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 Articles: Activity and the Rheumatic Diseases

Cover image: The figure on the cover (from Bremander et al, page 170) depicts finger flexion, pincer grip, and toe-standing from the Signals of Functional Impairment index.

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AMERICAN COLLEGE OF RHEUMATOLOGY
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ACTIVITY AND THE RHEUMATIC DISEASES

Introduction to the Special Theme Section: Activity and the Rheumatic Diseases

Marian T. Hannan

In this issue of *Arthritis Care & Research*, we present the latest in a series of themed issues that are deemed highly relevant in clinical practice and rheumatologic research. These themed issues are specifically designed to bring needed attention to current information and observations in the field of rheumatology. The current theme focused on the effects and consequences of activity in rheumatic diseases, including activities that are linked with pain, depression, disability, or other factors. Also considered were topics emphasizing chronic disease management and public health strategies that address activity in the population. Manuscripts submitted for the themed issues of *Arthritis Care & Research* undergo the same peer-review procedures as do all other scientific manuscripts, and therefore meet the same rigorous standards as articles in this or any other issue.

Many pertinent aspects of activity or activities as related to outcomes and issues in the rheumatic diseases were reported. The call for papers for this special section resulted in 48 submissions covering a broad range of topics related to the activity theme. Of these, 14 were accepted and spanned topics from patterns and types of physical activity as well as influencing factors (both positive and negative) to measurement properties of self-reported physical activity instruments. Not unexpectedly, more than half of the articles focused on osteoarthritis, a well-known target for activity interventions, with our understanding expanded into types, dose, mechanisms, consequences of activity and inactivity, arthroplasty, and a review article addressing the gap between clinical guidelines and current clinical recommendations for physical activity. Activity concerns in patients with rheumatoid arthritis, fibromyalgia, back pain, and juvenile idiopathic arthritis were also evaluated, along with cardiovascular factors during activities.

These articles document the consequences of both activity and inactivity, and help clinicians, researchers, and patients with rheumatic conditions identify specific areas to address and target for improvement. Although solutions appear to be available and may be tailored to specific conditions, concern remains that improvements in physical activity and its components remain elusive not only in the rheumatic diseases but in the general population as well. Not dissimilar to many population interventions to increase access for persons with disabilities, it may well be that society needs to consider global changes in access to physical activity, possible barriers, and school-, work-, or societal-based reinforcements to make it easier to be more active. The long-term consequences of inactivity make it imperative that we continue our quest to improve activity for people with rheumatic diseases. Thus, the field of rheumatology continues to challenge the current status quo concerning activity. The solution may be closer than we think, and focusing on the details of activity research and integrating with practice will help close the knowledge gap across rheumatic diseases and perhaps in the underlying populations.

AUTHOR CONTRIBUTIONS

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

Marian T. Hannan, DSc, MPH: Hebrew SeniorLife, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, Massachusetts (Editor-in-Chief, *Arthritis Care & Research*).

Address correspondence to Marian T. Hannan, DSc, MPH Hebrew SeniorLife 1200 Centre Street, Boston, MA 02131. E-mail: Hannan@hsl.harvard.edu.

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ACTIVITY AND THE RHEUMATIC DISEASES

Importance of Measuring Hand and Foot Function Over the Disease Course in Rheumatoid Arthritis: An Eight-Year Follow-Up Study

Ann Bremander,[1] Kristina Forslind,[2] Kerstin Eberhardt,[3] and Maria L. E. Andersson[4]

Objective. To assess function using the Signals of Functional Impairment (SOFI) instrument over 8 years, to study clinical variables associated with the change, and to study change over time of the SOFI items.

Methods. In total, 1,223 patients with early rheumatoid arthritis (RA) from the Better Anti-Rheumatic Farmacotherapy (BARFOT) cohort (mean ± SD age 56.9 ± 15.4 years, 67% women) were included in the analysis. Data from baseline and from 1 and 8 years were studied. The SOFI instrument includes measures of range of motion in the hand, shoulder/arm, and lower extremity (range 0–44, best to worst). The effects of baseline variables (sociodemographic, disease activity, joint destruction, and function) on change in SOFI scores were studied by linear regression analysis.

Results. During the first year, the improvement in mean ± SD SOFI scores was 2.7 ± 5.7 ($P < 0.001$). Worse scores in the Disease Activity Score in 28 joints and Health Assessment Questionnaire score at baseline were associated with this improvement ($r^2 \leq 0.11$). During the next 7 years, the deterioration in SOFI scores was mean ± SD 1.5 ± 4.9 ($P < 0.001$). Based on change scores, we found that finger flexion, pincer grip, and toe-standing were the most important items to measure, explaining 58–61% of the total SOFI score, and these items were also associated with radiographic changes at the 8-year follow-up.

Conclusion. Function as assessed with SOFI scores improved during the first year in patients with early RA, but it deteriorated slowly thereafter. Impaired hand and foot function was associated with joint destruction at the 8-year follow-up. Measures of hand and foot function will complement self-reported and medical data, both in clinical work and in long-term research studies.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting approximately 0.5% of the adult Swedish population, with a female:male ratio of 3:1 (1–3). RA is characterized by pain, morning stiffness, and joint swelling, resulting in activity limitations that seriously affect a patient's quality of life. Nonmodifiable factors, including older age, female sex, and autoantibodies such as rheumatoid factor (RF) and anti–citrullinated protein antibodies, may predict a worse prognosis, and a history of smoking not only may increase the risk of developing the disease but can also affect disease severity (4).

In the last decade, there have been great improvements in pharmacologic treatment, but despite these advances, disease progression is unpredictable, and disease activity and long-term functional disability may vary, depending on the outcome measure studied (5). A sustained clinical remission is associated with less radiographic progression and better patient-reported outcome measures (PROMs) (6).

It is well known that PROMs and measures of observed physical function are not highly correlated (7,8), which is why in a clinical setting both measures should be examined. The performance-based measures vary considerably between countries, and in Sweden the Signals of Functional Impairment (SOFI) instrument

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[1]Ann Bremander, PT, PhD: Lund University, Lund, and Halmstad University and Spenshult Research and Development Center, Halmstad, Sweden; [2]Kristina Forslind, MD, PhD: Lund University, Lund, and Helsingborg Hospital, Helsingborg, Sweden; [3]Kerstin Eberhardt, MD, PhD: Lund University, Lund, Sweden; [4]Maria L. E. Andersson, BMSc, PhD: Lund University, Lund, and Spenshult Research and Development Center, Halmstad, Sweden.

Address correspondence to Ann Bremander, PT, PhD, Spenshult Research and Development Center, Bäckagårdsvägen 47, SE-30274 Halmstad, Sweden. E-mail: ann.bremander@fou-spenshult.se.

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SIGNIFICANCE & INNOVATIONS

- A performance-based instrument such as the Signals of Functional Impairment is sensitive to long-term changes in rheumatoid arthritis.
- Finger flexion, pincer grip, and toe-standing appear to be the most important items to measure, and these were also found to be associated with joint damage.
- We suggest that measures of hand and foot function should be included in clinical work and in long-term research studies.

(9) has been included in some large-scale longitudinal cohort studies (10–12). This instrument is used to rate performance tests according to range of motion in the hand, the upper extremity, and the lower extremity. The SOFI instrument was developed to allow recognition of early joint impairments, and a previous longitudinal study (12) showed that the value of SOFI to some extent could explain the outcome of the disease, regarding both development of disability and joint damage, in the long term. Age, sex, and comorbidity were also found to be of importance for the variation of SOFI scores over time (12). Performance-based measures are time-consuming and expensive and are often not included in larger prospective cohort studies and registry studies. However, their added value for understanding and predicting disease outcome is important to study. To better understand the possible added value of SOFI, data from different RA cohorts are needed.

The aim of this study was to investigate change over 8 years in physical function measured with the SOFI instrument in a well-defined Swedish RA cohort, and to learn whether clinical variables at baseline were associated with the change. We also wanted to study whether any of the separate items included in SOFI are of greater importance when measuring change over time.

PATIENTS AND METHODS

Patients. This study included a subset of patients from the BARFOT (Better Anti-Rheumatic Farmacotherapy) cohort, based on available SOFI data. Patients with RA were included in the BARFOT study at the time of diagnosis and recruited between 1992 and 2006. Four of 6 BARFOT centers reported both summary scores (SOFI index) and item scores of SOFI (SOFI items), and these data were included in the study. All the patients fulfilled the American College of Rheumatology criteria for classification of RA (13) and had a disease duration of ≤12 months. The patients were assessed according to a structured protocol at inclusion, after 3 and 6 months, and after 1, 2, 5, and 8 years. The patients were treated with disease-modifying antirheumatic drugs (DMARDs) in accordance with the recommended treatment strategy in Sweden, as described in earlier studies (14). At inclusion, 43% of the patients started treatment with methotrexate, 17% with sulfasalazine, 16% with glucocorticoids alone, and 5% were treated with other DMARDs, such as D-penicillamine and antimalarials alone or in combination with methotrexate and sulfasalazine. Data were retrieved from the BARFOT register; all centers reported a SOFI index, while reports of SOFI items were optional.

Clinical assessments. Physical function was evaluated by trained assessors using SOFI (9), which has 3 parts for measurement of hand, arm (upper extremity), and leg (lower extremity) function. Hand function is tested using 4 movements: opening grip (H1), finger flexion (H2), pincer grip (H3), and opposition of the thumb (H4). Arm function is assessed using 3 movements: ability to touch cervical spine processes with fingers (A1), elbow extension (A2), and elbow supination (A3). Leg function is tested using 4 movements: ability to touch the opposite knee with the heel while sitting (L1), knee extension in the supine position (L2), dorsiflexion of the foot while standing on a balance board (L3), and toe-standing without shoes (L4). The patient's ability to perform the different tests on the right and left sides is scored on an ordinal scale (where 0 = normal, 1 = partly impaired, and 2 = unable to perform), with a SOFI index with a range of 0 of 44 (where 0 = best and 44 = worst).

Disease activity was measured using the composite index Disease Activity Score in 28 joints (DAS28) (15). C-reactive protein level and RF were measured at the hospitals according to the current laboratory standards. Smoking (never smoker,

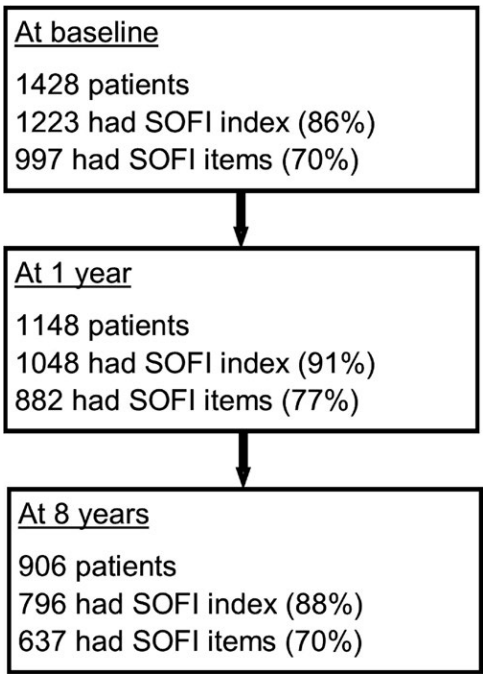

Figure 1. Flow chart of the study. SOFI = Signals of Functional Impairment.

smoker, or previous smoker), pain intensity (measured with a 0–100 mm visual analog scale, where 0 = best and 100 = worst), and disease duration (in months) were patient-reported measures. Daily life activities were measured using the Swedish version of the Health Assessment Questionnaire (HAQ) with a total score with a range of 0 to 3 (where 0 = best and 3 = worst) (16).

Radiographic assessment. Posteroanterior radiographs of the hands and feet were assessed according to the modified Sharp/van der Heijde score (SHS) method: total SHS (range 0–448), hand score (range 0–280), and foot score (range 0–168) (17). The radiographs were read by 1 of 2 experienced readers. Double readings of a proportion of the radiographs showed good agreement between the 2 readers. The intra- and interrater reliabilities of the readers were assessed by calculating intraclass correlation coefficients and were in the range of 0.940 to 0.998.

Statistical analysis. To study the differences between groups, the chi-square test and independent *t*-test were used when appropriate. Data of the SOFI index were split into 2 separate models because of the nonlinearity of the SOFI curve: from baseline to 1 year follow-up, and from 1 to 8 years of follow-up. Clinical and radiographic associations with change in the SOFI index (dependent variable) were entered into separate models because of high correlations between the variables ($r > 0.5$). In all models, the data were adjusted for age and sex. Statistical analyses were performed using SPSS software, version 21.

Ethical considerations. All patients gave their informed consent, and the study was approved by the regional ethics committees (Dnr: Gbg Ö 282-01; LU 398-01). The study was performed in accordance with the Declaration of Helsinki.

RESULTS

Clinical characteristics. At baseline, SOFI index data were available for 1,223 of 1,428 eligible patients; data were also available for 1,048 patients at 1 year, and 796 had data at the 8-year follow-up. SOFI items were available for 997 patients at baseline, for 882 patients at 1 year, and for 637 patients at the 8-year follow-up (Figure 1). The SOFI index from all 3 time points was available for 712 patients, and SOFI items were available for 569 patients. The patients who did not have a SOFI index at baseline (n = 205) had a worse mean DAS28 (higher number of

Table 1. Sex-specific characteristics of patients at baseline and at the 8-year follow-up*

	Baseline				8-year follow-up			
	All (n = 1,223)	Women (n = 820)	Men (n = 403)	*P*	All (n = 769)	Women (n = 538)	Men (n = 231)	*P*
Age, years	56.9 ± 15.4	54.9 ± 15.6	60.9 ± 14.2	<0.001	–	–	–	–
Disease duration, months	6.2 ± 3.2	6.4 ± 3.2	6.0 ± 3.0	0.049	–	–	–	–
RF positive, %	61	60	64	0.174	–	–	–	–
Never-smoker, %	42	47	32	–	–	–	–	–
Smoker, %	28	28	30	<0.001	–	–	–	–
Previous smoker, %	30	25	38	–	–	–	–	–
DAS28	5.01 ± 1.27	5.04 ± 1.26	4.95 ± 1.30	0.227	2.93 ± 1.31	3.07 ± 1.28	2.59 ± 1.30	<0.001
DAS28 <2.6, %	–	–	–	–	46	40	58	<0.001
Pain (range 0–100)	45.7 ± 24.6	47.6 ± 24.5	41.8 ± 24.3	<0.001	29.4 ± 25.2	31.6 ± 25.2	24.2 ± 24.2	<0.001
HAQ (range 0–3)	0.96 ± 0.63	1.05 ± 0.63	0.78 ± 0.58	<0.001	0.63 ± 0.62	0.70 ± 0.64	0.47 ± 0.56	<0.001
SOFI index (range 0–44)	7.6 ± 6.2	7.3 ± 6.1	8.4 ± 6.4	0.006	5.8 ± 5.6	5.7 ± 5.6	6.2 ± 5.1	0.217
SOFI hand (range 0–16)	3.4 ± 3.0	3.3 ± 3.0	3.7 ± 3.1	0.024	2.1 ± 2.6	2.0 ± 2.6	2.4 ± 2.6	0.113
SOFI upper (range 0–12)	1.8 ± 2.3	1.5 ± 2.1	2.2 ± 2.4	<0.001	1.2 ± 1.8	1.1 ± 1.8	1.4 ± 1.8	0.037
SOFI lower (range 0–16)	2.7 ± 2.8	2.7 ± 2.8	2.5 ± 2.7	0.297	2.4 ± 3.0	2.5 ± 3.0	2.2 ± 3.0	0.168
SHS total (range 0–448)	5.3 ± 9.1	5.3 ± 9.0	5.3 ± 9.4	0.934	23.0 ± 25.0	24.5 ± 27.3	19.7 ± 20.5	0.015

* Values are the mean ± SD unless indicated otherwise. RF = rheumatoid factor; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; SOFI = Signals of Functional Impairment; SHS = modified Sharp/van der Heijde score.

painful joints and higher patient's global assessment scores) than the patients who did have a SOFI index at baseline (mean ± SD 5.37 ± 1.24 versus 5.01 ± 1.27; $P < 0.001$). No other differences were found.

Of the patients who were included, 820 (67%) were women and 403 (33%) were men. These patients had a baseline mean ± SD age of 56.9 ± 15.4 years, a mean ± SD disease duration of 6.2 ± 3.2 months, a mean ± SD DAS28 of 5.01 ± 1.27, and a mean ± SD HAQ score of 0.96 ± 0.63; 61% were RF positive and 42% were never-smokers (Table 1). At baseline, 18% of patients did not start any pharmacologic treatment, and 82% were started on treatment with DMARDs (methotrexate, sulfasalazine, or a combination of these); 52% of patients were also being treated with glucocorticoids, and 1 patient was being treated with a biologic DMARD.

SOFI instrument. At baseline, the mean ± SD SOFI index was 7.6 ± 6.2, and at the 1-year follow-up there was a mean ± SD improvement of 2.7 ± 5.7 ($P < 0.001$). From year 1 to year 8, there was a mean ± SD deterioration in the index of 1.5 ± 4.9 ($P < 0.001$). When studying hand, upper extremity, and lower extremity function separately, sex differences were only found in SOFI scores for the upper extremity, in which women performed better than men at both time points ($P = 0.001$ for year 1; $P = 0.037$ for year 8) (Table 1 and Figure 2).

Clinical variables associated with a 1-year change in the SOFI index. In the linear regression models, an improvement in the SOFI index at 1 year was associated with a higher DAS28 (β value −1.272 [95% confidence interval (95% CI) −1.542, −1.001]), higher pain intensity (β value −0.049

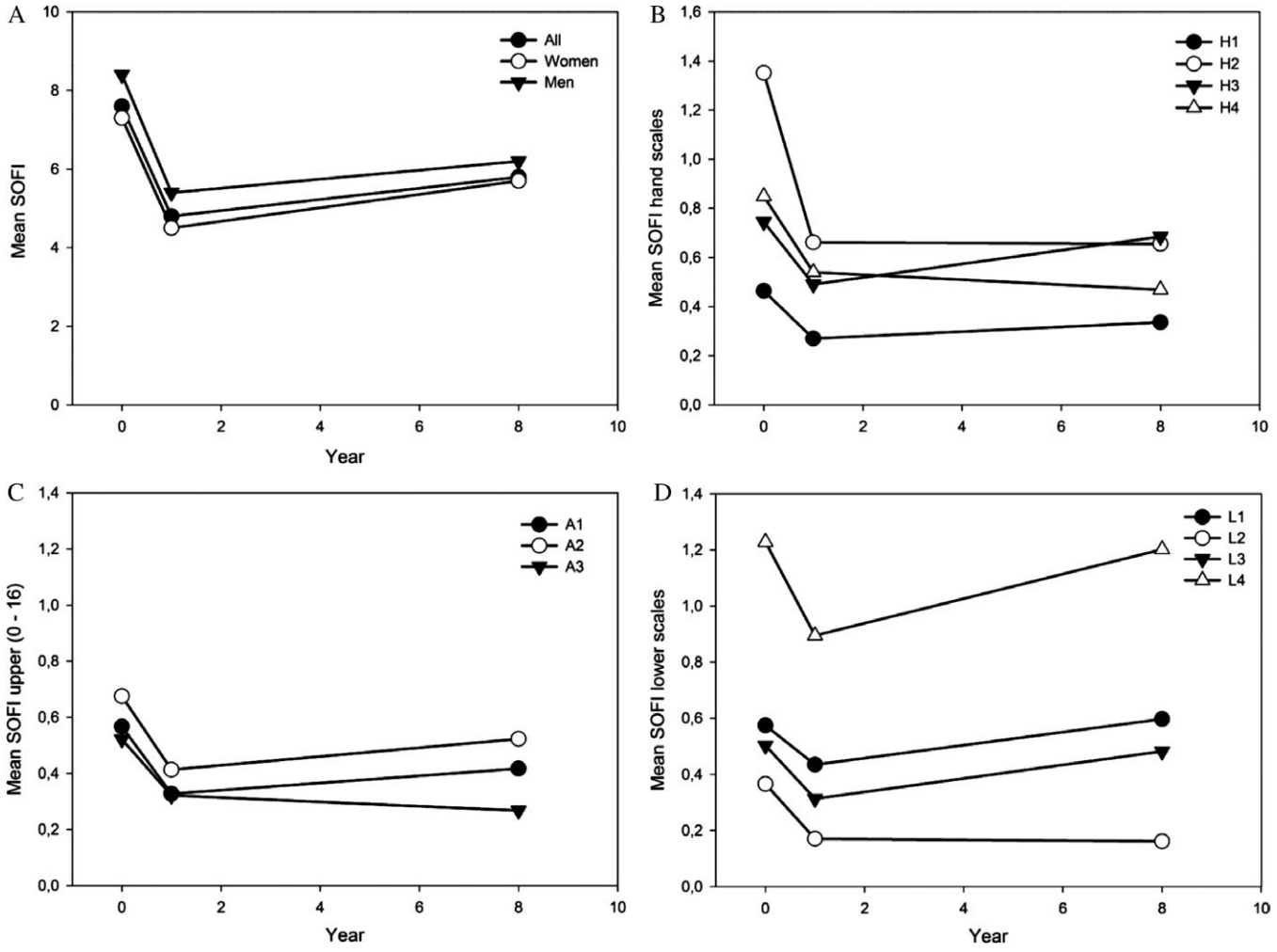

Figure 2. Signals of Functional Impairment (SOFI) over 8 years. **A**, SOFI index (range 0–44). **B**, Hands subscale (range 0–16). **C**, Upper extremities subscale (range 0–12). **D**, Lower extremities subscale (range 0–16). For hand function, H1 = opening grip; H2 = finger flexion; H3 = pincer grip; H4 = opposition of the thumb; for arm function: A1 = ability to touch cervical spine processes with fingers; A2 = elbow extension; A3 = elbow supination; for leg function: L1 = ability to touch the opposite knee with the heel while sitting; L2 = knee extension in supine position; L3 = dorsiflexion of the foot while standing on a balance board; L4 = toe-standing without shoes.

[95% CI –0.064, –0.035]), and a higher HAQ score (β value –2.943 [95% CI –3.505, –2.380]) at baseline, adjusted for age and sex (Table 2). The coefficient of determination ranged from 0.05 to 0.11 for significant associations in the linear regression models.

Clinical variables associated with a change in the SOFI index between year 1 and year 8. Older age (β value 0.056 [95% CI 0.026, 0.086]) and RF positivity (β value 1.313 [95% CI 0.447, 2.179]) were associated with deterioration in the SOFI index between the 1-year and the 8-year follow-up, adjusted for age and sex (Table 2). The coefficient of determination ranged from 0.02 to 0.03 for significant associations in the linear regression models.

Impact of specific SOFI items. When we studied all 11 SOFI items separately, 2 items improved the most during the first year: finger flexion (baseline mean ± SD 1.3 ± 1.3 versus 1-year mean ± SD 0.7 ± 1.0; $P < 0.001$) and toe-standing (mean ± SD 1.2 ± 1.3 versus 0.9 ± 1.2; $P < 0.001$). From 1 to 8 years, pincer grip (mean ± SD 0.4 ± 0.8 versus 0.7 ± 0.9; $P < 0.002$) and toe-standing (mean ± SD 0.8 ± 1.1 versus 1.2 ± 1.4; $P < 0.001$) were the items that deteriorated most (Figure 3). Assessment of finger flexion, pincer grip, and toe-standing explained 58–61% of the SOFI index, with the highest rate at 8-year follow-up ($r^2 = 0.61$).

SOFI items and radiographic changes. At the 8-year follow-up, patients with impaired function scores in SOFI for items opening grip, finger flexion, and pincer grip had higher SHS scores in the hands than patients who did not report having impaired hand function. This finding was also the case for toe-standing and SHS in the feet (Table 3).

Table 2. Linear regression models with the dependent variable change in the Signals of Functional Impairment index between baseline and 1 year, and change between 1 and 8 years*

Independent variables	Baseline to 1 year β (95% CI)†	1–8 years β (95% CI)‡
Age	−0.026 (−0.048, −0.003)	0.056 (0.026, 0.086)
Men	−0.309 (−1.049, 0.431)	−0.373 (−1.299, 0.554)
Smoker	0.698 (−0.159, 1.554)	0.712 (−0.317, 1.740)
Previous smoker	0.222 (−0.634, 1.078)	−0.142 (−1.174, 0.891)
RF positive	−0.014 (−0.736, 0.707)	1.313 (0.447, 2.179)
DAS28	−1.272 (−1.542, −1.001)	0.049 (−0.262, 0.359)
Pain (range 0–100)	−0.049 (−0.064, −0.035)	−0.011 (−0.029, 0.007)
HAQ (range 0–3)	−2.943 (−3.505, −2.380)	−0.666 (−1.486, 0.154)
SHS (range 0–448)	0.039 (−0.008, 0.086)	0.013 (−0.025, 0.051)

* All data were adjusted for age and sex. 95% CI = 95% confidence interval; RF = rheumatoid factor; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; SHS = modified Sharp/van der Heijde score.
† Data at baseline were included in the model.
‡ Data at 1 year were included in the model.

DISCUSSION

We evaluated the usefulness of performance-based outcome measures in a longitudinal study, and our findings support the idea that the SOFI index may be useful not only in clinical settings but also in research. We found that patients with early RA who had worse disease, with higher disease activity, more pain, and more functional limitations at baseline improved the most during the first year, as measured with the SOFI index. We also found that worse SHS were associated with impaired hand and foot function. SOFI items such as finger flexion, pincer grip, and toe-standing showed the greatest change over time, which is why we suggest including them in research and in clinical practice, instead of the full SOFI index, if saving time and costs is an issue.

The improvement in physical function at 1 year, measured with the SOFI index and occurring mostly in patients who reported having many problems, is supported by earlier studies in other RA populations (18,19). Effective antiinflammatory treatment will reduce disease activity and improve function, and a prompt clinical remission can reduce physical dysfunction in patients with early RA (20,21). The association between function and radiographic changes has been debated. In a different Swedish cohort, Kapetanovic et al (12) found that the change in the SOFI index over 20 years was mostly explained by disease activity, by radiographic damage assessed by the Larsen score, and to some extent by age. At 8 years, we only found an association between change in the SOFI index and age, but not radiographic changes assessed by the SHS. The most obvious difference between the 2 studies is the length of follow-up. In addition, the assessment protocol in the 2 studies differed, especially regarding the radiographic scoring methods, which may

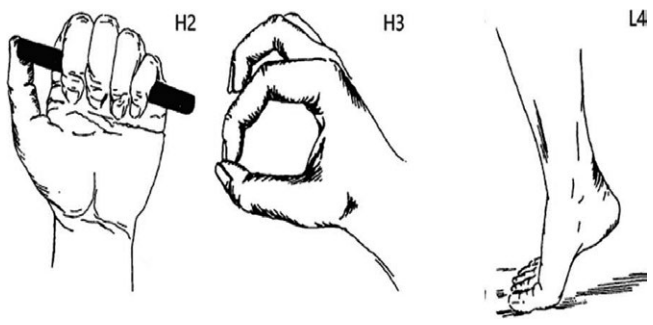

Figure 3. Finger flexion (H2), pincer grip (H3), and toe-standing (L4) from the Signals of Functional Impairment index.

Table 3. Sharp/van der Heide score in hands and feet at the 8-year follow-up in patients with normal performance (0), and those with partly impaired performance or unable to perform the SOFI items (≥1)*.

SOFI item	0	≥1	*P*
H1. Opening grip	13.50 ± 16.30	26.47 ± 23.67	<0.001
H2. Finger flexion	12.83 ± 16.01	23.00 ± 21.95	<0.001
H3. Pincer grip	13.98 ± 16.29	19.54 ± 21.95	0.002
H4. Opposition of thumb	15.99 ± 17.52	16.73 ± 22.00	0.713
L3. Dorsiflexion of the foot	8.46 ± 11.66	8.82 ± 10.47	0.785
L4. Toe-standing	5.62 ± 7.89	9.80 ± 11.67	<0.001

* Values are the mean ± SD unless indicated otherwise. SOFI = Signals of Functional Impairment.

affect the comparability, though long-term changes may occur in RA, despite earlier and more aggressive pharmacologic treatment. Earlier data from the BARFOT cohort showed that almost 4 of 10 patients did not respond sufficiently to treatment, as measured by the absence of DAS28 remission over 8 years, with a considerable impact on joint damage, pain, and function (11).

Even though we found that change in SOFI scores was associated with higher disease activity, higher pain intensity, and a higher HAQ score, the coefficient of determination ranged from 0.03 to 0.11, indicating that inclusion of a performance-based measure in research will complement information from physician-generated and patient-reported measures. This practice is in line with a core set for evaluation of rehabilitation, in which the inclusion of performance-based measures is proposed because it will add information to data reported by the patients (22). The validity of the SOFI instrument as an appropriate measure for patients with RA is supported by findings from an earlier study in which men and women with RA had higher SOFI hand scores in comparison with healthy controls (no other SOFI subscales were studied) (23). The patients with RA included in the study had SOFI, HAQ, and pain scores comparable to those in our studied cohort, supporting the representability of our data.

We also found that the SOFI items that had the greatest impact for measuring change in the SOFI index were finger flexion, pincer grip, and toe-standing. These 3 items are quick and easy to perform, and will reveal reduced function at all stages of RA. Reducing the number of items from 11 to 3 will also lower the costs for health professionals. Further studies are needed to support our results, but pain and swelling in the hands and feet are well-known early symptoms of RA (24), thus supporting our findings. Pain in the hand may cause activity limitations despite active control of the disease in terms of inflammation with drug treatment. Although the disease activity appears limited, often synovitis can still be present (25), which may partly contribute to the persistent pain. The SOFI index, or these 3 SOFI items, may help to reveal the remaining pathology, so that following SOFI scores over time is important, because they may be a measure of treatment response (26). In addition, other studies have supported the use of the SOFI index over a longer period of time. In a previous study, deterioration in function measured with the SOFI index was observed 20 years after inclusion, while changes in HAQ scores leveled off at 10 years (12).

While hand dysfunction is often assessed with questionnaires or using grip strength, foot problems are less often regarded as important. The omission from the DAS28 of swelling and pain in the feet (15) has been questioned (27). Foot synovitis can be present in a third of the patients categorized as being in remission, highlighting the importance of also examining the feet. Unrecognized foot synovitis (defined by the presence of swollen and tender joints in the ankles, middle foot, and forefoot) may influence the progression of erosion scores (27).

SOFI is an instrument developed in Sweden, with limited use in international studies. However, the 11 SOFI items are all commonly used as measures of function and range of motion in patients with RA. A limitation of this study is that only 58% of the patients had SOFI index data at all 3 time points. Since no linear relationship was found between baseline, the 1-year follow-up, and the 8-year follow-up, we included all patients with SOFI data at any time point in our statistical analysis. We found that the patients lost to follow-up reported a greater number of painful joints and a higher patient's global assessment score in DAS28 compared with the studied patients, which may affect the representability. However, the proportion of patients lost to follow-up was only 14% of the whole cohort, and the 2 groups of patients did not differ in age, sex, HAQ score, or erythrocyte sedimentation rate at baseline, supporting the idea that the results reported in this study are representative and accurate for evaluating the usefulness of the SOFI instrument in patients with RA.

Function assessed with SOFI scores improved during the first year in patients with early RA, and it deteriorated slowly thereafter. Finger flexion, pincer grip, and toe-standing showed the greatest changes over time and were also associated with joint damage at 8 years. We suggest that these 3 performance measures should be included in the clinical follow-up and in prospective research studies to complement patient-reported information.

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. Bremander 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. Bremander, Forslind, Eberhardt, Andersson.

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ACTIVITY AND THE RHEUMATIC DISEASES

Chronic Inflammation in Rheumatoid Arthritis and Mediators of Skeletal Muscle Pathology and Physical Impairment: A Review

Beatriz Y. Hanaoka, Matthew P. Ithurburn, Cody A. Rigsbee, S. Louis Bridges Jr., Douglas R. Moellering, Barbara Gower, and Marcas Bamman

INTRODUCTION

The prevalence of physical function impairment and lower levels of physical activity among patients with rheumatoid arthritis (RA) is high compared to matched non-RA controls (1–3), despite tight control of disease activity. More striking is the observation that patients whose RA is in clinical remission lead a more sedentary lifestyle with decreased physical function and worse body composition abnormalities compared to sedentary age- and sex-matched healthy individuals (1,4). The reason for these differences is not clear, but may be due to inflammation-induced pathology to skeletal muscle and associated impairment of physical function.

It is generally accepted that in the majority of patients decreased physical function occurs in the early stages of RA and progresses over time (5). Varying degrees of pain, limited joint mobility, impaired muscle strength, decreased aerobic capacity, fatigue, and low levels of physical activity have been identified as contributing factors to lower physical function in patients with RA (6,7). It is well established that joint inflammation and damage strongly contribute to functional limitations in RA (8), but the deleterious effects of chronic systemic inflammation on skeletal muscle are being increasingly recognized (9).

Physicians and other health care providers recommend exercise for patients with RA, without the existence of much evidence-based knowledge on the optimal duration, frequency, and intensity of exercise in order to maximize health benefits in individuals with RA. As the focus on precision medicine grows (10), and the cellular and molecular mechanisms of physical activity–induced health benefits are elucidated, precision exercise prescription will likely have an increasingly prominent role in the treatment and prevention of chronic conditions like RA and other forms of arthritis (11).

In the current review, we focus on the deleterious effects of chronic inflammation on skeletal muscle homeostasis and function. We discuss the importance of skeletal muscle in the regulation of whole-body glucose and lipid metabolism and the evidence for the beneficial effects of physical activity and exercise training in RA. Additionally, we identify knowledge gaps that may be important for the development of both pharmacologic and nonpharmacologic interventions (e.g., proper exercise regimens) in order to mitigate progressive physical impairment in individuals with RA.

EFFECTS OF CHRONIC INFLAMMATION AND INSULIN RESISTANCE ON SKELETAL MUSCLE MASS AND FUNCTION

Proinflammatory cytokines (i.e., tumor necrosis factor [TNF], interleukin-1β [IL-1β], and IL-6) are thought to be the key mediators of inflammation responsible for stimulating proteasome-dependent proteolysis and inhibiting anabolic and/or anticatabolic signals, which lead to low skeletal muscle mass in chronic inflammatory conditions, such as RA (12,13). TNF can also affect skeletal muscle function by depressing muscle fiber contractility through increasing general oxidant activity and nitric oxide activity (14). Interestingly, in a study involving individuals with RA (15), muscle cytokine levels did not reflect systemic cytokine levels, but were two times higher in the muscles of RA patients. This finding suggests that muscle cytokines were produced locally by myofibers, resident inflammatory cells, and/or adipocytes.

Inflammation plays a critical role in ectopic fat accumulation, underscoring the intimate interplay between the immune system and adipose tissue. Proinflammatory cytokines, such as TNF, can decrease the storage capacity of adipocytes in

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Beatriz Y. Hanaoka, MD, Matthew P. Ithurburn, PT, PhD, DPT, Cody A. Rigsbee, MD, S. Louis Bridges Jr., MD, PhD, Douglas R. Moellering, PhD, Barbara Gower, PhD, Marcas Bamman, PhD: University of Alabama, Birmingham.

Address correspondence to Beatriz Y. Hanaoka, MD, 1825 University Boulevard, Shelby, AL, 35233. E-mail: bhanaoka@uabmc.edu.

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primary fat depots (e.g., gluteofemoral adipose tissue) by inhibiting preadipocyte differentiation and increasing lipolysis (16), which then leads to increased ectopic adipocytes in "nonadipose" tissues, including skeletal muscle. Fat infiltration within the muscle is associated with greater disability, lower quadriceps strength and physical activity level, poorer objectively measured physical function performance, as well as insulin resistance in individuals with RA (17,18). Adipocytes are metabolically active and are capable of synthesizing a number of biologically active compounds such as proinflammatory adipocytokines (19). The stromovascular fraction of adipose tissue includes macrophages (19), which are the primary source of TNF in adipose tissue (20). Results of a recent study showed that a higher abundance of macrophages in the adipose tissue of individuals with RA versus non-RA controls matched on demographics and body mass index is a potent source of inflammatory cytokines in RA (21).

Inflammation is also linked with dysregulation of mitochondrial function and biogenesis, and, consequently, disruption of muscle oxidative metabolic capacity in the general population (22). Muscle oxidative metabolic capacity is essential for the generation of ATP in order to fuel skeletal muscle contraction, locomotion, and maintain homeostatic cellular electrolyte balance (i.e., sodium-potassium pumps). In a metabolic profiling study (15), the concentration of pyruvate in muscle in individuals with RA was significantly higher than in muscle from controls, and the expression of genes controlling glycolytic metabolism was also significantly up-regulated in those with RA versus controls. Pyruvate is the end-product of glycolysis, and normally feeds into the tricarboxylic acid cycle, generating energy intermediates that are critical for mitochondrial ATP synthesis through oxidative phosphorylation. Therefore, pyruvate accumulation in RA muscle could be a sign of poor mitochondrial function. However, further studies are needed to fully elucidate the role of substrate metabolism and mitochondrial function in the skeletal muscle of individuals with RA and their effects on disease outcomes.

INSULIN RESISTANCE IN RA

Insulin resistance has been associated with low skeletal muscle mass in patients with RA (23), but the precise mechanism or the extent to which it contributes to the metabolic and physiologic derangements is unknown. Insulin, along with insulin-like growth factor 1, is an important regulator of skeletal muscle mass through stimulation of cell growth and proliferation via Akt signaling (24). Under physiologic conditions, insulin also regulates substrate utilization in multiple tissues, including skeletal muscle, and liver and adipose tissue (25). Insulin resistance associated with diminished mitochondrial content and function, resulting in lower skeletal muscle oxidative capacity and higher levels of intramyocellular lipid content (26).

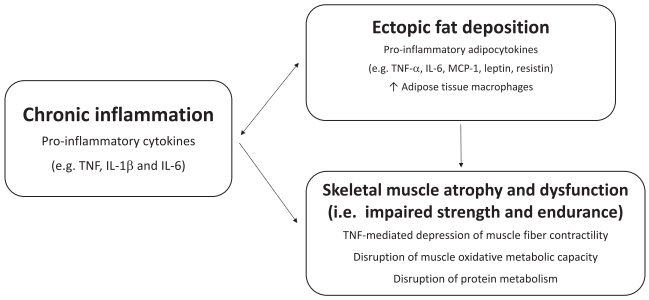

Figure 1. Conceptual model of biologic mechanisms involved in skeletal muscle dysfunction in rheumatoid arthritis. TNF = tumor necrosis factor; IL = interleukin; MCP-1 = monocyte chemotactic protein 1.

In older adults and individuals with type 2 diabetes mellitus, insulin resistance is an independent correlate of poor muscle strength (27–29). Therefore, the high prevalence of insulin resistance among patients with RA may play a very important role in skeletal muscle dysfunction.

Insulin resistance is much more prevalent in patients with RA compared to the general population (51% in recent-onset RA; 58% in longstanding RA; and 19% in non-RA controls) (30). Risk factors for insulin resistance in RA include rheumatoid factor seropositivity, prednisone use, higher RA disease activity, and visceral and thigh intermuscular adiposity (2,18,31). A recent study (18) demonstrated that adiposity, but not systemic inflammation was associated with insulin resistance in patients with RA. There is substantial evidence linking both inflammation and excess adiposity with insulin resistance in the general population and in individuals with RA (32–34), and adipose tissue itself can be an important source of inflammatory mediators that can induce insulin resistance. Low muscle mass may be another important contributing factor of insulin resistance in RA (34), although it has not received much attention. Skeletal muscle plays a critical role not only in movement and locomotion, but also in the regulation of whole-body carbohydrate and lipid metabolism (35). In humans, skeletal muscle is the principal site of glucose uptake in the postprandial state (36), and low appendicular lean mass has been shown to be significantly associated with insulin resistance in early RA (37). This underscores the importance of maintaining lean mass, and the need to better understand the complex interplay among chronic inflammation, ectopic fat accumulation, and skeletal muscle dysfunction. Figure 1 shows the potential mechanisms of skeletal muscle dysfunction in patients with RA that is covered in the current review.

BENEFICIAL EFFECTS OF PHYSICAL ACTIVITY AND EXERCISE TRAINING

Free-living physical activity is defined as "the level of physical activity that individuals, within their physical limitations, at their own pace, and in their own environment, typically perform."

Free-living physical activity and prescriptive exercise are associated with a myriad of health benefits in individuals with RA, including improvement of disease activity, fatigue, pain, quality of life, physical performance, aerobic capacity, cardiovascular risk, and bone and joint health (38–40). A recent systematic review that guided the 2016 update of the European League Against Rheumatism recommendations for the management of early arthritis supports the beneficial effect of exercise programs on pain and physical function (41). Additionally, a recent Cochrane review showed that there was moderate evidence that both short-term (<3 months) and long-term (>3 months) land-based dynamic exercise programs (endurance training and/or strength training) have positive effects on aerobic capacity and muscle strength in individuals with RA, with no adverse effects on disease activity (42). Endurance and resistance training improve body composition (i.e., increase lean mass and decrease adiposity) as well as physical function in individuals with RA (43–45). The observed positive effects of endurance training could be due to increased mitochondrial biogenesis and respiratory function, blood flow, and insulin sensitivity (46–48), but published studies on the cellular and molecular effects of resistance training in individuals with RA are almost nonexistent; we identified only 1 case report (44).

It is well established that exercise training enhances insulin sensitivity in the general population (35). According to a recent review on the effects of physical activity on insulin sensitivity, many studies support a dose-response relationship between physical activity and whole-body insulin sensitivity, whereby higher energy expenditures and higher exercise intensities yield greater benefits (49). Additionally, exercise regimens including both aerobic and resistance training have been shown to be more efficacious in improving insulin sensitivity than either exercise mode alone (49). Although there are no published studies on the effect of exercise training on insulin sensitivity in individuals with RA, we speculate individuals with RA would derive similar benefits.

PHYSICAL ACTIVITY AND EXERCISE TRAINING BARRIERS AND RECOMMENDATIONS

In spite of the well-documented evidence that physical activity and exercise are beneficial, most patients with RA are sedentary. A study of 5,235 individuals with RA across 21 different countries found that the overwhelming majority (71%) did not participate in any regular physical activity, and only 14% exercised ≥3 times a week (50). Lack of time and motivation have been the two most frequently reported perceived barriers to physical activity and exercise by patients with RA (51). Conversely, support and encouragement from instructors and health care professionals has been identified as the most prominent RA-specific perceived facilitating factor for regular physical activity and exercise (51). A recent study (52) also suggests self-managed physical activity programs using a pedometer may also promote increased physical activity level among individuals with RA. In this study, participants were followed up for only 21 weeks, but other studies (53,54) support the long-term effectiveness of pedometer-based interventions. Unfortunately, rheumatologists feel they do not have sufficient time to counsel patients on nonpharmacologic treatment, and have low confidence in their competence to prescribe exercise and to motivate patients (51,55). This underscores the importance of placing greater emphasis on treatment approaches utilizing nonpharmacologic and psychosocial strategies to complement the effects of medications in order to address many unmet needs of RA patients across key domains, such as physical function, fatigue, pain, and mental function (56).

Moreover, additional studies are needed to determine the optimal duration, frequency, and intensity of exercise required to safely produce substantial health benefits for individuals with RA, and to improve their adherence to exercise. For the time being, general physical activity recommendations for adults can be obtained from the 2018 Physical Activity Guidelines for Americans (57).

Some studies (58,59) have assessed whether behavioral interventions that foster autonomous motivation and self-efficacy can decrease sitting time, improve physical function and pain, and effectively promote long-term participation in physical activity among RA patients. Developing a multidisciplinary treatment team including physical therapists, occupational therapists, and exercise physiologists with expertise in rehabilitation and exercise prescription may also be critical for promoting increased physical activity and exercise among individuals with RA. Recent pilot research has explored expanding the role of physical therapists in administering a health-enhancing physical activity program in individuals with RA (60).

In conclusion, there is mounting evidence that treatment with disease-modifying antirheumatic drugs and biologic agents is insufficient to restore physical function, body composition, and metabolic homeostasis in individuals with RA. To advance our understanding of RA pathophysiology and improve RA patient care, key knowledge gaps that are ideal for future research include better understanding of the interrelationships of inflammation, ectopic adipose, and muscle dysfunction; and optimization of exercise prescription for RA via dose response trials. Expansion of our understanding of the complex etiology of the reduced physical function and identification of therapeutic targets offers a tremendous opportunity to improve morbidity and mortality in RA. Team science, with more collaboration among researchers and clinicians across different fields may be key to achieving these goals.

AUTHOR CONTRIBUTIONS

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

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ACTIVITY AND THE RHEUMATIC DISEASES

Leisure Time and Transportation Walking Among Adults With and Without Arthritis in the United States, 2010

Jennifer M. Hootman, Kristina A. Theis, Kamil E. Barbour, Prabasaj Paul, and Susan A. Carlson

Objective. Walking is a joint-friendly activity for adults with arthritis. The aim of this study was to estimate, among adults with arthritis, the prevalence of leisure and transportation walking overall (by arthritis status and by sociodemographic and health characteristics), the number of total minutes walking per week in each domain, and the distributions of walking bout length (i.e., short periods of activity) in minutes.

Methods. Data were obtained from the 2010 National Health Interview Survey. Prevalence estimates (percentages and 95% confidence intervals [95% CIs]) of leisure and transportation walking in the past 7 days and walking bout times were calculated (in minutes), as were multivariable Poisson regression models, which account for the complex sample design.

Results. Prevalence of leisure walking was 45.9% (95% CI 44.2–47.6) for adults with arthritis versus 51.9% (95% CI 50.9–52.9) for those without. Transportation walking prevalence was 23.0% (95% CI 21.7–24.4) for adults with arthritis versus 32.0% (95% CI 31.0–33.0) for those without. The total time of leisure walking per week did not differ in adults with arthritis compared to those without (77.3 versus 78.3 minutes, respectively; $P = 0.62$), while total time of transportation walking did differ (49.8 versus 58.1 minutes, respectively; $P = 0.03$). The most common walking bout length differed between leisure (26–40 minutes) and transportation (10–15 minutes) walking, but not by arthritis status. In separate adjusted multivariable models, obesity was consistently negatively associated with both walking outcomes, and being physically active was positively associated with both; lower extremity joint pain was not associated.

Conclusion. By adding short bouts, leisure and transportation walking could be adopted by large proportions of adults with arthritis. Existing evidence-based programs can help increase physical activity.

INTRODUCTION

In October 2015, the US Surgeon General released "Step it up! The Surgeon General's Call to Action to Promote Walking and Walkable Communities" (1,2). This call to action proposed to increase walking among all Americans by calling for improved access to safe and convenient places to walk and wheelchair roll, as well as for a culture that supports these activities (1,2). The 2008 Physical Activity Guidelines for Americans stipulate 3 criteria for achievement of meaningful health benefits through aerobic activity, including moderate (e.g., brisk walking) to vigorous (e.g., jogging) intensity activity, a total of ≥150 minutes per week of moderate intensity activity or ≥75 minutes per week of vigorous intensity activity (or the equivalent), and activity comprised of bouts (i.e., short periods of activity) lasting ≥10 minutes each (3). Walking can be an easy way to start and maintain a physically active lifestyle because it is inexpensive, convenient, does not require special facilities or equipment, and can be done for many reasons, such as for leisure (e.g., walking the dog) and transportation (e.g., getting to and from places such as work) (1,2).

For adults with arthritis, low impact physical activity, such as walking, is a recommended approach for symptom management, but few get sufficient physical activity (4–9). Prior studies among people with arthritis have shown walking improves symptoms (pain, stiffness, and fatigue), function (self-reported and physical performance measures), mood, and quality of life

The findings and conclusions contained herein are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Jennifer M. Hootman, PhD, ATC, FACSM, FNATA, Kristina A. Theis, PhD, Kamil E. Barbour, PhD, Prabasaj Paul, PhD, Susan A. Carlson, PhD: Centers for Disease Control and Prevention, Atlanta, Georgia.

Address correspondence to: Jennifer M. Hootman, PhD, ATC, FACSM, FNATA, Centers for Disease Control and Prevention, 4770 Buford Highway MS#F78, Atlanta, GA, 30341. E-mail: tzh7@cdc.gov.

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SIGNIFICANCE & INNOVATIONS

- This study expands knowledge of leisure walking prevalence among adults with arthritis to include information on average minutes walked per week and bout length distribution.
- To our knowledge, this is the first nationally representative report of transportation walking among adults with arthritis and includes prevalence, average weekly minutes walked, and bout length distribution for a comprehensive description of transportation walking behavior.
- The prevalence and correlates of both leisure and transportation walking behaviors vary with the presence of arthritis, the specific walking measure, and sociodemographic characteristics.

(10–15). Recently, among people with knee osteoarthritis, walking has been shown to be protective for incident functional limitation (16) and, among adults at risk for or with mild knee osteoarthritis, has not been associated with harmful changes in cartilage and joint structure (17). Qualitative studies among adults with arthritis also support walking as an appropriate, feasible, enjoyable, and favored activity (18–20). Recent studies that have demonstrated estimates of walking among adults with arthritis either capture walking in only 1 domain (e.g., leisure) or total daily walking using motion sensors (no differentiation of context or domain of walking) (21–25). Currently there are no distinct data on transportation-specific walking for adults with arthritis, which, along with leisure-time walking, may be a viable target for increasing walking within the arthritis population.

Estimates of the number and distribution of adults with arthritis who walk can inform intervention efforts in order to increase recommended physical activity, especially among low-level or nonwalkers. Knowing relevant sociodemographic and other characteristics may inform health communication messaging and marketing of evidence-based programs to all groups. The purpose of this study was to estimate, among US adults, the prevalence of leisure and transportation walking overall (by arthritis status and by selected sociodemographic and health characteristics), the total number of minutes of walking per week in each domain, and the prevalence and distributions of walking bout length in minutes for each domain.

MATERIALS AND METHODS

Study design and population. We used data from the National Health Interview Survey (NHIS), an ongoing, in-person, cross-sectional interview survey conducted by the National Center for Health Statistics that is representative of the civilian, noninstitutionalized US population. The NHIS uses a complex sampling frame in which blacks, Hispanics, and Asians are oversampled, including minorities over age 65. Interview data were collected by trained interviewers in individuals' homes. Participation is voluntary.

We used NHIS 2010 sample adult questions consisting of the core questionnaire (basic health and demographic questions) and the cancer control supplement (asked of a subset of sample adults), which have data on walking (26). The 2010 final sample adult response rate was 60.8% (26). The overall sample included 27,157 adults. We analyzed 24,350 responses after excluding those who could not walk (555 adults), and those for whom we were missing data on arthritis or walking (1,910 adults), or missing demographic variables (342 adults). For each sample adult, sampling weights were applied to raw estimates to generate nationally representative estimates, which also accounted for nonresponse and post-stratification adjustments (26).

Definitions of terms and walking outcomes. Arthritis was defined as a "yes" response to the question "Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?" Leisure walking was defined as a "yes" response to the question "Sometimes you may walk for fun, relaxation, exercise, or to walk the dog. During the past 7 days, did you walk for at least 10 minutes for any of these reasons? Please do not include walking for transportation." Transportation walking was defined as a "yes" response to the question "During the past 7 days, did you walk to get some place that took you at least 10 minutes?"

Those answering "yes" to either of the leisure or transportation walking questions were subsequently asked the following questions: "In the past 7 days, how many times did you do that?" (frequency); and "On average, how long did those walks take?" (bout length). The mean minutes of walking per week in each domain were calculated by multiplying the frequency by the bout length. Respondents who did not walk for at least 10 minutes or who averaged <10 minutes in both domains (leisure and transportation) were classified as nonwalkers (<10 minutes of walking in the past 7 days).

Covariates. The demographic variables were sex, age, race/ethnicity, and education. Other variables included body mass index (BMI; weight [kg]/height [m^2] where <25 = under/normal weight; 25 to <30 = overweight; and ≥30 = obese), lower extremity joint symptoms (yes/no), and a 3-level aerobic physical activity variable. Physical activity was assessed by asking 1 question each about the frequency of vigorous activity (that which causes heavy sweating or large increases in breathing or heart rate) and light-to-moderate activity (that which causes only light sweating or a slight to moderate increase in breathing or heart rate) for at least 10 minutes. Participants with ≥1 bout of either activity were then asked

for details about the frequency and duration of moderate and vigorous activity, which were translated into weekly minutes of activity (1 minute of vigorous-intensity activity was equal to 2 minutes of moderate activity). Respondents were then categorized into 3 levels of moderate intensity–equivalent aerobic physical activity: active (≥150 minutes), insufficient (some but did not meet the active definition), and inactive (zero minutes per week).

Statistical analysis. We calculated prevalence (percentages and 95% confidence intervals [95% CIs]) of leisure and transportation walking in the past 7 days, overall by arthritis status and stratified by all covariates among those with arthritis. To measure associations with each walking domain, we used multivariable Poisson's regression models, including all 7 covariates, to estimate adjusted prevalence ratios (APRs; 95% CIs) for participation in leisure and transportation walking, separately, using Taylor Series Linearization for variance estimation (27). Poisson's regression has been shown to be a robust estimator in cross-sectional studies and produces a prevalence ratio that may be more easily interpreted compared to odds ratio (28).

We calculated the mean and 95% CIs for minutes walked per week in each domain. We estimated adjusted volume ratios (AVRs) using linear regression models on a log-transformed model of total minutes walking in each domain, adjusting for all covariates; volume ratios represent total minutes per week of walking across both domains. To account for the complex sample design, we conducted all analyses using R statistical software, version 2.14.1, and survey package, version 3.29 (R Foundation for Statistical Computing). Statistical testing between adults with and without arthritis was performed using Pearson's chi-square test, with first- and second-order corrections using the Rao-Scott test (for unadjusted prevalence estimates) and a regression model of log (volume) (for the volume models). For all independent variables, responses of "don't know" or "refused" were treated as missing for modeling purposes.

RESULTS

Leisure walking. *Prevalence overall and by study characteristics*. The unadjusted prevalence of leisure walking was lower for adults with arthritis compared to those without (45.9% [95% CI 44.2–47.6] versus 51.9% [95% CI 50.9–52.9] $P < 0.05$) (Table 1). The only groups of adults with arthritis who reported ≥50% prevalence of leisure walking were those ages 18–34 and 35–44 years, non-Hispanic others, college graduates, those with under/normal weight BMI, and those reporting insufficient or active for physical activity. Leisure walking was reported least by those who were inactive (21%). Groups with ≤40% prevalence of leisure-time walking included high school graduates (39%), non-Hispanic blacks (37%), adults ages ≥75 years (36%), and those without a high school degree (34%). Those without lower extremity joint pain reported ~6 percentage points higher prevalence of leisure walking than those with lower extremity joint pain, which was statistically significant (49.6% [95% CI 46.7–52.5] versus 43.5% [95% CI 41.5–45.6]).

Multivariable adjusted associations (APRs) between study characteristics and leisure walking. Among adults with arthritis, the magnitude of the APRs for leisure walking were similar and were not significant by age group and sex, with even the most extreme association (those adults ages ≥75 years), failing to reach statistical significance (APR 0.88 [95% CI 0.77–1.02]) (Table 1). The APR for the Hispanic race/ethnicity category was significantly associated with a higher prevalence of leisure-time walking versus non-Hispanic whites (APR 1.19) and was 16% higher for college graduates (APR 1.16) versus those with less than a high school education. There was a 15% lower prevalence of walking associated with obesity (APR 0.85) compared to adults who were under/normal weight. The differences in associations for physical activity level were considerable. Compared with those who were inactive, those with insufficient physical activity (<150 minute/week), were 2.4 times more likely and those who were active were 3 times more likely to report leisure walking.

Total minutes of leisure walking per week overall and by study characteristics. The total minutes of leisure walking per week were similar between adults with and without arthritis (77.3 versus 78.3 minutes per week; $P = 0.62$) (Table 2). The mean minutes of leisure walking per week were generally tightly dispersed from the upper 60s to the low 80s across the studied sociodemographic groups, with some expected outliers. For example, the lowest mean minutes of walking were observed for those who were inactive or had insufficient physical activity, 57.6 and 55.4 minutes, respectively. The highest mean minutes of walking were observed for under/normal weight adults and those who were physically active, 92.7 and 99.7 minutes, respectively.

After adjustment for all characteristics studied, among adults with arthritis, the only statistically significant, positive associations with minutes of leisure walking were among those ages 55–64 years (AVR 1.30 [95% CI 1.07–1.57]) and ages 65–74 years (AVR 1.30 [95% CI 1.08–1.57]) versus those adults ages 18–34 years and active adults (AVR 1.71 [95% CI 1.52–1.92]) versus inactive adults. The only statistically significant, negative associations were among those who were overweight or obese (AVR 0.81 [95% CI 0.73–0.90] and AVR 0.78 [95% CI 0.70–0.87]) versus under/normal weight adults.

Leisure walking bout length by arthritis status. There was no discernable difference in the distribution of leisure walking bout lengths between adults with and without arthritis who reported walking (Figure 1). The most commonly reported leisure walking bout length was 26–40 minutes followed by 10–15 minutes for adults both with and without arthritis. Walking bout lengths of

Table 1. Unadjusted prevalence and multivariable APRs of leisure and transportation walking in the past 7 days among US adults with and without arthritis, by selected characteristics, National Health Interview Survey 2010*

Characteristic	Leisure walking, arthritis (n = 5,565)		Leisure walking, no arthritis (n = 18,785)		Transportation walking, arthritis (n = 5,565)		Transportation walking, no arthritis (n = 18,785)	
	Weighted % (95% CI)	APR (95% CI)	Weighted % (95% CI)	APR (95% CI)	Weighted % (95% CI)	APR (95% CI)	Weighted % (95% CI)	APR (95% CI)
Total	45.9 (44.2–47.6)	–	51.9 (50.9–52.9)	–	23.0 (21.7–24.4)	–	32.0 (31.0–33.0)	–
Sex								
Men	47.4 (44.7–50.0)	ref.	49.7 (48.3–51.0)	ref.	24.3 (22.2–26.5)	ref.	34.7 (33.3–36.1)	ref.
Women	44.8 (42.8–46.9)	1.0 (1.0–1.1)	54.2 (52.9–55.4)	1.1 (1.1–1.2)	22.1 (20.5–23.9)	1.0 (0.9–1.1)	29.2 (28.0–30.5)	0.9 (0.8–0.9)
Age group, years								
18–34	51.6 (45.4–57.9)	ref.	50.9 (49.3–52.5)	ref.	31.2 (25.6–37.5)	ref.	36.6 (34.9–38.4)	ref.
35–44	51.4 (46.0–56.7)	1.0 (0.9–1.2)	53.3 (51.4–55.3)	1.1 (1.0–1.1)	27.2 (22.8–32.0)	0.9 (0.7–1.2)	30.2 (28.5–32.0)	0.8 (0.8–0.9)
45–54	48.4 (44.8–52.1)	1.0 (0.9–1.2)	53.4 (51.4– 55.4)†	1.2 (1.0–1.1)	25.2 (22.3–28.2)	0.9 (0.7–1.1)	29.8 (27.9–31.8)†	0.9 (0.8–0.9)
55–64	48.4 (45.0–51.9)	1.0 (0.9–1.2)	54.2 (51.7–56.8)†	1.1 (1.1–1.2)	24.9 (22.3–27.7)	0.9 (0.7–1.1)	30.0 (28.0–32.1)†	0.9 (0.8–0.9)
65–74	44.1 (41.0–47.2)	1.0 (0.9–1.1)	53.2 (49.8–56.6)†	1.2 (1.1–1.3)	20.8 (18.2–23.6)	0.7 (0.6–0.9)	26.4 (23.8–29.2)†	0.8 (0.7–0.9)
≥75	35.6 (32.3–39.1)	0.9 (0.8–1.0)	38.9 (35.1–42.8)	1.0 (0.9–1.1)	14.8 (12.6–17.2)	0.6 (0.4–0.7)	20.5 (18.0–23.3)†	0.7 (0.6–0.8)
Race/ethnicity								
Non-Hispanic white	46.8 (44.8–48.9)	ref.	53.9 (52.7–55.2)	ref.	21.9 (20.4–23.5)	ref.	30.7 (29.4–32.0)	ref.
Non-Hispanic black	37.1 (33.1–41.2)	0.9 (0.8–1.0)	43.6 (41.2–46.0)†	0.9 (0.9–1.0)	26.1 (22.8–29.8)	1.3 (1.1–1.5)	33.1 (30.9–35.4)†	1.2 (1.1–1.3)
Hispanic	46.4 (41.0–51.9)	1.2 (1.1–1.3)	48.5 (46.6–50.5)	1.1 (1.0–1.1)	26.7 (22.7–31.2)	1.3 (1.1–1.5)	34.7 (32.7–36.8)†	1.2 (1.1–1.3)
Non-Hispanic other	50.2 (43.8–56.6)	1.0 (0.9–1.2)	54.4 (51.3–57.5)	1.0 (1.0–1.1)	30.0 (23.9–36.8)	1.3 (1.0–1.6)	35.6 (32.9–38.4)	1.1 (1.0–1.2)
Education								
<High school	34.4 (31.1–37.9)	ref.	39.8 (37.7–42.0)	ref.	22.0 (19.1–25.3)	ref.	31.6 (29.5–33.8)	ref.
High school graduate	39.3 (36.7–41.9)	1.0 (0.9–1.1)	45.7 (43.9–47.6)†	1.1 (1.0–1.1)	17.6 (15.4–20.0)	0.7 (0.6–0.9)	26.9 (25.4–28.4)†	0.9 (0.8–0.9)
Some college	48.3 (45.2–51.5)	1.1 (1.0–1.2)	52.4 (50.7–54.2)†	1.1 (1.0–1.2)	24.0 (21.5–26.7)	0.9 (0.8–1.1)	31.3 (29.7–32.9)†	0.9 (0.9–1.0)
College graduate	58.6 (55.1–62.0)	1.2 (1.0–1.3)	62.1 (60.4–63.7)	1.2 (1.1–1.3)	29.4 (26.7–32.3)	1.1 (0.9–1.3)	37.1 (35.5–38.7)†	1.1 (1.0–1.2)
Body mass index								
Under/normal weight	50.7 (47.4–53.9)	ref.	53.7 (52.2–55.2)	ref.	24.5 (21.9–27.2)	ref.	34.8 (33.4–36.3)	ref.
Overweight	48.4 (45.6–51.2)	0.9 (0.8–1.0)	52.6 (51.0–54.1)†	1.0 (1.0–1.0)	24.5 (22.1–27.0)	0.9 (0.8–1.1)	32.6 (31.2–34.1)†	0.9 (0.9–1.0)
Obese	40.8 (38.3–43.4)	0.9 (0.8–0.9)	48.3 (46.7– 49.9)†	1.0 (1.0–1.0)	20.9 (18.9–23.1)	0.8 (0.7–0.9)	26.8 (25.1–28.4)†	0.8 (0.8–0.9)

(continued)

Table 1. *(Cont'd)*

Characteristic	Leisure walking, arthritis (n = 5,565)		Leisure walking, no arthritis (n = 18,785)		Transportation walking, arthritis (n = 5,565)		Transportation walking, no arthritis (n = 18,785)	
	Weighted % (95% CI)	APR (95% CI)	Weighted % (95% CI)	APR (95% CI)	Weighted % (95% CI)	APR (95% CI)	Weighted % (95% CI)	APR (95% CI)
Lower extremity joint symptoms‡								
No	49.6 (46.7–52.5)	ref.	52.1 (51.0–53.3)	ref.	22.5 (20.4–24.8)	ref.	32.2 (31.2–33.3)	ref.
Yes	43.5 (41.5–45.6)	1.1 (1.0–1.1)	50.6 (48.4– 52.7)†	1.1 (1.0–1.1)	23.3 (21.6–25.1)	0.9 (0.8–1.1)	30.5 (28.6–32.4)†	1.0 (0.9–1.1)
Aerobic physical activity§								
Inactive	21.0 (18.9–23.2)	ref.	26.5 (25.1–28.0)	ref.	15.7 (13.9–17.8)	ref.	23.0 (21.6–24.6)	ref.
Insufficient	52.4 (49.2–55.6)	2.4 (2.2–2.8)	53.2 (51.2–55.2)	2.0 (1.8–2.1)	23.8 (21.2–26.6)	1.5 (1.2–1.7)	29.1 (27.4–30.9)†	1.3 (1.2–1.4)
Active	67.1 (64.6–69.6)	3.0 (2.7–3.4)	66.1 (64.8–67.4)	2.4 (2.3–2.6)	30.0 (27.7–32.3)	1.7 (1.5–2.0)	38.3 (36.9–39.7)†	1.6 (1.5–1.7)

* Prevalence ratios adjusted for all characteristics included in the table. APR = adjusted prevalence ratio; 95% CI = 95% confidence interval; ref. = reference

† Arthritis versus no arthritis, $P < 0.05$.

‡ Pain, aching, or stiffness in or around hip, knee, ankle, and/or toes during the past 30 days.

§ Physical activity level is defined as active (≥150 minutes/week moderate-intensity equivalent activity), insufficiently active (some moderate-intensity equivalent activity, but not enough to meet active definition), and inactive (no moderate-intensity equivalent activity that lasted at least 10 minutes).

Table 2. Unadjusted mean walking time per week and AVRs among US adults who reported walking with and without arthritis, by selected characteristics, National Health Interview Survey 2010*

Characteristic	Leisure walking, arthritis (n = 2,435)		Leisure walking, no arthritis (n = 9,601)		Transportation walking, arthritis (n = 1,342)		Transportation walking, no arthritis (n = 6,314)	
	Mean mins/wk (95% CI)	AVR (95% CI)	Mean mins/wk (95% CI)	AVR (95% CI)	Mean mins/wk (95% CI)	AVR (95% CI)	Mean mins/wk (95% CI)	AVR (95% CI)
Total	77.3 (74.0–80.8)	–	78.3 (76.4–80.2)	–	49.8 (46.5–53.3)	–	58.1 (56.0–60.3)	–
Sex								
Men	79.8 (74.2–85.9)	ref.	77.1 (74.3–80.0)	ref.	52.2 (46.4–58.8)	ref.	60.2 (57.3–63.2)†	ref.
Women	75.4 (71.3–79.8)	0.98 (0.89–1.08)	79.4 (76.8–82.0)	1.07 (1.02–1.12)	48.0 (44.1–52.1)	0.94 (0.81–1.09)	55.6 (52.9–58.5)†	0.93 (0.87–1.00)
Age group, years								
18–34	68.3 (57.9–80.6)	ref.	69.0 (66.2–71.9)	ref.	51.6 (42.0–63.5)	ref.	58.0 (55.0–61.2)	ref.
35–44	74.8 (66.0–84.8)	1.11 (0.90–1.38)	75.2 (71.8–78.7)	1.12 (1.05–1.19)	40.4 (33.5–48.8)	0.81 (0.62–1.06)	56.7 (52.8–60.9)†	1.01 (0.93–1.10)
45–54	74.7 (68.3–81.7)	1.19 (0.99–1.43)	86.1 (81.5–90.9)†	1.28 (1.20–1.37)	51.6 (44.4–60.1)	1.06 (0.82–1.37)	57.1 (52.1–62.5)	1.03 (0.94–1.14)
55–64	81.8 (73.5–91.0)	1.30 (1.07–1.57)	92.4 (86.9–98.2)†	1.40 (1.31–1.50)	54.6 (48.1–61.9)	1.15 (0.91–1.45)	62.8 (57.4–68.8)	1.15 (1.04–1.28)
65–74	81.5 (74.5–89.2)	1.30 (1.08–1.57)	98.2 (90.6–106.5)†	1.53 (1.41–1.66)	48.8 (41.3–57.7)	0.98 (0.76–1.27)	59.2 (51.6–67.9)	1.05 (0.91–1.22)
≥75	74.0 (64.8–84.6)	1.23 (0.98–1.54)	85.1 (74.3–97.4)	1.38 (1.20–1.60)	45.4 (38.1–54.1)	0.97 (0.75–1.25)	53.0 (44.5–63.0)	0.93 (0.78–1.11)
Race/ethnicity								
Non-Hispanic white	78.6 (74.8–82.5)	ref.	80.2 (77.8–82.6)	ref.	46.8 (43.2–50.8)	ref.	55.3 (52.7–58.0)†	ref.
Non-Hispanic black	73.7 (64.0–84.8)	1.07 (0.94–1.23)	71.0 (65.8–76.6)	0.96 (0.89–1.04)	54.4 (46.2–64.0)	1.25 (1.04–1.50)	60.4 (55.8–65.4)	1.07 (0.97–1.18)
Hispanic	65.1 (56.1–75.4)	0.97 (0.83–1.13)	75.5 (71.7–79.5)	1.04 (0.98–1.11)	60.1 (49.1–73.6)	1.37 (1.10–1.71)	68.3 (62.8–74.3)†	1.19 (1.08–1.32)
Non-Hispanic other	84.0 (71.9–98.1)	1.03 (0.89–1.20)	76.5 (70.8–82.8)	1.02 (0.94–1.10)	72.1 (55.1–94.4)	1.54 (1.15–2.06)	56.5 (50.7–63.0)	1.04 (0.92–1.17)
Education								
<High school	66.1 (58.3–75.0)	ref.	74.5 (69.4–80.1) †	ref.	51.1 (43.9–59.6)	ref.	67.0 (61.8–72.8)†	ref.
High school graduate	73.6 (68.0–79.6)	1.00 (0.86–1.17)	76.2 (72.2–80.4)	0.99 (0.91–1.09)	45.0 (38.8–52.2)	0.94 (0.75–1.18)	62.0 (57.3–67.2)	0.97 (0.87–1.09)
Some college	75.9 (70.0–82.4)	1.04 (0.90–1.21)	77.7 (74.4–81.2)	1.00 (0.91–1.09)	48.0 (42.6–54.0)	0.96 (0.78–1.17)	57.5 (54.1–61.2)	0.92 (0.82–1.03)
College graduate	87.3 (80.8–94.3)	1.06 (0.91–1.23)	81.2 (78.1–84.6)	0.97 (0.89–1.06)	55.4 (48.8–62.9)	1.06 (0.85–1.33)	53.2 (50.1–56.4)	0.84 (0.76–0.93)

(continued)

Table 2. *(Cont'd)*

Characteristic	Leisure walking, arthritis (n = 2,435)		Leisure walking, no arthritis (n = 9,601)		Transportation walking, arthritis (n = 1,342)		Transportation walking, no arthritis (n = 6,314)	
	Mean mins/wk (95% CI)	AVR (95% CI)	Mean mins/wk (95% CI)	AVR (95% CI)	Mean mins/wk (95% CI)	AVR (95% CI)	Mean mins/wk (95% CI)	AVR (95% CI)
Body mass index								
Under/normal weight	92.7 (85.2–100.7)	ref.	79.6 (76.6–82.7)	ref.	49.4 (43.1–56.6)	ref.	60.1 (57.0–63.3)†	ref.
Overweight	75.9 (70.5–81.7)	0.81 (0.73–0.90)	79.8 (76.5–83.2)	1.00 (0.94–1.06)	52.3 (46.7–58.5)	1.03 (0.86–1.24)	59.3 (56.1–62.6)	0.94 (0.87–1.02)
Obese	68.4 (63.7–73.5)	0.78 (0.70–0.87)	74.0 (70.6–77.6)	0.97 (0.92–1.03)	47.7 (42.9–53.0)	0.99 (0.84–1.17)	52.6 (48.7–56.7)	0.85 (0.78–0.93)
Lower extremity joint symptoms‡								
No	80.6 (75.2–86.4)	ref.	78.4 (76.4–80.4)	ref.	52.8 (47.2–59.0)	ref.	58.3 (56.0–60.6)	ref.
Yes	75.0 (70.8–79.4)	1.03 (0.94–1.12)	77.6 (72.4–83.1)	1.03 (0.96–1.10)	48.0 (44.3–52.1)	1.10 (0.97–1.24)	57.0 (52.3–62.2)†	1.0 (0.91–1.09)
Aerobic physical activity§								
Inactive	57.6 (52.5–63.2)	ref.	63.5 (59.5–67.8)	ref.	48.1 (42.2–55.0)	ref.	65.9 (60.6–71.6)†	ref.
Insufficient	55.4 (51.3–59.8)	0.95 (0.84–1.07)	54.5 (52.1–57.0)	0.86 (0.79–0.94)	39.5 (35.1–44.5)	0.82 (0.69–0.99)	44.6 (41.9–47.4)	0.71 (0.64–0.79)
Meets recommendations	99.7 (94.6–105.1)	1.71 (1.52–1.92)	92.2 (89.3–95.2)†	1.50 (1.39–1.62)	56.8 (51.2–63.1)	1.19 (0.99–1.44)	60.2 (57.4–63.1)	0.97 (0.87–1.07)

* Volume ratios estimated using linear regression models on a log-transformed model of minutes walking in each domain, adjusted for all characteristics included in the table. AVR = adjusted volume ratio; mins/wk = minutes per week; 95% CI = 95% confidence interval; ref. = reference.
† Arthritis versus no arthritis, $P < 0.05$.
‡ Pain, aching, or stiffness in or around hip, knee, ankle, and/or toes during the past 30 days
§ Physical activity level is defined as active (≥ 150 minutes/week moderate-intensity equivalent activity), insufficiently active (some moderate-intensity equivalent activity but not enough to meet active definition), and inactive (no moderate-intensity equivalent activity that lasted at least 10 minutes).

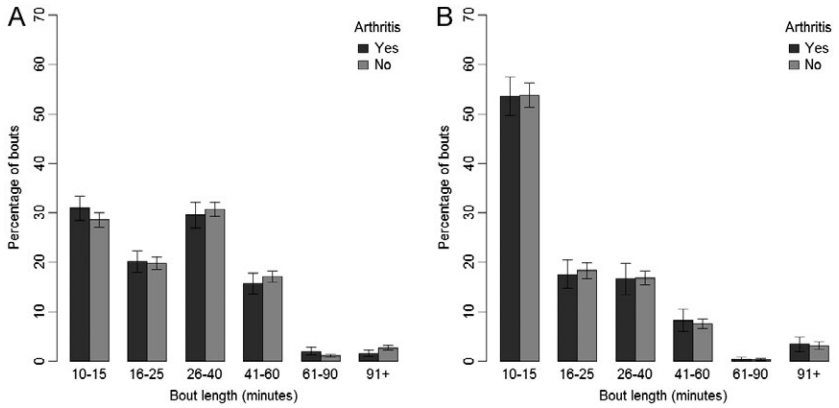

Figure 1. Distribution of mean minutes per bout of leisure (**A**) or transportation (**B**) walking, among US adult walkers with and without arthritis, NHIS, 2010.* * The initial survey lead-in question asked about walking in bouts of at least 10 minutes, however, responses of <10 minutes were allowed when individuals were later asked about bout length (n = 157 leisure, n = 189 transportation walking).

61–90 minutes and ≥91 minutes were reported with approximately equal frequency for those with and without arthritis.

Transportation walking. *Prevalence overall and by study characteristics*. Overall, the prevalence of transportation walking for adults with and without arthritis was 23.0% (95% CI 21.7–24.4) and 32.0% (95% CI 31.0–33.0), respectively ($P < 0.01$) (Table 1). No groups reported ≥40% prevalence of transportation walking. The highest prevalence of transportation walking was 31.2%, reported by adults ages 18–34 years, followed by 30% prevalence reported by physically active adults and 29.4% reported by college graduates. Fewer than 20% of the following groups reported transportation walking: high school graduates (17.6%), physically inactive adults (15.7%), and those ages ≥75 years (14.8%).

Multivariable adjusted associations (APRs) between study characteristics and transportation walking. Among adults with arthritis, associations with transportation walking did not differ by sex. The likelihood of transportation walking was lower for those adults ages 65–74 years (27%) and ≥75 years (45%) compared to those 18–34 years, but 27% and 28% higher for non-Hispanic blacks and Hispanics, respectively, compared to non-Hispanic whites. The APR was 26% lower for high school graduates versus those with less than a high school education. Adults with obesity and arthritis were 19% less likely to report transportation walking than those with underweight/normal BMI. As with leisure walking, associations with transportation walking were strongest for physical activity level, 46% and 74% higher for those who were insufficiently active and active, respectively, compared to those who were inactive.

Total minutes of transportation walking per week overall and by study characteristics. Adults with arthritis reported fewer minutes of transportation walking compared to adults without arthritis (49.8 versus 58.1 minutes per week; $P = 0.03$) (Table 2). As with leisure-time walking, there was only moderate variation in total transportation minutes walked per week across sociodemographic groups. The fewest total transportation minutes walked per week were reported by those with insufficient physical activity (39.5 minutes) and among those ages 35–44 years (40.4 minutes). The most transportation minutes walked per week were reported by physically active adults (56.8 minutes) and Hispanics (60.1 minutes).

Among adults with arthritis, after adjustment for all characteristics studied, the only statistically significant associations were for Hispanics and non-Hispanic others, with AVRs of 37% and 54%, respectively, which were higher compared to non-Hispanic whites. There were no significant negative associations.

Transportation walking bout length by arthritis status. Among those who reported transportation walking, there was no significant difference in the distribution of bout lengths between adults with and without arthritis ($P > 0.05$) (Figure 1). More than 50% of both people with and without arthritis reported a walking bout length of 10–15 minutes. The next most common bout lengths, reported by 16–19% of both those with and without arthritis were 16–25 minutes and 26–40 minutes. The least reported bout lengths were 61–90 minutes, followed by ≥91 minutes.

DISCUSSION

Among adults with arthritis, only an estimated 46% engaged in leisure walking and only 23% engaged in transportation walking. Prevalence of both leisure and transportation walking was lower among adults with arthritis compared to those without arthritis. For the leisure walking domain, both average minutes walked per week and the distribution of average minutes per bout of walking were similar regardless of arthritis status. Conversely, for the transportation domain, average minutes walked per week were significantly lower for adults with arthritis compared to those without arthritis, while the distribution of average minutes per bout of walking was still very similar.

The prevalence of walking varied by demographic group in both the leisure and transportation walking domains. Among adults with arthritis, leisure walking did not differ by sex. This pattern was different than that which was shown in a study by Paul et al (29) of the general US population in which women had a higher prevalence of exclusively leisure walking than men (29). Patterns in race/ethnicity, however, were also similar to those reported by Paul et al (29). Hispanics and non-Hispanic others had higher adjusted prevalences of transportation walking than non-Hispanic whites. Studies of Hispanics with and without arthritis have already demonstrated that this group walks for transportation more than other subgroups and may be receptive to positive messaging about health benefits of walking, both for transportation and leisure. These results may also be an opportunity to engage with all community members regarding efforts to create and enhance walkability in communities, including improved infrastructure, street safety, sidewalk continuity, traffic calming, lighting, and other measures to encourage walking through environmental improvements (2).

Despite the lower prevalence of leisure walking time among adults with arthritis, people with and without arthritis spend about the same amount of leisure-time walking (a single bout) when they do walk, suggesting that there are not arthritis-specific differences in established walking behavior. In addition, lower extremity joint pain, a common feature of many types of arthritis, had a minor significant effect in decreasing the prevalence of leisure walking but was no longer significant after adjustment for all studied characteristics. For the lower prevalence behavior of transportation walking, lower extremity joint pain had no significant associations with the outcome. It was somewhat surprising that lower extremity joint pain did not have stronger associations with either walking behavior for those with or without arthritis, especially given that lower extremity mobility limitation is a known and frequent limitation among people with arthritis (30). However, our measurement of lower extremity joint pain was dichotomous without assessment of pain severity, duration, or exact cause, so it is difficult to interpret the meaningfulness of these results. On the other hand, it is promising, from a public health perspective, to establish in a national sample that the presence of lower extremity joint pain does not necessarily represent a deterrent to walking or, more broadly, mobility.

Nevertheless, people with arthritis may have trouble interacting with their environment due to poor walkability, for example while using transportation for work (2). A study by Brittain et al demonstrated that 15% of people with arthritis reported their neighborhood was unsafe, 19% reported the sidewalks were bad, and 21% said that local and state laws do not facilitate being active (31). Improvements in neighborhood walkability that require physical improvements may be expensive (such as building curb cuts and fixing broken sidewalks), which can cause resistance to adoption. Local and state policies that facilitate physical activity, such as active commuting strategies and comprehensive street design, may improve perceptions of safety and encourage people, including those with arthritis, to increase their amount of walking.

The low prevalence of leisure and transportation walking among people with arthritis overall and by subgroups calls attention to the many specific audiences for the delivery of relevant messages regarding the attainable health benefits of walking. For nonwalkers or those who are not physically active in other ways, these messages could include recommendations to begin walking. For walkers, these messages could include suggestions to walk more and to meet recommended physical activity guidelines through walking for their arthritis and general health. Public health practitioners and other allied health professionals are ideally positioned to interface with receptive adults and can use findings from the present study and other studies to give context to encouraging messages about being active to people with arthritis.

For example, a combination of leisure and transportation walking may add up to achievement of physical activity recommendations and improvement of health outcomes. The most common transportation bout length reported among adults with arthritis was 10–15 minutes. Increasing the number of errands done on foot or combining transportation walking and use of public transportation (where available) to event or leisure destinations could increase walking overall. Since the majority of the 53 million people with arthritis are of working age (18–64 years) (30), walking to lunch, at lunch, or during breaks, when possible, might be a manageable way to fit additional bouts of walking into peoples' routines. Another bout of 10–15 or 16–25 minutes of leisure walking on most days per week could help people meet the aerobic physical activity guideline and expect to experience the observed improvements in pain, function, and mood which are associated with these levels of physical activity (10–15). Walking is a favored activity among people with arthritis (18,32), and it is likely that health communication messages stating that physical activity can be broken down in to 10–15 minute bouts could resonate with people with arthritis.

For those adults with arthritis who worry that an increase in walking will worsen their joint pain and arthritis, or who are unsure about how to walk safely with arthritis, evidence-based, community-delivered physical activity interventions (which educate participants about the safety and importance of exercise and teach joint-friendly techniques for people with arthritis) are a promising area of community-clinical linkages to manage and reduce arthritis effects (33). One of these programs focuses specifically on walking. Walk With Ease is a 6-week program that meets 3 times per week, is available in English and Spanish (*Camino Con Gusto*), and is led by trained leaders. Results of the program show significant improvements in disability, pain, fatigue, stiffness, self-efficacy, muscle strength, balance, walking pace, mood, and workplace limitations (15,34,35). While some interventions described above, such as a sidewalk policy, may have greater applicability depending on the area of residence (particularly where a community falls on the urban-rural continuum), Walk

with Ease is an evidence-based intervention focused on skill and behavior change that can be successfully applied in a group or individual setting.

This study is subject to several limitations. First, all variables were based on self-report, including the arthritis, walking, and physical activity measures. The case-finding question that was used to identify people with self-reported, doctor-diagnosed arthritis has been found to be sufficiently reliable and valid for public health surveillance purposes (36,37). Physical activity may be overestimated, likely due to recall and social desirability biases, which may also be the case with reports of walking (38). But it is unlikely that there is differential recall bias based on arthritis status and other variables used in this study. Second, these cross-sectional data describe patterns among those with and without arthritis but cannot be used to infer a causal relationship between arthritis status and walking behaviors. Third, the NHIS walking questions do not capture the intensity of walking. It is recommended that, for health benefits, walking should be of at least moderate intensity (~3.0 miles/hour) or equivalent to a "brisk" pace (1,2). Self-selected walking pace of inactive adults has been shown to be within this intensity and can be maintained for at least 10 minutes, suggesting that participant self-reports are likely in this range (39). Additionally, it was not possible to control for environmental factors that could affect walking such as street connectivity, crime, weather, etc., because the NHIS survey did not capture environmental factors. Also, due to small sample sizes, we were unable to examine potential interactions between subgroups in order to identify potential groups with very low prevalence of leisure and transportation walking.

Strengths of this study include the large, nationally representative sample of US adults with and without arthritis and the availability of a substantial number of health and descriptive variables in the survey. To our knowledge, this is the first nationally representative report of transportation walking among adults with arthritis and the first to use population-based data to provide arthritis-specific estimates on leisure walking among adults. Having information on both leisure and transportation walking allows us to extend our knowledge of walking behaviors among adults with arthritis and provide context by using a non-arthritis comparison group. This is important for helping to frame health communication messages aimed to increase walking among adults with arthritis.

In conclusion, less than 50% of adults with arthritis engage in leisure-time walking and less than 25% engage in transportation walking. Interventions to support or encourage walking may be most successful if they are targeted to address demographic groups as well as prevalence, average weekly walking minutes, or walking bout length distributions, as these measures have shown different associations with correlates and patterns depending on whether the outcome was in the leisure or transportation walking domain. Establishment of each of these 3 measures of walking behavior among US adults with and without arthritis provides insight into unique aspects of walking behavior that are important for surveillance. Multidimensional surveillance of walking is necessary for public health planning, intervention development, implementation, and evaluation, and for policymakers and other partners. Messages for clinicians and people with arthritis are that, in addition to organized community-delivered, evidence-based walking programs, individuals with arthritis can increase their total walking per week by increasing frequency, rather than duration, and can benefit in terms of meeting physical activity guideline recommendations and achieving long-term health goals through this easily accessible means of being active.

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. Hootman 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. Hootman, Theis, Barbour, Paul, Carlson.
Acquisition of data. Hootman, Theis, Barbour, Paul, Carlson.
Analysis and interpretation of data. Hootman, Theis, Barbour, Paul, Carlson.

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ACTIVITY AND THE RHEUMATIC DISEASES

Physical Activity Intervention in Primary Care and Rheumatology for the Management of Knee Osteoarthritis: A Review

Esther Waugh,[1] Lauren King,[2] Natasha Gakhal,[3] Gillian Hawker,[1] Fiona Webster,[2] and Daniel White[4]

INTRODUCTION

Knee osteoarthritis (OA) is a leading cause of functional limitation in older adults and is associated with serious cardiovascular events and early all-cause mortality (1–3). Clinical practice guidelines from international OA organizations recommend physical activity (PA) as an essential component of first-line management of knee OA (4–6). PA has been consistently shown to reduce pain and improve physical function in people with knee OA and has few contraindications (7,8). Moreover, PA, particularly if adopted early in the disease process, is important to protect against future functional limitation (9) and adverse health outcomes due to inactivity such as obesity, diabetes mellitus, and cardiovascular disease (10). Importantly, PA increases cardiorespiratory fitness in the face of increased risk of cardiovascular morbidity and mortality in individuals with knee OA. Even levels of PA below the published recommendations for the general population may protect against functional decline and increased mortality (11,12). Few patients with knee OA engage in PA, and the reasons for this inactivity are unclear. A meta-analysis published in 2013 showed that only 13% of participants with knee OA met current PA guidelines of at least 150 minutes per week of moderate to vigorous exercise (13).

Primary care physicians (PCPs) and rheumatologists can play a key role in promoting PA as an integral component of knee OA management. Although a recommendation from a physician is not the only determinant of whether a patient will participate in PA long-term, patients view medical doctors as credible and authoritative sources of health information and patients may, therefore, be particularly motivated to be physically active if it is recommended by their PCP or rheumatologist (14,15). In fact, specifically in patients with arthritis, receiving advice from a physician was a key predictor of participation in physical activity (16). As a first step towards developing PA interventions, it is important to know the extent to which PA recommendation is occurring in primary care and rheumatology and to understand the underlying barriers to PA recommendation. Targeting PCPs and rheumatologists for PA interventions is logical given the important influence these health professionals may have on people with OA because of their broad-based patient contact and high likelihood of providing care to this patient population. The aim of this review is to provide an overview of current practice regarding PCP and rheumatology prescribed PA intervention for the management of knee OA and to explore barriers to implementing PA intervention in primary and rheumatology care.

PATIENTS AND METHODS

PA has been defined as "any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level" (17). Exercise, which is a subcategory of physical activity, has been defined as being planned, structured, and repeated (17). For purposes of the current review, we will refer primarily to PA, with the knowledge that this definition includes exercise. PA intervention is defined as advising, counseling, recommending, or prescribing PA; it does not include referral to another health care provider such as a physiotherapist.

A Medline search was conducted from January 2000 to April 21, 2017. Medical subject headings (MeSH) key words included "physicians, primary care," or "family practice," or "physicians, family," "general practitioners" or "rheumatologists" or "primary care" or "general practice" and "osteoarthritis" or "arthritis" or "osteoarthritis, knee." To provide an overview of current practice, these search terms were combined with "exercise," "physical activity," "exercise prescription," "exercise counseling," "physi-

[1]Esther Waugh, BScPT, MSc, PhD, Gillian Hawker, MD, FRCPC: Women's College Hospital, and University of Toronto, Toronto, Ontario, Canada; [2]Lauren King, MD, Fiona Webster, PhD: University of Toronto, Toronto, Ontario, Canada; [3]Natasha Gakhal, MD, FRCPC, MSc: Women's College Hospital, Toronto, Ontario, Canada; [4]Daniel White, PT, ScD, MSc: University of Delaware, Newark.

Address correspondence to Esther Waugh, BScPT, MSc, PhD, Women's College Hospital, 76 Grenville Street, Toronto, Ontario, Canada M5S 1B2. E-mail: e.waugh@utoronto.ca.

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cal activity counseling," "guideline adherence," "practice guidelines," "quality of health care," "quality indicators, health care." To explore barriers to providing PA intervention, additional search terms used were "attitudes," "perceptions," and "barriers." References from relevant articles were manually reviewed.

Inclusion criteria were studies that reported clinical practice by PCPs or rheumatologists regarding PA intervention (as defined above) for knee OA across Europe, US, and Canada, published from the year 2000 and later, in order to represent current practice. Both quantitative and qualitative studies from the same time period describing barriers to PA intervention for adults in primary and rheumatology care were included and were not limited to people with knee OA, in order to identify both general nondisease-specific barriers and OA-specific barriers. Studies not specific to PCPs or rheumatologists, not specific to knee OA (for current practice search), or focused on exercise referral to other health professionals were excluded. Studies were limited to English. Once the initial search for studies of current practice was complete, there was a paucity of results for rheumatology practice; therefore the search time period for rheumatology studies was subsequently broadened to those published from 1996 and later.

Results of current practice studies were summarized descriptively by country because different methodologies were used across studies. Barriers to PA intervention were summarized by frequency of barriers reported and in a descriptive narrative review format because the results were descriptive and qualitative in nature.

RESULTS

The initial search yielded 848 abstracts, which were reviewed for relevance according to our inclusion criteria; 817 were excluded, leaving a total of 31 articles. An additional 36 articles were identified from a manual search of reference lists, providing a total of 67 articles available for detailed review. After full review, 45 articles were subsequently excluded, leaving a total of 22 articles included in this review; 11 articles described current practice of PCPs and rheumatologists and 12 articles described barriers to PA intervention (1 article described both current practice and barriers). (Figure 1).

Current practice regarding PA intervention. Eight studies described the practice of PCPs, including 1 study that also described rheumatology practice (18–25); an additional 3 studies described rheumatology practice (26–28). Different methodologies were used, including patient self-report by questionnaire (18,19), physician self-report by questionnaire (23,24,26) or in response to specific patient case scenarios (20,21,25), or chart review (28). Details of these studies are provided in Table 1. Overall, the studies show that the proportion of patients who said they received a recommendation for PA from their PCPs was 49–83%. PCPs who reported providing PA recommendation for knee OA varied widely from 9% to 87%. Overall, the majority of studies (5 of 8) reported either <50% of patients received a PA recommendation or <50% of PCPs provided a PA recommendation for their knee OA patients. The percentage of rheumatologists who provide PA recommendation is 47–58%. Together, these studies provide data on 7 countries. Across 5 European countries 49–83% of patients reported having been provided with information about exercise from their PCP (18,19). Additional studies in France and the UK found that 9–87% of PCPs said they would recommend exercise, based on case scenarios (20–22,25). There was only one study of PCPs in the US and it showed that less than one-third (30.2%) of physicians would provide exercise advice for a patient depicted in a video with symptoms of moderate-severe knee OA (25). Few studies provided information about the current practice of rheumatologists. Two US-based studies were conducted in the 1990s, well before current OA management guidelines. The results of one study showed that 54% of rheumatologists stated that they always or frequently recommended therapeutic exercise for knee OA patients (26). The second study (27) demonstrated that patients of rheumatologists were slightly more likely to have been recommended aerobic exercise than those receiving care from

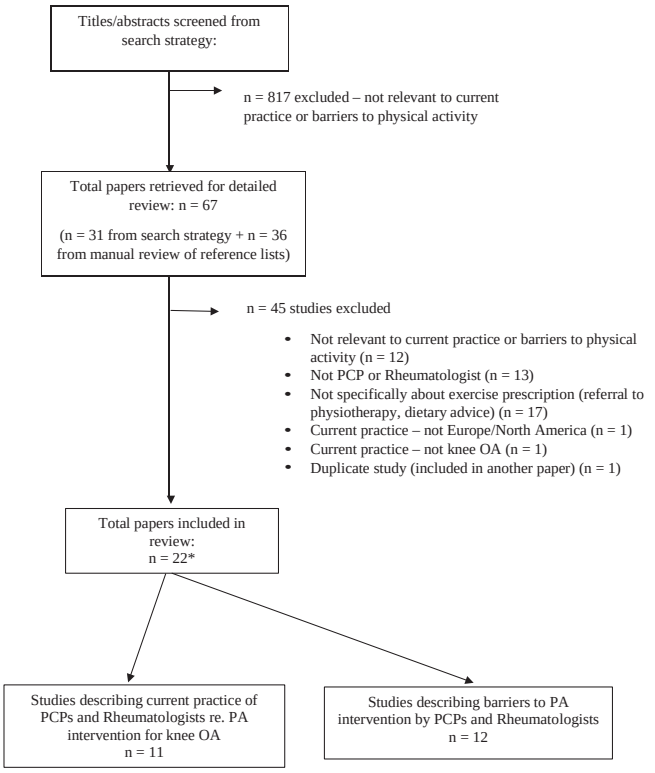

Figure 1. Flow chart demonstrating the search strategy.
*One study described both current practice and barriers to physical activity intervention. PCP = primary care physician; OA = osteoarthritis; PA = physical activity.

Table 1. Summary of studies of current practice regarding physical activity intervention for knee OA by PCPs and rheumatologists*

Study, country	Study population, (response rate)	Study methods	PA intervention findings
Primary care physicians			
Osteras et al (18), Denmark, Norway, Portugal, UK	354 adults ≥45 years of age PCP consultation with knee OA recorded in medical records (NA)	Patient self-report by questionnaire with set of QI items for OA care	Overall, 67% given "information about exercise"; Norway 83%, Denmark 53%, Portugal 65%, UK 66%
Osteras et al (19), Norway	351 adults recruited for larger population survey, clinically confirmed to have OA (58%)	Patient self-report by questionnaire with set of QI items for OA care	49% given "information about the importance of physical activity and exercise"
Cottrell et al (20), UK	835 PCPs chosen by random from database (17%)	Physician self-report by questionnaire that provided a clinical scenario of a patient with chronic knee pain	87% of PCPs would prescribe exercise for this patient
Bedson et al (21), UK	447 PCPs chosen by random sampling of 1,000 physicians from list of 37,000 registered doctors (45%)	Physician self-report by questionnaire that provided clinical scenario consistent with knee OA and choice of treatments including "advice on exercise"	66% of PCPs would "advise on knee joint exercises" for male OA patient and 76% for female OA patient
Chevalier et al (22), France	Questionnaires sent to 4,000 PCPs in France, completed by 3,491 (70%)	Physician self-report by questionnaire that provided clinical scenario consistent with knee OA presenting from mild to severe; multiple choice answers for therapies provided	9% of PCPs felt exercise was helpful in stage 1; <15% felt exercise was helpful at any stage
Richette et al (23), France	1,194 PCPs randomly selected from Cegedim registry participated and provided data on 1,570 patients with knee OA (16%)	Physicians asked to record data for 2 consecutive patients with symptomatic knee OA and complete questionnaire regarding mgmt.	PCPs prescribed exercise to 33.9% of these patients
Denoeud et al (24), France	967 PCPs randomly selected from database of physicians in France and provided data on 2,430 patients with knee OA (94%)	Physicians asked to record data for 3 consecutive patients with symptomatic knee OA and complete questionnaire regarding mgmt.	PCPs prescribed "physical exercise" to 48.7% of these patients
Maserejian et al (25), US	192 PCPs recruited from lists of licensed physicians in 6 states (NA)	Physicians randomized to view video vignettes of 2 patients (with sciatica or knee OA) and interviewed to determine their medical decisions regarding evaluation and mgmt.	30.2% of PCPs would "provide exercise advice" for knee OA patient
Rheumatologists			
Hochberg et al (26), US	594 rheumatologists randomly sampled from member roster of the ACR across regions of US (59%)	Rheumatologists completed questionnaire asking about preferences for use of various pharmacologic and nonpharmacologic methods for mgmt. of knee OA in patients	53.8% of rheumatologists "always" or "frequently" prescribed exercise
Mazzuca et al (27), US	419 patients followed for symptoms of knee OA by family doctor (n = 143), general internal medicine specialist (n = 75), or a rheumatologist (n = 201) (NA)	Patient self-report by questionnaire	56% of rheumatologists' patients advised to do aerobic activity and 31% isometric quadriceps vs. 52% and 12% of family doctor patients, respectively

(continued)

Table 1. *(Cont'd)*

Study, country	Study population, (response rate)	Study methods	PA intervention findings
DeHaan et al (28), Canada	105 patients randomly selected from 3 rheumatologists at teaching hospital (NA)	Chart review	Overall, exercise recommendation provided to 58% of patients; 2 rheumatologists recommended to 68%; 1 rheumatologist to 37%
Richette et al (23), France	225 rheumatologists randomly selected from Rheumatology Registry provided information on 251 patients with knee OA (12.7%)	Physicians asked to record data for 2 consecutive patients with symptomatic knee OA and complete a questionnaire regarding mgmt.	Rheumatologists prescribed exercise to 47.4%

* PA = physical activity; PCP = primary care physician (NOTE: In Europe/UK, PCPs are called general practitioners [GPs]); OA = osteoarthritis; QI = quality indicators; mgmt. = management; ACR = American College of Rheumatology; NA = not available.

a PCP (56% versus 52%, respectively), and rheumatologists were also more likely to provide specific exercise instruction such as quadricep strengthening (31% of rheumatologists versus 12% of PCPs). A chart review published in 2007 of patients who had received care from 3 rheumatologists at a hospital in Toronto, Canada showed that exercise recommendation was provided to 58% of patients (28). However, there was variability across the 3 rheumatologists, with 2 providing exercise recommendations to 67% of their patients while 1 rheumatologist only provided recommendation to 37%. In the most recent study conducted in France (2011), rheumatologists indicated that they recommended exercise to 47% of their knee OA patients versus PCPs who recommended it to only 36% of their patients (23).

Barriers to implementing PA intervention. A total of 12 studies included in this review addressed barriers to implementing PA intervention by PCPs (20,29–39). No studies that included rheumatologist-addressed barriers were found. Only 1 study directly addressed barriers to PA inter-

Table 2. Summary of studies of barriers to physical activity intervention by primary care physicians*

Study, country	Study population (response rate)	Study methods	PA intervention findings, key barriers (% of PCPs, if reported)
O'Brien et al (29), Canada	113 physicians who attended Exercise is Medicine Canada workshop (NA)	Self-reflection questionnaire completed prior to workshop	Barriers in order of impact: lack of patient interest/motivation, resources, time
Leemrijse et al (30), Netherlands	340 PCPs from random sample taken from Netherlands Health Services database (43%)	Questionnaire about perceived role in PA stimulation, referral for exercise, barriers, and motivators to giving PA advice	Limited patient motivation (44.4%), patient health status (34.1%), lack of time of PCP (26.2%), patient cultural/familial situation (15.9%), no thought of giving advice (11.2%)
Douglas et al (31), UK	376 PCPs from mailing list from Information Services Division, Scotland (47%)	Cross-sectional questionnaire survey regarding knowledge of PA recommendations, practice regarding PA advice, and associated attitudes	PCPs more likely than nurses to report lack of time as key barrier, that financial incentive might change practice, and that patients not motivated to follow advice
Puig Ribera et al (32), Spain†	145 PCPs randomly chosen from 7 Health Regions of Catalan Health System (overall, 58%)	Survey regarding behaviors, barriers (+ qualitative study regarding stage of change for PA promotion)	Lack of time, very limited training, not having PA protocols
Guo et al (33), US	110 family practice residents from 4 residency clinics in Texas (93.2%)	Questionnaire to assess behavioral counseling practices including PA	Major barriers identified were lack of the following: time (61.8%), patient interest (58.2%), available health educators (33.9%), systems promoting preventative care (33.9%), financial reimbursement (20%), effective patient educational material (17.6%)

(continued)

Table 2. *(Cont'd)*

Study, country	Study population (response rate)	Study methods	PA intervention findings, key barriers (% of PCPs, if reported)
Kennedy et al (34), Canada	330 PCPs randomly chosen from 6 provinces (61.1%)	Cross-sectional survey to assess confidence, current practice and barriers to exercise, counseling (list of 12 barriers provided)	Barriers rated most important: lack of time (65.7%), lack of exercise education in medical school (64.8%), guidelines on counseling (54.6%), personal knowledge (50.6%), patients not interested (49.7%), not paid enough (46.6%)
Petrella et al (35), Canada	362 PCPs identified from national directory of physicians representing 6 provinces across Canada (90.5%)	Questionnaire collected as phase 1 of RCT evaluating Step Test Exercise Prescription to assess current counseling behaviors, confidence, barriers	Key barriers in order of impact: inadequate time, lack of necessary skills and tools, lack of reimbursement
Abramson et al (36), US	84 PCPs randomly selected from AMA database (25%)	Cross-sectional survey on personal exercise habits, counseling practices, and barriers to counseling	Inadequate time (61%), inadequate knowledge (16%), patient disinterest (11%)
Persson et al (37), Sweden‡	15 PCPs from 16 health centers purposively selected (NA)	Focus groups to explore PCPs experiences and perspectives on prescribing PA using written prescription	Personal attitudes as potential barriers: role of PCP to counsel PA but not provide written prescription, skeptical about effectiveness of written prescription over verbal counseling, not comfortable prescribing due to lack of training/education
Bélanger et al, 2015 (38), Canada‡	9 PCPs selected from those who competed a web survey about prescribing PA (NA)	Individual interviews to identify barriers and enablers of written PA prescription in those who regularly prescribed vs. those who did not	No particular value seen in written prescription, lack of resources, fear of patients' rebuttal and non-compliance, PA prescription lower priority than other elements that need to be addressed
Patel et al (39), New Zealand‡	15 PCPs from Auckland region (NA)	Individual interviews to examine views and experiences with written prescription, "The Green Prescription"	Time constraint only barrier identified
Cottrell et al (20), UK	835 PCPs randomly selected from GP database (17%)	Cross-sectional questionnaire survey to identify factors that influence use of exercise for chronic knee pain using attitude statements, free-text questions, multiple response questions	Barriers/facilitators identified were perceived role in initiating exercise, beliefs about efficacy of exercise for knee OA, beliefs about their capability, and experience in prescribing exercise

* RCT = randomized controlled trial; AMA = American Medical Association. See Table 1 for additional definitions.
† Mixed methods utilized.
‡ Qualitative study.

vention specifically for the management of knee OA (20). Nine studies used questionnaires to identify key barriers (20,29–36), and 3 studies used qualitative methods to examine attitudes and behaviors regarding exercise prescription (37–39). (Table 2)

Numerous barriers were identified across these studies. The most commonly reported barriers were lack of time (reported in 9 of 12 studies), lack of patient motivation/compliance, lack of resources (including the absence of specific PA protocols and guidelines, educational materials for patients), lack of knowledge and training (each reported in 6 of 12 studies), and lack of financial reimbursement (reported in 4 of 12 studies). Lack of time was reported the most frequently and was also most often cited as the most important barrier (Table 3).

The 3 qualitative studies included in this review addressed the use of written exercise prescriptions with detailed recommendations including intensity, duration, and activity type. In addition to lack of time (37,39), another key barrier identified was that PCPs did not feel that a written prescription had greater efficacy over verbal counseling (37,38). Additionally, a lack of training was

Table 3. Key barriers to PA intervention by number of times reported and relative importance*

Barrier	No. of studies (n = 12)	No. of studies in which barrier is ranked in top 3 of importance	References
Time	9	9	(29–36,39)
Lack of patient motivation, compliance, or interest	6	5	(29,31,33,34,36,38)
Lack of resources including PA protocols, educational materials	6	4	(29,32–35,38)
Lack of knowledge, experience, or training	6	4	(20,32,34–37)
Lack of financial reimbursement	4	2	(31,33–35)
Patient health status	1	1	(30)
Prescription of PA not perceived as "normal" role of PCP	2	0	(20,30)
PCP beliefs about efficacy of exercise for OA	1	Not ranked	(20)

* Only 9 of 12 studies provided ranking of barriers. See Table 1 for definitions.

particularly emphasized because PCPs felt that they were not adequately trained or experienced in providing detailed exercise prescription, and while they felt they had a role in PA counseling, other health care providers such as nurses or physiotherapists were more skilled at prescribing PA (37).

While these previous studies offer important insights into factors influencing PA interventions in primary care, providing PA interventions to patients with knee OA may have unique disease-specific barriers. The current review included 1 study, by Cottrell et al (20), which sought to determine key influences associated with PCP-reported use of exercise intervention, explicitly, for patients with clinical knee OA. The factors most strongly associated with including or excluding PA into PCPs' management of knee OA in a patient were their beliefs about their role in initiating exercise, beliefs about the efficacy of exercise for patients with knee OA, moral norm (agreement that they should prescribe exercise to all knee OA patients), and beliefs about their own capabilities. Time limitations, patient preferences, and disease-related factors such as symptom and x-ray severity were less influential on PCP use of exercise intervention.

DISCUSSION

This review provided details on the clinical practice patterns of PA recommendations for people with knee OA in primary care and rheumatology. Overall, results indicated that the recommendation of PA is suboptimal, as the majority of studies reported that <50% of PCPs and rheumatologists make this recommendation to individuals with knee OA. Addressing the practice gap of recommending PA provides an opportunity for improving OA care and ultimately, the health and quality of life of those with OA.

This gap in practice may be due to the barriers to PA intervention identified in the current review. Overall, we found that lack of time, patient compliance, resources, training, and reimbursement were the most important barriers to PCPs' administration of PA intervention. These 5 barriers were also identified in a prior review by Hébert et al (40), but they did not rank the importance of the barriers, and their review was not limited to PCPs but included multiple types of primary care providers. The key barriers identified in the current review were not necessarily specific to the delivery of PA for the management of knee OA but might pose even greater obstacles for this patient population. OA patients often present with comorbidities, thus adding to time constraints where there are competing health priorities that need to be addressed during a consultation. In fact, a barrier to overall management of OA has been found to be a perception among health care providers that OA is less important as a comorbidity and leads to prioritization of other health conditions (41). As well, specific training and resources for prescribing PA that is appropriate for patients in various stages of knee OA is lacking. This may be a particularly critical barrier as patients with arthritis have indicated that receiving concrete details about the amount and type of activity that is safe and appropriate for them is a key factor in initiation and maintenance of exercise (42).

Future research should focus on development and evaluation of the best ways to address these barriers and facilitation of PA intervention for OA within primary care. Most PCPs consider PA to be important for health and that they have a role in promoting PA to their patients (40). However, holding these positive attitudes are not predictive of PA prescribing behavior (43) and specific, practical solutions need to be developed, implemented, and tested in clinical practice. Other studies have proposed strategies to enhance general PA counseling in primary care (44,45). These strategies include organizational prioritization and support of PA counseling as an essential service, system-wide structural supports such as use of electronic medical records to assist in integration of PA into patient visits, and inclusion of exercise prescription as an essential component in medical school curricula and continuing education.

In considering specific strategies, studies have shown that the first step in promotion of PA in primary care is the assessment of PA and procedures need to be in place to ensure assessment is standard practice (46,47). The Exercise is Medicine (EIM) initiative, started by the American College of Sports Medicine in conjunction with the American Medical Association, has recommended that PA assessment be considered a "vital sign" and become a standard part of a medical consultation (48). Kaiser Permanente, one of the largest health care providers in the US, incorporated a brief PA assessment tool into their electronic health records (EHR). The assessment involves asking 2 questions about current PA level, usually by a medical assistant at the start of the clinic visit, which is then viewed and discussed by the PCP. Kaiser Permanente reported that this action alone resulted in increased exercise counseling by physicians (46).

To address barriers related to time constraints, patient motivation, and resources, investigators in the UK have developed and tested "very brief interventions" (VBI) for physical activity in primary care. To date, their research has shown that the most promising VBI in terms of efficacy, feasibility, and cost is the pedometer VBI. This tool is deliverable within 5 minutes and involves a brief face-to-face consultation discussing the benefits of increasing PA, a goal of 10,000 steps/day, instructions in pedometer use, and a step chart to set and track daily step goals. Patients are also provided with an information booklet (49,50).

These strategies can be applied to PA intervention in OA management. For example, a brief written prescription for a walking program, easily accessible from an EHR system, may be an effective way to simplify the recommendation for both physicians and patients while also being time efficient. Walking has been shown to be effective in decreasing pain and improving quality of life in patients with OA (51) and suitable for most patients including those with cardiovascular disease and diabetes, which are common comorbid conditions (52). However, a specific protocol that can be individualized for OA patients has not been developed and is a necessary next step. Given the stated importance by patients for concrete and tailored advice, and the reported concerns of physicians regarding lack of knowledge about detailed exercise prescription, the development of a PA/exercise prescription specific to knee OA is required, including starting dose, titration, and pain management.

It is certainly not feasible for PCPs to prescribe exercise programs for complex patients with OA. Therefore, clinics need to develop a reliable exercise referral community, such as physiotherapists or exercise professionals certified by EIM to provide PA programs for patients with comorbidities. However, because these health care professionals may not be accessible to every patient, it is our view that PA counseling by PCPs remains imperative.

Given the evidence described above, we believe that modest changes that address the key barriers to PA intervention such as the addition of regular brief screening of patients for PA levels, the development and implementation of a simple walking protocol for patients with knee OA (potentially using a pedometer), or the addition of easily accessible PA assessment tools and protocols in EHRs, could generate increased PA intervention in primary care and ultimately result in more individuals with knee OA increasing their activity level. We suggest that potential interventions be tested in real-life situations through pragmatic trial methodology (53) or by using a quality improvement (QI) approach where changes are implemented incrementally and iteratively with repeated testing and revisions to improve patient care (54). The current review exposed the sparsity of data about rheumatology practice patterns and specific barriers and facilitators to PA intervention among patients with knee OA. This is a notable knowledge gap, given that rheumatologists are considered experts in the management of OA. A clearer picture of rheumatologists' practice patterns is important for a comprehensive understanding of current delivery of OA care.

The limitations of this review are the broad inclusion of studies with differing methodologies, and the fact that studies were not excluded based on quality criteria. Different methodologies may have contributed to the varying practice patterns reported, and patient and physician self-report may not reflect actual clinical practice. However, the purpose was to provide an overview of current practice patterns, and barriers and broad inclusion criteria were necessary to meet this objective. As well, it is acknowledged that since the current review was not a systematic review, authors' biases may have influenced the selection and interpretation of the results.

In conclusion, clinical guidelines recommend PA as a key component of knee OA management. Yet, there is a gap between what is recommended in guidelines and what is happening in clinical practice. This is an important gap to address, because PA has been shown to reduce pain, improve function, and protect against morbidity and all-cause mortality related to physical inactivity. While this gap exists across management of all chronic diseases, it is particularly consequential for OA given the absence of disease-modifying drugs in its treatment regimen. And while PA interventions by PCPs and rheumatologists are not the only solution to increasing PA, they are an important element given their pivotal role in the overall management of knee OA. Efforts should focus on development and evaluation of strategies to address key barriers to PA intervention within primary care and rheumatology practices.

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. Waugh 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. Waugh, King, Gakhal, Hawker, Webster, White.

Acquisition of data. Waugh.

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ACTIVITY AND THE RHEUMATIC DISEASES

Physical Activity and Worsening of Radiographic Findings in Persons With or at Higher Risk of Knee Osteoarthritis

Prakash Jayabalan, Masha Kocherginsky, Alison H. Chang, Gerald W. Rouleau, Kimberly L. Koloms, Jungwha Lee, Dorothy Dunlop, Rowland W. Chang, and Leena Sharma

Objective. The benefits of physical activity among persons with or at higher risk for knee osteoarthritis are well established. However, activity levels in this population are low, in part due to concern that activity will damage the knee joint. We hypothesized that sedentary and moderate-vigorous physical activity are each associated with greater risk of radiographic worsening of knee OA.

Methods. In Osteoarthritis Initiative participants with or at higher risk for knee OA enrolled in an accelerometer substudy at 48 months (study baseline), physical activity was measured by a uniaxial accelerometer (ActiGraph GT1M). Radiographic progression was defined as any 48 month to 96 month worsening of Kellgren/Lawrence (K/L) grade scores. All analyses were knee-level; we used multivariable logistic regression with generalized estimating equations, adjusting for key covariates.

Results. Of the 1,206 participants, 631 (52%) were female, the mean ± SD age was 64 ± 9 years, and mean ± SD body mass index (BMI) was 28 ± 5. The mean ± SD average daily sedentary activity was 602 ± 86 minutes, average daily light activity was 284 ± 75 minutes, and average daily moderate-vigorous activity was 20 ± 20 minutes. In 1,978 knees, 267 (14%) had worsening of K/L grade scores. In the multivariable model, age, sex, BMI, and pain, were associated with K/L grade worsening, but neither sedentary activity (adjusted odds ratio [OR] 0.99 [95% confidence interval (95% CI) 0.97–1.01]) nor moderate-vigorous activity (adjusted OR 1.00 [95% CI 0.91–1.09]) were associated with K/L grade worsening.

Conclusion. In persons with or at higher risk for knee OA, age, sex, BMI, and pain, but not objectively measured average daily minutes of sedentary or moderate-vigorous activity, were associated with subsequent worsening of K/L grade. Whether findings differ in persons with more severe knee OA and/or engaged more frequently in moderate-vigorous activity should be examined in future studies.

INTRODUCTION

The benefits of physical activity for overall health, wellness, and prevention of poor outcome in the general population and in those with chronic conditions including knee osteoarthritis (OA) are well established. There is evidence that physical activity is specifically associated with a reduced risk of subsequent function decline (1,2) and disability (3,4) in persons with or at higher risk for knee OA. However, the proportion of these individuals engaging in the recommended levels of physical activity is very low (5,6). This low level of physical activity relates in part to concerns that physical activity will damage the knee joint (7–9).

With few exceptions (10,11), longitudinal studies that evaluated the association between physical activity and worsening of

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Prakash Jayabalan, MD, PhD, Masha Kocherginsky, PhD, Alison H. Chang, DPT, MS, Gerald W. Rouleau, MS, Kimberly L. Koloms, MS, Jungwha Lee, PhD, Dorothy Dunlop, PhD, Rowland W. Chang, MD, MPH, Leena Sharma, MD: Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Address correspondence to Leena Sharma, MD, Division of Rheumatology, Feinberg School of Medicine, Northwestern University 240 E. Huron, M300, Chicago, IL 60611. E-mail: L-Sharma@northwestern.edu.

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SIGNIFICANCE & INNOVATIONS

- Among persons at higher risk of knee osteoarthritis, the proportion engaging in recommended levels of physical activity is low, in part due to concerns that such activity will damage the knee. The available literature concerning physical activity and worsening of knee OA disease features is limited in most studies by reliance on patient self-report of activity, which is vulnerable to reporting bias and imprecise recall. This study is the largest accelerometry study to date in this population and represents the best current opportunity to address these questions.
- Accelerometry provides an objective and valid means to assess both potentially deleterious extremes of activity intensity, i.e., sedentary activity and moderate-vigorous activity. To our knowledge, this is the first report of an investigation of the association between sedentary activity and structural outcome (by radiographs or magnetic resonance imaging).
- We uniquely examined physical activity objectively assessed using accelerometry, including knees at all baseline stages of disease.

radiographic knee OA have relied on self-report to quantify physical activity (12–18) however; self-report is vulnerable to reporting bias and imprecise recall. Accelerometry provides an objective method to quantify physical activity intensity and duration in daily-life settings. Radiographic worsening is a long established, widely accepted, and easily interpreted means to evaluate disease worsening in the setting of knee OA.

In theory, both extremes of activity (prolonged inactive periods or periods of heavy activity), may be deleterious to joint tissues (19–22). At a cellular level, articular cartilage health, proteoglycan content, and tissue stiffness require functional loading for healthy joints (22–29). Temporary or permanent periods of immobilization may be associated with cartilage thinning (30–32). To our knowledge, no previous study has evaluated the association between sedentary behavior and radiographic worsening of knee OA, perhaps due to the inadequacy of self-report to assess sedentary behavior.

The Osteoarthritis Initiative (OAI), a comprehensive, state-of-the-art longitudinal cohort study of persons with or at higher risk for knee OA, incorporated objective physical activity assessment in an accelerometry substudy, and therefore is an ideal setting to evaluate these questions. The objective of our study was to examine the association between objectively measured physical activity at baseline and radiographic worsening of knee OA over a 4-year period in OAI participants with or at higher risk for knee OA (e.g., older age, overweight/obese, prior knee injury, prior knee surgery, family history of knee replacement, hand OA, or occupational risk factors as detailed below). We hypothesized that objectively measured sedentary and moderate-vigorous physical activity at baseline are each associated with a greater risk of radiographic worsening of knee OA.

PATIENTS AND METHODS

Sample. The OAI is a prospective, observational cohort study including 4,796 men and women, ages 45–79 years, with or at increased risk of developing symptomatic, radiographic knee OA, who were enrolled at 1 of 4 sites (Baltimore, Maryland; Columbus, Ohio; Pittsburgh, Pennsylvania; and Pawtucket, Rhode Island). Adults eligible for the OAI were required at enrollment to have symptomatic knee OA defined as the presence of pain, aching, or stiffness in at least 1 knee on most days for at least 1 month during the past 12 months, a definite tibiofemoral osteophyte (Kellgren/Lawrence [K/L] grade ≥2 or characteristics that placed them at increased risk for developing symptomatic knee OA (e.g., overweight [defined using sex- and age-specific cutpoints for weight], prior knee injury causing difficulty walking for a least 1 week, history of any knee surgery, family history of a total knee replacement for OA in a biologic parent or sibling, Heberden's nodes, repetitive knee bending at work or outside work, or age 70–79 years). The OAI excluded individuals with rheumatoid or inflammatory arthritis; severe joint space narrowing in both knees on the baseline knee radiograph, or unilateral total knee replacement and severe joint space narrowing in the other knee; bilateral total knee replacement or plans to have bilateral knee replacement in the next 3 years; inability to undergo a magnetic resonance imaging (MRI) examination (inability to fit in the scanner or in the knee coil [including men weighing ≥285 pounds and women ≥250 pounds]); positive pregnancy test, inability to provide a blood sample; use of ambulatory aides other than a single straight cane for >50% of the time during ambulation; comorbid conditions that might interfere with the ability to participate in a long-term study; and current participation in a double-blind randomized trial.

A total of 2,679 participants enrolled in an OAI accelerometer substudy, which began at the 48-month follow-up evaluation, (baseline for our study). For the current study, we excluded participants with <4 valid days of physical activity monitoring and end-stage OA at baseline (i.e., using alternative definitions of end-stage disease, 48-month lateral or medial joint space narrowing grade 3 or K/L grade 4). We used follow-up data through the 96-month study visit. Institutional review board approval was obtained at each of the participating sites.

Physical activity. Trained OAI research personnel gave participants scripted in-person instructions on how to wear the ActiGraph GT1M accelerometer (on a belt at the natural waistline

on the right hip in line with the right axilla for 7 consecutive days from the time of arising in the morning until retiring, except during water activities). Accelerometer output is an activity count, which is the weighted sum of the accelerations measured over a minute, where the weights are proportional to the magnitude of acceleration. Non-wear periods were defined as ≥90 minutes with zero activity counts (allowing for 2 consecutive interrupted minutes with counts ≤100). Accelerometer data included ≥4 valid monitoring days for each participant. A valid day was defined as ≥10 wear hours in a day, as required for reliable estimates of physical activity (33). Intensity thresholds on a minute-by-minute basis developed by Troiano et al (33) and used by the National Cancer Institute were applied to identify sedentary activity (0–99 counts/minute), light intensity (≥100 counts/minute and <2,020) and moderate to vigorous intensity (≥2,020 counts/minute) activity. Average daily minutes spent in sedentary or moderate-vigorous intensity activity were used in primary analyses.

Outcome. Worsening was defined as any increase in K/L grade between 48 months and 96 months, (i.e., either by 72 months or by 96 months). Knee radiographs in the OAI were taken using the posteroanterior fixed-flexion weight-bearing protocol (34,35) with a SynaFlexer (Synarc) frame positioner. K/L grade was assessed by 2 experts in centralized readings at Boston University (36), blinded to each other's reading, hypotheses, and all other data (37). A third reader adjudicated any disagreements on K/L grade ≥2 versus K/L <2 at any time point, and also adjudicated any disagreement on change in K/L between any time points (36). It is widely accepted that knee OA begins before the radiographic definition of knee OA (K/L grade ≥2), but it is not clear at what point a high-risk state becomes disease. By including all knees that could worsen (i.e., K/L grade <4), we capitalized on the strength of the OAI in capturing the full spectrum of baseline disease severity, not one that is truncated at K/L grade 2.

Covariates. In the OAI study, body weight was measured using a standard balance beam scale, with the subject in lightweight clothes, with empty pockets, and without shoes or any heavy jewelry (details available at URL: http://oai.epi-ucsf.org/datarelease/operationsManuals/WeightV1_0p.pdf). Height was measured using a wall-mounted stadiometer, with the subject barefoot or wearing thin stockings or socks (details available at URL: http://oai.epi-ucsf.org/datarelease/operationsManuals/HeightV1_0p.pdf). Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Race was assessed by self-report and analyzed as nonwhite versus white (reference group). Knee pain was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subcale (38), adapted by the OAI to score pain separately for each knee. Knee injury was defined as ever injured either knee badly enough to limit ability to walk for at least 2 days, prior to study baseline versus no injury (reference group). Knee surgery was defined as having had any knee surgery or arthroscopy prior to study baseline versus no surgery (reference group). In the OAI, standing bilateral full-limb radiographs were acquired either at 12 months or 24 months (35). The hip-knee-ankle angle (i.e., the OAI variable HKANGJD) was calculated from 3 landmarks (39), as the angle subtended between the line through the femoral

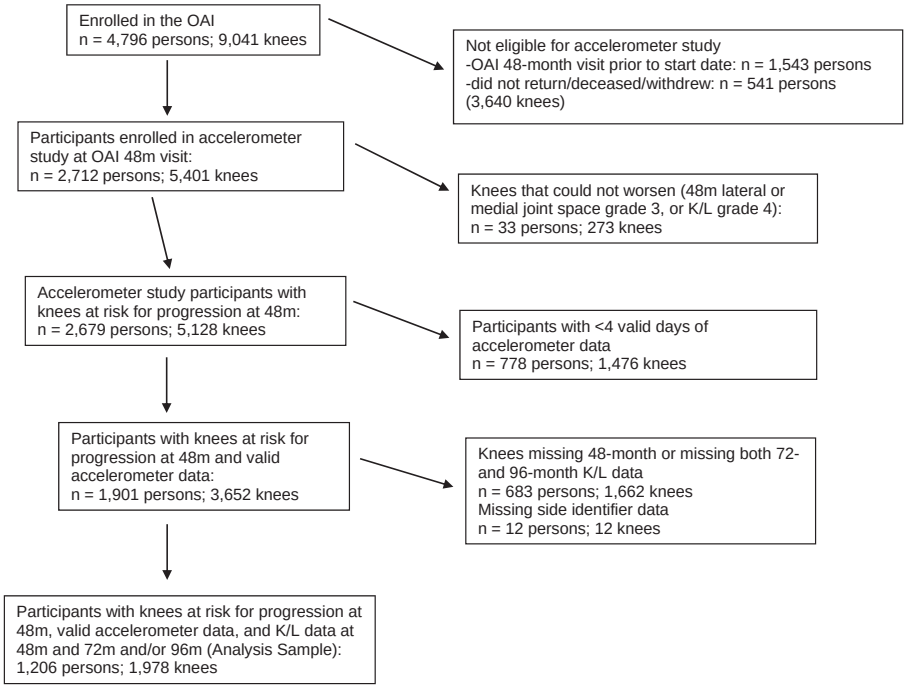

Figure 1. Derivation of analysis sample.

head and knee centers and the line through knee and tibiotalar joint centers, with varus as negative and valgus as positive (39).

Statistical Analysis. Person-level and knee-level variables were summarized using descriptive statistics. Person-level continuous variables were compared between groups using a 2-sample *t*-test, and categorical variables were compared using chi-square test. Continuous knee-level variables were compared between groups using a random-effects model with person as the random effect, and categorical variables were compared using the Cochran-Mantel-Haenszel test. Correlation between average daily activity counts spent in sedentary or moderate-vigorous activity type was assessed using Pearson's correlation coefficient (r).

Multivariable generalized estimating equations (GEE) logistic regression models were used to examine the effect of physical activity at baseline on subsequent progression, adjusting for other baseline demographic and clinical characteristics. The outcome variable of radiographic knee OA worsening was defined as an increase of at least 1 K/L grade at either the 72- or the 96-month visit. GEE models account for the within-subject correlation between knees, and use all available person-level and knee-level data. Three types of models were fitted: model 1 included only key baseline variables (age, sex, and BMI); model 2 examined the effect of sedentary and moderate-vigorous activity adjusted for covariates in model 1 and average daily wear time; and model 3 additionally adjusted for race and potential confounders, knee injury, knee surgery, and WOMAC pain. Linearity constraints and the need to control for wear time precluded the further addition of light activity into these models. These three models were fitted in order to first obtain the estimated effects of the usual risk factors on radiographic worsening in the study sample (model 1), as well as estimated effects of the different physical activity types adjusted for these factors (model 2), and both demographic and clinical (model 3) factors. Odds ratios (ORs) and their associated 95% confidence intervals (95% CIs) are presented for each of these models. Analyses were performed using SAS software, version 9.4.

RESULTS

Figure 1 depicts the derivation of the analysis sample, which included 1,206 participants who contributed 1,978 knees. The characteristics of the participants at study baseline are shown in Table 1. The main reasons for study exclusion in the 2,679 accelerometry substudy participants were having <4 valid days of physical activity monitoring and missing ≥1 of the radiographic assessments. Participants who were eligible for the accelerometer substudy and had knees at risk for worsening but were excluded from the study (n = 1,473) were older, were more likely to be female and African American, and had a higher BMI and a higher rate of prior surgery. The rate of prior knee injury was similar between these groups. Baseline knee-level characteristics of these participants included greater pain, higher K/L grade disease, and fewer knees with a neutral alignment.

The average wear time in the study sample was mean ± SD 14.9 ± 1.3 hours per day. Consistent with other studies, the majority of time was spent in sedentary activity, followed next by light activity. Little time was spent in moderate-vigorous activity (mean ± SD 20.0 ± 20 minutes per day). Distributions of average daily minutes spent in sedentary, light, and moderate-vigorous activity for the full study sample are shown in Figure 2. The average daily minutes spent in activity was similar between men and women (Figure 3). The correlation between sedentary and moderate-vigorous activity was low (r = -0.13).

Radiographic worsening was observed in 267 (14.0%) of 1,978 knees. Results from GEE logistic regression models with different sets of predictors are shown in Table 2. Age, female sex, and BMI were significantly associated with OA worsening (model 1). Neither sedentary activity time ($P = 0.17$) nor moderate-vigorous activity time ($P = 0.63$) at baseline was associated with OA worsening when adjusting for age, sex, BMI, and wear time (model 2), and when additionally adjusting for knee injury, knee surgery, and WOMAC pain scores (model 3). We repeated these models in secondary analyses including knees with radiographic OA (K/L grade ≥2) at baseline; neither sedentary (adjusted OR 1.03 [95% CI 0.98–1.08]) nor moderate-vigorous (adjusted OR 0.84, [95% CI 0.67–1.07]) activity at baseline was associated with OA worsening, adjusting for age, sex, BMI, wear time, knee injury, knee surgery, and WOMAC pain.

In sensitivity analyses using the Freedson cut-points for activity intensity, findings were similar. We also considered whether there was an interaction between sex and time spent at each activity level in model 3. The interaction was not statistically significant for sedentary activity. For moderate-vigorous activity, the interaction was marginally statistically significant (P = 0.046), but the estimated ORs for OA worsening per 10-minute increase in moderate-vigorous activity were not statistically significant among women (OR = 1.07; $P = 0.21$) or among men (OR = 0.93; $P = 0.21$). Interactions between K/L grade at baseline and time spent in sedentary or moderate-vigorous activity were not significant when added to model 3.

DISCUSSION

In persons with or at higher risk for knee OA, age, sex, BMI, and pain, but not objectively assessed average daily minutes of sedentary or moderate-vigorous intensity physical activity, were associated with subsequent worsening of radiographic knee OA. There is abundant evidence of the health benefits of reducing sedentary time and increasing physical activity; our findings do not reveal any evidence that physical activity, at least as engaged in by the study participants, is detrimental to joint structure.

Our findings are in keeping with previous longitudinal studies of self-reported physical activity and radiographic outcome. Par-

Table 1. Person-level and knee-level characteristics at study baseline*

Characteristics	Included†	Excluded†	*P*
Person-level			
Age, mean ± SD	64.1 ± 9.0	66.1 ± 9.2	<0.001
Age group, no. (%) years			
45–54	195 (16.1)	181 (12.3)	<0.001
55–64	455 (37.7)	474 (32.2)	
65–74	349 (28.9)	482 (32.7)	
≥75	207 (17.2)	335 (22.8)	
Sex, no. (%)			
Male	575 (47.7)	645 (43.8)	0.04
Female	631 (52.3)	828 (56.2)	
BMI, mean ± SD	28.0 ± 4.6	29.2 ± 5.1	<0.001
BMI, no. (%)			
<25.0	343 (28.4)	320 (21.7)	<0.001
≥25.0 and <30.0	489 (40.6)	547 (37.2)	
≥30.0	374 (31.0)	605 (41.1)	
Race, no. (%)			
African American	140 (11.6)	304 (20.7)	<0.001
White	1,048 (86.9)	1,119 (76.1)	
Asian	6 (0.5)	13 (0.9)	
Other non-white	12 (1.0)	35 (2.4)	
Any knee injury prior to baseline, no. (%)			
Yes	369 (30.6)	483 (33.3)	0.14
No	837 (69.4)	969 (66.7)	
Any knee surgery prior to baseline, no. (%)			
Yes	163 (13.5)	271 (18.7)	0.004
No	1,043 (86.5)	1,181 (81.3)	
Activity, mean ± SD (minimum–maximum) minutes			
Sedentary	601.5 ± 86.4 (241.4–849.6)	594.1 ± 90.5 (342.3–842.3)	0.07
Light	283.8 ± 74.7 (42.3–545.1)	277.0 ± 84.0 (62.5–647.0)	0.01
Moderate-vigorous	20.0 ± 20.0 (0.0–142.9)	14.8 ± 17.3 (0.0–136.1)	<0.001
Average daily wear time, mean ± SD	14.9 ± 1.3	14.6 ± 1.5	<0.001
(minimum–maximum) hours	(10.6–19.5)	(10.25–19.9)	
Knee-level			
Baseline WOMAC pain, mean ± SD	1.4 ± 2.5	2.1 ± 3.1	<0.001
Baseline K/L, no. (%)			
0	1,122 (57)	708 (25)	<0.001
1	550 (28)	329 (12)	
2	199 (10)	1,129 (40)	
3	107 (5)	650 (23)	
Baseline alignment, no. (%)			
Neutral	873 (49.3)	1,209 (43.5)	<0.01
Varus	692 (39.1)	1,145 (41.2)	
Valgus	207 (11.7)	424 (15.3)	

(Continued)

Table 1 *(Cont'd)*

Characteristics	Included†	Excluded†	*P*
Radiographic progression, baseline to 4-year follow-up, no. (%)			
Full sample	267 (14)	NS‡	NS‡
Men	102 (11)		
Women	165 (15)		

* BMI = body mass index; WOMAC = Western Ontario and McMaster Universities Osteoarthritis index; K/L = Kellgren/Lawrence grade. Most common reasons for being excluded were having <4 valid days of physical activity monitoring or missing radiographic outcome data for 48-month assessment or for both 72-month and 96-month assessment.
† Person-level included subjects (n = 1,206), excluded subjects (n=1,473); knee-level included knees (n = 1,978), excluded knees (n = 3,150).
‡ NS = Not shown because <20% of the sample had data to determine frequency of radiographic progression.

ticularly significant among these is the Framingham study, in which habitual physical activity (hours at various levels of activity) uniquely assessed at 2 time points, did not predict knee OA (12). A case–control study of subjects ages ≥55 years revealed no association between knee OA and lifetime leisure activities including walking, cycling, gardening, dancing, and outdoor sports (13). In a longitudinal study of the Chingford cohort, physical activity, assessed at baseline in categories of walking, job, and sport, was not linked to incident knee OA (14). The MOST (Multicenter Osteoarthritis) Study and OAI participants at higher risk for knee OA who were in the highest quartile of physical activity (assessed at baseline by the Physical Activity Scale for the Elderly) stratified by sex were not at higher risk for developing radiographic knee OA (15). Meeting Department of Health and Human Services physical activity guidelines was not associated with incident knee OA in middle-aged or older adults in the Johnston County Osteoarthritis Project (16).

Our findings are in keeping with the few previous studies that utilized objective measures of physical activity. In the MOST Study, in persons at higher risk or with mild OA, there was no association between daily walking, measured objectively using a StepWatch or with time spent walking at a moderate to vigorous intensity at the 60-month visit and radiographic progression by the 84-month visit (10). In OAI participants at higher risk of knee OA but free of the outcome of interest, ≥150 minutes per week of moderate-vigorous physical activity was not associated with incident radiographic knee OA, symptomatic knee OA, or joint space narrowing versus <10 minutes of moderate-vigorous activity per week (11). Longitudinal studies using MRI-based outcomes have also mostly relied on self-reported physical activity (40–44), with some exceptions (10,45); these studies have had mixed results.

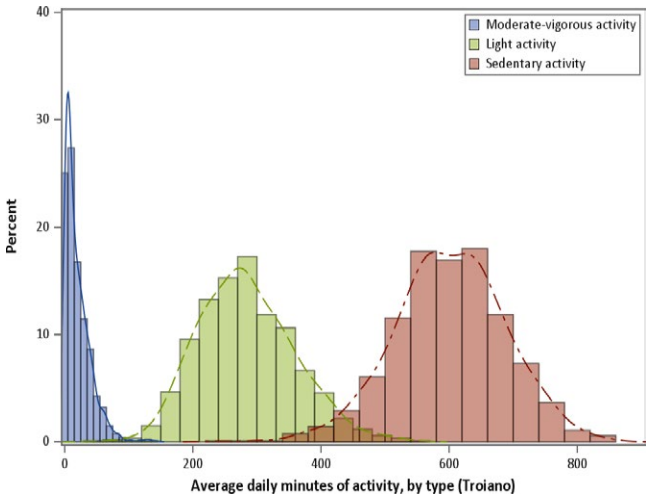

Figure 2. Distribution of average daily minutes of physical activity. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23756/abstract.

It is believed that articular or peri-articular abnormalities in knees without OA may increase the physical activity-associated risk of incident OA, and that abnormalities due to OA itself may increase the activity-associated risk of disease progression. Similar to our study and to the studies described above, it is likely that most participants were not involved in heavy activity. Previous studies that have sought to specifically examine heavy activity have had somewhat mixed results. In the Framingham study, involvement in more than 4 hours per day of heavy physical activity assessed at mid-study was associated with increased odds of developing knee OA between 2 examinations that occurred 8 years apart; the greatest risk was in the top BMI tertile (17). Moderate or light physical activity, number of blocks walked, or number of flights of stairs climbed daily were not associated with increased risk. In contrast, a subsequent study showed neither recreational walking, jogging, frequently working up a sweat, or high activity levels relative to peers by self-report at baseline altered the risk of knee OA or joint space loss, even in persons with higher BMI (18).

Although our findings are reassuring, uncertainty remains. Because our study required longitudinal radiographic readings, the sample of the current study only included 63.4% of the accelerometry substudy sample with 4–7 days of valid monitoring. Comparison of attributes to the study sample of persons and knees who were eligible but were not included, revealed small but potentially important differences in BMI (higher), race (higher proportion African American), previous knee surgery (more frequent), light activity (lower), and moderate-vigorous activity (lower), pain (greater), disease severity (worse), and malalignment (worse). Reasons for exclusion were a large number of missing baseline radiographic assessments, which made it impossible to assess radiographic progression. Since it is impossible to know what impact the inclusion of these individuals would have had

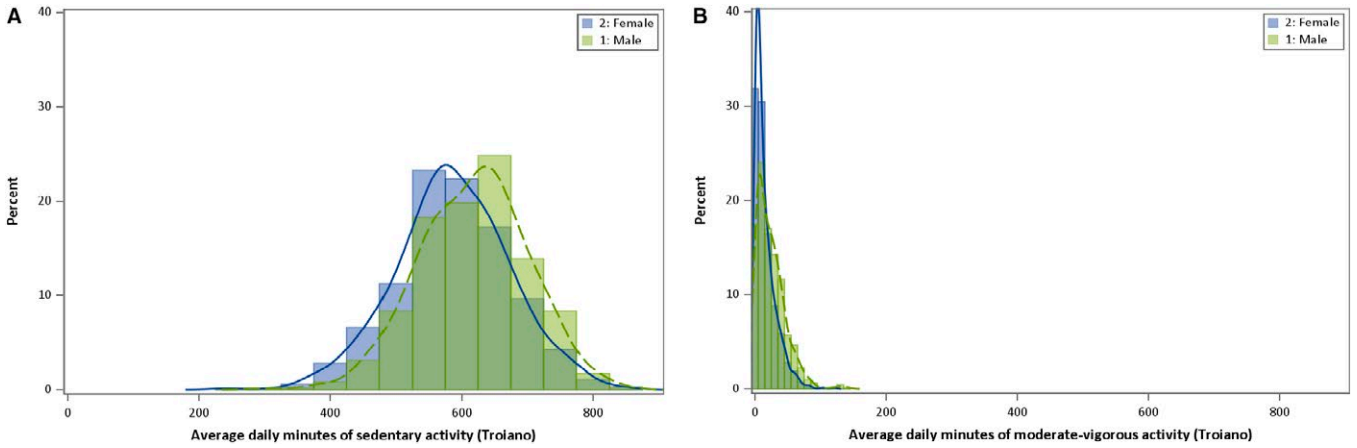

Figure 3. Distribution of average daily minutes of **A**, sedentary activity by sex, and **B,** moderate-vigorous activity by sex.

on our findings, we cannot make definitive conclusions regarding effects of either sedentary or moderate-vigorous activity. The current study has additional limitations. The vast majority of knees in our analysis sample had mild OA at baseline and time spent in moderate-vigorous activity was relatively low; vigorous activity was too infrequent to separately analyze. Whether findings differ in persons with more severe knee OA and/or in persons who engaged more frequently in moderate or vigorous activity should be examined in future studies. Physical activity was only measured at baseline; due to the likely decline in activity over the 4-year study period among these older adults, this baseline analysis is conservative, i.e., potentially overestimating the relationship of physical activity to worsening.

Although widely used and inexpensive, radiography has inherent weaknesses. Given the decades-long trajectory of knee OA, our follow-up period of up to 4 years was relatively short. As is an inherent issue with large-scale studies, not all participants remained in the study through the 96-month visit. Of 1,978 knees, 1,831 (92.6%) had no missing assessments (i.e., they had 48, 72, and 96 months), 69 of 1,978 knees (3.5%) were missing only the 72-month assessment, and 76 of 1,978 knees (3.8%) were missing only the 96-month assessment. Because the number of missing knees is similar at 72 and 96 months, it is likely to be missing at random, as opposed to a systematic pattern of higher omissions later in the study. In addition, because the overall proportion of knees with missing assessments is very low, we do not expect this to have an impact on our findings.

Nevertheless, it is important to present these findings. Although the OAI accelerometer substudy was designed to examine function and disability outcomes, the comprehensive data collection in the OAI afforded an excellent opportunity to explore the association between objectively measured physical activity and worsening of radiographic features of knee OA. To our knowledge, this substudy represents the largest accelerometry study in persons with or at higher risk for knee OA and the best opportunity that currently exists to examine these questions. It is

Table 2. Logistic regression models using generalized estimation equations for physical activity at baseline and radiographic worsening of knee osteoarthritis over the subsequent 4 years (dependent variable).

Predictor	Model 1	Model 2	Model 3
Age (per 5 years)	1.11 (1.03, 1.20)†	1.13 (1.03, 1.23)†	1.15 (1.05, 1.26)†
Female sex	1.44 (1.09, 1.92)†	1.37 (1.01, 1.88)†	1.40 (1.02, 1.93)†
BMI (per 1 kg/m^2)	1.07 (1.04, 1.11)†	1.07 (1.04, 1.11)†	1.07 (1.03, 1.10)†
Sedentary/10 minutes		0.99 (0.96, 1.01)	0.99 (0.97, 1.01)
Moderate-vigorous/10 minutes		0.98 (0.90, 1.07)	1.00 (0.91, 1.09)
Wear time		1.10 (0.95, 1.27)	1.10 (0.95, 1.28)
Race			0.68 (0.41, 1.11)
Knee injury			0.96 (0.70, 1.32)
Knee surgery			1.27 (0.81, 1.99)
WOMAC pain			1.13 (1.07, 1.19)†

* Adjusted odds ratios for sedentary and moderate-vigorous activity are per 10-minute increments. BMI = body mass index; WOMAC = Western Ontario and McMaster Universities Osteoarthritis index.
† Significant at $P < 0.05$.

notable that many previous studies and the current study focused on persons without or at mild stages of knee OA. Less is known about the impact of physical activity in persons with moderately severe knee OA. The ideal study, i.e., including a more balanced representation of various stages of knee OA disease severity along with more frequent moderate-vigorous activity, may not be realizable, particularly given the relative inactivity of this population. This inactivity is likely to be multifactorial, but relates in part to concerns about potential adverse effects of physical activity on the knee joint itself (79). A large-scale pragmatic design may be better, although it would have to adapt methods to objectively measure physical activity and knee joint structure to meet this scale. In conclusion, in a subset of OAI participants with or at higher risk for knee OA, there was no association between objectively measured moderate-vigorous physical activity at baseline and worsening of radiographic knee OA over 4 years of follow-up.

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AUTHOR CONTRIBUTIONS

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

Study conception and design. Kocherginsky, Dunlop, Sharma.

Acquisition of data. Dunlop.

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ACTIVITY AND THE RHEUMATIC DISEASES

Participation in Regular Physical Activity After Total Knee or Hip Arthroplasty for Osteoarthritis: Prevalence, Associated Factors, and Type

Justine M. Naylor,[1] Natasha Pocovi,[2] Joseph Descallar,[1] and Kathryn A. Mills[2]

Objective. To describe the rates of participation in regular physical activity presurgery and at 3 years follow-up after knee or hip arthroplasty, and to describe factors associated with participation postsurgery and types of activity undertaken.

Methods. A previously acquired multicenter, prospective cohort of knee or hip arthroplasty recipients was followed up for 3 years postsurgery. Regular participation in physical activity was defined as participation in physical activity ≥1 time/week, excluding incidental activities. Participants were interviewed about current participation as well as participation in the year presurgery. Joint-specific and health-related quality-of-life scores and information on experience of major complications were obtained. Information about comorbidity and body weight were updated. Factors associated with 3-year physical activity participation were determined using multivariable logistic regression modeling.

Results. In total, 73.4% of the eligible cohort (1,289 of 1,757) were followed up (718 patients with total knee arthroplasty, and 571 patients with total hip arthroplasty). Participation profiles were similar regardless of the joint replaced. Participation in physical activity increased postsurgery in the combined cohort (from 45.2% to 63.5%; $P < 0.001$). Participation at 3 years was associated with participation presurgery ($P < 0.0001$), better 3-year quality of life ($P < 0.001$), younger age ($P = 0.002$), better 3-year joint scores ($P = 0.01$), >1 lifetime arthroplasty ($P = 0.02$), and higher education level ($P = 0.04$). Low-impact and nonambulatory activities significantly increased postsurgery with no change in high-impact activities.

Conclusion. Participation rates increased postsurgery when recovery was stable, but approximately one-third of arthroplasty recipients did not engage in physical activity at least once per week. Because participation is associated with habitual activity presurgery, a potential role for behavior change interventions is suggested. The increase in nonambulatory activities indicates that current devices measuring ambulatory activity alone are inadequate for capturing physical activity.

INTRODUCTION

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are recognized as cost-effective interventions for end-stage knee or hip arthritis (1). Recovery from either surgery is multidimensional and includes joint-specific improvements as well as improvements in health-related quality of life (2–4). Secondary to alleviation of joint pain and functional impairment, arthroplasty recipients also have the potential to become more physically active. When compared to the period immediately preceding surgery, participants may increase their engagement in sports, exercise, or physical activity in the months or years following surgery, when their recovery is uncomplicated. Clearly, an increase in such activity is not only desirable for musculoskeletal and mental health (5), but it may also help manage concomitant medical conditions or health risk factors amenable to exercise common among arthroplasty

[1]Justine M. Naylor, PhD, BAppSc(Phty), Joseph Descallar, MBiostat, BSc: Ingham Institute Applied Medical Research, Sydney, New South Wales, Australia; [2]Natasha Pocovi, MPhty, BExPhys, Kathryn A. Mills, PhD, BPhty: Macquarie University, Sydney, New South Wales, Australia.

Address correspondence to Justine M. Naylor, PhD, BAppSc(Phty), Whitlam Orthopaedic Research Centre, Ingham Institute Applied Medical Research, 1 Campbell Street, Liverpool, NSW 2170, Australia. E-mail: Justine.Naylor@health.nsw.gov.au.

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SIGNIFICANCE & INNOVATIONS

- Compared to the year prior to surgery, the reported rate of participation in physical activity at least once per week increased by 40% at 3 years postsurgery.
- Approximately one-third of arthroplasty recipients did not perform physical activity at least once per week at a time when recovery was stable.
- Habitual physical activity presurgery was found to have a strong association with participation postsurgery, pointing to a potential role for behavior change interventions to improve engagement in physical activity.
- Nonambulatory activities are more common postsurgery, highlighting the inadequacy of current methods to objectively measure activity, given their reliance on ambulatory activity alone.

cohorts (6), including diabetes, obesity, hypertension, and hyperlipidemia (4,7–14).

Prospective longitudinal studies (15–18), cross-sectional studies (19,20), and several systematic reviews (21–24) have attempted to quantify or infer changes in activity volume (frequency, intensity, duration) after TKA or THA. Currently, due to limitations in measuring physical activity, differing study designs, and inadequate control of potentially confounding patient covariates, to what extent physical activity increases postsurgery, if at all, is unclear (24). In fact, many researchers have suggested that if activity volume increases, it still falls short of the recommended weekly levels stipulated in exercise prescription guidelines (17,19,20). Regarding physical activity participation rates, the literature varies with respect to the population prevalence of participation postsurgery and whether rates increase after surgery compared to presurgery levels. Estimates for participation postsurgery range from 21% to 83% (6,25–29), with some studies indicating an increase and others a decrease compared to presurgery. Variation between studies may reflect methodologic or population differences (30) such as sample size or age differences, how physical activity is defined (e.g., competitive sport versus regular recreational activity), the presurgical benchmark (e.g., the year prior to surgery [29] or several years before [6]), and differences in reporting change (e.g., change in activity among those reporting that they are active presurgery [6] versus the whole cohort [17,29]).

Variation in participation in physical activity within cohorts has been infrequently studied, and yet one can readily appreciate that differences in patient-level characteristics (both modifiable and unmodifiable) could affect participation. Only a few studies have explored patient factors (6,28,31,32), and these are typically confined to commonly collected variables such as age, sex, body mass index (BMI), and comorbidity. Few studies have hinted at the presence of persistent (poorly defined) joint problems or have diagnosed joint-related complications as confounders (6,25,29,31), and those that have done so have not accounted for their effects while controlling for other factors (30).

Regarding the types of activities or sports typically undertaken by TKA or THA recipients, they appear in general to be similarly reported across cohorts, regardless of country of origin (6,25–28,33). Walking, hiking, swimming, cycling (biking), golf, or lawn bowls are typically reported, and this type of reporting is true regardless of surgery type (hip or knee). Less consistent across studies are the observations concerning whether participation in each of these specific activities increases or decreases after surgery (25–29), or whether there is a shift from high-impact exercise to low-impact exercise or vice versa (26,27,30). Again, this variability in reporting may be attributable to inconstancy between studies in definitions of the presurgery time period or the scope of activities included.

The overarching objective of this study was to profile physical activity participation at 3 years after TKA or THA. Specifically, the study aimed to describe the rates of participation in regular physical activity presurgery and at 3 years postsurgery, to determine factors, both modifiable and unmodifiable, associated with participation in regular physical activity postsurgery, and to describe the types of activity undertaken pre- and postsurgery.

The knowledge derived from this study is useful for informing patient and clinician expectations about physical activity after surgery and identifying strategies to improve participation in physical activity, if indeed any of the associated factors are modifiable. Data about types of activity are particularly useful in informing future methodology for quantifying physical activity after arthroplasty.

MATERIALS AND METHODS

Design and ethics approvals. This study used both prospective and retrospective survey methods to examine current (at 3 years) and past (in the year leading up to surgery) physical activity behavior. The study was approved by the relevant institutional ethics committees (Hunter New England Human Reserach Ethics Committee, 16/07/20/5.05; Macquarie University HREC, Ref. 5201600658).

Participants. Participants from a previous observational cohort of primary TKA or THA recipients with osteoarthritis registered between August 2013 and December 2014 (12,34) were invited to take part in the 3-year follow-up interview. Of the original 1,900 recipients, 1,773 provided verbal agreement at the time of their last study follow-up to be contacted after 1 year. Patients who died between 1 and 3 years postsurgery and those who developed dementia were subsequently excluded from the eligible sample.

Participant recruitment. Letters informing prospective participants of the study were sent in the month prior to their

3-year anniversary. Patients were free to opt out by contacting the investigators; otherwise they were called shortly after the letter was sent and invited to complete the interview. The interview proceeded if verbal consent was obtained. Patients were deemed lost to follow-up after a minimum of 5 unsuccessful attempts to reach them.

Survey interview content. In addition to questions pertaining to physical activity (detailed below), the interview comprised questions concerning recovery of the index joint using the Oxford Knee Score and Oxford Hip Score (35), current ("today") general health using the EuroQol 5-domain instrument (36), joint-related complications experienced between years 1 and 3 postsurgery, details about further arthroplasty surgery (other joint), and development of new comorbid conditions (see Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23604/abstract). Current weight was also obtained if the participants had weighed themselves within the last month. Interviews were conducted by researchers familiar with all survey fields, including those requiring probing and potential clarification.

Physical activity. In the absence of a gold standard for capturing rates of participation, we developed our own approach, incorporating an established definition for physical activity (37): any bodily movement produced by skeletal muscles that requires energy expenditure undertaken for health and fitness. Our definition excluded incidental walking or activity that related to work or shopping and activities such as gardening or child-minding. Similarly, the minimum weekly frequency for a physical activity to be considered a regular activity was informed by an Australian state-based activity survey (38): participation in physical activity or exercise ≥1 time/week (minimum 4 times/month).

Participants were asked whether they currently engage in regular physical activity and whether they engaged in the same or other activities in the year leading up to surgery. For each activity they currently participated in, they were asked about frequency in the last week and month. For those who reported that the week or month prior to the survey was unusual (that is, they had been unwell or had been away), the activity profile for the month prior was included. We also asked respondents for reasons why they did not get back to an activity or why they were not active. These reasons were subsequently categorized by theme and coded by 2 investigators independently (JMN and KAM). Disparities were resolved through discussion. Using a 5-point Likert scale for level of agreement (strongly disagree, disagree, neither, agree, or strongly agree), we also asked participants whether prior to having surgery, they felt that participation in regular physical activity for them was an important goal of surgery.

Test–retest reliability. The reliability of the specifically developed activity questions was examined using a test–retest study involving 63 respondents (see Supplementary Appendix B, part 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23604/abstract). The kappa statistic (39–41) and percent agreement were used to describe week-to-week reliability. For participation in physical activity presurgery and results at 3 years postsurgery, substantial agreement between kappa values (0.77 and 0.68, respectively) and high agreement (88% and 86%, respectively) were obtained. A fair kappa (0.24) and excellent agreement (92%) were obtained for the question pertaining to activity as a goal. For the latter, the kappa statistic did not reflect overall agreement, because it was affected by the low prevalence of participants reporting strongly disagree, disagree, or neither, a fundamental limitation of the kappa statistic (39–41).

Statistical analysis. Assuming a minimum follow-up rate of 70% based on reported rates of follow-up (56–81%) in studies in this field (6,26,27,29,31,33), a sample size of 1,241 could reasonably be expected. Assuming a participation to nonparticipation rate ratio of 1:1, with approximately 600 in each group, we would have an event-to-variable ratio of 20:1, using a maximum of 30 variables that we defined a priori (see below), including past (previously acquired) and 3-year data.

Descriptive statistics (mean ± SDs or proportions) were used to describe the definitive TKA and THA cohorts separately and combined. To determine nonresponse bias, comparisons of characteristics between those lost to follow-up and those with 3-year data were conducted using parametric and nonparametric tests

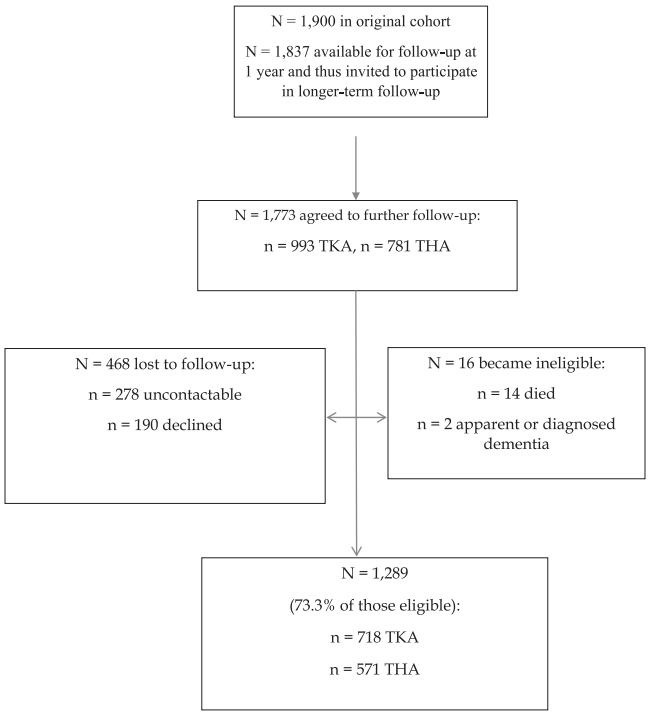

Figure 1. Cohort recruitment. TKA = total knee arthroplasty; THA = total hip arthroplasty.

as appropriate. For differences in rates, or prevalence, in activity and activity type across time, McNemar's test was used. The chi-square test was used to analyze the goal-related question.

Multivariable logistic regression was used to determine the variables significantly associated with participation in physical activity ≥1 time/week at 3 years. Decisions on the variables to be examined were in part informed by a recent systematic review (30) and our own knowledge about recovery after arthroplasty. The categorical variables were sex, joint, unilateral or bilateral procedure, global improvement at 3 years, presurgery physical activity involvement, education level, American Society of Anesthesiologists [ASA] score, insurance status, rehabilitation pathway, the presence of other lower extremity or back problems limiting mobility at 3 years, a major joint complication within the first 3 years, a history of >1 lower-extremity arthroplasty, the presence of comorbidity requiring daily medication, and the presence of ongoing index joint issues otherwise not defined as a major complication. In addition, we included continuous variables (age at the time of surgery and BMI) at the time of surgery or at 3 years, the Oxford score presurgery and at 3 years, and EuroQol visual analog scale [VAS] score presurgery and at 3 years. All data were stored in Redcap. All analyses were performed using SAS Enterprise Guide, version 7.15.

RESULTS

Figure 1 shows cohort recruitment. From an initially eligible sample of 1,773, 468 were lost to follow-up, 16 were excluded (died or had dementia), and 73.4% (1,289 of 1,757) were successfully followed up. Comparisons between those patients retained and those lost to follow-up indicated that the 2 groups were very similar, except that the latter were more likely to be publicly insured and to have attained a lower level of education (Table 1).

Table 1. Comparison of patients followed up and those lost to follow-up*

	Retained (n = 1,289)	Lost (n = 468)	*P*
Age at time of surgery, mean ± SD years	67.2 ± 9	66.6 ± 10	0.30
Women	708 (55)	251 (54)	0.63
BMI at time of surgery, mean ± SD	30.9 ± 6	30.7 ± 7	0.66
Total knee arthroplasty	718 (56)	266 (57)	0.67
Unilateral surgery	1,220 (95)	19 (95)	0.35
ASA score			0.44
1	146 (12)	42 (9)	
2	733 (58)	255 (57)	
3	370 (29)	145 (32)	
4	20 (2)	6 (1)	
Comorbidity requiring daily medication	842 (65)	287 (61)	0.12
Publicly insured	518 (40)	238 (51)	<0.001
Education level			0.003
≤ year 8	103 (8)	63 (14)	
year 9–10	725 (57)	251 (54)	
year 11–12	154 (12)	63 (13)	
Degree	298 (23)	90 (19)	
12-month Oxford score, mean ± SD	43.2 ± 6.4	43.0 ± 6.2	0.50
12-month EuroQol VAS, mean ± SD	82.5 ± 14.3	81.4 ± 15.0	0.157
Other lower extremity or back problems limiting mobility at 3 years	674 (52)	227 (49)	0.16
Major complication within first year	130 (10)	48 (10)	0.91

* Values are the number (%) unless indicated otherwise. Percentages are rounded to the nearest whole number. BMI = body mass index; ASA = American Society of Anesthesiologists; EuroQol VAS = current ("today") visual analog scale.

Participation in physical activity at least once per week. Overall, at 3 years, 819 participants (63.5%) reported that they were regularly participating in physical activity at least once per week. Regardless of surgery type, the prevalence of participation in physical activity increased from presurgery to postsurgery (for TKA from 40.8% to 60.6% [$P < 0.001$]; for THA from 50.6% to 67.3% [$P < 0.001$]; for all from 45.2% to 63.5% [$P < 0.001$]). While the majority of patients either agreed or strongly agreed that activity was an important goal of surgery, compared to those not active, a greater proportion of those reporting that they were physically active at 3 years answered "strongly agree" and a lesser proportion answered "disagree" (Table 2). Of those not reporting that they were regularly active, 64 (13.6%) reported undertaking incidental exercise such as gardening, child-minding, or volunteering (for TKA, n = 37; for THA, n = 27).

Factors associated with participation in physical activity at least once per week. *Univariate analysis.* Table 3 shows the characteristics of those reporting that they were regularly active at 3 years versus those who were not, by surgery type and overall. On univariate analysis, the pattern of characteristics between those patients who were physically active and those who were not was broadly similar for the TKR and THR groups. Those who were physically active were significantly younger, had a lower BMI (at the time of surgery and at 3 years), had fewer comorbidities requiring daily medication, had better ASA scores, had fewer other lower extremity or back problems impairing mobility, were more commonly physically active presurgery, had attained a higher education level, were more commonly privately insured, had better health-related quality of life and joint-specific scores presurgery and

Table 2. Descriptive summary of responses to whether physical activity was a goal of surgery based on activity status at 3 years*

	Total knee arthroplasty		Total hip arthroplasty		All	
	Yes	No	Yes	No	Yes	No
Strongly agree	184 (43)	77 (29)	199 (55)	55 (30)	383 (49)	132 (30)
Agree	207 (48)	116 (43)	142 (39)	78 (43)	349 (44)	194 (43)
Neither	24 (6)	58 (21)	18 (5)	35 (19)	42 (5)	93 (21)
Disagree	7 (2)	16 (6)	3 (1)	11 (6)	10 (1)	27 (6)
Strongly disagree	2 (1)	3 (1)	3 (1)	2 (1)	5 (1)	5 (1)

* Values are the number (%). Percentages are rounded to the nearest whole number (n = 1,240 who provided an answer). The pattern of responses between the physically active (Yes) and not physically active (No) respondents was highly significantly different ($P < 0.001$) for the knee, hip, and all cohorts.

at 3 years, and had not experienced a major joint-related complication within the first 3 years.

Multivariable analysis. Two multivariable logistic regression models were evaluated, one including BMI at the time of surgery, the other including BMI at the time of follow-up (Table 4). The latter was necessary because not all respondents could provide updated weight information. Including BMI at time of surgery, participation in physical activity prior to surgery ($P < 0.0001$), better 3-year EuroQol VAS score ($P = 0.0005$), younger age ($P = 0.0018$), a better Oxford score ($P = 0.014$), >1 lifetime arthroplasty ($P = 0.016$), and a higher education level ($P = 0.038$), were significantly associated with regular physical activity at 3 years. Similar associations were found in the model including BMI at 3 years, though >1 lifetime arthroplasty and BMI were of borderline significance ($P = 0.05$).

Types of physical activity. Table 5 shows the types of activity respondents reported being regularly engaged in, both prior to surgery and at 3 years. Types and patterns were broadly similar regardless of surgery type. Walking significantly increased ($P < 0.001$) after surgery and was the predominant activity reported both before (27.7%) and after surgery (46.9%). For the combined cohort, the prevalence of several low-impact, nonambulatory activities significantly increased after surgery (swimming, cycling, and gym exercise), while there was no change for higher-impact activities, including golf and tennis. Though uncommon generally, jogging significantly decreased postsurgery across the whole cohort, but this finding was due to a decrease among respondents with THA only.

Barriers to exercise participation and other reasons for nonparticipation at 3 years. Reported barriers to exercise participation at 3 years postsurgery or reasons for nonparticipation are shown in Supplementary Appendix B, part 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23604/abstract. The most common barrier reported (for both TKA and THA) was the presence of other musculoskeletal problems (9.7%). Index joint problems were the next most common barrier for respondents with TKA (5.2%), while believing their lifestyle was sufficiently active without engaging in formal physical activity was the next most common reason for THA respondents (3.3%).

DISCUSSION

Older people presumably have much to gain from participation in regular physical activity. Many within this population require daily medication for age-related and inactivity-related conditions, and physical activity can serve as an alternative cost-effective therapeutic strategy devoid of the risks associated with pharmaceutical agents (42). This argument is readily extrapolated to arthroplasty recipients, given their age and the high level of comorbidity in part attributable to the sedentary lifestyle that often precedes their surgery (30).

Despite the overwhelming majority of respondents agreeing that participation in regular physical activity was an important goal of surgery, and despite the fact that the rate of participation in physical activity increased, only approximately two-thirds reported that they were physically active at least once per week postsurgery, according to our definition. This finding raises concern about the extent to which arthroplasty recipients are truly taking advantage of their new symptom-reduced state 3 years after surgery, when recovery is stable. The fact that we identified modifiable factors affecting participation (namely, the goal of surgery and presurgery habitual behavior) indicates that this outcome can potentially be improved through behavior change strategies. Notably, the participation rate we observed is slightly less than, if not consistent with, those observed in the most recent population-based Australian state-based survey (38), in which 67% of patients ages 55–64 years and 64% of those ages ≥65 years, reported engaging in physical activity at least once per week. This finding suggests that TKA and THA recipients behave very much like the general older population, at least for participation rates. Our study provides no insights into other parameters of participation, such as duration and intensity, however.

Table 3. Characteristics of patients physically active and those not physically active at 3 years*

	Total knee arthroplasty (n = 718)			Total hip arthroplasty (n = 571)			All (n = 1,289)		
	PA	Not PA	*P*	PA	Not PA	*P*	PA	Not PA	*P*
Age at time of surgery, mean ± SD years	67.8 ± 8.2	69.0 ± 8.9	0.07	64.8 ± 10.1	67.3 ± 10.5	0.005	66.4 ± 9.3	68.4 ± 9.6	<0.001†
Women	55	61	0.08	54	49	0.32	54	56	0.43
Bilateral surgery	9	6	0.10	2	1	0.64	6	4	0.19
BMI at time of surgery, mean ± SD	31.7 ± 6.3	33.0 ± 6.9	0.01	28.5 ± 5.2	30.7 ± 6.3	<0.001	30.2 ± 6.0	32.0 ± 6.8	<0.001†
BMI at 3 years, mean ± SD (n = 1,202)	31.5 ± 6.7	33.0 ± 7.3	0.006	28.3 ± 5.3	30.8 ± 6.8	<0.001	30.0 ± 6.3	32.1 ± 7.2	<0.001†
Comorbidity requiring daily medications at 3 years	70	75	0.17	55	63	0.07	63	70	0.01†
ASA score			0.03			<0.001			<0.001
1	11	8		6	10		13	9	
2	57	51		65	55		61	53	
3	31	39		18	33		25	37	
4	1	3		1	2		1	2	
Other lower extremity or back pain limiting mobility at 3 years	46	58	0.001	52	59	0.11	49	59	<0.001†
Regular physical activity, 1 year prior to surgery	53	23	<0.001	66	19	<0.001	59	21	<0.001†
Education level			0.08			<0.001			<0.001
≤ year 8	8	14		4	9		6	11	
year 9–10	59	62		48	60		54	61	
Completed school	11	10		15	13		13	11	
Degree	21	16		33	19		27	17	
Publicly insured	43	53	0.008	28	41	0.003	36	48	<0.001†
Rehabilitation pathway			0.02			0.41			0.15
Unmonitored HP (least intervention)	6	12		34	34		19	21	
Monitored HP (≤3 community visits)	20	18		19	21		20	19	
Community treatments only	36	34		21	22		29	29	
Inpatient rehabilitation only‡	5	9		6	9		6	9	
Inpatient + community (most intervention)	33	28		19	14		26	22	
OKS or OHS presurgery, mean ± SD	22.7 ± 8.6	20.9 ± 7.5	0.004	22.8 ± 9.1	19.4 ± 8.5	<0.001	NA	NA	
OKS or OHS at 3 years, mean ± SD	41.3 ± 7.3	38.9 ± 8.8	<0.001	45.0 ± 4.7	41.9 ± 8.1	<0.001	NA	NA	

(continued)

Table 3. *(Cont'd)*

	Total knee arthroplasty (n = 718)			Total hip arthroplasty (n = 571)			All (n = 1,289)		
	PA	Not PA	*P*	PA	Not PA	*P*	PA	Not PA	*P*
EuroQol VAS, presurgery, mean ± SD	73.1 ± 17.9	69.5 ± 17.1	0.008	72.1 ± 18.7	68.6 ± 20.1	0.04	72.6 ± 18.3	69.1 ± 18.3	0.001†
EuroQol VAS at 3 years, mean ± SD	78.5 ± 16.3	72.5 ± 17.9	<0.001	81.6 ± 13.1	74.4 ± 16.3	<0.001	80.0 ± 14.9	73.2 ± 17.2	<0.001†
Global joint improvement (much better/ slightly better)	92	91	0.90	97	92	0.02	94	92	0.10
Major complication within first 3 years	9	13	0.16	6	10	0.11	8	12	0.03†
Ongoing undiagnosed index joint symptoms	11	13	0.41	7	11	0.08	9	12	0.07
>1 knee/hip arthroplasty (lifetime)	42	40	0.47	41	42	0.85	42	41	0.66

* Values are the percentage unless indicated otherwise. Percentages are rounded to the nearest whole number. Major joint complication includes deep infection, manipulation under anesthetic, revision surgery, dislocation, fracture, or soft tissue repair. PA = physically active; BMI = body mass index; ASA = American Society of Anesthesiologists; HP = home program; OKS = Oxford Knee Score; OHS = Oxford Hip Score; NA = not applicable; EuroQol VAS = current ("today") visual analog scale.
† Significant.
‡ Discharged to an inpatient rehabilitation facility postsurgery.

Several unmodifiable factors were associated with undertaking physical activity at least once per week (age, education), but some patients simply stated that they believed they were very active doing incidental activity alone. The latter observation is consistent with observations in a recent systematic review of patient perceptions of physical activity after TKA or THA (43). The authors of that study concluded that people desire to be active postsurgery, not to improve health or address health issues, but for social reasons and enjoyment. Furthermore, increases in obligatory physical activities, such as those of daily living, were highly regarded and potentially deemed more important than more extraordinary physical activity (43). Taking our observations together with those of Smith et al (43), we believe that future behavior change interventions intended to address the arguably suboptimal participation in activity would ideally focus on altering knowledge and attitudes toward healthy levels of activity. Our observations concerning why people do not undertake regular physical activity postsurgery are also consistent with previous studies, citing the presence of comorbidities and problems with the index or other joints as barriers to participation (6,29,31,44).

Meaningful comparisons with other studies are limited by lack of a common definition of physical activity, including a lack of clarity regarding the presurgery reference period. Comparing our study to the 1 study in which the presurgery period was restricted to the year prior to surgery (29), our participation rates prior to surgery for TKA are similar (41% versus 42%), but our rate for THA is higher (50% versus 36%).

As for the presurgery period, meaningful comparison with other observed postsurgery rates is limited. The prevalence observed for regular engagement in physical activity after surger**y** varies widely in the literature (for TKA, 32% [25], 34% [29], 47% [28], 75% [26], and 76% [31]; for THA, 52% [29] and 83% [27]). We feel that differences in how physical activity is defined and captured (such as using only low-impact sports [28], the tool used, e.g., Grimby Score [26], or the criteria applied to qualify as physically active, e.g., at least once a week independent of duration or intensity, as was used here) combined with differences in the follow-up period (1–5 years), and patient characteristics associated with physical activity (which are often underreported or not reported), are contributing to these differences. Because the definition used here could be regarded as conservative, that is, designed to capture the low-hanging fruit, our prevalence rates could be interpreted as optimistic (for TKA 61%, for THA 67%).

In this study, we observed increases in participation rates after surgery, regardless of the joint replaced. Increases have previously been reported in THA cohorts (27,29), but decreases have more typically been observed in TKA cohorts (6,25,26,28,29). The divergent results may in part be explained by the fact that for most of those studies in which decreases were observed, the presurgery rate was comparatively high and the presurgery period was not restricted to the year leading up to surgery (6,26) or was undefined (25,28). Additionally, in 1 study, a change in rate was reported only for those patients previously active, while those new to physical activity after surgery were ignored (6).

Table 4. Multivariable logistic regression analysis of variables associated with being physically active at 3 years*

	BMI, time of surgery		3-year BMI	
	OR	*P*	OR	*P*
Age at time of surgery	0.974	0.0018†	0.971	0.0008†
Sex, male vs. female	0.881	0.371	0.872	0.349
Index joint, THA vs. TKA	0.915	0.571	0.854	0.335
Side, unilateral vs. bilateral	0.807	0.518	0.752	0.404
BMI	0.984	0.184	0.977	0.052
Comorbidity requiring daily medication at 3 years, no (A) vs. yes (B)	1.02	0.900	0.907	0.553
American Society of Anesthesiologists score				
1 vs. 4	2.258	0.521	2.71	0.437
2 vs. 4	2.288	0.521	2.663	0.437
3 vs. 4	2.289	0.521	2.643	0.437
Other lower-extremity or back pain limiting mobility at 3 years, no (A) vs. yes (B)	1.191	0.215	1.211	0.192
Presurgery participation in regular PA (year leading up to surgery), no (A) vs. yes (B)	0.188	<0.0001†	0.188	<0.0001†
Education level, years				
None or ≤8 vs. degree	0.462	0.0376†	0.442	0.016†
9–10 vs. degree	0.718	0.0376†	0.735	0.016†
Completed school vs. degree	0.964	0.0376†	1.146	0.016†
Insurance status, public (A) vs. private (B)	0.82	0.280	0.802	0.251
Rehabilitation pathway				
Unmonitored HP vs. inpatient + community	0.8	0.291	0.899	0.280
Monitored HP vs. inpatient + community	1.277	0.291	1.419	0.280
Community vs. inpatient + community	0.989	0.291	1.088	0.280
Inpatient vs. inpatient + community	0.744	0.291	0.728	0.280
Oxford Knee or Hip Score, presurgery	0.998	0.868	0.996	0.730
Oxford Knee or Hip Score at 3 years	1.032	0.014†	1.034	0.012†
EuroQol VAS, presurgery	1.002	0.655	1.002	0.667
EuroQol VAS at 3 years	1.017	0.0005†	1.017	0.001†
Global joint improvement				
Much better/slightly better (A) vs. same/slightly worse/much worse (B)	1.344	0.345	1.675	0.115
Major joint complication within first 3 years, no (A) vs. yes (B)	1.405	0.157	1.356	0.232
Ongoing undiagnosed index joint issues, no (A) vs. yes (B)	0.937	0.805	1.007	0.980
>1 knee/hip arthroplasty (lifetime), no (A) vs. yes (B)	0.71	0.016†	0.751	0.0531

* For categorical variables with A vs. B, B is the reference value. BMI = body mass index; OR = odds ratio; THA = total hip arthroplasty; TKA = total knee arthroplasty; PA = physical activity; HP = home program; EuroQol VAS = current ("today") visual analog scale.
† Significant.

Although observations in individual studies vary, a recent systematic review concerning activity post-TKA showed that there was, in general, a switch to low-impact activities (30). We likewise observed this result for both the TKA and THA cohorts. The conclusion of the systematic review and our observations is consistent with recommendations by orthopedic surgeons for patients to avoid specific activities (45–47). The fact that many respondents participated in nonambulatory, low-impact activity (cycling, swimming, and gym exercise) supports the contention that current estimates of objectively measured physical activity, which capture ambulatory activity only, may be grossly underestimating true physical activity levels after surgery (24).

A recent systematic review concluded that prior studies in this area inadequately reported and controlled for confounders,

Table 5. Activities undertaken in the year prior to surgery and at 3 years postsurgery*

	Total knee arthroplasty (n = 718)			Total hip arthroplasty (n = 571)			All (n = 1,289)		
	Presurgery	Postsurgery	*P*	Presurgery	Postsurgery	*P*	Presurgery	Postsurgery	*P*
Walking (outside or treadmill)	183 (26)	328 (46)	<0.001†	174 (31)	277 (49)	<0.001†	357 (28)	605 (47)	<0.0001†
Swimming or aqua classes	48 (7)	62 (9)	0.060	36 (6)	59 (10)	<0.001†	84 (7)	121 (9)	<0.001†
Cycling (stationary or road)	24 (3)	46 (6)	0.0005†	31 (5)	49 (9)	0.001†	55 (4)	95 (7)	<0.001†
Gym exercise	26 (4)	54 (8)	<0.001†	43 (8)	77 (14)	<0.001†	69 (5)	131 (10)	<0.001†
Yoga	3 (0)	3 (0)	1.0	11 (2)	12 (2)	1.0	14 (1)	15 (1)	1.0
Tai chi	3 (0)	11 (2)	0.008†	0	2 (0)	NE	3 (0)	13 (1)	0.002†
Pilates	5 (1)	2 (0)	0.250	10 (2)	12 (2)	0.727	15 (1)	14 (1)	1.0
Lawn bowls	29 (4)	30 (4)	1.0	14 (3)	18 (3)	0.388	43 (3)	48 (4)	0.424
Golf, with or without cart	32 (5)	36 (5)	0.525	37 (7)	43 (8)	0.286	69 (5)	79 (6)	0.174
Tennis (doubles or singles)	9 (1)	4 (1)	0.180	14 (3)	12 (2)	0.791	23 (2)	16 (1)	0.210
Squash	3 (0)	0	NE	2 (0)	0	NE	5 (0)	0	NE
Running or jogging	1 (0)	2 (0)	1.0	17 (3)	5 (1)	0.004†	18 (1)	7 (1)	0.012†

* Values are the number (%). Percentages are rounded to the nearest whole number. Other activities not included in the table, but undertaken uncommonly, include dancing, horseback riding, and motorbike riding. NE = nonestimatable.
† Significant.

such as presurgical activity level, comorbidities, sex, BMI, complications, and rehabilitation pathways (30). In the current study, we comprehensively collected information on all these variables (and more) and statistically accounted for them. Earlier studies have likewise observed, either qualitatively or statistically, that presurgical participation in activity as an important variable associated with participation in activity postsurgery (25,29,30,32). Other variables that we identified are consistent with what is known about the propensity to be physically active in the general community (higher education level, younger age) (38). Similar to others, we observed univariate associations between major joint-related complications and being physically active after TKA (31,34). Interestingly, we observed that the relationship lessens (becomes nonsignificant) when other covariates are considered, and the presence of ongoing joint problems was not associated at all with being physically active. Our explanation for why current joint-related issues were not statistically related (i.e., those with problems being less likely to be physically active and vice versa) lies in our incidental observation that many of those with problems used physical activity as a method to address the problem, while many of those without problems simply were not interested in being physically active or believed being busy was sufficiently active. As may be expected, we observed that current (3-year) Oxford and quality-of-life scores and BMI appear to be more important than presurgical values, though we cannot assign cause or effect. The rehabilitation pathway in the subacute period did not appear relevant to longer-term participation, and in light of the consistent high-level evidence demonstrating no superiority of 1 pathway over another across a range of outcomes (48,49), this finding is perhaps not surprising.

Our large and well-defined cohort (restricted to osteoarthritis patients and primary surgeries), coupled with our clear definitions of participation in regular physical activity and presurgery time period, and coupled with the fact that our activity questions were reliable, aids the reader in interpreting the observations made here and confers confidence in these observations. Our response rate compares favorably with those observed in other studies in this field (6,26,27,29,31,33), and the differences between our retained cohort and those lost to follow-up would suggest that our observations may be optimistic. Our statistical accounting for many variables that may be associated with physical activity, including both commonly and uncommonly considered variables, along with our method of follow-up (a probing interview as opposed to a written survey), renders our study unique in this field.

The partially retrospective nature of the survey potentially introduces recall bias for physical activity prior to surgery. This potential is especially true given the relatively long timeframe and the advanced age profile of the respondents. Further, response shift may have occurred such that their experience of the surgery and subsequent recovery altered respondents' recollection of prior activity levels. This possibility notwithstanding, we note that our findings concerning past behavior concur with other studies in which such data were collected prospectively (29,32). Due to an inability to collect

both objectively measured and patient-reported volume data from a national cohort, we did not seek to determine the proportion of respondents achieving the recommended levels of weekly physical activity pre- and postsurgery. Based on previous studies demonstrating that very few patients achieve the levels recommended (17,20), we feel that many are possibly not achieving the recommended levels and, thus, future behavior change interventions will need to focus on both type and quantity of activity, not just participation, if the health of arthroplasty recipients is to be improved.

This study provides new insights concerning patient-reported participation in regular physical activity following TKA or THA from a large Australian national cohort. The participation rate improves, but a significant minority of participants (almost one-third) do not participate in physical activity at least once per week, despite an absence of a major complication or ongoing joint symptoms. Of those who are active, many participate in activity types that would normally be ignored by traditional measurement devices, such as an accelerometer used to quantify volume of activity. Translational research undertaken to improve the activity profile of TKA or THA recipients should focus on using devices that capture all physical activity (if possible) and incorporate behavior change techniques known to encourage physical activity, given that attitude or understanding of healthy activity levels appear to be a very important barrier. We echo the recommendations shown in recent systematic reviews articles (24,30) calling for uniformity in how physical activity is defined and measured.

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. Naylor 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. Naylor, Pocovi, Mills.
Acquisition of data. Naylor, Pocovi, Mills.
Analysis and interpretation of data. Naylor, Descallar, Mills.

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ACTIVITY AND THE RHEUMATIC DISEASES

Moderate Physical Activity and Prevention of Cartilage Loss in People With Knee Osteoarthritis: Data From the Osteoarthritis Initiative

Alessio Bricca,[1] Wolfgang Wirth,[2] Carsten B. Juhl,[3] Jana Kemnitz,[4] David J. Hunter,[5] C. Kent Kwoh,[6] Felix Eckstein,[2] and Adam G. Culvenor[7]

Objective. To examine the impact of physical activity on cartilage thickness loss in knee osteoarthritis (OA).

Methods. A total of 689 participants with radiographic knee OA at baseline (Kellgren/Lawrence grade ≥2) from the Osteoarthritis Initiative completed the Physical Activity Scale for the Elderly (PASE) questionnaires at annual intervals over 4 years. Magnetic resonance imaging–based cartilage thickness change in the medial femorotibial compartment (MFTC) over 4 years was the main outcome. The impact of PASE tertiles (low, moderate, or high) on changes in MFTC cartilage thickness was estimated using a mixed-effects model adjusted for baseline characteristics. Furthermore, stratification by sex was performed for secondary analyses.

Results. Structural progression of MFTC cartilage loss of –0.20 mm (95% confidence interval [95% CI] –0.22, –0.17) was observed in the entire cohort, with no significant difference between physical activity levels after adjustment for baseline characteristics. An interaction between sex and physical activity was observed in the adjusted analysis (P = 0.02). Stratification by sex showed that women with low physical activity had a statistically greater cartilage loss than women with moderate physical activity (adjusted between-group difference –0.09 mm [95% CI –0.16, 0.02]), whereas no significant differences were observed in men.

Conclusion. While physical activity was not associated with cartilage thickness loss in the whole cohort, this relationship significantly differed between sexes. In women, but not in men, moderate physical activity may slow down structural disease progression compared to low physical activity levels. For both men and women, high physical activity levels do not appear to be more detrimental than lower physical activity levels for cartilage thickness loss.

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[1]Alessio Bricca, PhD: University of Southern Denmark, Odense, Denmark, and University of Aberdeen, Aberdeen, UK; [2]Wolfgang Wirth, PhD, Felix Eckstein, MD: Paracelsus Medical University Salzburg and Nuremberg, Salzburg, Austria, and Chondrometrics GmbH, Ainring, Germany; [3]Carsten B. Juhl, PhD, PT: University of Southern Denmark, Odense, University of Copenhagen, Herlev, and Gentofte Hospital, Copenhagen, Denmark; [4]Jana Kemnitz, MSc: Paracelsus Medical University Salzburg and Nuremberg, Salzburg, Austria; [5]David J. Hunter, PhD: Royal North Shore Hospital and University of Sydney, Sydney, New South Wales, Australia; [6]C. Kent Kwoh, MD: University of Arizona, Tucson; [7]Adam G. Culvenor, PhD, PT: Paracelsus Medical University Salzburg and Nuremberg, Salzburg, Austria, and La Trobe University, Bundoora, Australia.

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Address correspondence to Alessio Bricca, PhD, Research Unit for Musculoskeletal Function and Physiotherapy, Department of Sport Science and Clinical Biomechanics, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark. E-mail: alessio.bricca8@gmail.com.

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SIGNIFICANCE & INNOVATIONS

- Physical activity was not associated with cartilage thickness loss in the whole cohort.
- Sex modifies the relationship between physical activity and cartilage thickness loss.
- In women, moderate physical activity appears to be protective of structural progression of knee osteoarthritis compared to low physical activity.
- In men and women, high physical activity does not appear to be more harmful than lower physical activity for cartilage thickness loss.

INTRODUCTION

Physical activity is commonly recommended as a first-line treatment for knee osteoarthritis (OA), because it has been suggested to reduce pain and improve physical function (1). While having positive effects on knee symptoms and activities of daily living, physical activity may have detrimental effects on structural progression through excessive mechanical loading (2). However, systematic reviews have shown large inconsistencies regarding the influence of physical activity on the incidence and progression of radiographic knee OA (3,4). The time between the detrimental physical activity exposure and development and progression of structural radiographic disease can be decades, and thus the true relationship can be difficult to capture. Assessment of articular cartilage with magnetic resonance imaging (MRI) may provide an ability to detect structural progression during a shorter window of disease.

Several studies have previously investigated the impact of physical activity on knee cartilage (5–10). Some of these studies showed that high (or very low) levels of physical activity had demonstrated detrimental effects on cartilage lesion scores or cartilage composition (10), in particular in knees with preexisting structural pathology (5). However, other studies did not observe an association between physical activity and knee cartilage morphology or composition (6,7). These inconsistent results may be attributed to the diversity of physical activity assessments (pedometer, accelerometer, or self-reported), outcome measures (cartilage volume/thickness, semiquantitative lesion scores, or compositional measures), and cohort composition (with or without symptomatic/radiographic knee OA). None of these studies, however, showed a relationship between physical activity and knee cartilage stratified by sex, despite men and women clearly having a different risk profile for OA development and structural progression (11–13). Further, only a single study that analyzed the association between physical activity and cartilage thickness loss in 100 Osteoarthritis Initiative (OAI) participants with full-thickness femoral cartilage defects (6) focused on participants with definite radiographic knee OA.

Considering the fact that physical activity is promoted worldwide for many health conditions, including OA, and the fact that people with OA avoid being physically active due to the belief that exercise damages their joints (14), it is important to investigate whether physical activity is related to cartilage thickness changes in men and women with established radiographic knee OA. The objective of this study, therefore, was to examine the impact of physical activity levels on the robust imaging biomarker longitudinal cartilage loss, as observed over 4 years by MRI in participants with radiographic knee OA. We additionally examined this relationship stratified by sex.

MATERIALS AND METHODS

Participants. This study used data from the OAI, an ongoing prospective observational cohort study of 4,976 participants designed to identify risk factors for the development and progression of radiographic knee OA. As part of the OAI, participants were recruited from 4 centers in the US and completed annual evaluations over a 4-year period, including image acquisition, clinical assessments, and questionnaires assessing physical activity levels. The OAI study and public use of clinical and imaging data were approved by the local institutional review board at each of the 4 clinical centers, and all participants gave informed consent. Inclusion criteria for the current study were the presence of baseline radiographic knee OA (Kellgren/Lawrence [K/L] grade ≥2 based on central readings), physical activity recorded at baseline and at every annual follow-up assessment up to year 4, and the availability of information on MRI-based cartilage thickness measurement, taken at baseline and at the 4-year assessment. If both knees were eligible, the one with less lateral joint space narrowing or the lower K/L grade was selected, and if these were identical, then the right knee was included (Figure 1).

Analysis of cartilage thickness. Cartilage thickness measurements were performed from 3T sagittal 3-dimensional double-echo steady-state MRIs based on a manual, quality-controlled segmentation of cartilage surfaces (15). Images from the baseline and 4-year follow-up visit were processed by the same reader using custom software (Chondrometrics GmbH), with blinding to image acquisition order. The mean cartilage thickness in the medial femorotibial compartment (MFTC) and in the combined central MFTC subregions (cMFTC) were computed for each visit individually, and change was calculated by subtracting the cartilage thickness at baseline from cartilage thickness at follow-up. We focused on longitudinal change in the MFTC and cMFTC, because the sensitivity to change of cartilage thickness measures depends on the radiographic disease stage and

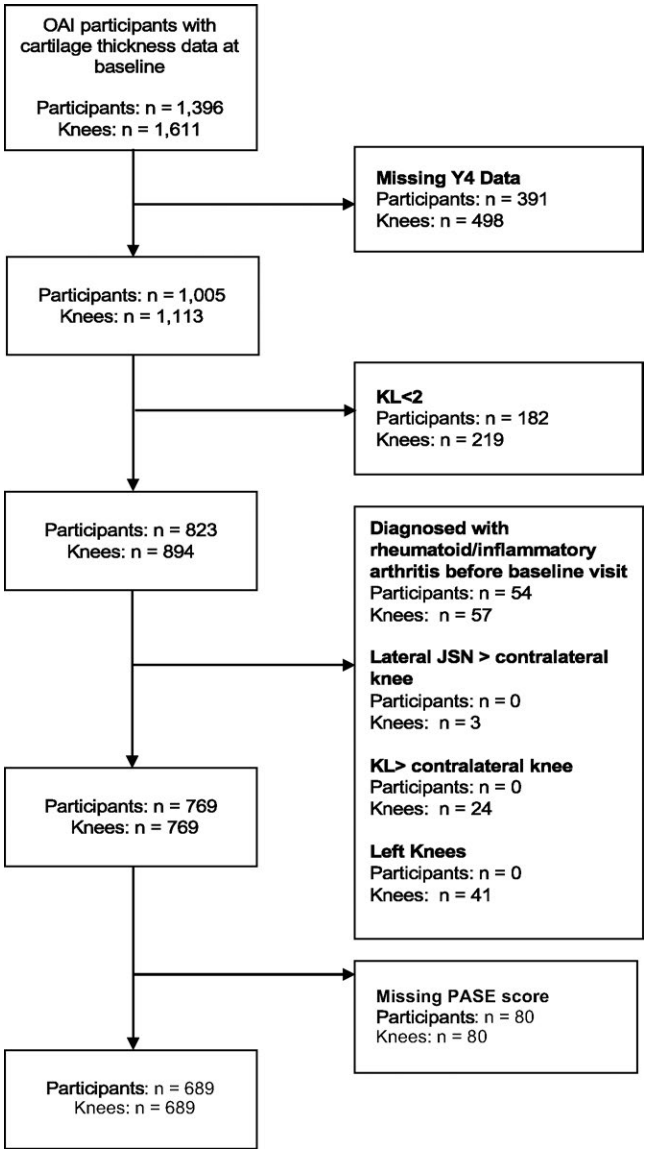

Figure 1. Flow chart of participants included in the study and reasons for exclusion. Y4 = year 4; KL = Kellgren/Lawrence grade; JSN = joint space narrowing; PASE = Physical Activity Scale for the Elderly.

the predominantly affected compartment (16), and because radiographic OA in the medial compartment is more prevalent than radiographic OA in the lateral compartment (17). Additionally, based on longitudinal changes in the 16 femorotibial subregions, location-independent cartilage thinning and thickening scores were computed for the change between the baseline and 4-year follow-up visits by summing all negative (thinning) and positive (thickening) changes across the 16 subregions within each knee (18). Location-independent measures have been suggested to be more sensitive to differences in change between groups than location-based measures, because these measures only depend on the magnitude of change (18–20). Precision errors in measurement for MFTC in people with mild to moderate OA using similar techniques were found to be 1.4% (21).

Physical activity assessment. Self-reported physical activity was assessed with the Physical Activity Scale for the Elderly (PASE) questionnaire at baseline, and at 1-, 2-, 3- and 4-year follow-up visits. The PASE is a valid and reliable questionnaire consisting of a numerical score assessing self-reported occupational, household, and leisure physical activity over a 1-week period (22) that has been previously used in knee OA studies (6,9,10,23). The overall score, ranging from 0 (completely sedentary) to 793 (extremely active), is calculated from weights and frequency values for each of the 12 components listed in the questionnaire (i.e., walking, sports [light/moderate/strenuous], muscular strength/endurance, job [standing/walking], housework [light/heavy], home repair, lawn work, outdoor gardening, and caring for another person). Participants in the current study were categorized into physical activity tertiles based on the PASE score, which was averaged over all 5 visits (low, moderate, and high physical activity).

Statistical analysis. The relationship between the 4-year (average) physical activity level (low, moderate, high) and 4-year cartilage thickness change was investigated in Stata software, version 14.2, using mixed-effects models (restricted maximum likelihood) to calculate mean differences and 95% confidence intervals (95% CIs). These differences were adjusted for baseline age, sex, body mass index (kg/m^2), knee pain using the Western Ontario and McMaster Universities Osteoarthritis Index pain scale (range 0–20, where 0 = no pain and 20 = worst pain [24] in the activities walking on flat ground, going up or down stairs, lying in bed at night, sitting or lying, and standing upright), K/L grade, knee alignment (assessed as frontal plane mechanical axis from full-limb radiographs), and comorbidities using the Charlson comorbidity index (25). In the primary analysis, the association between physical activity level and change in cartilage thickness was analyzed for the entire sample. Following evaluation of the interaction term for physical activity and sex, the primary analytical approach was repeated in secondary analyses stratified by sex (using sex-specific physical activity tertiles). Finally, we explored whether baseline radiographic disease stage (early radiographic OA [K/L grade 2] versus advanced radiographic OA [K/L grades 3/4]), baseline physical activity level, or percent changes in MFTC and cMFTC modified the relationship between physical activity and cartilage thickness loss. The primary outcome measure was defined as cartilage thickness change in the MFTC, because this region is strongly associated with knee OA progression (26,27). Changes in the cMFTC and location-independent thinning and thickening scores were considered exploratory.

Table 1. Demographic characteristics of the participants included in the analysis*

Characteristics	Total cohort (n = 689)	4-year physical activity level		
		Low (n = 231)	Moderate (n = 230)	High (n = 228)
Baseline age, years	61.6 ± 8.9	65.0 ± 8.7	62.8 ± 8.6	57.1 ± 7.5
Men, no. (%)	285 (41)	95 (41)	96 (42)	94 (41)
Baseline BMI (kg/m^2)†	30.0 ± 4.8	29.9 ± 4.4	30.2 ± 5.4	29.9 ± 4.7
Baseline knee injury, no. (%)‡	264 (38)	82 (35)	85 (37)	95 (42)
Baseline knee pain (WOMAC pain)	3.3 ± 3.5	3.6 ± 3.7	3.3 ± 3.5	3.1 ± 3.2
Charlson comorbidity index, no. (%)§				
0	514 (75)	162 (70)	164 (72)	188 (83)
≥1	171 (25)	68 (30)	65 (28)	38 (17)
Baseline knee OA severity, no. (%)				
K/L grade 2	387 (56)	126 (55)	121 (52)	140 (61)
K/L grade 3	277 (40)	98 (42)	96 (42)	83 (36)
K/L grade 4	25 (4)	7 (3)	12 (5)	6 (3)
Baseline knee alignment (degrees)¶				
Men and women	−1.7 ± 3.8	−2.1 ± 3.7	−1.3 ± 3.6	−1.7 ± 4.0
Men	−2.9 ± 3.7	−3.6 ± 3.6	−2.1 ± 3.8	−3.0 ± 3.7
Women	−0.8 ± 3.5	−1.0 ± 3.3	−0.6 ± 3.4	−0.7 ± 3.8
Baseline MFTC cartilage thickness, mm				
Men and women	3.3 ± 0.7	3.2 ± 0.7	3.3 ± 0.7	3.5 ± 0.7
Men	3.6 ± 0.8	3.5 ± 0.7	3.6 ± 0.8	3.8 ± 0.8
Women	3.2 ± 0.6	3.1 ± 0.6	3.2 ± 0.6	3.2 ± 0.6
4-year PASE overall score				
Men and women	153 ± 65	87 ± 23	145 ± 19	227 ± 45
Men	164 ± 69	91 ± 26	156 ± 19	244 ± 42
Women	145 ± 61	84 ± 19	137 ± 16	215 ± 43
4-year PASE household activity				
Men and women	83 ± 31	60 ± 21	90 ± 27	99 ± 29
Men	87 ± 31	63 ± 23	93 ± 28	103 ± 27
Women	81 ± 30	59 ± 58	87 ± 26	96 ± 30
4-year PASE work-related				
Men and women	44 ± 50	8 ± 14	29 ± 31	94 ± 49
Men	46 ± 52	6 ± 11	31 ± 32	102 ± 46
Women	42 ± 49	10 ± 15	28 ± 30	89 ± 51
4-year PASE sport/recreational				
Men and women	25 ± 19	18 ± 13	25 ± 18	33 ± 24
Men	30 ± 21	21 ± 14	31 ± 19	38 ± 27
Women	22 ± 17	15 ± 11	21 ± 15	28 ± 21

* Values are the mean ± SD unless indicated otherwise. Low = Physical Activity Scale for the Elderly (PASE) first tertile, moderate = PASE second tertile, high = PASE third tertile. BMI = body mass index; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; OA = osteoarthritis; K/L = Kellgren/Lawrence; MFTC = medial femorotibial compartment.
† One missing value in men.
‡ 107 missing values (38 men and 69 women).
§ 4 missing values (1 man and 3 women).
¶ 3 missing values (1 man and 2 women). Negative values represent varus alignment.

RESULTS

Participant characteristics. Of the 4,976 OAI participants ages 45–79 years at baseline, 689 knees from 689 participants (404 women) met the inclusion criteria. Demographic data are shown in Table 1.

Relationship between physical activity and cartilage thickness change. A cartilage thickness change in MFTC of –0.20 mm (95% CI –0.22, –0.17) was observed in the entire cohort. Cartilage thickness loss (MFTC and cMFTC) was greater in participants with low physical activity, although it did not differ significantly from cartilage thickness loss in participants with high physical activity (adjusted between-group difference MFTC –0.03 mm [95% CI –0.10, 0.03], cMFTC –0.06 mm [95% CI –0.16, 0.04]), or in participants with moderate physical activity (adjusted between-group difference MFTC –0.04 mm [95% CI –0.10, 0.02], cMFTC –0.04 mm [95% CI –0.13, 0.06]) (Table 2).

Changes in cartilage thinning scores were also greater in the low physical activity compared to the moderate (adjusted between-group difference –0.19 mm [95% CI –0.46, 0.09]) and high physical activity groups (adjusted between-group difference –0.20 mm [95% CI –0.50, 0.95]), but the differences did not reach a level of significance. Thickening scores did not differ significantly between the physical activity tertiles (Table 2 and Figure 2).

A significant interaction between sex and physical activity was observed in the adjusted analysis (P = 0.02), indicating

Table 2. Four-year change in cartilage thickness in Osteoarthritis Initiative participants with established radiographic osteoarthritis stratified by physical activity*

Thickness, mm	Low physical activity	Moderate physical activity	High physical activity	Low vs. moderate *P*		High vs. moderate *P*		Low vs. high *P*	
				Nonadj.	Adjusted†	Nonadj.	Adjusted†	Nonadj.	Adjusted†
Overall (n = 689)									
MFTC	−0.23 (−0.28, −0.19)	−0.17 (−0.21, −0.13)	−0.18 (−0.22, −0.14)	0.04	0.27	0.80	0.66	0.07	0.55
cMFTC	−0.41 (−0.48, −0.34)	−0.33 (−0.39, −0.26)	−0.33 (−0.39, −0.26)	0.10	0.55	0.97	0.87	0.09	0.48
Thinning	−1.81 (−2.02, −1.62)	−1.63 (−1.80, −1.45)	−1.61 (−1.79, −1.44)	0.15	0.27	0.93	0.93	0.13	0.35
Thickening	0.45 (0.40, 0.50)	0.51 (0.46, 0.57)	0.53 (0.47, 0.58)	0.10	0.14	0.77	0.22	0.05	0.80
Men (n = 285)									
MFTC	−0.27 (−0.34, −0.19)	−0.25 (−0.32, 0.18)	−0.21 (−0.28, −0.14)	0.77	0.31	0.40	0.07	0.26	0.43
cMFTC	−0.45 (−0.57, −0.32)	−0.47 (−0.58, −0.35)	−0.37 (−0.48, −0.27)	0.82	0.13	0.25	0.03	0.36	0.52
Thinning	−1.85 (−2.15, −1.55)	−1.90 (−2.20, −1.59)	−1.76 (−2.03, −1.50)	0.81	0.16	0.51	0.19	0.68	0.88
Thickening	0.40 (0.32, 0.48)	0.43 (0.36, 0.50)	0.43 (0.37, 0.50)	0.56	0.52	0.90	0.86	0.48	0.67
Women (n = 404)									
MFTC	−0.21 (−0.27, −0.16)	−0.12 (−0.16, −0.07)	−0.16 (−0.21, −0.11)	0.01	0.01	0.21	0.06	0.14	0.50
cMFTC	−0.38 (−0.47, −0.29)	−0.23 (−0.30, −0.15)	−0.29 (−0.37, −0.21)	0.01	0.02	0.28	0.16	0.13	0.34
Thinning	−1.79 (−2.08, −1.51)	−1.43 (−1.63, −1.24)	−1.51 (−1.74, −1.29)	0.03	0.02	0.65	0.38	0.10	0.17
Thickening	0.49 (0.42, 0.56)	0.58 (0.50, 0.66)	0.59 (0.51, 0.67)	0.10	0.20	0.80	0.18	0.06	0.96

* Values are the mean (95% confidence interval) unless indicated otherwise. Nonadjusted (Nonadj.) mean cartilage thickness changes and 95% confidence intervals were stratified by physical activity tertiles for the whole cohort and separately for men and women. Negative values represent cartilage thickness loss. MFTC = medial tibiofemoral compartment; cMFTC = central medial femorotibial compartment.
† All values are significant. Adjusted for age, sex, body mass index (BMI), knee injury, Kellgren/Lawrence grade, knee alignment, comorbidity index, and Western Ontario and McMaster Universities Osteoarthritis Index pain. A total of 113 participants (41 men and 72 women) were not included in the adjusted analysis due to missing data on knee alignment, comorbidities index, previous knee injury, and BMI.

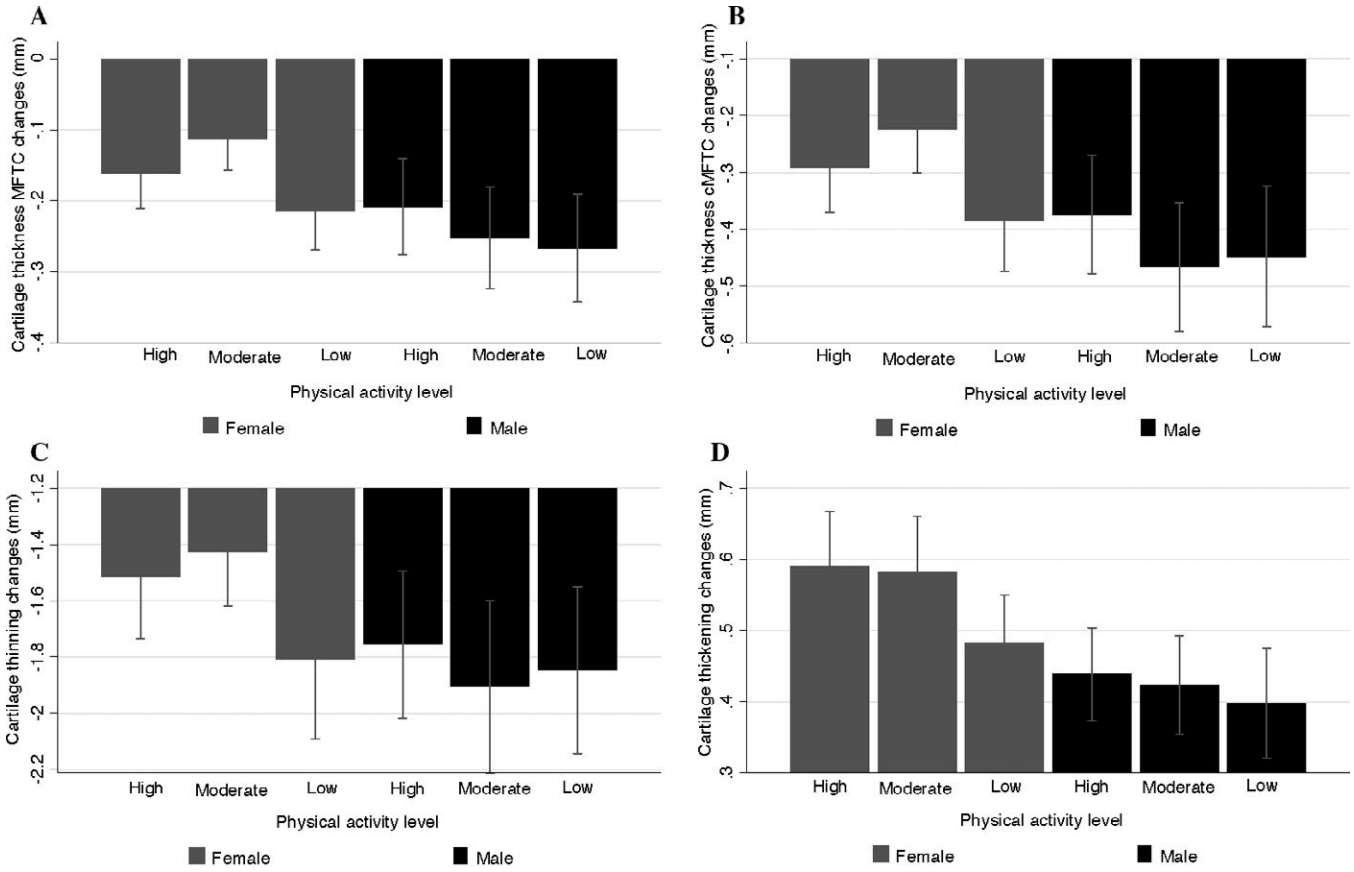

Figure 2. Cartilage thickness changes and 95% confidence intervals between baseline and year 4, stratified by sex and physical activity tertiles. **A**, Medial tibiofemoral compartment (MFTC). **B**, Central medial femorotibial compartment (cMFTC). **C**, Location-independent cartilage thinning score. **D**, Location-independent cartilage thickening score.

a different effect of physical activity in men and women. The analysis stratified by sex showed that women with low physical activity had a significantly larger MFTC and cMFTC cartilage thickness loss and cartilage thinning compared to women with moderate physical activity (adjusted between-group difference MFTC –0.09 mm [95% CI –0.16, –0.02], cMFTC –0.14 mm [95% CI –0.26, –0.02], and thinning –0.42 mm [95% CI –0.80, –0.05]) (Table 2). Interestingly, cartilage thickness loss in the MFTC and cMFTC of women with high physical activity tended to be slightly larger than the observed loss in women with moderate physical activity (adjusted between-group difference MFTC –0.06 mm [95% CI –0.13, 0.02], cMFTC –0.07 mm [95% CI –0.19, 0.05]). In contrast, men with moderate physical activity had a significantly larger cMFTC thickness loss compared to the high physical activity group (adjusted between-group difference cMFTC –0.18 mm [95% CI –0.35, –0.02]) (Table 2). Exploratory analyses showed that the relationship between physical activity and cartilage thickness loss did not differ between K/L grades (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23791/abstract), and the results for the MFTC and cMFTC percent changes are in line with the primary analysis (see Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23791/abstract). Finally, the baseline PASE score did not influence cartilage thickness loss over the 4-year follow-up (see Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23791/abstract).

DISCUSSION

In this evaluation of the relationship between physical activity and MRI-assessed structural cartilage changes in people with knee OA over a 4-year period, we observed that sex modifies the relationship between physical activity and cartilage thickness loss. Although no association was observed between physical activity and cartilage loss in the whole cohort, in women, moderate physical activity may slow down structural disease progression compared to low physical activity levels. Furthermore, high physical activity does not seem to be more harmful than lower physical activity levels for structural changes, either in women or men.

Our findings that physical activity levels did not influence cartilage thickness loss in the overall cohort add to the information from a systematic review on randomized controlled trials, showing that exercise does not harm articular cartilage (28), and also from 2 previous studies that showed no association between physical activity and cartilage loss or cartilage composition in people with cartilage defects or at risk of OA (6,7). Importantly, the evaluation of sex-specific relationships showed that physical activity levels, particularly in women, influenced cartilage thickness loss, which has not previously been reported. More precisely, the observation that moderate physical activity may be structurally protective in women with radiographic knee OA extends previous findings from studies using OAI data, suggesting that moderate physical activity may slow cartilage compositional change (specifically cartilage MRI transverse relaxation time T2) in those patients without radiographic knee OA (10). Although the greatest amount of cartilage thickness loss was observed in men and women with low physical activity, the differences in structural progression between physical activity tertiles were more pronounced in women than in men. The typical annual rate of cartilage loss in the MFTC of knees with radiographic knee OA is 0.06 mm (26), suggesting that the moderate, and high, physical activity observed in the current study may be protective against cartilage loss (annualized loss 0.04 mm and 0.05mm, respectively), whereas low physical activity appears to be associated with structural progression (annualized cartilage loss 0.06 mm). Although only small annualized differences over 4 years were seen, high physical activity does not appear to be as detrimental as low physical activity for structural progression of knee OA.

The specific type of physical activity preferably selected by women or men may partly explain the sex-specific association we observed in the current study. Men had higher absolute PASE scores than women, and the differences between men and women were most pronounced in the subscale related to sports activities, indicating that the type of activity might also have an impact on cartilage thickness loss. Nevertheless, a higher physical activity level may be related to a higher frequency of trauma and injury (29), and thus to a greater loss of cartilage, but we adjusted for knee injury in our analyses. Muscle weakness may have also influenced the sex-specific relationship between physical activity and cartilage thickness. Quadriceps weakness in particular is closely related to physical activity (30) and has been shown to be a risk factor for developing radiographic knee OA (13), for worsening of joint space narrowing (13,31), and for undergoing knee replacement surgery (32) in women, but quadriceps weakness did not display such relationships in men. The influence of quadriceps weakness on the relationship between physical activity levels in women and cartilage thickness should be considered in future analyses.

The results we observed for the location-independent cartilage thinning score were similar but not superior to the results obtained from the primary, location-based outcome measures. Importantly, the location-independent analysis showed that the differences between PASE groups were driven by differences in cartilage thinning (i.e., cartilage loss) and not by differences in cartilage thickening, which could be caused by swelling or hypertrophy (33).

An important consideration in interpreting the results of this study is the use of self-reported PASE scores for defining physical activity tertiles. The PASE questionnaire covers only a limited period of time before each assessment (i.e., 7 days), and in hip OA, the questionnaire has been considered insufficiently sensitive to detect differences that may be important to structural progression (34). In addition, patients with knee OA tend to overestimate their activity level when self-reporting (35), and the aggregate PASE data reported in the OAI limited our ability to analyze individuals based on specific types of activities within each PASE component. Not surprisingly, such a limited window of physical activity assessment was not associated with cartilage loss over time (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23791/abstract) and was an important reason for our use of the mean PASE score over the 4-year study window. Moreover, the mean PASE score in the moderate physical activity tertile was in the range previously suggested to be associated with a recommended waist circumference (36), which reassures that the level of moderate physical activity observed in the current study is clinically important. Furthermore, although participant selection was based on the availability of cartilage thickness measurements performed as a part of previous studies (26,37,38), we adjusted for potential covariates to minimize their impact on results. The phenomenon of index event (collider) bias, while influencing risk factor studies for disease progression, is less likely to have influenced the current study, because both underload and overload are risk factors for incident radiographic disease (39). A limitation of the current study is also the relatively modest sample size compared to the total OAI population, which may have limited the power to detect significant differences. However, we included all eligible participants from the OAI, and to maximize power we focused our primary analysis on the whole cohort (men and women combined; n = 689). Finally, the study sample was not randomly selected from the general population. Instead, participants were from the OAI progression cohort and by definition had more severe disease than the average OAI participant, which included those without knee OA, limiting the generalizability of our findings to other samples.

Patients with knee OA should be counseled and reassured that high physical activity levels do not appear to be more harmful than lower physical activity levels for structural progression of the disease. In the context of current clinical practice guidelines, this assurance is important, because exercise therapy, a first-line treat-

ment for knee OA, is clinically effective, regardless of the physical activity level (40). Although we cannot be sure whether the moderate physical activity level in our study, assessed by tertiles, reflects the actual physical activity guidelines of moderate physical activity, in a non-OA population the PASE questionnaire has been shown to discriminate between participants' physical activity level and physical activity guidelines, where participants who met the physical activity guidelines had a higher PASE score than sedentary participants (41). Although it was outside the scope of the current study (only 66, 16, and 70 participants maintained low, moderate, and high physical activity, respectively), future studies should focus on the influence of physical activity changes over time, since, for example, a sudden increase in physical activity and the consequent increased load may have a different effect on cartilage that is unaccustomed to such a spike in load.

Physical activity was not associated with cartilage thickness loss in the whole cohort, but this relationship significantly differed between men and women. Particularly in women, moderate physical activity may slow down cartilage thickness loss compared to low physical activity levels. For both men and women, high physical activity does not appear to be detrimental for cartilage thickness loss. People with knee OA can be informed that higher activity levels do not further damage their knee joints.

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. Bricca 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. Bricca, Wirth, Kemnitz, Culvenor.
Acquisition of data. Wirth.
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ACTIVITY AND THE RHEUMATIC DISEASES

Using Physical Activity Trackers in Arthritis Self-Management: A Qualitative Study of Patient and Rehabilitation Professional Perspectives

Jenny Leese,[1] Graham G. Macdonald,[1] Bao Chau Tran,[1] Rosalind Wong,[2] Catherine L. Backman,[1] Anne F. Townsend,[3] Aileen M. Davis,[4] C. Allyson Jones,[5] Diane Gromala,[6] J. Antonio Avina-Zubieta,[1] Alison M. Hoens,[7] and Linda C. Li[1]

Objective. To compare and contrast the perspectives of patients with arthritis and those of rehabilitation professionals regarding starting and sustaining use of physical activity trackers (PATs).

Methods. We conducted focus group sessions with patients, physiotherapists, and occupational therapists in Ontario, Alberta, or British Columbia, Canada. To be eligible, patients must have self-reported a diagnosis of inflammatory or osteoarthritis. Rehabilitation professionals reported that at least 40% of their caseload was dedicated to arthritis care. Participants had any level of experience with PATs. A thematic analytic approach was used.

Results. The following 3 themes were identified: 1) anticipating sharing objective measures of physical activity. Participants agreed that use of PATs had the potential to improve consultations between patients with arthritis and rehabilitation professionals but were uncertain how to achieve this potential; 2) perceived or experienced barriers to start or continue using a PAT. Participants shared doubts about whether existing PATs would meet specific needs of patients with arthritis and expressed concerns about possible negative impacts; and 3) bolstering motivation? Although there was agreement that use of PATs could bolster the motivation of patients who were already active, patients and rehabilitation professionals had different opinions regarding whether use of PATs alone would motivate patients to start increasing activity levels.

Conclusion. Our study highlights similarities and differences between the perspectives of patients and rehabilitation professionals regarding the potential value and risks of integrating PATs into arthritis self-management. Despite agreement about the potential of PATs, participants were uncertain how to effectively incorporate these tools to enhance patient–clinician consultations and had differing views about whether use of PATs would support a patient's motivation to be active.

INTRODUCTION

Physical activity is widely recommended as an essential component of optimal self-management among patients with several types of arthritis, including osteoarthritis (OA) (1–3). It is well known that physical activity can improve pain, fatigue, and functional limitation, and can enhance patients' quality of life (4–8). Because patients with arthritis have a higher risk for complications

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[1]Jenny Leese, MA, Graham G. Macdonald, MA, Bao Chau Tran, MSc, J. Antonio Avina-Zubieta, MD, PhD, Catherine L. Backman, PhD, J. Antonio Avina-Zubieta, MD, PhD, Linda C. Li, PhD: University of British Columbia and Arthritis Research Canada, Vancouver, British Columbia, Canada; [2]Rosalind Wong, HBSc: Krembil Research Institute, University Health Network, Toronto, Ontario, Canada; [3]Anne F. Townsend, PhD: Arthritis Research Canada, Vancouver, British Columbia, Canada, University of Exeter, Exeter, UK, and Lancaster University, Lancaster, UK; [4]Aileen M. Davis, PhD: Krembil Research Institute, University Health Network and University of Toronto, Toronto, Ontario, Canada; [5]C. Allyson Jones, PhD: University of Alberta, Edmonton, Alberta, Canada; [6]Diane Gromala, PhD: Simon Fraser University, Burnaby, British Columbia, Canada; [7]Alison M. Hoens, MSc: University of British Columbia, Vancouver, British Columbia, Canada.

Address correspondence to Linda Li, PhD, Arthritis Research Canada, 5591 No. 3 Road, Richmond, BC, Canada V6X 2C7. E-mail: lli@arthritisresearch.ca.

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SIGNIFICANCE & INNOVATIONS

- Our study identifies potential benefits and risks of using physical activity trackers (PATs) to support arthritis self-management, as anticipated by arthritis patients and rehabilitation professionals (physiotherapists and occupational therapists).
- Our findings draw attention to anticipated tensions between patients and clinicians that could impact their communication if use of PATs are integrated into clinical practice.
- Our study presents divergent views between arthritis patients and rehabilitation professionals regarding whether use of PATs would increase the physical activity levels of patients with arthritis. Combining these perspectives provides a nuanced view of the potential value that PATs realistically offer for arthritis self-management, which can help to guide future research.

such as hypertension, cardiovascular diseases, and diabetes, being physically active is also important for secondary prevention (9–12). Physical activity levels among patients with arthritis, however, typically fall below the recommendations of experts (13–18).

Recent advances in self-monitoring technology could potentially support patients with chronic diseases to be active (19–21). Physical activity trackers (PATs) are self-monitoring tools that include wearable technology (e.g., pedometers, accelerometers), websites, and mobile apps designed to record and provide feedback on an individual's movement (e.g., by number of daily steps, time spent in physical activity) (22). In a recent meta-analysis (8 randomized controlled trials and 18 observational studies, including 2,767 patients with chronic diseases) by Bravata et al (23), a mean increase of 2,491 steps per day among pedometer users compared to controls was reported. Evidence also exists to demonstrate that it is feasible that use of PATs may increase the amount of time spent engaging in physical activity (24–27). In a 2018 observational study of 157 patients with rheumatoid arthritis and patients with axial spondyloarthritis, participants considered the use of a PAT to be very acceptable (with a mean score of 8 on a 10-point scale), based on their experiences using the tool for 3 months (28).

In a focus group study including 21 patients with OA, most of whom were unfamiliar with PATs, participants reported that they expected to obtain clearer information about their health if they used a wearable device while undergoing rehabilitation in community settings (29). They also expected that sharing the data collected from the tool with a clinician could improve the clarity of information exchanged, assist them in being involved in the conversation, and enable clinicians to better tailor their treatment (30). Privacy, however, was a concern expressed by the patients, because they questioned whether wearing the tool would draw attention to themselves, thereby becoming "labeled as patients" (29).

In a separate study, orthopedic surgeons, general practitioners, and physiotherapists agreed regarding the potential benefit of using wearables in their practice to monitor patients' progress and guide conversations to tailor and evaluate treatment (31). Little is known, however, about how concordant the perceptions of patients and clinicians may be with regard to the use of PATs in arthritis self-management and how their use may affect patient–clinician relationships. Research in this area is in its infancy, but if PATs are to be used to support arthritis self-management, it is important that future research, intervention design, and implementation strategies take the combined perspectives of patients and clinicians into account (32). In the current study, we used an interpretive, naturalistic approach that aims to compare and contrast the perspectives of patients with arthritis and those of rehabilitation professionals regarding starting and sustaining use of PATs (33).

PATIENTS AND METHODS

Eligible patient participants had self-reported a diagnosis of OA or inflammatory arthritis. Eligible rehabilitation professional participants were physiotherapists (PTs) or occupational therapists (OTs) who were currently practicing and reported that at least 40% of their practice was dedicated to arthritis care. Both patients and rehabilitation professionals were English-speaking, resided in Ontario, British Columbia, or Alberta, Canada, and had any level of experience with PATs, from none to extensive. From February 2014 to April 2015, recruitment flyers were posted in hospitals and clinics in the 3 provinces and on social networking sites (e.g., Craigslist, Kijiji). They were also distributed via e-newsletter, Twitter, and Facebook by patient groups, including Arthritis Consumer Experts and Arthritis Research Canada's Arthritis Patient Advisory Board. Rehabilitation professionals were recruited online (e.g., e-newsletter) through the Arthritis Health Professions Association (Canada). Flyers were also distributed through The Arthritis Society (Ontario Division) and the Mary Pack Arthritis Program in British Columbia.

The research team conducted focus groups separately for patients and rehabilitation professionals. Our focus group design has overtones of constructivism, which is appropriate for exploring multiple subjective perspectives on our phenomena of interest (34–36). Social interaction in a focus group can also provide rich data to allow better understanding of how perspectives coexist within a community, for example, by offering an opportunity for participants to interact and ask questions of each other while exploring agreements and disagreements (34). Because some participants were not available to attend a focus group session,

Table 1. Sample questions for patient and rehabilitation professional focus groups

Section heading in topic guide	Sample questions
Use of online tool for general health/fitness	Please tell me what kind of online tool(s) you have used/your patients use for general health or fitness*
	Probes
	What do you/your patients like about them?
	What don't you/your patients like about them?
	How did you/your patients start using them?
	How do you/your patients use them?
	How helpful or unhelpful are they?
Potential benefits and challenges to using physical activity–monitoring tools†	What do you think are the similarities and differences of these online tools compared with the ones you/your patients have used or know about to track physical activity?
	Can you think of both positive and negative aspects of using these tools?
	These tools have the ability to transfer information between patients and doctors or therapists. What do you think about this feature? What are the benefits? Do you see any downsides to this?
	For some of you, the tools you see today may be new to you. If given the opportunity, would you use them? What might help or be a barrier to using them in your everyday life?
Use of online physical activity–monitoring tools and patient–health professional communication†	Can you think of examples of:
	… how these tools affect your communication with your health professionals/patients?
	… how these tools affect your involvement in your health care and how you keep track of your physical activity?

* This question was intended to serve as an ice-breaker and provide an opportunity for the facilitator to assess the level of experience with physical activity trackers (PATs) among the group.
† A brief presentation of some examples of PATs preceded the questions asked in this section.

we made the pragmatic decision to offer the option of a one-to-one telephone interview in the interests of generating a diverse range of perspectives. The topic guide was designed to encourage participants to contribute to the discussion by sharing their perspectives, regardless of their degree of experience with PATs (Table 1).

The 2-hour focus group sessions were organized into 3 sections examining perceptions regarding 1) using online tools for general health and fitness, 2) potential benefits and challenges to using PATs, and 3) how using PATs may potentially affect communication between patients and clinicians in clinical practice. Focus groups were moderated by members of the research team who had experience in qualitative research (JL, RW). During the session, facilitators gave a brief presentation to propose a definition of commercially available PATs and support common understanding of terminology. They encouraged group discussions during which participants voiced their priorities. Audio recordings of focus groups were transcribed verbatim, and transcripts were de-identified. Ethics approval was granted by the University of British Columbia Behavioural Research Ethics Board (H13-01894), Vancouver Coastal Health (V13-01894), and the University of Alberta Health Research Ethics Board (Pro00042758). In Ontario, approval was granted by the University Health Network Research Ethics Board (13-6782-AE) and Queensway Carleton Hospital Research Ethics Board (14-11).

Our study was conducted based on an inductive thematic analysis method, the following 6 phases of which are described by Braun and Clarke: 1) familiarization with data, 2) generating initial codes, 3) searching for themes, 4) reviewing themes, 5) defining and naming themes, and 6) producing the report (37). Transcripts from patient focus groups were read repeatedly by authors JL and BCT. No preselected codes were identified prior to analysis. After focus group sessions were completed, initial codes were generated manually using all data from a selection of the transcripts. Focus group sessions ceased when the research team judged that the data generated were sufficiently detailed and varied enough to provide a description rich enough to satisfy our research objective (38). We constantly compared codes within each selected transcript and across these transcripts, seeking to identify inconsistent codes and potential patterns.

We then considered how to combine all codes generated from the selected transcripts and sorted them into potential themes (37). Next, we used NVivo version 10 software to sort data from the remaining transcripts of patient focus group sessions within the potential themes. Inconsistent codes from these remaining transcripts were sought, and potential themes were reworked in order for data within each theme to cohere meaningfully. Author GGM followed the same process of analysis with transcripts from focus groups and interviews with rehabilitation professionals. Once themes were identified, authors JL, GGM, and BCT held meetings to discuss how themes compared and contrasted across the separate data sets of the patient and rehabilitation professional focus groups and interviews. Through discussion, themes across the entire data set (including data for patients and rehabilitation professionals) were further defined and refined. To enhance the precision of the findings, analyses were carried out in consultation with co-authors who had generated the data or were familiar with the entire data set.

RESULTS

Forty patients (31 women) participated in 9 focus groups, with 3–6 participants in each group. The median age of the patient participants was 59 years (range 23–78 years) (Table 2). Eighteen participants (45%) reported a diagnosis of OA, 15 (37%) reported a diagnosis of inflammatory arthritis, and 7 (17%) reported a diagnosis of both OA and inflammatory arthritis. Thirty-seven patients (93%) provided information about their previous use of PATs. Of those, 16 (38%) used a PAT 1–2 times per year, 2 (5%) used a PAT 1–2 times per month, and 13 (33%) used a PAT 1–2 times per week. Participants using a PAT 1–2 times per year or per month had often tried a PAT but stopped for reasons such as feeling frustrated when the PAT did not work in the way they expected. Participants who used a PAT 1–2 times per week often accessed their PAT data records via their cell phones. Six participants (15%) had no experience with PATs. A total of 25 clinicians (21 PTs and 4 OTs) participated in 5 focus groups (3 in British Columbia, 1 each in Alberta and Ontario) and 3 interviews (2 in Alberta and 1 in British Columbia). Among 17 clinicians, 9 (36%) reported having used a PAT with their patients in the past (Table 3).

Table 2. Characteristics of the patient participants (n = 40)*

Age, median (range) years	59 (23–78)
Female sex	31 (77)
Self-reported diagnosis	
Osteoarthritis	18 (45)
Inflammatory arthritis†	15 (37)
Both osteoarthritis and inflammatory arthritis	7 (17)
Education	
University (attended/graduated)	22 (55)
High school graduate	15 (38)
Unknown‡	3 (7)
Employment status	
Employed	19 (48)
Retired/homemaker	14 (35)
Disability leave	2 (5)
Unknown‡	5 (12)
Urban/suburban residence	40 (100)
Annual household income (Canadian dollars)	
<$40,000	8 (20)
$40,000–80,000	12 (30)
>$80,000	9 (23)
Unknown‡	11 (27)

* Except where indicated otherwise, values are the number (%).
† Includes rheumatoid arthritis, lupus, psoriatic arthritis, gout, Sjögren's syndrome, polymyositis, and ankylosing spondylitis.
‡ Participants did not provide the information.

Table 3. Characteristics of the rehabilitation professional participants (n = 25)*

Age, median (minimum, maximum) years	47 (28, 61)
No. of years in practice, median (minimum, maximum)	22 (5, 38)
Female sex	23 (92)
Practice setting	
Outpatient (includes clinic and hospital)	14 (6)
Inpatient (hospital)	15 (6)
Home care	3.5 (14)
Unknown†	6 (24)
Employment status	
Full-time	11 (44)
Part-time	7 (28)
Unknown†	7 (28)
Practice location	
Urban/suburban	16 (64)
Rural/remote	2 (8)
Unknown	6 (28)
Experience using PATs with patients	
Used PATs before with patients	9 (36)
No experience using PATs with patients	8 (32)
Unknown†	8 (32)

* Except where indicated otherwise, values are the number (%). PATs = physical activity trackers.
† Participants did not provide the information.

Three themes were identified: 1) anticipating sharing objective measures of physical activity, 2) perceived or experienced barriers to start or continue using a PAT, and 3) bolstering motivation? Patients cited relationships with a variety of clinicians, e.g., mentioned data-sharing with their doctor(s) and did not limit themselves to rehabilitation encounters during which rehabilitation professionals focused on their own rehabilitation practice encounters. Participant quotes are labeled with R (Rehabilitation Professional) or P (Patient) followed by numbers and letters corresponding to their speaker number in their focus group, province, and group (e.g., R2B3 is Rehabilitation professional number 2 from British Columbia focus group number 3), or by the number assigned to the interview (e.g., RI2 is Rehabilitation professional Interview 2).

Theme 1. Anticipating sharing objective measures of physical activity. There was agreement among patients and rehabilitation professionals that establishing a "concrete" baseline of patients' activity levels using objective measures from PATs had the potential to make consultations more effective and efficient. Both patients and rehabilitation professionals expected that objective measures from PATs would help rehabilitation professionals to develop treatment plans with their patients. Rehabilitation professionals also emphasized that the objective

Table 4. Supporting quotes from participants for theme 1 (anticipating sharing objective measures of physical activity)*

Participants
Patient participants
Patient 2 (experience with PATs was not reported). I mean it might be useful for the physiotherapist to know whether you're actually doing your exercises or not … You know with the physios maybe, I know with the data there's lots of automated ways of saying you haven't done enough, here's a prod to say remember to do your exercises. That might be helpful (British Columbia group 2).
Patient 4 (uses a PAT 1–2 times per year). I don't know 'cause I haven't done it, but it seems to me like I would like it if my physio said we're going to do an eight-week plan and I am going to follow your activity and I am going to see you every week and we are going to talk about it and we're signing up that your goal is to progress and you're going to be accountable on a weekly basis and I will see that information. And I think for me that level of accountability would be helpful … (British Columbia group 2).
Patient 1 (never used a PAT). I have to wonder what doctors would think about this influx of all this information that they'd be getting from patients. They're pressed for time as it is (British Columbia group 1).
Patient 2 (uses a PAT 1–2 times per week). That's true, you don't want to overwhelm them because they got so much other stuff but, to me, it would be similar to getting a lab report or an x-ray (British Columbia group 1).
Patient 3 (uses a PAT 1–2 times per week). I see it like they'll just get this information and file it … I just don't see them interpreting it and doing something with it and I can't expect them to because they're very busy and they have so many patients … (British Columbia group 1).
Patient 2 (experience with PATs was not reported). I think also too it depends what rapport you have with the doctor and how they're relating to your disease (British Columbia group 1).
Patient 3 (never used a PAT). I'd certainly be interested in working with it [accelerometer] with my health professional as long as I have a health professional who knows me. I mean I think that's very important … (British Columbia group 3).
Rehabilitation professional participants
Rehabilitation professional 3. I think people are subjective when they give you feedback … It's a lot more time effective to have something that's objective than to sort through subjectively […] They could clear up a lot of confusion I would think, perception versus reality, yeah, if they're seeing me because they want help with managing their chronic disease and one of the pieces of evidence is that activity assists that and if I can get them to agree at least to that premise, then we can start having the conversation of okay, what's your activity today and where do you want to go, how important is that to you. But without having that data, that baseline, we can't have that conversation (Alberta group 2).
Rehabilitation professional 4. Potentially it could help your visit with them to be a lot more effective (Alberta group 2).
Rehabilitation professional 2. It would just be one more tool to use to help you set your targets with the patient, to figure out what your next goal should be, to help you be able to develop a treatment plan … It has the potential to help you be more effective within a visit and to help navigate through some those conversations that are difficult where you're trying to tease out that information that might help with that piece … it's just another tool […] (Alberta group 1).
Rehabilitation professional 1. I think it changes our role too as a health care practitioner and how do we interact with our patients and what is our role with them to help guide them through this as a coach … I think it offers a really nice place to start a conversation because you can always ask them how they feel about the information that they're being given … How are they interpreting it? How do they feel about their health? Where do they wanna go next with it in terms of their next steps? (Alberta group 1).
Rehabilitation professional 3. I would love to use it as a baseline. I think it would be really useful … to just get a sense of how much they are not doing or are doing because you get people both ends where they say I don't do anything but when you start probing, they actually are doing a lot of walking but they're not considering that as exercise. And then you have the other people who say oh yeah, I'm doing enough and you find out they're doing absolutely nothing. So it would be just helpful to clarify that … (British Columbia group 1).
Rehabilitation professional 2. I also think it would be a good feedback for you if your treatment is working and the reason why I say that is you know we're giving them these exercises and they don't see the difference but you know it takes like six to seven weeks to see maybe functional gains or you, they're noticing changes in how they're feeling in fatigue. But maybe if they see in the short term, oh, I've increased this, then it's like some form of like physical proof that okay you know maybe my symptoms aren't any better but I'm doing a bit more … (British Columbia group 1).
Rehabilitation professional 4. I think it is very helpful … we talk so much about pacing, pacing exercise, pacing activity, housework, desk work. We talk about pacing so much and it could be a useful teaching tool because people aren't always aware of or they might be feeling pretty good so they decide to keep doing something a little bit longer than they should or they take too long a break between activities. It could be helpful in terms of that education awareness for pacing (Alberta group 4).

* PATs = physical activity trackers.

measures could potentially be used as a "teaching tool" to assist patients in understanding how activity levels could be linked to arthritis symptoms (Table 4).

Many rehabilitation professionals and patients believed that physical activity data recorded by PATs could be used to enhance their communication with each other during clinical visits. For example, rehabilitation professionals suggested that their patients' data could be a "starting point for conversation" by adding objective information to subjective accounts. Although many patients echoed this belief, some also anticipated a nega-

Table 5. Supporting quotes from participants for theme 2 (perceived or experienced barriers to start or continue using a PAT)*

Participants
Patient participants
Patient 3 (never used a PAT). It's a vanity for a few months. You know I used to have an MP3 player and a couple of little things. For the first couple of weeks it was fancy and then it is sitting there in my desk, I don't use it at all. I think it's just like anything else, I think unless we see a dire need for something like that it just sits there (Alberta group 1).
Patient 5 (never used a PAT). With so many gadgets around … I really don't know whether we need it or not … 'cause you know physically, I'm active. Whenever I get a chance, I go walking. I used to walk like 15 kilometers a day going to the office and coming back even though I could use my car but I preferred to do that (British Columbia group 2).
Patient 3 (uses a PAT 1–2 times per week). When the novelty wears off, I think the Fitbit will come off and then that's a hundred dollars wasted so … I don't know … I would like to try one of these and see if it made a difference for me. I'm skeptical … I'm not sure I would get my hundred dollars' worth, so like I can see the benefits of it but my little app that was free has served me very well right now (Ontario group 3).
Patient 2 (experience with PATs was not reported)…. the apps they're just so specific … I do such a combination between yoga and swimming and walking and skating that there's just been nothing that actually would let me put the energy in, or the exercise in or make it work. So I found that frustrating and I just stopped using it (Alberta group 1).
Patient 3 (uses a PAT 1–2 times per year)…. mostly when I stopped using it was because I would forget and then it would be like a week later, I'm like oh, I should start again but now I've lost all that progress and I don't really want to go back to zero, not really (Alberta group 2).
Patient 4 (uses a PAT 1–2 times per month). I agree with you, it's just forgetting to wear it (Alberta group 2).
Patient 1 (experience with PATs was not reported). I don't think any of us ever want to go back to zero (Alberta group 2).
Patient 3. No (Alberta group 2).
Patient 2 (never used a PAT). When I'm fit, it's great. When I have an attack, it's like the last attack I was off work for five days, six days, and one day I think I got out of bed maybe twice … I know that I can probably count how many steps I made in that day, that one particular day, and that's not really a fitness thing, that's a my God this hurts I don't want to move thing, so seeing how many steps I didn't take wouldn't really help my morale I guess (Alberta group 2).
Rehabilitation professional participants
Rehabilitation professional 3. We do deal with a lot of people who are on very minimal incomes and income assistance and there's just no way that they could afford the walkers, never mind, so this would be a way above an adjunct (British Columbia group 3).
Rehabilitation professional 1. They're a good initial tool. I don't think [patients] should rely on them. So I think the cost of them being $150 may prohibit some people from doing them and then it just goes in the drawer after (British Columbia group 3).
Interviewer. What is it about the clip that makes it harder for the person with arthritis? (British Columbia group 3).
Rehabilitation professional 1. Hand function, it's hard to push the clip, and it doesn't open enough (British Columbia group 3).
Interviewer. Are there other conditions that prevent you from introducing these as well? Macular degeneration. A lot of people we see can't see (British Columbia group 3).
Rehabilitation professional 1. Is it giving appropriate information to a patient who has a certain health problem? Well, I have a lot of people who are deteriorating, so instead of actually being inspired by walking a little bit further, they are going to be uninspired by walking not as far even though they may be doing their best (British Columbia group 3).

* PATs = physical activity trackers.

tive response from a clinician if they shared their PAT records with them (Table 4). Despite believing that it would be "for my benefit, I share that information with my doctor so that he can tell me what I'm doing wrong," one participant expected there may also be times when "I don't want my doctor to know otherwise he will yell at me" (P3A1 [never used a PAT]). Patients suggested that the quality of their relationship with clinicians could play an important role in determining whether they felt comfortable sharing their PAT records (Table 4). One patient (P1A2 [uses a PAT 1–2 times per month]) commented "I will share with [a clinician] sometimes … if they seemed competent, I'd be more willing to share."

Many patients and rehabilitation professionals indicated that they were uncertain how information from PATs would be integrated into the consultation. Some patients questioned whether clinicians would welcome information from PATs. Indeed, one rehabilitation professional (R1O1) worried that analyzing information provided by a patient's PATs may mean rehabilitation professionals doing "more in less amount of time." While one patient wondered whether clinicians would find the information useful, others doubted that it would be realistic for clinicians to make use of the information, given perceived time constraints that already exist for clinician visits (Table 4).

Theme 2. Perceived or experienced barriers to start or continue using a PAT. Both patients and rehabilitation professionals expressed uncertainty about whether PATs could provide sufficient benefit for patients to justify their use. Among the patient participants who had never used a PAT, some did not think that

Table 6. Supporting quotes from participants for theme 3 (bolstering motivation)*

Participants
Patient participants
Patient 3 (uses a PAT 1–2 times per week) …. the motivator for me would be oh my God, I've only gone 9000 steps, I'd better get off the subway earlier and walk (Ontario group 4).
Patient 2 (experience with PATs was not reported). There was one I tried … you put a goal of how much hours you want to work per week … in my mind if I go no, I promised myself I would do this many a week and I've gotta get there, so even though my body's saying maybe you should take it easy this week, that I'm pushing to do more (Alberta group 1).
Patient 2 (experience with PATs was not reported)…. again they're nice to have but if I didn't have my RunKeeper would I still be running? Yeah. So I mean … (British Columbia group 2).
Patient 5 (never used a PAT). In a way it's kind of feel good factor (British Columbia group 2).
Patient 2. Yeah. It's nice reinforcement but it's, it's whether you, whether you think the tools are actually going to be enough to get people out there or not … […] (British Columbia group 2).
Patient 5. I don't think it's going to prod me to do something that I was not doing, okay, I was not doing earlier … (British Columbia group 2).
Patient 3 (experience with PATs was not reported). Same thing, yeah (British Columbia group 2).
Patient 5. So it's all about self-motivation right, and … (British Columbia group 2).
Patient 3. Self-motivation, if it's not there then these devices are not useful yeah if you don't have self-motivation (British Columbia group 2).
Patient 2. If you're not going to do the exercises, I don't, if you don't have the motivation to do it in the first place or to do enough exercise, I'm not sure if the tool is going to be enough to push you over that edge to say you should be going (British Columbia group 2).
Patient 4 (never used a PAT). We already have the motivation. We know if we don't show up at the pool three times or four times a week, we won't be walking as easily and as well … we already have that internal motivation (Alberta group 1).
Rehabilitation profession participants
Rehabilitation professional 5. One patient told me that when they did first get their app or their pedometer, it was a Fitbit style, they said they were absolutely shocked at how little they were doing, and they never actually tracked themselves that way before and I think you know it was like 2000 steps or less. And just a wakeup call because oh, I am so sedentary, I had no idea. So in that way it kind of oh, we gotta do something now so that was a good benefit to her having it (British Columbia group 1).
Rehabilitation professional 1 …. if you take an inactive person even if, in my mind, it matters to me less which one they choose as long as it motivates them and if it gives them some empowerment to go ahead and say no I can do this. Cause there's definitely people out there who think I don't have the knowledge or I don't have the motivation and I can't afford a personal trainer, I can't do this on my own (Alberta group 1).
Rehabilitation professional …. some patients don't think they've done anything all day but really they've been on their feet all day moving around, and we could look at that together and say like oh, well what do you think, like this says that you didn't really take any rest or something. Or the opposite. And I guess it would be good for sort of like self-management … monitor their own activity … then they take it and they go off on their own so they don't have to be like dependent on a physio or someone to give them that feedback (Alberta interview 1).
Rehabilitation professional …. especially in arthritis, I think if people feel more accountable then they're more likely to follow you know what it is that you prescribe to them and … it be more *them*-centered as opposed to you trying to get them to do this activity … That it's for their, you know their long term health or managing their symptoms (Alberta interview 2).
Rehabilitation professional. It would motivate them if they knew I was checking on them because then they would say oh, you know I need to, for those who need that or benefit from that. Not everybody benefits from that but you know if you, it's like you know if you don't the teacher's going to check your homework then you're going to do it. If you know that you do your homework and the teacher never checks it, well, you're going to slide (Alberta interview 3).

* PATs = physical activity trackers.

they had a genuine need for the tools, often because they reasoned that they were already active. Both rehabilitation professionals and patients (including a patient who used a free PAT online 1–2 times per week) were uncertain about whether purchasing a PAT would be a wise financial investment for patients, anticipating that the novelty of the tool may wear off (Table 5).

Some patients indicated that they had stopped using a PAT after using it for a period of time. Furthermore, a few participants experienced difficulties setting up the tool due to pain and stiffness in the joints. For example, one patient (P1B3 [uses a PAT 1–2 times per year]) commented "I've got the Fitbit One … it's got the rubber on there that's difficult to fit the Fitbit into … If you've got good hands it's not an issue but, nine weeks of having a splint on, it's really awkward to do … [the dongle is] a tiny, tiny, little piece, try and fit that into the USB with bad hands." Some rehabilitation professionals also expected that problems with hand function or eyesight would prevent the use of some models of PATs by patients with arthritis (Table 5).

Another concern was the potential for PATs to have a negative effect on patients' emotions. Patients described experiencing fluctuations in their ability to be physically active from day to day due to their symptoms and, in this case, were of the opinion that they would not want to be reminded by a PAT of their physical activity levels. These concerns were echoed by rehabilitation professionals, who noted that the use of PATs could be "uninspiring" to patients with "deteriorating" health (Table 5).

Theme 3. Bolstering motivation? Despite uncertainties, there was agreement among rehabilitation professionals and patients that using PATs had the potential to bolster patients' motivation to be active (Table 6). Based on past experiences using PATs in their day-to-day lives, some patients expressed that PATs had bolstered their motivation by improving awareness of their activity levels, with one patient (P3O3 [uses a PAT 1–2 times per week]) recounting "I look and see well it's that fourth kilometer that I slow down the most so it motivates me to try and do a little bit more." These already-active patients described their use of PATs as a "nice reinforcement" of their motivation, providing incentive to push themselves a bit further and reach a physical activity goal they had set (Table 6).

Patients and rehabilitation professionals did not agree, however, about the value of patients sharing their PAT records with clinicians. Rehabilitation professionals often speculated that PAT records could be useful for coaching patients to be "good self-managers of their chronic disease," expecting that some patients may be motivated to be active if they knew their performance was being monitored (Table 6). One rehabilitation professional reported "It would motivate [some patients] if they knew I was checking on them" (RI3).

On the other hand, the views of patients were mixed. For example, one patient (P2B1 [uses a PAT 1–2 times per week]) agreed that she may feel more accountable if a clinician was monitoring the PAT records, commenting "I like the idea that if [data] went to my doctor, 'cause then I'm more accountable … Because they get the information and then I get the phone call or the email saying … we need to discuss some stuff you know. I think that would keep you maybe a little more on track," while another patient (P2B2 [experience with PATs was not reported]) doubted that having PAT records monitored by a clinician would be enough to motivate a patient. She said "I think being diagnosed with arthritis … that was enough to say right, better change the way you live … even if [the tools] were given to you by your doctor to say you need to do this so I'm giving this to track whether you're doing it or not … I don't think it would make the difference. You're either going to do it or you're not." Regardless, the sentiment among patients was that the use of PATs was not a replacement for a patient's own motivation (Table 6).

Finding the motivation to be physically active was perceived by patients to be a personal responsibility. One patient (P4B2 [uses a PAT 1–2 times per year]) remarked "I really get the sense with my doctor and even my physios, you know, they all say well it's 95 percent me … if I wasn't doing it well that's for me to motivate myself, right? … it's for me to find the means and the motivation … ." From patients' perspectives, PATs would be ineffective in bolstering motivation if patients were not already motivated to be active but were a nice addition for those who were already active and wanted to "do a little bit more."

DISCUSSION

By comparing and contrasting the perspectives of patients with arthritis and those of rehabilitation professionals, this study provided valuable insight into possible benefits and risks of using of PATs in arthritis self-management. Divergent perspectives regarding the effectiveness of PATs to increase physical activity levels in patients with arthritis were also examined. By combining these relevant and varied perspectives, we are able to present a nuanced view of the potential that PATs offer for arthritis self-management, which could help to guide future research, intervention design, and implementation strategies in ways that are meaningful to those who are likely to be impacted most. For example, although both patients and rehabilitation professionals commonly envisioned that sharing records from PATs had the potential benefit to improve their consultations, many were also uncertain about how this potential could be realized in practice. Patients and rehabilitation professionals were similarly uncertain about whether it would be realistic for clinicians to analyze PAT records during clinic visits, given the perceived time constraints. Some patients also questioned whether they would feel comfortable sharing their PAT records with their clinicians, with one patient anticipating that he might receive a hostile response. Some patients highlighted that the quality of their interaction with their clinician would be important in determining whether or not they felt comfortable sharing their PAT records.

Our findings align with existing studies that foreground how interactions between patients and clinicians impact and are impacted by patients' use of technologies with clinicians (39–43). Although our findings align with those in the current literature suggesting that use of PATs has the potential to enhance communication between patients and clinicians (29–31), they also provide a more balanced view of expectations of what PATs may realistically offer in terms of supporting arthritis self-management.

Although both patients and rehabilitation professionals believed that PATs could bolster the motivation of patients who were already active, there were contrasting views with regard to whether PATs would motivate less-active patients to start increasing their activity. It was suggested by rehabilitation professionals that PATs would motivate some less-active patients to start increasing their activity if they knew their performance was being monitored by a rehabilitation professional. There was strong agreement among patients, however, that using PATs (with or without involvement of a clinician) would have no effect on whether less-active patients would start increasing their activity if they were not already motivated to do so. An important implica-

tion is that a patient's stage of readiness for physical activity is critical for determining whether or not using a PAT would be effective for increasing physical activity levels among patients with arthritis (44). It is to caution against any expectation that using PATs would increase physical activity levels among patients with arthritis regardless of their level of readiness for physical activity. If use of PATs is successfully integrated into arthritis self-management, further research is needed to determine how effectively PATs can be used to encourage patients with arthritis to be physically active at various stages of their readiness for physical activity.

Theory-driven modifications in the future design of interventions involving PATs may be helpful if these tools are to be used to increase activity levels among less-active patients who are not already motivated. Originating from social cognitive theory, behavior change techniques (e.g., providing feedback on performance, action-planning, and goal-setting) have been implemented in clinical interventions associated with successful increases in physical activity (45,46). In a systematic content analysis, Lyons et al (47) compared 13 wearable devices and observed that these systems rarely contained certain behavior change techniques, including problem-solving, action-planning, commitment, instruction on how to perform the behavior, and behavior practice. Clinicians could provide these behavior techniques in interventions that involve a patient's use of PATs. Indeed, both patient and rehabilitation professional participants in our study anticipated potential difficulties if patients were to use PATs without guidance from a clinician. There was agreement, for example, that the emotional well-being of some less-active patients (e.g., due to disease flares) may be negatively affected if a clinician was not involved in setting realistic goals with the patient. Lyons et al also highlighted that because wearables are available commercially and can be used without consultation with clinicians, there is potential for patients' use of PATs to increase the risk of negative outcomes if, for example, activity programs with default pre-set goals were implemented without oversight from a clinician experienced in arthritis care (47). Further research is warranted to evaluate the clinician's role in supporting theory-based interventions that involve PATs as safe self-management support.

It is important to note that most patient participants were not habitual users of PATs, and most rehabilitation professional participants were not habitually using PATs with their patients. Rehabilitation professional participants also were not necessarily involved in the care of the patient participants in the current study. Although insight into how the use of PATs impacts and is impacted by actual encounters between rehabilitation professionals and patients with arthritis is thus limited, our study contributes new insights regarding the perceived values and risks associated with use of PATs in arthritis self-management, which can guide the direction of future research.

We also recognize limitations regarding the transferability of the findings in the current study. It is possible, for example, that the shared perspectives of our participants do not reflect those of patients and rehabilitation professionals from regions beyond British Columbia, Alberta, and Ontario, where arthritis rehabilitation services are currently concentrated. In addition, our data did not include the perspectives of patients with arthritis in rural and remote areas. Nonetheless, this study offers new insights into understanding the use and perception of PATs in arthritis care from relevant and varied perspectives of arthritis patients and rehabilitation professionals in Canada.

In conclusion, our findings shed light on issues that may hinder optimal use of PATs to support physical activity in patients with arthritis. Although participants agree that there is great potential for PATs to improve arthritis self-management, they also share doubts about the value of incorporating existing PATs and are uncertain about how to successfully incorporate PATs to enhance patient–clinician consultations and encourage patients to be physically active. We suggest a possible path forward to evaluate the effectiveness of theory-driven interventions involving the use of PATs by patients, with support from their clinicians.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Li 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. Backman, Townsend, Davis, Jones, Gromala, Avina-Zubieta, Li.

Acquisition of data. Leese, Macdonald, Tran, Wong, Davis, Jones, Li.

Analysis and interpretation of data. Leese, Macdonald, Tran, Wong, Backman, Townsend, Hoens, Li.

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ACTIVITY AND THE RHEUMATIC DISEASES

Identification and Evaluation of Self-Report Physical Activity Instruments in Adults With Osteoarthritis: A Systematic Review

Robert D. Smith,[1] Krysia S. Dziedzic,[2] Jonathan G. Quicke,[2] Melanie A. Holden,[2] Gretl A. McHugh,[3] and Emma L. Healey[2]

Objective. To identify and evaluate the measurement properties of self-report physical activity instruments suitable for patients with osteoarthritis (OA).

Methods. We conducted a comprehensive 2-stage systematic review using multiple electronic databases, from inception until July 2018. In the stage 1 review, we sought to identify all self-report physical activity instruments used in individuals with joint pain attributable to OA in the foot, knee, hip, or hand. In the stage 2 review, we searched for and appraised studies investigating the measurement properties of the instruments identified. In both stages of the review, we screened all articles for study eligibility criteria, completed data extraction using the Qualitative Attributes and Measurement Properties of Physical Activity questionnaire checklist, and conducted methodology quality assessments using a modified COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) checklist. Measurement properties for each physical activity instrument were evaluated and combined, using narrative synthesis.

Results. In the **s**tage 1 review, we identified 23 unique self-report physical activity instruments. In the stage 2 review, we identified 54 studies that evaluated the measurement properties of 13 of the 23 instruments identified. Instrument reliability varied from inadequate to adequate (intraclass correlation coefficient ≥0.7). Instrument construct and criterion validity assessment showed small to moderate correlations with direct measures of physical activity. Instrument responsiveness was assessed in only 1 instrument and was unable to detect changes in comparison to accelerometers.

Conclusion. Although many instruments were identified as being potentially suitable for use in patients with OA, none demonstrated adequate measurement properties across all domains of reliability, validity, and responsiveness. Further high-quality assessment of self-report physical activity instruments is required before such measures can be recommended for use in OA research.

INTRODUCTION

Osteoarthritis (OA) is a clinical syndrome of joint pain with varying degrees of limitation in physical function and reduced quality of life and most commonly affects the knee, hip, hand, and foot (1). Physical activity, such as therapeutic strengthening exercises or aerobic exercise, can reduce joint pain symptoms and improve physical function. Physical activity is recommended

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[1]Robert D. Smith, PhD, MSc Public Health, BSc Sport Science: University of Hong Kong, Hong Kong, China; [2]Krysia S. Dziedzic, PhD, Jonathan G. Quicke, PhD, MSc, BSc (Hons) Physiotherapy, Melanie A. Holden, PhD, Emma L. Healey, PhD: Research Institute for Primary Care and Health Sciences, Keele University, Keele, UK; [3]Gretl A. McHugh, PhD, MSc Public Health, B.Nurs (Hons): University of Leeds, Leeds, UK.

Address correspondence to Robert D. Smith, PhD, MSc Public Health, BSc Sport Science, 3/F William M. W. Mong Block, 21 Sassoon Road, Hong Kong, Pokfulam, Hong Kong. E-mail: robsmith@hku.hk.

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SIGNIFICANCE & INNOVATIONS

- Physical activity is a recommended core treatment for patients with osteoarthritis (OA) and is a commonly used outcome in clinical trials. Therefore, accurately measuring current physical activity levels and changes in physical activity in patients with OA is vital.
- This systematic review updates and builds on a previous systematic review examining the measurement properties of physical activity instruments suitable for adult patients with OA, collecting evidence from 54 studies.
- This study highlights the need for high-quality assessment (following COSMIN [COnsensus-based Standards for the selection of health Measurement INstruments] guidelines) across all measurement properties of self-report physical activity instruments before such measures can be recommended for use in OA research.

as a core treatment for patients with foot, knee, hip, or hand OA (2,3). However, pain is an important predictor of physical inactivity (4), and less than half of adult patients with OA are meeting the current guideline of 150 minutes of moderate-intensity physical activity per week (5,6). Accurately measuring current physical activity levels and changes in physical activity in patients with OA is important in terms of research.

Physical activity can be measured using direct methods such as accelerometry or indirect methods such as self-report physical activity instruments (7). Use of self-report physical activity instruments is a popular approach for measuring levels of physical activity in larger population studies (8), because such instruments are easy to use and allow immediate access to information about an individual's physical activity, and because of the low cost involved in their administration in a large number of study participants (9). To accurately measure physical activity using self-report instruments, the appropriate instrument must be selected according to the demographics of the participants (10). For instance, some instruments are developed specifically to measure physical activity in adults ages ≥65 years (11).

Multidomain instruments such as the Western Ontario and McMaster Universities Osteoarthritis Index and the Knee Injury and Osteoarthritis Outcome Score have been designed specifically for use in patients with OA. Although these multidomain instruments do measure physical activity as a component or subscale score, they have been excluded from this review because their purpose is not to assess physical activity levels explicitly in terms of frequency, duration, and intensity; such an assessment is required to make comparisons with current physical activity guidelines.

To date, there is still no consensus regarding which self-report physical activity instrument is the most suitable for use in OA research. In 2011, Terwee et al evaluated the measurement properties of physical activity instruments in patients with OA but focused solely on patients with a diagnosis of knee or hip OA (12). This previous systematic review identified 9 studies; however, none of these included the Physical Activity Scale for the Elderly (PASE) (13), an instrument that has more recently been used in OA research (14–16). Other systematic reviews that have evaluated the measurement properties of physical activity instruments in populations without joint pain were restricted to adults ages 18–65 years or those ages 65 years or older (7,8,11). Therefore, there is a gap in the literature for a comprehensive, broader, and updated systematic review that captures relevant information regarding the measurement of physical activity in patients with OA, a group comprised of individuals who are most commonly ages ≥45 years. By including studies that have evaluated the measurement properties of relevant instruments in other populations (i.e., those with joint pain attributable to OA in the foot, knee, hip, or hand, and community-dwelling adults in the same age bracket as that for OA) rather than focusing only on patients with a diagnosis of OA, it will be possible to identify and evaluate the measurement properties of a range of instruments suitable for use in patients with OA.

To our knowledge, no instrument measuring physical activity levels has been developed specifically for use in populations of patients with OA. Instruments developed for other populations, such as general adult or elderly adult populations, have been used in OA research. It is therefore important to understand how well these instruments reflect the construct of physical activity levels in populations of patients with OA by assessing the instruments' measurement properties as defined in the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) taxonomy (17). The aim of this 2-stage systematic review was to identify and evaluate the measurement properties of self-report physical activity instruments suitable for use in patients with OA.

PATIENTS AND METHODS

In the stage 1 review, we identified all self-report physical activity instruments used in published research involving populations of individuals ages ≥45 years who have joint pain attributable to OA in the feet, knee, hips, or hands. The age range and joint sites were selected based on the National Institute for Health and Care Excellence guideline for the management of OA and the most common peripheral joints affected by OA (1). In the stage 2 review, we subsequently identified all of the published evidence on the measurement properties of the instruments identified in stage 1. Both stages of the systematic review involved electronic database searches of Medline, Embase, and Web of Science from inception until July 19, 2018, combined

Table 1. Criteria for inclusion and exclusion of articles in stage 1*

Inclusion criteria	Exclusion criteria
Age range that includes participants ages 45 years or older (1)	
At least 50% of the study participants have OA or joint pain attributable to OA in the foot, knee, hip, or hand (1)	More than 50% of the study participants have inflammatory arthritis
Measurement of PA using a reproducible self-report questionnaire	A measure of physical fitness rather than a measure of daily PA participation
Self-reported PA used as a primary or secondary outcome measure	Direct measures of PA; e.g., accelerometers and calorimetry
All research settings (hospital, primary care, community settings, etc.)	Not written in English
All quantitative research methodologies (RCTs, cross-sectional, etc.)	Single-case research design

* OA = osteoarthritis; PA = physical activity; RCTs = randomized controlled trials.

with hand searching of reference lists in the included articles. The primary reviewer (RDS) screened all titles and abstracts, full articles were independently double-reviewed by the primary reviewer and at least 1 of the secondary reviewing team (KSD, JGQ, MAH, and GAM); any disagreements were resolved via consensus discussions between reviewers. Titles and abstracts were reviewed by the primary reviewer only because of time limitations of the secondary reviewers. To minimize the risk of reviewer error, 10% of all titles and abstracts were independently reviewed by at least one member of the secondary review team.

Stage 1. *Selection criteria.* The selection criteria for stage 1 were quantitative research studies that focused on populations with joint pain attributable to OA in the foot, knee, hip, or hand and measured self-reported physical activity (Table 1). Individuals were included if other sites of pain were present alongside pain in the foot, knee, hip, or hand. Because some study samples included both patients with OA and patients with inflammatory arthritis, we included only studies in which >50% of the sample had OA or joint pain attributable to OA. Search terms for articles reviewed in stage 1 were synthesized from previous joint pain and physical activity systematic review search strategies (18,19). The full search strategy for stage 1 is shown in Appendix 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23787/abstract).

Data extraction. Data extraction for stage 1 involved extracting the citation of the included studies and identifying the self-report physical activity instrument used. Data extraction was conducted by 2 different reviewers independently (the primary reviewer and one of the secondary reviewers). Because the aim of the stage 1 review was simply to identify studies and instruments, no further data extraction or quality assessment was conducted.

Stage 2. *Selection criteria*. The selection criteria for the stage 2 review were studies that included an evaluation of at least one measurement property of the instruments identified in stage 1 in individuals with joint pain attributable to OA or community-dwelling adults in a similar age group (ages ≥45 years). For purposes of describing all instruments included in the stage 2 review, articles in which the instruments' attributes (settings, recall period, purpose) were described were also retrieved. The search strategy for stage 2 was constructed using a high-sensitivity search term filter for identifying studies involving the properties of measurement tools (20). This filter was combined with the name of the instrument identified during stage 1. The full search strategy for stage 2 is shown in Appendix 2 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23787/abstract).

Data extraction and quality assessment. In stage 2, the Quality Assessment of Physical Activity Questionnaires (QAPAQ) checklist was used to extract data and conduct a preliminary quality assessment (21). The QAPAQ checklist is a comprehensive checklist of all the measurement properties and qualitative attributes of self-report physical activity instruments and has been used in previous systematic reviews evaluating the measurement properties of self-reported physical activity (7,11,12). A comprehensive quality assessment of the studies identified during stage 2 was conducted using the COSMIN checklist (22), which has been used in previous systematic reviews that assessed the quality of other self-report instruments (23–26). To reduce reviewer burden in this systematic review, the COSMIN checklist was modified by removing items on generalizability and interpretability already covered in the QAPAQ (21).

Following quality assessment, a previously designed grading system was used to assign a quantitative score to the strength of the evidence in each instrument's measurement properties (23–25). The grading system combined the strength of evidence (using the COSMIN checklist) (see Appendix 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23787/abstract) to a criterion for each measurement property (10) (see Appendix 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/

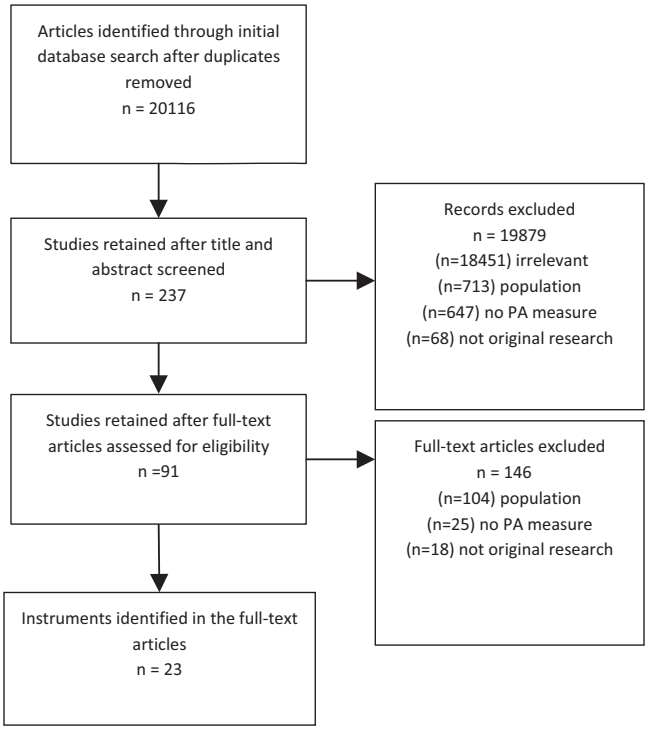

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of included articles from stage 1. PA = physical activity.

acr.23787/abstract), instruments' measurement properties were extracted using the QAPAQ (21). For the purposes of this systematic review, construct validity was defined in terms of convergent construct validity in which the self-report instrument reflects physical activity measured objectively (e.g., using accelerometers or heart rate monitoring). To evaluate criterion validity, the gold standard measurement for physical activity used in this review was considered to be doubly-labeled water (DLW). Measurement error was not formally assessed as a COSMIN criterion, as we could not identify a minimal important change reported for any of the instruments, measurement error has been reported when evaluated by studies.

RESULTS

Stage 1 results. From the search of the electronic databases and hand searching of reference lists of included studies, 20,292 articles were identified; this number of articles was reduced to 20,116 following removal of duplicates. Ninety-one studies comprising 23 unique self-report physical activity instruments met the inclusion criteria and were included in the review. Figure 1 shows a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the included articles from stage 1. Included studies focused on patients with knee OA (n = 52), those with knee and/or on hip OA (n = 22), patients with hip OA (n = 8), those with general joint pain or OA at multiple sites (n = 4), patients with foot pain or foot OA (n = 3), and patients with knee pain (n = 2). Thirty-two of the studies were longitudinal cohort studies, 29 were randomized controlled trials, 18 were cross-sectional studies, 9 examined the measurement properties of instruments, and 3 were systematic reviews. Seventeen studies were conducted in the US, 13 in Australia and the UK, 12 in the Netherlands, 5 in Canada and Germany, 4 in Switzerland and Denmark, 3 each in Sweden, Brazil, and Portugal, and Norway, 1 each in Greece, Spain, Japan, and Iran, and 2 studies were multi-country studies across Europe.

PA instruments identified. The self-report instruments of physical activity (n = 23) used in the included studies identified in stage 1 are shown in Appendix 5 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23787/abstract). The most common physical activity instruments used were the PASE (used in 34 studies) and the International Physical Activity Questionnaire Short Form (IPAQ-SF) (used in 17 studies). Nineteen of the instruments identified were multi-item self-report physical activity questionnaires, and 5 were single-item physical activity instruments.

Stage 2 results. In stage 2 of the systematic review, 3,661 studies were identified, and 54 of those studies met the inclusion

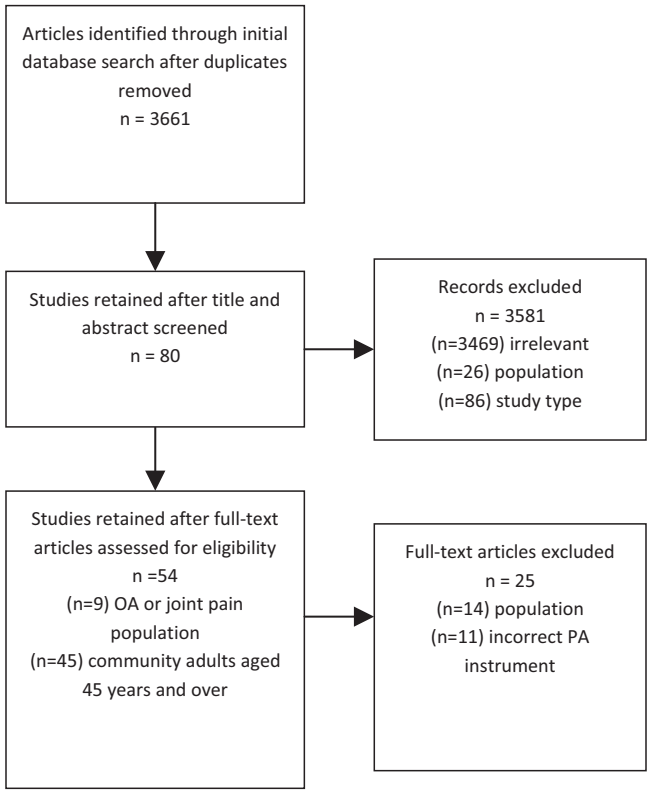

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of included articles from stage 2. OA = osteoarthritis; PA = physical activity.

criteria (Figure 2). Of those 54 studies, 9 (16%) evaluated the measurement properties of ≥1 of the identified physical activity instruments in adults with joint pain attributable to OA (3 with knee OA, 3 with hip OA, and 3 with both hip OA and knee OA). Forty-five studies (84%) evaluated the measurement properties of the physical activity instruments in community-dwelling adults ages ≥45 years (20 individuals ages ≥65 years and 25 individuals ages 45–64 years). The majority of these studies were conducted in Australia (n = 9), the US (n = 8), the Netherlands (n = 5), Japan (n = 4), and China (n = 4). Thirty-five studies evaluated construct validity, 36 evaluated reliability or measurement error, 2 studies examined content validity, 2 examined criterion validity, 2 evaluated internal consistency, and 1 evaluated responsiveness. A summary of the characteristics of the articles included in stage 2 is shown in (Appendix 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23787/abstract). Of the 23 instruments identified in the stage 1 review, 13 (56.5%) had at least 1 measurement property evaluated in either a population with joint pain attributable to OA or a community-dwelling adult population ages ≥45 years. Table 2 shows the characteristics of these instruments.

Measurement properties of the physical activity instruments in individuals with joint pain attributable to OA. No instruments were identified in stage 1 and evaluated in stage 2, which demonstrated full adequacy across all measurement property domains in individuals with joint pain attributable to OA (Table 3). Criterion validity, internal consistency, content validity, structural validity, and responsiveness were not assessed in any of the instruments. There was no evidence of any measurement properties assessed in the Active Australia Survey (AAS), modified Baecke questionnaire, Incidental and Planned Activity Questionnaire for Older People (IPEQ), IPAQ-SF, Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH), the Short Telephone Activity Recall questionnaire (STAR), or the Zutphen Physical Activity Questionnaire in individuals with joint pain attributable to OA.

In terms of reliability, the only multi-item instruments with a correlation or an intraclass correlation coefficient (ICC) >0.7 in studies deemed to be of good-to-excellence methodologic quality were the Baecke questionnaire, Human Activity Profile (HAP) questionnaire, IPAQ-SF, and PASE in populations of individuals with joint pain attributable to OA (27–30). In terms of reliability of the single-item instruments, the quality of evidence was rated as fair, all of the single-item instruments (Activity Rating Scale, Tegner scale, and University of California, Los Angeles Activity scale) demonstrated correlations >0.7 in populations with joint pain attributable to OA (29). The measurement error in the HAP, IPAQ-SF, and PASE has been evaluated, while there is no minimally important change index to assess the adequacy of measurement error in these instruments. The standard error of measurement in the IPAQ-SF and PASE was large compared to their maximal possible scoring range, while that in the HAP was small, which suggests large measurement error in populations with joint pain attributable to OA in the IPAQ-SF and PASE (28,30–33) (Table 3). For construct validity in populations with joint pain attributable to OA, the Baecke questionnaire, IPAQ-SF, and PASE demonstrated only low-to-moderate correlations (range 0.06–0.49) with accelerometers (30–33) (Table 3).

Measurement properties of the physical activity instruments in community-dwelling adults ages ≥45 years. No instruments identified in stage 1 and evaluated in stage 2 demonstrated full adequacy across all measurement property domains in community-dwelling adults ages ≥45 years (Table 3). Structural validity was not assessed in any of the instruments (Table 4).

In terms of reliability, the AAS displayed adequate reliability in 1 study (34) but inadequate reliability in 2 studies (35,36). The modified Baecke questionnaire demonstrated reliability across 3 studies (37–39). The HAP, IPEQ, and STAR demonstrated adequate reliability in 1 study each (40–42), the IPAQ-SF in 7 studies (43–50), and the PASE in 8 studies both showed results of a mix of reliability above and below adequate reliability (13,51–56). Measurement error in the PASE had been assessed in 1 study, showing a relatively small standard error of measurement (range 3.3–8.5) compared to the maximal scoring range of the PASE (range 0–400) (56).

The PASE and modified Baecke questionnaire were the only instruments for which criterion validity was evaluated, and this was in community-dwelling older adults ages ≥45 years. Both instruments demonstrated a moderate correlation with DLW, and in another study the PASE also demonstrated a nonsignificant correlation with DLW (51,57,58). The AAS was evaluated for construct validity in 5 studies, and correlation coefficients with accelerometers ranged from 0.39 to 0.61, demonstrating moderate correlations (34,36,43,59,60). The modified Baecke instrument demonstrated a nonsignificant correlation with heart rate monitoring (37). The HAP showed moderate correlations with accelerometers in a single study (40). IPAQ showed a low correlation with accelerometers in a single study (61). The IPAQ-SF was evaluated for construct validity in 9 studies, and correlations with accelerometers ranged from nonsignificant to moderate (44,46–49,62–65). The PASE was evaluated for construct validity in 5 studies, and correlations with accelerometers ranged from low to moderate (51–53,66,67). The SQUASH demonstrated high agreement with heart monitoring in a single study (68). The STAR demonstrated low correlations with accelerometers in a single study (42). The Zutphen Physical Activity Questionnaire demonstrated moderate correlations with accelerometers (69).

The IPAQ-SF and PASE were evaluated for internal consistency, each in a single study. In both the IPAQ-SF and PASE, internal consistency was deemed adequate. Cognitive interviews about understanding the items in the instrument were used to

Table 2. Characteristics of the physical activity (PA) instruments included in stage 2*

Instrument (ref.)	Construct	Setting	Recall period	Purpose	Target population	Justification	Format	Interpretability	Ease of use
Multi-item									
AAS (78)	Leisure-time PA	Leisure-time activities at different intensities	7 days	To assess knowledge of health benefits of PA in adult populations	Developed for adults ages 18–65 years, can be used internationally	Provides data on PA that can be implemented in self-report survey or interviewing	9 items, self-report of time spent during activities or frequency of activities	Total score for time spent in PA during 1 week and time spent sedentary	Takes a short time to complete
Baecke questionnaire (79)	Habitual PA across 3 domains: work-related, leisure-time, and sports activities	Activities in occupation, sports, and leisure time	Usual week	To assess habitual PAs for use in epidemiologic studies	Young adults	At the time of development, no appropriate instrument was available for use in epidemiologic studies	16 items, self-report questionnaire with closed-end questions	Scores given in 3 indices (work, sports, leisure time); scores are not interpretable outside of the Baecke questionnaire	Small number of multiple choice questions
Modified Baecke questionnaire (39)	PA during household, leisure-time, and sports activities	Household, leisure-time, and sports activities	1 year	Modified version of the Baecke questionnaire to better suit use in an elderly population	Elderly adults, ≥ages 65 years	Original Baecke questionnaire not appropriate for use in elderly populations	Interviewer-administered, not self-report	Time spent (hours) in PA for 1 week; scores can be compared to recommended PA levels for health benefits	Interviewer required, takes 30 minutes to complete
HAP (28)	Energy expenditure or physical fitness	Daily activities	Same day	Originally developed as an indicator of quality of life in pulmonary rehabilitation	Clinical and healthy populations	Previously developed instruments had floor and ceiling effects	94 items in a list, each a daily activity	Scores give average levels of activity and maximal achievable activity	Closed-ended questions, takes 1–2 minutes to complete
IPEQ (41)	Incidental and planned PA	Gym, home, and daily life activities	7 days or 3 months	Used in longitudinal epidemiology studies to assess levels of PA	Frail elderly populations	Other instruments for adults ages 45 years and older have too many items for use in surveys	10 items, on planned or structured exercises and activities of daily living	Scores are interpretable to time spent physically active	Self-report instrument, takes short time to complete

(continued)

Table 2. *(Cont'd)*

Instrument (ref.)	Construct	Setting	Recall period	Purpose	Target population	Justification	Format	Interpretability	Ease of use
IPAQ-SF and IPAQ-LF (44)	Energy expenditure in 1 week; there is a long version and a short version	Long version includes different settings, and short version does not separate settings	2 versions: last week and usual week	Research to compare populations according to levels of PA	Adults, ages 18–65 years; different languages available	Generic outcome measure of PA to be used in any adult population internationally	4 items in short 27 items in long version; closed-ended questions, some with continuous-scale answers	Scores given in energy expenditure per week; scores can be compared to recommended PA levels for health benefits	Short version requires minimal time and effort; long version takes longer and requires recall in different aspects of PA
PASE (79)	Time spent engaging in PA	PA in various settings: at work, at home, and during leisure time	Leisure-time activities, work-related activities, and household activities	Research to assess PA in elderly adults	Elderly adults, ages ≥65 years	None of the generic measures of PA are appropriate for elderly adults	32 items within 6 different domains	Scores given as a total score; total score not interpretable in a meaningful way	Questionnaires are easy to fill out, with full instruction, short recall period; 32 items is a high number
SQUASH (68)	Habitual activities	Leisure-time travel, household and work-related activities	Normal week over past few months	Self-report measure with scores comparable to recommended levels of PA for health benefits	All adult populations	Required a measurement in which scores were interpretable to quantify weekly PA levels	11 items asking questions on PA in different settings	Scores can be classified for recommended PA levels	Very short, simple to complete
STAR (42)	Classification of PA in moderate and vigorous levels of PA	All PA	Last 7 days	Telephone-administered short instrument to classify individuals in different levels of PA	All adult populations	Need for a quick-to-complete measure of PA by telephone	3 items, 2 versions available; open responses and closed responses	Responders can be classified into different levels of PA	Very quick to administer
Zutphen questionnaire (69)	Daily PA	Leisure-time, walking, household activities, sports activities, and hobbies	7 days, although some items differ	Used to assess PA levels in a longitudinal study	Designed for a study in older male adults but has since been used in male and female adults	Developed as an appropriate measure of PA over time for a longitudinal study	17 items, open-ended and closed-ended questions	Total score given as energy expenditure	Short with minimal requirements for completion

(continued)

Table 2. *(Cont'd)*

Instrument (ref.)	Construct	Setting	Recall period	Purpose	Target population	Justification	Format	Interpretability	Ease of use
Single-item									
ARS (29)	PA	All PA	Past year	To assess level of PA in 1 item	Patient with knee disorder	No valid single-item measure of PA	1 item, 5-point scale	Scoring range 0–4	Only 1 item
Tegner (29)	PA	All PA	Past week	To assess level of PA in 1 item	Knee injury	No valid single-item measure of PA	1 item, 10-level response	Each value on the scale identifies individuals at an interpretable level of PA	Only 1 item
UCLAA (29)	PA	All PA	Past week	To assess level of PA in 1 item	Joint replacement surgery	No valid single-item measure of PA	1 item, 10-level response	Each value on the scale identifies individuals at an interpretable level of PA	Only 1 item

* IPAQ-SF International Physical Activity Questionnaire; SF = Short Form; LF = long form; HAP = Human Activity Profile; IPEQ = Incidental and Planned Activity Questionnaire for Older People; PASE = Physical Activity Scale For The Elderly; SQUASH = Short Questionnaire To Assess Health Enhancing Physical Activity; STAR = Short Telephone Activity Recall Questionnaire; UCLAA = University Of California, Los Angeles Activity Scale.

Table 3. Summary of the measurement properties of each instrument included in stage 2*

Instrument	Reliability (quality) [ref.]	Measurement error (quality) [ref.]	Criterion validity (quality) [ref.]	Construct validity (quality) [ref.]	Other measurement properties (quality) [ref.]
Individuals with joint pain attributable to OA, multi-item					
AAS	0	0	0	0	0
Baecke questionnaire	ICC = 0.87 (good) [27]	0	0	Convergent construct validity, correlation to accelerometer = 0.49 (good) [27]	0
Modified Baecke questionnaire	0	0	0	0	0
HAP	ICC = 0.95, 0.96 (excellent) [28]; ICC = 0.60, 83 (poor) [72]	SEm = 3 (excellent) [28]	0	0	0
IPEQ	0	0	0	0	0
IPAQ-SF	ICC = 0.76, 0.87 (excellent) [29]; ICC = 0.5 (fair) [31]	SEm = 2,487, SDC = 1,039 (fair) [31]	0	Convergent construct validity, correlation to accelerometer = 0.29 (fair) [31]	0
PASE	ICC = 0.77 (poor) [33]; ICC = 0.58, 0.77 (poor) [32]; ICC = 0.77 (fair) [30]	SEm = 23–35%, SDC = 63–97% (fair) [30,32]; SEm = 31, SDC = 87 (poor) [33]	0	Convergent construct validity, correlation to accelerometer = 0.3 (poor) [33]; correlation to accelerometer = 0.06, 0.45 (poor) [32]; correlation to accelerometer = 0.27 (good) [30]	0
SQUASH	0	0	0	0	0
STAR	0	0	0	0	0
Zutphen	0	0	0	0	0
Single-item					
ARS	κ = 0.65, 0.88 (fair) [29]	0	0	0	No floor or ceiling effect (fair) [29]
Tegner	κ = 0.54, 0.84 (fair) [29]	0	0	0	No floor or ceiling effect (fair) [29]
UCLAA	κ = 0.80, 0.86 (fair) [29]	0	0	0	No floor or ceiling effect (fair) [29]
Community-dwelling adults ages ≥45 years, multi-item					
AAS	r_s = 0.58, 0.64 (good) [35]; r_s = 0.32 (fair) [36]; r_s = 0.76 (fair) [34]	0	0	Correlation to accelerometer = 0.48, 0.52 (good) [35]; correlation to accelerometer = 0.42 (good) [59]; correlation to accelerometer = 0.39, 0.49 (good) [36]; correlation to accelerometer = 0.49, 0.56 (good) [60]; correlation to accelerometer = 0.45, 0.61 (good) [34]	Wide range of limitations in items in terms of content validity (excellent) [70]

(continued)

Table 3. *(Cont'd)*

Instrument	Reliability (quality) [ref.]	Measurement error (quality) [ref.]	Criterion validity (quality) [ref.]	Construct validity (quality) [ref.]	Other measurement properties (quality) [ref.]
Baecke questionnaire	0	0	0	0	0
Modified Baecke questionnaire	r_s = 0.65, 0.89 (fair) [38]; correlation = 0.73, 0.82 (poor) [37]; r_s = 0.86 (poor) [39]	0	Correlation with DLW, r = 0.54 (poor) [57]	Correlation to heart rate monitoring = NS (poor) [37]; correlation to PASE (good) [80]	0
HAP	ICC = 0.79, 0.94 (good) [40]	0	0	Correlation to accelerometer = 0.52, 0.55 (good) [40]	0
IPEQ	ICC = 0.80, 0.84 (good) [41]	0	0	Correlation to accelerometer = 0.17 (excellent) [61]	IPAQ responsiveness index = 0.31, ActiGraph responsiveness index = 0.65 (excellent) [61]
IPAQ-SF	ICC = 0.68 (excellent) [43]; r_s = 0.46–0.96 (good) [44]; ICC=0.84 (excellent) [45]; r_s = 0.54 (poor) [46]; ICC= 0.5, 0.65 (excellent) [47]; ICC = 0.86 (good) [48]; r_s = 0.26 (good) [49]; ICC = 0.99 (good) [50]	0	0	Correlation to accelerometer = 0.30–0.33 (good) [44]; correlation to accelerometer = NS (good) [62]; correlation to accelerometer = 0.30–0.33 (poor) [46]; correlation to accelerometer = 0.38–0.56 (good) [47]; correlation to accelerometer = 0.39 (good) [48]; correlation to accelerometer = 0.33 (excellent) [63]; correlation to accelerometer = 0.29 (good) [49]; correlation to accelerometer = NS (excellent) [64]; correlation to accelerometer = NS (poor) [64]	Content validity showed that definitions were confusing and recall was difficult; good quality (7). Internal consistency, α = 0.70, good quality (50)
PASE	ICC = 0.60 (good) [51]; ICC = 0.60 (good) [52]; ICC = 0.65 (good) [53]; ICC = 0.75 (good) [66]; ICC = 0.68–0.84 (good) [13]; ICC = 0.81 (fair) [54]; ICC = 0.79 (good) [55]; ICC = 0.90–0.98 (good) [56]	SEm = 3.3–8.5 (good) [56]	Correlation to DLW = NS (good) [51]; correlation to DLW = r = 0.58 (poor) [58]	Correlation to accelerometer = 0.36 (good) [51]; correlation to accelerometer = 0.43 (good) [52]; for correlation to accelerometer, r_s = 0.16 (fair) [53]; correlation to accelerometer = 0.52, 0.59 (good) [66]; correlation to accelerometer = 0.49 (poor) [67]	Internal consistency, α = 0.71–0.75 (good) [56]
SQUASH	0	0	0	Agreement with heart monitors = 97.6% (fair) [68]	0
STAR	κ = 0.57–0.76 (excellent) [42]	0	0	Correlation to accelerometer = 0.14–0.15 (good) [42]	0
Zutphen	0	0	0	Correlation with accelerometer = 0.34 (good) [69]	0

* ref. = reference; OA = osteoarthritis; AAS = Active Australia Survey; ICC = intraclass correlation coefficient; SEm = standard error of measurement; SDC = smallest detectable change; ARS = Activity Rating Scale; DLW = doubly-labeled water; NS = not significant (see Table 2 for other definitions).

Table 4. Grading of the measurement properties of each instrument using the COSMIN checklist and QAPAQ*

	Reliability and measurement error		Criterion validity		Construct validity using objective measure		Internal consistency		Content validity		Structural validity		Responsiveness	
	Joint pain	Older adults	Joint pain	Older adults	Joint pain	Older adults	Joint pain	Older adults	Joint pain	Older adults	Joint pain	Older adults	Joint pain	Older adults
AAS	0	++	0	0	0	–	0	0	0	–	0	0	0	0
ARS†	+	0	0	0	0	0	0	0	0	0	0	0	0	0
Baecke questionnaire	++	0	0	0	0	0	0	0	0	0	0	0	0	0
Modified Baecke questionnaire	0	?	0	?	0	?	0	0	0	0	0	0	0	0
HAP	+++	0	0	0	0	–	0	0	0	0	0	0	0	0
IPAQ-SF	+++	±	0	0	?	–	0	+	0	–	0	0	0	0
IPEQ	0	++	0	0	0	–	0	0	0	0	0	0	0	+++
PASE	++	±	0	–	–	–	0	+	0	0	0	0	0	0
SQUASH	0	0	0	0	0	+	0	0	0	0	0	0	0	0
STAR	0	±	0	0	0	–	0	0	0	0	0	0	0	0
Tegner†	+	0	0	0	0	0	0	0	0	0	0	0	0	0
UCLAA†	+	0	0	0	0	0	0	0	0	0	0	0	0	0
Zutphen	0	0	0	0	0	–	0	0	0	0	0	0	0	0

* The strength of the evidence was based on the quality of the articles assessed by the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) (6). Joint pain refers to joint pain attributable to osteoarthritis. Instruments were given a positive, negative, or zero score for the corresponding measurement property based on quality criteria (10) (see also Appendices 3 and 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23787/abstract). QAPAQ = Quality Assessment of Physical Activity Questionnaire; AAS = Active Australia Survey; ARS = Activity Rating Scale; ? = Findings unclear due to study quality; ± = conflicting findings (see Table 2 for other definitions).
† Single-scale items.

assess the content validity of the AAS and IPAQ-SF (50,56). In both the AAS and IPAQ-SF, the terminology used in items was confusing or unclear to participants, making recall difficult (70,71). Responsiveness was evaluated in the IPEQ and was shown to be less responsive to changes in PA levels compared to accelerometers (61).

Methodologic quality of the included studies. For reliability, 8 studies were evaluated as being of poor quality, because a small sample size was used (<50 individuals) (29,31–33,38,39,46,72); sample sizes of <50 are considered to be too small for evaluating measurement properties (10). Five studies that assessed reliability were evaluated as being of fair quality because their sample size was >50 individuals, and a correlation rather than a test for agreement (ICC) was used (35–37,43,54). Fourteen studies were evaluated as good quality (sample sizes >50 but <100) (10), and 7 studies were evaluated as excellent quality (sample sizes >100) (10). One good-quality study evaluated measurement error in a sample of <100 individuals (56).

The 2 studies that evaluated criterion validity were evaluated as being of poor quality due to their sample size (57,58). Of the studies evaluating construct validity, 7 were evaluated as poor quality due to sample size (31–33, 38, 39, 46, 60, 67); 3 were evaluated as fair quality (although the sample size was deemed appropriate, these studies used pedometers or heart monitors rather than accelerometers) (45,59,68); 12 studies were evaluated as good quality, with sample sizes >50 but <100 (27, 30, 34, 36, 42, 48, 49, 51, 52, 66, 69, 73); and 10 studies were evaluated as excellent quality, with sample sizes >100 (35,40,43,47,53,61–64,74). Only 1 of the studies in this review used hypothesis testing to evaluate construct validity (49). Responsiveness was assessed in 1 study, which was evaluated as excellent quality due to a large sample size (>100) and a comparison with an accelerometer. Two studies of excellent quality used cognitive interviews to assess content validity (70,71).

DISCUSSION

In stage 1 of this systematic review, we identified 23 self-report physical activity instruments that have been used previously in populations of individuals with joint pain attributable to OA. However, based on our findings in the stage 2 review, it is still not clear which instrument is most appropriate for use in patients with OA. This lack of clarity is attributable to the lack of evidence of adequate measurement properties for all of the instruments identified. In both populations in the current study, most self-report instruments demonstrated adequate test–retest reliability, although methodologic quality ranged from poor to excellent, which suggests that these self-report instruments are reliable for measuring levels of physical activity in test–retest evaluations. Two studies evaluated internal consistency (1 in the IPAQ-SF and 1 in the PASE), both of which were of good methodologic quality and indicated adequate consistency of all of the items ($\alpha \geq 0.70$).

None of the instruments demonstrated strong correlations (>0.70) with direct measures of physical activity such as accelerometers or heart monitors in patients with joint pain attributable to OA or community-dwelling older adults ages ≥45 years. Two studies evaluated criterion validity and instruments correlated poorly to the gold standard measurement of physical activity (DLW) (57,58), based on small samples (<50 participants). The implication of low-to-moderate criterion and construct validity of these instruments is that researchers cannot be certain regarding the degree to which instruments reflect actual physical activity levels, particularly because there were no clear patterns in the self-report instruments regarding overestimating or underestimating physical activity level compared to direct measures (75).

Notably, only 2 studies evaluated content validity. Both were conducted in community-dwelling adult populations ages ≥45 years and examined the AAS and IPAQ-SF (5,34). These studies highlighted participant misinterpretation of both physical activity definitions and the questions used within these instruments. To gain a clearer understanding of the difficulties associated with interpreting definitions of physical activity and the questions contained within, self-report physical activity instruments would be useful more generally.

None of the studies examined the responsiveness of the instruments in patients with joint pain attributable to OA, and only 1 study evaluated responsiveness (using the IPEQ) in community-dwelling older adults ages ≥45 years. It is therefore unclear how sensitive the identified self-report physical activity instruments are for detecting changes in physical activity levels in individuals with joint pain attributable to OA. This lack of clarity regarding sensitivity is a major limitation when evaluating physical activity interventions aimed at increasing physical activity levels in these populations (76). None of the studies identified in this review evaluated formally addressed structural validity or cross-cultural validity in any of the instruments in any of the populations of interest. The studies that evaluated measurement properties in patients with joint pain attributable to OA identified in this review were limited to only those in the knee and hip. None of the studies reviewed in stage 2 included individuals with joint pain in the foot or hand attributable to OA. This lack of evidence also limits comparisons of the measurement properties between different joints of individuals with pain attributable to OA.

This systematic review used a comprehensive search strategy including multiple electronic databases, and reference list screening from included studies. The study is also original because it included studies in populations with joint pain attributable to OA and community-dwelling adults ages ≥45 years. This study has used the gold standard tool for assessing study quality in outcome measures (22), as well as a previously published standardized form for extracting data on measurement properties of physical activity instruments (21).

Although we identified many studies in the stage 2 review (n = 54), it is difficult to determine the extent to which the find-

ings in community-dwelling adults ages ≥45 years are generalizable to adults in the same age group who have OA or joint pain attributable to OA. The current review focused on the most common sites of OA in adults ages ≥45 years, the group with the highest prevalence of OA (1), and the findings may not be generalizable to younger patients with posttraumatic OA.

This systematic review showed that there is limited evidence for the measurement properties of previously used self-report physical activity instruments in populations with joint pain attributable to OA. Further high-quality methodologic evaluation of additional measurement properties is required for commonly used instruments in this population. It is particularly recommended that such studies use larger sample sizes (≥50 or ideally >100 participants) (10). Such studies will allow researchers to make appropriately informed decisions when selecting self-report physical activity instruments for use in OA research. Although we observed adequate test–retest reliability in a couple of instruments, overall evidence for validity and responsiveness was lacking. Investigations into content validity may particularly help researchers to identify areas within self-report physical activity instruments that may cause participants to misinterpret the questions and therefore report physical activity inaccurately. Evaluation of the responsiveness of physical activity instruments commonly used in randomized controlled trials focused on OA is highly recommended (76), especially if physical activity is the primary outcome. In future studies, investigators should also consider building an evidence base focused on the reliability of physical activity instruments by examining correlations with direct measures of physical activity in patients with OA.

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

Study conception and design. Smith, Dziedzic, McHugh, Healey.
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Analysis and interpretation of data. Smith, Dziedzic, Quicke, Holden, McHugh, Healey.

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ACTIVITY AND THE RHEUMATIC DISEASES

Osteoarthritis-Related Walking Disability and Arterial Stiffness: Results From a Cross-Sectional Study

Kenth L. Joseph,[1] Kåre B. Hagen,[1] Anne T. Tveter,[1] Karin Magnusson,[2] Sella A. Provan,[1] and Hanne Dagfinrud[1]

Objective. To compare the 6-minute walking distance (6MWD) in a population-based cohort of patients with osteoarthritis (OA) with that in matched peers from the general population, and to explore the associations between walking ability and risk of cardiovascular disease (CVD) in the OA cohort.

Methods. This cross-sectional study included individuals (ages 40–80 years) who had self-reported OA (n = 500) in a previous population-based study and age- and sex-matched peers from the general population (n = 235). Clinical examinations of the patients with OA included classification according to the American College of Rheumatology criteria, blood sampling, and measuring arterial stiffness (PWV; pulse wave velocity). Group differences in the 6MWD were calculated with *t*-tests. The association between walking ability and CVD risk in the OA cohort was examined using multivariate regression models.

Results. In the age-stratified analyses, the largest mean difference in the 6MWD was observed in the youngest age groups (40–49 years); female patients in the OA group walked 84.6 fewer meters compared with the reference group (579.4 meters and 663.9 meters, respectively; $P < 0.001$), and male patients walked 88.3 fewer meters compared with the reference group (619.9 meters and 708.3 meters, respectively; $P = 0.001$). In the OA group, the 6MWD was significantly associated with PWV in the adjusted analysis ($P = 0.001$); an increase in the walking distance of 100 meters corresponded to a reduction in PWV of 0.3 meters/second.

Conclusion. Even at age 40 years, patients with OA had a significantly shorter mean walking distance compared with their matched peers, underlining the importance of an early clinical approach to OA. Furthermore, in the OA group, the 6MWD was significantly associated with arterial stiffness, suggesting that walking ability is important for the CVD risk profile in patients with OA.

INTRODUCTION

The results of recent systematic reviews (1,2) and population-based cohort studies (3–5) indicate that osteoarthritis (OA) is associated with an increased risk of cardiovascular disease (CVD). Fernandes and Valdes (6) recently reported risk factors shared by both conditions, including age, obesity, chronic inflammation, treatment with nonsteroidal antiinflammatory drugs (NSAIDs), physical inactivity, and walking disability (6). Patients with hip OA and those with knee OA tend to avoid painful physical activity, resulting in walking disability and physical inactivity (7–9), which in turn result in reduced cardiorespiratory fitness. Because cardiorespiratory fitness is an important independent predictor of CVD (10,11), OA may be considered to be an indirect cause of CVD (3,4,6). The co-existence of OA and CVD reinforces the negative health impact and increases the disease burden (6,12).

No cure for OA is available; therefore, it is important to identify modifiable factors that can contribute to limiting negative long-term consequences. Even if the underlying mechanisms for the association between OA and CVD are not fully elucidated, it seems clear that OA-related disability increases the risk of CVD beyond what can be explained by common risk factors such as aging and obesity (6). Arterial stiffness is a validated marker of the risk of cardiovascular events and a predictor of mortality (13,14).

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[1]Kenth L. Joseph, MSc, Kåre B. Hagen, PhD, Anne T. Tveter, PhD, Sella A. Provan, MD, PhD, Hanne Dagfinrud PhD: Diakonhjemmet Hospital, Oslo, Norway; [2]Karin Magnusson, PhD: Diakonhjemmet Hospital, Oslo, Norway and Lund University, Lund, Sweden.

Address correspondence to Kenth L. Joseph, MSc, Research Fellow, Norwegian National Advisory Unit on Rehabilitation in Rheumatology, Department of Rheumatology, Diakonhjemmet Hospital, PO Box 23 Vinderen, NO-0319 Oslo, Norway. E-mail: kenth-louis.joseph@diakonsyk.no.

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SIGNIFICANCE & INNOVATIONS

- Individuals with OA have a high risk of cardiovascular disease (CVD), and co-existence of the 2 disorders reinforces and increases the disease burden.
- Walking disability measured by a standardized 6-minute walking distance test was significantly associated with arterial stiffness, which is an independent risk factor for cardiovascular disease.
- The results emphasize the importance of an early and broad clinical approach to OA, addressing prevention and management of CVD risk along with treatment of joint-related symptoms.

An inverse association between the level of physical exercise and arterial stiffness has been observed in healthy individuals as well as in patients with chronic diseases (15,16), indicating that arterial stiffness can be modified with exercise. The performance-based 6-minute walking distance (6MWD) is known to be a valid measure of walking (dis)ability and cardiorespiratory fitness. The aim of this population-based study was to compare the 6MWD in patients with OA with that in age-matched peers from the general population, as well as to explore the association between walking ability and CVD risk as measured by arterial stiffness.

SUBJECTS AND METHODS

Study design and population. This cross-sectional study was part of the Musculoskeletal pain in Ullensaker STudy (MUST), a population-based study in a rural community in Norway, in which musculoskeletal pain was examined (17). Initially, 12,155 inhabitants ages 40–80 years in Ullensaker municipality were invited to participate in a postal survey (questionnaire 1), which was mailed at 3 time points (March 2010, November 2010, and September 2011). Responders who self-reported OA based on the question "Have you ever been diagnosed with osteoarthritis in hip/knee/hand by a medical doctor and/or x-ray?" and consented (n = 1,019) were invited to participate in medical examinations and physical testing at Diakonhjemmet Hospital, Oslo, Norway, and to respond to a second questionnaire (questionnaire 2) addressing OA and CVD. The 1-day medical examinations (i.e., radiography and pulse wave velocity [PWV]) and physical testing (6MWD test) were scheduled to be initiated within 2–5 months after mailing the initial postal survey. The protocol, including the project timeline and other methodologic details, has been described previously (17). The MUST study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (2009/812a and 2009/1703a).

The current study is based on participants who self-reported OA in the initial postal survey and participated in medical examinations and physical testing. We excluded those who reported inflammatory rheumatic diseases (rheumatoid arthritis, psoriasis arthritis, spondyloarthritis, systemic lupus erythematosus) and/or had a history of CVD (Figure 1). The definition of CVD was based on a reported history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, cerebral insult or transitory ischemic attack, or angina pectoris in addition to patient-reported pain relief with nitroglycerine.

OA classification criteria and clinical features. At the time of the physical examination, participants were screened for OA, as classified using the American College of Rheumatology (ACR) criteria (18–20). Conventional bilateral radiographs of the hip, knee, and hand joints were obtained, and blood samples were drawn, according to a previously published protocol (17).

In the current study, hip OA was classified according to clinical, laboratory, and radiography criteria (18). The presence of joint space narrowing (superior or medial) and osteophytes (femoral or acetabular) in the hips was determined by a grade of ≥1 according to the Osteoarthritis Research Society International atlas criteria (21). Knee OA was classified according to clinical and radiography criteria (20). A Kellgren/Lawrence grade of ≥2 was used to determine the presence of osteophytes in the knees (22) (1 participant with missing knee radiographs was classified according to clinical criteria). Hand OA was classified according to clinical criteria (19).

Based on fulfillment of the ACR criteria, we created the following 3 OA phenotypes: 1) hand OA (unilateral or bilateral), 2) hip/knee (lower extremity) OA (unilateral or bilateral in hip and/or knee), and 3) non-ACR–classified OA (OA not fulfilling the ACR classification criteria). Joint pain (average pain last week) was self-reported during clinical examinations, based on a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (unbearable pain).

Walking ability. Walking ability in individuals who self-reported OA was determined by the performance-based 6MWD test. The test was administered by physiotherapists, performed according to the American Thoracic Society statement guidelines, and measured in meters (23), and allowing use of walking aids (e.g., canes).

Reference values for the 6MWD. Reference values for the 6MWD were based on individual-level data from a general population, including men and women, ages 18–90 years (n = 370). The cohort was initially established for the purpose of providing reference values for health-related physical fitness measures in patients with musculoskeletal disorders. Participants were recruited from several settings (e.g., work, college/university, community centers for older adults), networks, and locations (e.g., urban, suburban, rural) to achieve a representative sample (mean reference values for 6MWD stratified by age group and sex have been reported previously [24]). In the current study, data for participants in the same age range as

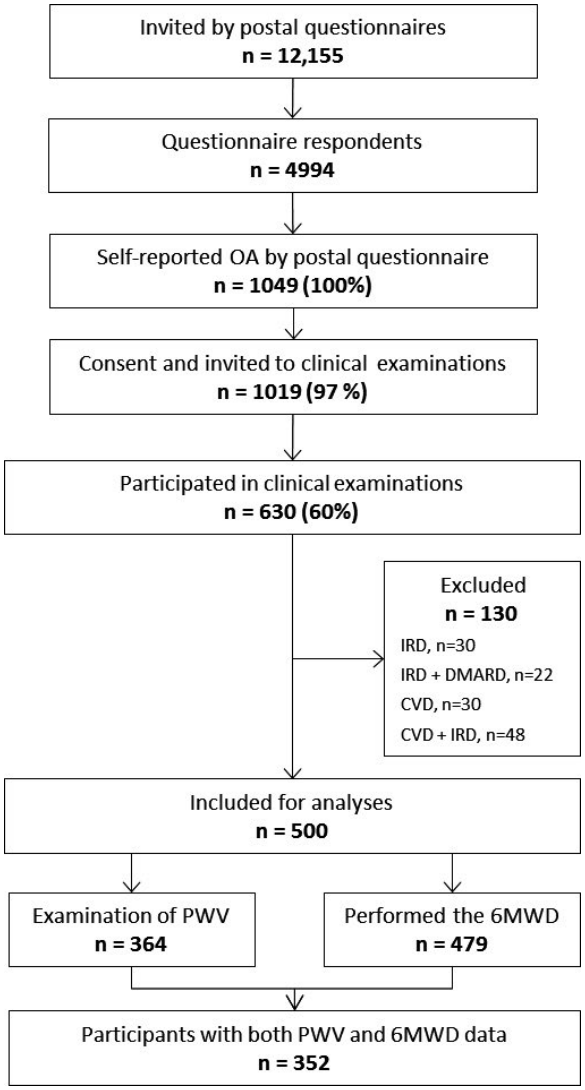

Figure 1. Flow chart showing creation of the population-based osteoarthritis (OA) cohort. IRD = rheumatic inflammatory disease; DMARD = disease-modifying antirheumatic drug; CVD = cardiovascular disease; PWV = pulse wave velocity; 6MWD = 6-minute walking distance.

that in the OA cohort (40–80 years) was used for a comparison of the 6MWD between OA patients and the general population (n = 235).

Arterial stiffness. Arterial stiffness was determined by measuring the PWV (17). The pulse wave between the carotid and femoral arteries and the resting heart rate were assessed using a SphygomoCor apparatus (Atcor). Brachial blood pressure was measured after a 5-minute rest, using an OMRON M7 monitor (Kyoto) according to the MUST protocol (17).

Background variables. Background variables included age, sex, smoking habits (daily, quit >6 months ago, never), education level (primary school, upper secondary school, 1–4 years of college/university, >4 years of college/university), and NSAID use over the last 7 days (no, occasionally, daily/almost daily) (17). NSAID use reported in questionnaire 1 was cross-checked against use of medication reported in questionnaire 2 (recorded by a study nurse) and was categorized accordingly.

For analytic purposes, background variables were collapsed into dichotomous responses: smoking habits (current smoker versus former smoker/never smoker), education (primary/upper secondary school versus ≥1 year of college/university), and NSAID use (no/occasionally versus daily/almost daily). Body height (cm) and weight (kg) were measured and recorded by trained personnel, and the body mass index (BMI) was calculated as kg/m^2.

Statistical analysis. Descriptive characteristics of the participants are shown as the mean ± SD (continuous data) or frequencies and percentages (categorical data). Differences in the 6MWD between patients in the OA cohort (n = 479) and age- and sex-matched peers from the general population (reference group) (n = 235) were analyzed by *t*-test for independent samples. Subgroup analyses to determine the mean difference (sex-matched) in the 6MWD between 1) the OA phenotype groups (hand OA, lower extremity OA, and non–ACR-defined OA) and 2) between OA groups and the reference group were performed using analysis of variance with the Bonferroni post hoc test.

Participants with data for both the 6MWD and PWV were included in the regression models (n = 352) (Figure 1). Univariate analysis was performed to examine the association between arterial stiffness (PWV) (dependent variable) and the 6MWD, resting heart rate, mean arterial blood pressure, age, sex, BMI, smoking, NSAID use, pain (on a numerical rating scale), and OA phenotypes as independent variables, using linear regression models (data not shown). Heart rate, mean arterial blood pressure, age, and sex were forced into the models, and independent variables with a *P* value of less than 0.25 were added to the final model. The final model included only patients with OA who fulfilled the ACR classification criteria. Results for the 6MWD test are presented as unstandardized coefficients (B) and 95% confidence intervals (95% CIs). Data were analyzed using IBM SPSS version 21.

RESULTS

In total, 630 (60%) of the participants who self-reported OA in the MUST study (n = 1,049) participated in clinical examinations and physical testing (Figure 1). No differences were observed between individuals who participated in the clinical examinations and those who did not (n = 419) with regard to age, sex ratio, self-reported height and weight, and educational status.

In the current study, 130 participants were excluded due to inflammatory rheumatic disease (n = 52) and/or CVD (n = 78); thus, 500 individuals were included in the analyses (Figure 1). The mean ± SD time gap between the initial self-report of OA and participation in the medical examinations and physical testing was 8.3

Table 1. Characteristics of the patients in the population-based OA cohort (n = 500)*

Demographics and anthropometrics	
Age, mean ± SD years	63.2 ± 8.8
Female sex	362 (72.4)
BMI, mean ± SD kg/m^2	27.96 ± 4.8
Overweight (BMI 25 to <30 kg/m^2)	183 (36.6)
Obese (BMI ≥30 kg/m^2)	159 (31.8)
Current smoker	80 (16.1)
Education level ≥1 year college/ university	146 (30.0)
ACR-defined OA	
Hand OA	189 (37.8)
Lower extremity OA	158 (31.6)
Non–ACR-defined OA	153 (30.6)
OA-related factors	
Daily/almost daily NSAID use	121 (24.3)
Joint pain on 0–10 NRS, mean ± SD	3.7 ± 2.2
Walking ability†	
6MWD, mean ± SD meters	551.4 ± 99.1
Arterial stiffness‡	
Pulse wave velocity, mean ± SD meters/second	8.82 ± 2.06
Mean arterial pressure, mean ± SD mm Hg	100.61 ± 11.45
Heart rate, mean ± SD beats per minute	64.64 ± 10.03

* Except where indicated otherwise, values are the number (%). OA = osteoarthritis; BMI = body mass index; ACR-defined = defined according to the American College of Rheumatology classification criteria; NSAID = nonsteroidal antiinflammatory drug; NRS = numerical rating scale; 6MWD = 6-minute walking distance.
† Only 479 patients were assessed.
‡ Only 364 patients were assessed.

± 4.0 months. The mean age of the participants was 63 years, and the majority (72%) were women (Table 1). More than two-thirds of the participants (68%) were classified as being overweight or obese. Approximately 1 of 4 patients reported using NSAIDs on a daily/almost daily basis. Most patients (78%) reported joint pain as ≤5 on the NRS. In total, 347 participants (69%) were classified as having OA in ≥1 joints according to the ACR criteria. Measures of arterial stiffness (PWV) in the OA group ranged from 4.65 to 18.30 meters/second (Table 1). Due to logistic reasons, PWV data for 136 patients were missing. There were no statistically significant differences in mean age ($P = 0.9$) or sex distribution ($P = 0.14$) between patients with and those without PWV measures, but the mean BMI in patients without PWV measures (1.40 [95% CI 0.45, 2.3], $P = 0.004$) was higher than that in patients with PWV measures.

OA cohort versus a general population cohort. Compared with that in the general population, the 6MWD was significantly shorter in patients in the OA cohort (in female patients with OA, 535.0 meters versus 589.3 meters in age-matched peers in the general population [$P < 0.001$]; in male patients with OA, 593.8 meters versus 642.9 meters in age-matched peers in the general population [$P < 0.001$]). In age-stratified analyses, the largest mean difference in the 6MWD was observed in the youngest age group (40–49 years); in this OA group female patients walked 84.6 fewer meters compared with the reference group (579.4 meters and 663.9 meters, respectively; $P < 0.001$), and male patients walked 88.3 fewer meters compared with the reference group (619.9 meters and 708.3 meters, respectively; $P = 0.001$) (Figure 2). These differences were attenuated gradually with increasing age increments; in the oldest age group (70–80 years), female patients walked 21.1 meters fewer compared with the reference group (488.8 meters and 509.9 meters, respectively; $P = 0.21$), and male patients walked 30.9 meters fewer than the reference group (544.6 meters and 575.5 meters, respectively; $P = 0.22$) (Figure 2).

In subgroup analyses, no significant differences in the mean 6MWD between OA phenotype groups were observed in either women or men ($P > 0.9$) (data not shown). With the exception of male patients with hand OA ($P = 0.196$), the walking distance in all of the OA phenotype groups was significantly shorter than that in the (sex-matched) reference groups ($P < 0.05$) (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23697/abstract).

Walking disability and arterial stiffness (PWV) in the OA cohort. The 6MWD was inversely associated with arterial stiffness after adjustment for heart rate, mean arterial blood pressure, age, and sex (Table 2). Furthermore, the 6MWD remained significantly associated with PWV in the final model, which had additional adjustments for smoking × BMI (interaction) (unstandardized coefficient –0.003; $P = 0.001$) (Table 2). This finding means that a 100-meter longer walking distance corresponded to a 0.3 meter/second reduction in arterial stiffness. In a sensitivity analysis of the final model including only patients in whom OA was diagnosed according to the ACR criteria, the 6MWD remained significantly associated with PWV (–0.003 meters/second [95% CI –0.005, –0.001], $P = 0.007$).

DISCUSSION

This study revealed that even at age 40 years, patients with OA had a significantly shorter walking distance (6MWD) compared with that in their age-matched peers in the general population. Furthermore, we also observed a significant inverse association between the 6MWD and arterial stiffness (PWV) in this population-based OA cohort, suggesting that walking ability is an important factor in the CVD risk profile.

Aging is a strong determinant of functional impairment and reduced physical capacity. Functional fitness is known to decline with increasing age, which may explain our findings that the dif-

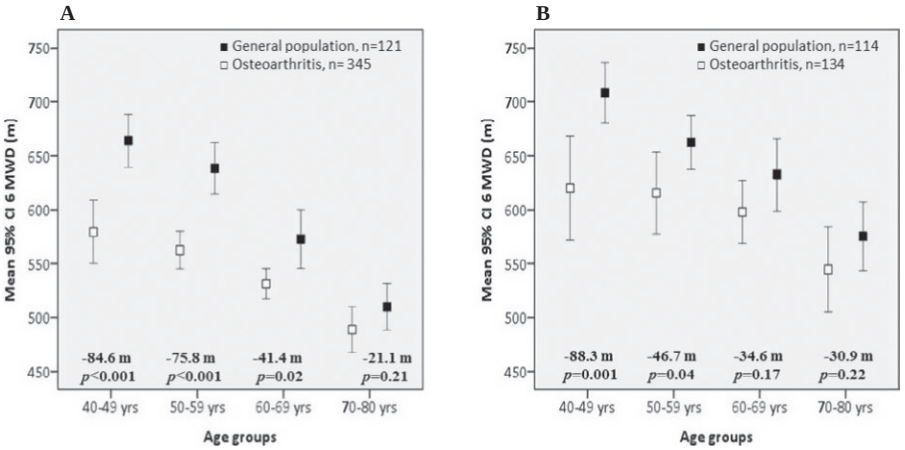

Figure 2. Six-minute walking distance (6MWD) in female subjects (**A**) and male subjects (**B**), according to age group. Values are the means (95% confidence intervals [95% CIs]).

ference in walking distance between the OA groups and age-matched peers was attenuated with increasing age. However, the significant and large differences in the youngest age groups emphasize the importance of an early approach in terms of individually adapted exercise programs, encouragement to stay physically active, and strategies for pain management. Nonpharmacologic treatment modalities are especially important, because the most relevant pharmacologic therapy for management of OA-related pain is use of NSAIDs, which are known to increase the risk of CVD (6,25).

The results of our study support those of previous studies showing that walking disability increases the risk of CVD in patients with OA (3,4). The importance of walking disability was also convincingly emphasized in a recent population-based study of the longitudinal relationship between OA and cardiovascular events (26). Even if OA severity, obesity, and hypertension significantly explained the subsequent risk for cardiovascular events in that longitudinal study, the relationship became nonsignificant when controlling for walking ability at baseline (26). The findings in these previous studies are clinically relevant, because they substantiate the importance of an early approach to treatment of patients with OA. Walking difficulty is a potentially modifiable factor that should be addressed in order to curb the adverse effects of the co-existence of OA and CVD.

The 6MWD test is a feasible clinical field test measuring patients' walking ability, but the test has also been shown to reflect cardiorespiratory fitness ($VO_{2\ max}$) in patients as well as healthy individuals (23,27–29). Burr et al (28) reported a "significant moderate strength association" between the 6MWD and $VO_{2\ max}$ (28) and that in adjusted regression equations, the 6MWD predicted 72% of the $VO_{2\ max}$ variance in healthy subjects (28). In the current study use of the 6MWD to compare patients with OA with their and age- and sex-matched peers increased insight into the early development of walking disability in patients with OA. The shorter walking distance in the OA group may reflect both walking disability and reduced cardiorespiratory fitness, therefore suggesting that treatment strategies should focus on a combination of pain management and cardiorespiratory (not cardiovascular) exercise.

Regular exercise is a prerequisite for maintenance and improvement of cardiorespiratory capacity (30), and walking ability is an important prerequisite for engaging in exercise. However, results from a recent population-based cohort study showed that hip OA or knee OA is a strong contributor to walking difficulty (9), and only a small-to-moderate proportion of patients with hip OA or knee OA meet the guidelines for physical activity (7). Many patients with OA spend a considerable amount of time being sedentary, leading to more impairment in physical function, reduced walking speed (31), and poorer cardiometabolic health (32) compared with their peers who had a less sedentary lifestyle. Therefore, assessment of cardiorespiratory fitness should be prioritized in clinical practice (33), and improved cardiorespiratory fitness

Table 2. Univariate and multivariate linear regression analyses of the association between the 6MWD and arterial stiffness*

	Unadjusted	Model 1	Model 2
B (unstandardized coefficient)	−0.006	−0.002	−0.003
95% CI	−0.008, −0.003	−0.004, −0.001	−0.005, −0.001
P	<0.001	0.007	0.001

* Arterial stiffness was measured using pulse wave velocity (meters/second). Model 1 was adjusted for heart rate, mean arterial blood pressure, age, and sex. Model 2 was adjusted for heart rate, mean arterial blood pressure, age, sex, smoking, and body mass index. The analyses were conducted in 352 participants. 6MWD = 6-minute walking distance (meters). 95% CI = 95% confidence interval.

should be a treatment goal, in order to prevent cardiovascular comorbidity in OA.

Based on results of studies in the general population, it is well known that improvement of cardiorespiratory fitness is associated with a better CVD risk profile and reduced CVD-related mortality (10,11,34). The reduced risk of CVD associated with aerobic exercise is partly attributable to improved vascular hemodynamic function, including arterial stiffness, and PWV is considered to provide clinically relevant information in addition to and beyond the traditional risk factors (15,35). A meta-analysis of 42 studies (n = 1,627 participants) including both healthy individuals and patients at risk for CVD showed that aerobic exercise improved arterial stiffness, and that higher-intensity exercise was associated with a greater reduction in arterial stiffness (15). Importantly, the authors of that review concluded that resistance exercise, alone or combined with aerobic exercise, had no significant effect on arterial stiffness (15), which emphasizes the importance of including aerobic exercise in the treatment program for OA patients.

According to the National Institute for Health and Care Excellence guidelines, radiologic findings are not required for the diagnosis of OA (36). In the current population cohort, participants were included based on self-reported OA even if they did not fulfill the ACR criteria (non–ACR-defined OA) (18–20). The association between the 6MWD and PWV was significant even when individuals who did not fulfill these criteria were included, indicating that self-reported OA is adequate for diagnostic purposes. Furthermore, a reduced walking distance was observed across all OA subgroups compared the walking distance in the matched control groups (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23697/abstract). The consistent findings in subgroup analyses may imply that OA per se, and not only OA affecting the lower extremities, causes a reduced walking distance.

A strength of this study is the comparison of the 6MWD between the patients in the OA cohort and their age- and sex-matched peers from the general population. The 2 cohorts were recruited during the same time period and from adjacent geographic areas. This approach is considered to be advantageous, because significant differences between countries have been reported for 6MWD (37). Other strengths are the comprehensive medical examination of a large population of patients with OA with several OA phenotypes, including the gold standard noninvasive assessment of arterial stiffness (PWV). Furthermore, the validity of the classification of OA subgroups applied in this study, including the group with non–ACR-classified OA, was confirmed by the sensitivity analyses that showed consistent results.

A limitation of our study is the cross-sectional design, which does not allow for conclusions regarding causality. In addition, the well-known association between NSAID use and CVD (25) was not supported by the findings in our study, possibly due to insufficient data with regard to use of NSAIDs.

This study provides new evidence regarding the early impact of walking disability in patients with OA and also underlines the associations between functional fitness and cardiovascular health in these patients. The results reinforce the strength of the guidelines for physical activity and emphasize the importance of an early and broad clinical approach to OA, addressing prevention and management of CVD risk along with treatment of joint-related symptoms.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Joseph 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. Joseph, Hagen, Magnusson, Tveter, Provan, Dagfinrud.

Acquisition of data. Hagen, Tveter, Provan.

Analysis and interpretation of data. Joseph, Hagen, Magnusson, Tveter, Provan, Dagfinrud.

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ACTIVITY AND THE RHEUMATIC DISEASES

Association Between Declining Walking Speed and Increasing Bone Marrow Lesion and Effusion Volume in Individuals with Accelerated Knee Osteoarthritis

Matthew S. Harkey,[1] Lori Lyn Price,[2] Timothy E. McAlindon,[1] Julie E. Davis,[1] Alina C. Stout,[3] Bing Lu,[4] Ming Zhang,[1] Charles B. Eaton,[5] Mary F. Barbe,[6] Grace H. Lo,[7] and Jeffrey B. Driban[1]

Objective. To determine whether a decline in walking speed during the year prior to disease onset is associated with concurrent changes in cartilage, bone marrow lesions (BMLs), or effusion in adults who develop common knee osteoarthritis (OA), accelerated knee OA, or no knee OA.

Methods. We identified 3 groups from the Osteoarthritis Initiative based on annual radiographs from baseline to 48 months: accelerated knee OA, common knee OA, and no knee OA. We used the cartilage damage index (CDI) to assess tibiofemoral cartilage damage and used a semiautomated program to measure BML and effusion volume. Walking speed was assessed as an individual's habitual walking speed over 20 meters. One-year change in walking speed and structural measures were calculated as index visit measurements minus measurements from the year prior visit. Logistic regression models were used to determine whether change in walking speed (exposure) was associated with change in each structural measure (outcome) for the overall group and then separately for the accelerated knee OA, common knee OA, and no knee OA groups.

Results. Adults who slowed their walking speed were almost twice as likely to present with increased BML volume, with a significant association (odds ratio 3.04 [95% confidence interval (95% CI) 1.03–8.95]) among adults with accelerated knee OA. Adults with accelerated knee OA who slowed their walking speed were approximately 3.4 times (95% CI 1.10–10.49) more likely to present with increased effusion volume. Walking speed change was not significantly associated with CDI change.

Conclusion. A change in an easily assessable clinical examination (i.e., 20-meter walk test) was associated with concurrent worsening in BML and effusion volume in adults who developed accelerated knee OA.

INTRODUCTION

Walking speed is an easily accessible clinical measure that reflects physical function in individuals with or at risk of knee osteoarthritis (OA) (1). Walking speed decline is a clinically relevant impairment that is a risk factor for developing radiographic knee OA and receiving a knee replacement (2,3). While walking speed decline is a prognostic marker of knee OA, how it relates to structural changes prior to the onset of radiographic OA remains unclear. Understanding whether

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[1]Matthew S. Harkey, PhD, Timothy E. McAlindon, MD, MPH, Julie E. Davis, BS, Ming Zhang, PhD, Jeffrey B. Driban, PhD: Tufts Medical Center, Boston, Massachusetts; [2]Lori Lyn Price, MAS, MLA: Tufts Medical Center and Tufts University, Boston, Massachusetts; [3]Alina C. Stout, BS: Northeastern University, Boston, Massachusetts; [4]Bing Lu, MD, DrPH: Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [5]Charles B. Eaton, MD, MS: Alpert Medical School of Brown University, Pawtucket, Rhode Island; [6]Mary F. Barbe, PhD: Temple University School of Medicine, Philadelphia, Pennsylvania; [7]Grace H. Lo, MD, MSc: Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston Texas.

Address correspondence to Jeffrey Driban, PhD, Tufts Medical Center, Division of Rheumatology, 800 Washington Street, Box 406, Boston, MA 02111. E-mail: jeffrey.driban@tufts.edu.

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SIGNIFICANCE & INNOVATIONS

- Understanding whether early changes in walking speed are associated with sensitive measures of knee structure may provide a better understanding of the early link to physical function and joint health decline.
- Individuals with accelerated knee osteoarthritis present with earlier worsening of knee structure as well as poorer patient-reported and physical function measures compared to individuals with a more common, gradual onset of knee osteoarthritis.
- Individuals with accelerated knee osteoarthritis who slowed their walking speed were 3.0 and 3.4 times more likely to demonstrate an increase in bone marrow lesion and effusion volume, respectively.
- Cartilage structure changes were not associated with walking speed decline in individuals with accelerated or common knee osteoarthritis.

early changes in walking speed are associated with commonly used sensitive measures of knee health that are related to OA onset and progression (e.g., changes in bone marrow lesions [BMLs; 4], effusion [5], or cartilage [6]) may provide a better understanding of the early link to physical function and joint health decline.

While knee OA is commonly considered a slowly progressive disorder, some individuals develop an accelerated form of the disease that progresses from a normal joint (Kellgren/Lawrence [K/L] grade 0–1) to advanced-stage disease (K/L grades 3–4) within 4 years (7–9). Individuals with accelerated knee OA present with earlier worsening of magnetic resonance imaging (MRI)–based structural measures (e.g., effusion) and poorer patient-reported and physical function measures (e.g., walking speed) compared to individuals with a more gradual onset of knee OA (common knee OA) (8,10). Thus, the association between walking speed decline and early structural changes may be more pronounced among patients with accelerated knee OA than in those patients with common knee OA.

Therefore, we aimed to determine whether a decline in walking speed during the year prior to disease onset is associated with concurrent worsening of tibiofemoral effusion, BMLs, and articular cartilage in 3 groups: adults who develop accelerated knee OA, common knee OA, and no knee OA. This information may help clarify the relationship between a decline in knee structure and physical function in individuals with incident knee OA. We hypothesized that an association exists between a change in walking speed and a change in structural features due to 2 possibilities: a decline in walking speed may alter loading at the knee and result in structural alterations, or alterations in structural features may lead to a decline in gait speed in an attempt to avoid pain or protect the joint from further damage. With either possibility, the results of this study may demonstrate that a clinically feasible physical function test may be a proxy for early structural changes and thus help identify individuals with early evidence of structural changes in a knee.

PATIENTS AND METHODS

Study design. To determine the association between changes in walking speed and changes in MRI-based knee structural measures, we conducted a longitudinal analysis of data from the Osteoarthritis Initiative (OAI). The OAI is a multicenter (Memorial Hospital of Rhode Island, Ohio State University, University of Maryland, Johns Hopkins University, and University of Pittsburgh) cohort study that recruited 4,796 adults with or at risk of symptomatic knee osteoarthritis between February 2004 and May 2006 (11). MRIs and walking speed information were obtained at the initial baseline study visit, as well as at the first 4 annual follow-up visits. Institutional review boards at all OAI clinical sites and the OAI coordinating center (University of California, San Francisco) approved the OAI study. Participants provided informed consent prior to participation.

Participant selection. We identified 3 groups within the OAI based on radiographs obtained at baseline and at the first 4 annual follow-up visits (9). All groups had at least 1 knee with no radiographic knee OA at baseline (K/L grade ≤1). Individuals with incident accelerated knee OA (n = 125) were defined as having 1 knee that developed advanced-stage knee OA (K/L grades 0–1 to 3–4, definitive osteophyte, and joint space narrowing) within 48 months (9). Individuals with incident common knee OA (n = 187) had no knee OA in both knees at baseline and were defined as having a more gradual onset of knee OA, with 1 knee increasing in K/L grade within 48 months (i.e., K/L grade from 0 to 1, from 0 to 2, or from 1 to 2). Individuals with no knee OA (n = 1,325) were defined as having no knee OA in both knees at baseline and had no change in K/L grade in either knee from baseline to the 48-month follow-up. To match individuals with common and no knee OA, we first identified those individuals with 1 or no missing MRIs. Next, we used SAS software to assign each male and female a random number from a uniform distribution, and we used this number to randomly match individuals with common or no knee OA to individuals in the accelerated knee OA group, stratified by sex (125 participants per group).

Index knee. For individuals with accelerated knee OA or common knee OA, the index knee was defined as the knee that first met the definition for incident accelerated knee OA or common knee OA. The index knee for individuals with no knee OA

was matched to the knee on the same side for that person's matched member of the accelerated knee OA group.

Index visits. For the individuals with accelerated knee OA and common knee OA, the index visit was defined as the visit at which the index knee met the criteria for accelerated OA or common OA. For individuals with no knee OA, the index visit was the same as their matched member of the accelerated knee OA group. For this study, we assessed walking speed and the MRI-based knee structure measures at the index visit and the visit in the year prior to the index visit (Figure 1).

Knee radiographs. To determine group assignment, we used readings of bilateral weight-bearing, fixed-flexion posteroanterior knee radiographs obtained at baseline and at each of the annual follow-up visits (9). Central readers blinded to the group assignment scored the K/L grade of each knee (K/L 0–4) The intrarater reliability agreement for the K/L grades was good (weighted κ = 0.70–0.80). These data are publicly available on the OAI website under Full Downloads, Knee X-Ray Image Assessments (files: kXR_SQ_BU##_SAS [versions 0.6, 1.6, 3.5, 5.5, and 6.3]) (12,13).

MRI acquisition. MRIs were acquired annually with 1 of 4 identical Siemens Trio 3T MRI systems at each clinical site using the OAI MRI protocol (12,13). BML and effusion quantitative measurements were performed using a sagittal intermediate-weighted, turbo spin-echo, fat-suppressed MRI sequence with the following parameters: field of view 160 mm, slice thickness 3 mm, skip 0 mm, flip angle 180°, echo time 30 msec, recovery time 3,200 msec, matrix 313 × 448 pixels, x resolution 0.357 mm, y resolution 0.511 mm, and total slice number 37. Cartilage was quantified using a 3-dimensional double-echo steady-state sequence with the following parameters: field of view 140 mm, slice thickness 0.7 mm, skip 0 mm, flip angle 25°, echo time 4.7 msec, recovery time 16.3 msec, matrix 307 × 384 pixels, x resolution 0.365 mm, y resolution 0.456 mm, and total slice number 160.

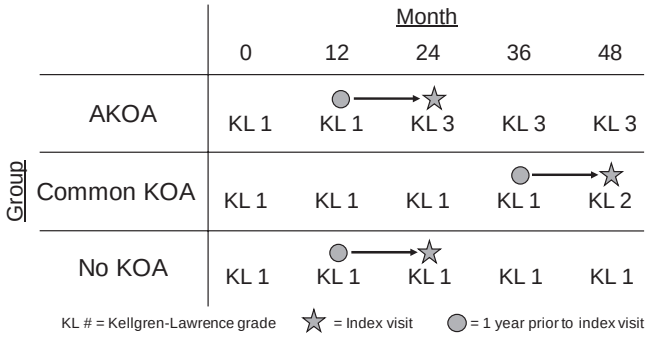

Figure 1. Walking speed and structural measures were assessed at the visit in the year prior to the index visit, as well as at the index visit. One-year change in walking speed and structural measures was calculated as the measurement from the index visit minus measurement from the year prior visit. AKOA = accelerated knee osteoarthritis; KOA = knee osteoarthritis.

MRI outcomes. For BML, effusion, and cartilage processing, the readers were unaware of group assignment. Additionally, during the processing of all MRI measures, the readers had both time points on the screen and were unblinded to the order of time, which is the standard method used to maximize the sensitivity to change (14,15).

BML volume. One reader (ACS) measured tibiofemoral BML volume with a semiautomated segmentation method (16,17). The only manual step required the reader to identify crude boundaries of the tibia and femur in each slice of the MRIs. The boundary furthest from the articular surfaces was marked just prior to the epiphyseal line or at the edge of the bone and soft tissue. The program software then automatically identified the precise bone boundaries and performed a thresholding and curve evolution process twice to segment areas of high signal intensity, which may represent a BML. We eliminated false-positive regions by operationally defining a BML based on 2 criteria: the distance between a BML to the articular surface should be <10 mm, and a BML needed to span >1 MRI. BML volume was expressed as a total tibiofemoral BML volume. A previous study used a similar total tibiofemoral BML volume and the results showed a significant association between change in BML volume and change in knee pain severity (17). The study principal investigator (JBD) reviewed all measurements with both time points on screen simultaneously. Our reader demonstrated excellent intrareader reliability (intraclass correlation coefficient [ICC](3,1) 0.91).

Effusion volume. We used a customized semiautomatic software to measure knee effusion/synovitis, which reflects effusion and synovitis volume but for simplicity is referred to only as effusion volume. Two readers used the software to mark the first and last MRI slice that included bone, the proximal border of the patella, and the apex of the fibular head on a central slice. The software then automatically segmented effusion between these limits based on an existing threshold. The senior reader (JBD) then manually adjusted the threshold to change the effusion boundaries and removed areas of high signal intensity that were not effusion (e.g., subchondral cysts, blood vessels). The effusion volume measurement was a total tibiofemoral effusion volume. The senior reader (JBD) demonstrated excellent intrareader reliability (ICC[3,1] 0.96).

Cartilage damage index. To quantify change in tibiofemoral cartilage damage we used the validated cartilage damage index (CDI) (18,19). One reader (JED) manually marked the bone-cartilage boundary on specific knee slices that were automatically selected based on the width of the knee. The reader then measured cartilage thickness at predefined informative locations, which the software automatically located. At that point, the software computed the CDI for the medial femur, lateral femur, medial tibia, and lateral tibia by summing the products of cartilage thickness, cartilage length (anteroposterior), and voxel size from 9 informative locations in

each compartment. All measurements were reviewed by the study principal investigator (JBD). Our reader demonstrated excellent intrareader reliability (ICC[3,1] 0.86–0.99).

Walking speed assessment. To assess habitual walking speed, we asked participants to perform 2 trials of a timed 20-meter walk at their usual, comfortable walking pace (1,2). The participants began each trial in a stationary, standing position, and timing began when the participant took the first step at the starting line and ended when they passed a cone positioned 20 meters away. Participants were instructed to maintain their usual walking pace for 3 steps past the cone to ensure they were not decelerating at the end of each trial. The time needed to complete the 20 meters was converted to walking speed (i.e., meters/second) and averaged across the 2 trials.

Clinical data. Demographic and other participant characteristics were acquired based on a standard protocol. We extracted OAI baseline age, body mass index (BMI), index knee Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score, self-reported Physical Activity Scale for the Elderly (PASE) score, frequent knee pain, and injury between the 2 study visits. The data are publicly available (files: allclinical0#; version 0.2.2, 1.2.1, 3.2.1, 5.2.1, and 6.2.1) (13).

Statistical analysis. *Data analysis.* Because cartilage thickness is largely dependent on an individual's height (20), we normalized the CDI of each tibiofemoral compartment (i.e., medial femur, lateral femur, medial tibia, and lateral tibia) to participant height. The one-year change in BML, effusion, and CDI for each compartment was calculated as the measurement from the index visit minus the measurement from the year prior to the index visit. If individuals were missing a structural measurement at one of the time points, we used the most proximate visit (e.g., if an individual was missing the year prior to the index visit, we used the visit from 2 years prior, and if missing the index visit, we used the year following the index visit) to calculate an annual rate of change over 2 years (n = 13). Total tibiofemoral CDI change was calculated as the sum of the change for each individual compartment CDI. The total tibiofemoral changes for BML, effusion, and CDI were then separated into tertiles and converted to a dichotomous variable, to subsequently compare the worst tertile (i.e., the highest BML and effusion, the lowest CDI) to the combination of the other 2 tertiles to facilitate the interpretation of the odds ratio. These binary change variables were used in our statistical analysis to compare individuals with the greatest increase in BML/effusion volume and greatest decrease in CDI to individuals with no change/decrease in BML/effusion volume and no change/increase in CDI.

Walking speed change was calculated as the index visit walking speed minus the walking speed of the year prior to the index visit. Based on a previous study, which detected an increase in the risk of knee OA in individuals decreasing their walking speed (2), we dichotomized walking speed change as slower/decline in walking speed (walking speed change less than or equal to –0.1 meter/second) and no change/increase in walking speed (walking speed change greater than –0.1 meter/second). This dichotomous variable allowed us to compare individuals with declining walking speed to individuals with no change/increase in walking speed.

Primary analysis: association between change in walking speed and change in structure. Three logistic regression models were used to determine whether the change in walking speed (predictor) was associated with the change in BML volume, effusion volume, and CDI (outcomes) for the overall group. Additionally, we separately explored these relationships for individuals with accelerated knee OA, common knee OA, or no knee OA. As a post hoc analysis, we replicated these analyses using a linear regression with each structural feature as a continuous variable for the overall group and separated for accelerated knee OA, common knee OA, and no knee OA.

Sensitivity analysis. We conducted 3 sensitivity analyses using the same logistic regression models above on 3 subsets: individuals who developed accelerated knee OA within 1 year, individuals who had no radiographic knee OA bilaterally at baseline (K/L grades 0–1), and excluding the 13 individuals with missing structural data that we imputed by calculating an annual rate of change over 2 years.

Table 1. Group demographics*

Variable	Overall (n = 346)	Accelerated knee OA (n = 106)	Common knee OA (n = 121)	No knee OA (n = 119)
Age, years	60.6 ± 8.6	64.5 ± 8.4	59.4 ± 8.4	58.3 ± 7.8
BMI, kg/m^2	28.2 ± 4.6	29.7 ± 4.5	28.0 ± 4.5	27.1 ± 4.6
WOMAC pain	2.0 ± 2.8	3.3 ± 3.5	1.8 ± 2.3	1.1 ± 2.1
PASE	162.8 ± 84.0	148.1 ± 89.1	161.6 ± 80.1	177.3 ± 81.6
Women, no. (%)	214 (62)	66 (62)	75 (62)	73 (61)

* Values are the mean ± SD unless indicated otherwise. OA = osteoarthritis; BMI = body mass index; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; PASE = Physical Activity Scale for The Elderly.

Table 2. Association between longitudinal walking speed change and knee structure change*

Group and walking speed change	Decrease/no change (BML and effusion) or decrease (CDI)	Increase (BML and effusion) or increase/ no change (CDI)	Adjusted OR (95% CI)†
BML change‡			
Overall			
Slower	35 (58)	25 (42)	1.79 (1.00–3.20)
Faster/no change	200 (70)	86 (30)	Ref.
Accelerated knee OA			
Slower	7 (30)	16 (70)	3.04 (1.03–8.95)
Faster/no change	46 (55)	37 (45)	Ref.
Common knee OA			
Slower	15 (68)	7 (32)	1.17 (0.41–3.32)
Faster/no change	72 (73)	27 (27)	Ref.
No knee OA			
Slower	13 (87)	2 (13)	0.60 (0.12–2.92)
Faster/no change	82 (79)	22 (21)	Ref.
Effusion change‡			
Overall			
Slower	36 (60)	24 (40)	1.48 (0.83–2.66)
Faster/no change	195 (68)	91 (32)	Ref.
Accelerated knee OA			
Slower	6 (26)	17 (74)	3.39 (1.10–10.49)
Faster/no change	41 (49)	42 (51)	Ref.
Common knee OA			
Slower	17 (77)	5 (23)	0.57 (0.19–1.73)
Faster/no change	67 (68)	32 (32)	Ref.
No knee OA			
Slower	13 (87)	2 (13)	0.80 (0.16–4.02)
Faster/no change	87 (84)	17 (16)	Ref.
CDI change§			
Overall			
Slower	18 (30)	42 (70)	0.89 (0.48–1.66)
Faster/no change	97 (34)	189 (66)	Ref.
Accelerated knee OA			
Slower	12 (52)	11 (48)	0.81 (0.30–2.16)
Faster/no change	51 (61)	32 (39)	Ref.
Common knee OA			
Slower	4 (18)	18 (82)	0.75 (0.22–2.55)
Faster/no change	22 (22)	77 (78)	Ref.
No knee OA			
Slower	2 (13)	13 (87)	0.49 (0.10–2.35)
Faster/no change	24 (23)	80 (77)	Ref.

* Values are the number (%) unless indicated otherwise. OR = odds ratio; 95% CI = 95% confidence interval; BML = bone marrow lesion; Ref. = reference; OA = osteoarthritis; CDI = cartilage damage index.
† Adjusted for baseline age, body mass index, Western Ontario and McMaster Universities Osteoarthritis Index pain score, and physical activity.
‡ Decrease/no change = reference.
§ Increase/no change = reference.

Covariates for all analyses included baseline age, BMI, WOMAC pain score, and PASE score. We used baseline covariates because the covariate means were stable throughout the study period and to prevent the loss of participants due to

Table 3. Association between longitudinal walking speed change and knee structure change among individuals who developed accelerated knee osteoarthritis within 1 year*

Group and walking speed change	Decrease/no change (BML and effusion) or decrease (CDI)	Increase (BML and effusion) or increase/ no change (CDI)	Adjusted OR (95% CI)†
BML change‡			
Overall			
Slower	19 (49)	20 (51)	2.17 (1.05–4.52)
Faster/no change	110 (68)	51 (32)	Ref.
Accelerated knee OA			
Slower	2 (13)	14 (87)	9.26 (1.52–56.50)
Faster/no change	22 (48)	24 (52)	Ref.
Common knee OA			
Slower	9 (64)	5 (36)	1.87 (0.49–7.21)
Faster/no change	43 (78)	12 (22)	Ref.
No knee OA			
Slower	8 (89)	1 (11)	0.37 (0.04–3.45)
Faster/no change	45 (75)	15 (25)	Ref.
Effusion change‡			
Overall			
Slower	22 (56)	17 (44)	1.27 (0.61–2.64)
Faster/no change	103 (64)	58 (36)	Ref.
Accelerated knee OA			
Slower	2 (13)	14 (87)	6.38 (1.04–39.38)
Faster/no change	19 (41)	27 (59)	Ref.
Common knee OA			
Slower	12 (86)	2 (14)	0.29 (0.06–1.51)
Faster/no change	37 (67)	18 (33)	Ref.
No knee OA			
Slower	8 (89)	1 (11)	0.46 (0.05–4.41)
Faster/no change	47 (78)	13 (22)	Ref.
CDI change§			
Overall			
Slower	15 (38)	24 (62)	1.19 (0.56–2.53)
Faster/no change	56 (35)	105 (65)	Ref.
Accelerated knee OA			
Slower	11 (69)	5 (31)	1.74 (0.45–6.70)
Faster/no change	30 (65)	16 (35)	Ref.
Common knee OA			
Slower	3 (21)	11 (79)	1.14 (0.25–5.19)
Faster/no change	14 (25)	41 (75)	Ref.
No knee OA			
Slower	1 (11)	8 (89)	0.47 (0.05–4.33)
Faster/no change	12 (20)	48 (80)	Ref.

* Values are the number (%) unless indicated otherwise. OR = odds ratio; 95% CI = 95% confidence interval; BML = bone marrow lesion; Ref. = reference; OA = osteoarthritis; CDI = cartilage damage index.
† Adjusted for baseline age, body mass index, Western Ontario and McMaster Universities Osteoarthritis Index pain score, and physical activity.
‡ Decrease/no change = reference.
§ Increase/no change = reference.

missing self-reported data between the 2 time points. We ran sensitivity analyses that used the frequent knee pain variable as a covariate instead of the WOMAC pain score and a sensitivity analysis that included injury between the 2 visits as a covariate.

Table 4. Association between longitudinal walking speed change and knee structure change in individuals with no radiographic knee OA bilaterally at baseline (K/L grades 0–1)*

Group and walking speed change	Decrease/no change (BML and effusion) or decrease (CDI)	Increase (BML and effusion) or increase/no change (CDI)	Adjusted OR (95% CI)†
BML change‡			
Overall			
Slower	10 (40)	15 (60)	3.67 (1.47–9.19)
Faster/no change	85 (69)	38 (31)	Ref.
Accelerated knee OA			
Slower	3 (25)	9 (75)	5.68 (1.00–32.39)
Faster/no change	19 (54)	16 (46)	Ref.
Common knee OA			
Slower	6 (50)	6 (50)	2.11 (0.47–9.57)
Faster/no change	29 (73)	11 (27)	Ref.
No knee OA			
Slower	1 (100)	0 (0)	Unable to calculate
Faster/no change	37 (77)	11 (23)	–
Effusion change‡			
Overall			
Slower	14 (56)	11 (44)	1.95 (0.78–4.85)
Faster/no change	85 (69)	38 (31)	Ref.
Accelerated knee OA			
Slower	4 (33)	8 (67)	6.37 (0.96–42.33)
Faster/no change	19 (54)	16 (46)	Ref.
Common knee OA			
Slower	9 (75)	3 (25)	0.49 (0.10–2.34)
Faster/no change	27 (68)	13 (32)	Ref.
No knee OA			
Slower	1 (100)	0 (0)	Unable to calculate
Faster/no change	39 (81)	9 (19)	–
CDI change§			
Overall			
Slower	9 (36)	16 (64)	1.34 (0.52–3.43)
Faster/no change	40 (33)	83 (67)	Ref.
Accelerated knee OA			
Slower	7 (58)	5 (42)	1.37 (0.31–5.98)
Faster/no change	19 (54)	16 (46)	Ref.
Common knee OA			
Slower	2 (17)	10 (83)	0.74 (0.11–4.85)
Faster/no change	9 (23)	31 (77)	Ref.
No knee OA			
Slower	0 (1)	1 (100)	Unable to calculate
Faster/no change	12 (25)	36 (75)	–

* Values are the number (%) unless indicated otherwise. OA = osteoarthritis; K/L = Kellgren/Lawrence; OR = odds ratio; 95% CI = 95% confidence interval; BML = bone marrow lesion; Ref. = reference; CDI = cartilage damage index.
† Adjusted for baseline age, body mass index, Western Ontario and McMaster Universities Osteoarthritis Index pain score, and physical activity
‡ Decrease/no change = reference.
§ Increase/no change = reference.

All analyses were performed using SAS Enterprise software, version 7.15.

RESULTS

Primary analyses. *BML volume and walking speed.* The group demographics are described in Table 1. Due to missing MRI or walking speed data, our final analyses included 106 individuals with accelerated knee OA, 121 individuals with common knee OA, and 119 individuals with no knee OA. Overall, adults who slowed their walking speed during 1 year had almost twice the odds of presenting with increased BML volume (adjusted odds ratio [OR] 1.8 [95% confidence interval (95% CI) 1.00–3.20]) (Table 2). Specifically, adults with accelerated knee OA who slowed their walking speed had 3 times the odds of increasing BML volume (adjusted OR 3.0 [95% CI 1.03–8.95]). However, among individuals who develop common knee OA or no knee OA, walking speed change was not significantly associated with a change in BML volume.

Effusion volume and walking speed. Adults with accelerated knee OA who slowed their walking speed had 3.4 times greater odds of presenting with increased effusion volume (adjusted OR 3.4 [95% CI 1.10–10.49]) (Table 2). However, in individuals who develop common knee OA or no knee OA, walking speed change was not significantly associated with a change in effusion volume.

CDI and walking speed. Walking speed change was not significantly associated with CDI change (Table 2). The results of our post hoc linear regression analyses using the continuous structural variables were in agreement with our primary results (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23613/abstract).

Sensitivity analyses. *Individuals who developed accelerated knee OA within 1 year.* Neither of the sensitivity analyses that included frequent knee pain or injury as a covariate significantly altered the odds ratios observed in our primary results. Similar trends with stronger odds ratios were observed when limiting our analysis to include individuals with accelerated knee OA who progressed from K/L grades 0–1 to 3–4 within 1 year, along with their matched individuals in the common knee OA and no knee OA groups (Table 3). Adults with accelerated knee OA who slowed their walking speed had 9.3 times (95% CI 1.52–56.50) and 6.4 times (95% CI 1.04–39.38) greater odds of presenting with increased BML and effusion volume, respectively. CDI change and walking speed change were not significantly associated in any of the groups.

Individuals with no radiographic OA bilaterally at baseline. Similar trends with stronger odds ratios were observed when limiting our analysis to individuals without radiographic knee OA at baseline (K/L grades 0–1) and their matched individuals in the common knee OA and no knee OA groups (Table 4). Adults with accelerated knee OA who slowed their walking speed had 5.7 times (95% CI 1.00–32.39) the odds of presenting with increased BML volume. However, due to the loss of power with this sensitivity analysis, the association between declining walking speed and increasing effusion volume had wide confidence intervals that crossed 1 (adjusted OR 6.38 [95% CI 0.96–42.33]). CDI change and walking speed change were not significantly associated in any of the groups.

Excluding the individuals who were included after imputing missing structural data. Similar trends with stronger odds ratios were observed when excluding the individuals who were included after imputing their missing structural data (Table 5). Adults with accelerated knee OA who slowed their walking speed had 3.6 times (95% CI 1.11–11.62) the odds of presenting with increased effusion volume. However, due to the loss of power with this sensitivity analysis, the association between declining walking speed and increasing BML volume had wide confidence intervals that crossed 1 (adjusted OR 3.04 [95% CI 0.99–9.30]). CDI change and walking speed change were not significantly associated in any of the groups.

DISCUSSION

Individuals with accelerated knee OA who slowed their walking speed had 3.0 times and 3.4 times greater odds of an increase in BML and effusion volume, respectively, when compared to individuals who did not decrease their walking speed. However, there was not a significant association between change in walking speed and cartilage damage in individuals developing accelerated knee OA. Additionally, individuals with no knee OA or common knee OA showed no significant associations between a change in walking speed and any of our knee structural measures. These findings build upon a growing body of work that shows a stark difference between individuals who develop accelerated and common knee OA (8,10,21–24), which highlights the potential need for future studies to separately analyze these individuals. These results are important, because they indicate that a 1-year change in an easy, clinically accessible examination (i.e., 20-meter walk) is associated with concurrent worsening in BML and effusion volume in adults developing accelerated knee OA.

Walking speed has been labeled a functional vital sign (25), because this physical function measure has been linked to the prediction of falls (26), hospitalization (27), and mortality (28) in older individuals. In knee OA specifically, declining walking speed is associated with decreased knee confidence (29), radiographic development of disease (29), and likelihood to undergo a knee replacement (3). This is the first study linking declining walking speed with concurrent worsening of specific knee structural measures in individuals with knee OA.

Table 5. Association between longitudinal walking speed change and knee structure change excluding individuals with imputed missing structural data*

Group and walking speed change	Decrease/no change (BML and effusion) or decrease (CDI)	Increase (BML and effusion) or increase/no change (CDI)	Adjusted OR (95% CI)†
BML change‡			
Overall			
Slower	34 (57)	26 (43)	1.95 (1.09–3.49)
Faster/no change	192 (70)	81 (30)	Ref.
Accelerated knee OA			
Slower	7 (30)	16 (70)	3.04 (0.99–9.30)
Faster/no change	39 (54)	33 (46)	Ref.
Common knee OA			
Slower	14 (64)	8 (36)	1.50 (0.54–4.21)
Faster/no change	71 (73)	26 (27)	Ref.
No knee OA			
Slower	13 (87)	2 (13)	0.60 (0.12–2.92)
Faster/no change	82 (79)	22 (21)	Ref.
Effusion change‡			
Overall			
Slower	37 (62)	23 (38)	1.44 (0.80–2.61)
Faster/no change	189 (69)	84 (31)	Ref.
Accelerated knee OA			
Slower	6 (26)	17 (74)	3.59 (1.11–11.62)
Faster/no change	35 (49)	37 (51)	Ref.
Common knee OA			
Slower	17 (77)	5 (23)	0.59 (0.20–1.79)
Faster/no change	66 (68)	31 (32)	Ref.
No knee OA			
Slower	14 (93)	1 (7)	0.40 (0.05–3.44)
Faster/no change	88 (85)	16 (15)	Ref.
CDI change§			
Overall			
Slower	19 (32)	41 (68)	0.98 (0.53–1.81)
Faster/no change	91 (33)	182 (67)	Ref.
Accelerated knee OA			
Slower	12 (52)	11 (48)	0.84 (0.31–2.30)
Faster/no change	45 (63)	27 (37)	Ref.
Common knee OA			
Slower	5 (23)	17 (77)	1.00 (0.32–3.13)
Faster/no change	22 (23)	75 (77)	Ref.
No knee OA			
Slower	2 (13)	13 (87)	0.49 (0.10–2.35)
Faster/no change	24 (23)	80 (77)	Ref.

* Values are the number (%) unless indicated otherwise. OR = odds ratio; 95% CI = 95% confidence interval; BML = bone marrow lesion; Ref. = reference; OA = osteoarthritis; CDI = cartilage damage index.
† Adjusted for baseline age, body mass index, frequent pain, and physical activity.
‡ Decrease/no change = reference.
§ Increase/no change = reference.

The mechanisms leading to this association between walking speed and knee structure are unknown, but we recognize 2 possibilities: declining walking speed is creating altered knee loading (30–32) that leads to worsening knee structure, or the worsening knee structure is leading to a protective gait strategy that decreases walking speed to minimize loading of the joint. Future work is needed to explain the causality of this association. Understanding this causality may lead to the development of 2 treatment possibilities: interventions targeting the maintenance of walking speed to prevent pathologic joint loading created by slower walking speed, or interventions that decrease BML and effusion volume to prevent the decline in walking speed.

Even though walking speed decline was associated with worsening BML and effusion volume in individuals who developed accelerated knee OA, there was no significant association between walking speed decline and knee articular cartilage change in any group. While we observed no significant association between walking speed and articular cartilage, results from prior cross-sectional studies and prognostic studies have suggested a link between walking speed and cartilage health (33,34). Specifically, slower walking speed is significantly associated with worse cartilage composition (33) (i.e., T1rho relaxation times) as well as with serum biomarkers of cartilage metabolism (34) (i.e., the ratio of type II collagen degradation to synthesis) in individuals at high risk of knee OA (i.e., young adults with a history of an anterior cruciate ligament reconstruction). Additionally, habitual walking speed is associated with acute femoral cartilage deformation following a 30-minute treadmill walk (35), indicating that walking speed may play a role in cartilage loading that is important in the maintenance of cartilage health. Our analysis determined the association between concurrent change in walking speed and change in cartilage structure, which is a more robust analysis technique than previous cross-sectional studies (33–35). However, this difference in analysis may be one reason why we did not observe a significant association between changes in walking speed and articular cartilage.

Another reason for our lack of significance in the association between change in walking speed and change in cartilage structure is that the change in walking speed may be eliciting subtle changes in the cartilage composition that may precede changes in cartilage thickness (36). Declines in cartilage thickness may be a downstream event that occurs later in the structural progression of knee OA, following significant increases in BML and effusion volume. Therefore, further studies are needed to determine whether changes in walking speed are associated with more sensitive measurements of cartilage composition in individuals with knee OA. Another reason why there is no association between change in walking speed and change in cartilage damage may be due to the fact that pain can influence the decline in walking speed, but early cartilage damage is typically not painful (37). Future studies should explore whether the change in walking speed contributes to future loss of articular cartilage.

While these results indicate that a decline in walking speed is associated with concurrent worsening of BML and effusion volume in individuals with accelerated knee OA, there are some limitations to this study that we must consider. We only included individuals who completed the walking speed assessment and MRI protocol at their index and year prior to the index visits. Thus, the individuals with potentially the largest change in outcomes may have been omitted from our analysis due to their inability to complete the study protocol. However, we expanded our analysis to the most proximate visit among the individuals with missing data (n = 13) to reclaim some of these excluded individuals. Due to the fact that our analysis used concurrent changes in walking speed and knee structure, we are unable to determine whether one outcome is generating the change in the other outcome. Future research is needed to determine whether slower walking speed is creating the alterations in knee structure, or whether early decline in knee structure is leading to declines in walking speed. Previous investigations have determined that individuals with accelerated knee OA often have self-reported and MRI-detected knee injuries (38), which may influence the change in the BML, effusion, and cartilage structure.

In conclusion, these results highlight a significant link between a decline in a clinically accessible physical function measure (i.e., walking speed) and specific changes in knee structure in individuals who develop accelerated knee OA. Specifically, walking speed decline was associated with concurrent worsening BML and effusion volume over the year prior to the development of accelerated knee OA, but not among individuals with incident common knee OA or no knee OA. Additionally, cartilage structure changes were not associated with walking speed decline in any group. Future studies are needed to determine whether interventions that target the declining walking speed will also create concurrent improvements in knee structure outcomes, and vice versa.

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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. Driban 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. Price, McAlindon, Lu, Eaton, Barbe, Lo, Driban.

Acquisition of data. Davis, Stout, Zhang, Driban.
Analysis and interpretation of data. Harkey, Price, McAlindon, Davis, Stout, Lu, Eaton, Barbe, Lo, Driban.

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ACTIVITY AND THE RHEUMATIC DISEASES

Specific Sports Habits, Leisure-Time Physical Activity, and School-Educational Physical Activity in Children With Juvenile Idiopathic Arthritis: Patterns and Barriers

Mette Nørgaard and Troels Herlin

Objective. Juvenile idiopathic arthritis (JIA) may cause functional impairment and reduced time engaged in physical activity. The aim of this study was to investigate the habits of patients with JIA regarding participation in club sports, leisure-time physical activity, and school-educational physical activity and relate this to objectively measured physical activity using accelerometry and to compare the findings with those in healthy controls.

Methods. Consecutive patients from the Aarhus University Hospital outpatient clinic were included. Clinical characteristics, functional ability, and exploration of specific habits in club sports, leisure-time physical activity, and school-educational physical activity (based on a standardized questionnaire) in patients were recorded and compared with those in healthy controls. The intensity and frequency of physical activity were measured by accelerometer monitoring, using ActiGraph GT1M.

Results. Sixty-eight patients with JIA and 118 healthy control subjects were included. Despite having low disease activity, children with JIA had significantly lower accelerometry-monitored physical activity levels compared with healthy controls. The distribution of specific club sport activities was the same among patients and controls. However, the proportion of patients spending >3 hours/week participating in club sports was significantly lower than the proportion of controls, whereas no difference in time spent engaging in physical activity during leisure-time was observed. Participation in compulsory school-educational physical activity was equally high in patients and controls, although participation by patients was significantly less consistent than that by controls. Patient reports of time spent with club sport and leisure-time physical activity was significantly related to accelerometry measures, whereas this was not observed for school-educational physical activity.

Conclusion. The results of this study indicate the need for structured guidance for all patients with JIA (including those with minimal disease activity) in both understanding and coping with the consequences of a low level of physical activity.

INTRODUCTION

Functional ability in patients with juvenile idiopathic arthritis (JIA) and their prognosis have improved considerably over the last decade due to early, targeted treatment with biologics such as etanercept (1,2). Consequently, a motivating approach to physical activity and participation in sport has emerged, because studies have shown that physical activity and exercise training in patients with JIA are both safe and beneficial in terms of numerous health and disease outcomes (e.g., quality of life, cardiovascular fitness, muscle strength, pain, number of swollen joints) (3–6). Nevertheless, children with JIA are still less physically active (7–10), participate less often in competitive sports, and spend more time sedentary compared with their peers without JIA (7,8). Moreover, using accelerometry as an objective measure of the intensity of physical activity, we recently showed that children with JIA are significantly less physically active compared with their healthy peers, and that approximately half of the patients had below-average levels of aerobic fitness (maximum oxygen consumption [VO_2max]), despite well-controlled disease activity, low pain intensity, and close-to-normal functional ability (10).

Mette Nørgaard, PT, Troels Herlin, MD, DMSc: Aarhus University Hospital, Aarhus, Denmark.

Address correspondence to Troels Herlin, MD, DMSc, Pediatric Rheumatology Clinic, Pediatrics and Adolescent Medicine, Aarhus University Hospital, 8200 Aarhus N, Denmark. E-mail: troeherl@rm.dk.

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SIGNIFICANCE & INNOVATIONS

- Patients with juvenile idiopathic arthritis (JIA) who participate in club sports and leisure-time physical activities demonstrated the potential to perform adequately compared with their healthy peers, despite having significantly lower values for objectively measured physical activity, as assessed by accelerometry.
- Patients with JIA who were active in sports chose the same types of club sports as those chosen by controls. However, significantly fewer patients participated in club sports compared with controls, and patients reported more barriers (both physical and psychosocial) to participation.
- For leisure-time physical activity, patients avoided high-intensity activities (e.g., running); for school-educational physical activity, they reported significantly more difficulty with specific modalities (handstanding, athletics, jumping, running on time) compared with controls.

Participation in leisure-time activities, both physical and psychosocial, is essential for a child's development, and long-term limitations to engaging in such activities may lead to less ability to make friends, social isolation, depression, and physical deconditioning (11–13). However, only few studies have explored patterns and barriers to participation in specific types of sport and leisure-time physical activity in patients with JIA (14–16). In 1993, Kirscheimer et al (14) observed that children with JIA preferred swimming and bicycling to other physical activities, at a time when children with JIA were advised to restrict participation in weight-bearing, strenuous, or contact sports because of the assumption that these activities may exacerbate disease. In 1995, Henderson et al (17) observed that children with JIA often had problems with school-educational physical activities, and in 2000 Huygen et al (18) reported that children with JIA perceived themselves as having a lower level of competency in sports compared with their healthy counterparts. Recently, Cavallo et al (15) reported decreased participation in both physical and psychosocial leisure-time activities among children with JIA. In that study, the investigators examined sociodemographic, disease-related, and contextual factors limiting participation in leisure-time activities. The results showed that parent-reported arthritis-related impairment accounted the most for the decreased leisure-time participation by children with JIA, and that the availability and affordability of desired activities as well as "the child not requiring assistance" were associated with greater participation in leisure-time activities (15).

Most studies of daily physical activity are based on subjective questionnaires, which may lead to overestimation of daily physical activity and information bias (19). To provide more accurate information on the frequency and intensity of physical activity, objective monitoring is warranted (10,16) as well as exploration of contextual barriers (e.g., lack of support) or motivators (e.g., being with friends) to involvement in physical activities and sports by patients with JIA (16). In general, the purpose is to facilitate advising patients regarding physical activity and engagement in sports and to motivate patients and their families to have an active lifestyle.

Thus, in the current study, we sought to explore specific physical activity habits (in club sports, leisure-time, and school-educational physical activities) in 10–16-year-old children with JIA. We used accelerometry to assess the frequency and intensity of all daily physical activities in the patients with JIA and compared the data with that for normative controls and with World Health Organization (WHO) recommendations (20). We also examined the types of physical activities and sports as well as the self-perceived impact of motivating factors and physical and psychosocial barriers (e.g., lack of experience, skills, support, or availability) to participation.

PATIENTS AND METHODS

Patients. Children ages 10–16 years who met the 2001 revised International League of Associations for Rheumatology classification of juvenile idiopathic criteria (21) were consecutively recruited (November 2008 to November 2009) from the rheumatology clinic. Exclusion criteria were co-morbidities associated with mental or physical limitations (e.g., severe asthma) and disease duration <6 months. Disease activity was quantified using the Juvenile Arthritis Disease Activity Score (JADAS) (22).

According to Danish law on medical ethics, it was not necessary to obtain approval from the Biomedical Ethics Committee. Participation was voluntary in both groups, and parents of the patients provided written informed consent when the child had agreed to participate. For controls, consent was provided by the school's headmaster and teachers; parents were informed in advance through the school's intranet. The study was approved by the Danish Data Protection Agency.

Evaluation of functional status, the intensity and frequency of physical activity, and pain intensity. Functional impairment was assessed using the revised Childhood Health Assessment Questionnaire including 38 items (C-HAQ38) (23). Daily physical activity was monitored with a hip-worn ActiGraph GT1M accelerometer measuring acceleration of the body in a biaxial plane. Only measurements in the vertical plane were used, as previously described in detail (10). The ActiGraph monitor has been validated and is one of the most commonly used accelerometers in both healthy children (24–26) and children with chronic diseases, including JIA (9,10).

Recordings were obtained over 7 consecutive days following the outpatient clinic visit, except during water activi-

ties. Movement was detected as a combination of frequency and intensity, and movement counts were averaged over 10-second intervals (lower limit of monitor) of recording (epochs). ActiLife software was used to convert the raw data to mean counts per minute (cpm) of accelerometer-assessed physical activity (PA-Acc), minutes/day with >1,000 cpm (moderate-to-high PA-Acc), and minutes/day with >2,500 cpm (high PA-Acc) (10). Values for minutes per day with >2,500 cpm that were above +5 SD of values for age- and sex-matched normative controls were considered to be outliers and were omitted from the study (10). Adjustments for overestimation or underestimation of PA-Acc during activities without monitoring or with difficulties in correct monitoring (e.g., swimming, bicycling) (9,10,27) were performed (10). Patients were matched with control subjects for age and sex, and and Z scores for PA-Acc were obtained as the mean deviation of the study population from the normative data from 2 large studies measuring PA-Acc in 2,055 healthy Danish school children (10,25,26). Children were instructed to complete an activity log indicating when the monitor was put on in the morning and removed in the evening, as well as activities performed while not wearing the monitor or those that are difficult to measure with the monitor. Only children providing a minimum of 3 separate days of at least 8 hours of valid recording were included (10).

To estimate daily physical activity of at least 60 minutes of moderate-to-high PA-Acc, as recommended by WHO (20), the levels in patient were compared with those in normative controls, using PA-Acc >1,500 cpm (28,29). In the clinic, pain intensity was measured as "current pain" or "worst pain during the last week" using the revised Faces Pain Scale (FPS-R) form (30). In addition, the children recorded their pain scores in the morning and evening for 1 week concurrent with the use of accelerometer (10).

Evaluation of specific club sports, leisure-time, and school-educational physical activities. We administered a questionnaire (the Physical Activity and Sport Questionnaire [PASQ]) with 31 questions on specific club sport habits and leisure-time and school-educational physical activities, including type of specific activity or sport, frequency, consistency, and intensity including type of specific activity of sport; frequency, consistency and intensity of participation; barriers to participation (e.g. disease related symptoms, adherence, competency, satisfaction with own effort); and strategy for those having difficulties during physical activity. When patients agreed to participate in the study, data from the questionnaires were collected in conjunction with an outpatient clinic visit that included initiation of accelerometry monitoring. The questionnaires were completed during individual interviews. Parents were present only during the visit when accelerometry was initiated, which included instructions, an activity log, and a pain diary.

Table 1. Cohort data for demographics, disease activity, functional ability, and accelerometry*

	Patients (n = 68)	Controls (n = 118)
Age, mean ± SD years	12.7 ± 1.7	12.4 ± 1.7
Sex, no. (%)		
Female	41 (60.3)	60 (50.8)
Male	27 (39.7)	58 (49.2)
BMI, mean ± SD kg/m^2	18.6 ± 2.7	
JIA subcategory, no. (%)		
Polyarticular, RF positive	6 (8.8)	
Polyarticular, RF negative	10 (14.7)	
Systemic	11 (16.2)	
Oligoarticular, persistent	19 (27.9)	
Oligoarticular, extended	16 (23.5)	
Psoriatic	4 (5.9)	
Enthesitis-related	2 (2.9)	
Disease activity, mean ± SD		
JADAS-27 (range 0–57)	4.8 ± 4.48	
ESR, mm/hour	8 ± 10.1	
Disease duration, months	69 ± 50	
Pain intensity, mean ± SD		
PGA score on VAS (range 0–100)	22.1 ± 20.3	
FPS-R current pain (range 0–10)	1.25 ± 1.77	
FPS-R worst pain last week (range 0–10)	3.29 ± 2.85	
Pain diary (FPS-R, 1 week) (range 0–140)†	20.4 ± 23.7	
Functional ability, mean ± SD		
CHAQ-38 (range 0–3)	0.19 ± 0.20	0.04 ± 0.08‡
Accelerometer-monitored physical activity		
Mean cpm (Z score)	−1.07 (−1.8, 0.3)	
Boys, mean ± SD	505 ± 176	
Girls, mean ± SD	426 ± 165	
Minutes/day with >1,000 cpm (Z score)	−1.00 (−2.1, −0.07)	
Boys, mean ± SD	118 ± 45§	
Girls, mean ± SD	83 ± 31	
Minutes/day with >2,500 cpm (Z score)	−1.42 (−2.7, −0.06)	
Boys	42 ± 23§	
Girls	25 ± 13	

* Z scores are expressed as the median (interquartile range). BMI = body mass index; JIA = juvenile idiopathic arthritis; RF = rheumatoid factor; JADAS-27 = Juvenile Arthritis Disease Activity score with 27 defined joints; ESR = erythrocyte sedimentation rate; PGA VAS = patient's global assessment score on a 0–100 visual analog scale; FPS-R = revised Faces Pain Scale; C-HAQ38 = revised Childhood Health Assessment Questionnaire including 38 items; cpm = counts per minute.
† Data were available for only 57 patients.
‡ $P < 0.001$.
§ $P < 0.001$, boys versus girls.

Healthy control subjects. One hundred forty-five healthy control subjects' ages 10–16 years were recruited from a public school (1 class per grade [fourth to ninth]). Only 2 questionnaires were administered to control subjects (the C-HAQ38 and the PASQ). In the PASQ, 5 JIA-related questions were removed, but questions regarding demography and co-morbidity were included. Subjects with a co-morbidity associated with functional limitation and those who did not complete the questionnaires were excluded. Data for each school class were collected (April 2009) via an appointment with the teacher. Children completed the questionnaires by themselves, after receiving oral instructions in plenum. Questionnaires were completed anonymously, but it was possible to obtain explanatory help from the instructor.

Statistical analysis. Data were entered and analyzed using Predictive Analysis Software and SPSS version 24. The level of significance was defined as less than 0.05. Data distribution was described as the mean ± SD for patients and controls. Pearson's chi-square test was used for comparison of dichotomous variables evaluating patients versus controls. Student's *t*-test was used to compare the means of continuous variables evaluating patients versus controls. One-way analysis of variance (ANOVA) was used to compare the mean scores in different groups.

RESULTS

Of the 70 patients who agreed to participate, 2 were excluded; 1 was excluded due to co-morbidity, and the other was excluded because of a revised diagnosis. Two patients failed to provide valid accelerometry recordings, and 5 patients were considered to be outliers, as previously described (10). In all patients, reply rates for the questionnaires were 100%. For analysis, accelerometry data were available for 61 patients, and data from questionnaires were available for 68. Of the 145 school children who were invited to complete the questionnaires (C-HAQ and PASQ), 137 gave consent. Ten were excluded due to co-morbidity, and incomplete responses led to exclusion of another 9 of these children. Thus, 118 healthy controls were available for analysis.

The mean ages of the patients and healthy controls were comparable (Table 1). The proportion of girls was 10% higher in patients compared with controls, although the difference was not significant. The body mass index in patients was within the normal range. All subtypes of JIA were represented. The mean ± SD disease duration was 69 ± 50 months, and disease activity was low (mean ± SD 27-joint JADAS [JADAS-27] score 4.8 ± 4.5; range 0–100) (Table 1). Twenty-one patients (30%) had active disease at the time of the investigation (ref. 10 and results not shown). The mean C-HAQ scores in patients indicated very mild functional impairment, although it was significantly higher than that in controls (Table 1). Pain intensity scores (FPS-R) in patients were relatively low (Table 1).

Accelerometry. According to data for accelerometer-monitored physical activity (PA-Acc), the mean ± SD number

Table 2. Specific club sport and leisure-time physical activities in patients and controls*

Activity	Patients (n = 45)	Controls (n = 88)	*P*†
Club sports			
Swimming	6 (8.0)	4 (3.4)	NS
Badminton	8 (11.8)	3 (2.5)	0.010
Handball	5 (7.4)	16 (13.6)	NS
Football (soccer)	18 (26.5)	35 (29.7)	NS
Gymnastics	7 (10.3)	7 (5.9)	NS
Sports dancing	0 (0)	10 (8.5)	0.014
Horse riding	8 (11.8)	7 (5.9)	NS
Athletics	1 (1.5)	6 (5.1)	NS
Martial arts	1 (1.5)	7 (5.9)	NS
Boxing	0 (0)	2 (1.7)	NS
Cycling (racing)	0 (0)	1 (0.8)	NS
Rowing	1 (1.5)	1 (0.8)	NS
Yachting	1 (1.5)	0 (0)	NS
Motor sport	1 (1.5)	0 (0)	NS
Fitness center	1 (1.5)	5 (4.2)	NS
Other‡	5 (7.4)	7 (5.9)	NS
Club sports, hours/week			0.025
0–3	25 (55.6)	31 (35.2)	0.025
>3	20 (44.4)	57 (64.8)	
Leisure-time			
Cycling (transportation)	44 (64.7)	68 (57.6)	NS
Trampoline	19 (27.9)	16 (13.6)	0.016
Skating/rollerblading	14 (20.6)	7 (5.9)	0.002
Playing ball	35 (51.5)	28 (23.7)	<0.001
Running	14 (20.6)	53 (44.9)	0.001
Walking (e.g., the dog)	28 (41.2)	25 (21.2)	<0.004
Part-time job that includes physical activity	2 (2.9)	2 (1.7)	NS
Other§	16 (23.5)	21 (17.8)	NS
Leisure hours/week			0.832
0–3	37 (56.9)	65 (58.6)	
>3	28 (43.1)	46 (41.4)	

* Values are the number (%) unless indicated otherwise. NS = not significant.
† By Pearson's chi-square test.
‡ Volleyball, basketball, running, yoga, Pilates.
§ Weight training, rope-skipping.

Table 3. Consistency in active participation in club sports and school-educational physical activity*

	Club sports			School-educational		
Consistency	Patients (n = 45)	Controls (n = 89)	*P*†	Patients (n = 68)	Controls (n = 118)	*P*†
Always	29 (42.6)	27 (22.9)	0.001	35 (51.5)	90 (76.3)	0.001
Almost always	16 (23.5)	25 (21.2)		22 (32.4)	28 (23.7)	
Half of time	0	20 (16.9)		7 (10.3)	0	
Almost never	0	15 (12.7)		2 (2.9)	0	
Never	0	2 (1.7		2 (2.9)	0	

* Values are the number (%) unless indicated otherwise.
† By Pearson's chi-square test.

of days of valid recordings in 66 patients was 5.97 ± 1.07. The mean ± SD cpm/day of PA-Acc was 458 ± 172, with 97 ± 40 minutes/day with >1,000 cpm (moderate-to-high physical activity) and 31 ± 19 cpm/day with >2,500 cpm (high physical activity); Z scores were higher in boys than in girls (Table 1) In a recent study in 61 patients with JIA and 2,055 age- and sex-matched normative controls, we observed that the values for patients were significantly lower than the values for controls, in all 3 PA-Acc levels ($P < 0.002$) (10). However, although the WHO recommended at least 60 minutes of accumulated daily moderate-to-vigorous physical activity in children ages 5–17 years (20), 68% of boys (17 of 25) and 39% of girls (16 of 41) in the patient group had PA-Acc values exceeding 60 minutes/day with >1,500 cpm. These proportions were comparable with the proportions in controls (61% of boys and 39% of girls) (28,29).

Participation in club sports reported in the PASQ. The distribution of club sport activities was the same among patients (n = 45) and controls (n = 88), although significantly more patients played badminton and significantly more controls participated in sports dancing (Table 2) . Surprisingly, no significant differences were observed between patients and controls involved in contact sports, and in both groups football (soccer) was the most prevalent club sport activity (Table 2). The proportion of control subjects spending ≥3 hours/week participating in club sports was significantly higher than the proportion of patients (Table 2). Consistency in active participation in club sport activities was significantly greater in patients compared with controls, with a higher proportion of patients participating "always" (Table 3). In patients who experience pain during club sport activities (data were available for 37 of 45 patients), the most commonly used strategies were taking a short break (86.6%), modifying or changing activity (67.6%), continuing despite pain (40.5%), and taking a long break or stopping activity (13.5%) (Table 4). Noninvolvement in club sports was more prevalent in patients (23 [34%] of 68) compared with controls (29 [25%] of 118; $P = 0.01$) (Table 5) , mainly due to joint pain (48%), shortness of breath/side stitches/sweating (35%), lack of competency/skills in sports (30%), and having the belief that club sports are harmful (17%); these proportions were significantly different from those in controls ($P < 0.02$) (Table 5).

Leisure-time physical activity reported in the PASQ. Equally high numbers of patients and controls reported engaging in informal leisure-time physical activities (96% and 94%, respectively). Significantly more controls than patients chose running ($P = 0.001$) (Table 2), whereas patients preferred playing ball, walking (e.g., the dog), trampoline jumping, and skating/roller blading (Table 2). No significant differences were observed in the number of subjects who were bicycling (e.g., to school), an activity in which more than half of the subjects in both groups participated. Similarly, no significant differences were observed in other unstructured leisure-time physical activities, in leisure-time jobs involving physical activity, or in the amount of leisure-time physical activity (Table 2).

Educational-school physical activity reported in the PASQ. All controls (n = 118) and all except 2 patients (n = 66 [97%]) were engaged in school-educational physical activities, although participation by patients was significantly less consistent, with only 51.5% participating always compared with 76.3% of controls (Table 3). Additionally, patients were more often challenged in school-educational physical activity and significantly more often reported difficulties with specific activities compared with controls (81% versus 5%; $P < 0.001$); these specific activities included running on time (32.8%), jumping (14.9%), handstanding (11.9%), and "other" (e.g., athletics) (17.9%) ($P < 0.001$) (data not shown). Ninety percent (n = 62) of patients reported pain aggravation in joints (81%) and muscles (30%) as the most common reasons for being less consistent regarding participation, but shortness of breath/side stitches (30%) and lack of competency in specific activities (30%) were also reported, as well as lack of support from teachers (25%). No controls reported any of the above reasons for decreased consistency of participation in school-education physical activity (Table 5). With regard to experiencing pain during school-

Table 4. Strategies used by patients when experiencing pain during club sports and school-educational physical activity*

Strategies when in pain	Club sports†	School-educational‡
Continue despite pain	15 (40.50)	23 (33.8)
Short break	32 (86.5)	50 (73.5)
Long break/stop activity	5 (13.5)	10 (14.7)
Modify/change activity	25 (67.6)	36 (52.9)
Other§	1 (2.7)	2 (2.9)

* Values are the number (%).
† Responses from 37 of a total of 45 patients.
‡ Responses from 62 of a total of 66 patients.
§ Tell the coach/teacher, or back out in advance.

educational physical activity, patients reported using the same strategies as those used during participation in club sports (Table 4).

PA-Acc compared with self-reported participation. When we compared the objectively measured accelerometry values (PA-Acc) in patients (adjusted for age- and sex-matched normative values [Z score]) with the self-reported weekly hours spent participating in physical activities (Figure 1), we observed higher Z scores related to an increasing amount of time spent engaging in club sports, which exceeded normative values in those engaging in club sports more than 7 hours/week. The one-way ANOVA showed significant group differences in Z scores for the mean cpm (P = 0.023) and in the number of minutes/day with >1,000 cpm (P = 0.046), but not in the number of minutes/day with >2,500 cpm (P = 0.067) (Figure 1). Similarly, a positive correlation between PA-Acc and self-reported weekly hours spent engaged in leisure-time physical activity was observed (Figure 1), with ANOVA showing significant group differences in Z scores for the number of minutes/day with >1,000 cpm (P = 0.035). This was not the case for Z scores for the mean cpm (P = 0.297) or the number of minutes/day with >2,500 cpm (P = 0.181). For school-educational physical activity, PA-Acc values in patients were equally low regardless of the reported frequency of participation (Figure 1).

Importance of physical activity as reported in the PASQ. Overall, physical activity was equally important to patients and controls (93% versus 88%) but for different reasons. Being with friends, liking competition, and forgetting pain were reported significantly more often by patients than by controls ($P \leq 0.003$), who reported having fun doing physical activity as the main reason but also "other" (e.g., tradition in family, talent in sports) significantly more than patients ($P \leq 0.018$) (Table 6). Enjoying being in motion was the main reason that physical activity was important to patients and was the second most-reported reason in controls (Table 6). No significant differences were observed between patients and controls in self-estimated competency in overall daily physical activity (83% versus 88%) or in satisfaction with one's own effort (69% versus 80%) (data not shown). Of the 68 patients, 27 (39.7%) received physical therapy, mostly 2–3 times/week (32%) (data not shown).

Table 5. Reasons for non-engagement in club sports and less-consistent participation in school-educational physical activity*

	Club sports			School-educational	
Reasons	Patients (n = 23)	Controls (n = 29)	P†	Patients, no./total no. (%)	Controls (n = 0)
Joint pain	11 (47.8)	1 (3.4)	<0.001	17/21 (81.0)	
Muscle pain	4 (17.4)	1 (3.4)	0.090	6/20 (30.0)	
Belief of harm	4 (17.4)	0	0.019	2/20 (10.0)	
Shortness of breath, side stitches, or sweating	8 (34.8)	2 (6.9)	0.011	6/20 (30.0)	
Lack of support from coach or peers	2 (8.7)	0	0.105	5/20 (25.0)	
Lack of skills	7 (30.4)	0		6/20 (30)	
Dislike	9 (39.1)	10 (34.5)			
Lack of availability	6 (26.1)	4 (13.8)			
Not knowing peers	3 (13.0)	2 (7.1)			
Lack of adherence	7 (30.4)	3 (10.3)			
Other‡	5 (27.8)	9 (31.0)		1/20 (5)	

* Values are the number (%) unless indicated otherwise.
† Versus controls, by Pearson's chi-square test.
‡ Lack of time, lack of interest, it is boring.

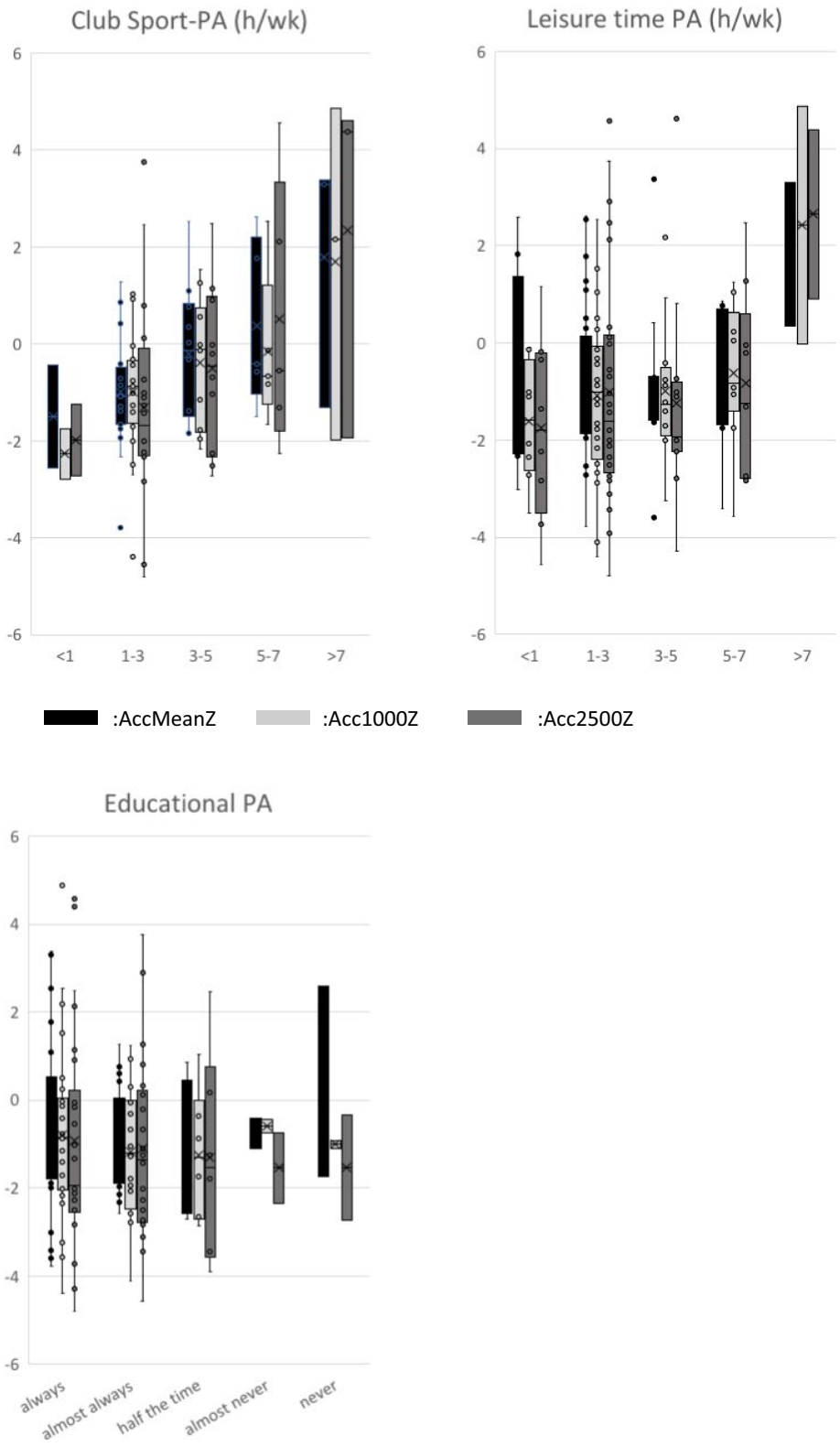

Figure 1. Accelerometry-based measures of free-living physical activity (PA) in patients with juvenile idiopathic arthritis (n = 61). Data are shown as box plots, representing the median and interquartile range of PA-Acc Z scores for mean counts per minute (cpm) (AccMeanPMinZ), Z scores for numbers of minutes/day spent with >1,000 cpm (Acc1000Z), and Z scores for numbers of minutes per day spent with >2,500 cpm (Acc2500Z) during club sport, leisure-time, and school-educational physical activities. AccMeanZ = Z score for mean accelerometer cpm; Acc1000Z = Z score for number of minutes of activity recorded with >1,000 cpm; Acc2500Z = Z score for number of minutes of activity recorded >2,500 cpm.

Table 6. Importance of overall physical activity (PA) and reason for participation*

Reason for importance of PA	Patients (n = 68)	Controls (n = 118)	*P*†
I believe PA is important for me	63 (92.7)	104 (88.1)	0.328
I like motion	53 (84.1)	78 (75.0)	0.164
I like competition	32 (50.8)	29 (27.9)	0.003
I forget pain	29 (46.0)	0	<0.001
I want to be with friends	50 (79.4)	42 (40.4)	<0.001
It is fun	37 (58.7)	85 (81.7)	0.001
It is healthy/keeps me in shape	27 (42.9)	58 (55.8)	0.106
Other‡	3 (4.8)	18 (17.3)	0.018

* Values are the number (%) unless indicated otherwise.
† By Pearson's chi-square test.
‡ Talent in the sport, tradition in the family.

DISCUSSION

To our knowledge, this study is the first to explore specific sport habits as well as leisure-time and school-educational physical activities in children with JIA, both objectively and subjectively, after the introduction of more targeted treatments, including biologic agents. Conceivably, the low values for disease activity (JADAS-27), basic pain intensity, and functional impairment observed in patients might have indicated close-to-normal physical activity levels and more engagement in regular physical activity and sports by patients. However, this study showed that objectively measured daily physical activity (using accelerometry) was significantly reduced in patients compared with normative controls and at all intensity levels (PA-Acc mean, number of minutes with PA-Acc >1,000 cpm and >2,500 cpm, respectively). In addition, the proportion of patients engaging in self-chosen club sports was significantly lower than the proportion of controls (66% versus 75%), although club sports–active patients (45 of 68) participated in the same number and types of sports as those in which control subjects participated. However, patients were relatively more engaged in individual, less intense, and weight-bearing sports (e.g., badminton, swimming, horse riding) than controls, who were more engaged in contact/team and strenuous sports (e.g., handball, martial arts, sports dancing). Nevertheless, in both groups playing football (soccer) topped the list.

More patients than controls were not engaged in club sports (34% versus 25%), and patients more often reported both physical (e.g., joint/muscle pain, shortness of breath, lack of skills) and psychosocial (e.g., dislike, belief of harm, lack of availability/support) barriers to participation. However, apart from the belief of harm to joints during sports, only physical barriers were reported significantly more often by patients than by control subjects. Equally high proportions of patients and controls engaged in informal leisure-time physical activity (96% and 94%, respectively). However, despite great diversity of self-reported leisure-time activities, significantly more patients reported non-strenuous activities (e.g., playing ball, walking, skating), whereas patients were less engaged in running activities compared with controls.

We previously reported that more than half of 61 patients with JIA (57%) had below-average VO_2max values (10), indicating a lower capacity to perform high-intensity physical activity. This finding might add to the explanation for the outcomes in the current study and is in accordance with findings in other studies showing low physical activity and capacity in patients with JIA (11,12,29). The proportion of patients spending ≥3 hours/week participating in club sports, but not in leisure-time physical activity, was significantly lower than the proportion of controls. In contrast, patients were significantly more consistent than control subjects when participating in club sports. Furthermore, in both club sports and leisure-time physical activity, PA-Acc levels increased in relation to the reported hours of participation per week even exceeded normative PA-Acc values in patients participating >7 hours/week.

An equally high proportion of patients and controls engaged in compulsory school-educational physical activities, although participation by patients was significantly less consistent. The ongoing diversity of content in school-educational physical activities challenged patients physically, resulting in difficulties and the feeling of being less competent in specific activities (e.g., handstanding, running, athletics). Patients also reported an escalation of joint pain significantly more often than controls as the main reason for not participating fully. In both club sports and school-educational physical activity, patients needed strategies to minimize pain/lack of stamina; the most commonly used strategies in both modalities were taking a short break or modifying activity.

Engagement in school-educational physical activity did not influence the levels of PA-Acc in patients, presumably due to the low number of physical education classes per week (2 45-minute classes/week). This finding is in accordance with the findings in a 1995 study by Henderson et al (17) that showed inadequate integration of school-educational physical activity in children with musculoskeletal problems (even those that are minor), stressing the need to address (specifically in the clinical setting) the importance of participation in school-educational physical activities.

Although patients and controls were not equally engaged in physical activity, the patients and controls did not differ in terms of their overall opinion of physical activity, equally indicating physical activity as being important to them, although for different reasons. Patients reported social and disease-related reasons (e.g., being with friends, forgetting pain), while controls found physical activity to be important for individual reasons (e.g., fun, tradition, talent). Surprisingly, patients favored competition significantly more compared with controls. The fact that 93% of patients reported that physical activity was important implies that patients are aware of

the necessity for physical activity, which could indicate a motivation to do more under the right conditions (e.g., with more support). In addition, reported competence in overall physical activities and satisfaction with their own efforts were equal in patients and control subjects. This might indicate that although being less engaged in physical activity, patients thought that they did their best when participating on their own terms.

In this study, the percentages of boys and girls in the patient group who fulfilled the WHO recommendations for physical activity (20) (i.e., 60 minutes/day of moderate-to-high physical activity) were equal to those reported for normative Danish controls (28). This was a surprise, because most other studies show the opposite (9,11,12,29). In fact, in a recent study by Bos et al, only 4% of children with JIA and 16% of controls met the WHO recommendations (31). However, our findings were based on the assumption that moderate-to-high levels of physical activity were seen at PA-Acc of >1,500 cpm, as previously described (29), which was achievable in a relatively high percentage of our patient group with low disease activity and in patients in other studies (10,32).

One limitation of this study is that the proportion of girls among patients was 10% higher than the proportion in controls, which may have skewed the data toward lower physical activity levels in patients (31,33). Due to the relatively low number of patients in the cohort, subdivision of patients into small sex- and age-matched groups did not seem meaningful. However, in the accelerometry calculations, data for each patient were matched with the data for age- and sex-matched controls (mean ± SD 239 ± 97 controls per patient), enabling a direct comparison (10). Other limitations are that hypoactivity, sedentary behavior, and sleep patterns were not addressed in this study, and that the study design (cross-sectional) did not include intervention or longitudinal follow-up data (34).

The strength of our study is use of a combination of objective and subjective assessments of both structured, informal, and compulsory physical activity in patients, as well as direct comparison with healthy controls and normative data, although the use of the same controls in both objective and subjective assessments would have been optimal. The investigators in a recent study suggested combining objective and subjective assessments in order to, e.g., better capture the limitations of both non-wear of accelerometers and biased self-reporting (35).

The results of this study indicate the need to identify individual and multifactorial barriers to participation in physical activities in patients with JIA and the need to provide support and individual guidance in order to avoid the consequences of a low level of participation. Participation and adequate performance in physical activities in patients with JIA seem closely related to physical capacities, positive experiences, and consistency of physical activity. Recognition of the importance of psychosocial motivation to overcome barriers (e.g., disliking physical activity, pain when active, believing physical activity is harmful) seems essential. Special attention and better integration are needed regarding school-educational physical activities, which may facilitate further participation in physical activities in patients and a life-long active lifestyle.

AUTHOR CONTRIBUTIONS

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

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ACTIVITY AND THE RHEUMATIC DISEASES

Substituting Sedentary Time With Physical Activity in Fibromyalgia and the Association With Quality of Life and Impact of the Disease: The al-Ándalus Project

Blanca Gavilán-Carrera,[1] Víctor Segura-Jiménez,[2] Rania A. Mekary,[3] Milkana Borges-Cosic,[1] Pedro Acosta-Manzano,[1] Fernando Estévez-López,[4] Inmaculada C. Álvarez-Gallardo,[2] Rinie Geenen,[5] and Manuel Delgado-Fernández[1]

Objective. There is an overall awareness of the detrimental health effects of sedentary time (ST) in fibromyalgia; however, data are limited on how replacement of ST with physical activity (PA) of different intensity may be related to health in this condition. The aim of this study was to examine how a substitution of ST with light PA (LPA) or moderate-to-vigorous PA (MVPA) is associated with quality of life and disease impact.

Methods. This study comprised 407 women with fibromyalgia, mean ± SD age 51.4 ± 7.6 years. The time spent in ST and PA was measured with triaxial accelerometry. Quality of life and disease impact were assessed using the Short Form 36 (SF-36) health survey and the Revised Fibromyalgia Impact Questionnaire (FIQR), respectively. The substitution of ST with an equivalent time of LPA or MVPA and the associated outcomes were examined using isotemporal substitution analyses.

Results. Substituting 30 minutes of ST with LPA in the isotemporal model was associated with better scores in bodily pain (B = 0.55), vitality (B = 0.74), and social functioning (B = 1.45) according to the SF-36, and better scores at all of the domains (function, overall impact, symptoms, and total impact) of the FIQR (B ranging from –0.95 to –0.27; all $P < 0.05$). When ST was replaced with MVPA, better physical role (B = 2.30) and social functioning (B = 4.11) of the SF-36 and function of the FIQR (B = –0.73) were observed (all $P < 0.05$).

Conclusion. In regression models, allocation of time of sedentary behavior to either LPA or MVPA was associated with better quality of life and lower disease impact in women with fibromyalgia.

INTRODUCTION

Fibromyalgia is a chronic condition with key symptoms of persistent and widespread pain (1). Other symptoms include, but are not limited to, fatigue, nonrestorative sleep, and/or cognitive difficulties (1). The disease impact of fibromyalgia includes physical disability, psychological distress, severe symptoms, and reduced work status (2). Moreover, patients with fibromyalgia usually have a reduced general quality of life (3), which is the individual perception of health in different spheres of life (physical, mental, and social). Because fibromyalgia has no cure, treatments focus on disease management and improvement of quality of life. Thus, it is relevant to identify modifiable factors that might be related to these fibromyalgia-specific (which pertains to the disease impact) and general (which pertains to the quality of life) health outcomes.

Compelling evidence supports the efficacy of physical exercise interventions in the management of fibromyalgia (4). However, although the benefits of physical exercise interventions in fibromyalgia are endorsed (4), literature regarding guidelines for physical activity (PA) generally do not answer the question of whether low-,

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[1]Blanca Gavilán-Carrera, BSc, Milkana Borges-Cosic, BSc, Pedro Acosta-Manzano, BSc, Manuel Delgado-Fernández, PhD: University of Granada, Granada, Spain; [2]Víctor Segura-Jiménez, PhD, Inmaculada C. Álvarez-Gallardo, PhD: University of Cádiz, Cádiz, Spain, and University of Granada, Granada, Spain; [3]Rania A. Mekary, PhD: Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts; [4]Fernando Estévez-López, PhD: University of Granada, Granada, Spain, Ulster University, Northern Ireland, United Kingdom, and Utrecht University, Utrecht, The Netherlands; [5]Rinie Geenen, PhD: Utrecht University, Utrecht, The Netherlands.

Address correspondence to Blanca Gavilán-Carrera, BSc, Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada, Granada, Spain. Carretera de Alfacar, s/n (Granada), Spain. E-mail: bgavilan@ugr.es.

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SIGNIFICANCE & INNOVATIONS

- In women with fibromyalgia, the substitution of 30 minutes of sedentary behavior with physical activity of any intensity was positively associated with different dimensions of quality of life and disease impact.
- The substitution of sedentary time with light physical activity was positively associated with more dimensions of quality of life and impact of fibromyalgia, while moderate-to-vigorous physical activity was related to stronger theoretical changes in the outcomes.

moderate-, or high-intensity physical exercise should be recommended. Moreover, patient acceptability, treatment adherence, premature termination and, most importantly, high dropout rates are serious concerns for exercise-based interventions in fibromyalgia (5). Moderate or even low-intensity physical exercise programs may be more appropriate to achieve long-term results in this group versus high-intensity programs, because individuals with fibromyalgia are so easily sensitized to pain and other symptoms (6). Greater insight into the relationship between PA levels and patient-reported outcome measures may indicate the potential usefulness of stimulating low- and moderate-to-vigorous intensity PA levels.

Whereas most effect studies in rheumatic diseases pertain to systematic physical exercise interventions in specific groups, the most frequent intervention is probably education and advice about daily PA given during a consultation or accessed through a brochure or via the internet (7). A positive relationship between total self-reported PA and quality of life in fibromyalgia has been described (8,9). Lifestyle interventions (10,11) and observational studies (12–14) have described the positive influence of light PA (LPA) in the physical function domain of quality of life (10,11) and on fibromyalgia symptoms (10,12–14). Furthermore, an increase of moderate-to-vigorous PA (MVPA) has been shown to promote better physical function and well-being (15), and greater levels of vigorous PA have been associated with less pain, fatigue, and overall impact of the disease (14). Despite these benefits, a high percentage of patients do not achieve the recommended 150 minutes of MVPA per week (16,17) and tend to be highly sedentary (16). While the relationship between PA and symptoms or physical domains of quality of life has been largely addressed in prior research (10–15), evidence is scarce in regard to the potential influence of a reduction of sedentary time (ST), which might be a more attainable goal for some patients. In order to gain insight into the benefits of pursuing this goal, it is necessary to examine how a decrease in ST, through an increase of time in different intensity levels of PA, is specifically related to quality of life and disease impact in fibromyalgia.

ST has been shown to exert a deleterious effect on health in the general population (18). In fibromyalgia, ST has been associated with worse pain regulation (12), overall pain, fatigue, and disease impact (14). Although the inverse relationship between ST and quality of life has been described in other conditions (19,20), the precise association between these 2 factors in fibromyalgia is unknown. Therefore, it would be relevant to determine the benefits of substituting ST with PA. Given that total daily time is finite (24 hours), a decrease of time in 1 specific behavior requires an increase of time in another. The isotemporal substitution model (21) allows study of the effect of time substitution while controlling for the confounding effect of other activities. Therefore, given that ST, LPA, and MVPA have been shown to be associated with fibromyalgia symptoms (12–15), it is possible to determine how replacing time spent in one specific behavior (e.g., ST) with an equal amount of time in another behavior (e.g., LPA) might be related to different health outcomes in individuals with fibromyalgia. Prior applications of isotemporal substitution models on replacement of ST with an equal amount of PA of different intensities have demonstrated positive effects on quality of life and health outcomes in adults (22–25) and the elderly (19,26,27). These findings, however, do not necessarily generalize to patients with fibromyalgia. Therefore, the aim of this study was to analyze how substitution of ST with LPA or MVPA was associated with quality of life and disease impact in women with fibromyalgia.

PATIENTS AND METHODS

Patients from southern Spain (Andalusia) were recruited through fibromyalgia associations via email, letter, and social media. After providing detailed information about the aims and study procedures, participants (n = 646) signed an informed consent. Inclusion criteria for the current study comprised a previous diagnosis by a rheumatologist and meeting the 1990 American College of Rheumatology (ACR) fibromyalgia criteria (28). Participants were excluded if they had either acute or terminal illness, severe cognitive impairment, or were age >65 years (to avoid the influence of other prevalent conditions, such as osteoarthritis). The study was approved by the ethics committee of the Hospital Universitario Virgen de las Nieves.

The assessment protocol was carried out on 2 alternate days. On day 1, a diagnosis of fibromyalgia according to ACR criteria (28) (widespread pain for >3 months and pain with ≤4 kg/cm^2 of pressure reported for 11 or more of 18 tender points) was confirmed. Body composition was also evaluated, and participants filled out self-reported sociodemographic and clinical data questionnaires. The Short Form 36 (SF-36) health survey and the Revised Fibromyalgia Impact Questionnaire (FIQR) were given to patients (along with other questionnaires) to be completed at home. On day 2, questionnaires were collected and checked by the researcher team. Subsequently, accelerometers were pro-

vided and participants received instructions on how to complete sleep diaries.

Quality of life. The SF-36 was used to assess the quality of life. This questionnaire has been validated in Spanish populations (29) and has demonstrated good reliability among patients with chronic pain (30). The SF-36 is composed of 36 items that assess 8 dimensions of health (i.e., physical functioning, physical role, bodily pain, general health, social functioning, emotional role, mental health, and vitality) and 2 component summary scores (i.e., physical and mental health). The score in each dimension is standardized and ranges from 0 (worst health status) to 100 (best health status).

Impact of the disease. The FIQR (31) is a disease-specific tool to assess overall fibromyalgia severity through a wide range of symptoms, and comorbidities, related to this chronic condition. It is a self-administered questionnaire with 21 individual questions (rated on a scale of 0–10), divided into 3 linked sets of domains: function, overall impact, and symptoms severity. The FIQR total score ranges from 0 to 100, with a higher score indicating greater impact of the syndrome on an individual's life.

Physical activity intensity levels and sedentary time. Each patient wore a triaxial accelerometer GT3X+ (Actigraph) around the hip (secured with an elastic belt) for nine 24-hour days, except for during water-based activities. Using the default mode filter option, data were collected at a rate of 30 Hz and at epochs of 60 seconds (32). Given that patients received the accelerometer at different times throughout day 1 and because time is needed to eliminate any reactivity to the awareness of being monitored, we excluded this familiarization day from the analysis. The last day (day of device return) was also excluded from the analysis. A total of 7 continuous days with a minimum of 10 valid hours/day were required to be included in the analysis. Data download, reduction, cleaning, and analyses were conducted using the manufacturer software (ActiLife desktop, version 6.11.7).

Accelerometer wear time was calculated by subtracting sleeping time and nonwear periods. Sleeping time was obtained from the sleep diaries, in which patients indicated the time they went to bed and the time that they woke up. According to the Choi algorithm (33), nonwear periods were considered to be any bouts of 90 continuous minutes (30 minutes small-window length and 2 minutes skip tolerance) of 0 counts. Light, moderate, and vigorous PA intensity levels were calculated based upon recommended PA vector magnitude cut points (32,34); 200–2,689, 2,690–6,166, and ≥6,167 counts per minute, respectively. ST was estimated as the time accumulated below 200 cpm during periods of wear time (33). Participants presented extremely low values of vigorous PA (0.4 minutes/day); therefore, vigorous PA was excluded from all of the analyses and MVPA was used instead. A 10-minute activity bout was defined as 10 or more consecutive minutes of ≥2,690 cpm (up to 2 minutes below the cut point allowance). The proportion of women meeting the current PA recommendations for adults ages 18–64 years (at least 150 minutes/week of MVPA accumulated in bouts ≥10 minutes) (17) was also calculated. All values were initially expressed in minutes/day but were converted to units of 30 minutes (1 represents 30 minutes) for better interpretation of the results. To complete this conversion, minutes/day spent in ST, LPA, MVPA, and total wear time were divided by 30.

Other variables. *Tenderness*. Following the 1990 ACR criteria for classification of fibromyalgia (28), we assessed 18 tender points using a standard pressure algometer (FPK 20; Wagner Instruments). We obtained the mean pressure of 2 measurements at each tender point. A tender point was considered as positive when the patient felt pain at pressure ≤4 kg/cm^2. The total number of positive tender points was recorded for each patient.

Sociodemographic and clinical data. We collected sociodemographic and clinical data by using a self-reported questionnaire, including date of birth, marital status (married/not married), education level (university/non-university), and occupational status (working/not working). Furthermore, patients reported the use of antidepressants (yes/no) during the previous 2 weeks. Additionally, to assess an exclusion criterion, participants were asked, "Are you currently diagnosed with an acute or terminal illness?"

Anthropometry and body composition. Weight (kg) and total body fat percentage were assessed using a portable eight-polar tactile-electrode bioelectrical impedance device (InBody R20; Biospace). The validity and reliability of this instrument has been reported elsewhere (35,36). As recommended by the manufacturer, participants were requested not to shower, practice intense PA, or ingest large amounts of fluid and/or food 2 hours before measurement. Patients were also asked not to wear either clothing (except for underwear) or metal objects during the measurement.

Statistical analyses. Descriptive statistics were used to examine the sociodemographic and clinical characteristics of the sample. Multiple linear regression models were used for isotemporal substitution models in order to examine how substituting ST with LPA and MVPA was associated with quality of life and impact of the disease in women with fibromyalgia. The description and rationale behind these analyses have previously been described in detail (21). Briefly, in this model, the finite nature of time was considered so that performing 1 activity results in displacing the time spent in another behavior. These regression models included the total time (sum of ST, LPA, and MVPA, which is the total accelerometer wear time variable) and all of the individual activities (e.g., LPA and MVPA) except for the activity of interest (e.g., ST) as independent variables. The coefficient from the regression analysis for each of the included variables is an estimation of the mean effect

on the outcome of substituting a fixed amount of time (e.g., 30 minutes) of the omitted activity with the same amount of each of the included activities (while holding time spent in other activities constant). For instance, an isotemporal substitution model can be expressed as follows: SF-36 scores = (β_1) LPA + (β_2) MVPA + (β_3) total time + (β_4) covariates.

Because ST is omitted from the model, β_1 expresses the change in quality of life (SF-36 scores of each dimension), which resulted from reallocation of 30 minutes of ST to LPA. The β_2 coefficient would provide the same information in relation to MVPA. Pearson's correlation coefficients were used to check for the association of potential confounders (age, marital status, education level, working status, fat percentage, antidepressant use) with quality of life and impact of the disease. As a result of significant associations ($P < 0.05$) with most of the outcomes, the confounders of age, current occupational status, fat percentage, and use of antidepressants were entered in all models.

Normal probability plots of the standardized residual and scatterplots of residuals were generated to test for normality, linearity, and homoscedasticity. Non-autocorrelation assumption was also met using the Durbin-Watson test ($1.5<d<2.5$ for all regression models). No multicollinearity problems among the predictor variables of the model were found (all variance inflation factor statistics <10.0). All analyses were performed using the Statistical Package for Social Sciences, version 20.0, and variables were significant at $P < 0.05$.

RESULTS

The flow chart of the participants included in this study is shown in Figure 1. The final sample size included in the analyses comprised 407 women with fibromyalgia. Table 1 provides an overview of the patients' sociodemographic and clinical characteristics according to the achievement of the PA recommendations (at least 150 minutes a week, per week of MVPA, in bouts of ≥10 minutes) (17).

In the isotemporal substitution models for the SF-36 scores (Table 2), replacing 30 minutes of sedentary behavior with 30 minutes of LPA was associated with better bodily pain ($B = 0.55$ [95% confidence interval (95% CI) 0.03, 1.07]), vitality ($B = 0.74$ [95% CI 0.09, 1.39]), and social functioning ($B = 1.45$ [95% CI 0.61, 2.30]), all $P < 0.05$. Replacement of 30 minutes of sedentary behavior with 30 minutes of MVPA was associated with better physical role ($B = 2.30$ [95% CI 0.2, 4.38]) and social functioning ($B = 4.11$ [95% CI 1.78, 6.44]), all $P < 0.05$.

When the FIQR was modeled as the outcome variable (Table 3), replacing 30 minutes of ST with the same amount of LPA was associated with better functioning ($B = –0.32$ [95% CI –0.55, –0.09]), overall impact ($B = –0.27$ [95% CI –0.45, –0.08]), symptoms ($B = –0.37$ [95% CI –0.63, –0.11]), and total impact of the disease ($B = –0.95$ [95% CI –1.52, –0.38), all $P < 0.01$.

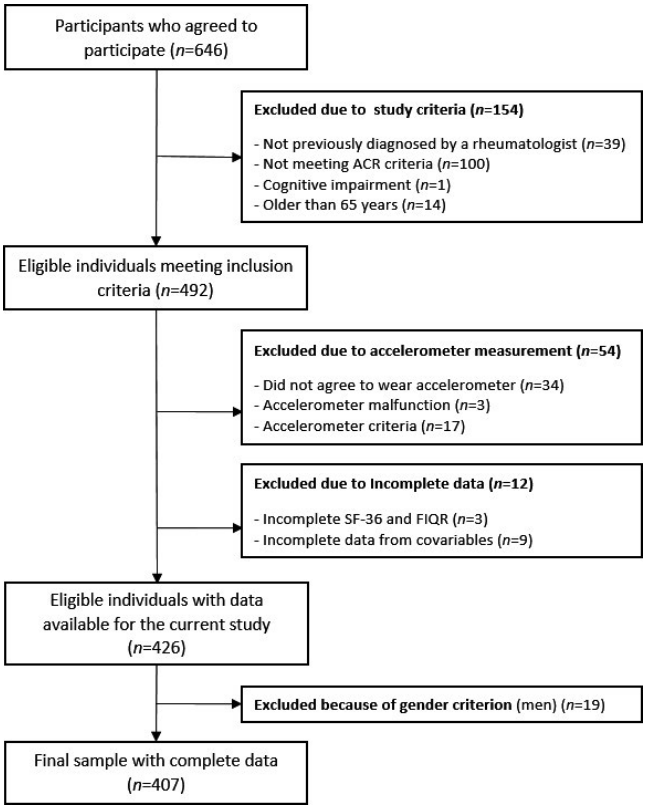

Figure 1. Flow diagram of inclusion of women with fibromyalgia from the al-Ándalus project included in the present study (n = 407). ACR = American College of Rheumatology; FIQR = Revised Fibromyalgia Impact Questionnaire; SF-36 = Short-Form 36 health survey.

Substituting 30 minutes of ST with 30 minutes of MVPA was only associated with better functioning ($B = –0.73$ [95% CI –1.37, –0.09]), $P = 0.025$.

DISCUSSION

Our study demonstrated that the substitution of 30 minutes of ST with LPA yielded better scores in the bodily pain, vitality, and the social functioning domains of the SF-36 and in all domains of the FIQR (function, symptoms, overall impact, and total impact). When this amount of ST was conferred instead to MVPA, patients presented better physical role and social functioning according to the SF-36 and better scores in the function domain of the FIQR. Our results complement previous research (8,9) by estimation of how varying the distribution of ST, LPA, and MVPA throughout the waking hours is related to patient quality of life and impact of the disease.

Overall, the results of the isotemporal substitution models allocation of ST to LPA showed smaller estimated effects, but in more dimensions (B rating from 0.55 to 1.4 in 7 dimensions) of quality of life and impact of the disease in comparison to those models

Table 1. Clinical and sociodemographic characteristics of women with fibromyalgia by achievement of PA recommendations*

	Total (n = 407)	Not meeting PA recommendations (n = 321)	Meeting PA recommendations (n = 86)
Age, years	51.4 ± 7.6	51.7 ± 7.6	50.3 ± 7.5
Married, no. (%)	311 (76.4)	250 (77.9)	61 (70.9)
College, no. (%)	58 (14.3)	46 (14.3)	12 (14.0)
Currently working, no. (%)	107 (26.3)	78 (24.3)	29 (33.7)
Total tender points (11–18)	16.7 ± 2.0	16.8 ± 1.9	16.5 ± 2.2
Algometer score (18–144)	43.2 ± 13.4	42.8 ± 13.3	45.0 ± 14.0
Total body fat percentage	40.1 ± 7.6	40.6 ± 7.7	38.3 ± 6.8
Antidepressant use, no. (%)	232 (57.0)	198 (61.7)	34 (39.5)
Disease impact, FIQR (0–100)			
Function	17.2 ± 6.4	17.9 ± 6.2	14.6 ± 6.7
Overall impact	12.5 ± 5.4	12.9 ± 5.2	11.1 ± 6.0
Symptoms	34.7 ± 7.6	35.5 ± 7.5	31.8 ± 7.5
Total score	64.4 ± 16.7	66.3 ± 16.0	57.5 ± 17.7
Health-related quality of life, SF-36 (0–100)			
Physical function	39.2 ± 18.9	37.9 ± 18.7	44.2 ± 18.8
Physical role	33.2 ± 21.2	31.8 ± 21.2	38.7 ± 20.2
Bodily pain	21.2 ± 14.7	19.8 ± 14.2	26.3 ± 15.5
General health	28.5 ± 15.3	27.9 ± 14.9	30.9 ± 16.6
Vitality	22.3 ± 17.7	21.3 ± 17.1	26.2 ± 19.3
Social functioning	43.7 ± 24.7	41.5 ± 24.2	51.7 ± 24.6
Emotional role	56.9 ± 27.9	55.8 ± 28.8	61.1 ± 24.2
Mental health	46.2 ± 19.7	45.0 ± 19.6	50.8 ± 19.5
Physical component	29.5 ± 6.9	29.1 ± 6.9	31.2 ± 6.7
Mental component	36.0 ± 11.6	35.3 ± 11.7	38.5 ± 11.3
PA and sedentary time (min/day)			
Accelerometer wear time	923.0 ± 78.9	921.2 ± 83.0	930.0 ± 61.3
Sedentary time	460.1 ± 104.1	473.3 ± 104.7	410.8 ± 86.1
Light PA	418.6 ± 91.8	414.2 ± 96.9	435.2 ± 67.2
Moderate PA	43.9 ± 29.5	33.5 ± 19.9	82.6 ± 27.6
MVPA	44.3 ± 30.1	33.7 ± 20.0	84.0 ± 28.1

* Values are the mean ± SD unless indicated otherwise. Physical activity (PA) recommendation = accumulation of ≥150 minutes of moderate-to-vigorous PA (MVPA)/week, in bouts of ≥10 minutes. FIQR = Revised Fibromyalgia Impact Questionnaire; SF-36 = Short Form 36 health survey.

allocating ST to MVPA (*B* rating from 0.73 to 4.1 in 3 dimensions). Although MVPA is recommended for health benefits (17), the intensity of PA that best correlates with quality of life in fibromyalgia is still unknown and presents mixed results in other populations. Replacement of ST with MVPA showed greater benefits for quality of life in adults (22), whereas increasing LPA might be more effective in the elderly (19,26), except for physical domains that were associated with higher intensities. The results of our study are more similar to those in the elderly population, probably due to similarities observed when demonstrating a reduced fitness level (37).

LPA is of special relevance among individuals with reduced physical capacity (17) or inactive individuals (38), given that low intensity levels of PA are shown to be stimuli that elicit improvements in health (17,38). In fibromyalgia, small increases in LPA have been associated with improvement of key symptoms (10). Because women with fibromyalgia are highly sedentary (16), it is plausible that in this group, PA at one of the adequate intensities (in order to achieve benefits) falls below the recommendations of moderate-to-vigorous intensity for the general population (17). Increases in daily MVPA might, however, also be of interest for patients with fibromyalgia because of its association with a lower physical disease impact, as shown in the current and in a previous study (15). Therefore, a graded sustainable and thus, feasible strategy to achieve health benefits in this condition might be

Table 2. Coefficients for the isotemporal substitution analyses examining the association of reallocating 30 minutes/day of sedentary time to LPA or MVPA with quality of life (n = 407)*

	LPA			MVPA		
	B	95% CI	*P*	*B*	95 % CI	*P*
SF-36 dimension						
Physical function	0.64	−0.06, 1.34	0.074	1.77	−0.16, 3.70	0.072
Physical role	0.47	−0.29, 1.22	0.227	2.30†	0.21, 4.38†	0.031†
Bodily pain	0.55†	0.03, 1.07†	0.040†	0.85	−0.59, 2.29	0.247
General health	0.08	−0.48, 0.65	0.768	0.15	−1.41, 1.70	0.853
Vitality	0.74†	0.09, 1.39†	0.026†	1.69	−0.10, 3.48	0.064
Social functioning	1.45†	0.61, 2.30†	0.001†	4.11†	1.78, 6.44†	0.001†
Emotional role	0.70	−0.28, 1.69	0.160	0.65	−2.07, 3.36	0.640
Mental health	0.08	−0.63, 0.78	0.829	0.88	−1.06, 2.82	0.374
Physical component	0.19	−0.06, 0.45	0.138	0.61	−0.10, 1.32	0.093
Mental component	0.31	−0.09, 0.72	0.129	0.73	−0.38, 1.85	0.197

* Isotemporal substitution model included all activity variables (light physical activity [LPA], moderate-to-vigorous physical activity [MVPA]), total wear time, and covariates [age, current occupational status, fat percentage, and antidepressant use]). Coefficients of 1 represent reallocation of 30 minutes/day. Sedentary time was reallocated to either LPA or MVPA. *B* = nonstandardized regression coefficient; 95% CI = 95% confidence interval; SF-36 = Short-Form 36 health survey.
† Significant values.

to first replace inactivity with LPA and to eventually increase PA to moderate intensity levels.

Increases of time in MVPA were positively related to the physical role domain of the SF-36 and in the function domain of the FIQR. In fact, this affinity is consistent with the closeness between these domains of both questionnaires (2). Similar to the results of our study, a previous study (15) showed improvements in the function domain of the FIQR after an intervention aimed at increasing MVPA among patients with fibromyalgia. The physical role in the SF-36 includes limitations in the kind and amount of work due to physical problems. Physical barriers to continue working, such as physical capacity and symptoms (39), have been associated with MVPA (15,17), which is in agreement with the results of the current study. Patients who increase their level of PA might also be more confident and present greater self-efficacy to engage in movement-related tasks of daily living that require physical effort (40) and perceive less limitations in functional status (8). Therefore, promotion of PA of moderate-to-vigorous intensity as an ultimate goal seems to be a safe strategy (15) of special interest for benefits in the physical domains of quality of life in women with fibromyalgia.

In the present study, when ST was substituted with LPA, better reported bodily pain, vitality, and lower impact of symptoms were observed. The results of our study are consistent with previous interventions where increasing steps per day resulted in better reported pain interference (11) and intensity (10). Moreover, low levels of PA have been previously linked to better brain responses in pain modulation regions of patients with fibromyalgia (13). The chronic widespread pain in fibromyalgia may be due to or modulated by an altered processing of nociceptive signals in the central nervous system, known as central sensitization (41). The pain relief promotion mechanisms of PA are thought to act on central pain facilitation (reduced *N*-methyl-D-aspartate receptor phosphorylation [41,42]) and endogenous inhibitory systems (reduced serotonin

Table 3. Coefficients for the isotemporal substitution analyses examining the association of reallocating 30 minutes/day of sedentary time to LPA and MVPA with impact of the disease (n = 407)*

	LPA			MVPA		
FIQR domain†	*B*	95 % CI	*P*	*B*	95% CI	*P*
Function	−0.32†	−0.55, −0.09†	0.008†	−0.73†	−1.37, −0.09†	0.025†
Overall impact	−0.27†	−0.45, −0.08†	0.006†	−0.26	−0.77, 0.26	0.331
Symptoms	−0.37†	−0.63, 0.11†	0.006†	−0.18	−0.90, 0.54	0.619
Total impact	−0.95†	−1.52, 0.38†	0.001†	−1.17	−2.74, 0.40	0.143

* Isotemporal substitution model included all activity variables (light physical activity [LPA], moderate-to-vigorous physical activity [MVPA]), total wear time and covariates [age, current occupational status, fat percentage, and antidepressant use]). Coefficients of 1 represent reallocation of 30 minutes/day. Sedentary time was reallocated to either LPA or MVPA. *B* = nonstandardized regression coefficient; 95% CI = 95% confidence interval; SF-36 = Short-Form 36 health survey; FIQR = Revised Fibromyalgia Impact Questionnaire.
† Significant values.

transporter expression, increased serotonin levels, and increased opioids in pathways, including different brain areas [12,13] such as the periaqueductal grey and rostral ventromedial medulla [42,43]). Although the amount of PA needed to elicit pain modulatory mechanisms is not clear, maintenance of even a low level of PA and/or avoidance of periods of sustained ST have been related to modulation of the central nervous system in fibromyalgia (12).

Fatigue, which is strongly linked to pain and its mechanisms (44), also has a great impact on quality of life (44). In agreement with our results in the vitality domain of the SF-36, the level of fatigue has been related to LPA in fibromyalgia (14) and other pain conditions such as arthritis (45). However, a lifestyle intervention increasing self-selected LPA, unlike the findings of our study, did not produce changes in the fatigue severity of patients with fibromyalgia (12). The heterogeneity in tools to assess the multiple facets of fatigue (44) and the use of different accelerometers and thresholds to categorize PA may be representative of the impediments to making direct comparisons to prior studies. Previous research in healthy women has also stressed the importance of meeting the recommended level of MVPA and reduction of prolonged sedentary behavior for a better energy and fatigue profile (46). In the present study, we also observed a borderline association between increasing MVPA and vitality, but our analyses only showed a significant estimated association derived from reallocation of ST to LPA. Accordingly, it has been observed that greater improvements in fatigue observed with moderate-intensity exercise in a healthy population may not extend to sedentary people with persistent fatigue (47), who can benefit from low-intensity activities (47). The central nervous system appears to also be involved in the relationship between PA and fatigue (48). More specifically, PA might perhaps have a positive influence on fatigue in fibromyalgia through changes in insulin-like growth factor 1 and resistin levels (48), yet further research is needed on this topic.

The estimated benefits of LPA in all domains of the FIQR are also in line with previous PA interventions, where a change from sedentary to low active habits reduced the total disease impact of patients with fibromyalgia (10). The magnitude of the effect, 10.2 points reduction in the total score in the previous study (10) versus 0.95 points reduction in the total score in the present study, differed notably from our estimations. Several underlying methodological issues that might account for these differences include that the FIQ (previous version of the FIQR) presents different weighting among domains, with more importance given to symptoms instead of function as opposed to the FIQR (2); the lifestyle intervention not only aimed to increase PA but also coping and adherence strategies; and there are differences in study designs. In light of these findings, strategies for health promotion among these patients might also target the replacement of sedentary behaviors with activities of light intensity, which are also the most likely activities in which patients would be expected to engage (13).

The greatest estimated benefits were detected in the social functioning domain of the SF-36 as a result of substituting ST with LPA or MVPA. Similar to the results of our study, a study by Suorsa et al (49) showed lower social contact in the most sedentary fibromyalgia patients. This group of patients usually present social isolation concerns (50) and a high prevalence of loneliness (51) that might be negatively influenced by the decreased communication that sedentary behaviors entail (52). Conversely, it is likely that the practice of PA provides opportunities for social interactions, especially during accessible activities that are shared experiences such as walking, which may support our findings. Nonetheless, further intervention designs are needed to ascertain the nature of this relationship.

Strengths of our study included a relatively large sample size of women with fibromyalgia represented from southern Spain (Andalusia) and the use of accelerometers to objectively assess PA instead of self-reported measures (53). In addition, we used general (SF-36) and disease-specific (FIQR) instruments, providing a more comprehensive view of the actual reported health status of these patients (54). Furthermore, the robustness of our analyses was also enhanced by considering a reasonable number of potential confounders.

Limitations included the cross-sectional study design; thus, the associations found in a between-subjects analysis cannot be explained via a causal pathway as a within-subject mechanism. Indeed, previous research has shown how quality of life can discriminate different levels of PA (8). Therefore, some of the relationships found work in both directions. Additionally, due to the large quantity of factors related to quality of life and the impact of the disease, it is difficult to ascertain the true association between the variables. Given that only women took part in this study, future studies should investigate whether these associations also occur in men.

In conclusion, this study showed preliminary evidence that replacement of 30 minutes of ST with PA of either light or moderate-to-vigorous intensity was positively associated with different domains of quality of life and impact of the disease in fibromyalgia. When ST was substituted with LPA, better bodily pain, social function, vitality, and disease impact were observed. When ST was substituted with MVPA, we detected better scores in physical role, social functioning, and function. These results may seem to be a simple message to communicate in clinical practice; however, longitudinal and intervention studies on actual behavioral reallocation effects are needed to further confirm our findings.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Ms Gavilán-Carrera 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. Segura-Jiménez, Borges-Cosic, Acosta-Manzano, Estévez-López, Álvarez-Gallardo, Geenen, Delgado-Fernández.

Acquisition of data. Segura-Jiménez, Borges-Cosic, Estévez-López, Álvarez-Gallardo, Delgado-Fernández.

Analysis and interpretation of data. Gavilán-Carrera, Segura-Jiménez, Mekary.

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ACTIVITY AND THE RHEUMATIC DISEASES

Risk Factors for Low Back Pain: A Population-Based Longitudinal Study

Rahman Shiri,[1] Kobra Falah-Hassani,[2] Markku Heliövaara,[3] Svetlana Solovieva,[1] Sohrab Amiri,[4] Tea Lallukka,[5] Alex Burdorf,[6] Kirsti Husgafvel-Pursiainen,[1] and Eira Viikari-Juntura[1]

Objective. To identify risk factors for low back pain (LBP) and lumbar radicular pain and to assess whether obesity and exposure to workload factors modify the effect of leisure-time physical activity on LBP and lumbar radicular pain.

Methods. The population of this 11-year longitudinal study consists of a nationally representative sample of Finns ages ≥30 years (n = 3,505). The outcomes of the study were LBP and lumbar radicular pain for >7 days or for >30 days in the past 12 months at follow-up.

Results. LBP and lumbar radicular pain were more common in women than in men. LBP slightly declined with increasing age, while lumbar radicular pain increased with age. Abdominal obesity (defined by waist circumference) increased the risk of LBP (adjusted odds ratio [OR] 1.40 [95% confidence interval (95% CI) 1.16–1.68] for LBP >7 days and adjusted OR 1.41 [95% CI 1.13–1.76] for LBP >30 days) and general obesity (defined by body mass index) increased the risk of lumbar radicular pain (adjusted OR 1.44 [95% CI 1.12–1.85] for pain >7 days and adjusted OR 1.62 [95% CI 1.16–2.26] for pain >30 days). Smoking and strenuous physical work increased the risk of both LBP and lumbar radicular pain. Walking or cycling to work reduced the risk of LBP, particularly LBP for >30 days (adjusted OR 0.75 [95% CI 0.59–0.95]), with the largest reductions among nonabdominally obese individuals and among those not exposed to physical workload factors. Using vibrating tools increased the risk of lumbar radicular pain.

Conclusion. Lifestyle and physical workload factors increase the risk of LBP and lumbar radicular pain. Walking and cycling may have preventive potential for LBP.

INTRODUCTION

Low back pain (LBP) is a global health problem, the top leading cause of years lived with disability in 2016 (1). Depending on the recall period, definition, and population, the prevalence of LBP varies considerably (2,3). Almost 25–40% of individuals report LBP in the past 12 months (4–7), and 4–25% report chronic LBP (6,8). Lumbar radicular pain is pain that radiates from the lower back along the sciatic nerve to the back of the thigh and down the leg (9). Sciatica is lumbar radicular pain that is accompanied by clinical findings suggestive of a herniated lumbar disc or nerve root irritation (9). Lumbar radicular pain is more severe but less prevalent than nonspecific LBP (3,10).

Among lifestyle risk factors, smoking (11) and excess body mass (12) increase the risk of transient and chronic LBP as well as health care consultation for LBP. Moreover, smoking (13,14) and overweight/obesity (14,15) increase the risk of lumbar radicular pain and hospitalization for sciatica. The role of leisure-time physical activity in LBP and sciatica is still uncertain. Leisure-time physical activity may reduce the risk of chronic LBP (16) and lumbar radicular pain (10). Recently, we found that walking or cycling to work reduces the risk of hospitalization for sciatica (14).

Approximately one-third of back pain cases may be attributed to occupational ergonomic risk factors (17,18). When considering psychological and psychosocial factors, results from previous studies have shown that depressive symptoms not only increase the risk of developing LBP (19) but also have an adverse

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[1]Rahman Shiri, MD, PhD, Svetlana Solovieva, PhD, Kirsti Husgafvel-Pursiainen, PhD, Eira Viikari-Juntura, MD, PhD: Finnish Institute of Occupational Health, Helsinki, Finland; [2]Kobra Falah-Hassani, PhD: Western University, London, Ontario, Canada; [3]Markku Heliövaara, MD, PhD: National Institute for Health and Welfare, Helsinki, Finland; [4]Sohrab Amiri, PhD: Urmia University, Urmia, Iran; [5]Tea Lallukka, PhD: Finnish Institute of Occupational Health and University of Helsinki, Helsinki, Finland; [6]Alex Burdorf, PhD: Erasmus MC, Rotterdam, The Netherlands.

Address correspondence to Rahman Shiri, MD, PhD, Finnish Institute of Occupational Health, P.O. Box 18, FI-00032 Työterveyslaitos, Helsinki. E-mail: rahman.shiri@ttl.fi.

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SIGNIFICANCE & INNOVATIONS

- To date, the role of leisure-time physical activity in the prevention of low back pain (LBP) and lumbar radicular pain is still uncertain. Moreover, whether obesity or exposure to occupational risk factors modify the effect of leisure-time physical activity on LBP and lumbar radicular pain is unknown.
- This study shows that abdominal obesity increases the risk of LBP and general obesity increases the risk of lumbar radicular pain.
- Walking and cycling to work reduce the risk of LBP, particularly LBP for >30 days in the past 12 months, with the largest reductions among nonabdominally obese individuals and among those individuals who are not exposed to physical workload factors.

effect on the prognosis of LBP (20). However, whether LBP and depression share similar risk factors is unknown. Moreover, previous studies did not control for all known confounders. The role of psychosocial factors in the occurrence and prognosis of LBP and lumbar radicular pain is still unclear (21–23).

To date, little is known about potential effect modifiers of the association between leisure-time physical activity and LBP. Whether obesity or exposure to occupational risk factors modify the effect of leisure-time physical activity on LBP and lumbar radicular pain is unknown. Leisure-time physical activity may compensate to some extent for the adverse effect of obesity on LBP (24). However, obese individuals may reduce their leisure-time physical activity. Individuals with physically active jobs are more likely to decrease their leisure-time physical activity and those individuals with sedentary occupations are more likely to increase their exercise (25). The aims of this study were to identify risk factors for LBP and lumbar radicular pain and to assess whether obesity and exposure to workload factors modify the effect of leisure-time physical activity on LBP and lumbar radicular pain.

SUBJECTS AND METHODS

Population. The current study is based on 2 Finnish population-based surveys, the Health 2000 Survey (26) and the Health 2011 Survey (27,28), carried out to achieve an overview of the population health. The Health 2000 Survey was conducted in 2000–2001 using a 2-stage stratified cluster sampling to obtain a representative sample of Finns (26). The data were collected using questionnaires, a face-to-face home interview, a clinical examination, and laboratory and functional capacity tests (26).

All the Health 2000 Survey participants were invited to take part in the Health 2011 Survey. The data were collected between August and December 2011 by 5 research teams in 60 localities in Finland. For those participants who were not able to attend the primary health examination, a shortened health examination was carried out at a participant's home, and those who did not want or were not able to participate were interviewed by phone between January and June 2012.

The original participants in the Health 2000 Survey were ages ≥30 years (n = 7,977). Of those participants, 6,986 (87.6%) were interviewed, and 6,354 (79.7%) took part in the health examination. Of the 7,977 original participants, 1,441 died during an 11-year follow-up (until the end of September 2011), and of the remaining participants, 3,756 responded to the questionnaire on LBP at follow-up. A total of 251 patients with a physician-diagnosed chronic back syndrome or probable sciatica at baseline were excluded from the study, leaving 3,505 participants for the final analysis.

All participants signed a written informed consent, and the Ethics Committee for Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa approved the Health 2000 Survey, and the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the Health 2011 Survey.

Characteristics at baseline. *Sociodemographic and lifestyle factors.* Information on age, sex, education, smoking, and the nature, frequency, and duration of participation in leisure-time physical activity, and walking or cycling to and from work was collected (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23710/abstract). Sedentary lifestyle was defined as participation in leisure-time physical activity for ≤2 to 3 times/month, and as reading, watching TV, or doing other activities that do not demand moving or straining physically during leisure time. The level of education was defined as low (basic comprehensive school certificate), medium (upper secondary or vocational school diploma), and high (college or university degree). As part of the health examination, body weight and height and waist and hip circumferences were measured. Body mass index (BMI) was grouped into 4 levels: underweight (BMI <18.5 kg/m^2), normal (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), and obese (BMI ≥30 kg/m^2). Waist circumference was classified into 3 groups: normal (<94 cm), increased (94–101.9 cm) and abdominally obese (≥102 cm) for men, and <80, 80–87.9 and ≥88 cm, respectively, for women (29). Height at baseline was grouped into 3 levels: <170, 170–179, and ≥180 cm for men, and <160, 160–169, and ≥170 cm for women.

Physical workload factors. Exposure to the following physical workload factors in the current job was assessed by the home interview (30): strenuous physical work (lift or carry heavy items, dig, shovel, or pound), manual handling of loads ≥5 kg ≥2 times/minute ≥2 hours/day, manual handling of loads ≥20 kg ≥10 times/day, work with vibrating tools ≥2 hours/day, work demanding

kneeling or squatting for 1 hour/day or longer, work requiring driving a vehicle for ≥4 hours/day for >3 months/year, work demanding standing or leaning forward without support for 1 hour/day or longer, work requiring sitting for ≥5 hours/day, and work demanding standing or walking for ≥5 hours/day.

Psychological and psychosocial factors. Depression and anxiety were assessed at the health examination using the computerized version of the Composite International Diagnostic Interview (31). Shift work, social support, job satisfaction, and job demands and job control were assessed by the home interview or a questionnaire.

LBP and disorders at baseline. As a part of the health examination, a specially trained nurse asked whether the participants had experienced pain, ache, or motion-related soreness in the back in the past 7 days or in the past 30 days. In addition, a physician who was not aware of records of the preceding interview carried out a standardized clinical examination, and according to preset criteria, diagnosed a definite or probable chronic back syndrome and sciatica (32). Definite chronic low back syndrome was defined as LBP in the past month and at least 3 months overall and had either convincing documented history of previously diagnosed low back syndrome or a clear clinical finding (e.g., at least moderately restricted mobility of the spine). The diagnosis of chronic low back syndrome was considered probable when a documented history of previously diagnosed low back syndrome was not convincing, and either the participant did not have LBP in the past month or a clinical finding was minor (e.g., slightly restricted mobility of the spine).

Outcome. At follow-up, information on the history of LBP was collected by a self-administered questionnaire. The records were checked and completed, if necessary, by a specially trained nurse at the examination. No physical examination of the spine was performed by a physician. LBP was assessed by several questions at follow-up in 2011. We used the following 4 questions to define the outcomes of this study: "Have you had back pain in the past 12 months (no/yes)?" and "Have you had back pain that radiates down the leg, beyond the knee in the past 12 months (no/yes)?" If the answer was yes, the next 2 questions addressed the number of days having LBP or lumbar radicular pain using a modified version of the validated Nordic Questionnaire (33). "Please, give an estimate on how many days you have had back pain in the past 12 months?" and "Please, give an estimate on how many days you have had lumbar radicular pain in the past 12 months?" The alternative responses for each question were: 1–7 days, 8–30 days, >30 days but not daily, and daily. For the current analysis, we defined 4 LBP outcomes: LBP longer than 7 days in the past 12 months (i.e., LBP for >7 days), radiating LBP >7 days in the past 12 months (i.e., lumbar radicular pain for >7 days), LBP >30 days in the past 12 months (i.e., LBP for >30 days), and radiating LBP >30 days in the past 12 months (i.e., lumbar radicular pain for >30 days).

Statistical analysis. The participants with chronic low back syndrome and sciatica at baseline were excluded. We studied the effects of baseline risk factors on the presence of LBP at follow-up and adjusted for the presence of LBP in the past 30 days at baseline. Moreover, we stratified the study sample by the presence of LBP in the past 30 days at baseline and identified the risk factors for new episodes of LBP and prognostic factors for recurrent or persistent LBP. We performed survey data logistic regression analysis by using Stata's svy prefix command. We first performed age- and sex-adjusted analyses. Second, the variables associated with the outcome of interest were included in the full models. The variables that were not associated with the outcome of interest were removed from the full model one at a time. Those variables associated with the outcome of interest with a *P* value less than or equal to 0.20 in the full model were kept in the final multivariable models. We also carried out sex-specific and age-specific analyses. We studied effect modification using stratified analysis. For stratified analyses, exposure to physical workload factors was defined as exposure to strenuous physical work, manual handing of loads ≥20 kg, or using a vibrating tool. We used Stata software, version 13, for the analyses.

RESULTS

Correlation between independent variables in baseline survey. The correlation between workload factors ranged from 0.26 to 0.53. The highest correlation was found between strenuous work and manual handling of loads ≥5 kg (Spearman's rank correlation coefficient $\rho = 0.53$) or ≥20 kg ($\rho = 0.53$). All workload factors were positively correlated with waist circumference and BMI (ρ ranged from 0.05 to 0.15), indicating that the participants who were exposed to a workload factor had a higher waist circumference and BMI than those who were not. The positive correlations were found among participants with low and medium levels of education, with the strongest correlations among those with a low level of education. Among participants with a high level of education, only driving a vehicle ≥4 hours/day was positively correlated with waist circumference and BMI.

Walking or cycling to work was inversely and weakly correlated with waist circumference ($\rho = -0.17$), BMI ($\rho = -0.13$), and workload factors (ρ less than -0.10 for all). We found that 28.8% of participants with normal BMI, 21.0% of overweight participants, and 16.9% of obese participants walked or cycled to work. The corresponding estimates for waist circumference were 29.5%, 20.6%, and 19.2%, respectively. Other leisure activity was also inversely and weakly correlated with waist circumference, BMI, and workload factors (ρ less than -0.10 for all).

The inverse correlations of walking or cycling to work and other leisure activity with BMI and waist circumference were found with all 3 levels of education, and among the participants younger than 60 years and in those ages ≥60 years. However, the correlations were stronger in younger participants and in participants with a low or medium level of education.

Age- and sex-adjusted analysis. The risk of LBP for >30 days and lumbar radicular pain for >30 days increased with age (Table 1). LBP and lumbar radicular pain were more common in women than in men. LBP was less common among highly educated individuals than among individuals with a low level of education. Smoking, general obesity defined

Table 1. Age- and sex-adjusted odds ratios for the effects of sociodemographic, lifestyle, and psychological risk factors on low back pain and lumbar radicular pain*

Characteristic	No.	Low back pain >7 days	Low back pain >30 days	Lumbar radicular pain >7 days	Lumbar radicular pain >30 days
Age, 1-year increase	3,366	1.00 (0.99–1.01)	1.01 (1.00–1.02)	1.01 (0.99–1.02)	1.01 (1.00–1.02)
Sex					
Men	1,516	1	1	1	1
Women	1,850	1.37 (1.19–1.57)	1.58 (1.34–1.85)	1.45 (1.20–1.75)	1.49 (1.14–1.95)
Education level					
Low	1,018	1	1	1	1
Medium	1,065	0.91 (0.76–1.09)	0.94 (0.76–1.17)	0.85 (0.67–1.09)	0.76 (0.57–1.01)
High	1,242	0.80 (0.66–0.97)	0.81 (0.64–1.01)	0.86 (0.68–1.09)	0.95 (0.73–1.25)
Smoking status					
Never	1,790	1	1	1	1
Former	688	1.28 (1.06–1.54)	1.21 (0.95–1.55)	1.46 (1.15–1.86)	1.22 (0.89–1.68)
Occasional	199	1.32 (0.94–1.85)	1.36 (0.92–2.01)	1.52 (1.03–2.22)	1.58 (1.02–2.46)
Current	648	1.38 (1.14–1.67)	1.39 (1.12–1.73)	1.49 (1.17–1.89)	1.64 (1.18–2.27)
Body mass index, kg/m^2					
Normal	1,368	1	1	1	1
Overweight	1,315	1.12 (0.96–1.30)	1.30 (1.07–1.57)	1.14 (0.91–1.43)	1.20 (0.87–1.65)
Obese	644	1.39 (1.14–1.69)	1.62 (1.29–2.03)	1.56 (1.21–2.00)	1.75 (1.27–2.41)
Waist circumference					
Normal	1,190	1	1	1	1
Increased	889	1.13 (0.94–1.35)	1.09 (0.87–1.36)	1.12 (0.88–1.42)	0.93 (0.67–1.29)
Obese	1,154	1.45 (1.22–1.72)	1.54 (1.25–1.88)	1.38 (1.10–1.73)	1.35 (1.00–1.81)
Leisure-time physical activity					
Low	760	1	1	1	1
Moderate	1,927	0.85 (0.70–1.02)	0.86 (0.69–1.06)	0.99 (0.77–1.26)	1.05 (0.77–1.43)
High	708	0.71 (0.56–0.90)	0.70 (0.53–0.92)	0.98 (0.71–1.35)	0.92 (0.62–1.37)
Walking or cycling to work					
No	2,537	1	1	1	1
Yes	775	0.75 (0.62–0.90)	0.68 (0.54–0.84)	0.81 (0.64–1.02)	0.75 (0.56–0.99)
Depression					
No	2,966	1	1	1	1
Yes	204	1.37 (1.04–1.79)	1.41 (1.03–1.94)	1.53 (1.10–2.12)	1.56 (1.03–2.37)
Anxiety					
No	3,045	1	1	1	1
Yes	125	1.38 (0.94–2.02)	1.46 (0.98–2.19)	1.65 (1.09–2.49)	1.35 (0.79–2.30)

* Values are the odds ratio (95% confidence interval) unless indicated otherwise.

Table 2. Age- and sex-adjusted odds ratios for the effects of occupational factors on low back pain and lumbar radicular pain*

Characteristic	No.	Low back pain >7 days	Low back pain >30 days	Lumbar radicular pain >7 days	Lumbar radicular pain >30 days
Social support					
High	1,254	1	1	1	1
Low	1,143	1.23 (1.03–1.47)	1.24 (0.99–1.55)	1.23 (0.98–1.53)	0.95 (0.70–1.29)
Job satisfaction					
Satisfied	2,141	1	1	1	1
Neither satisfied nor unsatisfied	254	1.05 (0.80–1.39)	1.03 (0.74–1.43)	1.19 (0.83–1.70)	0.56 (0.29–1.06)
Unsatisfied	81	1.42 (0.91–2.22)	1.80 (1.08–3.00)	1.78 (1.07–2.95)	2.77 (1.53–5.02)
Job strain					
Low	1,918	1	1	1	1
High	494	1.09 (0.88–1.34)	1.11 (0.87–1.41)	1.11 (0.84–1.45)	1.15 (0.81–1.64)
Shift work					
No	2,159	1	1	1	1
Yes	316	0.93 (0.72–1.20)	0.74 (0.53–1.04)	0.83 (0.61–1.14)	0.79 (0.52–1.21)
Strenuous physical work					
No	2,306	1	1	1	1
Yes	964	1.42 (1.20–1.67)	1.36 (1.12–1.65)	1.59 (1.29–1.96)	1.52 (1.18–1.96)
Manual handling of ≥5 kg					
No	2,686	1	1	1	1
Yes	582	1.34 (1.11–1.62)	1.46 (1.15–1.85)	1.56 (1.21–2.00)	1.73 (1.27–2.36)
Manual handling of ≥20 kg					
No	2,660	1	1	1	1
Yes	611	1.22 (0.99–1.50)	1.29 (1.04–1.60)	1.49 (1.20–1.85)	1.47 (1.12–1.95)
Work with vibrating tools ≥2 hours/day					
No	3,025	1	1	1	1
Yes	247	1.49 (1.11–1.98)	1.61 (1.19–2.16)	1.94 (1.40–2.68)	2.11 (1.45–3.07)
Kneeling/squatting ≥1 hour/day					
No	2,473	1	1	1	1
Yes	798	1.24 (1.05–1.45)	1.45 (1.17–1.79)	1.32 (1.08–1.61)	1.45 (1.14–1.84)
Driving ≥4 hours/day					
No	2,866	1	1	1	1
Yes	404	1.23 (0.95–1.58)	1.11 (0.83–1.48)	1.32 (0.97–1.79)	1.10 (0.72–1.67)
Standing/leaning forward, without support					
No	2,245	1	1	1	1
Yes	1,027	1.31 (1.10–1.55)	1.47 (1.20–1.81)	1.30 (1.07–1.59)	1.36 (1.05–1.75)
Sitting ≥5 hours/day					
No	2,023	1	1	1	1
Yes	1,247	0.91 (0.78–1.06)	0.98 (0.82–1.16)	0.92 (0.76–1.12)	1.01 (0.81–1.27)
Standing/walking ≥5 hours/day					
No	1,635	1	1	1	1
Yes	1,636	1.20 (1.04–1.39)	1.15 (0.96–1.38)	1.13 (0.95–1.34)	1.11 (0.88–1.40)

* Values are the odds ratio (95% confidence interval) unless indicated otherwise.

by BMI, abdominal obesity defined by waist circumference, and depression increased the risk of LBP and lumbar radicular pain. There was no association of height with LBP or lumbar radicular pain. Walking or cycling to work reduced the risk of LBP and lumbar radicular pain, whereas leisure-time physical activity reduced only the risk of LBP. Frequency of exercise (times/week) and a sedentary lifestyle were not associated with LBP or lumbar radicular pain.

Job satisfaction, strenuous physical work, manual handling of loads ≥5 kg or ≥20 kg, work with vibrating tools, kneeling or squatting, and standing or leaning forward without support increased the risk of LBP and lumbar radicular pain after adjustment for age and sex (Table 2). Social support and standing or walking for ≥5 hours/day only weakly increased the risk of LBP. Job strain, shift work, sitting for ≥5 hours/day, and driving a vehicle for ≥4 hours/day were not associated with LBP or lumbar radicular pain.

Multivariable analysis. After controlling for confounding factors, LBP and lumbar radicular pain in particular were more common among women than men (Table 3). Abdominal obesity increased the risk of LBP, whereas general obesity increased the risk of lumbar radicular pain (Table 3). Smoking increased the risk of both LBP and lumbar radicular pain, but its effect was stronger on lumbar radicular pain than on LBP. Walking or cycling to work at baseline reduced the risk of LBP, particularly LBP for >30 days (Table 3). This effect was seen among participants who walked or cycled to work both at baseline and follow-up or only at baseline, but not among those who walked or cycled only at follow-up (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23710/abstract). Strenuous physical work increased the risk of both LBP and lumbar radicular pain, while using vibrating tools and having depression increased the risk of lumbar radicular pain only.

Subgroup analysis. Limiting the analysis to individuals ages ≤60 years changed the effects of workload factors and depression on LBP and lumbar radicular pain (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23710/abstract). Among individuals ages ≤60 years, using vibrating tools increased the risk of both LBP and lumbar radicular pain, while depression and strenuous physical work did not significantly increase the risk of LBP or of lumbar radicular pain.

In sex-specific analyses, obesity was a statistically significant risk factor for LBP and lumbar radicular pain among women, but not among men (see Supplementary Tables 4 and 5, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23710/abstract). Walking or cycling to work reduced the risk of LBP among women only. Among men, using vibrating tools increased the risk of LBP and lumbar radicular pain, while among women it increased the risk of lumbar radicular pain only. Furthermore, depression and strenuous physical work increased the risk of LBP and lumbar radicular pain among women only. Women who were exposed to manual handling of loads ≥20 kg were at lower risk of LBP than women who were not.

Effect modification. Table 4 shows that obesity and exposure to physical workload factors modify the effects on LBP of leisure-time physical activity and walking or cycling to work. Walking or cycling to work reduced the risk of LBP and LBP for >30 days in nonobese individuals, but not in abdominally obese individuals. A high level of leisure-time physical activity also reduced the risk of LBP for >30 days in nonobese individuals only. Using BMI as an indicator of obesity did not change the results for lumbar radicular pain. Among individuals who were not exposed to physical workload factors, walking or cycling to work reduced the risk, while among those exposed to workload factors, only a high level of leisure-time physical activity reduced the risk of LBP.

Supplementary Table 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23710/abstract, shows whether exposure to physical workload factors modifies the effects of excess body mass on LBP and lumbar radicular pain. Among individuals not exposed to physical workload factors, obesity increased the risk of LBP, while among those exposed to workload factors, the effect of obesity was weak. For lumbar radicular pain, the effect of obesity was stronger among individuals exposed to workload factors than among those not exposed.

Among individuals without LBP at baseline, abdominal obesity increased the risk of LBP, and excess body mass strongly increased the risk of lumbar radicular pain (see Supplementary Table 7, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23710/abstract). Moreover, strenuous physical work increased the risk of LBP and lumbar radicular pain. Standing or leaning forward without support was associated with LBP for >30 days only.

In individuals with LBP in the past 30 days at baseline, smoking increased the risk of recurrent or persistent LBP and lumbar radicular pain, and using vibrating tools increased the risk of recurrent or persistent lumbar radicular pain (see Supplementary Table 8, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23710/abstract). Walking or cycling to work reduced the risk of recurrent or persistent LBP and lumbar radicular pain. The estimate, however, reached statistical significance for LBP only. The presence of LBP at baseline did not affect the associations of risk factors with LBP at the end of the follow-up.

Table 3. Multivariable models for the risk factors of low back pain*

Characteristic	Low back pain >7 days	Low back pain >30 days	Lumbar radicular pain >7 days	Lumbar radicular pain >30 days
Age, 1-year increase	0.992 (0.985–0.999)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.01 (1.00–1.02)
Sex, women vs. men	1.33 (1.12–1.58)	1.54 (1.28–1.85)	1.65 (1.32–2.05)	1.68 (1.26–2.23)
Smoking				
Former	1.22 (0.99–1.49)	1.18 (0.92–1.53)	1.40 (1.09–1.79)	1.20 (0.86–1.67)
Occasional	1.25 (0.88–1.78)	1.29 (0.83–2.02)	1.49 (0.99–2.44)	1.60 (0.99–2.61)
Current	1.28 (1.04–1.59)	1.30 (1.02–1.64)	1.39 (1.07–1.80)	1.61 (1.14–2.28)
Body mass index (ref. normal)				
Overweight	–	–	1.09 (0.85–1.38)	1.13 (0.81–1.57)
Obese	–	–	1.44 (1.12–1.85)	1.62 (1.16–2.26)
Waist circumference (ref. normal)				
Increased	1.07 (0.88–1.31)	0.98 (0.77–1.26)	–	–
Obese	1.40 (1.16–1.68)	1.41 (1.13–1.76)	–	–
Leisure-time physical activity (ref. low)				
Moderate	0.96 (0.78–1.17)	–	–	–
High	0.83 (0.65–1.06)	–	–	–
Walking or cycling to work at baseline	0.82 (0.67–1.00)	0.75 (0.59–0.95)	0.86 (0.67–1.11)	0.81 (0.59–1.10)
Depression	1.27 (0.95–1.70)	1.32 (0.94–1.86)	1.38 (1.00–1.91)	1.34 (0.89–2.01)
Strenuous physical work	1.24 (1.02–1.51)	–	1.35 (1.06–1.71)	1.28 (0.96–1.71)
Using vibrating tools	–	–	1.48 (1.03–2.11)	1.62 (1.09–2.41)
Kneeling or squatting	–	1.17 (0.92–1.49)	–	–
Standing or leaning forward without support	–	1.21 (0.95–1.53)	–	–
Low back pain, past 30 days	3.33 (2.82–3.94)	3.30 (2.75–3.95)	2.28 (1.89–2.75)	1.91 (1.48–2.46)

* Values are the odds ratio (95% confidence interval). Odds ratios are adjusted for all factors in the table.

DISCUSSION

The findings of this study indicate that obesity increases the occurrence of LBP and lumbar radicular pain, while smoking increases recurrence rates of LBP and lumbar radicular pain. Mechanical workplace risk factors increase both onset and recurrence of LBP and lumbar radicular pain. Walking or cycling to work reduces recurrence rates, and depression increases the rates. In subgroup analysis, walking or cycling to work reduced the risk of LBP among nonabdominally obese individuals and among those not exposed to physical workload factors.

In line with our previous meta-analyses (11,13), the current study shows that smoking increases the risk of both LBP and lumbar radicular pain. Moreover, the current study adds new evidence that smoking is a weak risk factor for onset of LBP and lumbar radicular pain, but a strong prognostic factor for their recurrence and persistence. Smoking may increase the risk of recurrence and persistence by causing intervertebral disc degeneration (34) and slowing down the healing process (35).

In line with our earlier meta-analyses (12,15), we found that obesity increases the risk of both LBP and lumbar radicular pain. In addition, this study adds new knowledge that obesity is a strong risk factor for the onset of both LBP and lumbar radicular pain, but a weak prognostic factor for their recurrence and persistence. Furthermore, the current study suggests that abdominal obesity increases the risk of LBP, and general obesity increases the risk of lumbar radicular pain. Obesity may contribute to nonspecific LBP by increasing the mechanical load on the lumbar spine and may be involved in the development of lumbar radicular pain by increasing the secretion of inflammatory mediators from excess adipose tissue (36) and interfering with the healing of the intervertebral discs (37).

In the current study we found that walking or cycling to work guards against LBP and lumbar radicular pain, particularly LBP for

Table 4. Effect of leisure-time physical activity on low back pain in abdominally obese and nonobese individuals and in individuals with or without exposure to physical workload factors*

Characteristic	Low back pain >7 days	Low back pain >30 days	Lumbar radicular pain >7 days	Lumbar radicular pain >30 days
Nonobese (n = 2,079)†				
Leisure physical activity (ref. low)				
Moderate	0.81 (0.62–1.05)	1.00 (0.73–1.37)	1.24 (0.88–1.75)	1.09 (0.71–1.68)
High	0.91 (0.72–1.16)	0.62 (0.42–0.93)	1.19 (0.76–1.88)	1.10 (0.62–1.93)
Walking or cycling to work	0.65 (0.49–0.86)	0.70 (0.50–0.98)	0.91 (0.66–1.26)	0.86 (0.56–1.31)
Abdominally obese (n = 1,154)†				
Leisure physical activity (ref. low)				
Moderate	1.01 (0.73–1.39)	1.01 (0.69–1.46)	0.99 (0.67–1.47)	1.27 (0.79–2.03)
High	1.26 (0.86–1.85)	1.24 (0.82–1.86)	1.14 (0.69–1.90)	0.99 (0.55–1.77)
Walking or cycling to work	0.82 (0.60–1.12)	0.82 (0.58–1.16)	0.73 (0.48–1.10)	0.65 (0.38–1.11)
Not exposed to workload (n = 2,129)‡				
Leisure physical activity (ref. low)				
Moderate	0.95 (0.72–1.26)	0.97 (0.73–1.28)	1.06 (0.76–1.49)	1.03 (0.68–1.56)
High	0.90 (0.66–1.22)	0.85 (0.60–1.21)	1.34 (0.91–1.97)	1.19 (0.74–1.90)
Walking or cycling to work	0.74 (0.59–0.93)	0.72 (0.54–0.95)	0.79 (0.58–1.08)	0.83 (0.56–1.21)
Exposed to workload (n = 1,140)‡				
Leisure physical activity (ref. low)				
Moderate	0.95 (0.68–1.33)	1.07 (0.71–1.60)	1.21 (0.81–1.81)	1.34 (0.79–2.28)
High	0.65 (0.44–0.95)	0.71 (0.43–1.18)	0.88 (0.52–1.50)	0.86 (0.43–1.71)
Walking or cycling to work	0.94 (0.65–1.36)	0.75 (0.47–1.18)	0.94 (0.64–1.38)	0.68 (0.40–1.16)

* Values are the odds ratio (95% confidence interval). ref. = reference.
† Odds ratios were adjusted for age, sex, low back pain at baseline, smoking, strenuous physical work, using vibrating tools, leisure activity, and walking or cycling to work.
‡ Workload defined as exposure to strenuous physical work, manual handing of ≥20 kg, or using a vibrating tool. Odds ratios were adjusted for age, sex, low back pain at baseline, smoking, overweight/obesity, leisure activity, and walking or cycling to work.

>30 days in the past 12 months. Moreover, walking or cycling to work had a stronger protective effect against recurrent or persistent LBP and lumbar radicular pain than against new episodes of LBP and lumbar radicular pain. In an earlier study, we also found that walking and cycling to work can lower the risk of hospitalization for sciatica (14). Walking and cycling are regular low-level physical activities that do not usually strain the lower back. Other sports activities may not reduce the risk of LBP because they may cause repeated lower back strains and sprains. Walking or cycling to work had a significant protective effect on LBP only among nonobese participants and among those not exposed to a workload factor. A possible reason is that obese participants were more likely to be exposed to physical workload factors, but less likely to be active during leisure time than nonobese participants. Individuals exposed to a workload factor were also less likely to be active during leisure time and were more likely to be obese than unexposed individuals. The correlations were, however, assessed for the baseline survey. Leisure-time physical activity, body weight, and exposure to workload factors may have been changed during the follow-up. Further prospective cohort studies are needed to confirm our findings.

Manual handling of heavy loads and bending forward without support (38,39) as well as whole-body vibration (40) increase the risk of LBP. In the current study, professional drivers exposed to whole-body vibration were not at increased risk of LBP and lumbar radicular pain, while using a vibrating tool increased the risk

of lumbar radicular pain. Using hand-held vibrating tools has not been suggested as a cause of lumbar radicular pain (41). This unexpected association is not due to the correlation of using vibrating tools with other workload factors. In the presence of other workload factors in the regression model, using a vibrating tool predicted lumbar radicular pain. Previous studies showed that drivers may over-report their occupational use of cars (41), and the association between the use of hand-held vibrating tools and lumbar radicular pain may be due to inaccurate exposure assessment (42) or unknown or unmeasured confounders. The question asking about using vibrating tools did not distinguish between vibrating tools (e.g., grinder, polisher) and tools that vibrate at such high magnitude that they jolt or impact the user (i.e., high magnitude of vibration). Furthermore, drivers may have responded yes to this question.

The strengths of the current study include a longitudinal design, a nationally representative population-based sample with a relatively high participation rate, a face-to-face interview, and physical examinations. This study also had some limitations. First, at follow-up we had data on LBP that lasted for > 30 days in the past 12 months, but we did not have information on chronic LBP, which is typically defined as pain that persists for 12 weeks or longer. Second, we included participants with LBP in the past 30 days at baseline in some of the analyses. LBP is a recurrent condition and in the current study the follow-up time was long. From 11 years of follow-up, we had information on LBP for the last year of the follow-up only. Participants without LBP at baseline may have experienced LBP and recovered from pain, and those with LBP at baseline may have recovered from LBP during the 11-year follow-up. The study population may no longer be a representative sample of the general population if the participants with transient LBP at baseline were excluded from the analysis. Lastly, we used only a single question to assess moderate and high levels of leisure-time physical activity and did not compute total weekly leisure-time physical activity.

In summary, obesity, smoking and mechanical workplace risk factors predict an increase in the risk of LBP and lumbar radicular pain, whereas walking and cycling are associated with reduced risk. Walking and cycling may have the potential to prevent LBP in the general population.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Shiri 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. Shiri, Heliövaara, Solovieva, Viikari-Juntura.

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Novel Approach to Estimate Osteoarthritis Progression: Use of the Reliable Change Index in the Evaluation of Joint Space Loss

Camille M. Parsons,[1] Andrew Judge,[2] Kirsten Leyland,[3] Olivier Bruyère,[4] Florence Petit Dop,[5] Roland Chapurlat,[6] Jean-Yves Reginster,[4] Mark H. Edwards,[7] Elaine M. Dennison,[1] Cyrus Cooper,[8] Hazel Inskip,[9] and the SEKOIA Study Group

Objective. Osteoarthritis-related changes in joint space measurements over time are small and sensitive to measurement error. The Reliable Change Index (RCI) determines whether the magnitude of change observed in an individual can be attributed to true change. This study aimed to examine the RCI as a novel approach to estimating osteoarthritis progression.

Methods. Data were from 167 men and 392 women with knee osteoarthritis (diagnosed using the American College of Rheumatology criteria) randomized to the placebo arm of the 3-year Strontium Ranelate Efficacy in Knee Osteoarthritis trial (SEKOIA) and assessed annually. The RCI was used to determine whether the magnitude of change in joint space width (JSW) on radiographs between study years was likely to be true or due to measurement error.

Results. Between consecutive years, 57–69% of participants had an apparent decrease (change <0) in JSW, while 31–43% of participants had annual changes indicating improvement in JSW. The RCI identified JSW decreases in only 6.0% of patients between baseline and year 1, and in 4.5% of patients between the remaining study years. The apparent increases in JSW were almost eliminated between baseline and year 1, and between years 1 and 2 only 1.3% of patients had a significant increase, dropping to 0.9% between years 2 and 3.

Conclusion. The RCI provides a method to identify change in JSW, removing many apparent changes that are likely to be due to measurement error. This method appears to be useful for assessing change in JSW from radiographs in clinical and research settings.

INTRODUCTION

Osteoarthritis (OA) is one of the most widespread musculoskeletal disorders worldwide (1,2), and the knee is a commonly affected joint (3). During natural disease progression, the joint affected will have dramatic structural changes, which lead to increasing levels of pain and disability for the patient.

Although pain is the most commonly reported manifestation of knee OA (4), quantifying structural disease progression is important to aid in understanding the risk factors for OA progression

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[1]Camille M. Parsons, PhD, Elaine M. Dennison, MD, PhD: University of Southampton, Southampton, UK; [2]Andrew Judge, PhD: University of Southampton, Southampton, and University of Oxford, Oxford, UK; [3]Kirsten Leyland, PhD: University of Oxford, Oxford, and University of Bristol, Bristol, UK; [4]Olivier Bruyère, PhD, Jean-Yves Reginster, MD, PhD: University of Liège, Liège, Belgium; [5]Florence Petit Dop, PhD: Innovative Therapeutic Pole of Rheumatology, Servier, Surenes, France; [6]Roland Chapurlat, MD, PhD: INSERM UMR 1033, Hôpital Edouard Herriot, Université de Lyon, Lyon, France; [7]Mark H. Edwards, MD, PhD: University of Southampton and Southampton General Hospital, Southampton, and Portsmouth Hospitals NHS Trust, Portsmouth, UK; [8]Cyrus Cooper, FMedSci: University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, and University of Oxford, Oxford, UK; [9]Hazel Inskip, PhD: University of Southampton, and University Hospital Southampton NHS Foundation Trust, Southampton, UK.

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Address correspondence to Cyrus Cooper, FMedSci, MRC, Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, SO16 6YD, UK. E-mail: cc@mrc.soton.ac.uk.

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SIGNIFICANCE & INNOVATIONS

- The aim of this research was to assess the effectiveness of the Reliable Change Index as a novel approach to estimating osteoarthritis progression. To date no studies have been identified that apply the Reliable Change Index methodology within musculoskeletal research.
- The Reliable Change Index provides a useful method to identify change in joint space width, removing many of the apparent changes that are likely due to measurement error. When compared with crude differences in joint space width measurements, implementation of the Reliable Change Index dramatically reduced the proportions of study participants who were identified as having statistically reliable change.
- This method appears to be useful for assessing change in joint space width in clinical and research settings from radiographs and may have wider applications to other imaging modalities.

and to evaluate nonpharmacologic and pharmacologic treatments. In epidemiologic studies of knee OA, monitoring of structural disease progression has conventionally been based on a radiographic definition of knee OA (5), and knee joint space width (JSW), as a continuous measure, is currently the only Food and Drug Administration–approved end point for clinical trials assessing potential disease-modifying OA drugs (6). JSW refers to measurement of the minimum medial tibiofemoral interbone distance and is assessed in a standard metric scale of millimeters. Knee JSW measurements are small, and in knees from healthy individuals, maximum values are approximately 8 mm (7). However, it has also been estimated that joint space measurements could be in error by up to 1 mm (8), making it difficult to distinguish real deterioration in disease from measurement error. Previous studies have shown that both the technique used to read the radiograph and positioning of the knee during the radiograph can have a substantial influence on measured JSW (9,10).

To date, no single gold standard statistical method has been recommended in epidemiologic studies that focus on disease progression through monitoring JSW measurements. When JSW measurements have been shown to be normally distributed, OA disease progression has been compared between groups using the simple method of calculating the mean difference between measurements and then testing whether group differences are significant, using such statistical techniques as paired *t*-tests (11). Nonparametric rank comparisons have also been used to compare structural change if JSW measurements have a skewed distribution (12). However, such statistical techniques will only reveal differences in means between groups or indicate whether a population mean joint space has changed over time; such methods give no information on changes within individuals. An individual's change is the observed difference between 2 measurements taken at different times, and this change may be dominated by measurement error in either 1 or both measurements. In addition to obscuring disease deterioration, measurement error may lead to an apparent increase in joint space being observed. Due to the pathologic process associated with OA, i.e., cartilage volume loss, with ultimate involvement of underlying bone, any significant observed increase in JSW could possibly arise as a result of measurement error. Therefore, in both research and clinical settings, minimizing the effect of measurement error is important, to identify differences that are more likely to be due to real change in disease. In research, ensuring that the effects of any treatment or behavioral factors related to disease progression are correctly identified is important. In a clinical setting, identification of rapid radiologic progression may inform clinical management.

The Reliable Change Index (RCI) is a statistical method for identifying whether an observed change within an individual is meaningful in the presence of measurement error (13). The RCI provides a method of determining whether an individual's observed change is likely to be true or whether the change is attributable to measurement error; the greater the error in the measurement under investigation, the lower the likelihood that an observed change can be attributed to deterioration.

To date, the RCI has been mainly used in health psychology, and little is known about its value outside this setting (14). We therefore assessed the use of the RCI in a clinical research setting by implementing the index as a novel approach to estimate OA progression. We considered measurements of knee JSW taken at yearly intervals, within the control arm of an international, multicenter, randomized controlled trial of therapy for knee OA. RCI results were compared with crude differences and with the well-recognized cut points of 0.5 mm and 0.8 mm in joint space narrowing (JSN) (15).

MATERIALS AND METHODS

Study design. This study used data from patients randomized to the placebo arm of the 3-year Strontium Ranelate Efficacy in Knee Osteoarthritis trial (SEKOIA) (16). This was an international trial established to assess the effect of a drug treatment, strontium ranelate, on radiologic and clinical progression of OA in the knee joint. Patients were recruited into the trial between 2006 and 2008 from 98 study centers across 18 different countries and were randomized to either a drug regimen of strontium ranelate 1gm/day, strontium ranelate 2 gm/day, or a placebo treatment. Participants were recruited from secondary care establishments where they were already receiving outpatient care for knee OA. To be eligible for entry into SEKOIA, ambulatory white men and women age ≥50

years had to have a primary diagnosis of knee OA as defined by the clinical criteria of the American College of Rheumatology (17). On radiographs, patients had to have knee Kellgren/Lawrence (K/L) grade 2 or 3 (18), JSW between 2.5 mm and 5 mm at an inclusion screen, and predominant OA of the medial tibiofemoral compartment. The SEKOIA study conformed to the principles of the Declaration of Helsinki.

Radiographs were taken at the time of selection and then annually on the target knee, using a standardized technique described elsewhere (19). The radiographer recorded a fixed-flexion posterioanterior view (fixed angle 10°), using a SynaFlexer positioning frame (BioClinica, formerly Synarc) (20). All radiographs were measured centrally (at INSERM UMR 1033, Lyon, France) by a single reader (OB or JYR) blinded to treatment allocation and participant identity. Minimal JSW in millimeters at the medial tibiofemoral compartment was measured using a standardized computer-assisted method (21). Radiologic progressors were defined as patients whose joint space changed by ≥0.5 mm or ≥0.8 mm over the 3-year duration of SEKOIA, as per the definition developed by Bruyere et al in 2005 (15,16).

RCI. The RCI was first developed in 1991 by Jacobson and Truax (13). The principle behind the index is to determine whether the magnitude of change observed in a study participant can be attributed to true change, i.e., the change observed is more than could be explained by the unreliability of the measure. Several variations of the RCI have been proposed (22), but all variations identify the extent to which study participants' current measurements differ from their previous measurements. All variations of the RCI follow the same fundamental expression:

$$\text{RC index} = \frac{Y - Y'}{SE}$$

where Y is the study participant's actual measurement at the latter time point, Y′ represents the predicted measurement for the study participant at the latter time point of interest, and SE is the standard error of the score. The different approaches to the RCI vary in how they determine the different elements of the RCI. The version that was explored within this study was developed by Christensen and Mendoza (23). The RCI formula for each study participant, which produced a standardized RCI score, is:

$$\text{RC index} = \frac{X_2 - X_1}{\sqrt{S_1^2 + S_2^2 - 2S_1S_2r_{xy}}}$$

The predicted score is represented by the study participant's measurement at time point 1 (X_1) and the same study participant's actual measurement at time point 2 (X_2). The SE is derived using S_1^2 and S_2^2, which are the variances of the measurements at time points 1 and 2, respectively. S_1 and S_2 are the SDs of the measurements at time points 1 and 2, respectively, and r_{xy} is Pearson's correlation coefficient between the measurements at the 2 time points. Using this version of the RCI does not require the assumption of equal variance in measurements between time points.

The RCI calculation yields a standardized Z score (i.e., the scores have a mean of 0 and an SD of 1). Following the convention of using a 5% level of significance, an RCI score of ±1.96 or greater in magnitude denotes a significant difference, indicating that the change observed reflects more than the fluctuations in the measurement procedure. Each study participant's RCI score can be categorized into 1 of 3 categories: an increase (RCI greater than 1.96), a decrease (RCI less than −1.96), or stable (RCI between −1.96 and 1.96). A magnitude of change thresh-

Table 1. Participant characteristics*

Characteristic	Men (n = 167)	Women (n = 392)	All (n = 559)
Age, years	63.8 ± 7.8	62.3 ± 7.3	62.8 ± 7.5
Body mass index, kg/m^2	29.8 ± 4.1	29.8 ± 5.5	29.8 ± 5.1
Severity of knee osteoarthritis			
JSW at baseline, mm	3.65 ± 0.85	3.44 ± 0.82	3.51 ± 0.83
JSW at 36 months, mm	3.20 ± 1.06	3.12 ± 0.98	3.15 ± 1.00
JSN, study duration, mm	−0.44 ± 0.68	−0.40 ± 0.60	−0.41 ± 0.63
JSW at baseline, min/max mm	0.99/5.43	0.65/6.11	0.65/6.11
JSW at 36 months, min/max mm	0.38/5.47	0.58/5.50	0.38/5.50
JSN, study duration, min/max mm	−2.25/1.59	−3.34/0.70	−3.34/1.59
Disease duration, median (range) months	58 (0–502)	49 (0–457)	51 (0–502)
K/L grade, no. (%)			
2	103 (61.7)	247 (63.0)	350 (62.6)
3	64 (38.3)	145 (37.0)	209 (37.4)

* Values are the mean ± SD unless indicated otherwise. JSW = joint space width; JSN = joint space narrowing; min/max = minimum/maximum; K/L = Kellgren/Lawrence.

Table 2. Crude changes and Reliable Change Index (RCI) results*

	Baseline to year 1	Year 1 to year 2	Year 2 to year 3
Total in study, no.	465	400	329
Crude increase	146 (31.4)	171 (42.8)	138 (41.9)
Crude decrease	319 (68.6)	229 (57.3)	191 (58.1)
RCI increase	5 (1.1)	5 (1.3)	3 (0.9)
RCI decrease	28 (6.0)	18 (4.5)	13 (4.0)
Progression threshold, mm, no.	0.91	0.82	0.88

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

old can be calculated from the SE derived during the calculation of the RCI, with a level of change in JSW that can be considered statistically reliable, calculated as:

$$1.96^{*}\sqrt{S_1^2+S_2^2-2S_1S_2r_{xy}}$$

Statistical analysis. Study participants' continuous characteristics were checked for normality and summarized using means ± SDs. Crude differences in JSW were calculated between each SEKOIA study visit to provide a change in JSW in millimeters per year between each study year. The RCI was calculated between each SEKOIA study visit as described above for all study participants. All analyses were undertaken using Stata software, version 13.

RESULTS

In the SEKOIA study, 559 patients were randomized to the placebo arm, with demographic characteristics shown in Table 1. On entry, participants had a median disease duration of slightly more than 4 years, with men having experienced knee OA longer than women. The majority of the participants (63%) had K/L grade 2 at baseline, and proportions were similar in men and women. The participants' mean ± SD age was 62.8 ± 7.5 years, with the mean for men being greater than that for women, at 63.8 ± 7.8 and 62.3 ± 7.3 years, respectively. The mean ± SD JSW at baseline was 3.51 ± 0.83 mm, which reduced to 3.15 ± 1.00 mm by the end of the study. The minimum JSW at baseline was 0.65 mm, reducing to 0.38 mm during the study, and the largest individual reduction in JSW over the study was 3.34 mm. The 472 intent-to-treat placebo patients were used here to assess change in JSW. Table 2 and Table 3 show the crude changes and RCI results across all SEKOIA study years.

Of the 465 study participants who had knee JSW measurement at baseline and year 1, nearly 70% had either no change or an apparent decrease in JSW over the year when assessed using crude change, and this figure was nearly 60% between the remaining study years (Table 2). An RCI value was calculated for the differences in measurements between each SEKOIA study visit for each study participant. The SD at baseline for all JSW measurements was 0.82, and therefore the variance of JSW measurements at baseline was 0.67, while for all JSW measurements at year 1 the SD was 0.92 and the variance 0.84. The correlation between the 2 time points was 0.84. As an example, for a participant with a baseline JSW of 4.841 mm and a JSW at year 1 of 3.981 mm, the RCI value would be:

$$\frac{3.981-4.841}{\sqrt{0.67+0.84-2*0.82*0.92*0.84}}=-1.75$$

Thus the RCI for the study participant indicates that no statistically significant change in JSW has occurred. Performing this calculation for each study participant between baseline and year 1 indicated that 28 participants (6.0%) had an RCI less than –1.96 when assessing the observed difference. Thus, only in these 28 study participants was a statistically reliable decrease in JSW observed that was larger than would be expected through fluctuation in the joint space measurements or through measurement error. A similar pattern was observed between year 1 and year 2, and between year 2 and year 3, with 4.5% and 4.0% of patients,

Table 3. Crude changes, radiologic progressors, and Reliable Change Index (RCI) results*

	Total duration, baseline to year 3
Total in study, no.	336
Crude increase	74 (22.0)
Crude decrease	262 (78.0)
Radiologic progressor (JSN 0.5 mm)	120 (35.7)
Radiologic progressor (JSN 0.8 mm)	62 (18.5)
RCI increase	1 (0.3)
RCI decrease	36 (10.7)
Progression threshold, mm, no.	1.23

* Values are the number (%) unless indicated otherwise. JSN = joint space narrowing.

respectively, having a significant reliable decrease in knee joint space measurements between these years.

Conversely, approximately 30% of study participants were identified as having an increase in crude JSW measurement between baseline and year 1, and approximately 42% of study participants were identified as having a crude increase between year 1 and year 2, or between year 2 and year 3. Using the RCI calculation, 5 study participants (1.1%) had an RCI >1.96 when the observed differences between baseline and year 1 were assessed. These 5 study participants are of note because they appear to have had an increase in JSW greater than can be explained by the fluctuations of an imprecise measurement procedure. Use of the RCI for measurements between year 1 and year 2 and between year 2 and year 3 showed that only 5 participants (1.3%) and 3 participants (0.9%), respectively, had an increase in JSW during those time periods. No study participants consistently had a statistically reliable increase or decrease across all the following time periods: between baseline and year 1, between year 1 and year 2, and between year 2 and year 3.

Of the 336 study participants with measurements at baseline and year 3, 78% had crude decreases in JSW over the 3-year duration, with nearly 36% having a decrease in JSW ≥0.5 mm, and 18.5% having JSN of ≥0.8 mm. This measure of progression also identified a greater number of study participants with a decrease in knee JSW than the 11% identified using the RCI score (Table 3). When considering those study participants who were identified as having a crude increase in JSW between baseline and year 3 (74 participants) only 1 participant (0.3%) was still identified as having an increase when using the RCI score.

All RCI values were normally distributed, and a magnitude of change in millimeters (threshold) was calculated by transforming the RCI results to give a change in JSW, above which a statistically reliable change occurred. When calculating the magnitude of change in millimeters using the RCI, the magnitude varied between 0.85 mm and 1.23 mm for the different study periods under consideration. Very similar patterns were seen when RCI scores were calculated for men and women, and by K/L grade separately.

DISCUSSION

The aim of this study was to assess the effectiveness of the RCI as a novel approach to estimating OA progression, through assessment of knee JSW at yearly intervals. Although individual disease progression would almost certainly not be classified using the crude difference alone, if the measurements of the crude differences were taken in isolation, they would lead to the conclusion that between baseline and year 1, 70% of those study participants under observation had a worsening of their knee OA. However, use of the RCI indicates that only 6.0% of study participants (24) had a statistically reliable decrease in observed JSW that was larger than would be expected through measurement error in joint space measurements between baseline and year 1. Therefore considerably fewer study participants than initially highlighted through simple differences can reliably be considered to have had a decrease in joint space. Similar patterns were observed between years 1 and 2, and between years 2 and 3. Considerably more study participants, 10.7% (n = 36), had a statistically reliable decrease in observed change in JSW across the total duration of the SEKOIA trial compared to the differences between singular study years, indicating that reliable change becomes easier to detect when longer time periods exist between joint space measurements. This fact may be explained in part by greater time for disease progression to occur, allowing for potentially greater deterioration, which can be more easily distinguished from the measurement error that is still present.

Conversely, approximately 31% of study participants between baseline and year 1, and approximately 42% of study participants between year 1 and year 2, or between year 2 and year 3, were identified as having an absolute increase in JSW. Because real increases are extremely unlikely, this finding shows the impact of measurement error. If crude differences are assessed, without taking any account of measurement error, more than one-third of study participants would appear to have had some improvement in their knee OA condition. Use of the RCI identified a markedly lower number of 5 participants (1.1%) between baseline and year 1, 5 (1.3%) between years 1 and 2, and only 3 (0.9%) between years 2 and 3 as having an increase in JSW.

To date, no studies have been identified that apply the RCI methodology within musculoskeletal research, not only to monitor joint space measurements but also to assess disease deterioration. The RCI has, however, been successfully applied within psychological and neurologic research. For example, Ferguson et al (25) used the RCI to determine clinically significant change between pre- and postintervention Short Form 36 health survey scores that provide a continuous measure of patient health. Ferguson highlighted the fact that the use of the RCI is an important technique, because assessing crude differences alone does not provide reliable information about whether an intervention has had clinically meaningful effects (26). However, an assumption of the RCI is the stability of measurements between time points, and thus this method has not been previously applied to assess deterioration. The natural disease progression of OA is a slow process, often taking many years. Therefore, the assumption would be that on an annual basis, little or no change in JSW in a study participant would have occurred, and in this novel application of the RCI the assumption of stability was upheld.

There are other statistical techniques and metrics currently used within musculoskeletal research to identify whether change has been significant, such as the standard error of the measurement or the standardized response mean. However, neither of these techniques is appropriate for assessment at the individual level rather than the cohort level. Therefore, an advantage of using the RCI is that reliability of an individual

study participant's change can be determined, and additionally the estimate of the SE used within the RCI calculation can be used to quantify the JSW change, above which change could be considered statistically reliable. Although the RCI has its merits, there has also been much debate and criticism of the technique (22,24). One of the major criticisms is that although all variations of the calculation can be simplified to the same fundamental expression, each approach differs slightly in how the elements of the RCI are calculated. For example, the original definition of the RCI developed by Jacobson and Truax (13) requires an externally derived test–retest reliability coefficient to be able to calculate the SE and assumes equal variance in the measurements at both time points. Hinton-Bayre (22) has made a comparison of the different RCI variations, but there is currently no consensus as to which RCI should be used.

A further criticism of the RCI is that it is specific but not very sensitive, though this fact is partly due to the magnitude of measurement error within longitudinal studies. Within this study, the conventional 5% level of significance was followed, meaning that the cut point for RCI scores was ±1.96, but this cut point is arbitrary, and to increase the sensitivity of the RCI a less strict cutoff could be used.

The RCI aims to distinguish true progression of JSN in those patients with knee OA from measurement error. Although use of JSW longitudinally is the current gold standard for monitoring disease progression, previous studies have shown that inconsistent knee positioning during radiographs can cause a systematic shift in JSW (9), and so change in JSW may be due to change in positioning of the knee during radiographs rather than disease progression. However, previous studies have shown that the use of the intermargin distance is optimal in reducing variation in JSW due to knee positioning (27). The minimal JSW in millimeters at the medial tibiofemoral compartment, the intermargin distance, was measured in SEKOIA annually from radiographs obtained under strict study protocol (17,19). Therefore, the data in this study were collected with all the associated safeguards around methodology and training, and all radiographs were assessed by 1 reader, reducing measurement error. Thus, the joint space measurements collected during the SEKOIA study probably contain less measurement error than routine clinical measurements. Because there are different radiographic techniques that can be used to obtain knee radiographs, assessing the use of the RCI in data where other methods have been used would be important, particularly in routine clinical practice. However, it is important to remember that the RCI only provides statistically reliable change and does not provide information about the reason for change. The RCI is thus unable to distinguish changes in JSW due to variability in the radiographic positioning from disease progression.

Because there is no gold standard method for assessing significant change in JSW when assessing OA disease progression, there is no comparator for the RCI. However, the use of this novel approach does take account of measurement error, unlike calculation of crude differences. The formula is also simple enough that summary statistics derived from the study population enable assessment of individual study participants' reliable change.

Despite its simplicity, a conceptual problem with the RCI is that no account is taken within the calculation of the duration between the study visits. However, application of the RCI informs of change thresholds that can be used to further explore OA disease progression, particularly in a clinical trial setting. The index can help with determining study duration and assist in sample size determination. In addition, once calculated, the RCI groupings and individual scores might also be used in further statistical analysis to investigate characteristics and phenotypes that may be associated with disease progression, after accounting for the presence of measurement error.

There are some limitations to this study. The study participants already had established OA when recruited into SEKOIA, and assessing the performance of the RCI in a population with wider variability in JSW would be of value. The RCI notably did not remove all apparent increases in JSW. No measure is entirely reliable, and there is always a balance between the sensitivity and specificity of the cut points chosen. To eliminate all apparent increases, a higher level of statistical significance could be used within the RCI calculation, though this practice would reduce the number of decreases identified. Alternatively, if the concern was about missing true deterioration, a lower level could be used.

Few studies have assessed long-term reduction of joint space in a population of patients with OA of the knee. Applying the RCI within knee OA disease progression studies should enable a greater understanding of the progression of JSN. If the value of the RCI is confirmed in other populations, it may aid research, lead to better management of patients with the disease, and assist in improving and/or maintaining the quality of life for a patient with knee OA.

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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. Cooper 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. Parsons, Judge, Leyland, Reginster.
Acquisition of data. Bruyère, Petit Dop, Chapurlat.
Analysis and interpretation of data. Parsons, Edwards, Dennison, Inskip.

ADDITIONAL DISCLOSURE

Dr. Petit Dop is an employee of Servier.

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Appendix A: Members of the SEKOIA Study Group

Executive Committee: J.-Y. Reginster (Chairman), C. Cooper (International Coordinator), C. Christiansen, P. Delmas (deceased 2008), R. Chapurlat (from 2008 onward), H. Genant, J. Zacher, N. Bellamy. Steering Committee: C. Cooper (International Coordination, Chair), National Coordinators (see below), and representatives from the Central Reading Centers. Safety Committee: C. Speirs, G. Bréart, O. Meyer. Central Reading Centre (Lyon): D. Gensburger, M. Arlot, J.-P. Roux, R. Chapurlat. Central Reading Centre (Liege): R. Deroisy, O Bruyère, J.-Y. Reginster. National Coordinators: P. Sambrook (Australia), B. Leeb (Austria), A. Verbruggen (Belgium), W. Bensen (Canada), T. Hala (Czech Republic), M. Holm-Bentzen (Denmark), I. Valter (Estonia), X. Chevalier (France), B. Swoboda (Germany), S. Adami (Italy), M. Kloppenburg (The Netherlands), E. Grazuleviciute (Lithuania), J. Badurski (Poland), J. Branco (Portugal), E. Nasonov (Russia), F. Navarro (Spain), T. Spector (UK). Investigators: Australia: L. Barnsley, S. Hall, G. Jones, A. Klestov, L. March, P. Nash, E. Romas, R. Will. Austria: L. Erlacher, F. B. Leeb, H. Resch, F. Rainer, O. Zamani. Belgium: T. Appelboom, J. P. Devogelaer, A. Kvasz, F. Raeman, A. Verbruggen. Canada: A. D. Beaulieu, W. G. Bensen, J. Brown, A. A. Cividino, F. Morin, W. P. Olszynski, J. P. Raynauld, J. C. Thorne. Czech Republic: T. Hala, K. Pavelka. Denmark: P. Alexandersen, H. C. Hoeck, M. Holm-Bentzen, P. Lundqvist. Estonia: I. Valter. France: L. Aim, P. Audouy, P. Beaunier, C. L. Benhamou, F. Berenbaum, E. Chabaud, D. Chalet, X. Chevalier, M. Cohen-Solal, D. Delbecq, L. Euller-Ziegler, P. Fardellone, P. Hilliquin, E. Jacquety, N. Jude, D. Lechevalier, J. C. Mouchet, P. Richette, E. de Sainte Lorette, T. Schaeverbeke, A. Sebbah, E. Vignot. Germany: T. Brabant, G. R. Burmester, J. Grifka, P. E. M. Müller, B. Swoboda, J. Zacher. Italy: S. Adami, G. Bianchi, W. Grassi, L. Di Matteo, V. Modena, O. Di Munno, S. Ortolani, L. Punzi, M. Zangari. Lithuania: E. Grazuleviciute. Netherlands: M. Kloppenburg, L. D. Roorda, P. L. C. M. Van Riel. Poland: J. Badurski, E. Czerwinski, A. Gorecki, W. Tlustochowicz. Portugal: J. Branco, J. Canas

Da Silva, J. A. Melo Gomes, L. M. Miranda. Romania: F. Radulescu. Russia: L. I. Alexeeva, A. V. Orlov-Morozov, E. G. Pikhlak, V. G. Pilyaev, N. A. Shostak, E. I. Shmidt, N. V. Zagorodniy. Spain: L. Arboleya Rodríguez, P. Benito Ruiz, E. Chamizo Carmona, E. Collantes Estévez, G. Herrero-Beaumont, E. Martín Mola, A. Moreno, A. Naranjo Hernández, F. Navarro Sarabia, J. M. Padrino, C. Palacios, A. Rodríguez De La Serna, J. A. Román Ivorra, A. Torrijos. UK: E. Abdulhakim, N. Arden, F. Birrell, H. Donnachie, W. Fraser, R. Keen, R. Sarmiento, M. D. Stone.

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Brain Correlates of Continuous Pain in Rheumatoid Arthritis as Measured by Pulsed Arterial Spin Labeling

Yvonne C. Lee,[1] Alexander Fine,[1] Ekaterina Protsenko,[2] Elena Massarotti,[1] Robert R. Edwards,[1] Ishtiaq Mawla,[2] Vitaly Napadow,[2] and Marco L. Loggia[2]

Objective. Central nervous system pathways involving pain modulation shape the pain experience in patients with chronic pain. The aims of this study were to understand the mechanisms underlying pain in patients with rheumatoid arthritis (RA) and to identify brain signals that may serve as imaging markers for developing targeted treatments for RA-related pain.

Methods. Patients with RA and matched control subjects underwent functional magnetic resonance imaging, using pulsed arterial spin labeling. The imaging conditions included 1) resting state, 2) low-intensity stimulus, and 3) high-intensity stimulus. Stimuli consisted of mechanical pressure applied to metacarpophalangeal (MCP) joints with an automated cuff inflator. The low-intensity stimulus was inflation to 30 mm Hg. The high-intensity stimulus was the amount of pressure required to achieve a pain intensity rating of 40 on a 100-point scale for each RA patient, with the same amount of pressure used in the matched control.

Results. Among RA patients, regional cerebral blood flow (rCBF) in the medial frontal cortex and dorsolateral prefrontal cortex increased during both low-pressure and high-pressure stimulation. No rCBF changes were observed in pain-free controls. Region-of-interest analyses in RA patients showed that baseline rCBF in the medial frontal cortex was negatively correlated with the pressure required for the high-intensity stimulus and positively correlated with pain induced by the low-intensity stimulus. Baseline rCBF was also marginally correlated with disease activity). Regional CBF during high pain was positively correlated with pain severity and pain interference.

Conclusion. In response to clinically relevant joint pain evoked by pressure applied to the MCP joint, neural processing in the medial frontal cortex increases and is directly associated with clinical pain in patients with RA.

INTRODUCTION

Pain is the main reason patients seek rheumatologic care, but little is known about the mechanisms of pain in rheumatoid arthritis (RA). Most rheumatologists conceptualize pain primarily in the context of inflammation at joint sites (1). However, even with treatment of inflammation, average pain levels often do not return to general population norms (2,3). The imperfect association between inflammation and pain intensity may be attributable to many factors, including differences in central nervous system (CNS) processing and modulation of joint-specific pain perception.

Historically, the need for invasive techniques to assess CNS pain mechanisms limited this area of study in humans, but the development of advanced functional magnetic resonance imaging (fMRI) techniques has enabled the noninvasive visualization of brain responses. Arterial spin labeling (ASL) is an fMRI technique in which water is used in arterial blood as a freely diffusible endogenous

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[1]Yvonne C. Lee, MD, MMSc (current address: Northwestern University, Chicago, Illinois), Alexander Fine, BA, Elena Massarotti, MD, Robert R. Edwards, PhD: Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [2]Ekaterina Protsenko, BA, PhD, Ishtiaq Mawla, BSc, Vitaly Napadow, PhD, Marco L. Loggia, PhD: Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

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Address correspondence to Yvonne C. Lee, MD, MMSc, 240 East Huron Street, M-300, Chicago, IL 60611. E-mail: yvonne.lee@northwestern.edu.

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SIGNIFICANCE & INNOVATIONS

- This study is the first to identify the medial frontal cortex (MFC) as a key area involved in the sensation and/or regulation of tonic, clinically relevant joint pain in patients with rheumatoid arthritis (RA).
- Joint pain exacerbation was associated with increases in regional cerebral blood flow (rCBF) in the MFC, and rCBF in the MFC was significantly associated with pain severity and pain interference.
- The results from this study will inform the development of targeted pharmacologic and nonpharmacologic interventions for pain in systemic inflammatory conditions such as RA.

tracer to measure blood perfusion in the brain, an indirect marker of neural activity, noninvasively (4). By using ASL, a quantifiable measurement of regional cerebral blood flow (rCBF) can be obtained by comparing images obtained with and those obtained without application of the tagging magnetic pulse, which inverts the natural magnetization of water in arterial blood (5).

Several studies have applied ASL to the study of experimental pain in healthy humans (6–8). More recently, ASL has also been applied to the investigation of the neural correlates of clinical pain. For instance, in individuals with chronic low back pain, acute pain exacerbations were shown to be associated with increases in rCBF in several brain regions, including the insular and medial prefrontal cortices (MPFCs) (9). Another study showed rCBF changes in the insular cortex and the MPFC related to clinical pain from carpometacarpal osteoarthritis (10). Both studies were able to capture brain responses to ongoing pain, a signal that evolves slowly (typically over minutes or hours) and, importantly, is not easily detected by traditional blood oxygen level–dependent (BOLD) fMRI in block or event-related designs, which require multiple, brief alternations between epochs of pain and no pain. These observations suggest that ASL imaging has the potential to be an important biomarker for pain in clinical studies. To our knowledge, no study has used ASL to measure rCBF changes associated with clinically relevant pain in patients with RA.

In this study, we used pulsed ASL (pASL) to identify changes in rCBF associated with pain provocations at the metacarpophalangeal (MCP) joints in patients with RA and pain-free control subjects. Using a similar experimental stimulus, Schweinhardt et al showed that brief, 2-second pressure provocation of hand joint pain resulted in increases in BOLD brain signal in portions of the MPFC and pregenual anterior cingulate cortex (pgACC) (11). Because brief pain stimuli are likely to be particularly salient, we designed our study to use longer (6-minute) tonic stimuli to minimize the effect of attentional reallocation associated with rapid perceptual changes. We were particularly interested in minimizing attentional responses, because previous studies have shown that the startle response is altered in patients with chronic illnesses associated with pain (12–15).

Because pASL is better equipped to assess brain activity for low-frequency stimuli (16), our hypothesis was that pASL would identify changes in rCBF associated with clinical tonic exacerbations of RA-related pain. This finding could have an important impact by furthering our understanding of the brain mechanisms mediating RA pain and by paving the way for the use of imaging markers to objectively assess pain in clinical trials, thereby decreasing heterogeneity and increasing the power to detect medication effects.

PATIENTS AND METHODS

Participants. Patients with RA were recruited from the outpatient rheumatology clinics at a single academic institution. Inclusion criteria for the RA patients were age 25–70 years, diagnosis of RA by a board-certified rheumatologist, chronic pain for ≥3 months with an average intensity of ≥3 on a 0–10 scale at the left MCP joints, and no or minimal glucocorticoid use (≤10 mg prednisone [or equivalent] daily). Exclusion criteria were history of surgery at the left MCP joints, current opioid and/or benzodiazepine use, and contraindications to MRI screening (e.g., metal in the body, cardiac pacemaker, claustrophobia, pregnancy). Age- and sex-matched pain-free controls were recruited through advertisements in Craigslist and a registry of individuals interested in clinical research. Exclusion criteria for controls were the same as those for the RA patients. Additional exclusion criteria for pain-free controls were history of RA and/or other systemic rheumatic diseases, history of chronic pain conditions, and acute pain at the time of the screening visit. All participants provided written informed consent. The Partners Institutional Review Board approved this study.

Study overview. Subjects participated in 2 sessions: a behavioral training visit and an imaging visit. The objectives of the training session were to familiarize participants with pressure-induced pain and rating procedures, and to identify the approximate pressure needed for the high-intensity stimulus during the imaging session. The objective of the imaging visit was to obtain the questionnaire and neuroimaging data for use in the analyses.

Training session. The subjects were instructed to lie on an examining table, and a Velcro-adjusted vascular cuff was secured around the left MCP joints. The cuff was connected to a Rapid Cuff Inflator (Hokanson) that increases pressure to a target level over ~2 seconds. This type of cuff pressure stimulus preferentially targets deep tissue nociceptors (17) and has been used in other neuroimaging studies of chronic pain (18,19). Testing began by inflating the cuff to 60 mm Hg and increasing the pressure by 20–30 mm Hg until a pain intensity rating of 70 on a 100-point scale (70/100) was obtained. Pressure was then de-

creased by 20–30 mm Hg every 15 seconds, until the subject did not feel any pain. Two trials were performed, with a 6-minute rest period between trials. The average pressure required to achieve a pain intensity rating of 40/100 was then applied to the left MCP joints for 6 minutes, to simulate what the subjects would experience in the MRI scanner during the imaging session.

Imaging session. The imaging session occurred within 2 weeks of the training session and included a physical examination, blood work, questionnaires, and MRI scanning at rest and during application of pressure stimuli.

Physical examination, blood work, and questionnaires. A trained assessor performed a standardized 28-joint count in all participants to assess tenderness and swelling, and blood was obtained to assess C-reactive protein (CRP) levels. The swollen joint–to–tender joint ratio was calculated as a measure of widespread, noninflammatory pain (20). All participants completed the following questionnaires: the Brief Pain Inventory (BPI), the Hospital Anxiety and Depression Scale (HADS), the Pain Catastrophizing Scale (PCS), and the Medical Outcomes Study (MOS) Sleep Scale. The BPI is a validated, 9-question survey that assesses the sensory and reactive aspects of clinical pain (21). The HADS is a validated, 12-item questionnaire that assesses anxiety and depression in chronically ill patients (22). The MOS Sleep Scale is a validated, 12-item questionnaire developed to assess sleep quality and quantity in individuals with chronic illnesses (23). The PCS is a validated, 13-item questionnaire used to examine catastrophic thinking about pain in individuals with chronic pain.

MRI scans. Using a 3T Siemens Magnetom Skyra scanner with a 32-channel head coil, 6-minute pASL scans (repetition time [TR] 3,000 msec, time to echo [TE] 17 msec, inversion time 1/inversion time 2 700 msec/1,700 msec, voxel size 4 × 4 × 5 mm, number of slices 17) were collected using the PICORE Q2TIPS MRI labeling method (24). Tag images were acquired by labeling a thick inversion slab (110 mm) proximal to the imaging slices (gap 21.1 mm). Tag and control images were acquired in an interleaved pattern. At the beginning of each pASL scan, an M0 calibration image scan was acquired for the purpose of rCBF quantification. A high-resolution anatomic volume image was also collected (TR 2,300 msec, TE 2.95 msec, voxel size 1.1 × 1.1 × 1.2 mm, number of slices 176) for anatomic localization purposes (9).

Pulsed ASL scans were collected under 3 conditions: baseline, low-intensity pressure stimulus, and high-intensity pressure stimulus. During scanning under all 3 conditions, participants were instructed to remain still, with their eyes open. During the baseline scan, the vascular cuff was wrapped around the left MCP joints, but no pressure stimulus was provided. During the low-intensity pressure scan, the vascular cuff was inflated around the left MCP joints to 30 mm Hg for 6 minutes.

The pressures used for the high-intensity scans were individualized to achieve a pain intensity rating of 40/100 for each RA patient. The required pressure was recalibrated immediately before the scan, using pressure values from the training session as the starting point. Each RA patient was age- and sex-matched to a pain-free control subject, and the pressures used for the control subject were the same as those used for the RA patient with whom they were matched, as has been done in previous studies (25). The rationale behind using stimulus-matched conditions was to demonstrate that patients are hypersensitive to pressure stimuli (e.g., they exhibit hyperalgesia or allodynia) and to identify brain patterns that might contribute to explaining such hypersensitivity. The order of the high-intensity and low-intensity pain provocation scans was randomized to minimize order effects. The high-intensity and low-intensity pain provocation scans were separated by at least 10 minutes to allow subjects to recover between pain provocations.

Data analysis. To characterize the RA patients and age- and sex-matched controls, means and frequencies were calculated. Wilcoxon's signed rank tests were used to compare responses to the pressure stimuli between RA patients and controls. Imaging data analysis was performed using a combination of analysis packages, including FMRIB Software Library version 5.0.7 (www.fmrib.ox.ac.uk/fsl) (26), FreeSurfer version 5.3.0 (https://surfer.nmr.mgh.harvard.edu) (27), and ASLtbx (https://cfn.upenn.edu/~zewang/ASLtbx.php) (28,29). Pulsed ASL time series were motion-corrected (by realigning tag and control images separately), co-registered to the M0 scan, spatially smoothed using a full-width half-maximum kernel of 6 mm and converted into rCBF maps in absolute values (ml/100 gm of tissue/minute) (30), using ASLtbx. This preliminary spatial smoothing, prior to rCBF calculation, was performed to prevent noise propagation, as recommended by the ASLtbx documentation.

Regional CBF maps were then brain-extracted using the Brain Extraction Tool, registered to high-resolution anatomic images using Freesurfer's boundary-based registration tool (BBregister) (31), and spatially normalized to the standard Montreal Neurological Institute (MNI) template (MNI152). To avoid differences in brain coverage (e.g., due to differences in head size or slice placement during acquisition) that may confound group imaging results, all MNI-normalized rCBF maps were masked by an "intersection volume," so that only voxels imaged in all participants were included in all analyses. The rCBF maps were then intensity-normalized by dividing each voxel by the global rCBF, computed within the intersection volume (as is commonly done in ASL or PET perfusion studies) (32,33), to improve sensitivity to regional changes.

Normalized rCBF maps were smoothed using a Gaussian kernel with a full width at half maximum of 8 mm to improve between-subject co-registration, the signal-to-noise ratio, and the validity of statistical tests. Group differences in baseline rCBF maps, as well as the effect of stimulation (low/high-

Table 1. Demographic and clinical characteristics of the study subjects*

Characteristic	RA patients (n = 14)	Controls (n = 16)	*P*†
Age, mean ± SD years	44.8 ± 9.3	47.1 ± 11.4	0.55
Female sex	100	93.8	0.34
Seropositive	78.6	–	–
Disease duration, mean ± SD years	11.4 ± 9.9	–	–
DAS28, mean ± SD	3.8 ± 1.0	–	–
Glucocorticoid use	14.3	–	–
DMARD use	57.1	–	–
Synthetic DMARD	35.7		
Biologic DMARD	42.9		
NSAID treatment	57.1%		
BPI score, mean ± SD			
Average pain severity (0–10 scale)	4.6 ± 1.9	0.6 ± 1.3	<0.01
Pain interference (0–10 scale)	3.9 ± 2.1	0.1 ± 0.4	<0.01
HADS Depression score, mean ± SD (0–21 scale)	5.4 ± 3.6	0.7 ± 1.6	<0.01
HADS Anxiety score, mean ± SD (0–21 scale)	7.0 ± 2.6	2.1 ± 3.1	<0.01
PCS score, mean ± SD (0–52 scale)	16.8 ± 10.5	6.2 ± 6.7	<0.01
MOS Sleep Problems II score, mean ± SD (0–100 scale)	45.8 ± 17.7	16.6 ± 15.1	<0.01

* Except where indicated otherwise, values are the percent. RA = rheumatoid arthritis; DAS28 = Disease Activity Score in 28 joints; DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal antiinflammatory drug; BPI = Brief Pain Inventory; HADS = Hospital Anxiety and Depression Scale; PCS = Pain Catastrophizing Scale; MOS = Medical Outcomes Study.
† By 2-sample *t*-test (continuous variables) and chi-square test (categorical variables).

intensity versus baseline), and condition x group interaction were assessed using general linear models (GLMs). The group-level analyses were performed using a mixed-effects analysis, and corrected for multiple comparisons with a voxel-wise cluster-forming threshold of Z = 2.3 and a corrected cluster significance threshold of $P = 0.05$. Because no subcortical effects were detected, and for ease of visualization, imaging results were visualized on the brain surface using FreeSurfer fsAverage.

In exploratory analyses, the cluster demonstrating significantly increased rCBF in RA patients in the "high-intensity stimulation versus baseline" contrast was used as a region of interest (ROI) to probe group differences in the mean rCBF signal, using GLMs. Pearson's correlations were used to assess the relationship between rCBF in this cluster and clinical measures. ROI analyses were performed with Statistica 10.0 (StatSoft), using an alpha level of 0.05.

RESULTS

Participant characteristics. We enrolled 16 RA patients and 16 pain-free control subjects. One male RA patient was excluded from analysis because his large head size would excessively limit brain coverage for the pASL scans. One female patient with RA was excluded from the analysis because she fell asleep during the scan. The final analytic cohort included 14 patients with RA and 16 pain-free control subjects (Table 1). The mean ± SD age of the RA patients was 44.8 ± 9.3 years and that of the controls was 47.1 ± 11.4 years. RA patients differed significantly from controls in terms of average pain intensity, pain interference, depression, anxiety, pain catastrophizing, and sleep problems. In the RA patients, the mean ± SD disease duration was 11.4 ± 9.9 years, and the mean ± SD Disease Activity Score in 28 joints (DAS28) was 3.8 ± 1.0. Nine RA patients (64.3%) were receiving disease-modifying antirheumatic drugs (DMARDs), 5 (35.7%) were receiving a synthetic DMARD, and 6 (42.9%) were receiving a biologic DMARD. Eight RA patients (57.1%) were receiving a nonsteroidal antiinflammatory drug (NSAID), and 2 RA patients (14.3%) were receiving prednisone.

Pressure pain induction in RA patients and controls. During application of the high-intensity pain stimulus, all RA patients and 11 (68.8%) controls reported pain. The mean pain severity in response to the high-intensity pain stimulus was significantly greater in RA patients compared with controls (51.6 ± 24.4 versus 14.8 ± 22.3; $P = 0.0006$) (Figure 1). During low-intensity stimulation, 10 RA patients (71.4%) and 2 control subjects (13.5%) reported pain. Mean ± SD pain severity in response to the low-intensity stimulus was significantly higher in RA patients compared with controls (24.6 ± 30.1 versus 0.6 ± 1.7; $P = 0.0005$).

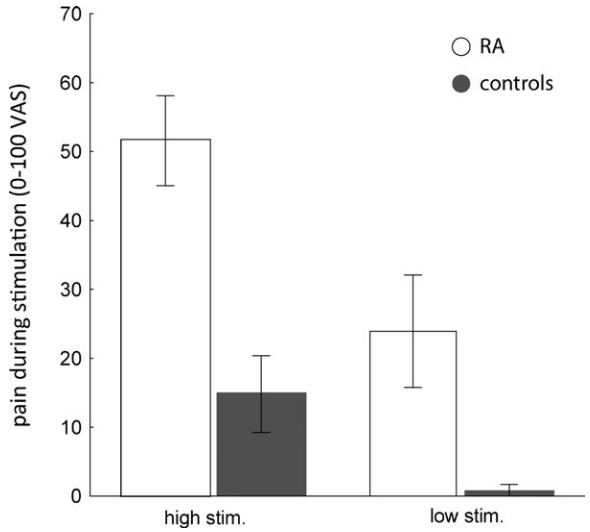

Figure 1. Mean pain ratings in response to the high-intensity (40–418 mm Hg) and low-intensity (30 mm Hg) stimuli (stim.) at the metacarpophalangeal joints in patients with rheumatoid arthritis (RA) and control subjects. Bars show the mean ± SEM. VAS = visual analog scale.

We also examined the effect of the order of high-intensity versus low-intensity pain stimulus scans on patient-reported pain. Although there was no order effect for patient-reported pain in response to the high-intensity pain provocation, there was a significant order effect for the low-intensity pain provocation. Specifically, RA patients perceived the low-intensity provocation as significantly more painful when it was preceded by the high-intensity stimulus than when the low-intensity provocation was given first (mean ± SD 43.4 ± 37.7 versus 10.6 ± 14.0; $P = 0.02$). This observation is suggestive of sensitization after the high-intensity provocation.

Group differences in imaging results. At baseline, resting-state whole-brain voxel-wise comparisons revealed no statistically significant differences in rCBF between RA patients and pain-free controls. In RA patients, low-intensity stimulation (which was perceived as mildly painful, on average) was accompanied by a statistically significant rCBF increase in the posterior medial frontal cortex (MFC) (34), including the anterior midcingulate cortex (aMCC), and the supplementary motor area (SMA) and pre-SMA, as well as in the precentral gyrus, the dorsolateral prefrontal cortex (dLPFC), and underlying white matter, compared with baseline (Figure 2A and Table 2). In RA patients, high-intensity stimulation (which was moderately painful, on average) led to rCBF increases similar to those of low-intensity stimulation in the posterior MFC, with the additional recruitment of more rostral portions of the MFC (expanding into the pgACC) and the dLPFC (expanding into the frontal pole) compared with baseline (Figure 2B and Table 2). In healthy pain-free subjects (for whom cuff stimulation was only mildly painful or not painful at all), these effects were

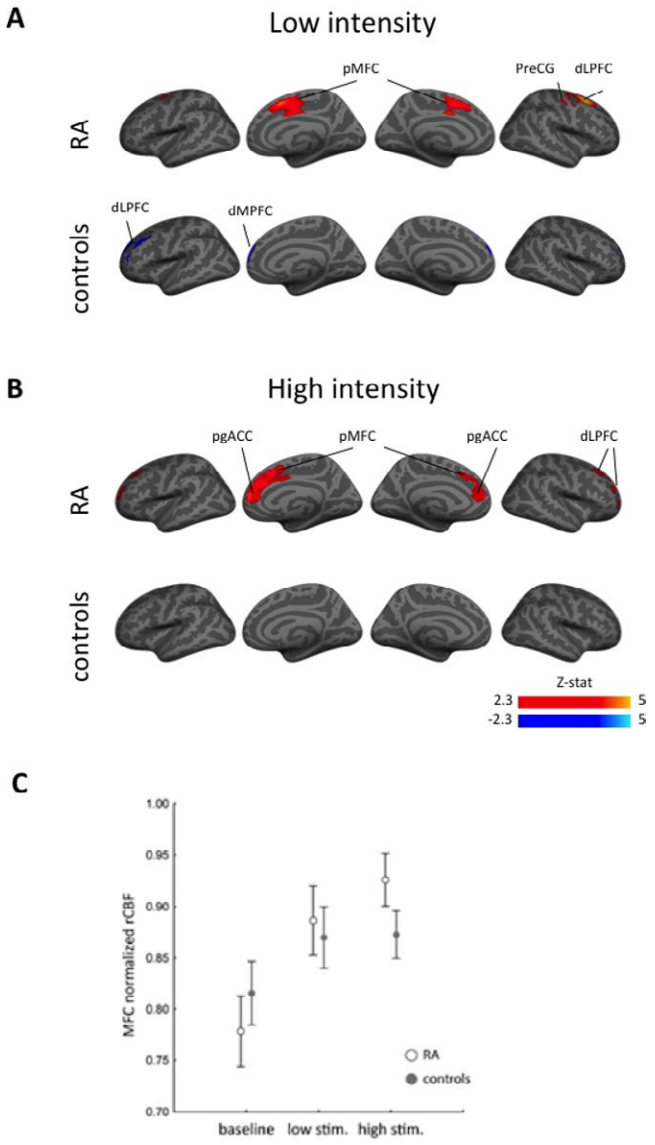

Figure 2. **A,** Regional cerebral blood flow (rCBF) in response to a low-intensity pressure stimulus (compared to baseline) at the metacarpophalangeal (MCP) joints in patients with rheumatoid arthritis (RA) and pain-free controls. **B,** Regional CBF in response to a high-intensity pressure stimulus at the MCP joints in RA patients and pain-free controls. **C,** Significant increases in rCBF in the medial frontal cortex (MFC) in response to high-intensity stimulation at the MCP joints in RA patients but not healthy, pain-free control subjects. Bars show the mean ± SEM. pMFC = posterior medial frontal cortex; Pre-CG = precentral gyrus; dLPFC = dorsolateral prefrontal cortex; dMPFC = dorso medial prefrontal cortex; pgACC = pregenual anterior cingulate cortex; Z-stat = Z statistic.

absent. The only statistically significant effect detected was a decrease in rCBF in the dorsomedial prefrontal cortex, dLPFC, and the frontal pole for the low-intensity stimulation.

A direct comparison of high-intensity and low-intensity stimulation scans, or any group interactions, did not yield results surviving statistical thresholding in voxel-wise analyses. A

Table 2. Brain regions showing significant rCBF changes in response to the stimuli*

Group/contrast	Cluster size†	Cluster *P*	Label	Local maxima			
				Z	x (mm)	y (mm)	z (mm)
RA/low-intensity stimulus > baseline	3,714	0.0023	R superior frontal sulcus	4.96	22	12	52
			R pre-SMA	3.58	10	10	52
			aMCC	3.56	0	2	42
			L aMCC/pre-SMA	3.41	−4	4	46
			R precentral gyrus	3.11	32	−12	56
RA/baseline > low-intensity stimulus	NS	NS					
RA/high-intensity stimulus > baseline	4,078	0.00161	R pgACC	3.55	8	48	12
			R pre-SMA	3.34	10	22	44
			L pgACC	3.08	−6	48	12
			L superior frontal sulcus	3.04	−16	22	46
			L pre-SMA	2.7	−10	24	40
RA/baseline > high-intensity stimulus	NS	NS					
Controls/low-intensity stimulus > baseline	NS	NS					
Controls/baseline > low-intensity stimulus	1,951	0.0336	L frontal pole	3.34	−38	58	14
			R medial prefrontal cortex	3.22	2	58	10
			L middle frontal gyrus	3.04	−30	32	38
			R frontal pole	2.89	10	58	32
Controls/high-intensity stimulus > baseline	NS	NS					
Controls/baseline > high-intensity stimulus	NS	NS					

* rCBF = regional cerebral blood flow; RA = rheumatoid arthritis; pre-SMA = pre–supplementary motor area; aMCC = anterior midcingulate cortex; NS = not significant; pgACC = pregenual anterior cingulate cortex.
† Number of voxels.

follow-up ROI-based analysis confirmed the response of an effect of stimulus (baseline, low-intensity, and high-intensity) on the average rCBF extracted from the significant cluster identified in the "high-intensity versus baseline" contrast in RA patients ($F[2,54] = 9.455$, $P < 0.001$). No statistically significant condition × group interaction was observed ($F[2,54] = 1.689$, $P = 0.19$). However, an exploratory post hoc decomposition of the interaction using Tukey's highest significant difference tests revealed that although in patients the high stimulation versus baseline comparison was significant (replicating the results of the voxel-wise analyses) ($P < 0.01$) and the low stimulation versus baseline comparison trended toward significance ($P = 0.053$), these comparisons did not yield statistically significant results in controls (both $P > 0.53$).

Imaging results showing correlations with clinical measures. In patients, baseline normalized rCBF in the MFC was negatively correlated with the amount of pressure required for the high-intensity pain stimulus ($r = –0.76$, $P < 0.01$). Baseline normalized rCBF in the MFC was also positively correlated with pain ratings in response to the low-intensity pain stimulus ($r = 0.56$, $P < 0.05$) and with the DAS28 (with borderline statistical significance; $r = 0.53$, $P = 0.05$) (Figure 3). In other words, the higher the rCBF in the MFC at baseline, the higher the disease activity and the sensitivity to experimental pain, as assessed in terms of both lower intensity of stimulation needed to achieve the target percept and higher pain ratings in response to a fixed, low-intensity stimulus. Furthermore, normalized rCBF during the

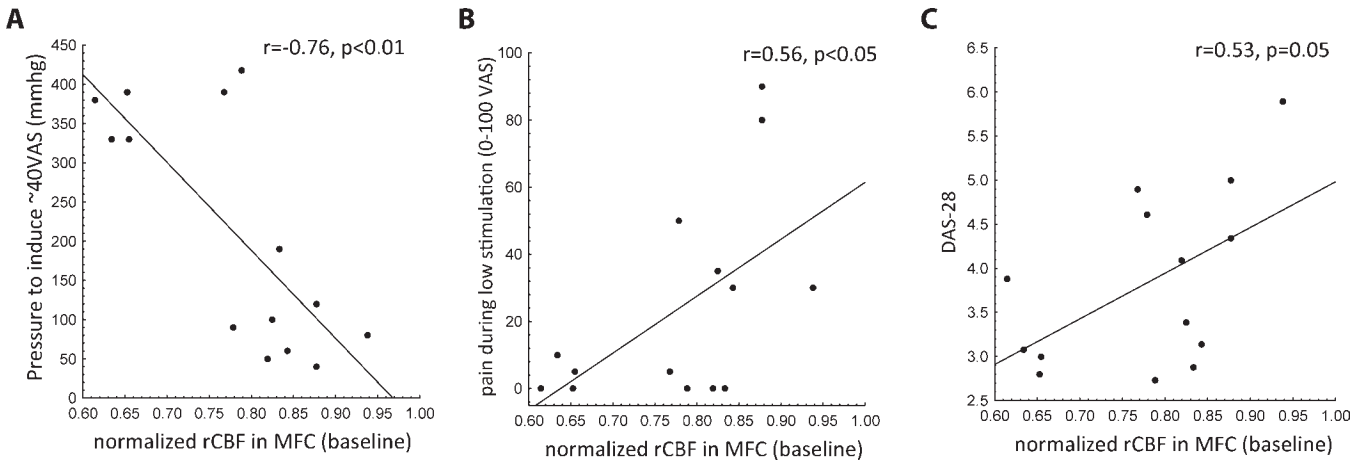

Figure 3. Region of interest analyses in the medial frontal cortex and associations with pain sensitivity and RA disease activity. **A,** Negative correlation between resting rCBF and the pressure required for high-intensity MCP joint stimulation. **B,** Positive correlation between resting rCBF and pain evoked by the low-intensity MCP joint stimulus. **C,** Positive correlation between the Disease Activity Score in 28 joints (DAS28) and resting rCBF. Each symbol represents an individual patient. VAS = visual analog scale (see Figure 2 for other definitions).

high-intensity stimulation was significantly correlated with both BPI average pain (r = 0.53, $P < 0.05$) and BPI pain interference ratings (r = 0.60, $P < 0.05$) (Figure 4). No statistically significant associations were observed with rCBF at baseline or during the high-intensity stimulation and measures of depression, anxiety, catastrophizing, sleep problems, and widespread, noninflammatory pain (ratio of swollen joint count to tender joint count).

DISCUSSION

Using pASL, we identified the MFC as a key area involved in the sensation and/or regulation of tonic, clinically relevant joint pain in patients with RA. Joint pain exacerbation was associated with increases in rCBF in the MFC, and rCBF in the MFC was significantly associated with measures of experimental pain sensitivity and clinical pain severity and pain interference. Moreover, the MFC was not shown to be involved in pain induction in our sample of healthy controls. Based on these observations, we interpret the rCBF response in the MFC to represent neural processing of tonic, clinically relevant pain in RA patients.

The MFC, including the MPFC, aMCC, and SMA/pre-SMA (35,36), is consistently activated in response to pain (37) and is part of a group of regions in which activity reliably predicts experimental pain (38). Activation of the posterior region of the rostral MFC is thought to be associated with cognitive endeavors, such as attending and monitoring actions, whereas activation of the anterior region of the rostral MFC is associated with emotional undertakings, such as evaluating emotions in

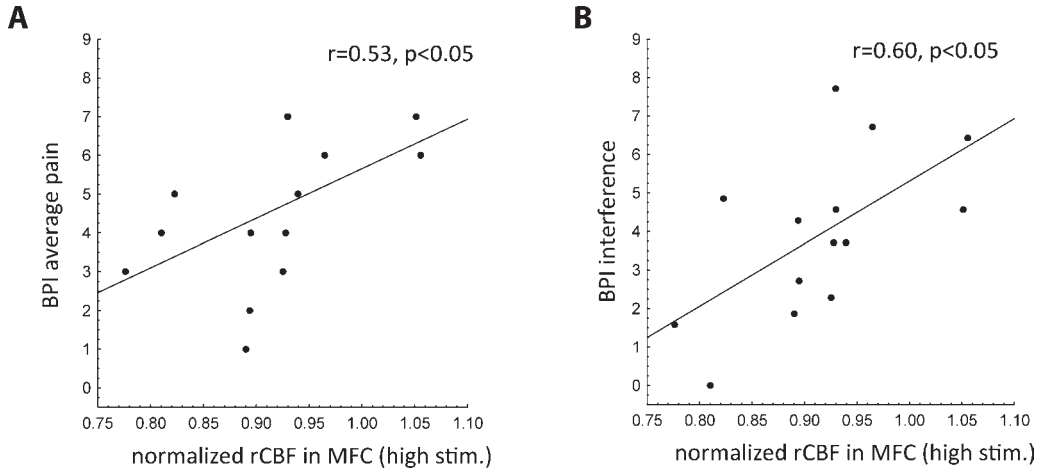

Figure 4. Region of interest analyses in the medial frontal cortex (MFC) and associations with clinical pain measures. **A,** Positive correlation between the Brief Pain Inventory (BPI) average pain level and regional cerebral blood flow (rCBF) in response to pain induced by a cuff wrapped around the metacarpophalangeal (MCP) joints. **B,** Positive correlation between the BPI pain interference score and rCBF in response to pain induced by a cuff wrapped around the MCP joints. Each symbol represents an individual patient. Stim. = stimulation.

reaction to positive and negative images (35). Additionally, the aMCC, also referred to as the dorsal anterior cingulate cortex, has been suggested to mediate the affective component of pain (39). In our study, both low-intensity and high-intensity stimuli activated a posterior component of the MFC, but only high-intensity stimulation significantly activated a more anterior component, possibly indicating the engagement of attentional resources in both the low-intensity and high-intensity conditions and recruitment of additional emotional processing in the latter (40). Furthermore, activation of the pgACC by the high-intensity stimulus might reflect activity of the descending pain modulatory system, because this region has been extensively associated with antinociceptive functions (41–43), likely exerted through its descending projections to the periaqueductal gray matter (44).

In addition, the MFC is also a component of the default mode network, a group of brain regions associated with self-referential cognitive processing (45), which our group and others have shown to exhibit alterations in chronic pain (46–53). Using the same imaging technique employed in the current study (pASL), our group demonstrated rCBF elevations in the MFC (including the dorsomedial prefrontal cortex and pre-SMA) in patients with chronic low back pain after the experimental exacerbation of their clinical pain (9). The recruitment of the MFC across different pain disorders supports a central role for this region in chronic pain perception.

During both low-intensity and high-intensity stimulation, the patients in this study also demonstrated activation of the dLPFC, another region that is commonly activated in response to noxious stimulation (54). Interestingly, dLPFC activation appeared to be stronger on the right side. A possible explanation for this finding is that the right dLPFC might be implicated more than the left side in the processing of fear and negative emotions (55), although this hypothesis needs to be further evaluated.

In contrast to the statistically significant rCBF elevations detected in the MPFC and dLPFC, 2 sets of negative results are particularly noteworthy. First, several regions commonly observed as being activated in imaging studies of acute pain (e.g., primary somatosensory, insula, and thalamus) (56) did not show a statistically significant increase in rCBF in our study. We speculate that this may be due to the fact that we used tonic stimuli, whereas prior studies used mostly brief, phasic stimuli.

Second, as opposed to the RA patients, the controls did not demonstrate any significant rCBF elevations in response to either high-intensity or low-intensity stimulation. Although the exact cause for this negative result remains uncertain, it is possible that the pain levels experienced by the controls, and/or the signal-to-noise ratio in our data set, were simply too low to yield a measurable change in rCBF in our control sample, particularly in the context of tonic stimuli. Despite these negative results, the observed patterns of stimulus-related brain changes in patients, and their association with clinical variables, suggest that pASL might be a promising tool to identify perfusion changes that are related to clinically relevant pain.

Prior to our current study, few studies have used fMRI to examine associations between brain function and pain in RA (11,57). Most recently, Basu et al examined functional connectivity between the default mode network, which includes the MPFC and the insula, in 54 RA patients with clinically significant fatigue (58). That study revealed that functional connectivity between the default mode network and insula was directly correlated with the modified American College of Rheumatology Preliminary Diagnostic Criteria scores for fibromyalgia (59), suggesting that connectivity between the default mode network and insula may serve as an imaging marker for pain centralization. Because the study was cross-sectional, however, it could not provide information on causality.

Interestingly, a small longitudinal study (n = 5 participants) demonstrated that treatment with infliximab, a monoclonal tumor necrosis factor (TNF) inhibitor, was associated with decreases in the fMRI BOLD signal in the ACC, MPFC, and other brain areas involved in pain perception (e.g., thalamus, secondary somatosensory cortex, and insula) within 24 hours (57). These changes were accompanied by significant decreases in pain intensity, whereas measures of inflammation (e.g., CRP level, interleukin-6 level, swollen joint count, and DAS28) were slower to change, with no statistically significant or clinically meaningful changes after 24 hours. These observations suggest that TNF may mediate nociception, independent of inflammation, in patients with RA. Future studies using longitudinal data on psychosocial factors are needed to determine whether depression may mediate the association between TNF inhibition and changes in rCBF and clinical pain intensity.

In addition to fMRI, positron emission tomography (PET), an invasive technique involving ionizing radiation, has been used to assess rCBF in patients with RA. Using PET, Jones and Derbyshire also identified the MPFC and ACC as regions in which rCBF differed in response to noxious stimuli in 6 RA patients versus 6 age- and sex-matched controls (60). In contrast to the current study, which showed increases in rCBF in these areas, that study showed dampened responses in the MPFC and ACC. The investigators postulated that the dampened responses may reflect cognitive coping strategies, which are more developed (and thus more effective) among RA patients who experience pain on a regular basis. Responses, however, may differ depending on the type of noxious stimulus (61,62). In the study by Jones and Derbyshire, the noxious stimulus was thermal heat applied to the back of the hand, whereas in our study, the noxious stimulus was a pressure cuff wrapped around the MCP joints. RA patients may be better able to cope with an experimental noxious stimulus applied to an area not typically affected by RA. In contrast, pressure on the MCP joints, which are actively inflamed due

to RA, may elicit maladaptive cognitive responses, resulting in the increases in rCBF in the MPFC and ACC observed in the current study.

Strengths of this study are inclusion of age- and sex-matched controls; detailed clinical data on pain, disease activity, and psychosocial factors; and use of the pASL technique. The pASL scan includes a 6-minute continuous stimulus that minimizes contributions from attentional, salience, and orienting responses.

The main limitations of our study are the small sample size and the absence of a higher-intensity pain stimulus that was universally painful in the control group. Due to the small sample size, our study may not have been powered to detect modest differences between RA patients and healthy, pain-free control subjects. Because the study design did not include a higher-intensity pain stimulus that was specifically constructed to be painful in the control subjects, nearly one-third of controls did not describe the high-intensity pain stimulus as being painful. Thus, the lack of differences in rCBF in the control group may reflect that the controls did not consider either the high-intensity or low-intensity stimulus to be significantly painful. As a result of these 2 limitations, ambiguity remains regarding the interpretation of our results. It is possible that the lack of significant group interaction effects in rCBF may be due to the small sample size, the lack of painful responses in the controls, or no differences in the way noxious pressure is processed centrally. In addition, this study is inherently limited by the assumption that data for acute experimental stimuli, even directed at the peripheral source of clinical pain as in our study, accurately reflect chronic pain processing. This assumption is universal to all neuroimaging studies that require an acute on/off stimulus, but it neglects the many nuances that differ between acute and chronic pain (63).

In conclusion, our results highlight the roles of the MFC in the sensation and regulation of pain in patients with RA. By identifying the CNS regions involved in the experience of pain, our study contributes important information regarding the pathophysiology of pain in systemic inflammatory conditions. In addition, this information may represent an early step toward the use of imaging markers to objectively assess pain in research studies. However, before imaging markers can be used in clinical trials to assess the efficacy of interventions to treat pain, further studies are necessary to evaluate the clinical utility of these markers and to determine the populations and scenarios in which imaging marker assessment is appropriate.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Lee 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. Lee, Edwards, Loggia.
Acquisition of data. Lee, Fine, Protsenko, Massarotti, Loggia.
Analysis and interpretation of data. Lee, Mawla, Napadow, Loggia.

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BRIEF REPORT

A Novel Method to Combine Assessment of Benefit and Harm: Outcome Measures in Rheumatology 3×3 Methodology Applied to Two Active Comparator Trials

Maarten Boers,[1] Jasvinder A. Singh,[2] Stacey S. Cofield,[3] S. Louis Bridges Jr.,[3] Larry W. Moreland,[4] James R. O'Dell,[5] Hongsheng Wu,[6] Sarah Leatherman,[6] and Jeffrey R. Curtis[3]

Objective. The Outcome Measures in Rheumatology (OMERACT) 3×3 method analyzes the occurrence of benefit and harm simultaneously at the individual patient level. We applied this method to 2 recent rheumatoid arthritis (RA) trial data sets.

Methods. The Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) and the Rheumatoid Arthritis Comparison of Active Therapies (RACAT) randomized trial outcomes for safety were defined according to OMERACT as having no adverse events (AEs), non-serious AEs, and serious AEs. Treatment efficacy was defined as good, moderate, or no response. A good treatment response without any AEs was labeled an unqualified success, and no treatment response but at least 1 AE was considered an unmitigated failure. The association between benefit and harm was assessed by chi-square or exact tests, as appropriate.

Results. In TEAR, 612 of 755 patients had response data at 48 weeks: 14% of patients experienced unqualified success and 9% had unmitigated failure, with no difference between the treatment arms. Treatment response and AE rates were not correlated. In RACAT, 309 of 353 patients had response data at 48 weeks: 6% of patients experienced unqualified success and 11% had unmitigated failure, with no differences between the treatment arms. Response and AE rates were negatively correlated. The frequency of AEs and serious AEs increased as response decreased (P = 0.008).

Conclusion. We found some evidence that clinical response may be reduced by the co-occurrence of AEs.

Introduction

Most clinical trial reports provide far more detailed benefit assessments than discussions of harms. Frequently, the expected benefit of the experimental treatment is expressed in a responder index, e.g., the proportion of rheumatoid arthritis (RA) patients experiencing relevant benefit (e.g., American College of Rheumatology criteria for 20% improvement [ACR20] or European League Against Rheumatism [EULAR] response criteria) (1,2). In contrast, adverse events (AEs) typically are counted and summarized as frequencies at the treatment group level. Differences between treatments in these outcomes are sometimes summarized both as the number of patients needed to treat or as the number needed to harm. However, the comparison of benefit and harm of interventions is therefore considered separately, leaving the reader unsure of how the interventions truly compare to each other.

The Outcome Measures in Rheumatology (OMERACT) initiative has suggested that trial reports can be enhanced by analyzing the occurrence of benefit and harm simultaneously, at the level of the individual patient rather than at the group treatment level (3). The underlying idea is that patients and physicians not only need to know what the chances of benefit and harm of a treatment are, but also whether these chances are correlated. In other words, the patients who are benefitting from the intervention could be the same patients who are more (or less) likely to experience harm. This approach has the potential ability to inform more

[1]Maarten Boers, MSc, MD, PhD: VU University Medical Center, Amsterdam, The Netherlands; [2]Jasvinder A. Singh, MD, MPH: University of Alabama at Birmingham and Birmingham VA Medical Center, Birmingham, and Mayo Clinic College of Medicine, Rochester, Minnesota; [3]Stacey S. Cofield, PhD, S. Louis Bridges Jr, MD, PhD, Jeffrey R. Curtis, MD, MS, MPH: University of Alabama at Birmingham; [4]Larry W. Moreland, MD: University of Pittsburgh, Pittsburgh, Pennsylvania; [5]James R. O'Dell, MD: University of Nebraska Medical Center, Omaha; [6]Hongsheng Wu, PhD, Sarah Leatherman, MA: Boston VA Medical Center, Boston, Massachusetts.

Address correspondence to Maarten Boers, MSc, MD, PhD, Professor of Clinical Epidemiology, Department of Epidemiology and Biostatistics, P.O. Box 7057 1007 MB Amsterdam, The Netherlands. E-mail: eb@vumc.nl.

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SIGNIFICANCE & INNOVATIONS

- Clinical trials mostly report on benefit, and the limited information on the occurrence of harm is not related to the benefit results.
- The Outcome Measures in Rheumatology 3×3 method analyzes the occurrence of benefit and harm simultaneously at the individual patient level.
- Application of this method to 2 recent trials in patients with rheumatoid arthritis showed some evidence that clinical response may be reduced by the co-occurrence of adverse events.

personalized care and improve shared decision-making, in that it can be conducted in important subgroups to understand the unique risk/benefit profile of interventions across heterogeneous patient phenotypes.

Patients and methods

The OMERACT method suggests creating 2 or 3 levels of benefit (e.g., good, moderate, or no response) and likewise 2 or 3 levels of harm (e.g., no AEs, non-serious AEs, and serious AEs [SAEs]). The trial outcome for each patient is expressed as a pair of values showing the level of both benefit and harm, and a contingency table (2×2 or 3×3) can be created. In the 3×3 table, patients achieving a good response without any AEs can be labeled as an unqualified success (4), and patients experiencing no response but at least 1 AE as an unmitigated failure. The 6- and 12-month data of 2 recent active comparator trials were reanalyzed according to this framework: the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial (5) and the Rheumatoid Arthritis Comparison of Active Therapies (RACAT) trial (6).

The TEAR trial used a factorial design and randomized 755 early RA patients to 1 of 4 treatments: 2 groups received immediate combination therapy of either methotrexate (MTX) plus etanercept or oral triple therapy with MTX, sulfasalazine, and hydroxychloroquine; and 2 groups initially received MTX monotherapy with a step-up to combination therapy at 24 weeks after insufficient response, based on the Disease Activity Score in 28 joints. In the primary study report, analysis at 6 but not at 12 months showed a better response in the immediate treatment groups compared to the delayed groups and no differences in safety between the 4 treatment groups.

The RACAT trial compared the addition of sulfasalazine and hydroxychloroquine or etanercept to MTX in the treatment of 353 RA patients who had an inadequate response to MTX. Patients were randomized to 1 of the 2 treatment strategies and were switched to the alternative strategy if they showed no clinical improvement after 24 weeks. At 24 and 48 weeks (primary analysis), triple therapy was noninferior to etanercept plus MTX.

For this post hoc analysis, initially 3 benefit/harm categories were made as described above, by applying the EULAR response criteria and examining AE reports for each patient. Patients dropping out prematurely for a patient- or investigator-reported reason of "side effects or any other medical issue" were assigned a code of AE even if such an event had not otherwise been explicitly reported. In addition, the data were further collapsed into 2×2 tables categorizing patients as experiencing harm according to 2 scenarios: harm = SAE or harm = any AE; and likewise, as experiencing benefit or no benefit according to 2 scenarios: benefit = good response or benefit = good or moderate response. We designed a new way to present these data: each cell of the 2×2 table also contains a color-coded bar with a length proportional to the percentage in that cell (Figure 1) . On the orange/blue (bottom left to top right) diagonal, one can see the balance between worst and best, and on the on the light grey/purple (top left to bottom right) diagonal, one can see the balance between the tradeoff categories, i.e., no benefit + no harm versus benefit + harm. The figure was designed in Microsoft PowerPoint and drawn by hand (using a line tool) where necessary. Colors were chosen to respect color blindness (7). The distributions were tested for significance by chi-square tests, without adjustment for multiple comparisons.

Results

TEAR trial. Of the 755 randomized patients, 693 had response data at 24 weeks and 617 at 48 weeks. In the 48-week results, 66% of patients had experienced a non-serious AE and 7% a serious AE (Figure 1, left top panel). Overall, 14% of patients experienced an unqualified success (EULAR good response and no AE) and 9% experienced an unmitigated failure (no EULAR response and either a non-serious AE or an SAE) (Figure 1). At 24 weeks, results were similar (data not shown). No clear pattern emerged to suggest that the occurrence of benefit and harm was correlated. In the 2×2 analyses, combining the counts of good and moderate responders increased the numbers of patients with unqualified success, as expected (24%), and combining those of moderate and nonresponse increased the numbers with unmitigated failure (36%). None of the statistical tests were significant, and none found differences in the distribution of benefits and harms across the 4 treatment groups (Figure 1, right top panel for 1 of the 2×2 analyses).

RACAT trial. Of the 353 randomized patients, 321 had response data at 24 weeks and 309 at 48 weeks. In the 48-week results, 73% of patients experienced a non-serious AE and 15% an SAE. Overall, 6% of patients experienced an unqualified success while 11% experienced an unmitigated failure. Benefit was negatively associated with harm: the frequency of AEs and SAEs

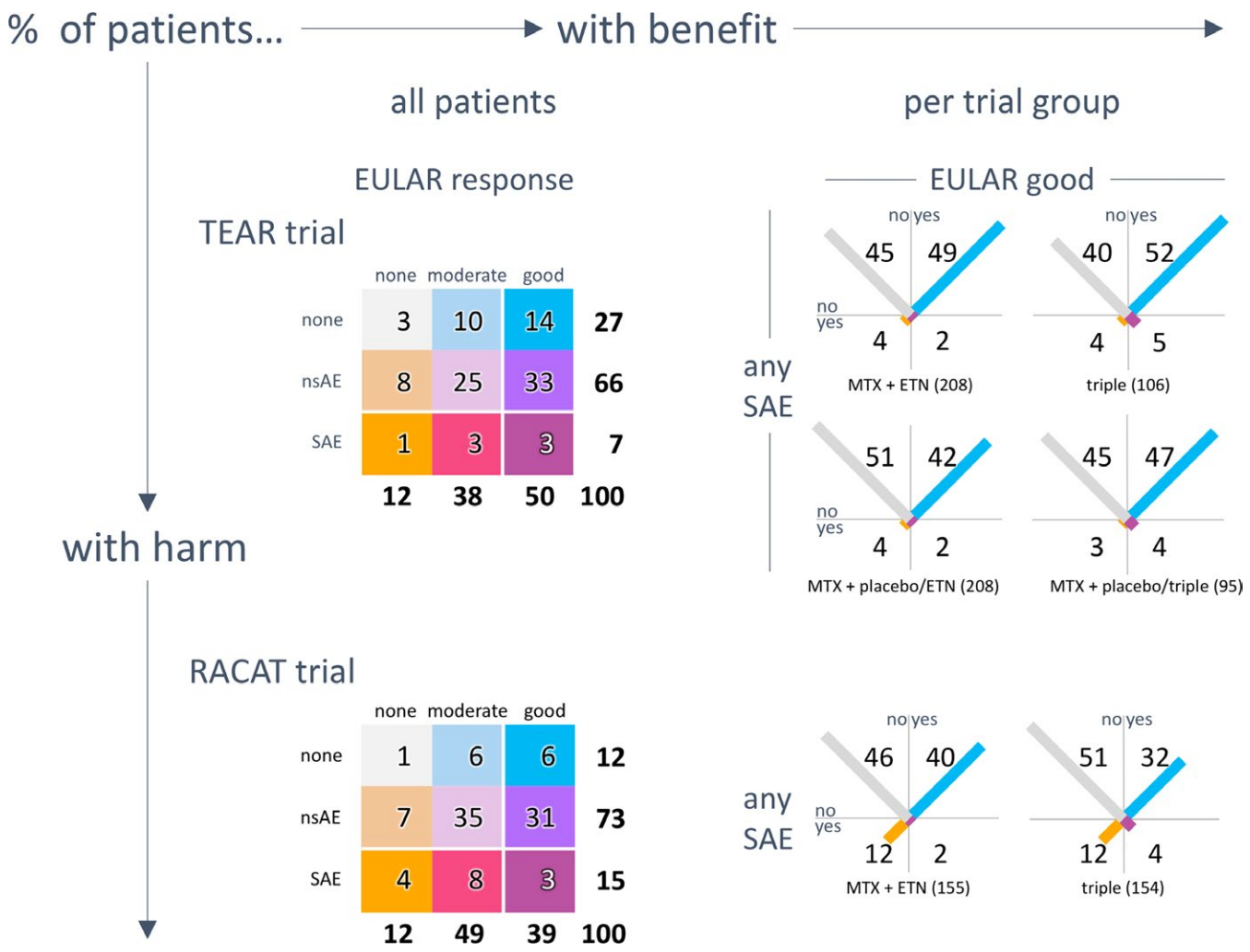

Figure 1. Results of the combined assessment of benefit and harm in 2 randomized trials. **Top**, Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial (617 evaluable patients). **Bottom**, Rheumatoid Arthritis Comparison of Active Therapies (RACAT) trial (309 evaluable patients). In each panel, benefit increases from left to right, and harm increases from top to bottom. In the panels on the left, results of treatment groups are pooled and categorized according to the combined occurrence of benefit and harm, each in 3 categories. Results are expressed as a percentage of the total group, corrected for rounding. White lines delineate the cutoffs for the 2×2 categorization in the right-hand panels. The panels on the right show the results (%) per treatment group, with the combined occurrence of benefit and harm, each in 2 categories: for benefit, the European League Against Rheumatism (EULAR) good response (yes/no); for harm, the occurrence of any serious adverse event (SAE; yes/no). Length of the diagonal bar in each cell is proportional to the percentage of patients in that cell. The orange/blue (bottom left to top right) diagonal shows the balance between worst and best. The light grey/purple (top left to bottom right) diagonal shows the balance between 2 types of tradeoff: no benefit + no harm, and benefit + harm. nsAE = non-serious adverse event; MTX = methotrexate; ETN = etanercept; triple = MTX, sulfasalazine, hydroxychloroquine.

increased as response decreased (P = 0.008) (Figure 1, left bottom panel). In the 2×2 table analysis, this association was significant in the scenarios that contrasted SAEs with no SAE (Figure 1, right bottom panel). Results for 24 weeks were similar, but the association between benefit and harm was not significant (data not shown).

Discussion

Reporting the occurrence of benefit and harm together is a new way to report trial results and makes the tradeoffs involved in choosing a particular therapy more explicit. This method of reporting would aid in discussions with patients and provide for further shared decision-making. We studied 2 active comparator trials, and in RACAT the occurrence of treatment benefit was associated with a lower occurrence of harm, regardless of treatment allocation. In addition, RACAT clearly had more patients with AEs, impacting the proportion of patients with an unqualified success.

This analysis method has limitations and should be regarded as complementary to, not a replacement of, current analysis and reporting strategies. One limitation is inherent in the way AEs are assessed and reported; unlike benefit, the AE experience

of a patient is not easily summarized. The 3 categories of harm proposed in this system are a simplification, and the largest category, non-serious AEs, is very broad. Even with this simplification, presenting a 2-arm trial with two 3×3 tables side by side requires the reader to compare 2×9 numbers, a difficult task. This comparison can be simplified by reporting the best and worst outcomes (unqualified success and unmitigated failure), by collapsing the results into 2×2 tables and adding a graphical representation. Graphs may ease interpretation through visual pattern recognition. The downside, of course, is further simplification and loss of accuracy, e.g., should we combine all AEs into 1 category, or should we contrast SAEs versus no SAE? In addition, our analysis strategy does not improve on well-known limitations of current AE definitions, the consideration of non-serious side-effects that can potentially limit adherence to treatment, as well as the likelihood of a relationship to treatment. In the case of the RACAT data set, the statistical analysis result depended on the definition of the categories.

An advantage of the method is that it is flexible, i.e., neutral to the definition of benefit and harm, to the preference weighting of harm (e.g., to incorporate the patient perspective), and to the attribution of harm to treatment. Such choices should be made in the protocol phase and the results interpreted accordingly. For example, some mild AEs may not be considered harm at all, and the definition of SAE is mandated by regulatory authorities, sometimes resulting in misclassification from the clinician's point of view. Some AEs are not grouped under the category of SAE, even though they are reported as severe in intensity, and some are categorized as SAE when the clinician reports them as moderate or mild in severity.

The finding of an association between less benefit and more harm in RACAT is unexpected and novel. Given its occurrence in only 1 of 4 comparisons (2 time points in 2 trials) the finding may also be the play of chance. The expectation would be to find a positive association, i.e., more benefit but also more harm, though perhaps this association requires a stronger contrast between therapies, as in a placebo-controlled trial. In addition, the treatments in TEAR and RACAT are known to be well tolerated.

In conclusion, we have applied the OMERACT methodology of combined reporting of benefit and harm to 2 active comparator trials in RA and suggested a new graphical summary. As a complement to existing methods, this approach is likely to provide a useful framework for simultaneously considering the risks and benefits of treatments at a patient level, both overall and for important patient subgroups such as older individuals and other patients with high comorbidity burdens, who are more likely to experience harms.

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. Boers 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. Boers.

Acquisition of data. Singh, Bridges, Moreland, O'Dell, Curtis.

Analysis and interpretation of data. Boers, Singh, Cofield, Wu, Leatherman, Curtis.

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Patient Concerns and Perceptions Regarding Biologic Therapies in Ankylosing Spondylitis: Insights From a Large-Scale Survey of Social Media Platforms

Eldin Dzubur,[1] Carine Khalil,[2] Christopher V. Almario,[2] Benjamin Noah,[2] Deeba Minhas,[1] Mariko Ishimori,[1] Corey Arnold,[3] Yujin Park,[4] Jonathan Kay,[5] Michael H. Weisman,[1] and Brennan M. R. Spiegel[2]

Objective. Few studies have examined ankylosing spondylitis (AS) patients' concerns about and perceptions of biologic therapies, apart from traditional surveys. In this study, we used social media data to examine the knowledge, attitudes, and beliefs of AS patients regarding biologic therapies.

Methods. We collected posts published on 601 social media sites between January 1, 2016 and April 26, 2017. In each post, both an AS keyword and a biologic were mentioned. To explore themes within the collection of posts in an unsupervised manner, a latent Dirichlet allocation topic model was fit to the data set. Each discovered topic was represented as a discrete distribution over the words in the collection, similar to a word cloud. The topics were manually reviewed to identify themes, which were confirmed using thematic data analysis.

Results. We examined 27,416 social media posts and identified 112 themes. The majority of themes (n = 67 [60%]) focused on discussions related to AS treatment. Other themes, including the psychological impact of AS, reporting of medical literature, and AS disease consequences, accounted for the remaining 40% (n = 45). In discussions regarding AS treatment, most topics involved biologics, and most subthemes involved side effects (e.g., fatigue, allergic reactions), biologic treatment attributes (e.g., dosing, frequency), and concerns about use of biologics (e.g., increased cancer risk). Additional implicit patient needs (e.g., support) were identified using qualitative analyses.

Conclusion. Social media revealed a dynamic range of themes governing AS patients' experience with and choice of biologic agents. The complexity of selecting biologics from among many such agents and navigating their risk/benefit profiles suggests the merit of creating online tools tailored to support patients' decision-making with regard to biologic therapies for AS.

INTRODUCTION

Conventional therapies used to treat ankylosing spondylitis (AS), such as nonsteroidal antiinflammatory drugs (NSAIDs), commonly fail to provide good results in patients with moderate to severe AS. Such lack of efficacy along with nonresponse to and dependence on glucocorticoids have spawned increased development of biologic therapies that neutralize proinflammatory cytokines. Biologic therapies attempt to supersede standard management of symptoms by preventing the long-term sequelae of AS (1). Over the past few decades, many new medications for treating AS have come on the market, and several promising "pipeline" therapies are being evaluated in various phases of clinical investigation. For example, tumor necrosis factor (TNF) inhibitors have been shown to effectively reduce symptoms of AS and improve spinal mobility (2,3). More recently, a biologic targeting interleukin-17A has also been shown to be effective and has been approved for use in patients with AS (4).

However, despite the benefits of biologic therapy, some of these agents are associated with important side effects, including potentially increasing the risk for serious infections, cancer, and immunologic reactions, among others. Considering the complex risk/

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[1]Eldin Dzubur, PhD, Deeba Minhas, MD, Mariko Ishimori, MD, Michael H. Weisman, MD: Cedars-Sinai Medical Center, Los Angeles, California; [2]Carine Khalil, PhD, Christopher V. Almario, MD, MSHPM, Benjamin Noah, BS, Brennan M. R. Spiegel, MD, MSHS: Cedars-Sinai Medical Center and Cedars-Sinai Center for Outcomes Research and Education, Los Angeles, California; [3]Corey Arnold, PhD: Medical Imaging Informatics, University of California, Los Angeles; [4]Yujin Park, PharmD: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; [5]Jonathan Kay, MD: University of Massachusetts Memorial Medical Center and University of Massachusetts Medical School, Worcester.

Address correspondence to Brennan M. R. Spiegel, MD, MSHS, Cedars-Sinai Health System, 116 North Robertson Boulevard, 8th Floor, Los Angeles, CA 90048. E-mail: Brennan.Spiegel@cshs.org.

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SIGNIFICANCE & INNOVATIONS

- In this study, we used innovative social netnography techniques to reveal ankylosing spondylitis patients' concerns about and perceptions regarding biologic therapies.
- Patients had a wide variety of preferences for side effects and treatment effects throughout the online discussions, suggesting that clinical decision-making tools may be useful to help patients identify biologic therapies that meet their treatment and lifestyle needs.
- Patients' uncertainty about medications and information-seeking, as identified using the mixed-methods approach, suggests the need for a greater presence of informed stakeholders (i.e., clinicians, patient advocacy societies, professional societies) on social media.

benefit profiles of the different biologics along with the increasing number of clinically available therapies for patients with AS, it is becoming more difficult for patients to make informed decisions when choosing from among the various options. As a result, ~40–60% of patients with AS have never been treated with biologics (5,6).

Thus far, few attempts have been made to examine patients' concerns about and perceptions of these therapies outside of traditional surveys and cognitive interviews (7,8). To address this gap, we used a novel research method known as social netnography—a type of ethnography used to analyze the free behavior of individuals on the internet (9). Specifically, in this study, we used social media data to examine AS patients' concerns about and perceptions regarding biologic therapies, using a mixed-methods approach. In contrast to traditional qualitative methods such as focus groups and interviews, social netnography allows for a wide sampling pattern and provides a contextually based study of unfiltered, free-flowing conversations that may more reliably be generalized to the AS population at large (10).

MATERIALS AND METHODS

Data collection. We collaborated with researchers from Treato (www.treato.com), a social media data mining service, to extract relevant social media and e-forum data. Treato is used to automatically collect, index, and analyze patient and caregiver content from >10,000 US-based and international-based websites, forums, blogs, and communities such as Spondylitis.org, KickAS.org, Facebook.com, and Twitter.com, among many others. Posts are indexed using a lexicon of >100,000 medical terms (based on the Unified Medical Language System), and a built-for-purpose "patient language" dictionary manually created by Treato researchers (11). The researchers then use proprietary natural language processing classification algorithms to index posts with this lexicon, which results in an easily searched data set that can be analyzed in aggregate (11).

Treato researchers extracted relevant posts from their database using a set of keywords validated by internet domain experts on the research team. All posts were written in English and published online between January 1, 2006 and April 26, 2017. The keyword search list included 2 categories: AS keywords and biologic medications. The AS keywords category included names, abbreviations, and common misspellings for AS. We also identified posts with phrases that contained "AS" (e.g., "diagnosed with AS," "treats my AS") as well as those published on AS-dedicated sites (e.g., Spondylitis.org, KickAS.org) or Facebook groups. The biologic medications category included brand and generic names for biologics and biosimilars used to treat AS. Table 1 shows a complete list of the keywords used as well as the data extraction strategy. Posts were selected for analysis if they included an AS word, phrase, site, or group and included a keyword from the biologic medications category (Boolean search for AS keyword AND biologic).

Quantitative methods. To explore themes within the collection in an unsupervised manner, a latent Dirichlet allocation (LDA) topic model was fit to the data set. Under LDA, each discovered topic is represented as a discrete distribution over the words in the collection, which may be thought of as a word cloud (i.e., words with increased representation in the collection are presented in a larger font size). Topics were manually examined by an expert panel of medical professionals and researchers and grouped into categories and subcategories based on keyword content. The grouping was confirmed by using a sample of posts most representative of each topic. Each primary category consisted of at least 1 subcategory identified as a specific theme within the topic.

LDA alpha hyperparameters were estimated and indicated the relative sparsity of data such that lower values indicate topics occurring less often throughout the data. Topics sharing common primary categories were aggregated, and the sums of the alpha hyperparameters were used as an approximate measure of the importance of a topic (e.g., sparsity) relative to the number of times the topic was identified. Topics for which the cumulative sparsity parameter was >1.0 were separated into the next lowest subcategory; the process was repeated until all categories had sparsity parameters of <1.0.

Qualitative methods. In addition to our quantitative analysis, we used a qualitative approach to understand, in depth, AS patients' perceptions regarding biologic therapies. The thematic

Table 1. Full list of keywords and data extraction strategy used by Treato researchers

Keyword	Data extraction strategy
Ankylosing spondylitis	"ankylosing spondylitis," "ankylosing," "ankylosign spondylitis," "ankylosingspondylitis," ankylsingspondlytis," "ank," "spond," "spondy," "ankspond," "ankspondylitis," ankylosingspondy," "ankylosingspond," "spondyloarthritis," "spondylithropathy," "spondylitis," "spondyliitis," spondyliti," "rheumatoid spondylitis," "sacroiliitis," "sacroilitis," "sacroiilitis," "axial spa," "axial," "axspa," "hlab27," "halb27," "b27," "enthesitis," "enthsitis," "dactylitis," "dactlitis," "dactyliitis," spondyloarthropathies," "spondyl arthropathies," "spondyloarthrosis," "spondyloarthropathy," "spondyl arthropathy"
OR phrases containing "AS"	"diagnosed with AS," "diagnosis of AS," "dx with AS," "dxd with AS," "dx'd with AS," "dx d with AS," "dxd with AS," "treat my AS," "treats my AS," "treating my AS," "treated my AS," "control my AS," "controls my AS," "controlling my AS," "controlled my AS," "I suffer from AS," "approved for AS," "I have AS," "patients with AS," "patient with AS"
OR ankylosing spondylitis websites	spondylitis.org kickas.org
OR Facebook groups	Spondylitis Association of America Ankylosing Spondylitis Awareness Spondyloarthropathy (Spondylitis, Iritis, Arthritis) Ankylosing Spondylitis-Invisible Illnesses
Biologic medications	"biologic," "biologics," "biologicals," "biological drugs," "biological drug," "tnf inhibitor," "tnf inhibitors," "TNFs," "TNF's," "Tumor Necrosis Factor Inhibiting Agents," "TNF blocker," "TNF drugs," "TNF drug," "DMARD TNF," "TNF alpha blocker," "TNF blockers," "TNF alpha blockers," "TNF antagonist," "TNF antagonists," "TNF antibody," "TNF antibodies," "tnfinihibitor," "Humira," "humra," "Humaria," Humera," "humria," "hmira," "adalimumab," adlimumab," "adalimuamb," "Enbrel," "Enbel," "Enbrels," "Embrel," "embril," "Enbral," "Enbrell," "enbril," "Enebrel," "ennbrel," "enbrl," "etanercept," "etenercept," "etancercept," "Simponi," "smponi," "simpony," "symponi," "symponi aria," "golimumab," "galimumab," "glimumab," "Cimzia," "cmzia," "simzia," "cimza," "certolizumab," "certolizumabpego," "Remicade," "Remicad," "remicaide," "remcaide," "Remicaid," "infliximab," "inflixmab," "Inflectra," "adalimumabatto," "attoadalimumab," "erelzi," "Amjevita," "Cosentyx," "cosentix," "cosintyx," "Secukinumab," "AIN 457," "AIN457," "il-17a," "il17a," "il17," "biosimilar," "biosimilars," "bio similar," "bio similars," biogeneric," "biogenerics," "bio generic," "generic versions of a biological," "generic version of biological," "GENERIC BIOLOGICal," "adalimumabatto," "attoadalimumab"

data analysis assists in understanding meanings and interpretations given to AS treatment–a prevalent category that was identified in the first round of our quantitative analysis.

Social media posts that focused on AS treatment and biologics were analyzed based on an inductive open coding approach. We assigned a reader (BN) to examine social media posts multiple times before the coding process. Throughout the reading, data texts were divided into distinctive meaning units or codes. Each unit or code provides sufficient information for the reader even without the context. Thus, numerous codes were defined and illustrated by text fragments. As different inductive codes emerged, they were regrouped into defined categories with more specific meanings. Additionally, these categories were iteratively revised and refined throughout the analysis process.

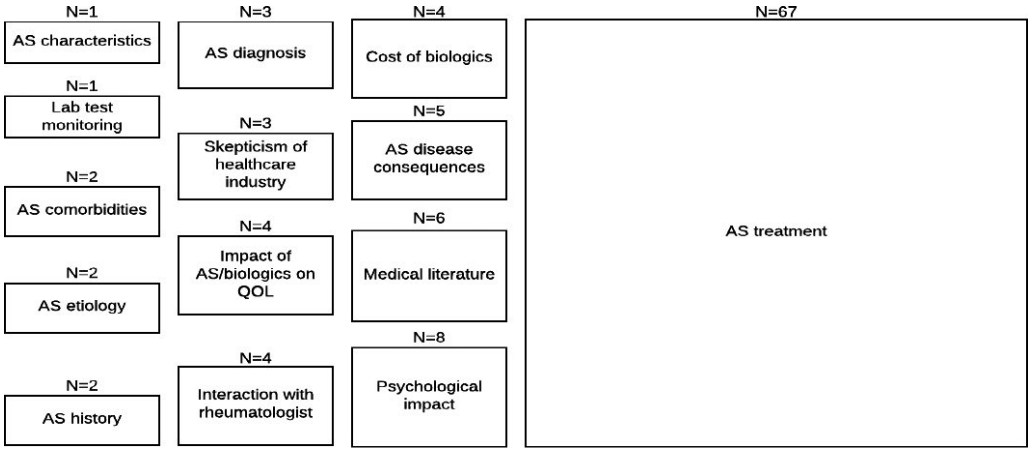

Figure 1. Main patient discussion themes identified by topic modeling. The sizes of the individual boxes represent the relative prevalence of the theme. AS = ankylosing spondylitis; QoL = quality of life.

While some categories were combined, others were linked under a superordinate category when the meanings were similar. This approach reduced redundancy among the categories, similar to the data analysis approach. Therefore, categories were conceptualized onto broader themes, and links between them were created. The thematic data analysis was presented with verbatim quotes and may contain some spelling or grammatical errors.

This study was reviewed by the Cedars-Sinai Medical Center Institutional Review Board and was deemed to be exempt from review, because it did not meet the definition of "human subject research" under Department of Health and Human Services or US Food and Drug Administration regulations.

RESULTS

Main themes identified by topic modeling in the quantitative analysis. We examined 27,416 social media posts made between January 1, 2006 and April 26, 2017 that focused on AS and biologics, and we identified 112 main themes (Figure 1). The posts were made by 13,262 users, resulting in a median of 1 post per user, with 1,210 users having more >1 post, and 27 of those users having >100 posts. Among individuals who posted, only 1 had >1,000 posts. The majority of themes (60% [67 of 112]) focused on discussions relating to AS treatment. Other main themes including the psychological impact of AS, reporting of medical literature, and AS disease consequences, among others, accounted for the remaining 40% of themes (45 of 112). Figure 2 shows the main themes within the AS treatment category, and most topics (61% [41 of 67]) involved discussions about pharmacologic treatment (for biologics, n = 36; for nonbiologic options, n = 5). Within the biologics category, 78% (28 of 36) of the identified subthemes centered on side effects related to use of these agents (e.g., fatigue, allergic reactions), biologic attributes (e.g., dosing, frequency), and concerns about use of these agents (e.g., increased cancer risk, reproductive health concerns).

Results of the quantitative analysis. Because each post can contain multiple themes, we conducted a topic sparsity assessment. After we adjusted for topic sparsity, we observed that 49% of the text consisted of content concerning the following 6 topics: 1) medication uncertainty, 2) psychosocial impact, 3) duration/time of biologic treatment, 4) interactions with rheumatologists, 5) attributes of biologics, and 6) personal experience with pharmacologic treatment of AS. The remaining 51% of the text consisted of content related to the remaining 106 themes.

Results of the qualitative analysis. In our qualitative analysis, we identified 8 inductive categorical groups that were identified as being related to AS treatments and biologics (Figure 3): 1, medication uncertainty/lack of information, 2) lack of trust in physician's decisions, 3) psychosocial challenges, 4) patient worries, 5) perceived biologic treatment effects, 6) medicine substitutions, 7) treatment determinants, and 8) seeking alternative treatments.

Although most of the identified topics were similar to those identified using topic modeling, an additional important category group emerged in our open coding analysis (patient needs) that was not identified in the quantitative analysis. The needs of patients were often expressed explicitly as advice from the community across domains such as information-seeking, support-seeking, and self-management (e.g., "I was just searching for support chats"; "you should discuss biologics with your rheumy"; "If you are still able to control your symptoms at this point, do

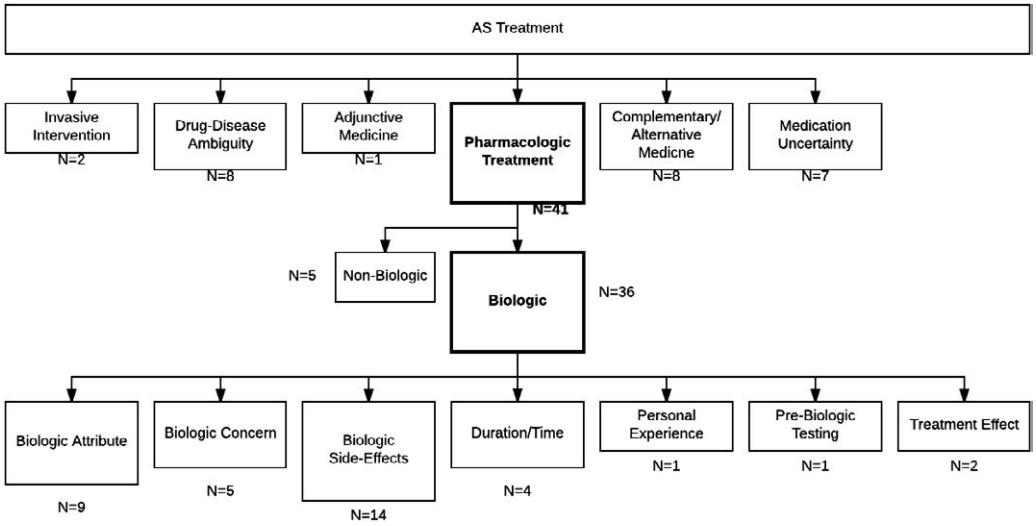

Figure 2. Main themes within the ankylosing spondylitis (AS) treatment category identified by topic modeling. "Pharmacologic Treatment" and "Biologic" emerged as predominant subthemes. The sizes of the individual boxes represent the relative prevalence of the theme.

not rush to start a strong medicine like [Biologic X]"). More often, however, such information could be derived from discussions in the AS patient community about medication uncertainty and determining treatment.

The thematic data analysis revealed 3 primary challenges faced by patients with AS in their everyday lives in the domains of understanding a complex treatment regimen, communicating with their provider, and coping with intrapersonal and interpersonal struggles. First, a broad theme of uncertainty regarding the use of medication was expressed primarily as a lack of information about a variety of topics related to biologics. Patients often lacked information regarding biologic treatment options (e.g., "I don't know much about all the options available"). Other patients reported that they were not familiar with medication protocols such as dosage and length of treatment (e.g., "Should I take [Biologic X] once a week instead of every other week?"). A lack of familiarity with medication side effects was reported, especially among individuals who had not yet

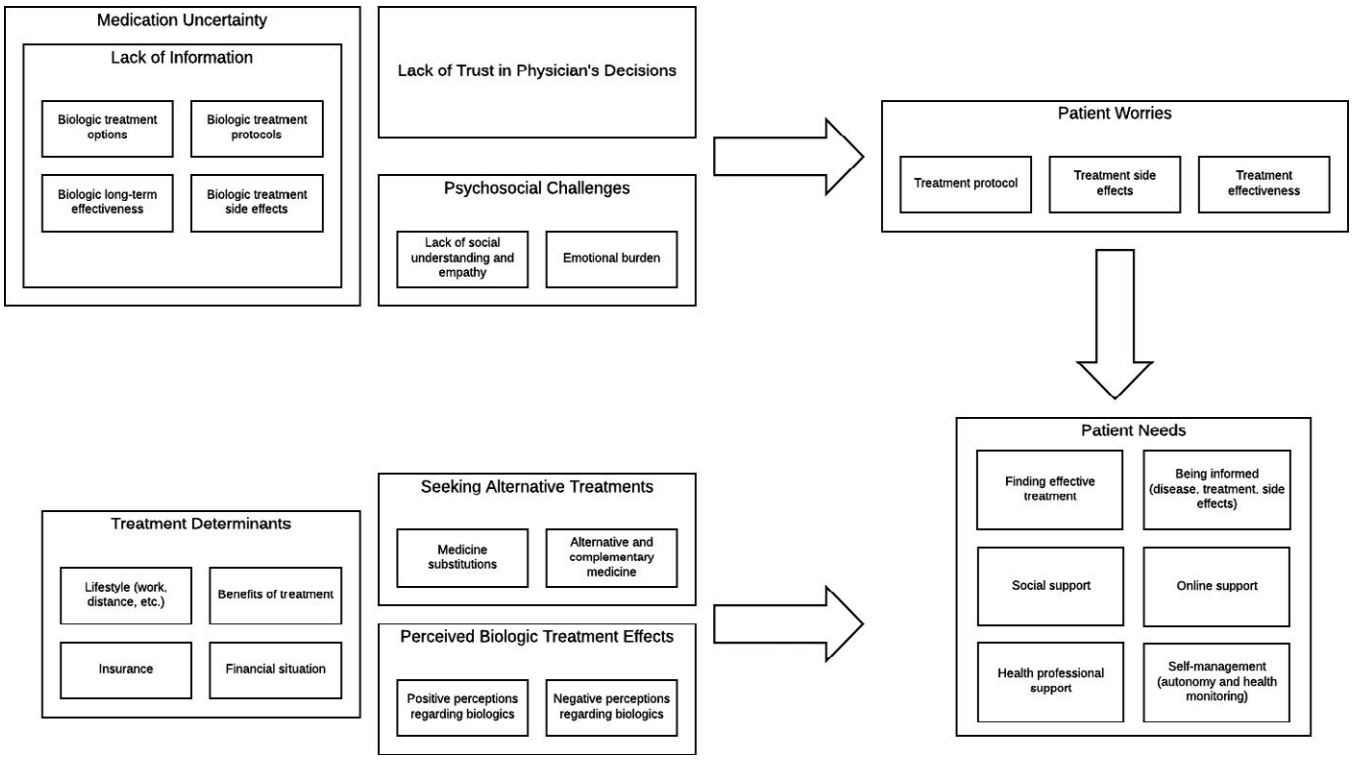

Figure 3. Thematic representation of data analysis based on predominant themes identified from the topic models.

started treatment (e.g., "I am just scared about injecting my body with something I am unsure about.. I am unsure what to do"). Among individuals who had started treatment with biologics, apprehension regarding the long-term effectiveness of these agents was prevalent (e.g., "Have any of you found that all of the biologics just don't last long enough?").

Second, patients expressed distrust in their physicians' decisions (e.g., "How would my rheumy know what biologic would work on me?"). Such concerns often escalated to eliciting medical advice from online communities (e.g., "Do you think I should try switching my medicine?"). Third, psychological and social challenges were expressed as the inability of friends and family to empathize with the symptoms of AS, even in the presence of support (e.g., "I have amazing support from my family but really no one understands unless they can spend a day in [my] body").

Patients reported internal struggles, often describing depressive symptoms and, in some cases, suicidality (e.g., "I am losing the will to live with AS"). Given the lack of information about biologics, trust in physicians, and empathy from others, patients with AS find themselves online seeking information, advice, and support from their peers in similar situations to assuage their concerns. Patients expressed worries about protocols (e.g., "I understand from previous discussions that [Biologic X] has more room for dosage customization"), side effects (e.g., "I worry that I may trade 2 bad days for a week or 2"), and the effectiveness of treatments (e.g., "I notice a lot of folks switch biologics due to losing effectiveness").

Additional thematic data analysis also revealed discussions regarding determining a course of treatment that balances a patient's lifestyle with his or her desire to be pain-free. Some patients expressed efficacy of biologics (e.g., "I am on [Biologic X]… so far it has helped out lots able to work again"); however numerous posts featured dissatisfaction due to poor efficacy and other factors (e.g., "Biologics never helped and made me sick"). Other treatment determinants included impact on patient lifestyle (e.g., "One reason I choose [Biologic X] for the once a month dosing is travel") and financial and insurance issues (e.g., "There is a process to go through first to make sure that the cheaper drugs are not effective"). As alternatives to treatment with biologics, pharmacologic treatments such as glucocorticoids, narcotics, and neuromuscular medicine for relieving pain were discussed. The discussions concerning alternatives to biologics also highlighted the role of complementary and alternative medicine such as chiropractor visits and acupuncture in helping patients with AS. In addition, the analysis revealed that alternative practices and physical activities such as ultrasound, exercising, and using ice and heat were perceived as beneficial in patients with AS.

DISCUSSION

Social netnography analysis revealed a wide range of themes governing the knowledge, attitudes, and beliefs of AS patients regarding biologics. Using more than 27,000 posts made by patients with AS on social media and health-related websites, we identified and grouped common themes among related posts, quantitatively examined the prevalence of each theme, and qualitatively generated themes with sample posts using thematic data analysis. Our approach leveraged data science and human insights to explore a large repository of social media posts both thoroughly and efficiently.

To our knowledge, this is the first study that used a mixed-methods approach and large-scale social media data to examine concerns and perceptions regarding biologic therapies among patients with AS. The study provides novel insights into patient experiences with biologics and identifies actionable needs that may improve patients' quality of life. The findings also highlight the distinct yet related contributions of topic modeling and thematic data analysis to examining health-related social media posts. Although quantitative approaches identified a greater variety of topics and more subcategories, they did not provide relational information between posts. In contrast, qualitative approaches were limited in the number of identified categories but integrated each topic as part of a larger relational model. Moreover, qualitative approaches identified patient needs, an implicit category with high utility due to its actionable subtopics.

As expected, topic modeling showed that patients predominantly discussed biologics as treatment for their AS, often posting about and seeking information concerning side effects and other personal experiences with biologics. Topics derived from discussions about biologics indicate that these discussions may refer to attributes of biologics that vary from patient to patient based on preferences. For instance, some patients may be able to tolerate certain side effects if treatment efficacy is increased and dosing schedules are more convenient. Conversely, other patients may want to avoid side effects at all costs, even at the expense of reduced efficacy and less convenient dosing regimens. These findings suggest that conjoint analysis, a survey methodology that is often used in market research to determine consumer preferences for products, may be adapted as a support tool for patient decision-making. In our prior research, we used conjoint analysis to examine how patients with inflammatory bowel disease (IBD) approached decision-making regarding biologic treatment, and how they balanced efficacy, side effect profiles, and mode of administration, among other attributes (12).

In the aforementioned study, we observed that the decision-making process in terms of biologic treatment was highly personalized, and that demographic and disease characteristics poorly predicted the preferences of individual patients. Because of this finding, we used the conjoint analysis developed and tested in that study to support an online decision aid called "IBD&me" (www.ibdandme.org). This online decision aid uses conjoint analysis to quantify and rank the attributes of biologics that drive an individual pa-

tient's decision-making preferences, which may help improve shared decision-making between the patient and clinician and optimize selection of a biologic in a more personalized and structured manner. The same highly individualized approach to selecting a biologic therapy in patients with IBD may also be seen in those with AS, but that possibility must be formally tested and is the subject of our future research.

In our analyses, we also observed that discussions regarding medication uncertainty were highly prevalent in the examined posts. Moreover, we discovered that many individuals expressed a lack of trust in their physicians' treatment recommendations and even turned to their online peers with questions and to seek validation. However, the quality and accuracy of AS information obtained through social media and other online forums are largely unknown. In studies of IBD, investigators noted that the quality of IBD websites varied widely, with many being too difficult to comprehend or contained out-of-date information (13–17). The same observation is likely to apply to AS-focused social media sites and e-forums. Because the number of individuals who go online seeking AS-specific information will only continue to grow (18), informed stakeholders (e.g., health care providers, patient advocacy societies, professional societies) should increase their presence on social media to improve the quality and accuracy of online AS-related and biologics-related information.

Results of previous studies examining patients' experiences with biologics were consistent with the results of our study. For instance, lack of information, especially about biologic treatment, was identified in a similar study among Italian patients with rheumatoid arthritis (19). Even though nearly all patients in that study reported satisfaction with disease-specific information, only approximately one-third of patients reported satisfaction with treatment information, indicating they would turn to other sources such as the internet to meet their needs. More importantly, a study using internet-based surveys among patients with chronic inflammatory rheumatic diseases demonstrated that treatment history, negative beliefs about treatment, and lack of perceived medical and social support were 3 determinants of self-discontinuation that were also identified in our analyses. Additionally, the same study showed that pain and self-administration of injections predicted discontinuation, which were specific examples of treatment side effects and treatment protocol, respectively (20). Furthermore, a study in patients with inflammatory arthritis showed that patients were significantly influenced by their social support network with respect to treatment decision-making related to biologics, reflecting our findings regarding the needs of patients to establish social support and an online support (8).

Our study has important limitations. First, the study may be limited in generalizability due to the nature of social media posts as a platform in which some persons who post may be responsible for a relatively large share of the discussions. Nonetheless, the posts obtained for this study were made by >13,000 users, included a highly diverse number of posters, and was not dominated by a few individuals. Second, the findings of the study can be generalized only to patients with AS who use social media. Although we do not have a true estimate of this distribution, ~88% of individuals younger than age 30 years and 80% of those younger than age 49 years use social media (21). Therefore, the use of social media as a source of data could be especially relevant for newly diagnosed patients, because disease onset usually occurs before age 30 years and rarely occurs after age of 40 years (22). Third, given that the inclusion criteria for posts required some mention of a biologic, discussions related to biologics were overrepresented and may not be generalizable to patients who choose to treat AS using nonbiologic options. Finally, there may have been patient misclassification, because we did not confirm AS diagnoses or have access to linked International Classification of Diseases, Tenth Revision codes. However, many previous studies evaluating the reliability of self-reported diagnoses of chronic diseases have shown high validity of such self-reports (23–28). Furthermore, AS is a specific diagnosis made by health care providers, and our study focused specifically on biologic therapies used in AS.

In summary, an investigation of social media revealed a dynamic range of themes governing AS patients' experience with and choice of biologics. The findings in this study can help researchers and clinicians anticipate the needs of patients with AS as well as provide insight into thoughts and concerns some patients may have throughout the course of their treatment. Moreover, these findings highlight the complexity that AS patients face when selecting among biologic treatment options. The increasing number of biologic therapies available to patients with AS indicates that further research and development of online decision-making tools that support patients in selecting a therapy that fits their treatment needs and lifestyles are warranted.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Spiegel 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. Almario, Arnold, Park, Spiegel.
Acquisition of data. Dzubur, Noah, Arnold.
Analysis and interpretation of data. Dzubur, Khalil, Almario, Noah, Minhas, Ishimori, Arnold, Park, Kay, Weisman.

ROLE OF THE STUDY SPONSOR

Novartis approved the final study design as drafted by the investigators. Novartis was not involved in data collection, data analysis, interpretation of data, and editing of the manuscript. Yujin Park, PharmD, funded by Novartis, provided assistance with interpretation of the data, editing of the manuscript, and approved the contents of the submitted manuscript along with other coauthors. Publication of the article was not contingent upon approval by Novartis.

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ARP Announcements

Association of Rheumatology Professionals
2200 Lake Boulevard NE, Atlanta, Georgia 30319
www.rheumatology.org

ACR/ARP Annual Meeting

November 8–13, 2019, Atlanta

New Division Name

Rheumatology is truly a people specialty: We often develop lifelong relationships with our patients as well as our colleagues. We increasingly recognize that providing the best rheumatologic care requires a team effort. The collegial nature of our specialty is reflected in the ACR's mission statement: To empower rheumatology professionals to excel in their specialty.

In keeping with this mission, we are pleased to announce that our health professionals' membership division is changing its name to Association of Rheumatology Professionals (ARP). This name change highlights the dedication of the ACR to serve the entire rheumatology community. It also reflects our broadened base of interprofessional members (administrators, advanced practice nurses, health educators, nurses, occupational therapists, pharmacists, physical therapists, physician assistants, research teams, and more).

The name is new, but our commitment and promise remain the same: We are here for you, so you can be there for your patients.

ARP Membership

The Association of Rheumatology Professionals (ARP), a division of the American College of Rheumatology, appreciates your continued membership and looks forward to serving you another year. Membership costs range from $30 to $140. ARP welcomes nurse practitioners, nurses, physician assistants, office staff, researchers, physical therapists, occupational therapists, assistants, and students. Student membership is complimentary; the Annual Meeting registration fee is waived for students who submit the required student verification letter. For information, go to www.rheumatology.org and select "Membership" or call 404-633-3777 and ask for an ARP staff member.

ACR Open Rheumatology Accepting Submissions

The American College of Rheumatology will be publishing the first issue of its third official journal, *ACR Open Rheumatology (ACROR)*, in early 2019. Editors-in-Chief Drs. Patricia P. Katz and Edward H. Yelin, and Clinical and Basic Science Deputy Editors Drs. David I. Daikh and Bruce N. Cronstein, will be heading *ACROR*'s editorial team.

ACROR will publish manuscripts describing potentially important findings of rigorously conducted studies in all aspects of rheumatology. As an open access journal, immediate access to full content of *ACROR* will be available to all readers. The electronic-only format of the journal, as well as other aspects of the review and production processes, will allow for faster review and publication, and liberal sharing of articles. The projected article publication fee (APC) for *ACROR* will be $2,500 with a discounted rate of $2,000 for articles in which the first or corresponding author is an ACR/ARP member. In addition, there will be waivers of the APC for all articles submitted through March 31, 2019.

New for 2019: Education for Rheumatology Professionals

Whether you are new to a rheumatology practice or just need a rheumatology refresher, kick off 2019 with high-quality education for the entire interprofessional team. All 19 Advanced Rheumatology Course activities have been updated with all-new interactive content, including mini-quizzes. You can also register for 11 brand new Advanced eBytes, which are complimentary to ARP members. For information on pricing, credits hours, and registration go to www.rheumatology.org, click the drop down box "I AM A" next to the Membership tab and select "Health Professional Education."