achieve remission (19) compared with other ethnicities. LLDAS in African American patients has not been fully elucidated. In this study, we determined the time to LLDAS and predictors of time to LLDAS in the Hopkins Lupus Cohort, a US cohort with both Caucasian and African American representation.

MATERIALS AND METHODS

The Hopkins Lupus Cohort is a prospective longitudinal single-center cohort of SLE patients ongoing since 1987, which was approved on an annual basis by the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave written informed consent to participate. Visits were scheduled quarterly by protocol. Patients were seen by 1 rheumatologist (MP). This analysis was based on cohort data from its inception until January 2019. A total of 2,512 patients with SLE diagnosed according to the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (20) or the classification criteria as defined by the American College of Rheumatology (ACR) (21,22) and as updated in 1997 (23), were included in the analyses. At each clinic visit, the PhGA score (range 0–3, visual analog scale) (24), the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLEDAI (SELENA-SLEDAI) (25,26), the SLICC/ACR Damage Index (SDI) (27), relevant serologies (anti-dsDNA, complement), and treatment were recorded.

In this study, we applied LLDAS (2) to the Hopkins Lupus Cohort. LLDAS was defined as a SELENA-SLEDAI score of ≤4 with no scores for renal, central nervous system, cardiopulmonary, vasculitis, or fever; no hemolytic anemia or gastrointestinal activity; no increase in any SELENA-SLEDAI component since the previous visit; a PhGA score of ≤1; and a prednisone dose of ≤7.5 mg/day. Immunosuppressant and hydroxychloroquine treatment were allowed for LLDAS. Patients were grouped according to LLDAS status at baseline.

SAS software, version 9.4, was used. A chi-square test for categorical variables, Wilcoxon's rank sum test, or the independent samples *t*-test for continuous variables (where appropriate) were used to determine whether there was a significant difference between baseline characteristics of patients grouped according to LLDAS status at baseline.

Patients who did not satisfy LLDAS at cohort entry were analyzed prospectively. The time to LLDAS was defined as the time between the cohort entry and the first clinic visit at which LLDAS was attained. We used the Kaplan-Meier approach to estimate the distribution of time to LLDAS and probability of patients achieving LLDAS after cohort entry, censoring patients who had a gap of ≥7 months in their follow-up time or who dropped out of the study before attaining LLDAS. We used Cox regression to identify patient characteristics that were associated with LLDAS. First, we assessed the relationship between each variable and time to LLDAS, one at a time. Those with significant association with time to LLDAS were then entered into the multivariable model and those that remained significant were retained in the final model. Variables that were highly collinear were included separately in a multivariable model.

RESULTS

Cohort entry. Table 1 details the patient characteristics according to LLDAS status at baseline. The cumulative classification criteria were 49% malar rash, 19% discoid rash, 52% photosensitivity, 53% oral ulcer, 72% arthritis, 49% serositis, 45% renal disorder, 12% neurologic disorder, 67% hematologic disorder, 83% immunologic disorder, and 97% antinuclear antibody positivity based on revised ACR classification criteria. Additional SLICC classification criteria included 21% direct Coombs test, 55% low C3, 48% low C4, and 16% low CH50. A total of 2,512 SLE patients were analyzed. In all, 1,086 patients (43.2%) were in LLDAS at the first cohort visit. Of these patients, 94% were female, 30.1% were African American, and 61.8% were Caucasian. The mean age at baseline was 40 years. Thirty-nine percent had been diagnosed with SLE within the past year, while 33.6% had SLE for 5 or more years. Patients who were not in LLDAS at baseline were significantly younger and were more likely to be male and African American. Disease duration was comparable between the groups.

Follow-up. Figure 1 shows the probability of patients achieving LLDAS at stated time points. Based on our Kaplan-Meier analysis, the estimated probability of LLDAS attainment within 1 year was 52% for Caucasian Americans and 36% for African Americans. Among those with renal involvement, the estimated probability of achieving LLDAS within 1 year was 33%. In total, 93% of Caucasian-Americans, 82% of African Americans, and 89% of

Table 1. Clinical and demographic characteristics of the patients in the Hopkins Lupus Cohort, grouped according to lupus low disease activity state (LLDAS) status at baseline*

Characteristic	LLDAS at cohort entry (n = 1,086)	No LLDAS at cohort entry (n = 1,426)	*P*
Female	1,021 (94)	1,294 (90.7)	0.0025
Ethnicity			<0.0001
African American	327 (30.1)	663 (46.5)	–
Caucasian	671 (61.8)	655 (45.9)	–
Other	88 (8.1)	108 (7.6)	–
Age at baseline, years			<0.0001
<30	284 (26.2)	526 (36.9)	–
30–39	298 (27.4)	422 (29.6)	–
40–49	252 (23.2)	266 (18.7)	–
≥50	252 (23.2)	212 (14.9)	–
Mean ± SD	39.8 ± 13.1	36.2 ± 12.6	<0.0001
History of smoking	395 (36.6)	514 (36.1)	0.8256
Duration of SLE prior to baseline			0.199
<1 year	426 (39.2)	524 (36.7)	–
1–5 years	295 (27.2)	374 (26.2)	–
>5 years	365 (33.6)	528 (37)	–
Median (IQR)	2.3 (0.3–7.5)	2.5 (0.3–8.1)	0.243
Baseline prednisone dose			<0.0001
≤10 mg/day	1,086 (100)	495 (34.7)	–
>10 mg/day	0 (0)	931 (65.3)	–
Baseline hydroxychloroquine	546 (50.3)	703 (49.3)	0.6274
Baseline immunosuppressant	120 (11.0)	425 (29.8)	<0.0001
Baseline low C3	186 (17.7)	523 (37.9)	<0.0001
Baseline low C4	170 (16.2)	431 (31.3)	<0.0001
Baseline anti-dsDNA positivity	201 (19.6)	586 (43.2)	<0.0001
Baseline PhGA ≤1	1,086 (100)	723 (50.7)	<0.0001
Baseline SLICC/ACR Damage Index score >1	200 (18.6)	400 (28.2)	<0.0001
Baseline SELENA-SLEDAI score			<0.0001
≤4	1,086 (100)	767 (53.8)	–
>4	0 (0)	659 (46.2)	–
Baseline musculoskeletal activity	27 (2.5)	258 (18.1)	<0.0001
Baseline cutaneous activity	199 (18.3)	380 (26.6)	<0.0001
Baseline renal activity	0 (0)	384 (26.9)	<0.0001
Baseline hematologic activity	59 (5.4)	146 (10.2)	<0.0001
Baseline serositis activity	0 (0)	87 (6.1)	<0.0001
Baseline vasculitis	0 (0)	43 (3.0)	<0.0001
Antiphospholipid antibodies			
Anticardiolipin	486 (46.2)	668 (48.2)	0.3385
Lupus anticoagulant (RVVT)	271 (25.6)	367 (26.5)	0.617

* Values are the number (%) unless indicated otherwise. SLE = systemic lupus erythematosus; IQR = interquartile range; anti-dsDNA = anti–double-stranded DNA; PhGA = physician global assessment; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology; SELENA-SLEDAI = the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE disease activity index; RVVT = Russell viper venom time.

patients with renal involvement would achieve LLDAS at the end of 5 years of follow-up.

Predictors of time to LLDAS. Table 2 shows the median time to LLDAS, with baseline characteristics of patients that were associated with time to LLDAS based on Kaplan-Meier models. Table 2 also shows estimated rate ratios for LLDAS attainment based on both univariate and multivariable Cox regression models. The median time to LLDAS was 1.1 years. We found that disease duration <1 year, taking prednisone <10 mg daily, taking hydroxychloroquine, normal levels of C3, C4, and anti-dsDNA, PhGA score of ≤1, a SELENA-SLEDAI score of ≤4, and cutaneous activity were associated with attaining LLDAS faster, while African American ethnicity, baseline renal activity, baseline damage accrual, and the presence of lupus anticoagulant were associated with later attainment of LLDAS.

In the multivariable model, African American ethnicity, taking prednisone >10 mg daily, baseline hypocomplementemia, baseline damage accrual, and baseline renal activity remained significant predictors of later attainment of LLDAS. Disease duration of <1 year and cutaneous activity remained significant predictors of earlier attainment of LLDAS.

We also performed a subgroup analysis of inception patients. A total of 536 patients, who entered the cohort within 18 months

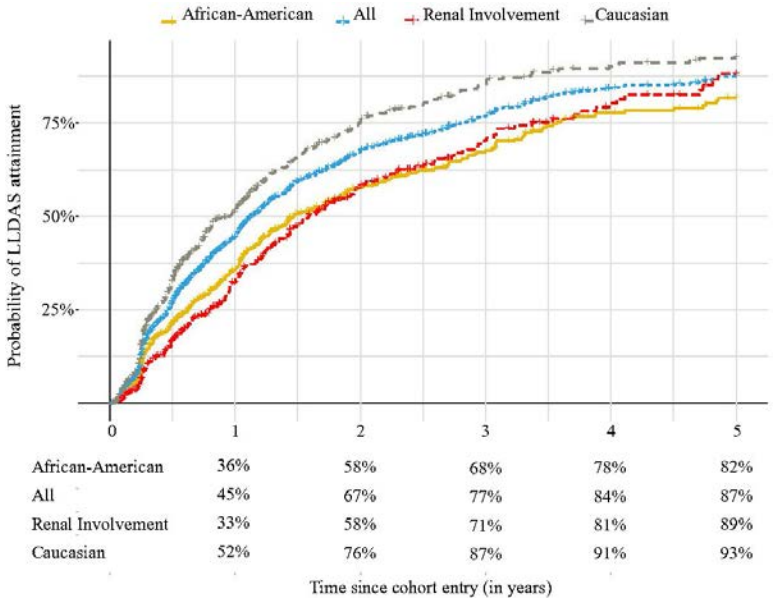

Figure 1. Graph showing the probability of lupus low disease activity state (LLDAS) attainment according to patients' ethnicity and renal involvement at the stated time points.

of SLE diagnosis date and were not in LLDAS at cohort entry were analyzed. African American ethnicity (95% confidence interval [95% CI] 0.50–0.76), taking prednisone >10 mg daily (95% CI 0.52–0.79), baseline hypocomplementemia (95% CI 0.61–0.92), and baseline renal activity (95% CI 0.59–0.94) were found to be predictors of later attainment of LLDAS.

DISCUSSION

In view of the ethnic disparities in SLE outcomes, studying results in cohorts that include different ethnicities is important. The Hopkins Lupus Cohort has a balanced representation of Caucasian and African American ethnicities. Other studies of LLDAS (2–5,10,11) cannot generalize to patients with SLE within the US. In general, though, studies of time to LLDAS are lacking. We applied the LLDAS definition to the Hopkins Lupus Cohort and identified the frequency of LLDAS, time to LLDAS, and clinical determinants of time to LLDAS.

First, African American SLE patients were found to require a longer time to achieve LLDAS. This is the first study confirming the association between African American ethnicity and its effect on LLDAS. Most SLE cohorts do not contain different ethnicities (3,11). One that was predominantly of Chinese patients (10) reported that ethnicity had no effect on LLDAS. However, disease prevalence, severity, and mortality are well-established as increased in the African American population compared to the Caucasian population (6,12–14,17,28,29). Moreover, lupus nephritis, discoid lupus, hematologic, serologic, and immunologic SLE manifestations are more common in African Americans (13,30–32). However, the longer time until LLDAS in African Americans persisted even after adjustment for renal activity. African Americans are significantly underrepresented in SLE clinical trials (33). Our findings further emphasize the importance of including African Americans in clinical and pharmaceutical research studies considering heterogeneity in outcomes among ethnicities.

Second, among patients who were not in LLDAS at cohort entry, we estimated that 45% of all and 36% of African American patients would achieve LLDAS within 1 year. In total, 87% of all and 82% of African American patients would achieve LLDAS at the end of 5 years of follow-up. Whether cross-sectional or longitudinal, cohorts that analyzed the frequency of LLDAS were in general agreement with our results (3–5,10). LLDAS should be an achievable treat-to-target goal in the majority of SLE patients, as opposed to remission. Although remission should remain the ultimate goal, our current therapies are insufficient to establish remission as the treat-to-target goal for standard of care. Our findings clarify that LLDAS is an achievable target for both African American as well as Caucasian patients.

Third, the median time to LLDAS was found to be 1.1 years. The range of the follow-up time until LLDAS was 0.3 to 180 months. Indeed, the importance of faster attainment of LLDAS comes from what we know about the association between preexisting damage and further damage accrual (34), between early damage and higher mortality (34,35), and between LLDAS and reduced risk of new damage. A desirable treat-to-target state should be reachable early in the disease course to prevent damage. We previously reported that the median time to remission ranged between 1.8 and 11.0 years depending on the definition of remission (19). This finding is noteworthy, since the median time to LLDAS showed that, in many patients, LLDAS is attainable in time to actually prevent early damage and within the duration of randomized clinical trials.

Table 2. Predictors of time to lupus low disease activity state (LLDAS)*

Predictor	Median time to LLDAS, years	Univariate		Multivariable	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Ethnicity					
Non-African American	0.95	Ref.	–	Ref.	–
African American	1.5	0.63 (0.55–0.73)	<0.001	0.61 (0.52–0.70)	<0.001
Duration of SLE†					
<1 year	1	Ref.	–	Ref.	–
1–5 years	1.2	0.75 (0.62–0.89)	0.001	0.8 (0.67–0.96)	0.016
>5 years	1.4	0.72 (0.62–0.85)	<0.001	0.79 (0.66–0.94)	0.007
Prednisone dose†					
≤10 mg/day	0.6	Ref.	–	Ref.	–
>10 mg/day	1.4	0.56 (0.48–0.64)	<0.001	0.57 (0.49–0.66)	<0.001
Hydroxychloroquine use†					
No	1.3	Ref.	–	–	–
Yes	1	1.23 (1.07–1.41)	0.004	–	–
Hypocomplementemia†					
No	0.9	Ref.	–	Ref.	–
Yes	1.5	0.66 (0.57–0.76)	<0.001	0.68 (0.59–0.79)	<0.001
Anti-dsDNA positivity†					
No	1.1	Ref.	–	–	–
Yes	1.3	0.85 (0.73–0.98)	0.026	–	–
PhGA†					
≤1	1	Ref.	–	–	–
>1	1.3	0.78 (0.68–0.90)	<0.001	–	–
SLICC/ACR Damage Index score†					
≤1	1	Ref.	–	Ref.	–
>1	1.4	0.79 (0.67–0.92)	0.003	0.84 (0.71–0.99)	0.041
SELENA-SLEDAI score†					
≤4	1	Ref.	–	–	–
>4	1.4	0.81 (0.70–0.92)	0.002	–	–
Cutaneous activity†					
Absent	1.2	Ref.	–	Ref.	–
Present	0.9	1.23 (1.06–1.44)	0.007	1.19 (1.01–1.39)	0.035
Renal activity†					
Absent	1	Ref.	–	Ref.	–
Present	1.6	0.70 (0.59–0.82)	<0.001	0.72 (0.61–0.85)	<0.001
Lupus anticoagulant					
Never	1.1	Ref.	–	–	–
Ever	1.3	0.85 (0.72–0.99)	0.042	–	–

* There was no significant association between time to LLDAS and baseline age, sex, history of smoking, immunosuppressant use, musculoskeletal activity, hematologic activity, serositis, and anticardiolipin antibody positivity. Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) and physician global assessment (PhGA) were not included in the final multivariable model due to their collinearity with cutaneous and renal activity. HR = hazard ratio; 95% CI = 95% confidence interval; Ref. = reference; SLE = systemic lupus erythematosus; anti-dsDNA = anti–double-stranded DNA; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology.
† Baseline.

Fourth, we found that renal activity independently predicted a longer time to LLDAS, which is in agreement with previous studies (10,11). Lupus nephritis remains associated with higher health care costs and remains an indicator of high morbidity and mortality (36,37). In particular, lupus nephritis is more common (38), develops earlier (39), and has worse outcomes (40,41) in African Americans (28). Achievement of LLDAS was found to predict statistically significant reductions in end-stage renal disease (ESRD) in our previous analysis (6). Thirty-three percent of our patients with baseline renal involvement would attain LLDAS within 1 year. Although renal involvement is a predictor of later attainment of LLDAS, LLDAS is still a potential target for patients with renal involvement, because it is associated with a low risk of progression to ESRD.

Fifth, we found baseline cutaneous activity as an independent predictor for early LLDAS attainment. Skin activity in SLE is an umbrella term for a family of manifestations with a wide range of prognosis. Unfortunately, our cohort database (based on the SLEDAI) did not subcategorize cutaneous manifestations at baseline and did not define discoid rash as a distinct variable. Golder et al (10) found discoid rash as a negative predictor of LLDAS attainment.

Sixth, we showed that patients with disease duration <1 year were able to attain LLDAS faster. This finding is in contrast

to that of Golder et al (10) in a multicenter cross-sectional study from 2016, which reported a shorter disease duration as a negative predictor of LLDAS attainment. However, the mean disease duration at baseline was 8.64 years. Only 8% of the patients had a disease duration of <1 year at enrollment, as opposed to 38% of our cohort. In addition, the study by Golder et al included patients who we excluded, i.e., those who were in LLDAS at baseline. SLE disease activity decreases over time (42). The discrepancy between our result and previous studies might be explained by sample selection. We analyzed only patients who were not in LLDAS at cohort entry. Inception patients are much more likely not to be in LLDAS, because their disease manifestations are evolving over time, irrespective of disease severity. However, patients with longer disease duration may have established (ingrained) SLE manifestations, and not being in LLDAS at cohort entry may imply that these patients had a more difficult disease to control.

We also performed a subgroup analysis of an "inception cohort" of our SLE patients with a disease duration <18 months at cohort entry. The results did not deviate from our main findings. African American ethnicity, taking prednisone >10 mg daily, baseline hypocomplementemia, and baseline renal activity were found to be predictors of later attainment of LLDAS in these patients, as well. As one might expect, damage accrual was similar between the groups and thus did not enter in multivariable analysis. Cutaneous activity became insignificant in the multivariable analysis in these inception patients.

Seventh, hydroxychloroquine is the cornerstone of the treatment of SLE, with multiple benefits, including improved survival (43–45), decreased frequency of lupus flares (46), and reduced risk of damage accrual (47). In the univariate model, hydroxychloroquine was significantly associated with earlier LLDAS attainment. However, this association was lost in the multivariable model. Our result was likely underpowered due to the high frequency of nonadherence we have previously reported (48).

Baseline damage, hypocomplementemia, and prednisone >10 mg daily were found to be independent predictors of longer time to LLDAS. This finding is expected, because these factors are associated with active or refractory disease. Furthermore, we found that patients with baseline lower SELENA-SLEDAI and PhGA scores more frequently and rapidly attained LLDAS, compared to those patients with higher scores at baseline. To differentiate the effects of different organ system involvement to the time to LLDAS, we did not include SELENA-SLEDAI and PhGA into the multivariable models because of the collinearity. Other multivariable models that did include SLENA-SLEDAI or PhGA instead of renal and cutaneous activity showed that SELENA-SLEDAI and PhGA are independent negative predictors of time to LLDAS, which agrees with previous studies (3,4).

A limitation of our analysis is the lack of sufficient other ethnicities such as Hispanic American and Asian American. SLE is also more severe in Hispanic American patients (13). Hispanic-American patients tend to have more acute disease onset, more lupus nephritis, and higher disease activity and damage, compared to Caucasian patients (14,28,32,49,50). Our cohort represents the Baltimore area, with predominantly African American and Caucasian patients.

This is the largest US study to assess predictors of time to LLDAS. Besides the large population and long follow-up time, the Hopkins Lupus Cohort is the only ongoing cohort in which patients were followed quarterly by 1 rheumatologist (MP) and which comprises both Caucasian and African American patients. Moreover, we censored patients with a gap of >7 months between visits to define time to LLDAS more accurately. This study is the first to include a large number of African Americans and the first to analyze time to LLDAS. We demonstrated the achievability of LLDAS in both African Americans and Caucasian patients, supporting the validity of LLDAS in multiple ethnicities. African American patients with SLE were found to take longer to achieve LLDAS. Characteristics of African American patients with SLE, such as renal activity and hypocomplementemia (38), were also independent predictors of longer time to LLDAS. These findings point to the need to include African American patients with SLE in both clinical and pharmaceutical research, because we cannot generalize from studies from Europe and Asia. LLDAS is an attainable and practical treatment target for both clinical trials and daily practice, as a part of the stepwise approach on the way to remission.

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. Petri had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Babaoğlu, Magder, Petri.
Acquisition of data. Li, Goldman, Petri.
Analysis and interpretation of data. Babaoğlu, Li, Magder, Petri.

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RHEUMATOLOGY REGISTRIES, BIG DATA, AND THE RHEUMATIC DISEASES

Accelerating Medicines Partnership: Organizational Structure and Preliminary Data From the Phase 1 Studies of Lupus Nephritis

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The Accelerating Medicines Partnership (AMP) Lupus Network was established as a partnership between the National Institutes of Health, pharmaceutical companies, nonprofit stakeholders, and lupus investigators across multiple academic centers to apply high-throughput technologies to the analysis of renal tissue, urine, and blood from patients with lupus nephritis (LN). The AMP network provides publicly accessible data to the community with the goal of generating new scientific hypotheses and improving diagnostic and therapeutic tools so as to improve disease outcomes. We present here a description of the structure of the AMP Lupus Network and a summary of the preliminary results from the phase 1 studies. The successful completion of phase 1 sets the stage for analysis of a large cohort of LN samples in phase 2 and provides a model for establishing similar discovery cohorts.

Introduction

LN is a serious complication of systemic lupus erythematosus (SLE) that affects nearly 40% of patients, with even higher rates in minority populations. Despite intense research efforts, treatment options remain inadequate, and the development of novel therapies has been slow. End-stage renal disease and death are common complications in patients with LN (1,2). While histologic classification drives the choice of treatment for LN, this classification is only loosely correlated with patient outcome (3–5). The presence of tubular injury, tubulointerstitial inflammation, and/or interstitial fibrosis is associated with a poorer prognosis of LN (6–8); however, these are late manifestations of LN that reflect the inability to detect early disease and to treat effectively. This failure likely reflects our limited knowledge of the molecular mechanisms driving kidney damage. Thus, there is a critical need for a comprehensive and high-resolution analysis of tissue and immune cells in LN to identify new drug targets and disease biomarkers.

A central challenge of LN has been identifying disease subsets among patients that can be therapeutically targeted. Pathogenic mechanisms inferred from genetic studies have not yet led to effective therapeutic interventions. Animal models are also imperfect because their relationship to human disease is not well defined, and successful interventions have not yet translated to improved patient outcomes. Some progress has been made in

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SIGNIFICANCE & INNOVATIONS

- Successful completion of phase 1 of the Accelerating Medicines Partnership Lupus Network has yielded an optimized set of protocols for state-of-the-art, high-throughput analysis of renal tissue, urine, and blood.
- The phase 1 studies have identified novel inflammatory renal cell populations and their origins and have begun to identify possible molecular biomarkers for disease response.
- Exploratory studies have revealed the potential of using noninvasive cell collections (urine and skin) to longitudinally study the renal landscape.

stratifying patients with lupus based on molecular analyses of whole blood and lymphocyte subsets. Longitudinal monitoring of whole-blood gene expression in 158 pediatric patients identified 7 lupus subgroups as well as a distinct neutrophil signature that is enriched in patients with LN and decreases after treatment. Abnormalities in cell activation remain even after treatment, with differences among nephritis subclasses that suggest differences in the underlying pathogenic mechanisms (9). A CD8 T cell exhaustion signature in the peripheral blood is associated with a better overall prognosis of patients with lupus but not with disease activity per se (10). Nevertheless, how pathogenic mechanisms drive molecular stratification of LN remains poorly understood both because whole blood profiling yields insufficient molecular resolution for mechanistic inferences and because changes in the peripheral blood may not reflect the disease processes in the tissue.

The primary goal of the AMP Lupus Network is to improve our understanding of LN pathogenesis by applying new technologies to the analysis of renal tissue, urine, and blood in order to identify novel targets for drug development and improve diagnostic classification. Supported by the National Institutes of Allergy and Infectious Diseases, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, pharmaceutical companies, and nonprofit organizations across the US, the AMP Lupus Network is comprised of academic centers and investigators focused on directly studying patient samples. The Network applies single-cell molecular profiling and other high-throughput approaches to generate disease-specific, publicly accessible data to the greater biomedical community for further investigations. The driving questions include: Which cell types, cell states, and molecular programs are associated with LN disease activity and responsiveness to therapy? Can surrogate molecular markers (e.g., from urine, blood leukocytes, and/or skin biopsy samples) be leveraged for diagnostic or prognostic purposes?

Structure of the AMP

The AMP Lupus Network consists of 5 technology and clinical centers and a network of clinicians who collect patient data and tissue samples. These centers are supported by an administrative arm, shared with the AMP Rheumatoid Arthritis Network, that oversees data collection, tissue storage, and other logistics and by a network of scientific subcommittees each focused on a particular cell subtype or analytic approach (Figure 1 and Table 1). Regularly scheduled conference calls ensure the cohesiveness of the geographically diverse groups, and face-to-face meetings occur as needed. Shared data has been loaded into ImmPort (www.immport.org; study SDY997).

Clinical design of the AMP and specimen collection

The goals and clinical design of each phase of the AMP Lupus Network are shown in Figure 2. Patients recruited into phase 1 of AMP for the SLE component met the following criteria: American College of Rheumatology (ACR) (11) or the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (12), clinical and laboratory data consistent with LN, and the need for a kidney biopsy to guide clinical care regardless of whether this was a first or repeat biopsy. For phase 1, only patients with urine protein-to-creatinine ratios (UPCRs) >1.0 gm/dl were included; however, for phase 2, patients with UPCRs >0.5 gm/dl are being included. Adult patients of any race/ethnicity or sex were enrolled. Only individuals with International Society of Nephrology/Renal Pathology Society histologic class III, IV, or V (or a mixed class that included 1 of these) were included in the pipeline analyses for phase 1 (Figure 3). Patients received standard-of-care therapy at the discretion of the treating physician. Clinical correlations will be performed in phase 2. Clinical follow-up was performed, and blood and urine samples were obtained according to protocol at 3, 6, and 12 months. If patients underwent a second biopsy, this sample was also collected. As expected, some technical variation was present across the various sites, including the size of the biopsy needle and length of the biopsy.

For the phase 1 program, 57 LN and 15 living transplant donor (LD) renal biopsy samples from unperfused freshly removed organs were collected from 10 sites over 15 months. A total of 45 individuals with class III, IV, or V pathology and 12 LD controls were included in the phase 1 analytic pipeline. Data collected for each enrolled participant included demographic information (Table 2), age at SLE diagnosis, ACR classification criteria, SLICC classification criteria, autoantibody titers, clinical laboratory values (such as C3, C4, creatinine, albumin), urinary parameters (urinalysis, UPCR), Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index scores, physician global assessment, Patient-Reported Outcomes Measurement Information System–29 profile, medications, and adverse events. Research electronic data capture forms were used for data entry; a study-specific database was created and maintained by the AMP Leadership Center.

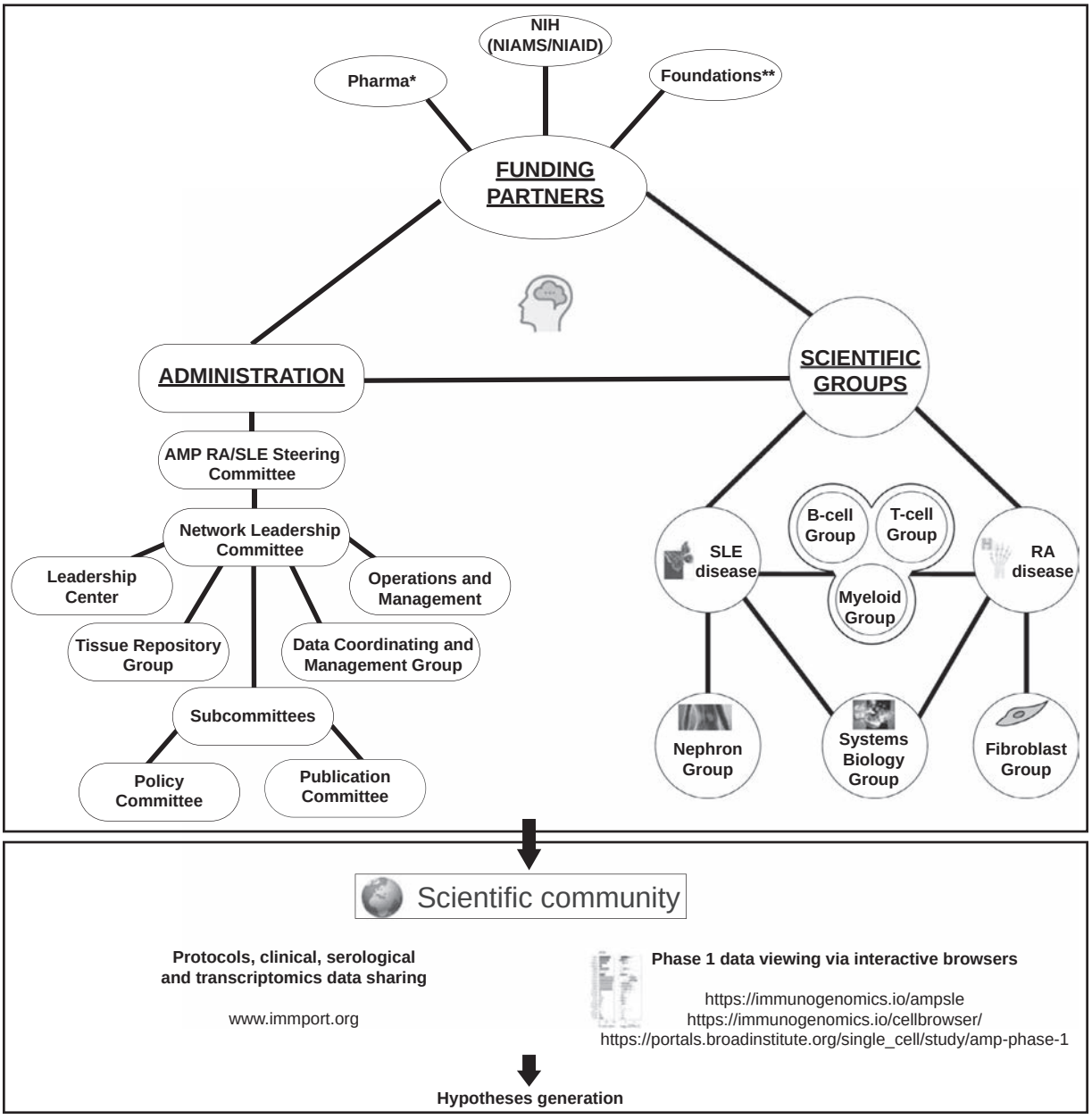

Figure 1. The structure and goals of the Accelerating Medicines Partnership (AMP): overall structure and integration of the AMP Lupus Network (footnotes shown in Table 1). NIH = National Institutes of Health; NIAMS = National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIAID = National Institute of Allergy and Infectious Diseases; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

Renal biopsies were collected and stored as described (13,14). Although some fresh samples were individually processed in the early phases of the study, protocol optimization performed in phase 0 and phase 1 showed that immediate freezing of tissue samples followed by later thawing and dissociation at a single technology site yielded high-quality RNA, ample for downstream applications without a freezing-associated molecular signature (13). This protocol was therefore adopted for all AMP tissue samples. Blood was processed for serum, plasma, peripheral blood mononuclear cells (PBMCs), and total blood leukocytes, and urine was collected and processed using optimized protocols (13,14). For phase 2, all samples will be shipped to a single site for storage and subsequent redistribution to the technology sites.

Single-cell RNA sequencing methods and reproducibility

Single-cell RNA sequencing (scRNAseq) is transforming biomedicine by uncovering new cell types and cellular functions in complex biologic tissues (15). Thousands of single cells from

Table 1. The AMP Lupus Network*

Funding partners
Pharma
AbbVie
Bristol-Myers Squibb
Merck Sharp & Dohme
Pfizer
Sanofi
Takeda Pharmaceuticals International
Janssen Pharmaceuticals
Foundations
Foundation for the National Institutes of Health
Arthritis Foundation
Lupus Research Alliance
Rheumatology Research Foundation
Lupus Foundation of America
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Martin Hodge (Pfizer) and Robert Carter (NIAMS)
Network Leadership Committee and Executive Committee
Michael Brenner and Jennifer Anolik
Policy Committee
Betty Diamond and Michael Weisman
Publication Committee
Betty Diamond and Michael Weisman
SLE Disease Focus Group
Jill Buyon and Betty Diamond
RA Disease Focus Group
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B Cell Group
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Fibroblast Group
Michael Brenner
Nephron Group
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Medical University of South Carolina
Zucker School of Medicine, Northwell Health
Texas Tech University, El Paso
University of Michigan
Temple University
University of Texas
Cedars-Sinai Hospital

* AMP = Accelerating Medicines Partnership; NIAMS = National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIAID = National Institute of Allergy and Infectious Diseases; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

individual tissue samples can now be processed in parallel for deep molecular profiling by next-generation sequencing (NGS). Unbiased bioinformatic analysis enables the identification, characterization, and molecular relationships among individual cells. Because scRNAseq is rapidly evolving, the AMP Lupus Network has adopted contemporary scRNAseq approaches to enable state-of-the-art cellular profiling.

The phase 1 studies used both plate-based (Cel-Seq2) (13) and Fluidigm platforms (C1 chip) (14) to profile transcriptomes of single cells. Plate-based technology enabled deep gene profiling of sorted CD45+ cells for improved cellular characterization but was labor intensive and low throughput; the Fluidigm platform was agnostic, easy to use, and improved throughput but captured fewer genes. These methods were applied to 45 patient samples (21 by Fluidigm and 24 by Cel-Seq2) to reveal for the first time the molecular details of diseased renal parenchymal cells and activated immune cells from tissue at unprecedented resolution (13,14).

Recently, droplet-based approaches have dramatically increased the number of cells that can be profiled in parallel as well as the number of genes detected (16). Single cells are partitioned into nanoliter-scale droplets containing barcoded beads that capture gene transcripts for NGS. Droplet-based scRNAseq (10x Genomics) will be applied to patient samples in phase 2. Thousands of renal cells will be analyzed per sample, thus allowing discovery of rare cell populations and enabling new molecular insights while presenting new challenges in data analysis. Several bioinformatic tools have recently been developed that enable analysis of multiple data sets by minimizing the effects of combined analysis of different scRNAseq technologies (17,18).

The general data analysis pipeline for the phase 1 studies is shown in Figure 3. First, major cell types were identified by

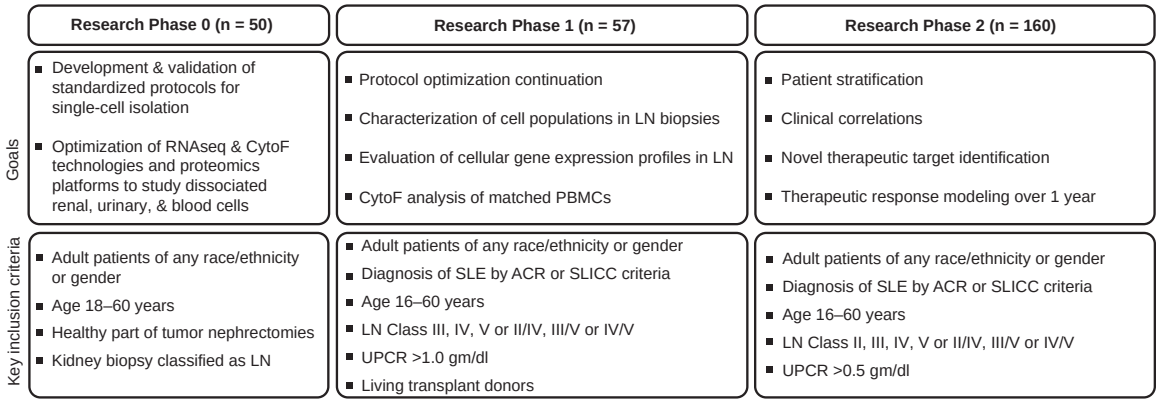

Figure 2. The structure and goals of the Accelerating Medicines Partnership (AMP): goals and enrollment criteria for each phase of the lupus nephritis studies. CytoF = cytometry by time-of-flight mass spectrometry; LN = lupus nephritis; PBMCs = peripheral blood mononuclear cells; SLE = systemic lupus erythematosus; ACR = American College of Rheumatology; SLICC = Systemic Lupus International Collaborating Clinics; UPCR = urine protein-to-creatinine ratio.

grouping the profiled cells into clusters sharing similar gene expression patterns, and then further subclustering was performed to reveal cell subtypes. Cluster labeling was done using a combined approach, taking into account the distribution of known lineage markers across clusters, the identity of genes specifically upregulated in each cluster, and by comparing the gene expression data of each cluster to those of published reference data sets (19–21). Understanding which pathways are active in each cell type was elucidated through pathway enrichment and gene ontology analyses (22,23) and enrichment programs such as DAVID (24) or Enrichr (25). Developmental trajectories were revealed by linking cell types to progenitor populations (26). Importantly, phase 1 established the feasibility for a much larger phase 2 study of 160 LN patients that is currently underway, with initial sample collection almost complete (Figure 2).

Single-cell RNAseq analysis of dissociated tissue raises powerful new hypotheses but has several important technical limitations (15). First, tissue disaggregation destroys spatial context among cell types and may deplete some cell populations for downstream analyses or introduce stress signatures. We have found, for example, that kidney epithelial cells are particularly sensitive to cell death and/or cell stress upon disaggregation. Second, low abundance RNAs may not be detected so that important information about cell function may be missed. Third, scRNAseq profiles RNA transcriptomes, which are only an indirect readout of protein expression and cellular function. Recent advances include multiplexed fluorescent in situ hybridization of tissue sections that gives critical information about the spatial context of multiple cell types, as well as multimodal analysis of single cells to add information about cell surface markers, protein abundance, and epigenomic state (15). These advances are occurring in parallel with the development of new methods to integrate multimodal data and compare data sets from different experiments. While these technologies are too new to be applied in the AMP studies, it is expected that they will soon become possible in the setting of cohort studies of disease such as those described here. Finally, construction of a Human Cell Atlas (https://www.humancellatlas.org) will allow easier comparisons of disease states with normal tissue.

Summary of scRNAseq data from the phase 1 studies

Studies of whole kidney and skin. Both kidney and skin were analyzed by the METRO group (Table 1). Biomarkers available from skin biopsies would be a desirable option, given the easier accessibility of skin as compared to kidney tissue. The concept that skin can reflect the immunologic milieu of SLE dates back to the original demonstration of immunoglobulin and complement deposition at the dermal–epidermal junction in both lesional and nonlesional skin (25). Activation of the microvasculature is found even in non–sun-exposed, nonlesional skin of patients with active lupus (26–28), and endothelial changes in the kidneys of patients with LN predict poor responses to therapy (29). Thus, serial analysis of noninvolved skin, although distant from the primary affected organ, may provide an opportunity to explore surrogates for renal tissue analyses so as to facilitate early identification critical to renal survival and follow treatment responses. Accordingly, 2-mm biopsy samples from nonlesional, non–sun-exposed skin (buttocks) were collected from patients donating renal tissue as part of AMP.

Using a C1 Autoprep system (Fluidigm), skin samples from subjects with LN, healthy skin samples from control subjects, and renal biopsy samples were examined by scRNAseq without presorting or cell-type selection. A total of 21 LN kidney biopsy samples and 17 skin biopsy samples were analyzed in phase 1 (14). Graph-based clustering and t-distributed Stochastic Neighbor Embedding visualization (30) resolved major skin and kidney cell populations, including tubular cells, keratinocytes, endothelial

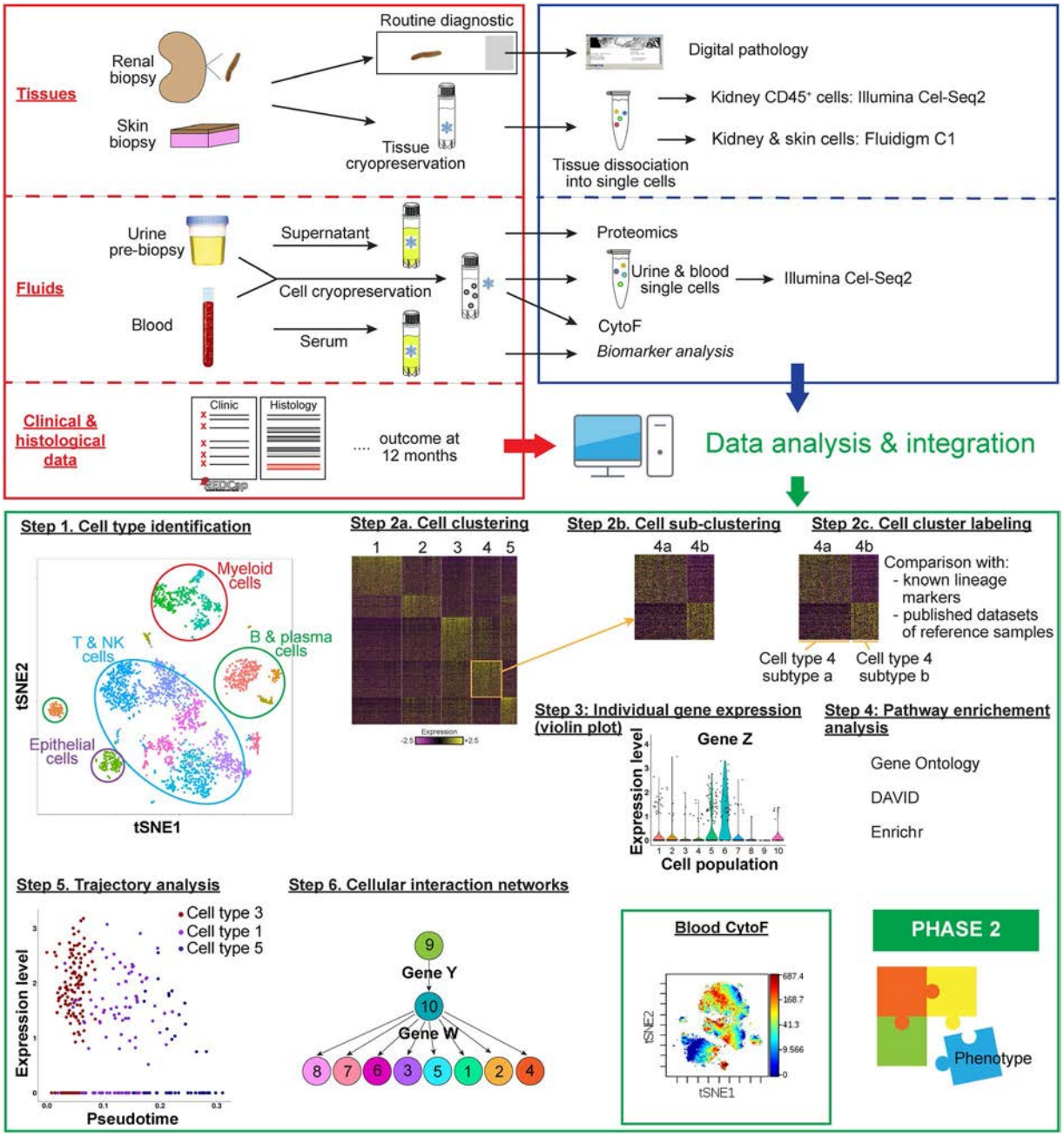

Figure 3. The Accelerating Medicines Partnership (AMP) Lupus Network Pipeline. Samples and clinical data are collected at point of care (**red box**). Patient data is loaded into research electronic data capture (REDCap) and samples are processed according to optimized protocols and shipped to the sample and tissue repository for distribution to the technical sites. Proteomic analyses, cytometry by time-of-flight mass spectrometry (CytoF), and single-cell RNA sequencing are each performed at different technical sites (**blue box**), and data analyses and integration (**green box**) are performed by the scientific groups. Examples of analyses and integration methods are shown in the bottom panel. Profiled cells are grouped into clusters sharing similar gene expression patterns (step 1). The dimensionality of the expression data of these genes is reduced using principal components analysis, and the resulting low-dimensional data is analyzed using graph-based clustering (step 2a). Further subclustering reveals cell subtypes (step 2b). Cluster labeling is performed by taking into account the distribution of known lineage markers across clusters and the identity of genes specifically upregulated in each cluster, and by comparing the gene expression data of each cluster to those of published data sets of reference samples (step 2c). Individual gene expression (violin plot) in each cell subtype can be generated (step 3). Pathway enrichment analysis using curated databases and gene ontology analysis provides information about which genes are active in each pathway (step 4). Developmental trajectories are constructed by linking cell types to progenitor populations (step 5), and regulatory relationships can be inferred between genes using cellular interdependency networks (step 6). Cluster analysis of CytoF data is displayed as a t-distributed Stochastic Neighbor Embedding (tSNE) plot (**box**). Phase 2 will integrate multimodal data to address the goals shown in Figure 2 and to generate hypotheses.

Table 2. AMP SLE phase 1 demographic information*

	Cases (n = 57)†	Controls (n = 15)†
Sex		
Female	52 (92)	11 (73)
Male	5 (9)	4 (27)
Race		
Asian	7 (12)	0
African American	23 (40)	3 (20)
Unknown or not reported	3 (5)	1 (7)
White	25 (43)	11 (73)
Ethnicity		
Hispanic or Latino	17 (30)	2 (13)
Not Hispanic	40 (70)	13 (87)
Age at biopsy, mean ± SD years	31.93 ± 10.50	35.54 ± 6.27
Medication		
Belimumab	3 (5)	
Prednisone	39 (68)	
Hydroxychloroquine	51 (89)	
Methotrexate	1 (2)	
Mycophenolic acid	1 (2)	
Mycophenolate mofetil	14 (25)	
dsDNA+ (n = 48)	40 (83)	
Low C3 (n = 56)	42 (75)	
Low C4 (n = 56)	37 (66)	
ISN/RPS class‡		
I	1 (2)	
II	2 (4)	
II/V	1 (2)	
III	10 (17)	
III/V	9 (16)	
IV	9 (16)	
IV/V	10 (17)	
V	15 (26)	
Activity, mean ± SEM (range) (n = 37)	4.69 ± 0.78 (0–16)§	
Chronicity, mean ± SEM (range) (n = 37)	1.95 ± 0.29 (0–7)¶	
ACR 1997 score (n = 57)	5.84	
SLICC score (n = 51)	7.80	
SELENA–SLEDAI score (n = 57)	12.93	
ACR/SLICC Damage Index (n = 51)	3.99	

* Values are number (%) unless indicated otherwise. AMP = Accelerating Medicines Partnership; SLE = systemic lupus erythematosus; ISN/RPS = International Society of Nephrology/Renal Pathology Society; ACR 1997 = American College of Rheumatology 1997 update of the SLE revised criteria; SLICC = Systemic Lupus International Collaborating Clinics; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index.
† A total of 45 lupus nephritis and 12 living transplant donor controls were analyzed in phase 1, and the others were rolled over to phase 2.
‡ Class VI biopsies were excluded.
§ Maximum 24.
¶ Maximum 12.

cells, fibroblasts, and leukocytes. Subtypes of skin and kidney epithelial cells were further resolved, including melanocytes, sweat gland cells, proximal and distal tubular cells, and collecting duct cells. This agnostic approach allowed us to focus on the epithelial cells of both tissues, which were analyzed for prognostic and diagnostic markers.

Previously published phase 0 studies of LN keratinocytes (31) demonstrated an upregulated interferon (IFN) response signature compared to healthy keratinocytes from control subjects. This finding was replicated in phase 1 and further extended to tubular cells. Preliminary analysis of small numbers of LN patients with available follow-up data found that tubular cells from patients who did not respond to conventional therapy at 6 months post biopsy showed a higher IFN score and increased expression of genes encoding extracellular matrix (ECM) proteins and ECM interaction proteins, suggesting a fibrotic process. A trend toward up-regulation of both ECM pathways was also observed in keratinocytes of nonresponders (32). Exploration of the cellular interactions between various cell types in the kidney and skin suggest that the fibrotic process may be mediated through fibroblast growth factor receptors on the tubular cells whose ligand is expressed in leukocytes. Further preliminary analyses suggested that there might be gene signatures that distinguish histologic subclasses of disease. These findings need to be confirmed in the phase 2 studies. Resident renal cells also expressed high levels of chemokines with receptors expressed by leukocytes, indicating a potential mechanism for immune cell infiltration into the glomeruli and tubulointerstitium (14).

Studies of infiltrating immune cells. Viable CD45+ immune cells were sorted from renal biopsies from 24 LN and 12 unperfused renal LDs, and scRNAseq was performed using Cel-Seq2 (13). Batch effects were minimal, allowing comparison of data from all the samples in a single analysis. We identified 21 immune cell clusters in the patients with LN, including 10 subsets of natural killer (NK) and T cells, 4 clusters of B cells, 6 clusters of macrophages and dendritic cells, and 1 mixed cluster of dividing cells. Memory CD4 T cells and resident macrophages were the most frequently identified subsets in LDs. Saturation analysis indicated that this initial cohort size was sufficient to identify most cell clusters. Comparisons between LN and LD cells indicated that an IFN signature is present in most cell types from the patients with LN.

Analysis of the transcriptome of each subset yielded several novel findings (13). Most of the dividing cells were CD8+ T cells and NK cells; these cells also expressed the most IFNγ. By contrast, Th1 and Th17 cytokine-expressing CD4 T cells were present in lower abundance without skewing to either subset. Novel CD8 T cell subsets were identified in the tissue, but exhausted CD8 T cells were not detected, although these were readily identified in the peripheral blood. B cells of naive and activated phenotypes were detected, including B cells with an age-associated phenotype and plasma cells. Follicular helper T cell–like CD4 T cells were also found, confirming previous data showing that T cell and B cell activation occur in situ (33). Macrophages, myeloid dendritic cells, and plasmacytoid dendritic cells were all found. Analysis of the macrophage subsets showed 3 subpopulations (CM0, CM1, and CM4) that appeared related by trajectory analysis. These cells

most resembled CD16+ peripheral monocytes (34). Of these, the subset most similar to peripheral blood monocytes (CM0) had an inflammatory phenotype, which was lost as the cells progressed along the trajectory; instead, these cells first acquired a phagocytic (CM1) and then an alternatively activated (CM4) phenotype. These alternatively activated cells were also a major immune cell source of chemokines, suggesting that they may help orchestrate immune cell infiltration and/or organization. CXCR4 and CX3CR1 were the most commonly expressed chemokine receptors among the immune cells (13).

The question of noninvasive methods for evaluation of renal status was addressed by analyzing urine samples from 8 patients with LN. Of note, not all of the renal immune cells have access to the urinary space or survive in the urine; compared to kidney cells, urine cells had a lower frequency of T cells and instead were dominated by a single cluster of CD16+ macrophages (cluster CM1). Despite the limited diversity of urine immune cells, their transcriptome faithfully reflected that of the kidneys, indicating that the urine can be used to estimate gene expression of the related kidney cells (13).

Analysis of urine using proteomics

Numerous proteins that participate in the pathophysiology of LN can be measured in the urine, and several distinguish the urine of patients with active LN from that of patients with inactive disease. Nevertheless, longitudinal studies have been few, and there is as yet no biomarker panel that is superior to standard clinical parameters for predicting LN outcomes (35,36). High-throughput proteomic analysis of urine from patients enrolled in the AMP and followed longitudinally for a year will accelerate the pace of discovery of useful LN biomarkers, identify proteomic signatures with greater specificity and sensitivity than a single protein, and help provide additional insights into the underlying biology of the disease process. Furthermore, the ability to correlate proteomic signatures with molecular signatures will greatly enhance the power of this approach.

Two urine proteomics platforms were tested in phase 1 to demonstrate feasibility and identify potential biomarker targets. The first was Quantibody, an array-based, multiplex, enzyme-linked immunosorbent assay (ELISA) system (Raybiotech) for simultaneous quantitative measurement of 1,000 proteins from small urine volumes, including multiple cytokines, growth factors, proteases, and soluble receptors. This assay is highly reproducible and combines the high specificity and sensitivity of ELISA with the high throughput of the glass chip-based array. For some molecules, the sensitivity of the arrays far exceeds that of ELISA assays (37,38). The second approach was a capillary electrophoresis/mass spectroscopy platform that separates and identifies up to 5,000 peptides in the urine with high resolution, sensitivity, and reproducibility. This technology can differentiate chronic kidney disease from LN using a classification panel of peptides (39). Preliminary screens of phase-1 urine samples have shown a large number of elevated proteins and peptides in the urine of patients with LN compared to urine from healthy controls, demonstrating the feasibility of using these 2 proteomic methods in AMP (Petri M: personal communication).

Questions that can now be addressed in phase 2 are whether it is possible to differentiate histologic classes or to identify treatment responders. In addition, with the large number of proteins identified in the urine, it may be possible to perform pathway analyses similar to those performed using transcriptomic data. Integration of the 2 data sets would likely expand our understanding of the pathophysiology of LN.

Analysis of peripheral blood subsets using cytometry by time-of-flight mass spectrometry (CytoF)

CytoF is a method for comprehensive and accurate, multidimensional single-cell phenotyping that employs antibodies tagged with rare-earth metal isotopes rather than fluorescent-tagged antibodies (38). This technology provides the opportunity to simultaneously stain cells with up to 45 different metal-tagged antibodies without major concern for signal spillover or background.

In phase 1 studies, optimization of cell processing and cryopreservation of both total leukocytes (TL) and PBMCs was followed by building of CytoF antibody panels designed to detect major immune cell subset markers. Three PBMC and 2 TL panels were developed for phase 1 to inform the development of phase 2 AMP CytoF panels. During the development period, pilot CytoF antibody panel stains were performed to assure proper staining antibody concentrations and to validate staining accuracy. Other approaches to improve data quality included flow cytometry confirmation of cell counts, an assessment of cell viability, use of platinum isotope barcoding reagents for batched sample acquisition, and normalization of signal intensity during data acquisition. To reduce batch effects, the same Helios instrument was used for the entire phase 1 project, and samples were randomized into groups to include mixtures of controls and patient samples.

The entire AMP phase 1 blood phenotyping project analyzed 34 control, 44 SLE, and 33 rheumatoid arthritis (RA) PBMC samples and 17 control, 36 SLE, and 21 RA TL samples (uploaded as a shared data set to ImmPort [www.immport.org; study SDY997]). No significant batch effects were detected by the AMP Systems Biology Group. CytoF staining data has been analyzed for significant immune cell cluster changes and to determine which markers provided the most useful information for single-cell phenotyping. In general, we observed that circulating immune cell subsets from patients with SLE were significantly more different from healthy controls than were blood immune cells from patients with RA. Several interesting findings included a significant increase in circulating activated CD57+ CD8 T cells, altered ratios of Vδ1 and Vδ2 γδ T cell receptor, and reduced NK cell percentages in patients with SLE compared with controls (Lederer J: personal communication).

The next generation phase 2 CytoF panels have removed uninformative antibodies and expanded marker detection on those immune cell subsets showing significant differences between SLE and RA patients and healthy controls. The phase 2 AMP panels will include 45 markers per panel with new advances in metal isotope antibody labeling methods. In phase 2, blood immune cells from as many as 400 SLE and RA patients will be profiled using newly designed antibody panels that are T cell, B cell, innate cell, and neutrophil centric. We anticipate that the results from AMP phase 2 will identify immune cell phenotypes that could be used to diagnose, predict, or better understand the pathobiology of the SLE disease process.

Conclusion

Phase 1 lupus AMP studies have identified novel inflammatory cell populations and their origins, have begun to identify possible molecular biomarkers for disease response, and have suggested that it may eventually be possible to use noninvasive cell collections to longitudinally study the renal landscape. Together, the phase 1 studies set the stage for phase 2 analysis of renal tissue from 160 well-characterized patients with LN from which both renal resident cells and immune cells will be analyzed using 10x Genomics technology. This will allow us to correlate peripheral blood cell phenotype by CytoF, the renal transcriptome, and the urine proteome with patient histologic subclass, response to therapy, and outcome at 12 months. New hypotheses can then be examined using more focused molecular and histologic analyses in new cohorts and examination of specific molecules and pathways in relevant mouse models.

The AMP studies have been completed within the prescribed timeframe and with organized input from many investigators, including multiple clinicians who are providing a rich clinical data set to accompany the genomic, proteomic, and CytoF studies. The phase 1 studies have demonstrated good patient safety, and the preliminary analyses have confirmed that the data is of high quality. Central storage and the ability to freeze and batch samples has been a key component in maintaining quality. The application and development of new bioinformatics tools such as trajectory analysis and Harmony (17) should enable further novel molecular insights from the larger cohort. As advanced technologies become available, such as histologic immunophenotyping with large numbers of markers, T cell and B cell repertoire analysis, barcoding, and epigenetic profiling, the AMP organizational model can be used as a template for new discovery cohorts.

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AUTHOR CONTRIBUTIONS

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

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RHEUMATOLOGY REGISTRIES, BIG DATA, AND THE RHEUMATIC DISEASES

Defining Depression and Anxiety in Individuals With Rheumatic Diseases Using Administrative Health Databases: A Systematic Review

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Objective. To conduct a systematic review to describe how administrative health databases have been used to study depression and anxiety in patients with rheumatic diseases and to synthesize the case definitions that have been applied.

Methods. Search strategies to identify articles evaluating depression and anxiety among individuals with rheumatic diseases were employed in Medline, Embase, CINAHL, Cochrane Database of Systematic Reviews, and PsycINFO. Studies included were those using administrative health data and reporting case definitions for depression and anxiety using International Classification of Diseases (ICD) codes. We extracted information on study design and objectives, administrative health database, specific data sources (e.g., inpatient, pharmacy records), ICD codes, operational definitions, and validity of case definitions.

Results. Of the 36 studies included in this review, all studies assessed depression, and 13 studies (36.1%) evaluated anxiety. A number of specific ICD-9/10 codes were consistently applied to identify depression and anxiety, but the overall combination of ICD codes and operational definitions varied across studies. Twenty-four studies reported operational definitions, and 19 of these studies (79.2%) combined claims from more than 1 type of administrative data source (e.g., inpatient, outpatient). Validated case definitions were used by 6 studies (16.7%), with sensitivity estimates for depression and anxiety case definitions ranging from 33% to 74% and 42% to 76%, respectively.

Conclusion. We identified numerous case definitions used to evaluate depression and anxiety among individuals with rheumatic diseases within administrative health databases. Recommendations include using case definitions with demonstrated validity as well as operationalizing case definitions within multiple data sources.

INTRODUCTION

Pain and disability along with complications such as cardiovascular disease (1–3) characterize the tremendous physical impacts of rheumatic diseases, which include rheumatoid arthritis (RA), systemic autoimmune rheumatic diseases (SARDs), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and gout. Beyond the physical complications associated with rheumatic diseases, there is also an increased burden and risk of mental illness, namely depression and anxiety (4,5). Recent systematic reviews report prevalence estimates for depression ranging from 15% to 39% in individuals with RA (5) and 24% to 39% in individuals with systemic lupus erythematosus (4). Moreover, a recent Canadian population-based study reported that individuals with

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SIGNIFICANCE & INNOVATIONS

- This systematic review of 36 studies identified and assessed case definitions applied to study depression and anxiety among individuals with various rheumatic diseases using administrative health databases.
- Practical implications of this systematic review include recommendations to use validated case definitions for depression and anxiety and to link multiple administrative data sources to optimize sensitivity for future studies.

RA have a 1.5-fold increased risk for incident depression and a 1.2-fold increased risk for incident anxiety (6). The negative impacts of these mental illnesses in the context of rheumatic diseases include increased disease activity (7,8), suboptimal treatment adherence (9,10), reduced treatment response (11), and decreased quality of life (12,13).

Along with findings of increasing burden and risk of mental illnesses in individuals with rheumatic diseases, the aforementioned publications also suggest the increasing use of administrative health databases to assess the impact of depression and anxiety. Administrative health databases refer to secondary data collected for billing purposes, which may be composed of several unique administrative data sources such as those capturing inpatient visits, outpatient visits, and prescription claims, and with data sources often linked at the individual level. Administrative health data are advantageous in their availability, and when assessed with an appropriate design, they have the ability to reduce common biases associated with hospital- and clinic-based studies. However, identifying depression and anxiety within administrative health databases presents challenges such as misclassification, and various definitions have apparently been used to define these mental illnesses (14,15). Indeed, the use of numerous case definitions to assess mental illness in individuals with rheumatic diseases may affect estimates, as suggested by 1 study showing that prevalence estimates of comorbid mental illnesses in individuals with diabetes mellitus can range from 13% to 34%, depending on the coding algorithm being applied (16). Because administrative health data will continue to be an important resource for epidemiologic and health services research of mental illness in individuals with rheumatic diseases, efforts to improve research approaches, such as applying consistent case definitions and reporting are necessary. Therefore, to optimize evaluation of mental illnesses among patients with rheumatic diseases, the aim of this systematic review was to understand the context in which administrative health databases have been used to study depression and anxiety in individuals with rheumatic diseases and to synthesize the case definitions that have been used.

MATERIALS AND METHODS

Literature search strategy. We constructed 5 search strategies (i.e., 1 search for each type of rheumatic disease) with a research librarian who used subject headings and key words to capture all original, peer-reviewed articles on depression and anxiety within RA, SARDs (including systemic lupus erythematosus, systemic sclerosis/scleroderma, Sjögren's syndrome, dermatomyositis/polymyositis, and systemic vasculitides), AS, PsA, and gout (see Supplementary Appendix 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24048/abstract). Subject headings were unique to each database but similar to the medical subject headings used in Medline. The research librarian conducted the searches in Medline (1946–), Embase (1974–), CINAHL (1982–), Cochrane Database of Systematic Reviews (2005–), and PsycINFO (1880–) from database inception to April 2018. All articles identified with the search strategy were imported to Endnote X6 to organize the study selection process.

Study selection. We concurrently screened titles, abstracts, and full texts with the following inclusion criteria: 1) observational study design using administrative health data; 2) patient population of RA, SARDs, AS, PsA, or gout; 3) depression and/or anxiety as a study variable (i.e., outcome, exposure, covariate); 4) cases of depression and/or anxiety defined using International Classification of Diseases (ICD) codes and/or providing the operational definition; 5) adult participants (age ≥18 years) in the study sample; and 6) publication in English. Case definitions for depression and anxiety that were reported in Supplementary material, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24048/abstract, or previously published work, were also accessed for this review. Further, we included studies that either combined depression and anxiety as a single variable or those that assessed depression/anxiety with another health-related diagnosis. Studies relying on administrative health databases that do not use the ICD coding system (e.g., the General Practice Research Database) or those where the definition of depression or anxiety were within the context of a comorbidity index (e.g., Elixhauser) were excluded.

Data extraction and assessment. Two study authors (AH and MADV) extracted information on year of publication, country, study design, study objectives, the administrative health database (e.g., Market Scan Database in the US, National Health Insurance Research Database in Taiwan), specific administrative data sources (e.g., ambulatory/outpatient, inpatient, pharmacy records), ICD codes, and operational definitions. The operational definition refers to the criteria (e.g., number of ICD codes) and administrative data sources used to identify cases within the administrative health database, and together the ICD codes and

operational definition form the case definition. In addition, we specified the ICD version (e.g., Ninth Revision [ICD-9] or Tenth Revision [ICD-10]) used as well as the variable type for depression or anxiety (e.g., primary outcome). We also assessed whether case definitions were validated, either within the study itself or in a previous publication.

Following data extraction, we reviewed articles for completeness with respect to 3 criteria: 1) reported ICD codes for depression and/or anxiety, 2) outlined protocol for operationalizing case definitions within the administrative health database, and 3) used a validated case definition for depression and/or anxiety. We awarded a single point for each criterion if present in the article, resulting in a maximum overall score of 3. Given the fact that we excluded studies in which both ICD codes and operational definitions were absent, each study inherently received a minimum score of 1.

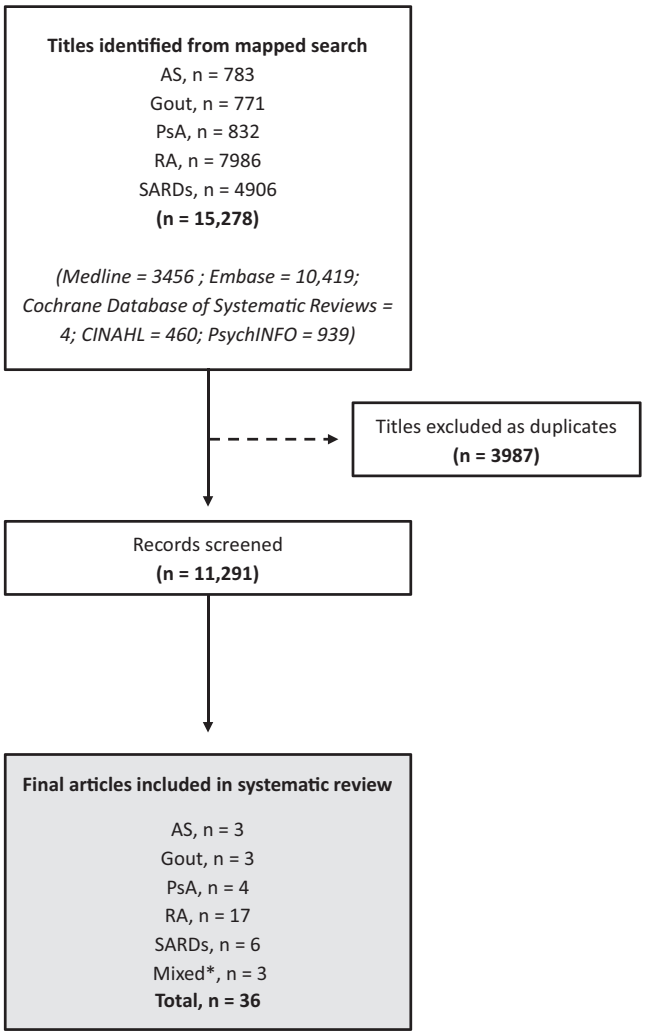

Figure 1. Review of search results. * = multiple types of rheumatic diseases combined as a single population sample; AS = ankylosing spondylitis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SARDs = systemic autoimmune rheumatic diseases.

RESULTS

Study characteristics. After the removal of duplicates, a total of 11,291 articles were identified in our literature search (Figure 1). Screening for eligibility criteria resulted in 36 studies being included. The majority of studies included were conducted in RA (n = 17), followed by SARDs (n = 6), PsA (n = 4), AS (n = 3), mixed rheumatic disease patient populations (n = 3), and gout (n = 3). The administrative health databases used were from the following countries: Taiwan (n = 14), US (n = 8), Canada (n = 4), Sweden (n = 4), Denmark (n = 2), UK (n = 1), Germany (n = 1), Finland (n = 1), and Japan (n = 1). The majority of studies (n = 31 [86.1%]) were published since 2010. A description of study characteristics is shown in Table 1. With regard to completeness of reporting, only 6 articles met all 3 criteria, describing the ICD codes, providing an operational definition, and using a validated case definition (6,17–21).

All 36 of the studies included in the review assessed depression, and 13 studies (36.1%) evaluated anxiety. Three studies combined multiple psychiatric diagnoses into a single variable, specifically: anxiety and depression (22), psychosis and depression (23), and affective/neurotic disorders (24). In addition, 1 study combined depression and insomnia into a single primary outcome (25). Anxiety and depression were evaluated as a primary outcome in 18 studies, as an exposure in 4 studies, and as both a primary outcome and exposure in 1 study. Last, there were 13 studies that included anxiety and depression as a covariate or comorbidity in their analyses.

ICD codes for defining depression and anxiety. Twenty-eight studies evaluated depression or anxiety according to the ICD-9 coding system, 13 using ICD-10, and 4 using ICD-8. The earliest study included in our review, by Allebeck et al (26) in 1985, employed a Swedish version of the ICD-8, for which the diagnostic codes for depression and anxiety were 300.40 and 300.00, respectively. Altogether, 7 studies included case definitions applying more than 1 edition of the ICD.

The most frequently used individual ICD-9/10 codes are shown in Table 2. For depression, the most commonly applied ICD-9 and ICD-10 codes are 311 and F32/F33, respectively. Authors identifying cases of anxiety predominantly used 300.0 from the ICD-9 and F40/F41 from the ICD-10. In terms of collective definitions, the most frequently used group of ICD codes using ICD-9 to identify cases of depression are: 296.2, 296.3, 300.4, and 311 (n = 12 studies). The most frequent combination of ICD-10 codes included both F32 and F33 (n = 5 studies). Among the few studies that did evaluate anxiety, 4 studies by Marrie et al (6,17–19) applied consistent combinations of ICD codes (ICD-9: 300.0 and 300.2; ICD-10: F40 and F41). Overall, while there is some observed similarity across studies with regard to ICD codes, the operational definitions are relatively inconsistent across studies.

Table 1. Characteristics of included studies that assessed depression and anxiety, using administrative health databases, among individuals with rheumatic diseases*

Author, year (ref.)	Country	Study design	Administrative health database	Objective
Ankylosing spondylitis (n = 3)				
Meesters, 2014 (37)	Sweden	Cohort	Skåne Healthcare Register	To evaluate the risk of depression in patients with AS
Shen, 2016 (38)	Taiwan	Cohort	National Health Insurance Research Database	To evaluate the risk of psychiatric disorders in patients with AS
Shen, 2016 (22)	Taiwan	Cohort	National Health Insurance Research Database	To evaluate the risk of sleep disorders in patients with AS
Gout (n = 3)				
Changchien, 2015 (39)	Taiwan	Cohort	National Health Insurance Research Database	To evaluate the risk of incident depression among patients with gout
Chen, 2015 (40)	Taiwan	Cohort	National Health Insurance Research Database	To evaluate the association between gout and erectile dysfunction
Hsu, 2015 (41)	Taiwan	Cohort	National Health Insurance Research Database	To evaluate the association between gout and erectile dysfunction
Psoriatic arthritis (n = 4)				
Ballegaard, 2018 (42)	Denmark	Cohort	Danish National Patient Register	To evaluate the relationship between comorbidities and tumor necrosis factor inhibitor treatment among patients with PsA
Feldman, 2015 (43)	US	Cohort	OptumHealth Reporting and Insights claims database	To assess health care utilization, costs, and comorbidities in patients with psoriasis and PsA
Shah, 2017 (21)	US	Cohort	MarketScan Database	To understand the rate of comorbidities in patients with PsA
Wu, 2016 (25)	Taiwan	Cohort	National Health Insurance Research Database	To evaluate the association between biologic therapy and risk of depression and insomnia in patients with psoriasis and PsA
Rheumatoid arthritis (n = 17)				
Allebeck, 1985 (26)	Sweden	Cohort	Stockholm County medical information system	To evaluate the rate of RA hospital visits among patients with psychiatric conditions
Bengtsson, 2016 (44)	Sweden	Cross-sectional	1. Anti-Rheumatic Therapy in Sweden register 2. Vega administrative health care register	To evaluate differences in demographics, comorbidities, and health care consumption among RA patients treated with or without biologics
Drosselmeyer, 2017 (45)	Germany	Cohort	Disease Analyzer database	To estimate the prevalence and risk factors for depression in patients with late-onset RA
Guelfucci, 2018 (46)	Japan	Cohort	Japan Medical Center claims database	To determine characteristics of health care utilization among patients with RA and comorbid depression
Jacob, 2017 (47)	UK	Cohort	Disease Analyzer database	To assess the risk of depression in patients diagnosed with RA
Joyce, 2009 (48)	US	Cohort	PharMetrics Patient-Centric Database	To compare health care utilization and costs among RA patients with and without cardiovascular disease and depression
Lin, 2015 (49)	Taiwan	Cohort	National Health Insurance Research Database	To estimate the incidence and risk factors of depression in patients with RA
Lu, 2016 (50)	Taiwan	Cohort	National Health Insurance Research Database	To estimate the incidence of depression in individuals with RA and the incidence of RA in patients with depression
Marrie, 2017 (18)	Canada	Cohort	Manitoba Population Research Data Repository	To estimate the incidence of psychiatric comorbidities in inflammatory diseases (including RA)
Marrie, 2018 (19)	Canada	Cohort	Manitoba Population Research Data Repository	To evaluate the relationship between physical comorbidities and psychiatric disorders among individuals with inflammatory diseases (including RA)
Marrie, 2018 (6)	Canada	Cohort	Manitoba Population Research Data Repository	To estimate the prevalence and incidence of psychiatric comorbidities in patients with RA

(Continued)

Table 1. (*Cont'd*)

Author, year (ref.)	Country	Study design	Administrative health database	Objective
Marrie, 2019 (17)	Canada	Cohort	Manitoba Population Research Data Repository	To evaluate if there is an increased risk of psychiatric comorbidity before diagnosis of an inflammatory disease (including RA)
Mikuls, 2013 (51)	US	Cohort	1. Veterans Affairs Rheumatoid Arthritis registry 2. Veterans Affairs Decision Support System	To evaluate the effect of post-traumatic stress disorder on RA disease activity
Scherrer, 2009 (20)	US	Cohort	Veteran Affairs National Administrative Databases	To examine if depression increases the risk of incident myocardial infarction in individuals with RA
Timonen, 2003 (52)	Finland	Cohort	Finnish Hospital Discharge Register	To describe the characteristics of patients with RA dying by suicide
Tsai, 2017 (53)	Taiwan	Cohort	National Health Insurance Research Database	To examine if depression increases the risk of incident stroke in individuals with RA
Wang, 2014 (54)	Taiwan	Cohort	National Health Insurance Research Database	To estimate the incidence and risk factors of depression in patients with RA
SARDs (n = 6)				
Chen, 2018 (55)	Taiwan	Cohort	National Health Insurance Research Database	To assess glucocorticoid use and adverse events in individuals with SLE
Liu, 2015 (56)	Taiwan	Cohort	National Health Insurance Research Database	To examine the risk of Parkinson's disease in individuals with SLE
Shah, 2013 (57)	US	Cohort	IMS LifeLink Health Plans Claims Database	To evaluate adverse events related to corticosteroid use and cost of adverse event treatment in individuals with SLE
Shen, 2015 (58)	Taiwan	Cohort	National Health Insurance Research Database	To evaluate the risk of psychiatric disorders in individuals with SS
Tang, 2016 (59)	Taiwan	Case-control	National Health Insurance Research Database	To examine determinants of suicide attempt by drug overdose in patients with SLE
Wells, 2010 (23)	US	Case-control	California Office of Statewide Health Planning and Development	To assess if nephritis and other comorbidities increase the risk of acute myocardial infarction among patients with SLE
Mixed patient population (n = 3)				
Benros, 2013 (60)	Denmark	Cohort	1. Danish Psychiatric Central Research Register 2. Danish National Hospital Registry 3. Danish Civil Registration System	To estimate the risk of mood disorders in patients with autoimmune diseases and severe infections
Sundquist, 2008 (24)	Sweden	Cohort	MigMed database	To analyze the association between AS, RA, and SLE and hospitalization for psychiatric disorders
Wu, 2017 (61)	US	Cohort	1. Group Health Cooperative 2. Kaiser Permanente Southern California	To evaluate the risk of depression, suicide ideation, and suicide attempt in patients with psoriasis, PsA, and AS

* ref. = reference; AS = ankylosing spondylitis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SARDs = systemic autoimmune rheumatic diseases; SLE = systemic lupus erythematosus; SS = Sjögren's syndrome.

Operational definitions for depression and anxiety using ICD codes. In total, 24 studies (66.7%) reported their approach to operationalizing ICD codes to identify cases of depression and anxiety within administrative health databases (Table 3). Four studies restricted cases of depression and anxiety to those diagnosed by a psychiatrist. Six of the included studies incorporated prescription claims in addition to ICD codes in their operational definitions. Among the studies reporting their operational definitions, 19 (79.2%) assessed claims from more than 1 type of administrative data source (i.e., inpatient, outpatient, emergency, prescription).

Validity of depression and anxiety case definitions. There were 6 studies that used validated case definitions for depression and anxiety using ICD-9/10 codes (6,17–21). Four of the studies in this review (6,17–19) applying a validated case definition evaluated depression and anxiety as a primary outcome among individuals with RA and used case definitions that had been previously validated in populations with multiple sclerosis and inflammatory bowel disease (6,17–19,27,28). These case definitions for depression and anxiety resulted in moderate (0.49) and fair (0.23) kappa scores, respectively (27). In addition, 1 study (20) assessing the impact of depression on the risk of myocar-

Table 2. Description of the ICD-9 and ICD-10 codes used in case definitions to identify depression and anxiety (selected ICD-9/10 codes with a minimum of 50% coverage for the included studies)*

Code (no. of studies)	Definition	Coverage†
Depression: ICD-9 (n = 28)		
311	Depressive disorder, not elsewhere classified	26 (93)
296.2	Major depressive disorder, single episode	25 (89)
296.3	Major depressive disorder, recurrent episode	25 (89)
300.4	Dysthymic disorder	24 (86)
Depression: ICD-10 (n = 13)		
F32	Major depressive disorder, single episode	13 (100)
F33	Major depressive disorder, recurrent episode	13 (100)
F34	Persistent mood (affective) disorders	8 (62)
Anxiety: ICD-9 (n = 11)		
300.0	Anxiety states	11 (100)
300.2	Phobic disorders	6 (55)
Anxiety: ICD-10 (n = 6)		
F40	Phobic anxiety disorders	6 (100)
F41	Other anxiety disorders	6 (100)

* ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = Tenth Revision.
† Number of studies (%).

dial infarction in individuals with RA applied a previously validated case definition for depression having an estimated positive predictive value (PPV) of 99.0% (20,29). Finally, 1 study assessing depression as a covariate among individuals with PsA applied a more inclusive case definition using ICD-9 codes (21). When the original article validated this case definition against clinical charts, the sensitivity was low (32.9%), but specificity, PPV and negative predictive value (NPV) were all ≥90% (14). The validation estimates for depression and anxiety case definitions from the original validation studies are shown in Table 4.

DISCUSSION

This systematic review aimed to understand the context in which administrative health databases have been used to study depression and anxiety in individuals with rheumatic diseases and to synthesize the case definitions for depression and anxiety in this patient population. All of the 36 studies identified in this review evaluated depression, while 13 of the studies (36%) assessed anxiety. A number of specific ICD codes were consistently included in the case definitions; for example, over 90% of studies evaluating depression using ICD-9 or ICD-10 included 311 or F32 and F33, respectively. The majority of studies reporting an operational definition included administrative data sources that capture inpatient and outpatient visits, and a number of operational definitions also incorporated pharmacy records. Although only one-sixth of the studies referenced the validity of their case definition, these demonstrated reasonable estimates of validity, with sensitivity ranging from 33% to 74% and specificity over 80% for depression. Altogether, our systematic review highlights the increasing use of administrative health databases to study the epidemiology and impacts of mental health in individuals with rheumatic disease. Moreover, our synthesis contributes to a necessary discussion on the use of administrative health data to evaluate depression and anxiety in the context of rheumatology and provides recommendations for future studies.

Previous systematic reviews on the use of administrative health data to assess depression and anxiety have focused on synthesizing studies that have used validated case definitions (14,15). In 2014, Fiest et al (14) identified 3 studies that validated case definitions for depression within the general population and the authors also developed 6 new case definitions using both ICD-9 and ICD-10 codes. The case definitions developed by Fiest et al (14) were classified as most restrictive, moderately inclusive, and most inclusive according to the increasing scope of ICD codes included. Both the published and developed case definitions were operationalized to require 1 ICD code for depression recorded in any diagnostic position within a single data source that captured inpatient visits and resulted in low sensitivity (1–36%), but over 90% for estimated specificity, PPV, and NPV (14). The most restrictive case definition developed by Fiest et al (14) (ICD-9: 296.2, 296.3, 300.4, 311) was the most frequently applied group of ICD codes identified in our systematic review. This restrictive case definition for depression using inpatient ICD-9 codes resulted in a sensitivity of 29%, PPV of 92%, and NPV of 91% (14). The low sensitivity estimates corresponding to each of the depression case definitions of Fiest et al (14) are presumably related to operational definitions being confined to data sources capturing inpatient encounters, while prior work has demonstrated that the majority of diagnostic codes for depression are recorded in data sources capturing outpatient encounters (30).

In addition, a 2012 systematic review by Townsend et al (15) identified 11 articles that validated case definitions for depression in any population and recommended the use of the same restrictive set of ICD codes described in the review of Fiest et al (14). However, the operational definition differed in that it required a minimum of 2 recorded ICD codes in the outpatient setting and/or prescriptions for antidepressants within a 12-month period (15). This definition resulted in a higher sensitivity (95%) but reduced specificity (65%) and PPV (49%) (31). Findings of these reviews emphasize the multitude of ICD codes that have been used to evaluate depression and the impact of operational definitions. Last, although the 2016 systematic review of Davis et al (32) has summarized validation statistics of case definitions for several mental illnesses, including anxiety, we were unable to find a systematic review that specifically described validated case definitions for anxiety. Overall, a number of validated case definitions to assess mental illnesses exist, but how ICD case definitions have been used to define depression and anxiety in the context of rheumatic diseases is unclear, and our systematic review provides that clarity.

Table 3. Case definitions for depression and/or anxiety using administrative health data among individuals with rheumatic diseases*

Author, year (ref.)	Rheumatic disease	Outcome	Type of variable	ICD codes	Operational definition	Validity indicated/ validation conducted	Completeness of reporting assessment†
Primary outcome and/or exposure (n = 23)							
Allebeck, 1985 (26)	RA	Depression	Exposure	ICD-8: 300.40	≥1 inpatient visit	No	2
		Anxiety	Exposure	ICD-8: 300.00	≥1 inpatient visit	No	
Benros, 2013 (60)	Mixed rheumatic diseases	Depression	Primary outcome	ICD-8: 296.09, 296.29, 296.99, 298.09, 300.49; ICD-10: F32 F33	1 inpatient visit or 1 emergency department visit or 1 outpatient visit as diagnosed by a psychiatrist	No	2
Changchien, 2015 (39)	Gout	Depression	Primary outcome	ICD-9: 296.2, 296.3, 300.4, 311	Not specified	No	1
Chen, 2018 (55)	SARDs	Depression	Primary outcome	ICD-9: 296.2x, 296.3x, 300.4, 311	Not specified	No	1
Drosselmeyer, 2017 (45)	RA	Depression	Primary outcome	ICD-10: F32, F33	Primary care documentation including diagnoses by psychiatrists	No	2
Jacob, 2017 (47)	RA	Depression	Primary outcome	ICD-10: F32, F33	Not specified	No	1
Lin, 2015 (49)	RA	Depression	Primary outcome	ICD-9: 296.2, 296.3, 300.4, 311	≥2 outpatient visits or ≥1 inpatient visit	No	2
Lu, 2016 (50)	RA	Depression	Primary outcome and exposure	ICD-9: 296.2, 296.3, 300.4, 311	≥3 outpatient visits or ≥1 inpatient visit	No	2
Marrie, 2017 (n = 1) (18), Marrie, 2018 (n = 2) (6,19), and Marrie, 2019 (n = 1) (17)	RA	Depression	Primary outcome	ICD-9: 296.2, 296.3, 298.0, 300.4, 311; ICD-10: F32, F33, F34; ATC: N06AA01, N06AA02, N06AA04, N06AA11, N06AA12, N06AA17, N06AA21, N06AB03, N06AB04, N06AB05, N06AB06, N06AB08, N06AB10, N06AF03, N06AF04, N06AG02, N06AX06, N06AX11, N06AX16, N06AX21, N06AX23	≥1 hospital visit or ≥5 physician visits or ≥1 physician visit and ≥7 prescription claims	Yes	3
		Anxiety	Primary outcome	ICD-9: 300.0, 300.2; ICD-10: F40, F41; ATC: N05AB12, N05AB06	≥1 hospital visit or ≥2 physician visits or ≥1 physician visit and ≥2 prescription claims	Yes	
Meesters, 2014 (37)	AS	Depression	Primary outcome	ICD-10: F32, F33	Doctor-diagnosed	No	2
Scherrer, 2009 (20)	RA	Depression	Exposure	ICD-9: 296.2, 296.3, 300.4, 311	2 outpatient visits or 1 inpatient visit in the same year	Yes	3
Shah, 2013 (57)	SARDs	Depression	Primary outcome	ICD-9: 300.0, 296.2, 296.3, 298.0, 311, 301.12, 292.84, 309.28, V79.0	Not specified	No	1
Shen, 2015 (58)	SARDs	Depression	Primary outcome	ICD-9: 296.2, 296.3, 300.4, 311	Psychiatrist-diagnosed	No	2
		Anxiety	Primary outcome	ICD-9: 300.0, 300.2, 300.3, 308.3, 309.81	Psychiatrist-diagnosed	No	
Shen, 2016 (38)	AS	Depression	Primary outcome	ICD-9: 296.2, 296.3, 300.4, 311	Psychiatrist-diagnosed	No	2
		Anxiety	Primary outcome	ICD-9: 300.0, 300.2, 300.3, 308.3, 309.81	Psychiatrist-diagnosed	No	

(Continued)

Table 3. (*Cont'd*)

Author, year (ref.)	Rheumatic disease	Outcome	Type of variable	ICD codes	Operational definition	Validity indicated/ validation conducted	Completeness of reporting assessment†
Sundquist, 2008 (24)	Mixed rheumatic diseases	Affective disorders	Primary outcome	ICD-8: 296, 298.A, 300.E, 309, 311; ICD-9: 296, 298.A, 300.E, 309, 311; ICD-10: F30-F39	1 inpatient visit	No	2
		Neurotic disorders	Primary outcome	ICD-8: 300.A, 300.B, 300.C, 300.D, 300.F, 300.G, 300.H, 300.W, 300.X; ICD-9: 300.A, 300.B, 300.C, 300.D, 300.F, 300.G, 300.H, 300.W, 300.X; ICD-10: F40-F48	1 inpatient visit	No	
Tsai, 2017 (53)	RA	Depression	Exposure	ICD-9: 296.2, 296.3, 300.4, 311	≥3 outpatient visits or ≥1 inpatient visit	No	2
Wang, 2014 (54)	RA	Depression	Primary outcome	ICD-9: 296.2x-296.3x, 300.4, 311.x	Psychiatrist-diagnosed	No	2
Wells, 2010 (23)	SARDs	Psychosis and depression‡	Exposure	ICD-9: 293, 294.9, 296, 297, 298, 323.8, 323.9	≥1 inpatient visit	No	2
Wu, 2016 (25)	PsA	Depression and insomnia‡	Primary outcome	ICD-9: 296.2, 296.3, 298.0, 300.4, 309.28, 311, and V790	Not specified	No	1
Wu, 2017 (61)	Mixed rheumatic diseases	Depression	Primary outcome	ICD-9: 296.2x, 296.3x, 300.4, 309.0, 309.1, 311	Not specified	No	1
Covariate or comorbidity (n = 13)							
Ballegaard, 2018 (42)	PsA	Depression	Comorbidity	ICD-10: F31-F34, F38-F39	Not specified	No	1
		Anxiety	Comorbidity	ICD-10: F40-F41	Not specified	No	
Bengtsson, 2016 (44)	RA	Depression	Comorbidity	ICD-10: F32, F33	Physician visits in primary and secondary health care or as discharge diagnosis after hospitalization	No	2
Chen, 2015 (40)	Gout	Depression	Comorbidity, covariate	ICD-9: 296.2, 296.3, 300.4, 311	Not specified	No	1
Feldman, 2015 (43)	PsA	Depression	Comorbidity	ICD-9: 296.2, 296.3, 298.0, 300.4, 309.1, 311	Not specified	No	1
		Anxiety	Comorbidity	ICD-9: 300.0	Not specified	No	
Guelfucci, 2018 (46)	RA	Depression	Comorbidity	ICD-10: F03, F32.0, F32.1, F32.2, F32.8, F32.9, F33.1, F33.2, F33.3, F33.9, F34.1, F34.9, F41.2, F53.0	≥2 diagnostic codes and ≥2 prescriptions for treatment of depression (e.g., SSRI, SNRI, TCA, and MAOI)	No	2
Hsu, 2015 (41)	Gout	Depression	Comorbidity, covariate	ICD-9: 296.2, 296.3, 300.4, 311	Not specified	No	1
		Anxiety	Comorbidity, covariate	ICD-9: 300.00	Not specified	No	

(Continued)

Table 3. (*Cont'd*)

Author, year (ref.)	Rheumatic disease	Outcome	Type of variable	ICD codes	Operational definition	Validity indicated/ validation conducted	Completeness of reporting assessment†
Joyce, 2009 (48)	RA	Depression	Comorbidity	ICD-9: 296.2x, 296.3x, 296.82, 296.90, 300.4, 311, 309, 309.1	Diagnostic code (inpatient, outpatient) plus evidence of antidepressant during the pre-index period	No	2
Liu, 2015 (56)	SARDs	Depression	Comorbidity, covariate	ICD-9: 296.2, 296.3, 296.82, 300.4, 311	Not specified	No	1
Mikuls, 2013 (51)	RA	Depression	Comorbidity, covariate	ICD-9: 296.2-296.36, 296.90, 311.xx	≥1 diagnostic code	No	2
		Anxiety	Comorbidity, covariate	ICD-9: 300.00, 300.01, 300.02, 309.xx (excluding 309.81)	≥1 diagnostic code	No	
Shah, 2017 (21)	PsA	Depression	Comorbidity	ICD-9: 296.2x, 296.3x, 300.4, 309.0, 309.1, 309.28, 311, 296.82, 296.90	≥1 diagnosis in any claim	Yes	3
Shen, 2016 (22)	AS	Anxiety and depression‡	Comorbidity, covariate	ICD-9: 296.2, 296.3, 300.00, 300.4, 311	Not specified	No	1
Tang, 2016 (59)	SARDs	Depression	Covariate	ICD-9: 296.2, 296.3, 300.4, 309.0, 309.1, 311	3 consecutive outpatient visits or 1 inpatient visit	No	2
Timonen, 2003 (52)	RA	Depression	Comorbidity	ICD-8: 2960, 2980, 3004; ICD-9: 2961, 2968, 3004; ICD-10: F32-34.1	Hospital-treated psychiatric disorders	No	2

* ICD = International Classification of Diseases (ICD-8 = Eighth Revision; ICD-9 = Ninth Revision; ICD-10 = Tenth Revision); RA = rheumatoid arthritis; SARDs = systemic autoimmune rheumatic diseases; ATC = Anatomic Therapeutic Chemical Classification System; AS = ankylosing spondylitis; PsA = psoriatic arthritis; SSRI = selective serotonin reuptake inhibitors, SNRI = serotonin noradrenaline reuptake inhibitors; TCA = tricyclic antidepressant; MAOI = monoamine oxidase inhibitors.
† Criteria for completeness of reporting were based on the reporting of ICD codes (1 point), operational definition (1 point), and use of a validated case definition (1 point) with a total maximum score of 3.
‡ Combined as a single variable.

Table 4. Validation statistics from original articles assessing ICD-9 and ICD-10 case definitions for depression and anxiety in administrative health databases*

Validation study, author, year (ref.)	Population	Reference standard	Type of database	ICD codes (operational definition)	Time period	Background prevalence, %	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Depression										
Fiest, 2014 (14)†	General	Clinical chart	Inpatient	ICD-9: 296.20–.25, 296.30–.35, 300.4, 311, 296.5, 296.6, 296.82, 296.90, 309.0, 309.1, 309.28 (≥1 inpatient visit)	Any	11.9	32.9 (28.7–37.3)	99.5 (99.2–99.7)	89.7 (84.2–93.8)	91.7 (90.7–92.5)
Marrie, 2013 (27)	Multiple sclerosis	Clinical chart	Inpatient, outpatient, prescription	ICD-9: 296.2, 296.3, 298.0, 300.4, 311; ICD 10: F32, F33, F34 (≥1 inpatient visit or ≥5 outpatient visits or ≥1 outpatient visit and ≥7 prescription claims)	2 years	27.5	62.2 (52.4–71.2)	86.7 (82.2–90.4)	63.9 (54.1–72.9)	85.8 (81.3–89.6)
Marrie, 2016 (28)‡	Inflammatory bowel disease	Self-reported physician diagnosis	Inpatient, outpatient, prescription	ICD-9: 296.2, 296.3, 298.0, 300.4, 311; ICD 10: F32, F33, F34 (≥1 inpatient visit or ≥5 outpatient visits or ≥1 outpatient visit and ≥7 prescription claims)	2 years	25.5	73.5 (63.0–84.0)	84.3 (79.2–89.4)	61.7 (51.1–72.3)	90.3 (86.0–94.5)
Solberg, 2006 (29)	General	Clinical chart	Inpatient, outpatient	ICD-9: 296.2x, 296.3x, 300.4, 311 (≥1 inpatient visit or ≥2 outpatient visits)	1 year	4.4	–	–	99.0	–
Anxiety										
Marrie, 2013 (27)	Multiple sclerosis	Clinical chart	Inpatient, outpatient, prescription	ICD-9: 300.0, 300.2; ICD 10: F40, F41 (≥1 inpatient visit or ≥2 outpatient visits or ≥1 outpatient visit and ≥2 prescription claims)	2 years	6.5	42.3 (23.3–63.1)	82.2 (78.0–85.9)	14.1 (7.25–23.8)	95.4 (92.5–97.4)
Marrie, 2016 (28)‡	Inflammatory bowel disease	Self-reported physician diagnosis	Inpatient, outpatient, prescription	ICD-9: 300.0, 300.2; ICD 10: F40, F41 (≥1 inpatient visit or ≥2 outpatient visits or ≥1 outpatient visit and ≥2 prescription claims)	2 years	15.8	76.2 (63.3–89.0)	61.2 (54.8–67.5)	26.9 (18.9–34.8)	93.2 (89.1–97.3)

* ICD = International Classification of Diseases (ICD-9 = Ninth Revision; ICD-10 = Tenth Revision); 95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value.
† Validation statistics presented are for the most inclusive case definition reported. Full article includes 9 validated case definitions for depression.
‡ Measures of validity were assessed using additional reference standards.

In addition to synthesizing articles evaluating depression and anxiety in individuals with rheumatic diseases within administrative health databases, we have detailed the ICD codes, operational definitions, and validity of each case definition in an effort to establish practical recommendations. Results from our systematic review make it apparent that several case definitions have been used to assess depression and anxiety in the area of rheumatology, and the majority of definitions employed are unvalidated, despite the availability of validated case definitions. Of the studies employing validated case definitions to assess depression and anxiety, 1 applied a depression definition developed by Fiest et al (14), and others applied definitions not included in the aforementioned systematic reviews (27,28). Specifically, these case definitions for depression and anxiety were validated in populations with multiple sclerosis and inflammatory bowel disease using both ICD-9 and ICD-10 codes and operationalized within inpatient, outpatient, and prescription data sources over a 2-year period (27,28). Besides the multiple administrative data sources and increased time-window for assessment, this case definition for depression differs from previously discussed case definitions with regard to ICD codes, specifically adding depressive-type psychosis (ICD-9: 298.0) (27,28). Further, as described by study authors, eligible prescriptions were those without "on or off-label" use for other conditions and needed to be in combination with an outpatient diagnosis of the respective mental illness (27,28). These differences likely contribute to the higher specificity (>80%) observed for this depression case definition (27,28). A recommendation resulting from our systematic review is for future research to prioritize the use of previously validated case definitions, such as those described by Marrie et al (27,28) or Fiest et al (14), when using administrative health data to evaluate mental health conditions in individuals with rheumatic diseases.

Although this systematic review suggests suboptimal use of validated case definitions to assess depression and anxiety in individuals with rheumatic diseases, we observed that nearly 80% of studies reporting their operational definition used multiple administrative data sources, that is, a combination of inpatient, outpatient, or prescription claims. Indeed, the use of multiple administrative data sources is a common and robust approach to identifying chronic conditions and is often employed in rheumatology (33,34). In contrast to physical chronic diseases such as inflammatory rheumatic diseases, individuals with a mental illness are less likely to seek professional care. For instance, the World Health Organization estimates that among high-income countries, up to 50% of individuals are untreated for their mental illness (35). Moreover, depression and anxiety may be misclassified in administrative health databases as a result of symptom overlap with comorbid diseases, variation in the number of digits for ICD codes available in administrative data sources for purposes of health research, treatments not recorded in administrative health databases (e.g., out-of-pocket counseling), and variability in coding practices among physicians and across jurisdictions (27,28). Therefore, administrative health data, which characterize the treatment and diagnosis only of individuals who seek care and discuss their mental health, risks underestimating cases of depression and anxiety. Given the underreporting and inadequate treatment of mental illnesses, linking multiple administrative data sources is ideal to optimize the identification of individuals with comorbid depression and anxiety.

Strengths of this systematic review include the comprehensive search strategy developed with a research librarian that covered multiple reference databases as well as several rheumatic diseases, including less common SARDs such as Sjögren's syndrome. Limitations of this study also deserve comment. Although we did not conduct a quality assessment of the included studies, such an assessment was beyond the aim of the review, and instead we assessed the reporting of case definitions for depression and anxiety based on 3 dimensions: ICD codes, operational definition, and use of a validated case definition. The focus on studies that used ICD codes within administrative health databases meant we excluded studies using other coding classifications such as Read codes. However, the ICD system is used internationally, and validated case definitions for mental disorders using Read codes are available (36).

Our systematic review highlights a fair degree of dissonance among the case definitions currently being applied in administrative health databases to evaluate depression and anxiety in individuals with rheumatic diseases. Results of our synthesis show that a number of ICD codes are consistently used to identify cases of depression and anxiety in administrative health data, but due to discrepancies in the entire combination of ICD codes and operational definitions, drawing comparisons across studies is challenging. Therefore, findings of this review lend to the recommendation of linking multiple administrative data sources when feasible and exploring the use of validated case definitions for depression and anxiety, such as those discussed in this study (14,15,27,28).

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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. De Vera 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. Howren, Aviña-Zubieta, De Vera.

Acquisition of data. Howren, De Vera.

Analysis and interpretation of data. Howren, Aviña-Zubieta, Puyat, Esdaile, Da Costa, De Vera.

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RHEUMATOLOGY REGISTRIES, BIG DATA, AND THE RHEUMATIC DISEASES

Mediation of Adverse Pregnancy Outcomes in Autoimmune Conditions by Pregnancy Complications: A Mediation Analysis of Autoimmune Conditions and Adverse Pregnancy Outcomes

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Objective. Autoimmune conditions are associated with an increased risk of adverse pregnancy complications and outcomes, suggesting that pregnancy complications may mediate the excess risk. We performed a causal mediation analysis to quantify the mediated effects of autoimmune conditions on adverse pregnancy outcomes.

Methods. We queried a California birth cohort created from linked birth certificates and hospital discharge summaries. From 2,963,888 births, we identified women with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriasis, and inflammatory bowel disease (IBD). Pregnancy complications included preeclampsia/hypertension, gestational diabetes mellitus, and infection in pregnancy. Adverse pregnancy outcomes were preterm birth, cesarean delivery, and small for gestational age. We performed a mediation analysis to estimate the total effects of each autoimmune condition and adverse pregnancy outcome and the indirect effects through pregnancy complications.

Results. All 4 autoimmune conditions were associated with preterm birth and cesarean delivery, and RA, SLE, and IBD were associated with offspring that were small for gestational age. The strongest mediator of RA, SLE, and psoriasis was preeclampsia/hypertension, accounting for 20–33% of the excess risk of preterm births and 10–19% of excess cesarean deliveries. Gestational diabetes mellitus and infections generally mediated <10% of excess adverse pregnancy outcomes. Of the 4 autoimmune conditions, selected pregnancy complications mediated the least number of adverse pregnancy outcomes among women with IBD.

Conclusion. We found evidence that some excess risk of adverse pregnancy outcomes is mediated through pregnancy complications, particularly preeclampsia/hypertension. Quantifying excess risk and associated pathways provides insight into the underlying etiologies of adverse pregnancy outcomes and can inform intervention strategies.

INTRODUCTION

The increased risk of adverse pregnancy outcomes associated with select autoimmune conditions is well documented and has been replicated across multiple data sources (1–9). Rheumatic conditions such as rheumatoid arthritis (RA), psoriatic arthritis, and systemic lupus erythematosus (SLE) have been associated with increased risk of preterm birth, low birth weight, caesarean delivery, and offspring who are small for gestational age (SGA) (1,2,5–7,9–11). Further, although less consistent, psoriasis and inflammatory bowel disease (IBD) have also been associated with increased risk for preterm birth and caesarean delivery (1,3,4,8,12). Many of these same autoimmune conditions are also associated with pregnancy complications, including preeclampsia (1,7,10,12,13), gestational diabetes mellitus (12,13), and infections (7,13,14). Taken together, these findings suggest

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SIGNIFICANCE & INNOVATIONS

- For rheumatoid arthritis, systemic lupus erythematosus, and psoriasis, preeclampsia/hypertension was the strongest mediator of all 3 pregnancy outcomes (preterm birth, caesarean delivery, and small for gestational age), accounting for approximately 10–33% of the excess risk.
- Infections were the next strongest mediator but generally accounted for <10% of the excess risk of pregnancy outcomes.
- Efforts to prevent or mitigate preeclampsia/hypertension would have the largest impact on reducing disparities in adverse pregnancy outcomes associated with rheumatoid arthritis, systemic lupus erythematosus, and psoriasis.

that autoimmune conditions may, in part, increase the risk of adverse pregnancy outcomes through their relationship with pregnancy complications. Termed "indirect" or "mediated" pathways, these models propose that in addition to autoimmune diseases directly causing adverse pregnancy outcomes, the autoimmune conditions are causing pregnancy complications, which in turn cause adverse pregnancy outcomes (15).

To determine whether or not, and to what extent, these mediated relationships exist, performing a mediation analysis is necessary, where the total effect is broken down into direct (nonmediated) and indirect (mediated) effects. Previous strategies for mediation analysis have included regression-based approaches of estimating the effect of the exposure on the outcome in the presence and absence of the mediator and assessing the difference in effect estimates (15). However, if there are unmeasured common causes of the mediator and outcome (Figure 1, variable U) (16), conditioning on the mediator will introduce a collider stratification bias (17,18). Further, if there is an interaction between the exposure and mediator, traditional regression-based approaches may result in incorrect estimates. To avoid these biases, a counterfactual approach may be employed, which is a framework for estimating causal effects from observational data. Through various methodologic techniques, including marginal structural models and inverse probability weighting, counterfactual models are robust to interactions between exposure and mediator variables and mediator-outcome confounding. Under this approach, one can estimate the total effect, the direct and indirect effects, and the proportion of the effect that is mediated through the indirect effect.

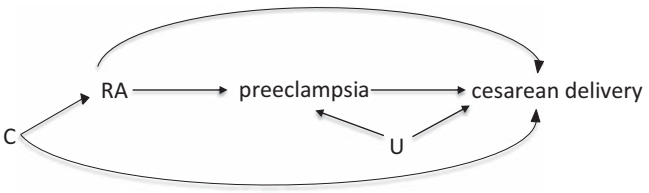

Figure 1. Simplified directed acyclic graph (16) of rheumatoid arthritis (RA) and caesarean delivery, with mediation by preeclampsia. Maternal characteristics (C) of prepregnancy body mass index, race and ethnicity, age, education, insurance provider, and smoking are assumed baseline confounders. U = potential unmeasured confounders of preeclampsia and cesarean delivery.

RA, SLE, psoriasis, and IBD are relatively rare, with prevalence estimates that range from <1% for RA to 3% for psoriasis (19–22). Similarly, pregnancy complications are not common, with 8% of patients experiencing gestational hypertension (23) and 6% experiencing gestational diabetes mellitus (24). The prevalence of the outcomes ranges from 8–10% (preterm birth and SGA) (25,26) to 30% (cesarean deliveries) (26). To partition the total effect into these component pathways, querying large data sets is necessary. Recently, the authors estimated the total effects of several rheumatic diseases in causing adverse pregnancy and birth outcomes from a retrospective birth cohort of 3 million singleton births in California (2). To extend that work, the objective of this study was to perform a causal mediation analysis to determine the extent to which pregnancy complications (preeclampsia/hypertensive disorder, gestational diabetes mellitus, and infections) mediate the association between selected autoimmune conditions (RA, SLE, psoriasis, and IBD) and adverse pregnancy outcomes (preterm birth, caesarean delivery, and SGA). Identifying pathways that mediate adverse pregnancy outcomes will inform the clinical care of pregnant women with autoimmune conditions through quantifying the potential impact of intervention on select mediators.

MATERIALS AND METHODS

Study population. Subjects in this retrospective cohort were women with live-born singletons in California between 2007 and 2012. Deliveries were identified from a hospital discharge database maintained by the California Office of Statewide Health Planning and Development, which includes linked birth certificates, detailed information on maternal and infant characteristics, hospital discharge diagnoses, and procedures recorded as early as 1 year before delivery (27). Clinical characteristics were based on International Classification of Diseases, Ninth Revision (ICD-9) 4-digit codes contained in the hospital discharge database (28). Of the 3,160,268 live births, the study was restricted to singletons born between 20 and 44 weeks of gestation (n = 3,067,839) and then further restricted to mother-infant dyads with linked hospital discharge records (n = 2,963,888). Methods and protocols for the study were approved by the Committee for the Protection of Human Subjects within the Health and Human Services Agency of the State of California.

Exposures, outcomes, and mediators. Autoimmune conditions were identified via ICD-9 codes as follows (29,30): RA: 714.0 (rheumatoid arthritis and other inflammatory polyarthropathies), SLE: 710.0 (systemic lupus erythematosus, organ or system involvement unspecified), psoriasis: 696.1 (other psoriasis), and

IBD: 555.5x (regional enteritis) and 556.x (ulcerative enterocolitis). Gestational age was determined using the best obstetric estimate and was obtained from birth certificate records. Preterm birth was defined as <37 weeks of completed gestation, and SGA was defined as birth weight in the lowest 10th percentile for gestational age (31). Cesarean delivery was identified from maternal ICD-9 codes (669.7: cesarean delivery without mention of indication) or infant codes (763.4: cesarean delivery affecting fetus or newborn), or maternal procedure codes (74.0, 74.1, 74.2, 74.4, 74.99). Potential mediators were identified as preeclampsia/hypertensive disorder (642: hypertension complicating pregnancy childbirth and the puerperium), gestational diabetes mellitus (648.0: diabetes mellitus complicating pregnancy childbirth or the puerperium, 648.8: abnormal glucose tolerance of mother complicating pregnancy childbirth or the puerperium), and any infection complicating the pregnancy (ICD-9 codes: 647 [infectious and parasitic conditions in the mother classifiable elsewhere but complicating pregnancy childbirth or the puerperium], 646.5 [asymptomatic bacteriuria in pregnancy], 646.6 [infections of genitourinary tract in pregnancy]), or infant ICD-9 codes 760.2 (maternal infections affecting fetus or newborn) or 760.1 (maternal renal and urinary tract diseases affecting fetus or newborn).

Covariates. Maternal age, race, and ethnicity were derived from birth record variables. Maternal prepregnancy body mass index (BMI) was created from height and weight variables on the birth records and categorized into <25, 25–30, and >30 kg/m^2. The expected source of delivery payment was categorized from birth records as private, public, or other, and maternal education was dichotomized as less than or equal to 12th grade. Finally, maternal smoking data were created from an indication of smoking from either birth records or ICD-9 codes (649.0).

Mediation analysis. Causal mediation analysis was performed using an SAS macro (%mediation) developed by Valeri and VanderWeele (15). This macro was selected for its ability to determine causal direct (nonmediated) and indirect (mediated) effects, allowance for interaction of exposure and mediator variables, and the ability to model binary outcomes with log-linear regression. In this analysis, we present the total effect (mediated

Table 1. Maternal characteristics of 3 million births in the state of California (2007–2012) stratified by autoimmune conditions*

Characteristic	All births (n = 2,963,888)	Rheumatoid arthritis (n = 3,129)	Systemic lupus erythematosus (n = 3,863)	Psoriasis (n = 1,255)	Inflammatory bowel disease (n = 2,714)
Sociodemographic characteristics					
Race/ethnicity					
Non-Hispanic white	773,352 (26.1)	1,134 (36.2)	1,050 (27.2)	543 (43.3)	1,703 (62.8)
Hispanic	1,445,356 (48.8)	1,313 (42.0)	1,568 (40.6)	353 (28.1)	509 (18.8)
African American	158,802 (5.4)	202 (6.5)	388 (10.0)	36 (2.9)	135 (5.0)
Asian	366,732 (12.4)	210 (6.7)	469 (12.1)	199 (15.9)	145 (5.3)
Other	219,646 (7.4)	270 (8.6)	388 (10.0)	124 (9.9)	222 (8.2)
Maternal age, years					
<18	85,717 (2.9)	26 (0.8)	36 (0.9)	11 (0.9)	9 (0.3)
18–34	2,351,645 (79.4)	2,228 (71.2)	2,917 (75.5)	934 (74.4)	1,998 (73.6)
>34	526,415 (17.8)	875 (28.0)	910 (23.6)	310 (24.7)	707 (26.1)
Prepregnancy BMI, kg/m^2					
<25	1,479,287 (49.9)	1,513 (48.4)	1,888 (48.9)	488 (38.9)	1,678 (61.8)
25–30	728,096 (24.6)	788 (25.2)	936 (24.2)	320 (25.5)	543 (20.0)
>30	556,623 (18.8)	655 (20.9)	805 (20.8)	369 (29.4)	351 (12.9)
Missing	199,882 (6.7)	173 (5.5)	234 (6.1)	78 (6.2)	142 (5.2)
Insurance provider					
Private	1,373,539 (46.3)	1,837 (58.7)	2,019 (52.3)	824 (65.7)	2,044 (75.3)
Public	1,475,205 (49.8)	1,199 (38.3)	1,705 (44.1)	403 (32.1)	599 (22.1)
Other	115,144 (3.9)	93 (3.0)	139 (3.6)	28 (2.2)	71 (2.6)
Education ≤12th grade	1,466,653 (49.5)	1,123 (35.9)	1,550 (40.1)	455 (36.3)	609 (22.4)
Missing	109,457 (3.7)	118 (3.8)	150 (3.9)	42 (3.3)	121 (4.5)
Pregnancy smoking	134,682 (4.5)	202 (6.5)	280 (7.3)	145 (11.6)	167 (6.2)
Pregnancy complications					
Preeclampsia or hypertension	212,590 (7.2)	448 (14.3)	875 (22.7)	175 (13.9)	258 (9.5)
Gestational diabetes mellitus	274,102 (9.3)	392 (12.5)	426 (11.0)	213 (17.0)	230 (8.5)
Infection in pregnancy	234,043 (7.9)	475 (15.2)	698 (18.1)	178 (14.2)	382 (14.1)
Adverse pregnancy outcomes					
Preterm birth	211,802 (7.2)	447 (14.3)	901 (23.3)	135 (10.8)	371 (13.7)
Cesarean delivery	956,710 (32.3)	1,317 (42.1)	1,823 (47.2)	528 (42.1)	1,097 (40.4)
Small for gestational age	252,848 (8.5)	376 (12.0)	636 (16.5)	98 (7.8)	279 (10.3)

* Values are the number (%). In total, 369 women had International Classification of Diseases, Ninth Revision codes for >1 autoimmune condition. BMI = body mass index.

and unmediated pathways), the natural direct (unmediated) effect, and the natural indirect (mediated) effect. The natural direct effect (Figure 1, arrow from RA to caesarean delivery) is the effect of the exposure if the effect of the mediator is what it would have been in the absence of the exposure. The natural indirect effect (Figure 1, arrow from RA to caesarean delivery through preeclampsia) is the effect when the exposure is present and the mediator is set to what it would have been without versus with the exposure. As an example, in the case of the risk of caesarean delivery with RA and mediation by preeclampsia (Figure 1), the natural direct effect compares the risk of caesarean delivery between those with and without RA if, in both cases, the occurrence of preeclampsia was what it would have been without RA. The natural indirect effect is the effect among those with RA, the risk of caesarean delivery if preeclampsia status was changed from the level in those without RA to the level in those with RA. Finally, the proportion mediated is also reported, which is the excess risk of the outcome among exposed women that is mediated by the variable of interest. Following the example, the proportion mediated is the excess risk of caesarean delivery among women with RA that is mediated through preeclampsia. Mathematically, the total effect is the product of the natural direct and indirect effects, and the proportion mediated is the ratio of the natural indirect effect over the total effect with a transformation of the ratio scale (15).

Statistical analysis. Women with ICD-9 codes for >1 autoimmune condition were considered exposed to each and included in each appropriate model. To prepare for mediation analyses, we first performed multivariable adjusted Poisson log-linear regression to estimate the risk of each autoimmune condition with each outcome. We then repeated models with the mediator and a mediator-exposure product term to assess interaction. Mediation analyses were then performed in SAS using the macro % mediation. All models had a Poisson distribution and log link and were adjusted for race and ethnicity, age, insurance provider, education, BMI, and smoking (all coded into dummy variables as required for the macro). For models with evidence of an exposure-mediator interaction, the model was coded to allow for interaction. SEs and confidence intervals were obtained via the default delta method. Separate models were constructed for each exposure/mediator/outcome combination, and total effect, natural direct effect, natural indirect effect, and proportion mediated were all reported. Of note, due to random fluctuations and estimations inherent to modeling, the total effects may vary slightly between models for each exposure/outcome pair. Thus, the total effects from each model are reported. When total effects were not statistically significant, mediation analyses were not performed. To assess whether mediation differs by race/ethnicity, we repeated all models stratified into samples of non-Hispanic white, Latina, African American, and Asian women.

RESULTS

In the full sample, there were 3,129 deliveries (0.11%) from women with RA, 3,863 deliveries (0.13%) from women with SLE, 1,255 deliveries (0.04%) from women with psoriasis, and 2,714 deliveries (0.09%) from women with IBD (Table 1). Compared to the full sample, women with an autoimmune disease were more likely to be older, have private insurance, and have more education. Mediators of interest also differed by the presence of autoimmune conditions. Women with autoimmune conditions were more likely to have preeclampsia/hypertension and infection, and all conditions with the exception of IBD

Table 2. Effect analysis of the influence of rheumatoid arthritis and potential mediators on adverse pregnancy outcomes in 3 million live births in the state of California*

Mediator	Total effect†	Direct effect‡	Indirect effect§	Proportion mediated, %¶
Preterm birth				
Preeclampsia/hypertension	1.97 (1.78–2.17)	1.77 (1.60–1.96)	1.11 (1.08–1.13)	20.4
Gestational diabetes mellitus	1.98 (1.80–2.19)	1.96 (1.78–2.17)	1.01 (1.00–1.02)	2.2
Infection in pregnancy	1.99 (1.81–2.20)	1.92 (1.74–2.12)	1.04 (1.03–1.05)	7.4
Cesarean delivery				
Preeclampsia/hypertension	1.22 (1.15–1.29)	1.19 (1.12–1.26)	1.02 (1.02–1.03)	13.3
Gestational diabetes mellitus	1.23 (1.16–1.30)	1.22 (1.15–1.29)	1.01 (1.00–1.01)	3.0
Infection in pregnancy	1.23 (1.16–1.30)	1.22 (1.15–1.29)	1.01 (1.00–1.01)	3.6
Small for gestational age				
Preeclampsia/hypertension#	1.53 (1.37–1.73)	1.49 (1.33–1.66)	1.03 (1.01–1.05)	8.3
Gestational diabetes mellitus	1.53 (1.37–1.73)	1.53 (1.38–1.71)	0.99 (0.99–0.99)	3.0
Infection in pregnancy	1.53 (1.37–1.73)	1.52 (1.36–1.69)	1.01 (1.00–1.01)	1.5

* Values are the adjusted risk ratio (95% confidence interval) unless indicated otherwise. Models adjusted for race/ethnicity, maternal age, insurance provider, maternal education, overweight/obesity, and smoking.
† Effect of rheumatoid arthritis on adverse pregnancy outcomes.
‡ Effect of rheumatoid arthritis on adverse pregnancy outcomes that is not mediated by each pregnancy complication.
§ Effect of rheumatoid arthritis on adverse pregnancy outcomes mediated by each pregnancy complication.
¶ Proportion of effect of rheumatoid arthritis on adverse pregnancy outcomes mediated by each pregnancy complication.
# Modeled with interaction term between exposure and mediator.

Table 3. Effect analysis of the influence of systemic lupus erythematosus and potential mediators on adverse pregnancy outcomes in 3 million live births in the state of California*

Mediator	Total effect†	Direct effect‡	Indirect effect§	Proportion mediated, %¶
Preterm birth				
Preeclampsia/hypertension	3.09 (2.87–3.32)	2.46 (2.29–2.63)	1.25 (1.23–1.28)	30.2
Gestational diabetes mellitus	3.12 (2.91–3.35)	3.10 (2.89–3.32)	1.00 (1.00–1.01)	1.0
Infection in pregnancy	3.11 (2.91–3.34)	2.96 (2.76–3.18)	1.05 (1.04–1.05)	7.0
Cesarean delivery				
Preeclampsia/hypertension	1.40 (1.33–1.47)	1.32 (1.26–1.39)	1.06 (1.05–1.06)	18.9
Gestational diabetes mellitus#	1.41 (1.35–1.48)	1.41 (1.34–1.48)	1.00 (1.00–1.00)	0.5
Infection in pregnancy	1.40 (1.34–1.48)	1.39 (1.32–1.46)	1.01 (1.01–1.01)	3.1
Small for gestational age				
Preeclampsia/hypertension#	1.89 (1.74–2.06)	1.73 (1.59–1.09)	1.09 (1.05–1.13)	17.6
Gestational diabetes mellitus	1.91 (1.76–2.06)	1.91 (1.76–2.07)	0.99 (0.99–0.99)	0.0
Infection in pregnancy	1.89 (1.76–2.07)	1.89 (1.74–2.05)	1.01 (1.01–1.01)	1.4

* Values are the adjusted risk ratio (95% confidence interval) unless indicated otherwise. Models adjusted for race/ethnicity, maternal age, insurance provider, maternal education, overweight/obesity, and smoking.
† Effect of systemic lupus erythematosus on adverse pregnancy outcomes.
‡ Effect of systemic lupus erythematosus on adverse pregnancy outcomes that is not mediated by each pregnancy complication.
§ Effect of systemic lupus erythematosus on adverse pregnancy outcomes mediated by each pregnancy complication.
¶ Proportion of effect of systemic lupus erythematosus on adverse pregnancy outcomes mediated by each pregnancy complication.
# Modeled with interaction term between exposure and mediator.

were more likely to have gestational diabetes mellitus. Further, women with RA, SLE, and psoriasis were more likely to have all outcomes of interest: preterm birth, caesarean delivery, and SGA, and women with IBD were more likely to have a preterm birth and a cesarean delivery. These findings prompt further investigation into mediation mechanisms.

Analysis of mediation. *RA*. Women with RA had a 2-fold increase in the risk for preterm birth compared with women without RA (Table 2). One-fifth of the excess preterm births associated with RA was due to preeclampsia/hypertension, while 7% was mediated by infection in pregnancy, and 2% by gestational diabetes mellitus. Relative to the excess risk of preterm birth, preeclampsia/hypertension accounted for less of the excess cesarean delivery and SGA in women with RA (13% and 8%, respectively).

SLE. There was a 3-fold increase in the risk of preterm birth, and almost a 2-fold increase in the risk of SGA among women with SLE compared to women without SLE (Table 3). Preeclampsia/hypertension was the strongest mediator for all outcomes, accounting for 18–30% of the excess adverse pregnancy outcomes among women with SLE. An additional 7% of the excess preterm births among women with SLE were attributable to infection in pregnancy. Gestational diabetes mellitus contributed essentially no excess risk of any of the pregnancy outcomes.

Table 4. Effect analysis of the influence of psoriasis and potential mediators on adverse pregnancy outcomes in 3 million live births in the state of California*

Mediator	Total effect†	Direct effect‡	Indirect effect§	Proportion mediated, %¶
Preterm birth				
Preeclampsia/hypertension#	1.46 (1.22–1.76)	1.31 (1.08–1.58)	1.11 (1.05–1.18)	32.9
Gestational diabetes mellitus	1.48 (1.25–1.78)	1.44 (1.19–1.74)	1.03 (1.00–1.06)	8.9
Infection in pregnancy#	1.49 (1.25–1.79)	1.41 (1.18–1.70)	1.06 (1.01–1.11)	15.9
Cesarean delivery				
Preeclampsia/hypertension	1.22 (1.11–1.33)	1.19 (1.09–1.31)	1.02 (1.01–1.03)	11.8
Gestational diabetes mellitus	1.22 (1.12–1.34)	1.21 (1.10–1.32)	1.01 (1.01–1.02)	7.3
Infection in pregnancy	1.22 (1.12–1.34)	1.22 (1.12–1.33)	1.01 (1.00–1.01)	3.3
Small for gestational age**				

* Values are the adjusted risk ratio (95% confidence interval) unless indicated otherwise. Models adjusted for race/ethnicity, maternal age, insurance provider, maternal education, overweight/obesity, and smoking.
† Effect of psoriasis on adverse pregnancy outcomes.
‡ Effect of psoriasis on adverse pregnancy outcomes that is not mediated by each pregnancy complication.
§ Effect of psoriasis on adverse pregnancy outcomes mediated by each pregnancy complication.
¶ Proportion of effect of psoriasis on adverse pregnancy outcomes mediated by each pregnancy complication.
# Modeled with interaction term between exposure and mediator.
** Total effects observed between psoriasis and small for gestational age were null (adjusted risk ratio 1.00 [95% confidence interval 0.81–1.24]); no mediation analysis performed.

Table 5. Effect analysis of the influence of inflammatory bowel disease and potential mediators on adverse pregnancy outcomes in 3 million live births in the state of California*

Mediator	Total effect†	Direct effect‡	Indirect effect§	Proportion mediated, %¶
Preterm birth				
Preeclampsia/hypertension#	2.01 (1.80–2.24)	1.97 (1.77–2.21)	1.02 (1.01–1.04)	4.9
Gestational diabetes mellitus	2.03 (1.82–2.26)	2.02 (1.81–2.24)	1.00 (1.00–1.01)	0.5
Infection in pregnancy#	2.02 (1.82–2.26)	1.90 (1.70–2.13)	1.06 (1.02–1.10)	11.5
Cesarean delivery				
Preeclampsia/hypertension#	1.24 (1.17–1.34)	1.23 (1.16–1.31)	1.00 (1.00–1.01)	1.4
Gestational diabetes mellitus	1.24 (1.16–1.31)	1.23 (1.16–1.31)	1.00 (1.00–1.01)	1.2
Infection in pregnancy	1.24 (1.16–1.31)	1.22 (1.15–1.30)	1.00 (1.00–1.00)	3.5
Small for gestational age				
Preeclampsia/hypertension	1.38 (1.22–1.56)	1.35 (1.20–1.53)	1.02 (1.00–1.03)	6.6
Gestational diabetes mellitus	1.38 (1.22–1.56)	1.38 (1.22–1.56)	1.00 (1.00–1.00)	0.0
Infection in pregnancy	1.38 (1.22–1.56)	1.38 (1.22–1.56)	1.01 (1.00–1.01)	1.9

* Values are the adjusted risk ratio (95% confidence interval) unless indicated otherwise. Models adjusted for race/ethnicity, maternal age, insurance provider, maternal education, overweight/obesity, and smoking.
† Effect of inflammatory bowel disease on adverse pregnancy outcomes.
‡ Effect of inflammatory bowel disease on adverse pregnancy outcomes that is not mediated by each pregnancy complication.
§ Effect of inflammatory bowel disease on adverse pregnancy outcomes mediated by each pregnancy complication.
¶ Proportion of effect of inflammatory bowel disease on adverse pregnancy outcomes mediated by each pregnancy complication.
# Modeled with interaction term between exposure and mediator.

Psoriasis. Women with psoriasis had a 50% increased risk of preterm birth and a 22% increased risk of caesarean delivery; there was no evidence of an increased risk of SGA offspring (Table 4). Approximately 33% of excess preterm births and 12% of excess cesarean deliveries in women with psoriasis were mediated by preeclampsia. Additionally, gestational diabetes mellitus accounted for an additional 9%, and infections in pregnancy an additional 16% of excess preterm births.

IBD. The total risk estimates for adverse pregnancy outcomes in women with IBD were quite similar in magnitude to women with RA. However, preeclampsia/hypertension, gestational diabetes mellitus, and infection in pregnancy explained much less of the excess risk of outcomes among women with IBD relative to the other autoimmune conditions (Table 5). Unlike the other autoimmune conditions, pregnancy complications mediated <10% of excess risk of any outcome, with the only notable mediation occurring through infections and the risk of preterm birth (11.5%).

Race/ethnicity. *RA and race/ethnicity*. Among women with RA, there was heterogeneity in the strength of the total effect of the disease on outcomes, with African American women having the highest risk of preterm birth, Latina women having the highest risk of cesarean delivery, and Latinas and Asian women having the highest risk of SGA (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24037/abstract). The proportion mediated by the select pregnancy complications also varied markedly. Of excess preterm births among women with RA, Latina women had the highest proportion attributed to preeclampsia/hypertension (25.6%) and infection in pregnancy (9%), while African American women had the highest proportion attributed to gestational diabetes mellitus (6.8%). Of excess SGA births among women with RA, African American women had the highest proportion attributable to preeclampsia/hypertension.

SLE and race/ethnicity. When stratified by race/ethnicity, the magnitude of the association between preterm birth and SLE was strongest in Latinas and Asian women, and equivalent among white and African American women (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24037/abstract). Of the excess preterm deliveries due to SLE, Latinas and Asian women had the highest proportion mediated by preeclampsia/hypertension (34.7% and 36.4%, respectively), and white women had the lowest (19.5%). The proportion of preterm births mediated by gestational diabetes mellitus or infection in pregnancy was substantially lower than the proportion mediated by preeclampsia/hypertension, with little heterogeneity between race/ethnicities. Although there was little heterogeneity by race/ethnicity in the overall risk of cesarean delivery, Latinas, African American, and Asian women had a much higher proportion mediated by preeclampsia/hypertension than white women.

Psoriasis and race/ethnicity. There was little heterogeneity in total effect estimates by race/ethnicity of psoriasis on preterm birth or cesarean delivery and little heterogeneity on the proportion mediated by pregnancy complications (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24037/abstract). Of note, the total effect of psoriasis on preterm birth or cesar-

ean delivery among African American women was not statistically significant; however, only 36 African American women in the sample had evidence of psoriasis, and thus statistical power was limited. There was also no evidence of an increased risk of cesarean delivery among Asian women with psoriasis.

IBD and race/ethnicity. While the total effect of IBD on preterm birth was strongest among African American women, the proportion mediated by preeclampsia/hypertension was highest among Latinas, although still <10% (see Supplementary Table 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24037/abstract). There was little other heterogeneity by race/ethnicity of the proportion mediated by pregnancy complications for any of the other outcomes.

DISCUSSION

The purpose of a causal mediation analysis is to investigate the underlying mechanisms that contribute to an observed relationship. We performed such an analysis to determine the extent to which select pregnancy complications contribute to the previously documented association between autoimmune conditions and adverse pregnancy outcomes. Using a large cohort of approximately 3 million births in the state of California, we found increased risks of preterm birth, cesarean delivery, and SGA among women with RA, SLE, and IBD, and increased risk of preterm birth and cesarean delivery among women with psoriasis. There was tremendous heterogeneity between and within autoimmune conditions with respect to the proportion mediated by pregnancy complications. In general, preeclampsia/hypertension accounted for the largest proportion of excess adverse pregnancy outcomes due to autoimmune conditions, particularly preterm births. There, the proportion mediated was highest among women with psoriasis (32.9%) or SLE (30.2%), followed by RA (20.4%). There was not an appreciable contribution from preeclampsia/hypertension to preterm birth among women with IBD. Generally, gestational diabetes mellitus and infections in pregnancy contributed to much less of the excess risk of adverse pregnancy outcomes across the autoimmune conditions, although infections did contribute >10% of the excess preterm births among women with psoriasis and IBD. Finally, there was variation in the proportion mediated by race/ethnicity. Among women with RA, pregnancy complications generally mediated higher proportions of preterm births in Latinas compared to white or African American women. Among women with SLE, excess preterm births and cesarean deliveries were more commonly mediated by preeclampsia/hypertension among Latinas, Asian, or African American women than among white women.

By performing a counterfactual mediation analysis, we quantified the extent to which select pregnancy complications contribute to associations between autoimmune conditions and adverse pregnancy outcomes. Although mediation of adverse pregnancy outcomes by pregnancy complications among women with autoimmune conditions has been suggested (10,32,33), to our knowledge it has never been formally investigated using causal mediation analyses. These results are clinically meaningful both in the findings of the proportion mediated and the proportion not mediated. From the knowledge that up to one-third of excess cases of preterm birth are mediated by preeclampsia/hypertension among women with psoriasis and SLE, we may better appreciate the mechanisms through which these conditions affect pregnancy outcomes. However, by recognizing that two-thirds of the excess cases of preterm births were not due to preeclampsia/hypertension, we demonstrate the work that remains in understanding the underlying etiology of this outcome. Similarly, the contrast in proportions mediated between autoimmune conditions, even though many of the conditions use the same medications in pregnancy, suggests that different mechanisms underlie the risk of adverse pregnancy outcomes in women with different autoimmune conditions. This contrast is the most pronounced in the results for IBD, where although total effects on adverse pregnancy outcomes are just as strong as in other autoimmune conditions, very little of the excess risk was attributed to any pregnancy complications studied. This finding strongly highlights the importance of continued investigation into each of the conditions individually.

Strengths of this study include the large sample created from birth records and hospital discharge summaries. This birth cohort has been used by other researchers to estimate associations between maternal conditions and pregnancy outcomes (2,34,35). By relying on a large, administrative database, we were able to quantify mediated pathways of relatively rare complications, with further stratification by race/ethnicity to improve generalizability to specific populations. Additional strengths include the use of a counterfactual mediation analysis that is robust to unmeasured confounding of the mediator-outcome, and estimation of natural indirect effects to allow for examination of exposure-mediator interaction. Limitations include the well-documented underreporting of certain behaviors or medical conditions in hospital discharge summaries and in birth records, including information on licit and illicit substances and mental health diagnoses. As with all observational data, unmeasured confounding should be assumed. If the frequency of unmeasured confounders differed by the presence of autoimmune conditions, our estimates may be biased. In addition, autoimmune conditions were likely under-recorded (as evidenced by our prevalence estimates being much lower than national estimates), potentially with biased capture toward more severe cases. This possibility may result in overstated effect estimates when applied to a less severe sample. In addition, with respect to models assessing preterm birth, we did not have information on the timing of pregnancy complications. Preeclampsia, gestational diabetes mellitus, and infections can occur after 37 weeks of gestation, resulting in a misclassification of exposure among individuals no longer at risk of preterm birth. We anticipate this misclassification would attenuate the total and indirect effect estimates due to misclassification of exposure, but we cannot guarantee the strength

or direction of the potential bias. Finally, these select autoimmune conditions were chosen based on frequency of occurrence and reported increased risk with adverse pregnancy outcomes. Exposures that occurred with less frequency in our sample (e.g., psoriatic arthritis [n = 116] [2] or ankylosing spondylitis [n = 128] [2]) could not be estimated with a mediation analysis but should be pursued in other data sets with more exposures. Likewise, we were only able to assess pregnancy complications that are coded in discharge summaries and occur with enough frequency to investigate. Other potential mediators of interest (smoking, weight gain) were not well defined or captured in this data source and could not be assessed but should be quantified using other sources of data. Furthermore, this database did not capture medications, so we were unable to assess whether medications like disease modifying antirheumatic drugs or corticosteroids mediate the severity of autoimmune conditions and adverse pregnancy outcomes.

In summary, by leveraging a large retrospective birth cohort, we were able to perform a causal mediation analysis to estimate direct and indirect effects across relatively rare exposures and outcomes. We confirmed previous findings of increased risk of adverse pregnancy outcomes associated with select autoimmune conditions and quantified the extent to which preeclampsia/hypertension, gestational diabetes mellitus, and infections in pregnancy mediate these associations. We showed that although the select pregnancy complications do mediate the outcomes, there is considerable heterogeneity by complication and by autoimmune condition. This analysis demonstrates that there are many unrecognized pathways that mediate risk for adverse pregnancy outcomes in women with autoimmune conditions. However, we simultaneously demonstrate the potential magnitude of improvement of these outcomes through intervention efforts targeted toward preventing pregnancy complications. Clinically, this intervention could be implemented by additional counseling and prevention efforts, particularly around preeclampsia/hypertension, extended to women with RA, SLE, and psoriasis.

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. Bandoli 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. Bandoli, Singh, Strouse, Chambers.
Acquisition of data. Baer, Jelliffe-Pawlowski.
Analysis and interpretation of data. Bandoli, Singh, Strouse, Donovan, Feuer, Nidey, Ryckman, Jelliffe-Pawlowski, Chambers.

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RHEUMATOLOGY REGISTRIES, BIG DATA, AND THE RHEUMATIC DISEASES

Growth and Puberty in Juvenile Dermatomyositis: A Longitudinal Cohort Study

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Objective. To study growth and puberty in a multinational longitudinal prospective cohort of children with juvenile dermatomyositis (DM).

Methods. Children from 31 countries who were ages <18 years and had juvenile DM in active phase were studied, and analyses of height, weight, and pubertal development were conducted in those who had follow-up visits during a 2-year period and for whom anthropometric data was available.

Results. A total of 196 of 275 children (71%) were included. We found a significant reduction in parent-adjusted height Z score over time in female patients ($P < 0.0001$) and male patients ($P = 0.001$), but with catch-up growth at the final study visit. Median body mass index Z score peaked at 6 months ($P < 0.0001$) and was still significantly above baseline at the final study visit, which was at a median of 26 months after baseline ($P = 0.007$), with no difference between sexes. Female patients with a disease duration ≥12 months after onset had significantly lower parent-adjusted height Z score ($P = 0.002$) and no 2-year catch-up growth. At the final study visit, growth failure was seen in 20 of 97 female patients (21%) and in 11 of 73 male patients (15%). Height deflection (Δheight Z score less than –0.25/year) was observed in 29 of 116 female patients (25%) and 25 of 80 male patients (31.3%). Delayed puberty was seen in 20 of 55 female patients (36.4%) and in 11 of 31 male patients (35.5%). Children in early pubertal stage at baseline had the highest risk of growth failure.

Conclusion. Juvenile DM in the active phase and/or its treatment has a significant impact on growth and puberty in affected children. Children with recent onset of puberty or previous growth failure have the highest risk of delayed pubertal development and further growth retardation.

INTRODUCTION

Juvenile dermatomyositis (DM) is a systemic connective tissue disease of childhood, mainly characterized by progressive muscle weakness and cutaneous rash and ulcerations. Even though it is a rare disease with an annual incidence of 2–4 per million (1), it is the most common of the idiopathic inflammatory myopathies in childhood. Before the era of corticosteroid

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SIGNIFICANCE & INNOVATIONS

- In this multinational 2-year follow-up cohort study of 196 children with juvenile dermatomyositis (DM), height deflection, defined as Δheight Z score less than –0.25/year from baseline, was present in 25.0% of girls and 31.3% of boys at the final study visit.
- While growth was significantly affected by reduction in parent-adjusted height Z score over time, a catch-up growth was seen within the final study visit. The body mass index increased significantly during the whole study period.
- An overall delay in pubertal onset, pubertal tempo, or menarche in girls were seen in 36.4% of girls and in 35.5% of boys.
- Growth and pubertal development in patients with juvenile DM must be carefully monitored to minimize the impact of chronic inflammation and high-dose steroid treatment on normal physiologic development.

treatment, juvenile DM was a life-threatening disease (1). Modern immunosuppressive treatment has improved outcome substantially, but still includes long-term corticosteroids to control the systemic vasculopathy (2–5). The treatment goal in juvenile DM is to achieve inactive disease and prevent permanent damage (6,7). Both the inflammatory activity of this severe chronic rheumatic disease and the well-known side effects of corticosteroid treatment may interfere with normal growth and pubertal development of children. The risk of growth failure and delayed puberty are special problems of the childhood rheumatic diseases, and the consequences may be lifelong. Prospective long-term follow-up studies are few, and there is very limited knowledge on growth and puberty in children with juvenile DM (6,8).

The main aim of this study was to assess the prevalence and possible determinants of growth failure and pubertal delay in children with juvenile DM who were followed for 2 years in a large multinational Paediatric Rheumatology International Trials Organisation (PRINTO) prospective observational cohort study.

PATIENTS AND METHODS

Patients and study design. We analyzed anthropometric data from a prospective, multinational PRINTO (9) study on juvenile DM, with an inclusion period between 2001 and 2004 (4,10–12). Inclusion criteria were fulfillment of the diagnostic criteria of juvenile DM (13), age <18 years at enrollment, and an active phase of disease, which was defined as the need to start or receive a major dose increase of corticosteroids and/or immunosuppressants (10,11). A major dose increase was defined according to the physician's decision to increase, modify, or add corticosteroid therapy and/or a new immunosuppressive agent, as per the protocol inclusion criteria. In the present study, we included all patients for whom anthropometric data was available at baseline and at the final study visit (at a median of 26 months) and those who had ≥1 of the second or third visits planned at 6 and 12 months after baseline. Further details on the juvenile DM population and study methods can be found in prior articles (4,10–12). Informed written or verbal consent was obtained from all parents/guardians, according to the requirements of the regional ethics committees.

Data on height and weight. Parents' heights were measured or self-reported, while height (cm) and weight (kg) of the participating children were measured at all study visits, preferably by the same evaluator, scale, and stadiometer (wall mounted or a Harpenden stadiometer). Body mass index (BMI) was defined as weight (kg)/height (m^2). Height and BMI were standardized to Z scores with the least mean squares method (14–16) with age adjustment according to the chronological age in months, according to the World Health Organization (WHO) 2007 growth reference standards (17). Parent-adjusted height Z score was defined as the difference between the child's height Z score for chronological age and the target height (calculated as the average of parents' height, + 6.5 cm for boys, and – 6.5 cm for girls) (18,19). Growth failure was defined as parent-adjusted height Z score less than –1.5 (20).

Data on pubertal maturation. Pubertal maturity stage was assessed clinically at all study visits, according to a standardized case report form that described in detail the different Tanner stages (18,19) according to breast (B1–B5) and pubic

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hair (PH1–PH5) in girls, and testicular volume (T1–T5), penis (P1–P5), and pubic hair (PH1–PH5) in boys. When available, the starting dates for female B2, PH2, menarche, and male T2, P2, and PH2 were registered, together with the type of menstruation (regular, irregular, or stopped) and the testis volume (ml). Definitions of pubertal onset, late or delayed pubertal onset, delayed pubertal tempo, and delayed menarche are based on current literature (12,21,22) and described in detail (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24065/abstract). Delayed puberty was defined as a delay in pubertal onset, pubertal tempo, or menarche. If date of pubertal onset or menarche were missing, the dates were estimated to be the date of the first visit in which male T2, P2, PH2, or female B2, PH2, or menarche was registered.

Statistical analysis. Longitudinal data were analyzed with repeated-measurements analyses of variance (Friedman's test), with post hoc comparison tests adjusted with Bonferroni correction. If data were missing at the second or third visit, we estimated the height and weight by calculating the mean of the percentile of the corresponding data of the previous and following visit. For pubertal data, the Tanner stage was estimated according to all available information on the pubertal stage at the previous and following visit. Cumulative corticosteroid dose from baseline visit to the last available assessment was calculated by the area under the curve with approximation of the trapezoidal formula. Prednisone doses were reported using calculations from the equivalent doses from methylprednisolone. Possible associations between baseline disease characteristics (Table 1) and cumulative corticosteroid dose (oral, intravenous, or oral and intravenous) with growth failure and pubertal delay were analyzed. In the bivariate analysis, comparisons between groups were performed using the Mann-Whitney U test for continuous data, and either the chi-square test or Fisher's exact test as appropriate for categorical data. Comparison of quantitative data at different time points was performed by Friedman's nonparametric analysis of variance and Friedman's test for repeated measurements. Comparison of categorical data collected at 2 different time points in the same individual were performed with McNemar's test. Logistic regression analysis was performed to evaluate the role of baseline variables significant in bivariate analyses (Table 1) and cumulative steroid dose with growth failure or pubertal delay at the last assessment. Odds ratios

Table 1. Demographic and clinical baseline characteristics of children with juvenile DM and comparison between participants included in the growth study and those excluded due to missing anthropometric data (n = 275)*

Baseline characteristics	No. included	Median (IQR)	No. excluded	Median (IQR)	*P*†
Female sex, no. (%)	196	116 (59.2)	79	52 (65.8)	0.31
Age at disease onset, years	196	7.4 (4.3, 10.6)	79	6.7 (4.2, 9.5)	0.17
Age at baseline, years	196	8.9 (6.2, 12.9)	79	8.4 (4.9, 11.0)	0.16
Disease duration, months	196	0.7 (0.2, 2.1)	79	0.5 (0.2, 2.2)	0.45
Height, Z score	196	−0.18 (−1.19, 0.74)	76	−0.51 (−0.94, 0.44)	0.51
Parent-adjusted height, Z score	170	−0.11 (−0.96, 0.65)	62	−0.40 (−1.09, 0.50)	0.52
Body mass index, Z score	196	0.18 (−0.73, 1.13)	76	0.35 (−0.67, 1.33)	0.26
Tanner stage ≥2, no. (%)‡	116	36 (31.0)	52	13 (25.0)	0.43
Growth failure, no. (%)§	170	23 (13.5)	62	9 (14.5)	0.85
CMAS (range 0–52)	194	26 (13, 38)	78	28 (18, 35)	0.81
DAS (range 0–20)	196	12 (10, 15)	79	12 (9, 15)	0.76
C-HAQ score (range 0–3)	194	1.6 (0.9, 2.6)	77	1.5 (0.9, 2.3)	0.58
CHQ physical (range 40–60)	169	31.9 (23.5, 42.4)	68	34.2 (23.8, 44.8)	0.67
PhGA of disease activity (0–10 cm)¶	195	5.5 (3.9, 7.2)	78	5.1 (3.0, 6.9)	0.35
PhGA of muscular disease (0–10 cm)	196	5.3 (2.9, 7.7)	79	5.0 (2.8, 7.1)	0.32
PhGA of disease damage (0–10 cm)#	195	0.2 (0.0, 0.9)	78	0.3 (0.0, 0.9)	0.54
PGA of child well-being (10 cm)	190	5.2 (2.6, 7.4)	76	5.3 (3.4, 7.4)	0.57
PGA of child pain (10 cm)	192	3.3 (0.4, 6.0)	76	2.6 (0.8, 5.2)	0.64
Children ever received oral corticosteroids at baseline, no. (%)	196	186 (94.9)	79	75 (94.9)	1.0
Corticosteroid oral dose (mg/kg)	186	1.1 (0.5, 1.6)	75	1.0 (0.5, 1.8)	0.79
Children ever received pulse corticosteroids at baseline, no. (%)	196	78 (39.8)	79	22 (27.9)	0.06

* Data are median (interquartile range [IQR]) unless indicated otherwise. DM = dermatomyositis; CMAS = Childhood Myositis Assessment Scale; DAS = Disease Activity Score for juvenile dermatomyositis; C-HAQ = Childhood Health Assessment Questionnaire; CHQ physical = physical summary score of the Child Health Questionnaire; PhGA = physician global assessment; PGA = parent global assessment.
† Difference between included and excluded patients (chi-square test, Fischer's exact test, and Mann–Whitney U test), as appropriate).
‡ Female patients ≥B2, male patients ≥T2, or testis volume ≥4 ml.
§ Defined as parent-adjusted height Z score less than −1.5.
¶ Physician global assessment (PhGA) of disease activity using the Myositis Disease Activity Assessment tool.
# PhGA of disease damage using the Myositis Damage Index.

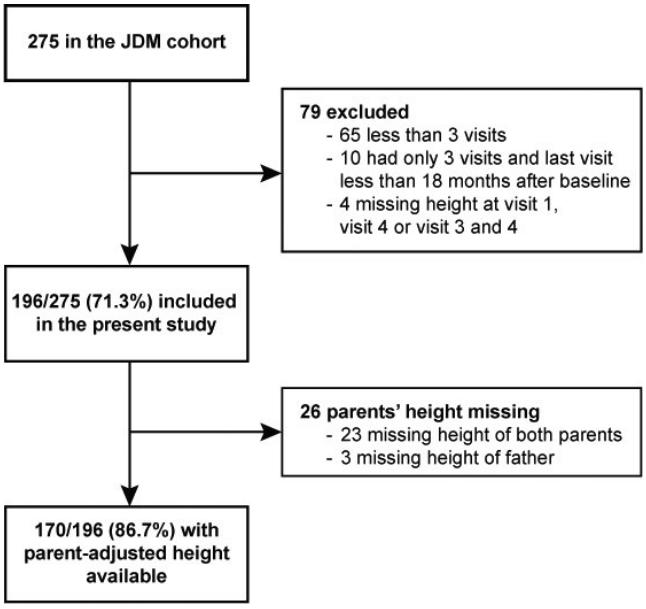

Figure 1. Flow chart of the participants in the juvenile dermatomyositis (JDM) multinational cohort study.

(ORs) and 95% confidence intervals (95% CIs) were reported. *P* values less than 0.05 were considered significant. Data were entered in Access XP database and analyzed by 2 authors (EN and AP) with Excel XP (Microsoft), Statistica 9 (StatSoft Inc.), and Stata 15.

RESULTS

Patients and study cohort. Height data from baseline and repeated measurements during a median of 26 months (first and third quarters) follow-up was available for 196 of 275 patients (71.3%) of the original cohort from 31 countries, and of these 196 patients, height data for both parents was available in 170 patients (86.7%) (Figure 1). Of the 784 visits, imputation was performed for missing height and/or weight in 31 visits and missing pubertal stage in 5 of the visits. The majority of the children were from Western Europe (55.6%) and South and Central America (25.5%), while Eastern Europe (13.8%) and North America (5.1%) were also represented. The included children had either recent-onset juvenile DM (n = 121) or a recent flare of juvenile DM (n = 75). No significant differences in sex, anthropometric data, or other baseline characteristics were found between the included children and the children excluded because of incomplete height data (Table 1). In the included cohort, 99 patients (50.5%) received methotrexate, 30 (15.3%) received cyclosporine A, 10 (5.1%) received cyclophosphamide, and 27 (13.8%) received intravenous immunoglobulins during the 2-year study period. The cumulative dose of oral corticosteroids was median 279 mg/kg (range 45–985 mg/kg) and the cumulative dose of combined oral and pulse steroid was 312 mg/kg (range 72–985 mg/kg) during the study period, and 85 (43.4%) received corticosteroid pulses.

Table 2. Longitudinal anthropometric characteristics in 196 children with juvenile dermatomyositis*

Characteristics	Baseline		6 months		14 months		26 months		*P*
	No.	Median (IQR)	No.	Median (IQR)	No.	Median (IQR)	No.	Median (IQR)	
Age at visit, years									
Female	116	8.8 (5.8, 12.9)	116	9.2 (6.2, 13.3)	116	10.1 (7.0, 14.1)	116	11.1 (8.1, 15.1)	–
Male	80	9.1 (6.3, 13.1)	80	9.7 (6.9, 13.5)	80	10.4 (7.8, 14.5)	80	11.8 (8.6, 15.4)	–
Disease duration									
Female	116	0.7 (0.3, 1.9)	116	1.1 (0.8, 2.5)	116	2.1 (1.5, 3.7)	116	3.1 (2.5, 4.8)	–
Male	80	0.7 (0.2, 2.2)	80	1.3 (0.7, 2.7)	80	2.0 (1.4, 3.5)	80	3.0 (2.5, 4.5)	–
Height, Z score									
Female	116	−0.26 (−1.21, 0.83)	116	−0.44 (−1.44, 0.57)	116	−0.33 (−1. 37, 0.55)	116	−0.34 (−1.19, 0.66)	<0.0001
Male	80	−0.08 (−1.02, 0.65)	80	−0.16 (−1.22, 0.45)	80	−0.20 (−1.08, −0.51)	80	−0.30 (−1.04, 0.56)	0.0005
Parent-adjusted height, Z score									
Female	97	−0.27 (−1.15, 0.43)	97	−0.63 (−1.34, 0.38)	97	−0.58 (−1.40, 0.19)	97	−0.50 (−1.38, 0.30)	<0.0001
Male	73	−0.01 (−0.70, 0.79)	73	−0.09 (−0.99, 0.62)	73	−0.14 (−0.81, −0.66)	73	−0.16 (−0.83, −0.67)	0.001
BMI, Z score									
Female	116	0.22 (−0.70, 1.10)	116	0.93 (−0.08, 1.74)	116	0.61 (−0.21, 1.54)	116	0.52 (−0.55, 1.52)	<0.0001
Male	80	0.15 (−0.86, 1.18)	80	0.93 (−0.16, 2.11)	80	0.62 (−0.37, 1.44)	80	0.43 (−0.66, 1.29)	<0.0001
Growth failure, no. (%)†									
Female	97	16 (16.5)	97	20 (20.6)	97	23 (23.7)	97	20 (20.6)	0.66
Male	73	7 (9.6)	73	9 (12.3)	73	8 (11.0)	73	11 (15.7)	0.77
Height deflection, no. (%)‡									
Female	116	NA	116	68 (58.6)	116	43 (37.1)	116	29 (25.0)	<0.0001
Male	80	NA	80	48 (60.0)	80	32 (40.0)	80	25 (31.3)	0.001

* Analyzed with nonparametric repeated-measures analysis of variance (Friedman's test) according to time or chi-square test for frequencies (female patients versus male patients at 26 months). IQR = interquartile range; BMI = body mass index; NA = not applicable.
† Parent-adjusted height Z score less than –1.5.
‡ Δheight Z score less than –0.25/year from baseline to the following assessments.

Height and BMI. The growth of 196 children during the 2-year study period is shown in Table 2. Height was mainly measured with a wall-mounted (74%) or a Harpenden (15%) stadiometer. The median parent-adjusted height Z score at baseline in girls was –0.27 (IQR –1.15, 0.43) and –0.01 (IQR –0.70, 0.79) in boys. At study visits 6 and 14 months, both actual and parent-adjusted height Z scores were statistically significantly lower compared to baseline, with girls more significantly affected than the boys ($P < 0.0001$ by Mann-Whitney U test). This reduction in parent-adjusted height Z scores was less pronounced and not significantly lower at the final study visit at a median of 26 months compared to baseline, showing that a catch-up growth took place (Table 2 and Figure 2A). Median BMI increased significantly during the whole study period, with a peak at 6 months with no sex differences (Table 2 and Figure 2B). Growth failure was observed in 16.5% of females and 9.6% of males at baseline and the increase during the study period was not significant. Height deflection, defined as Δheight Z score less than –0.25/year from baseline, was present in a majority of the participants at 6 months, and still present in 25.0% of girls and 31.3% of boys at the final study visit. The number of girls with height deflection was significantly higher at 6 months compared to later study visits, indicating that a catch-up growth took place in girls, but no significant catch-up growth took place in boys from the visit at 14 months to 26 months.

Pubertal development. The pubertal stage was assessed at each study visit, and the developmental characteristics of the 86 evaluable adolescents are shown in Table 3. Among these adolescents, 38 of 60 (63%) were late maturing, defined as onset of puberty >11 years of age in girls and >12 years of age in boys. A delayed pubertal onset, defined as B2 >13 years of age in girls and T2 >14 years in boys, was found in 11 of 62 evaluable adolescents (18%), with a mean pubertal onset age of 11.1 years for B2 in girls and 12.8 years for T2 in boys. An overall delay in pubertal onset, pubertal tempo, or menarche (in girls) was seen in 36.4% of girls (95% CI 23.8–50.4%) and in 35.5% of boys (95% CI 19.2–54.6%).

The median age at menarche was 14.0 years in the subgroup of 31 girls with menarche registered before the last study visit, and 7 of 31 girls (23%) had delayed menarche. Irregular menses was registered in 8 of the 28 girls (29%) with information on menses type. None of the girls reported postmenarchal amenorrhea. Altogether, 110 of 196 children were not evaluable for pubertal development, including 17 who were already sexually mature at study inclusion and 93 who were prepubertal during the whole study period (data not shown). Among the 116 girls included in the study, only 55 were evaluable for pubertal development. The remaining 61 girls were either Tanner stage B5 at baseline (n = 9), or <13 years of age and prepubertal at the last available assessment (n = 52). Among the 80 boys included in the study, only 31

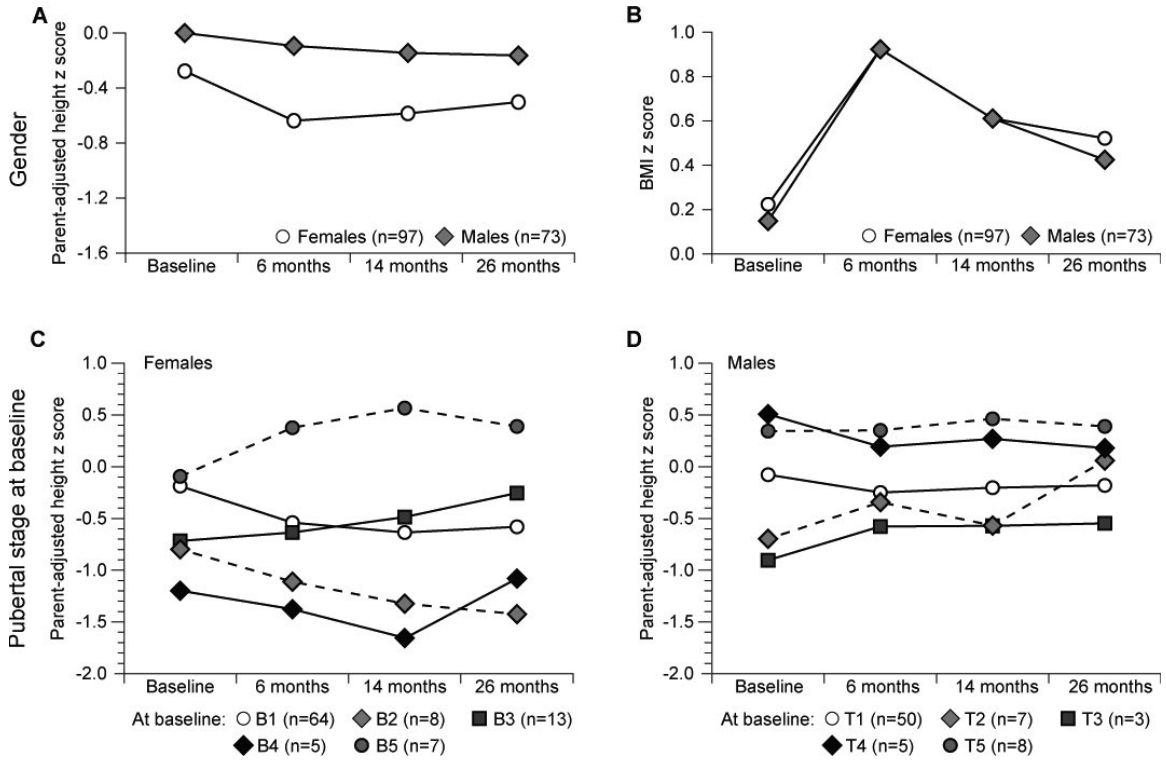

Figure 2. Median parent-adjusted height Z score and body mass index (BMI) Z score in 26 months of follow-up of 196 children with juvenile dermatomyositis according to sex (**A** and **B**) and pubertal stage (**C** and **D**). B = Tanner stage for breast development; T = Tanner stage for testicular development.

Table 3. Pubertal characteristics of participants in pubertal development during the study period (n = 86 [43.9%])*

	Female, no./ total no. (%)	Male, no./ total no. (%)
Stage at last visit, ≥B2 or ≥T2	55/55 (100.0)	31/31 (100.0)
Mean ± SD age, years, stage B2 (n = 37) or T2 (n = 23)	11.1 ± 1.9	12.8 ± 1.6
Late pubertal onset, stage B2 or T2	23/37 (62.2)	15/23 (65.2)
Delayed pubertal onset†	6/37 (16.2)	5/25 (20.0)
Delayed pubertal tempo‡	11/50 (22.0)	6/26 (23.1)
Menarche	31/55 (56.4)	NA
Delayed menarche§	7/31 (22.6)	NA
Secondary amenorrhea	0/31 (0)	NA
Age at menarche, mean ± SD years	14.0 ± 1.6	NA
Irregular menses	8/28 (28.6)	NA
Delayed puberty¶	20/55 (36.4)	11/31 (35.5)

* A total of 110 of 196 patients (56.1%) were excluded as they were too mature or too young to be evaluable for pubertal development. NA = not applicable.
† Age at B2 (Tanner stage: breast) ≥13 years for female patients; T2 (Tanner stage: testicular volume) ≥14 years for male patients.
‡ Stable Tanner stage for ≥1 year in late maturing child or ≥2 years in normal maturing child.
§ Age at menarche ≥15 years or no menarche and age at last follow-up ≥15 years.
¶ Delayed pubertal onset, delayed pubertal tempo, or delayed or absent menarche.

were evaluable for pubertal development. The remaining 49 boys were either ≥14 years of age and T5 at baseline (n = 8) or <14 years and prepubertal at the last available assessment (n = 41).

Impact of puberty and disease duration on height and BMI. The impact of the disease and treatment on growth pattern in female patients was influenced by the pubertal stage at baseline (Figure 2C). Female patients entering the study in Tanner stage B2 had significantly lower parent-adjusted height Z scores at the end of study compared to those entering the study in more mature stages, including B3, B4, or B5 (P = 0.01 by Mann-Whitney U-test). The growth pattern was less affected by pubertal stage in male patients (Figure 2D) and in female patients who were prepubertal at baseline.

Similarly, analyses of growth based on pubertal stage at the final study visit show that adolescents with Tanner stage B3/B4 or T3/T4 at the final study visit had a statistically significant reduction in parent-adjusted height Z scores during the study period. In comparison, the adolescents in Tanner stage 5 who were fully mature at baseline had a normal growth pattern (results not shown). Female patients who had longer disease duration (defined as ≥12 months at baseline) had significantly lower parent-adjusted height Z scores, with a baseline median ± SD Z score of –0.95 ± 1.21 that remained low throughout the study period (Supplementary Figure 1A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24065/abstract). Female patients with shorter disease duration had significantly lower parent-adjusted height Z scores at second and third visits, but not at the final study visit at 26 months after baseline. Disease duration had no impact on growth in male patients (results not shown). Children with shorter disease duration had significantly higher rise in BMI Z score, with a peak at 6 months and no sex differences (see Supplementary Figure 1B, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24065/abstract). Of the 170 patients, 15 were mature, T5 and B5, and 25 were T4/T5 and B4/B5 at baseline. There were no sex differences in baseline disease activity nor in cumulative corticosteroid dose.

Predictors and associations of growth failure and pubertal delay. For the 3 most important outcomes, including growth failure, height deflection, and pubertal delay, we evaluated the potential baseline determinants of age at onset, age at first study visit, disease duration, disease activity measures (such as the Childhood Myositis Assessment Scale, the Manual Muscle Testing measure, and physicians' and parents' global assessment of disease activity), cumulative oral and/or pulse corticosteroid dose, Central- or Latin-American origin, and growth failure at baseline. Growth failure, height deflection, and/or delayed puberty was found in 94 of the 196 children (48.0%) at the last study visit. Neither growth failure (P = 0.21 by chi-square test) nor height deflection (P = 0.42) was significantly associated with delayed puberty in female or male patients. The associations and over-

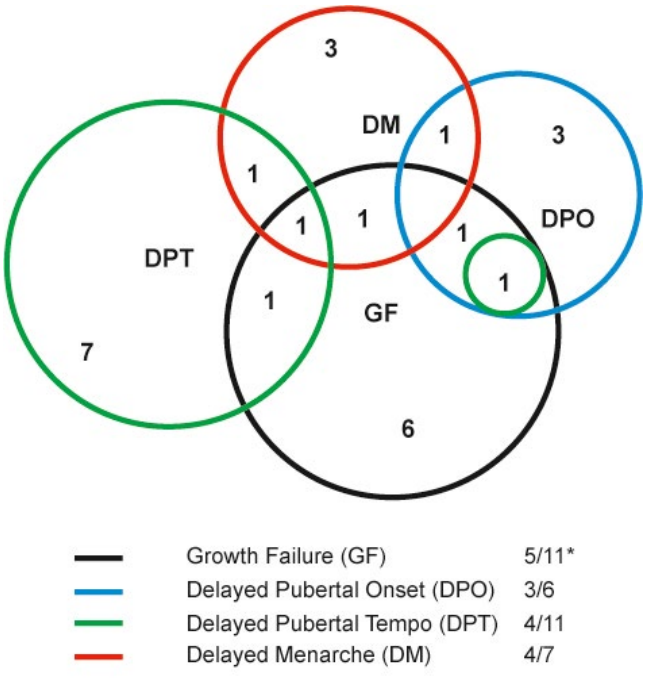

Figure 3. Venn diagram depicting the prevalence and overlap between growth failure (GF), delayed pubertal onset (DPO), delayed pubertal tempo (DPT), and delayed menarche (DM) in 55 females with juvenile dermatomyositis and evaluable pubertal development in the 2-year study period. One patient with GF, DPO, and DPT is depicted in a separate circle.

lap between growth failure and the different aspects of delayed puberty are shown in Figure 3.

In the bivariate analysis, an association was found between growth failure at final study visit and growth failure at baseline (OR 14.6 [95% CI 5.6–38.2]), while no significant associations were found for height deflection. No statistically significant association was found between growth failure at final study visit and cumulative oral and pulse corticosteroid dose given during the study period (median 455 mg/kg in children with growth failure and median 322 mg/kg in children with no growth failure; $P = 0.16$). There was also no statistically significant association between growth failure at final study visit and cumulative corticosteroid dose given during the study period in the 121 children with recent-onset juvenile DM. Statistically significant associations were found between growth failure at baseline and delayed puberty during the study period (OR 7.4 [95% CI 2.3–24.6]).

Growth failure at baseline was the only significant baseline determinant for growth failure in the logistic regression model (OR 14.6 [95% CI 5.6–38.2]) and in a regression model for delayed puberty (OR 7.4 [95% CI 2.3–24.6]). No significant effects of higher cumulative steroid doses, disease activity, or geographic origin on height or pubertal development were seen.

DISCUSSION

To the best of our knowledge, this is the first large prospective, longitudinal study to present results primarily on growth and puberty in juvenile DM. Parent-adjusted height Z scores decreased significantly during the first year of the study, but the decrease was less pronounced and not significantly lower at the final study visit compared to baseline, indicating that a catch-up growth took place within 2 years after the baseline visit. Children with onset of puberty at the time of the first study visit had the highest risk of growth retardation. Height deflection at the final study visit was found in 25% of female patients and 31% of male patients.

Growth failure has been reported in some outcome studies as 1 of 38 items included in the Myositis Damage Index (MDI) (10,23). Our study cannot clarify the unsolved question of whether the adverse impact on growth and puberty in juvenile DM is due to the ongoing active inflammation, side effects of the treatment, or likely a complex interplay between both of these factors, with individual variations in vulnerability. A large cross-sectional multinational study by Ravelli et al (6) demonstrated growth failure in 8% of 462 patients with juvenile DM, with a mean disease duration of 7.7 years. In a cross-sectional study, Sanner et al found growth failure in 10% of 60 juvenile DM patients for whom retrospective clinical information was available from a median of 16.8 years disease duration (8). Growth retardation was found in 14% of 143 children with idiopathic inflammatory myopathy in a study by Rider et al (24). The studies by Sanner et al and Rider et al included patients receiving the treatment regimens that were used up to 25 years ago, and growth failure was reported as part of the MDI, which was defined as a height less than –3 SD for age, growth velocity over 6 months less than the third percentile for age, or crossing at least 2 centiles (5%, 10%, 25%, 50%, 75%, 95%) on a growth chart (8,24).

An important clinical relevance of our findings is that children with juvenile DM may have pubertal delay without growth retardation, or isolated growth retardation. In follow-up, clinicians should therefore be aware of both the pubertal development and the growth of the child, assess the milestones of development, and ensure that the children reach as much as possible of their genetic potential. The observed BMI increase throughout the study period, peaking at 6 months, should be noted, and was probably due to the high doses of corticosteroid given to control active disease early after disease onset or flare.

Unexpectedly, we did not find a significant association between growth failure and cumulative corticosteroid dose. Use of intravenous high-dose corticosteroids may have less impact on growth than higher oral doses, but our study was not designed to examine potential differences in side effects of treatment administration routes.

In a study by Rygg et al (of similar design as the present study) on growth and puberty in juvenile systemic lupus erythematosus (SLE), a significant reduction in parent-adjusted height Z score was found from baseline also to the final study visit in both sexes, with male patients most affected (12). Similar rates of pubertal delay (as those found in the present study on juvenile DM) were observed and similar cumulative doses of corticosteroids were given in the study period. Baseline determinants of growth failure were previous growth failure, higher age at first visit, and a higher cumulative steroid dose. Juvenile SLE is, however, a disease in which onset is usually around or after puberty (25). The onset age in the juvenile SLE cohort in the study by Rygg and colleagues was a median of 14 years of age and clearly higher than the median of 9 years of age in our juvenile DM cohort. The chronicity of juvenile SLE implies that children with juvenile SLE may need immunosuppressive treatment for active disease in a longer time period than children with juvenile DM; therefore, corticosteroids may be given during the whole pubertal development more often in juvenile SLE (12,26). In juvenile DM, a chronic continuous disease course >2 years was found in 34.4% of a cohort of 121 children in a study by Rider et al (24), and active juvenile DM disease in long-term follow-up was demonstrated in studies by Ravelli et al (41.2–60.5%) (6) and Sanner et al (51–73%) (27).

Multiethnicity makes our results relevant worldwide but may also mask findings that may have shown clearer results reaching significance in a more homogeneous study population. The 2007 WHO growth reference was chosen (17,28), because national growth references were not available for all participating countries and would have made the analyses and interpretation less uniform. In order to eliminate the genetic and environmental impact, it was essential that parent-adjusted height scores were used in our study. Pubertal onset and menarche have changed over time in

different cultures and is influenced by ethnic and socioeconomic factors. Due to these secular trends, defining delayed pubertal development is a challenge (22,29).

In the multivariate model, the determinants for both growth failure and puberty were growth failure at first assessment. In line with findings of the similar study of juvenile SLE, our findings suggest that once a patient has growth failure it may be more difficult to achieve catch-up growth, and they have an increased risk of further growth impairment. These children may also represent a group with a more severe disease course.

Limitations of our study include that in a 2-year follow-up, assessment of pubertal development taking place over years will only be possible for a limited number of participants. Also, anthropometric data were not available for all patients in the original cohort. Only a few children were mature at the end of the study period, and therefore the impact on final height was not possible to ascertain. The cumulative steroid dose was estimated from reports at each visit of the present dose and adjustments of the steroid dose, therefore steroids given during the disease course before the study period in children with a flare were not registered, and the impact of this pre-study treatment could not be analyzed.

In conclusion, our study demonstrates that children with juvenile DM have a substantial risk of delayed pubertal development, increased BMI, and height deflection. However, the overall frequency of growth failure was not significantly higher at the final study visit 2 years after baseline, indicating that the very high doses of corticosteroid treatment given during the study period are reasonably well-tolerated with regards to growth. Children with previous growth failure, and children with disease onset in early pubertal development are most at risk of impaired growth and/or pubertal development, and careful clinical monitoring is essential.

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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. Nordal 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. Nordal, Pistorio, Rygg, Ruperto.

Acquisition of data. Nordal, Rygg, Ruperto, Giancane, Maghnie, Di Iorgi, Flemming, Hofer, Melo-Gomes, Bica, Brunner, Dannecker, Gerloni, Harjacek, Huppertz, Pratsidou-Gertsi, Nielsen, Stanevicha, Ten Cate, Vougiouka, Pastore, Simonini, Ravelli, Martini.

Analysis and interpretation of data. Nordal, Pistorio, Rygg, Ruperto.

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Reduction in Upper Limb Joint Surgery Among Rheumatoid Arthritis Patients: An Interrupted Time-Series Analysis Using Danish Health Care Registers

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Objective. Joint replacement surgery is a proxy of severe joint damage in rheumatoid arthritis (RA). The aim of this study was to assess the impact of the introduction of biologic disease-modifying antirheumatic drugs (bDMARDs) on the incidence rate (IR) of upper limb joint replacements among newly diagnosed RA patients.

Methods. Using the Danish National Patient Register, patients with incident RA from 1996–2012 were identified. Each patient was matched on age, sex, and municipality, with up to 10 general population controls. The age- and sex-standardized 5-year IR per 1,000 person-years of a composite outcome of any first joint replacement of the finger, wrist, elbow, or shoulder was calculated, and an interrupted time-series analysis was undertaken to investigate trends and changes of the IR in the pre-bDMARD (1996–2001) and the bDMARD eras (2003–2012), with a 1-year lag period in 2002.

Results. In total, 18,654 incident patients with RA were identified (mean age 57.6 years, 70.5% women). The IR of joint replacements among patients with RA was stable at 2.46 per 1,000 person-years (95% confidence interval [95% CI] 1.96, 2.96) from 1996 to 2001 but started to decrease from 2003 onwards (–0.08 per 1,000 person-years annually [95% CI –0.20, 0.02]). Compared with patients with RA, the IR among controls in 1996 was 1/17 and increased continuously throughout the study period.

Conclusion. The IR of upper limb joint replacements started to decrease among patients with RA from 2002 onwards, whereas it increased among controls. Our results suggest an association between the introduction of bDMARDs and a lower need of joint replacements among patients with RA.

INTRODUCTION

In patients with rheumatoid arthritis (RA), joint replacement surgery is considered a proxy for end-stage or severe joint damage (1). Joint damage occurs with persisting and longstanding inflammation, but even short periods of severe inflammation can also result in significant joint damage (2). Moderate or high disease activity in the first 5 years after diagnosis are risk factors for joint surgery (3). Up to 10% of patients with RA require surgery of the upper limbs within the first 5 years after disease onset (1) and,

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SIGNIFICANCE & INNOVATIONS

- The incidence of joint replacements in the shoulder, elbow, wrist, and fingers among patients with newly diagnosed rheumatoid arthritis (RA) was fairly stable prior to the introduction of biologic disease-modifying antirheumatic drugs (bDMARDs) but nonetheless ~17 times higher than in the general population.
- Following introduction of bDMARDs, the incidence rate of upper limb joint replacement surgery started to decrease among patients with RA, whereas it increased in the nonrheumatoid background population.
- However, the overall need of upper limb joint replacements in the first 5 years following diagnosis of RA was low in this Danish cohort.

following RA diagnosis, upper limb surgery is generally performed sooner than lower limb surgery (4,5).

The introduction of biologic disease-modifying antirheumatic drugs (bDMARDs) in the late 1990s and early 2000s has expanded the treatment repertoire and increased the chances of more favorable clinical and radiographic outcomes for RA patients (6–8). Whether the improved clinical outcomes observed with bDMARDs have resulted in lower rates of upper limb joint surgery is less clear (9,10). There are studies reporting decreases in upper limb joint replacements among patients with RA during recent decades, but in most studies, these changes started in the mid-1990s before bDMARDs were available (10–16). Other studies suggest that no changes have occurred for rates of joint replacements among RA patients during recent decades (13,17,18).

We therefore thought it of interest to assess whether there was an association between the introduction of bDMARDs in the treatment of patients with RA and the incidence rate (IR) of shoulder, elbow, wrist, and finger joint replacement surgery among patients with incident RA compared to a cohort of general population controls. To investigate this, we used data from a Danish health care register in an interrupted time-series design. As a secondary aim, we investigated the impact of bDMARD introduction on non–joint replacement surgeries in the shoulder and elbow and in the wrist and fingers.

PATIENTS AND METHODS

Study design. The present study is a nationwide interrupted time-series analysis (19,20) from Denmark investigating whether there was an association between the introduction of bDMARDs for the treatment of RA in 2002 and the 5-year IR of upper limb joint replacement and upper limb non–joint replacement surgery. The interrupted time series is an ecologic study method to investigate population-level time trends following a specific intervention at a specific point in the time series. Study methods and results are reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology guidelines (21).

Setting. In Denmark, the health care system is tax-financed and offers free access for all residents to hospitals and essential operations. Every resident receives a 10-digit personal identification number at birth or date of immigration. This personal identifier is consistent throughout all national registers, making register linkage possible. The study period was from January 1, 1996 to December 31, 2017.

Data sources. *The Civil Registration System (CRS) and The Danish National Patient Register (DNPR)*. The CRS captures all births, migrations, and deaths among Danish residents (22). The DNPR contains information on all inpatient (since 1977) and outpatient (since 1995) contacts at private and public hospitals in Denmark (23,24). Discharge diagnoses are registered in accordance with the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) (since 1994). Surgical interventions have been registered and coded in accordance with the Nordic Medico-Statistical Committee (NOMESCO) Classification (since 1996). When patients are discharged, information is provided on 1 main diagnosis and up to 19 additional secondary diagnoses along with any surgeries that are performed during the hospital stay. We used the DNPR to identify all patients with RA and all joint surgeries, and to obtain information on preexisting comorbidities for descriptive purposes solely (for ICD-10 and NOMESCO codes used, see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23835/abstract).

The Danish Registry for Biologic Therapies in Rheumatology (DANBIO). DANBIO is a nationwide register in Denmark established in 2000 to monitor the use and efficacy of bDMARDs (25). Each year the DANBIO steering committee publishes online reports (26). We used data from these annual reports to establish the time of the interruption (intervention) in the present study.

Study population. *Patients with RA*. In the DNPR, all patients with a diagnosis of RA between 1996 and 2012 were identified (ICD-10 codes M05.1, M05.3, M05.8, M05.9, M06.0, M06.8, and M.06.0). Some degree of misclassification is expected when using health care registers in epidemiologic studies. To minimize this risk, we restricted our case definition of RA in the primary analysis to patients having RA listed as their main diagnosis at 2 hospital contacts within 90 days, and each of these had to originate from a department that specialized in rheumatology or general internal medicine (27).

General population comparator. Each patient with RA who was identified in the DNPR was matched with up to 10 non-RA individuals from the general population of Denmark. Matching criteria were sex, year of birth, and municipality at time of diagnosis. Matching was carried out only once and

with no replacement following patient exclusions (see exclusion criteria below). In the present study, the date from which patients and controls were followed up (i.e., the date of the second RA diagnosis and corresponding matching date for controls) was termed "index date."

Exclusion criteria. Patients with prevalent RA with a first diagnosis of RA recorded prior to January 1, 1996 were excluded, as were individuals ages <18 years at the index date. Furthermore, patients and controls who had received upper limb joint replacement prior to their index date were excluded for the primary analysis. Accordingly, patients who had a secondary outcome of interest prior to the index date were excluded in the respective secondary analyses.

Outcomes. *Primary outcome*. The primary composite outcome was any first joint replacement of the shoulder, elbow, wrist, or fingers within 5 years of the index date. NOMESCO codes were used for identification of the procedures in DNPR (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23835/abstract, for specific codes). If an individual had multiple surgeries within the 5 years of maximum allowed follow-up, only the first joint replacement counted in the analysis.

Secondary outcomes. We had 2 secondary outcomes of interest, which included any first joint or soft tissue surgery in the shoulder or elbow excluding joint replacements and any first joint or soft tissue surgery in the wrist or fingers excluding joint replacements (for specific procedures and NOMESCO codes, see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23835/abstract).

Follow-up. In our primary analysis, follow-up started at the index date and ended at the date of first joint replacement surgery, death, emigration, or no later than 5 years of follow-up, whichever occurred first. In secondary analyses, follow-up started at the index date and ended at whichever occurred first of non–joint replacement surgery of interest, death, emigration, or 5 years of follow-up at the latest. To ensure equal follow-up time regardless of whether patients were diagnosed at the start or end of the study period, we exclusively looked at the first 5 years after the diagnosis for all patients and controls; thus, patients diagnosed later than December 31, 2012 (who were thus unable to contribute a full 5 years of follow-up) were not included in the present study.

Intervention. The intervention in our interrupted time-series analysis was the introduction of bDMARDs for the treatment of patients with RA in Denmark. Although infliximab was available in 1999, there were 3 reasons why 2002 was the appropriate choice as the intervention time point: (1) data from DANBIO showed that it was not until 2002 that the use of tumor necrosis factor inhibitors (TNFi) dramatically increased (26); (2) in 2002, 3 different TNFi were available (adalimumab, etanercept, and infliximab), and each of them were increasingly being used (26); and (3) the now defunct Danish Institute for Rational Pharmacotherapy published their first national treatment guideline for TNFi therapy in RA in 2002. Changes in prescription patterns and guideline implementation were likely phased in rather than instantaneously changed, and thus, to account for this in our time-series analysis, we applied a 1-year lag period starting January 1, 2002 and ending December 31, 2002.

Statistical analyses. Descriptive data of the study populations are presented in mean and SD and absolute numbers and percentages, as appropriate. Within each 6-month period from 1996 to 2012, we calculated the 5-year age-and sex-standardized IRs of upper limb joint replacement surgery among incident RA patients and controls. The time series thus consisted of 32 data points when excluding the 1-year lag period in 2002. The interrupted time-series analysis was then carried out with 2 time segments, including the pre-bDMARD era (1996–2001) and the bDMARD era (2003–2012), interrupted by the lag-period in 2002. Using segmented linear regression, we estimated the baseline IR in 1996 (IR per 1,000 person-years), the trend in IR from 1996 to the end of 2001 (Δ IR per 1,000 person-years per 6-month period), the immediate change in the level of the IR in 2003 (Δ IR per 1,000 person-years), and the changes in trend (Δ IR per 1,000 person-years per 6-month period) from 2003 to 2012 in the bDMARD era. Using a backward-stepwise procedure, the most parsimonious models were specified (P at entry < 0.05 and P at exit ≥ 0.20). This model selection strategy is commonly used in interrupted time-series studies (19,28,29). Results were presented as the 1996 baseline IR (intercept of the model), the pre-bDMARD era trend per year (slope coefficient × 2), the level change in IR at the start of the bDMARD era (difference between level in IR at the end of 2001 and start of 2003), and trend in bDMARD era (slope regression coefficient in pre-bDMARD era × 2 + slope regression coefficient in bDMARD era × 2). All model parame-

Table 1. Demographics of adult patients with incident RA and matched general population controls, 1996–2012*

	RA	Controls	*P*
No.	18,654	183,065	
Age, mean ± SD years	57.6 ± 15.1	57.4 ± 15.1	0.048
Women	13,142 (70.5)	129,239 (70.6)	0.683
Chronic obstructive pulmonary disease	756 (4.1)	6,432 (3.5)	<0.001
Cardiovascular disease	1,829 (9.8)	16,917 (9.2)	0.019
Diabetes mellitus	661 (3.5)	7,005 (3.8)	0.045

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

Table 2. Changes in the 5-year IR of upper limb joint replacement surgery among newly diagnosed RA patients following introduction of bDMARDs compared with secular trends in age-, sex-, and municipality-matched general population controls in an interrupted time-series model*

Cohort	No.	Person-years	Joint replacements, no.	Baseline†	Pre-bDMARD era‡	Start of bDMARD era§	bDMARD era¶
RA	18,654	89,196	193	2.46 (1.96, 2.96)	No change	No change	−0.08 (−0.20, 0.02)
Controls	183,152	838,001	291	0.14 (0.07, 0.21)	0.01 (−0.00, 0.02)	0.17 (0.03, 0.31)	0.01 (−0.00, 0.02)

* Values are the incidence rate per 1,000 person-years (95% confidence interval) unless indicated otherwise. Stepwise-backward elimination to produce most parsimonious model: $P < 0.05$ at entry and $P > 0.2$ at exit. IR = incidence rate; RA = rheumatoid arthritis; bDMARDs = biologic disease-modifying antirheumatic drugs.
† In 1996.
‡ Change per year based on biannual data, 1996–2001.
§ Change in level, January 1, 2003.
¶ Change per year, 2003–2012.

ters were presented with 95% confidence intervals (95% CI). Statistical analyses were carried out using Stata, version 13.1 and R software, version 3.1.4.

Sensitivity analyses and model testing. For sensitivity, we used another, less strict case definition from a study by Eriksson et al (30). This definition included patients who had RA listed as a main or contributory diagnosis at 2 hospital contacts within 1 year in the DNPR. This case definition had no requirements with regards to the specialization of the departments at each contact. All interrupted time-series models were tested for first order autocorrelation using Durbin-Watson tests (20).

Ethics. According to Danish legislation, the registration and publication of data from clinical registers and databases do not require patient consent or approval by ethics committees. Approval was given by the Danish Data Protection Agency (GEH-2014-043, I-Suite: 03166).

RESULTS

We identified 18,654 adult patients with RA who were diagnosed between January 1, 1996 and December 31, 2012 and those who had no prior upper limb joint replacements (Table 1 and Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23835/abstract).

Primary outcome. Overall, 193 of 18,654 patients with RA (1.0%) had upper limb joint replacements within the first 5 years from the index date; with a total of 89,196 person-years of follow-up, this resulted in a crude IR of 2.16 per 1,000 person-years (95% CI 1.87, 2.49) for the entire period of 1996–2012.

In the interrupted time-series analysis, the 1996 baseline IR was 2.46 (95% CI 1.96, 2.96) per 1,000 person-years and remained so until 2001 (Table 2 and Figure 1). From 2003, the IR started to decrease by 3% annually.

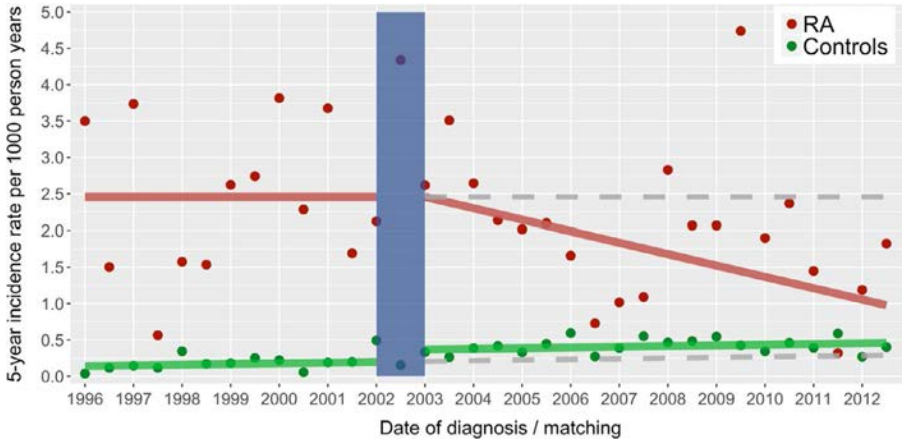

Figure 1. Results of interrupted time-series regression analysis investigating the association between introduction of biologic disease-modifying antirheumatic drugs and the 5-year incidence rate (per 1,000 person-years) of any first upper limb joint replacement among patients newly diagnosed with rheumatoid arthritis (RA) and matched controls from the general population. Broken lines represent estimated counterfactual scenarios had there been no change after 2002.

Table 3. Changes in the 5-year IR of upper limb joint surgery (excluding joint replacements) among newly diagnosed RA patients following introduction of bDMARDs compared with secular trends in age-, sex-, and municipality-matched general population controls in an interrupted time-series model*

Outcome	No.	Person-years	Surgeries (no.)	Crude IR/1,000 person-years†	Baseline IR/1,000 person-years	Annual change in IR/1,000 person-years‡	Level change/1,000 person-years§	Trend¶
Shoulder and elbow surgeries								
RA patients	18,545	88,577	216	2.44 (2.13, 2.79)	2.76 (2.32, 3.20)	No change	No change	−0.07 (−0.16, 0.02)
Controls	182,831	835,782	529	0.63 (0.58, 0.69)	0.23 (0.12, 0.33)	0.01 (−0.01, 0.03)	0.39 (0.19, 0.59)	No change
Finger and wrist surgeries								
RA patients	18,321	86,928	437	5.03 (4.58, 5.52)	7.98 (6.99, 8.97)	−0.13 (−0.32, 0.06)	−2.33 (−4.29, −0.37)	−0.13 (−0.32, 0.06)
Controls	181,874	830,768	760	0.91 (0.85, 0.98)	0.90 (0.82, 0.98)	No change	No change	No change

* Values are the incidence rate per 1,000 person-years (95% confidence interval) unless indicated otherwise. Stepwise backward elimination to produce most parsimonious model: $P < 0.05$ at entry and $P > 0.2$ at exit. Change per year based on biannual data. IR = incidence rate; RA = rheumatoid arthritis; bDMARDs = biologic disease-modifying antirheumatic drugs.
† 1996–2015.
‡ 1996–2001.
§ 2003.
¶ 2003–2015.

Among controls, the IR was much lower at 0.14 (95% CI 0.07, 0.21) per 1,000 person-years in 1996. Conversely to that observed for RA patients, these rates increased annually by 7% from 1996 to 2002 and a level increase of 0.17 (95% CI 0.03, 0.31) following the lag period in 2002 (Table 2 and Figure 1). At an IR of 0.37 in the beginning of 2003, the rate subsequently increased annually from 2003 to 2012 by the same magnitude as in the pre-bDMARD era.

The IR ratio (IRR) comparing RA and controls using regression-based values decreased from 17.6 in 1996 to 12.9 in 2001 (end of pre-bDMARD era), to 6.8 in 2003 (beginning of bDMARD era), and 3.5 in 2012 (end of the study period).

Secondary outcomes. *Shoulder and elbow surgery*. The IR of shoulder and elbow surgery was stable at 2.76 (95% CI 2.32, 3.20) per 1,000 person-years among RA patients in the pre-bDMARD era from 1996 to 2001 (Table 3 and Figure 2). From 2003, the IR started to decrease by 1% annually. Among matched controls, the baseline IR was 1/12 that in the RA cohort (0.23 [95% CI 0.12, 0.33] per 1,000 person-years) but with an annual increase of 0.01 (95% CI –0.01, 0.03) from 1996 to

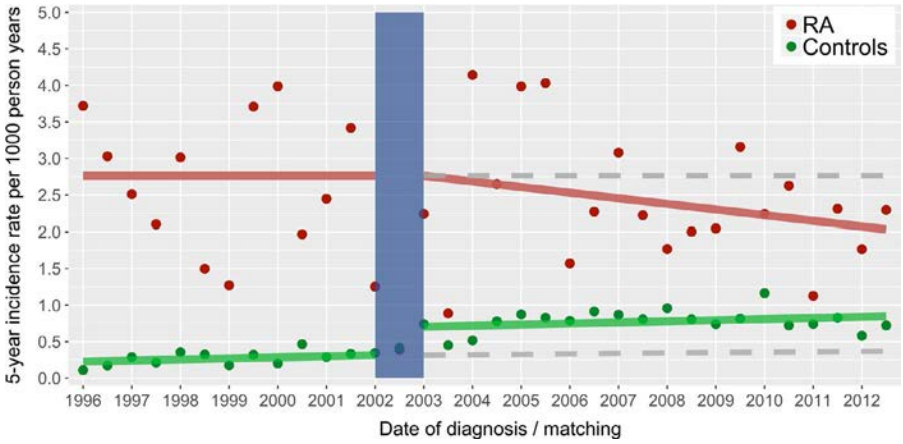

Figure 2. Results of interrupted time-series analysis investigating the association between introduction of biologic disease-modifying antirheumatic drugs and the 5-year incidence rate (per 1,000 person-years) of any first shoulder or elbow surgery (excluding joint replacement) among patients newly diagnosed with rheumatoid arthritis (RA) and matched controls from the general population. Broken lines represent counterfactual scenarios had there been no change after 2002.

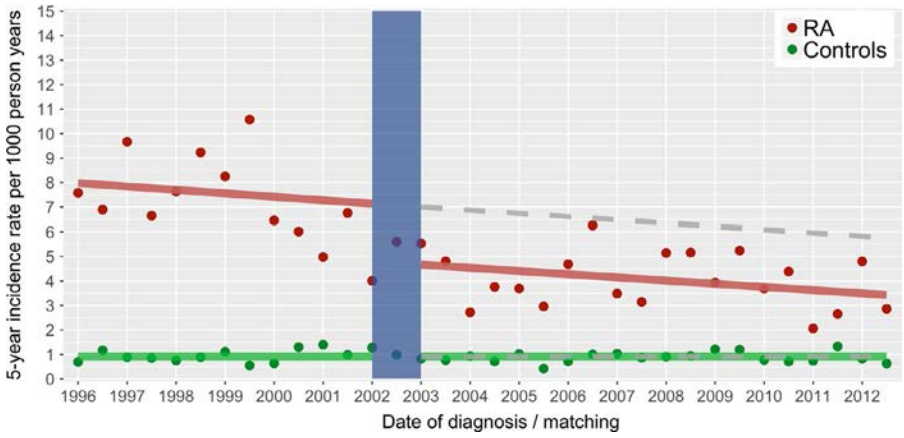

Figure 3. Results of interrupted time-series analysis investigating the association between introduction of biologic disease-modifying antirheumatic drugs and the 5-year incidence rate (per 1,000 person-years) of any first finger or wrist surgery (excluding joint replacement) among patients newly diagnosed with rheumatoid arthritis (RA) and matched controls from the general population. Broken lines represent counterfactual scenarios had there been no change after 2002.

2017. There was a level increase of 134% from the end of 2001 to 2003 following the lag period.

Finger and wrist surgery. In the regression models, the 5-year IR of finger and wrist surgeries in 1996 was 7.98 (95% CI 6.99, 8.97) with an annual decrease of 2% from 1996 to 2001 (see Table 3 and Figure 3). In 2003, at the start of the bDMARD era, there was a decrease of 32% followed by an annual decrease in IR with the same magnitude as in the pre-bDMARD era. Among controls, the IR was 0.90 (95% CI 0.82, 0.98) surgeries per 1,000 person-years from 1996 to 2017 with no observed changes throughout the interrupted time series.

Sensitivity analyses. Using the more liberal case definition, 32,584 patients with RA were identified. Applying this case definition resulted in a slightly older cohort (mean age 59.0 years versus 57.6 years) but with the same proportion of females (70.4% versus 70.5%) (see Supplementary Table 2). Overall, 372 of 32,584 patients (1.1%) with RA had a first primary upper limb joint replacement during follow-up. The regression model differed from the main analysis in that there was a level increase in 2003 in the RA cohort, but the rate of decline during 2003 to 2012 was the same as in the main analysis (see Supplementary Table 3 and Supplementary Figure 2). Overall, the results for the secondary outcomes using the liberal case definition were no different than when using the more strict definition (see Supplementary Table 4 and Supplementary Figures 3 and 4).

DISCUSSION

In a nationwide study, we investigated whether there was an association between the introduction of bDMARDs for treatment of patients with RA and the 5-year IR of upper limb joint replacements among newly diagnosed RA patients in an interrupted time-series design. Our main finding was that following a constant IR of upper limb joint replacements in the pre-bDMARD era from 1996 to 2001, the IR started to decrease after bDMARDs were introduced from 2003 to the end of the study period in 2012. Among controls from the general population, the IR was 1/17 that in the RA cohort in 1996 but, in contrast with the trend among RA patients, the rate increased among controls throughout the whole study period.

Our study contributes to a slowly growing body of evidence that suggests that, among patients with RA, the need for upper limb joint replacements and joint surgery in general is decreasing. Moreover, what this study further adds is that in Denmark this decrease mainly started after bDMARDs became a viable treatment option in 2002. In this study, we were able to demonstrate the use of surgery and changes therein following this major addition to the treatment repertoire in RA. Furthermore, the gradually increasing use of joint replacement in the general population from 2003 and onward is supported by data from the Danish Shoulder Arthroplasty Register (31,32). We looked at the main diagnoses of the controls who had upper limb joint replacement in the DNPR and found that primary and secondary osteoarthritis along with fracture sequelae were more often the indication for surgery from 2002 onward.

In the RA population, treatment with conventional synthetic DMARDs (and the introduction of the treat-to-target strategy in RA is likely to have also contributed to the decreased need for joint surgery (33). Accordingly, some studies have shown that rates of joint surgery had already started to decrease before the introduction of bDMARDs. A study by Nikiphorou et al (13) that investigated the temporal development in joint surgery in 2 inception cohorts from the UK (covering the period from 1986 to 2011) showed that rates of wrist, hand, and hindfoot/forefoot joint reconstructive procedures started to decrease before the year 2000. In addition, Nystad et al (10) found that in Norway, the incidence

of finger joint replacements among patients with RA decreased significantly from 1994 to 2012, as did the rates of shoulder and elbow replacements and non–joint replacement surgery of these joints, although this was not statistically significant. In all of these prior studies, these decreasing trends started before the millennium.

There are also studies with findings that compare well with those presented in the current study. A study from Finland showed a 60% reduction in shoulder and elbow replacements from 1995 to 2010. The rates of elbow replacements in that study showed a pattern similar to those presented in our study despite the use of a different denominator population. It would have been interesting to apply the interrupted time-series method to the data from Finland, as the biggest reduction in IR occurred post 2003. Likewise, findings from a study by Jenkins et al (34) showed the same decreasing pattern starting in the early 2000s for total elbow replacements performed due to RA using data from the Scottish Arthroplasty Project. Also in accordance with our results, Louie and Ward (16) showed in a serial cross-sectional time-trend study that among RA patients ages ≥40 years living in California, rates of total wrist arthroplasty and arthrodesis had started to decrease in the early 1990s, but there was a significant and steep decrease from 2003–2007. Young et al (35) have recently reported the time trends in joint replacement surgery from the US Nationwide Inpatient Sample, and they too reported a relative decrease in prevalence of RA patients among recipients of total elbow and total shoulder replacements from 2002 to 2012, as did Triplet et al (36). However, in the study by Young et al, although the proportion of patients with RA among shoulder replacement recipients decreased, the absolute numbers of RA patients undergoing shoulder surgery looked as if they increased (35). In a study from Japan, Momohara et al (18) reported an increase in finger arthroplasty surgery, whereas the number of elbow and wrist joint replacements remained constant from 1998 to 2008.

The overall pattern in the existing literature seems to be a decrease in use of joint surgery among RA patients since the 1990s, but in a few studies, the incidence has not changed. A possible explanation as to the different results could be that many studies include prevalent cohorts of RA. As suggested by Momohara et al (18), it is possible that patients with RA have become more fit for surgery in recent decades, but an increased use of surgery in RA populations due to this phenomenon would mostly affect prevalent RA patients. As we only included newly diagnosed patients with RA, the fit-for-surgery theory does not seem to be the most likely explanation for the present findings.

Our study has some limitations that need be mentioned. The interrupted time-series analysis is an ecologic method, and our results do not allow for commenting on causality. There is an alternative or contributory explanation for the decreasing rates of surgery among patients with RA: the more intensive treat-to-target strategy with increased use of csDMARD combination therapy. Although this strategy was not specifically introduced in 2002, it is likely that this has contributed to our results (33,37,38). To investigate the true impact of bDMARDs on the need for joint surgery, studies using individual-level based information on DMARD treatment are needed. Another limitation is the inherent risk of misclassification of RA patients when using health care register–based data, but by using 2 different case definitions we tried to account for this. A recent Danish study found that using the case definition in our primary analysis resulted in a positive predictive value of ~80% (27). Applying the 1-year lag period to the analysis of the time series in general population controls can result in models with no biologic or meaningful interpretation given that the introduction of bDMARDs would have no effect on this nontreated population. For instance, we have no biologic, political, or practical meaningful explanation for the significant level increase observed in shoulder and elbow surgery among controls in 2003, other than it is merely the result of applying the same flexible regression modelling as in the RA population.

All patients and controls were only followed up for the first 5 years following diagnosis, allowing us to only capture joint replacements performed within the first years after disease onset. Although this could underestimate the true long-term impact of bDMARDs on our outcomes, it allowed for all patients and controls to have an equal amount of follow-up time, regardless of entering the study in the pre-bDMARD or the bDMARD era, and therefore made comparisons across the time series more valid. It is worth noting that other studies have shown that a non-negligible number of RA patients require joint replacement surgery within 5 years of diagnosis, and upper limb surgery is reported to be the first type of surgery in at least 2 studies (3–5). Another limitation is the possibility that the new diagnostic criteria for RA introduced in 2010, with emphasis on earlier diagnosis, could have affected the 5-year IR of surgery in the last 2 years of the study period. Furthermore, it is also possible that rheumatologists have changed their threshold for referral to orthopedic surgery.

The strengths of the current study include the nationwide population-based design ensuring complete follow-up in a large population of RA patients as well as matched controls in a universal, tax-funded health care system. The ability of our study to compare the observed trends in patients with RA to the secular trends among matched non-RA individuals is another strength. We also believe that the interrupted time-series method is a strength of this study. When analyzing time -series data where interventions occur in the midst of the time series, it is beneficial to know the trend before and after a given intervention and to not only calculate the mean change over the entire period or to calculate only IRRs where information on trends within each calendar period is lost.

In conclusion, we found that the 5-year IR of upper limb joint replacements among newly diagnosed RA patients started to decrease following the introduction of bDMARDs. However, given the ecologic design of the study, it is a possibility that other factors contributed to this finding. In 1996, the IR of upper limb joint replacements was 17-times higher among RA patients compared to individuals without RA. In 2012, it was only 3.5 times higher. In context, our study supports previous reports of improved outcomes in patients newly diagnosed 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. Cordtz 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. Cordtz, Prieto-Alhambra, Kristensen, Overgaard, Odgaard, Dreyer.

Acquisition of data. Cordtz, Odgaard, Dreyer.

Analysis and interpretation of data. Cordtz, Hawley, Prieto-Alhambra, Højgaard, Zobbe, Kristensen, Overgaard, Soussi, Odgaard.

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Three Quality Improvement Initiatives and Performance of Rheumatoid Arthritis Disease Activity Measures in Electronic Health Records: Results From an Interrupted Time-Series Study

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Objective. Applying treat-to-target strategies in the care of patients with rheumatoid arthritis (RA) is critical for improving outcomes, yet electronic health records (EHRs) have few features to facilitate this goal. We undertook this study to evaluate the effect of 3 health information technology (health-IT) initiatives on the performance of RA disease activity measures and outcomes in an academic rheumatology clinic.

Methods. We implemented the 3 following initiatives designed to facilitate performance of the Clinical Disease Activity Index (CDAI): an EHR flowsheet to input scores, peer performance reports, and an EHR SmartForm including a CDAI calculator. We performed an interrupted time-series trial to assess effects on the proportion of RA visits with a documented CDAI. Mean CDAI scores before and after the last initiative were compared using *t*-tests. Additionally, we measured physician satisfaction with the initiatives.

Results. We included data from 995 patients with 8,040 encounters between 2012 and 2017. Over this period, electronic capture of CDAI scores increased from 0% to 64%. Performance remained stable after peer reporting and the SmartForm were introduced. We observed no meaningful changes in disease activity levels. However, physician satisfaction increased after SmartForm implementation.

Conclusion. Modifications to the EHR, provider culture, and clinical workflows effectively improved capture of RA disease activity scores and physician satisfaction, but parallel gains in disease activity levels were missing. This study illustrates how a series of health-IT initiatives can evolve to enable sustained changes in practice. However, capture of RA outcomes alone may not be sufficient to improve levels of disease activity without a comprehensive treat-to-target program.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, affecting up to 1% of adults living in the US and causing significant disability, excess mortality, and economic burden (1). The disease is characterized by pain and swelling in the joints, fatigue, and profound joint stiffness. Over time, inflammation can cause joint deformities and impair physical functioning. Although inflammation can be measured by blood tests, such as the erythrocyte sedimentation rate or C-reactive protein level, these tests are nonspecific and frequently do not correlate with how patients are feeling (2). The nature of RA makes clinical assessments and patient-reported outcomes (PROs) critical to understanding disease activity and its functional consequences.

There is strong evidence that treat-to-target strategies can improve RA outcomes (3–6). As with approaches to the treatment of

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

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SIGNIFICANCE & INNOVATIONS

- Applying treat-to-target strategies in the care of rheumatoid arthritis (RA) patients is critical for improving outcomes; however, electronic health records (EHRs) have few features to facilitate this goal.
- We evaluated 3 health information technology initiatives designed to standardize the collection of RA disease activity measures in the EHRs.
- Modifications to the EHR, provider culture, and clinical workflows effectively improved capture of RA disease activity scores and physician satisfaction, but we did not see parallel gains in patients' disease activity levels.
- Capture of RA outcomes alone may not be sufficient to improve levels of disease activity without a comprehensive treat-to-target program.

diabetes mellitus or hypertension, a treat-to-target approach in RA involves 1) regular assessment of quantitative disease activity measures and 2) changes to medications in order to achieve remission or low disease activity. In order to promote the use of a treat-to-target strategy for RA, the National Quality Forum endorsed a quality measure that requires documentation of a standardized RA disease activity score in the electronic health record (EHR) (7,8). This measure was incorporated into several pay-for-performance programs targeting US rheumatologists (9). However, the collection of disease activity measures remains inconsistent. Data from the American College of Rheumatology's national Rheumatology Informatics System for Effectiveness (RISE) Registry showed that among the 178,931 unique RA patients, only 50% had an RA disease activity score recorded in the EHR, indicating that collection and utilization of these measures are inconsistent in clinical practice (10,11).

Little has been published about how to best implement disease activity measures to guide treatment in routine clinical work (12). Existing EHRs often require customization to collect RA disease activity measures as structured data, and current efforts to collect these RA outcomes, through mechanisms that require intensive data entry, such as EHR flowsheets, are inefficient, disrupt clinical workflow, and decrease provider usage, leading to suboptimal performance of RA quality measures and inadequate implementation of treat-to-target strategies (13). Optimization of the EHR to facilitate collection of RA outcomes has the potential to make it easier to apply treat-to-target strategies in routine practice and to comply with national quality performance measures (14).

In this study we implemented a multifaceted quality improvement strategy, including 3 initiatives to standardize the collection and documentation of a formal disease activity measure in a large academic rheumatology clinic, including changes to clinic workflows, clinic culture, and modifications of the EHR itself. We examined the effect of each of the 3 initiatives on the proportion of encounters in which a disease activity score was documented in the EHR. Additionally, we assessed whether the initiatives resulted in concomitant improvements in both physician satisfaction and clinical outcomes over time.

PATIENTS AND METHODS

Study setting. This study was conducted in an academic rheumatology clinic at University of California, San Francisco (UCSF), which uses an Epic EHR system. Patients seen by all providers were included in the analysis. Over the study period, providers included at least 18 rotating rheumatology fellows and residents, 1 nurse practitioner, and 35 attending physicians. The Committee on Human Research at UCSF approved this study.

Patient and data sources. All patients age ≥18 years with at least 2 International Classification of Diseases, Ninth Revision (ICD-9) codes for RA (ICD-9: 714.0 and ICD-10: M05.9) in the EHR between June 1, 2012 and October 31, 2017 were included. We extracted information from the UCSF Epic Clarity Data Warehouse on patient demographics (age, sex, self-reported race/ethnicity, preferred language, insurance), comorbid conditions, encounter dates, encounter provider, and disease activity scores.

Outcomes. The main outcome of interest was whether a disease activity score was captured in structured fields in the EHR during a patient visit. To measure RA disease activity, this clinic used the Clinical Disease Activity Index (CDAI), a validated composite RA disease activity measure (15). It is based on the simple summation of a patient global score on a scale of 0 to 10, a physician global score on a scale of 0 to 10, and the count of swollen and tender joints out of 28 joints. In practice, CDAI scores are translated into 4 categories as follows: remission (≤2.8), low disease activity (>2.8 to ≤10), moderate disease activity (>10 to ≤22), or high disease activity (>22) in order to guide clinical decision making.

In addition to the process outcome above, we assessed changes in clinical outcomes after implementation of each of the 3 initiatives. We examined changes in mean CDAI scores before and after the 2 final initiatives. We were not able to compare CDAI scores prior to the first initiative (flowsheet) because disease activity scores were neither routinely performed nor captured in structured fields at that time. We also calculated the proportion of patient visits with a CDAI score in the low disease activity or remission categories (≤10).

Interventions. Over a 5.5-year period, 3 quality improvement initiatives were implemented in the clinic. Additional detail about each of the initiatives can be found in Table 1.

Initiative 1 (began January 2013). Initiative 1 consisted of EHR flowsheet and workflow changes. With the help of the health system's clinical informatics department, we built an Epic-based flowsheet that allowed providers to input and track disease activity scores using structured fields in the EHR. Workflow changes

Table 1. Three quality improvement initiatives implemented in the University of California, San Francisco clinic*

Initiative 1, January 2013: EHR flowsheet and workflow changes	Background and objective: very few providers in our clinic were routinely collecting disease activity scores. For the few that did, these scores were typed into the clinical notes and so were not readily accessible at future encounters or for population health management. Before the interventions discussed in this study, we did not have a built-in method to calculate the CDAI score, but as part of a research study, a research coordinator had built a third-party application whereby, through single and double clicks, providers could designate tender and swollen joints on a homunculus and, by entering values for patient and physician global scores, a total score could be calculated. Our clinical faculty decided as a group to make routine disease activity score collection a priority. As a first step, we focused on 1) expanding the use of the third-party CDAI calculator and 2) creating a way for disease activity and functional status to be entered as a structured field in the EHR. Intervention: with the clinical systems team of the health system, we built an Epic-based flowsheet that allowed providers to input and track disease activity scores using structured fields in the EHR. Workflow changes were made such that clerks handed out a single-item questionnaire in the waiting room to collect patient global assessments, nursing staff entered the patient global assessment into a template in the EHR, and providers entered the remaining CDAI components into a third-party application available on the desktop of all clinic computers. This application calculated the total CDAI score and the provider would subsequently manually enter the total score into a structured template ("flowsheet") within the EHR. Targeted providers: the initial intervention targeted all providers in the clinic, including faculty and fellows. We held several division-wide education seminars on treat-to-target, the value of disease activity collection, and upcoming changes to national pay-for-performance programs (although our providers were not subject to financial incentives around disease activity collection). PDSA cycles: although the process was somewhat cumbersome and required clicking in and out of the EHR and into the third-party application, this first step did make it possible for providers to input a disease activity score into a structured field into the EHR. For PDSA cycles, we experimented with workflows to appropriately identify RA patients in advance of their visits so clerks could collect patient global scores on the correct patients (RA visits now have a distinct designation for scheduling purposes). We educated fellows on the importance of using a treat-to-target strategy in the care of their RA patients and most full-time clinicians agreed to model this strategy for the fellows by reliably collecting a disease activity score. The active phase of this project lasted 6 months and involved multiple small tests of workflow changes as we implemented the EHR changes and championed adoption of the new workflows.
Initiative 2, February 2014: Peer performance reporting	Background and objective: despite the success of our first intervention, we saw wide variation in the collection of CDAIs across providers. As a group, we brainstormed about ways we could benchmark different provider performance on CDAI collection. Intervention: a monthly report was generated by a research coordinator in the clinic, by extracting data on all RA encounters from the EHR, including provider name and whether a CDAI was recorded. The report containing information on all providers and their individual CDAI performance was then disseminated by the rheumatology clinic chief to rheumatology providers via email. The report was unblinded (names and performance were included), and showed a color-coded grid to indicate on-target (green or CDAI performed at >50% of encounters) or below-target (orange if CDAI performed 1–49% of encounters), or not performed at all (red). It allowed physicians to benchmark their performance against their peers. Targeted providers: we targeted faculty only for this intervention. PDSA cycles: the active phase of this project lasted 3 months as we made changes to the components and presentation of the reports, such as varying the time intervals for measurement.
Initiative 3, April 2016: EHR optimization with a SmartForm	Background and objective: now that we had more buy-in and multiple providers reliably collecting CDAI scores, we focused on streamlining the process for inputting the CDAI score by reducing the number of EHR clicks required. Intervention: in a series of improvements to the existing CDAI flowsheet, which required exiting the note to enter information in a separate window, we implemented an Epic SmartForm, a structured template that could be embedded in the provider's note. The SmartForm included a homunculus tool to help clinicians document the location and number of tender and swollen joints and a CDAI score calculator that automatically called for information from the homunculus and other fields from the EHR (specifically, the patient global score, which was elicited by medical assistants and input into a flowsheet during the patient check-in to clinic). This replaced the third-party application that we had been using as part of Intervention 1. Finally, information from the SmartForm and CDAI calculation populated a "synopsis report" that allowed providers to display a graph of scores over time for each patient. Targeted providers: providers received education upon implementation on using the new tool, and the SmartForm was immediately available to both faculty and fellows. The performance report (initiative 2) was continuously sent out to keep motivating providers to document. PDSA cycles: once the new user interface was built, we piloted its use among 2 providers in the clinic before rolling out to all faculty and fellows. PDSA cycles consisted of testing a broad array of adjustments to the workflow and design of the SmartForm. Examples included different EHR location for accessing the SmartForm, the appearance of the synopsis report, and how values flowed between the SmartForm and the documentation flowsheet. The active phase of this project lasted 6 months as we implemented the EHR changes and championed adoption of the new workflows.

* CDAI = Clinical Disease Activity Index; EHR = electronic health record; PDSA = Plan-Do-Study-Act; RA = rheumatoid arthritis.

were made such that clerks handed out a single-item questionnaire in the waiting room to collect patient global assessments, nursing staff entered the patient global assessment into a template in the EHR, and providers entered the remaining CDAI components into a third-party application available on the desktop of all clinic computers. This application calculated the total CDAI score, and the provider would subsequently enter the total score manually into a structured template (flowsheet) within the EHR.

Initiative 2 (began February 2014). Initiative 2 consisted of peer performance reporting. A monthly report disseminated by the rheumatology clinic chief to rheumatology providers contained information on all providers and their individual CDAI performance. The report allowed physicians to benchmark their performance against their peers.

Initiative 3 (began April 2016). Initiative 3 consisted of EHR optimization with a SmartForm. In a series of improvements to the existing CDAI flowsheet, which required exiting the note to enter information in a separate window, we implemented an Epic SmartForm, which is a structured template that could be embedded in the provider's note. The SmartForm included a homunculus tool to help clinicians document the location and number of tender and swollen joints, as well as a CDAI score calculator that automatically retrieved information from the homunculus and other fields in the EHR (specifically, the patient global score, which was elicited by medical assistants and input into a flowsheet during the patient's clinic check-in). Finally, information from the SmartForm and CDAI calculation populated a "synopsis report," which allowed providers to display a graph of scores over time for each patient.

Provider satisfaction. In order to assess the impact of changing clinical workflows on rheumatologists, we assessed provider satisfaction with disease activity collection and documentation processes by administering a survey to providers immediately before and 24 months after the third initiative. Providers were asked to rate several domains on scales of 1 to 10, where 10 represented "very satisfied" and 1 represented "not satisfied." The domains were as follows: 1) overall satisfaction with disease activity score documentation, 2) satisfaction with the time spent recording this information in the EHR, 3) satisfaction with the homunculus as a tool to denote tender and swollen joint counts, and 4) satisfaction with disease activity score visual presentation. Additionally, providers were asked to self-report their time spent documenting disease activity (in minutes) during a typical visit with an RA patient. Survey responses were gathered from 10 providers (4 fellows, 6 attending physicians) pre-implementation and from 12 providers (5 fellows, 7 attending physicians) post-implementation.

Statistical analysis. We used descriptive statistics to summarize patient age, sex, self-reported race/ethnicity (white, African American, Hispanic, Asian, and other/multiple), preferred language (English, Spanish, Chinese, and other), baseline Charlson comorbidity index (CCI) score, and insurance type (private, Medicaid, and Medicare). The effect of each of the health information technology (health-IT) initiatives on CDAI documentation was assessed in 3 ways.

Control chart. First, we created a control chart (p-chart) to describe the overall trend and stability in performance of CDAI scores over time. Performance was calculated as the proportion of eligible patients with a documented CDAI score, aggregated into monthly intervals. Upper and lower control limits varied based on the number of RA patient encounters in the denominator. A continuous improvement of ≥6 points in a row or the occurrence of ≥8 points on the same side of the centerline is considered a significant trend (16).

Interrupted time-series (ITS) analysis. Second, quantifiable changes in CDAI performance following each of the initiatives were assessed with an ITS analysis. ITS is a strong quasi-experimental study design that is used to estimate the causal impact of an intervention on its target population without random assignment and is useful when evaluating new health system interventions (17–19). We used 2-week increments and estimated the coefficients using ordinary least square linear regression models, in which the errors were assumed to follow a first-order autoregressive process. We further specified the model to base the pooled autocorrelation estimate on the autocorrelation of the residuals, and added robust SEs (20). We expressed the effect of our initiatives on the outcome (whether a CDAI was recorded) as intercept and slope changes.

Generalized estimating equation (GEE) model. Third, we used GEE to estimate CDAI performance, adjusting for individual-level factors and accounting for clustering by provider (21). The outcome in this model was CDAI score documentation (yes/no for each patient visit). The primary predictors were each of the 3 health-IT initiatives, and they were encoded to reflect the period following each individual implementation, with the post-implementation period of intervention 1 serving as the baseline. Individual-level factors included age, sex, race/ethnicity, insurance, preferred language, and CCI scores. All included patients had a CCI score of ≥1 due to their RA diagnosis (22). For regression analysis, the CCI score was therefore dichotomized to 1 or ≥2. All covariates were tested for noncollinearity.

To assess changes in clinical outcomes over time, the proportion of scores reflecting remission/low disease activity (CDAI score of ≤10) each month was examined using a control p-chart for the subgroup of visits where a CDAI score was recorded. Additionally, using *t*-tests, we compared mean CDAI scores during the 12 months before and after the peer performance reporting initiative and 19 months before and after the SmartForm initiative. Paired *t*-tests were performed on a subgroup of patients with a CDAI score of ≥1 before and after initiatives 2 and 3.

Analyses were performed using Stata 15 Statistical Software, release 15. For all analyses, *P* values less than 0.05 were considered statistically significant.

Table 2. Characteristics of the University of California, San Francisco, academic rheumatoid arthritis clinic population (n = 995)*

Age, mean ± SD	58.9 ± 15.9
Sex, no. (%)	
Female	815 (81.9)
Male	180 (18.1)
Race/ethnicity, no. (%)	
Non-Hispanic white	508 (51.1)
African American	61 (6.1)
Asian	158 (15.9)
Hispanic	158 (15.9)
Other†	70 (7)
Missing‡	40 (4)
Preferred language, no. (%)	
English	871 (87.5)
Spanish	57 (5.7)
Chinese	41 (4.1)
Other	26 (2.7)
CCI score, median (IQR)	1.0 (1.0–2.0)
Insurance, no. (%)	
Medicaid	138 (13.9)
Medicare	445 (44.7)
Private	412 (41.4)

* CCI = Charlson comorbidity index; IQR = interquartile range.
† Includes "mixed."
‡ Includes "declined" and "unknown/declined."

RESULTS

The analysis included 995 RA patients with a total of 8,040 in-person encounters in the UCSF rheumatology clinic during the study period. The sample was 81.9% female and had a mean ± SD age of age of 58.9 ± 15.9 years (Table 2). This group was racially and ethnically diverse: 51.1% were non-Hispanic white, 15.9% were Asian, 15.9% were Hispanic, and 6.1% were African American, and 12.4% reported a language other than English as their preferred language (primarily Chinese or Spanish).

Control chart. The longitudinal control p-chart presents monthly proportions of visits with a CDAI score documented in the EHR (Figure 1A). We included 58 monthly time points; the number of visits for each month ranged from 94 to 161. Overall, CDAI documentation increased over time from 0% in 2012, prior to any of the initiatives, to 64% in October 2017, after successful implementation of all 3 initiatives. We found a substantial improvement in the proportion of patient visits with a CDAI documented in the EHR during the first 12 months after implementation of the first initiative. Following the second initiative, i.e., the peer perfor-

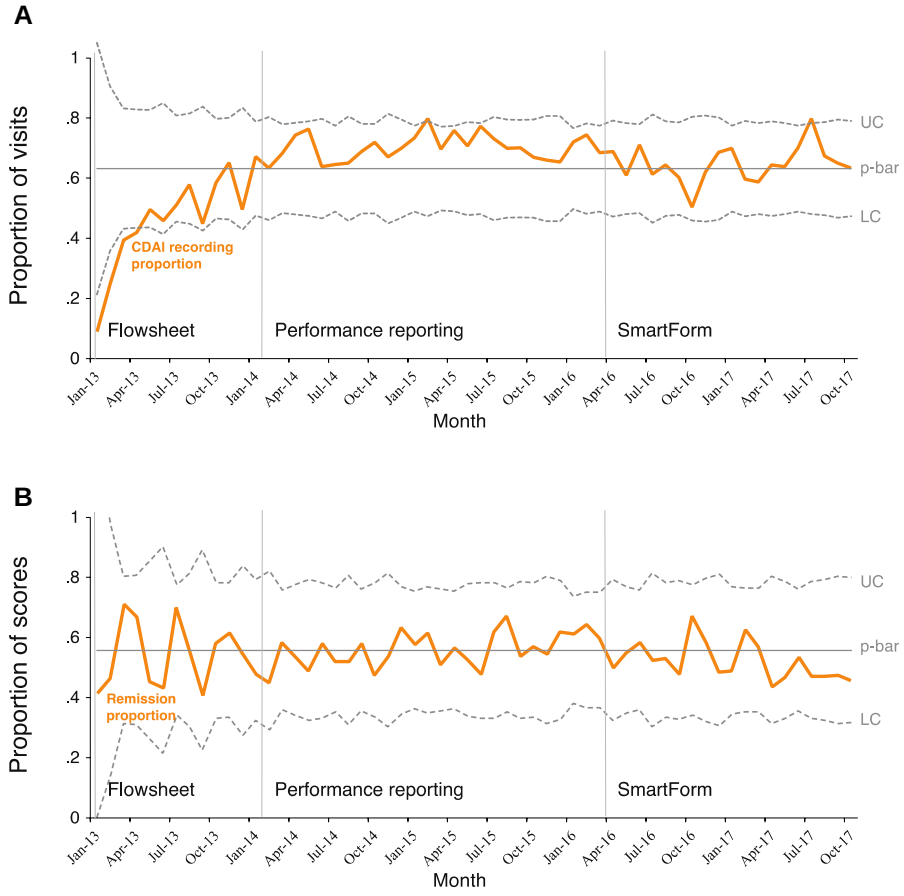

Figure 1. P-charts showing the proportion of visits per month with a Clinical Disease Activity Index (CDAI) score documented in the electronic health record (**A**) and the proportion of the documented CDAI scores in remission/low disease activity categories per month (**B**), during implementation of 3 quality improvement initiatives in an academic rheumatology clinic. Vertical lines indicate the onset of each initiative. UC = upper confidence limit; LC = lower confidence limit; p-bar = overall mean of monthly proportion.

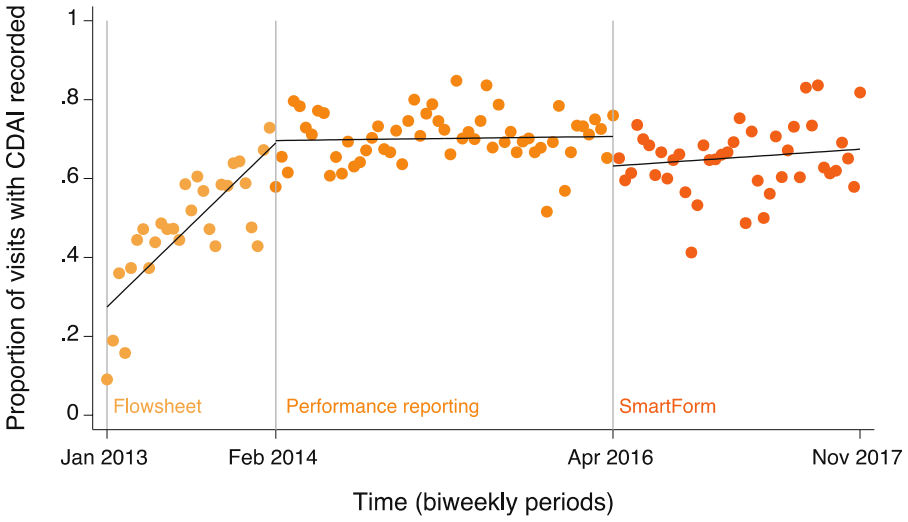

Figure 2. Interrupted time-series analysis showing mean proportion of Clinical Disease Activity Index (CDAI) scores recorded in the electronic health record in biweekly time periods after implementation of 3 quality improvement initiatives. Vertical lines indicate the onset of each initiative.

mance reporting, all 27 points on the control p-chart were seen above the centerline (p-bar), indicating that the improvement had stabilized around a new, slightly higher set point. After the SmartForm initiative, we identified a stable CDAI score capture trend throughout the entire period, with points varying around the centerline.

ITS analysis. The ITS analysis confirmed that changes seen in the control p-chart were statistically significant. Our results showed that in the first 2-week period immediately following implementation of the first initiative (EHR flowsheet and workflow), there was a significant increase in documentation of CDAI scores from 0% to 28% (95% confidence interval [95% CI] 17.9, 38.4) (Figure 2 and Table 3). The post-intervention estimate showed that after the introduction, documentation rate increased at a rate of 1.4% (95% CI 0.7, 2.1) per 2-week period.

Immediately following initiative 2 (peer performance reporting), there was a small, but not significant, increase in documentation rate (4% [95% CI –6.2, 14.2]) and subsequent stabilization in the post-intervention slope.

In the first 2-week period following the third initiative (EHR optimization with SmartForm), we observed a small reduction in CDAI score documentation (–7.3%; $P < 0.05$). The post-intervention trend showed a slight, though nonsignificant, increase of 0.1% per 2-week period (95% CI –0.1, 0.4), which resulted in a rise back to near pre-intervention levels over the following 18 months.

GEE model. The GEE results supported the findings of the ITS with respect to the interventions (initiative 2, odds ratio [OR] 2.28 [95% CI 1.73, 2.10]; initiative 3, OR 1.77 [95% CI 1.19, 2.65]). Additionally, the odds for having a CDAI recorded following initiative 2 and 3 were similar for adjusted and unadjusted models and improvements in documentation remained significant in both models (Table 4).

Clinical outcomes. Mean CDAI was stable before and after peer performance reporting (12.4 both before and after) and increased slightly after SmartForm implementation, from 11.3 to 13.4 ($P < 0.05$). Paired *t*-test analysis detected small disease activity improvements after peer performance reporting (n = 237, mean CDAI score from 12.0 to 10.7 [$P < 0.05$]) but slightly worse scores after SmartForm implementation (n = 341, mean CDAI score from 11.2 to 12.7 [$P < 0.05$]). Though these changes were statistically significant, they did not exceed the minimum clinically important difference thresholds for CDAI scores (23). The overall proportion of visits with a CDAI score in the remission/low disease activity category increased slightly from 42% to 46% during the study period (Figure 1B).

Table 3. Results from interrupted time-series analysis examining trends in CDAI score documentation rate after implementation of 3 quality improvement initiatives*

	Coefficient (95% CI)	*P*
Initiative 1: flowsheet		
Level change	28.1 (17.9, 38.4)	<0.001
Post-intervention trend	1.4 (0.7, 2.1)	<0.001
Initiative 2: peer performance reporting		
Level change	4.0 (−6.2, 14.2)	0.441
Post-intervention trend	0.01 (−0.10, 0.1)	0.927
ΔTrend†	−1.4 (−2.1, −7.1)	<0.001
Initiative 3: SmartForm		
Level	−7.3 (−14.4, −0.1)	0.048
Post-intervention trend	0.1 (−0.1, 0.4)	0.427
ΔTrend	0.1 (−0.2, 0.4)	0.498

* CDAI = Clinical Disease Activity Index; 95% CI = 95% confidence interval.
† ΔTrend = change in trend after intervention compared to trend in previous intervention.

Table 4. Generalized estimating equation logistic regression model to account for individual-level factors and clustering by providers on documentation of CDAI scores*

	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)†	*P*
Interventions				
1: Flowsheet	1.0 (reference)		1.0 (reference)	
2: Peer performance reporting	2.28 (1.73, 2.10)	<0.001	2.10 (1.64, 2.70)	<0.001
3: SmartForm	1.77 (1.19, 2.65)	0.005	1.70 (1.13, 2.56)	0.010

* CDAI = Clinical Disease Activity Index; OR = odds ratio; 95% CI = 95% confidence interval.
† Adjusted for age, preferred language, self-reported race/ethnicity, sex, Charlson comorbidity index score, and insurance category. Clustered on provider.

Provider satisfaction surveys. Results from provider surveys showed that on a scale from 1 to 10, mean ± SD overall provider satisfaction with disease activity documentation increased from 5.4 ± 2.5 to 7.5 ± 1.4. Similarly, mean ± SD satisfaction with time spent recording necessary information and visual presentation of data increased from 5.6 ± 2.6 to 8.2 ± 1.7 and from 6.4 ± 1.9 to 8.3 ± 1.4, respectively. Mean ± SD self-reported time for RA patient outcome documentation, including the time to conduct joint counts, calculate the total CDAI score, and input this score into the EHR, decreased from 6.5 ± 5.3 minutes to 3.2 ± 1.9 minutes.

Engagement of support staff. Additionally, we reviewed the encounters where a CDAI score was not collected to assess engagement and activation of support staff. We found a total of 2,605 encounters (36%) where a CDAI score was not collected during this period. The patient global assessment score was missing in 52.2% of these encounters, and this proportion decreased slightly, but significantly, during the study period.

DISCUSSION

Applying treat-to-target strategies in the routine care of patients with RA is critical for improving outcomes, yet EHRs have few features to facilitate this strategy. This study evaluated 3 targeted health-IT initiatives designed to standardize the collection of an RA disease activity measure score in a large academic rheumatology clinic.

Overall, the 3 initiatives increased and sustained performance of RA disease activity measures. Introduction of an EHR flowsheet in addition to workflow changes and monthly peer performance reporting significantly improved capture of CDAI scores, and the institution of additional workflow changes and an EHR SmartForm maintained these gains. By the end of the 5.5-year study period, performance of disease activity scores had increased from 0% to 64% of eligible clinic visits. We did not see parallel improvements in RA clinical outcomes, including the proportion of patients experiencing remission or low disease activity, but we did see important gains in physician satisfaction after optimization of workflows to capture RA disease activity scores.

The optimizations made to our EHR to improve performance on disease activity measures are not without precedent. Newman et al successfully built and incorporated a health-IT tool, RheumPacer, for documentation of disease activity and other outcomes in a large US rheumatology practice (12). These authors reported a CDAI score documentation rate of 61% over 2 years, which is comparable to the results demonstrated in the current study. Additionally, Newman et al showed significant improvements in quality of care, efficiency of care, and productivity. Collier et al likewise developed a rheumatology-specific tool with a disease activity score (Disease Activity Score in 28 joints) calculator integrated into their EHR (24). In that study, most physicians were satisfied with the application and reported that use of the calculator and visualizing trends of disease activity improved patient care. Our initiatives were unique because our IT tools were designed within the EHR rather than in a third-party application.

Our study demonstrates how quality improvement involving health-IT evolves in stages, with an initial focus on technical feasibility and subsequent attention paid to culture and clinical workflows. Before the first initiative, it was not technically possible to capture crucial RA measures in structured fields within the EHR, and there was no process for collecting PROs, such as the patient global assessment score, leaving each provider with a highly inefficient and cumbersome workflow for measuring disease activity. A few providers in the UCSF rheumatology clinic already used a free-standing application to calculate CDAI scores, and they had asked for a streamlined way to import the scores into the clinical note. After discussion during faculty meetings of the rationale behind routine assessment of disease activity as a new quality measure in RA, it was decided to pursue this through technical alterations to the EHR. The large increase in documentation seen after implementation of the first initiative seems, therefore, to suggest an evident, untapped potential, i.e. the clinic was ripe for a technological update. Once capturing the CDAI score became technically possible, we were able to maintain gains with changes to the clinic culture; peer performance reports sent out by the clinic leader on a regular basis highlighted how important this activity was for all providers, emphasizing individual provider accountability. Additional modifications, with the introduction of the Epic SmartForm and changes to clinic workflows, solidified a culture of measurement by improving provider efficiency and ultimately satisfaction.

The Consolidated Framework for Implementation Research suggests that many factors influence the adoption and maintenance of an initiative: the outer setting (events happening outside a practice that influence change, such as pay-for-performance programs incentivizing performance on nationally endorsed quality measures); the inner setting (specific characteristics of the practice itself); initiative characteristics (adaptability, complexity of the EHR flowsheets and Smart Forms); implementation process (planning and evaluation activities); and individuals within the practice (their beliefs and readiness for change) (25). The combination of the 3 initiatives described here may have been successful in improving performance of disease activity measures because in aggregate they addressed each of these components.

Interestingly, following implementation of our last initiative (EHR optimization with SmartForm), we detected a small but significant decrease in disease activity documentation. This might have been because providers needed to adapt to new EHR functionality, including a new EHR-based homunculus. With the SmartForm, the providers additionally had to learn a new, more complex electronic workflow, and this might not have been immediately prioritized in a busy clinic. This phenomenon has been described previously and could have accounted for the temporary decline in documentation rate (26,27). After this brief decrease, documentation increased again, possibly because providers gained familiarity and noted efficiency gains with the new tool.

The active phases of the initiatives occurred over a 5.5-year period, which reflects some of the challenges of doing quality improvement work in an academic environment. First, we had limited resources for EHR programming, which resulted in our having to wait in a queue to gain access to an implementation engineer to make changes to the EHR. After waiting, we were able to implement rapid PDSA (Plan-Do-Study-Act) cycles, although our time with the engineer was limited. Second, although our center has a handful of full-time providers, many of our faculty and fellows have just a half-day of clinic practice each week and might see just 3–5 patients during a given session, only a subset of whom would be RA patients. Cycles to change workflows thus required that we found a day with multiple providers and multiple RA patients to inform them of changes and solicit input.

Despite sustained improvements in disease activity measure performance, we observed no parallel improvements in clinical outcomes as measured by CDAI scores. This demonstrates that recording CDAI scores is not, by itself, sufficient to improve disease outcomes, and that a more comprehensive treat-to-target program is needed to affect change in clinical outcomes (28). Such a program could include personalized specification of a disease activity target, effective visualization of disease activity levels and targets for both patients and providers, utilization of interprofessional teams to identify and provide more intensive care to patients who would benefit from tighter disease control, and greater use of shared decision-making when medication changes are required (29).

Although this study provides important insights into health-IT modifications to improve disease activity measure performance, there are limitations that should be considered. We did not have a control group of providers in our clinic who were not exposed to the interventions, so it is possible that disease activity documentation could have increased over time without our initiatives (17,30). However, our ITS analysis still addresses important threats to internal validity, because the documentation levels and trends of the pre-intervention periods serve as a control for the post-intervention period. In addition, patients could enter the denominator for the study based on having at least 2 ICD codes for RA. We reviewed a random sample of 36 charts from the study period (June 2016) with at least 1 missing CDAI score and found that 11% of these patients did not have a diagnosis of RA. For this reason, it is possible that we underestimated the proportion of RA patients with a CDAI score collected. Finally, our study was conducted in an academic rheumatology clinic and may have limited generalizability to other settings where implementation of health-IT interventions may be challenging.

In conclusion, modifications to the EHR, clinic culture, and clinical workflows proved to be effective in increasing performance of disease activity measures for patients with RA while improving provider satisfaction. Future work at our center will address whether the addition of a comprehensive treat-to-target program to our clinics can improve clinical 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. Schmajuk 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. Gandrup, Ellingsen, Yazdany, Schmajuk.
Acquisition of data. Gandrup, Li, Yazdany, Schmajuk.
Analysis and interpretation of data. Gandrup, Li, Izadi, Gianfrancesco, Yazdany, Schmajuk.

ROLE OF THE STUDY SPONSOR

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

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ARP Announcements

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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*.

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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).