ARP Announcements

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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.

New ACR Journal Twitter Account (@ACR_Journals) and Social Media Editor

The ACR journals are heightening our focus on social media, to benefit authors and readers. Among our first activities is the introduction of an official ACR Journals Twitter account: @ACR_Journals. Followers will enjoy special features and the opportunity to engage with authors and other fellow professionals about studies published in *Arthritis Care & Research, Arthritis & Rheumatology,* and *ACR Open Rheumatology*. Authors of published articles will have the opportunity to use @ACR_Journals to share their work and engage in dialogue with others interested in the research. The journals welcome Dr. Paul Sufka of Minneapolis as our first Social Media Editor.

Submissions Invited for 2022 Themed Issue

Submissions are invited for the 2022 Themed Issue of *Arthritis Care & Research*: Rehabilitation Sciences and the Rheumatic Diseases.

Arthritis Care & Research is soliciting manuscripts for a themed issue addressing pertinent aspects of Rehabilitation Sciences or Rehabilitation as related to outcomes and issues in the rheumatic diseases. Rehabilitation Sciences include physical and occupational therapies, as well as varieties or types of rehabilitation activities, uses of technology to measure rehabilitation levels or outcomes, and community-level rehabilitation activities or clinical trials based on Rehabilitation Sciences.

Manuscripts covering a broad range of topics related to the major theme are invited; e.g. the effects and consequences of rehabilitation interventions in rheumatic diseases (rheumatoid arthritis, lupus, osteoarthritis, psoriatic arthritis, and others), rehabilitation as linked with symptoms and conditions (pain, depression, or disability among persons with rheumatic conditions), and intervention studies addressing improvement in the mechanics of rehabilitation levels, cost-benefit analyses, and outcomes (physical limitations, severity of disease, drug interactions, and health behaviors). Chronic disease management and/or public health strategies in the population that address rheumatic diseases and rehabilitation are also encouraged. Both Original Research and Review articles will be considered.

The 2022 Themed Issue will include regular submissions as well, but a certain number of pages will be reserved for manuscripts accepted in response to this solicitation. All manuscripts will be peer reviewed. The Editor will select papers for publication in the themed issue based on reviewer ratings and the balance of subject matter. It is possible that manuscripts submitted for the themed issue may be accepted for publication in a regular issue of *Arthritis Care & Research* rather than the themed issue.

Please follow the formatting requirements found in the Author Guidelines section at https://onlinelibrary.wiley.com/page/journal/21514658/homepage/ForAuthors.html. The deadline for submission is March 31, 2021. For further information, contact the Editor of *Arthritis Care & Research*, Dr. Marian T. Hannan; email: Hannan@hsl.harvard.edu.

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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Cover image: The image on the cover (from Iijima et al, page 328) shows a graphic presentation of a significantly higher prevalence of recurrent falls in people with knee osteoarthritis with moderate-to-severe low back pain. Falls frequently occurred by tripping/stumbling during walking and primarily in the forward direction.

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American College of Rheumatology
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EDITORIAL

Community-Engaged Research to Address Health Disparities in Systemic Lupus Erythematosus

R. Ezequiel Borgia[1] and Graciela S. Alarcón[2]

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by evidence of autoantibodies and multiorgan system involvement leading to significant physical and functional disability. The reported incidence and prevalence of SLE in the US vary by region but are estimated to be approximately 5.5 per 100,000 persons per year and 72.8 per 100,000 persons, respectively. Several social determinants of health, including educational level, health insurance, household income, and social support, as well as environmental and occupational exposures may impact lupus outcomes (1). The association of race/ethnicity with SLE outcomes has also been reported, with non-White minorities experiencing a more severe disease phenotype with increased damage accrual and higher rates of renal involvement when compared to White individuals (2–5). The goals of Healthy People 2020, a set of national public health objectives released by the US Department of Health and Human Services, include achieving health equity, eliminating health disparities, and overall improving the health of the nation's population through collaboration among diverse groups (6). Socioeconomic inequalities are a common cause of health disparities; therefore, addressing social determinants of health would enable health professionals to enhance prevention approaches and health promotions that reduce health inequities. In this editorial, we highlight several Community-Based Participatory Research (CBPR) principles and potential applications to address health disparities in SLE.

CBPR is one of the most recognized Community Engaged Research frameworks. According to the Centers for Disease Control and Prevention, "community engagement is the process of working collaboratively with and through groups of people affiliated by geographic proximity, special interests, or other situations to address issues affecting their well-being. CBPR often involves partnerships and coalitions that help mobilize resources and influence systems, change relationships among partners, and serve as catalysts for changing policies, programs, and practices" (7). Community is defined as a social unit where participants share different characteristics affecting their identity and degree of cohesiveness, such as norms, values, religion, race/ethnicity, socioeconomic status, beliefs, and risks, among others. CBPR is research performed in equitable partnership with communities for the benefit of the community involved. Even though investigators' interests in knowledge generation may be paramount, priority should be given to community interests and needs. CBPR not only promotes community empowerment, but it also incorporates social and ecologic health paradigms that reduce health disparities through social action, thereby ultimately improving health outcomes (7–11). CBPR is an expanding field and it has been increasingly recognized as an effective approach to address health inequalities in several chronic diseases (12,13). However, there are limited data on its use and outcomes in rheumatology, specifically in SLE. To tackle this issue, the American College of Rheumatology launched a new program in 2019, Uniting Collaborators for Innovation, to fund programs that demonstrate engagement in innovation efforts among communities in order to reduce health disparities in rheumatic diseases.

Several CBPR principles may guide the implementation of community engagement efforts through three stages: pre-engagement, continuous engagement, and sustained engagement. The pre-engagement stage provides the foundation upon which engagement approach is implemented (continuous engagement). Moreover, the established partnership between investigators and communities should be extended beyond the study completion (sustained engagement) to ensure long-term benefits to communities (7). Getting to know the community in the pre-engagement phase would enable the identification of factors that may affect the implementation of CBPR efforts, such as context, health concerns, community capacity, common interests, and action needs, as well as potential barriers and facilitators of the engagement approach. A better knowledge of community culture, socioeconomic status, power structure, norms, and values will provide a better understanding of physical and sociocultural

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features and how they interact with individual health behaviors. This socioecologic approach is essential to address health disparities in vulnerable populations. Likewise, identifying and working with key community leaders and stakeholders would contribute to coalition building for a more effective partnership and should be pursued earlier rather than later in any engagement effort (7). Moreover, building strengths and respectful relationships within the community is crucial to ensure effectiveness of the community engagement initiative. These relationships, along with community involvement in all stages of the research process including study design and outcome measures, enhance community empowerment and build trust, which encourages cooperation and mutual commitment, qualities that are lower within minority groups when compared to the general population (14).

Leveraging CBPR principles may improve patient engagement and participation in patient-centered outcomes research, which would provide valuable evidence-based information in order to make informed health care decisions (15). Randomized controlled trials provide the gold standard of scientific evidence to test the efficacy of medical interventions that influence health care practices and policy. Participation in lupus clinical trials has been reported to be lower in African American individuals when compared to the SLE prevalence of that ethnic group in the general population (16). As a result, the limited available data on the effectiveness and safety of different therapies among vulnerable groups compromise the generalizability of research findings, thereby contributing to health disparities. The use of CBPR approaches to guide the development and implementation of more culturally tailored clinical trial interventions was demonstrated to be promising in improving participants' engagement in cancer clinical trials (17). Similar approaches have not been tried in SLE; however, efforts currently exist to improve engagement of minority ethnic groups in lupus clinical trials. The Improving Minority Participation and Awareness in Clinical Trials for Lupus is an innovative educational partnership program between faith-based communities and several stakeholders to raise awareness of participation in lupus clinical trials among African American individuals with SLE.

Health disparities exist among vulnerable SLE groups. CBPR principles may be used to work in an equitable partnership with communities ensuring a better understanding of context and its impact on health at the physical, mental, and social levels. Research engagement may be challenging in ethnic minority groups due to many factors, including mistrust in health care research. The implementation of contextualized interventions enhances research engagement and increases the best available evidence that would optimize health care and management, thereby reducing health disparities in vulnerable populations. Moreover, dissemination of CBPR findings to policy makers and stakeholders can facilitate larger community efforts and policy changes advancing community actions at a broader scale (18). The National Lupus Advocacy Summit is the principal lupus advocacy event in the nation supported by the Lupus Foundation of America where lupus advocates and members of Congress meet every year with leading lupus researchers and physicians on Capitol Hill to learn about the latest lupus breakthroughs. The aim of this program is to support and further advance policy priorities that will increase funding for lupus research and accelerate the development of new therapies. To date, the National Lupus Advocacy Summit has helped generate more than $119 million in federal funding for lupus research and education programs. Likewise, the National Institutes of Health have increasing funding mechanisms for implementation of practices that promote health equity, reduce health disparities, and translate research findings into practice. Nevertheless, there are still limited initiatives using CBPR in rheumatology, and specifically in SLE, a rheumatic disease with one of the most striking health inequalities in our field. Hence, more CBPR efforts addressing health disparities in underrepresented groups are needed in SLE. Perhaps implementing more educational and training CBPR programs among the rheumatology community would raise awareness and encourage more research partnerships between academia and communities. The implementation of CBPR approaches not only promotes community empowerment, trust, and research engagement, but it also fosters translation of knowledge into social action, as well as sustaining the established partnership beyond the study completion, thereby ensuring the benefit of communities in the long term. One of the main goals of CBPR is to improve patient outcomes through reducing and ultimately eliminating health disparities in vulnerable populations.

REFERENCES

1. Carter EE, Barr SG, Clarke AE. The global burden of SLE: prevalence, health disparities and socioeconomic impact. Nat Rev Rheumatol 2016;12:605–20.
2. Pons-Estel BA, Catoggio LJ, Cardiel MH, Soriano ER, Gentiletti S, Villa AR, et al. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". Medicine (Baltimore) 2004;83:1–17.
3. Alarcón GS, Friedman AW, Straaton KV, Moulds JM, Lisse J, Bastian HM, et al. Systemic lupus erythematosus in three ethnic groups: III. A comparison of characteristics early in the natural history of the LUMINA cohort. Lupus 1999;8:197–209.
4. Alarcon GS. Lessons from LUMINA: a multiethnic US cohort. Lupus 2008;17:971–6.
5. Alarcón GS, McGwin G Jr, Sanchez ML, Bastian HM, Fessler BJ, Friedman AW, et al. Systemic lupus erythematosus in three ethnic groups. XIV. Poverty, wealth, and their influence on disease activity. Arthritis Rheum 2004;51:73–7.
6. US Department of Health and Human Services. The secretary's advisory committee on national health promotion and disease prevention objectives for 2020. Phase I report: recommendations for the framework and format of Healthy People 2020 Section IV: Advisory committee findings and recommendations. 2010. URL: http://www.healthypeople.gov/sites/default/files/Phasel_0.pdf.
7. US Department of Health and Human Services. Principles of community engagement (PCE). 2nd ed. NIH Publication No. 11-7782.

2011. URL: https://www.atsdr.cdc.gov/communityengagement/pdf/PCE_Report_508_FINAL.pdf.

8. Israel BA, Schulz AJ, Parker EA, Becker AB. Review of community-based research: assessing partnership approaches to improve public health. Annu Rev Public Health 1998;19:173–202.
9. Wallerstein N, Duran B. Community-based participatory research contributions to intervention research: the intersection of science and practice to improve health equity. Am J Public Health 2010;Suppl 1:S40–6.
10. Thompson B, Molina Y, Viswanath K, Warnecke R, Prelip ML. Strategies to empower communities to reduce health disparities. Health Aff (Millwood) 2016;35:1424–8.
11. Chau TS, Islam N, Tandon D, Ho-Asjoe H, Rey M. Using community-based participatory research as a guiding framework for health disparities research centers. Prog Community Health Partnersh 2007;1:195–205.
12. Harris DA, Pensa MA, Redlich CA, Pisani MA, Rosenthal MS. Community-based participatory research is needed to address pulmonary health disparities. Ann Am Thorac Soc 2016;13:1231–8.
13. Nicolaidis C, Raymaker D, Kapp SK, Baggs A, Ashkenazy E, McDonald K, et al. The AASPIRE practice-based guidelines for the inclusion of autistic adults in research as co-researchers and study participants. Autism 2019;23:2007–19.
14. Perry E, Swartz J, Brown S, Smith D, Kelly G, Swartz R. Peer mentoring: a culturally sensitive approach to end-of-life planning for long-term dialysis patients. Am J Kidney Dis 2005;46:111–9.
15. Kauffman KS, Dosreis S, Ross M, Barnet B, Onukwugha E, Mullins CD. Engaging hard-to-reach patients in patient-centered outcomes research. J Comp Eff Res 2013;2:313–24.
16. Falasinnu T, Chaichian Y, Bass MB, Simard JF. The Representation of gender and race/ethnic groups in randomized clinical trials of individuals with systemic lupus erythematosus. Curr Rheumatol Rep 2018;20:20.
17. Seifer SD, Michaels M, Collins S. Applying community-based participatory research principles and approaches in clinical trials: forging a new model for cancer clinical research. Prog Community Health Partnersh 2010;4:37–46.
18. Cacari-Stone L, Wallerstein N, Garcia AP, Minkler M. The promise of community-based participatory research for health equity: a conceptual model for bridging evidence with policy. Am J Public Health 2014;104:1615–23.

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How Are Neighborhood Characteristics Associated With Mental and Physical Functioning Among Older Adults With Radiographic Knee Osteoarthritis?

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Objective. To examine how neighborhood characteristics are associated with health outcomes among older adults with osteoarthritis.

Methods. In multilevel, cross-sectional, and longitudinal analyses we examined whether 4 neighborhood characteristics were associated with depressive symptoms and reported knee impact scores, and whether the neighborhood characteristics interacted with race/ethnicity among older adults with radiographic knee osteoarthritis (n = 656 for cross-sectional analyses and n = 434 for longitudinal analyses). The data came from the Johnston County Osteoarthritis Project, a prospective cohort study in North Carolina designed to examine risk factors for osteoarthritis.

Results. Although few longitudinal associations were found, cross-sectional results suggested that greater perceived neighborhood social cohesion (B = –0.04, $P < 0.001$) and perceived neighborhood resources for physical activity and walking (B = –0.03, $P < 0.001$) were associated with fewer depressive symptoms, and that greater perceived neighborhood resources for physical activity and walking were associated with higher (better) knee impact scores (B = 0.48, $P = 0.008$). We also observed 2 significant interactions among neighborhood characteristics and race/ethnicity related to depressive symptoms ($P < 0.01$); for African American adults, greater perceived neighborhood resources for physical activity and walking were associated with fewer depressive symptoms (B = –0.03, $P < 0.001$), but for White adults, greater perceived neighborhood safety was associated with fewer depressive symptoms (B = –0.04, $P = 0.003$).

Conclusion. In a sample of older adults with radiographic knee osteoarthritis, neighborhood context mattered, but in nuanced ways. Interventions aiming to improve mental and physical functioning of older adults with knee osteoarthritis can look to this study as evidence for the importance of neighborhood characteristics.

INTRODUCTION

Arthritis is one of the most common chronic diseases in the US (1), particularly among older adults, the majority of whom report having arthritis (2). There is now growing evidence that aspects of the neighborhood one lives in are associated with arthritis outcomes (3–15). Despite the growing body of evidence that neighborhoods influence the health and well-being of individuals with arthritis, several notable gaps in the literature remain.

First, relatively few studies have examined how neighborhood socioeconomic status (SES) affects the mental health of individuals with osteoarthritis (OA). Previous research has shown that neighborhood SES is associated with reduced quality of life (8) and depression (16) among individuals with self-reported arthritis. However, no studies to our knowledge have examined how neigh-

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SIGNIFICANCE & INNOVATIONS

- Few studies of neighborhoods and osteoarthritis (OA) have focused on mental health outcomes, examined multiple neighborhood characteristics simultaneously, analyzed associations longitudinally, and assessed cross-level interactions.
- This study examined how 4 neighborhood characteristics were associated with depressive symptoms and knee impact scores among adults with knee OA and used appropriate and novel methods (e.g., multilevel models, longitudinal analyses, multiple imputation, and cross-level interactions) to examine associations.
- This study demonstrated perceived neighborhood context to be associated with depressive symptoms and knee impact scores in expected directions among individuals with knee OA.
- This study also demonstrated that associations among neighborhood characteristics and health outcomes were different for White adults with knee OA compared to African American adults with knee OA.

borhood SES is associated with psychological well-being among individuals with OA. This lack of examination is surprising, given the relatively high prevalence of depression and anxiety among individuals with OA (17–19) and research suggesting that comorbid depression and OA are associated with worse outcomes than either condition alone (20).

Second, the majority of studies have focused only on neighborhood SES without investigating how other neighborhood characteristics are associated with OA outcomes, such as neighborhood cohesion, though there are some exceptions (13,15). Third, few studies have examined how neighborhood SES may interact with individual-level characteristics to influence OA outcomes. For instance, research has found that African Americans have more than double the prevalence of severe knee OA than White people (21), they are more likely to have significantly worse pain, stiffness, and function (22,23), and they are less likely to seek or receive joint replacement therapy or pain medication (24–26). Yet, only 1 previous study to our knowledge has examined interactions among neighborhoods and race by analyzing whether neighborhood SES moderates the effects of income and race on reports of arthritis (5). Finally, as is common with research on neighborhoods and health more generally (27), most studies have examined associations among neighborhood-level characteristics and OA outcomes cross-sectionally.

The current study examined whether neighborhood context is associated with mental and physical health outcomes among individuals with radiographic knee OA. It also addressed limitations of previous research by answering the following research questions: 1) Is neighborhood context associated with mental and physical health outcomes? 2) Is neighborhood context associated with health outcomes over time? and 3) Does race/ethnicity interact with neighborhood context to influence health outcomes?

To guide our research questions, we used a conceptual model from Diez Roux and Mair (27), which posits that both physical and social neighborhood environments influence health and that their influence likely depends on individual-level characteristics. Based on this model, 1) we selected multiple neighborhood characteristics, including neighborhood poverty, social cohesion, resources for physical activity and walking, and safety, to understand how neighborhood physical and social environments influence health, and 2) we examined how race/ethnicity (an important individual-level characteristic for OA research) interacts with neighborhood context to influence health outcomes. We chose to examine both mental and physical health outcomes, given the importance of both outcomes for individuals with OA (28).

MATERIALS AND METHODS

Participants and procedures. The data for this study came from a population-based prospective cohort of knee and hip OA among African American and White individuals (the Johnston County Osteoarthritis Project) (29). Recruitment occurred in Johnston County, North Carolina, which, at the time of this study, was classified as a mostly rural county (30). Details on the study design, data collection procedures, and study population are detailed in previous publications (29). Briefly, the study was designed to be representative of civilian, noninstitutionalized African Americans and White individuals ages <45 years who resided in 1 of 6 towns or townships in Johnston County for at least 1 year, were living in the county at the time of study enrollment, and were physically and mentally capable of completing the study protocol. All participants provided informed written consent at the time of recruitment. The study was approved by the institutional review boards of the University of North Carolina Schools of Medicine and Public Health and the Centers for Disease Control and Prevention.

Study analytical sample. The analytical sample for this study uses data from 2 waves of the Johnston County OA study: T2 and T3. For convenience, we refer to these time points as baseline and follow-up. Baseline data were collected between 2006 and 2011, and follow-up data were collected between 2013 and 2015. For the purposes of this study, we restricted analyses to individuals with radiographic knee OA, defined as a score of 2, 3, or 4 on the Kellgren/Lawrence scale (9,31).

Since we hypothesized that neighborhood variables would have the greatest effect on knee OA outcomes (given plausible links between neighborhood variables, exercise, and mobility), we only analyzed data for individuals with radiographic knee OA, rather than individuals with radiographic knee and hip OA, or individuals with radiographic hip OA. Among adults with radiographic knee OA at baseline (n = 729), cases in which individuals were missing data on any control variables (n = 73) were dropped

from the sample, yielding a sample size of 656 for cross-sectional analyses. Among adults with radiographic knee OA at follow-up (n = 485), cases in which individuals were missing data on any control variables (n = 51) were dropped from the sample, yielding a sample size of 434 for longitudinal analyses.

Measures. A comprehensive list of all measures and how they were coded can be seen in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24125/abstract. We measured 2 outcomes: depressive symptoms and knee impact scores.

Depressive symptoms. For cross-sectional analyses, we used the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item scale to assess depressive symptoms that occurred in the past week (32). We summed item responses, which ranged from 0 to 3, to create a total score that ranged from 0 (best possible score) to 60 (worst) (Cronbach's α = 0.86).

Between baseline and follow-up, the parent study switched depression measures from the CES-D to the Patient-Reported Outcomes Measurement Information System Depression (PROMIS-D) scale (33). Thus, for longitudinal analyses, we used the PROMIS-D scale as a measure of depression, with the CES-D entered into models as the corresponding measure at baseline. The PROMIS depression scale has shown strong correlations with the CES-D (>0.80) among the general population (34). We used an 8-item short form of the PROMIS-D, in which items were rated on a 5-point scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often, and 5 = always). The higher scores indicated greater severity of depression (35). We summed responses and then converted the raw scores to standardized scores, in line with scoring guidelines (35) (Cronbach's α = 0.94).

Reported knee impact scores. We used 3 subscales (Knee-Related Quality of Life, Function in Daily Living, and Pain) from the Knee Injury and Osteoarthritis Outcome Score (KOOS) to assess the impact of knee OA (36). Because of high observed correlations in these separate subscales (>0.85 in this study), we calculated a composite score from the items comprising the subscales and named it "knee impact." Response options determine the frequency of problems in the past week, and each item is scored from 0 to 4. We calculated the mean of the 30 items and transformed scores to a 0–100 scale, with 0 representing extreme problems and 100 representing no problems (Cronbach's α = 0.98). The KOOS and its subscales have been extensively validated among individuals with OA (36) and are shown to have adequate reliability (37), and have been used in a number of OA studies (38,39).

At baseline, items from the KOOS subscales were asked without regard to a specific knee, whereas at follow-up, items from the KOOS subscales were asked of each knee. To make scores comparable in longitudinal analyses, and since our objective was not to look at changes in KOOS scores, we took the highest score for each set of knees at follow-up, rather than the score for each knee. Using the same example from above, if an individual scored their left knee to be a 4 and their right knee to be a 0 on the same item, we calculated the score for that set of items to be a 4. We analyzed scores this way on the intuitive assumption that individuals think of their most painful knee when asked to evaluate overall knee functioning. We calculated the mean of the 8 items and transformed scores to a 0–100 scale (Cronbach's α for knee impact scores at follow-up = 0.99).

Independent variables. We measured 4 neighborhood characteristics as our independent variables: neighborhood poverty (defined as the percentage of households with income below the poverty line within a census block group and compiled from the 2010 US Census), perceived neighborhood social cohesion (using the 5-item measure of Social Cohesion and Trust [40]), perceived neighborhood resources for physical activity and walking (using 11 items from the Walking and Exercise Environment scale [41]), and perceived neighborhood safety (using 3 items). For the 3 perceived neighborhood variables, Cronbach's α = 0.067–0.85.

We assessed cross-level interactions among each of the 4 neighborhood characteristics and race/ethnicity as a moderator. The control variables that were assessed included standard demographic variables as well as health-related variables that we hypothesized could be independently associated with outcomes. The control variables that were assessed were race/ethnicity (White or African American), education (categorized as less than high school or high school or greater), body mass index, sex (male or female), age, health insurance status (categorized as health insurance or no health insurance), number of comorbidities (defined using a disease inventory index at baseline and the Charlson Comorbidity Index [42] at follow-up), and physical activity (categorized as inactive, insufficiently active, or sufficiently active using questions from the Behavioral Risk Factor Surveillance System).

Data analysis. *Descriptive statistics.* We first examined distributions of the data, checked for multicollinearity (all variance inflation factor scores were <3), and looked at bivariate associations among neighborhood characteristics and health outcomes.

Centering. Before modeling the data in multilevel models, we created group means for the 3 perceived neighborhood variables based on average scores within census block groups. We then grand-mean centered these variables at the neighborhood level, which means that we calculated the deviation of each neighborhood's score from the overall mean of each neighborhood variable (labeled as neighborhood estimates of neighborhood effects). We also group-mean centered these variables at the individual level, which means that we calculated the deviation of each individual's score from the mean for the individual's cluster (neighborhood census block group in this case, labeled as individualized estimates of neighborhood effects) (43).

Multilevel models. After centering, we used multilevel models to examine the associations among neighborhood characteristics and outcomes, adjusting for control variables and modeling the neighborhood variables as fixed effects. We observed that scores for depression were highly positively skewed, in that more individuals had lower CES-D and PROMIS-D scores. Accordingly, we used a multilevel Poisson regression to model CES-D and PROMIS-D scores, as has been done in previous research (44).

Longitudinal analyses. In longitudinal analyses, we used residualized change scores to model change in outcomes, controlling for prior levels of the measured outcome. For instance, when we modeled PROMIS-D scores as the outcome at follow-up, we controlled for CES-D scores measured at baseline.

Interactions. After conducting separate multilevel models for each outcome cross-sectionally and longitudinally, we added interaction terms for each neighborhood characteristic with race/ethnicity. Given the number of potential interactions, we only probed and graphed interactions that were significant at $P < 0.01$. Otherwise, we set critical alpha equal to 0.05 and used 2-tailed statistical tests. For all analyses, we used SAS software, version 9.4 survey procedures.

Sensitivity analyses. We conducted 2 sensitivity analyses for the cross-sectional analyses. First, we used multiple imputation to impute missing data. Using SAS Proc MI, we created 20 multiply imputed complete data sets, analyzed multilevel results via the SAS Proc MIANALYZE procedure, and determined whether the use of multiple imputation produced different results than listwise deletion by comparing the parameter estimates and *P* values. Second, we excluded individuals who resided in a census block group with <5 other individuals (n = 37), since small neighborhood size might bias neighborhood estimates.

RESULTS

Participant characteristics. At baseline, our sample included adults who were mean ± SD age 70.0 ± 9.0 years (Table 1). The participants were diverse, with a substantial number of African American participants (34.0%) and individuals without a high school degree (25.5%). Additionally, at baseline, participants reported low CES-D scores (mean ± SD 6.6 ± 7.4, possible range 0–60), although 11.7% had scores at or above 16 (indicative of moderate or severe depression) and reported high knee impact scores (mean ± SD 77.5 ± 22.3, possible range 0–100).

Correlations. At baseline, CES-D scores were associated with all neighborhood variables except poverty, with correlations ranging from –0.19 to –0.25, all *P* values < 0.001 (Table 2). Reported knee impact scores were associated with all neighborhood variables, including poverty, and in the expected direction, with correlations ranging from –0.10 to 0.21; $P < 0.01$ for all.

At follow-up, none of the neighborhood variables estimated at baseline were significantly associated with PROMIS-D or reported knee impact scores, with the exception of perceived neighborhood safety, which was positively associated with reported knee impact scores at follow-up (r = 0.11, $P = 0.02$). CES-D scores at baseline and PROMIS-D scores at follow-up were significantly moderately correlated (r = 0.40, $P < 0.001$), while reported knee impact scores at baseline and follow-up were significantly moderately correlated (r = 0.66, $P < 0.001$).

Neighborhood context and mental and physical health outcomes. A summary with results from all main effects is shown in Table 3. For the individualized estimates and after adjusting for control variables, we found that perceived

Table 1. Participant characteristics of adults with radiographic knee OA, from the Johnston County Osteoarthritis Project, Johnston County, North Carolina, 2006–2011 (n = 656) and 2013–2015 (n = 434)*

Characteristic	Baseline, 2006–2011	Follow-up, 2013–2015
Age, years	70.0 ± 9.0	72.5 ± 7.8
Sex, no. (%)		
Male	215 (32.8)	148 (34.1)
Female	441 (67.2)	286 (65.9)
Race, no. (%)		
White	433 (66.0)	288 (66.4)
African American	223 (34.0)	146 (33.6)
Education, no. (%)		
High school or greater	489 (74.5)	367 (84.6)
Less than high school	167 (25.5)	67 (15.4)
Health insurance, no. (%)		
No	27 (4.1)	27 (6.2)
Yes	629 (95.9)	407 (93.8)
Body mass index	33.1 ± 7.9	32.0 ± 6.9
Number of comorbidities, assessed using a disease inventory	1.9 ± 1.3	–
Number of comorbidities, assessed using the Charlson Comorbidity Index	–	4.0 ± 1.8
Neighborhood poverty (range 0–44)	17.2 ± 10.7	17.2 ± 11.2
Perceived neighborhood social cohesion (range 5–25)	18.9 ± 3.6	19.1 ± 3.5
Perceived neighborhood resources for physical activity and walking (range 11–55),	35.5 ± 6.1	36.2 ± 6.0)
Perceived neighborhood safety (range 3–15)	11.1 ± 2.2	11.1 ± 2.2
Physical activity, no. (%)		
Inactive	225 (34.3)	356 (59.0)
Insufficiently active	234 (35.7)	125 (28.8)
Sufficiently active	197 (30.0)	53 (12.2)
CES-D scores (range 0–60)	6.5 ± 7.4	–
PROMIS-D scores (range 8–40)	–	10.7 ± 4.5
Reported knee impact scores (range 0–100)	75.6 ± 23.3	70.0 ± 25.9

* Values are the mean ± SD unless indicated otherwise. CES-D = Center for Epidemiologic Studies Depression Scale; OA = osteoarthritis; PROMIS-D = Patient-Reported Outcomes Measurement Information System Depression.

Table 2. Correlations among neighborhood characteristics, physical activity, and health outcomes among adults with radiographic knee OA, from the Johnston County Osteoarthritis Project, Johnston County, North Carolina, 2006–2011 (n = 656) and 2013–2015 (n = 434)*

	Neighborhood poverty	Perceived neighborhood social cohesion	Perceived neighborhood resources for physical activity and walking	Perceived neighborhood safety	CES-D, baseline	PROMIS-D, follow-up	Reported knee impact, baseline	Reported knee impact, follow-up
Neighborhood poverty	–	−0.21†	0.03	−0.23†	0.05	−0.06	−0.10‡	−0.08
Perceived neighborhood social cohesion	–	–	0.27†	0.53†	−0.23†	−0.08	0.15†	0.01
Perceived neighborhood resources for physical activity and walking	–	–	–	0.36†	−0.19†	0.00	0.18†	0.08
Perceived neighborhood safety	–	–	–	–	−0.25†	−0.06	0.21†	0.11§
CES-D, baseline	–	–	–	–	–	0.40†	−0.40†	−0.34†
PROMIS-D, follow-up	–	–	–	–	–	–	−0.25†	−0.35†
Reported knee impact, baseline	–	–	–	–	–	–	–	0.66†
Reported knee impact, follow-up	–	–	–	–	–	–	–	–

* CES-D = Center for Epidemiologic Studies Depression Scale; OA = osteoarthritis; PROMIS-D = Patient-Reported Outcomes Measurement Information System Depression.
† Statistically significant at $P < 0.001$.
‡ Statistically significant at $P < 0.01$.
§ Statistically significant at $P < 0.05$.

Table 3. Summary of results, using data from the Johnston County Osteoarthritis Project, Johnston County, North Carolina, 2006–2011 and 2013–2015*

Neighborhood characteristics	Cross-sectional results		Longitudinal results	
	Depression scores, baseline	Knee impact scores, baseline	Depression scores, follow-up	Knee impact scores, follow-up
Individualized estimates				
Perceived neighborhood social cohesion	▼	–	–	–
Perceived neighborhood resources for physical activity and walking	▼	▲	–	–
Perceived neighborhood safety	–	–	–	–
Neighborhood estimates				
Neighborhood poverty	–	–	–	–
Perceived neighborhood social cohesion	▼	–	–	▽
Perceived neighborhood resources for physical activity and walking	–	–	–	
Perceived neighborhood safety	–	–	–	▲

* An arrow facing downward indicates that there was a negative association between the independent variable and outcome for the specified cell, so that the arrow in the upper left quadrant, for instance, indicates that there was a significant negative association between perceived neighborhood social cohesion and depression scores. In other words, greater perceived neighborhood social cohesion was associated with lower depression scores, or less depressive symptoms. The white arrow indicates findings contrary to expectations.

neighborhood social cohesion (B = –0.04, $P < 0.001$) and perceived neighborhood resources for physical activity and walking (B = –0.03, $P < 0.001$) were both associated with CES-D scores in expected directions (Table 4). We found no significant effect of perceived neighborhood safety on CES-D scores. Turning to the neighborhood estimates, we found that perceived neighborhood social cohesion (B = –0.07, $P = 0.02$) was associated with lower CES-D scores, while neighborhood poverty, perceived neighborhood resources for physical activity and walking, and perceived neighborhood safety were not.

For knee impact, for the individualized estimates, we found that perceived neighborhood resources for physical activity and walking was associated with higher (better) reported knee impact scores (B = 0.48, $P = 0.008$), but no other effects of perceived neighborhood social cohesion or safety on reported knee impact scores (Table 5). For neighborhood estimates, we found no significant effects of neighborhood characteristics on knee impact scores.

Neighborhood context and depressive symptoms and knee impact over time. In longitudinal analyses (see Supplementary Tables 2 and 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24125/abstract), we found few statistically significant relationships. For PROMIS-D scores, we found no significant main effects for the individualized or neighborhood estimates of the neighborhood variables. For associations among neighborhood estimates and reported knee impact scores, we found that increasing perceived neighborhood social cohesion was unexpectedly associated with lower (worse) reported knee impact scores (B = –1.65,

Table 4. Effects of neighborhood variables on CES-D scores among individuals with radiographic knee OA (n = 656), from the Johnston County Osteoarthritis Project, Johnston County, North Carolina, 2006–2011*

Variable	Model 1†	*P*	Model 2†	*P*
Intercept	1.78 (0.05)‡	<0.001‡	1.76 (0.05)‡	<0.001‡
Individualized estimates				
Perceived neighborhood social cohesion	–0.04 (0.01)‡	<0.001‡	–0.04 (0.01)‡	<0.001‡
Perceived neighborhood resources for physical activity and walking	–0.02 (0)‡	<0.001‡	–0.03 (0)‡	<0.001‡
Perceived neighborhood safety	–0.02 (0.01)	0.10	–0.02 (0.01)	0.10
Neighborhood estimates				
Neighborhood poverty	–	–	–0.01 (0.01)	0.34
Perceived neighborhood social cohesion	–	–	–0.07 (0.03)‡	0.02‡
Perceived neighborhood access to physical activity and walking resources	–	–	0 (0.01)	0.99
Perceived neighborhood safety	–	–	0.04 (0.05)	0.46

* Values are the regression coefficient (SE) unless indicated otherwise. CES-D = Center for Epidemiologic Studies Depression Scale; OA = osteoarthritis.
† Results are adjusted for sex, race, age, body mass index, education, health insurance status, number of comorbidities, and physical activity. Results were estimated using a Poisson multilevel model.
‡ Statistically significant at $P < 0.05$.

Table 5. Effects of neighborhood variables on reported knee impact scores among individuals with radiographic knee OA (n = 656), from the Johnston County Osteoarthritis Project, Johnston County, North Carolina, 2006–2011*

Variable	Model 1†	*P*	Model 2†	*P*
Intercept	75.63 (0.81)‡	<0.01‡	75.63 (0.8)‡	<0.001‡
Individualized estimates				
Perceived neighborhood social cohesion	–0.11 (0.29)	0.71	–0.1 (0.29)	0.74
Perceived neighborhood resources for physical activity and walking	0.47 (0.18)‡	0.008‡	0.48 (0.18)‡	0.008‡
Perceived neighborhood safety	0.94 (0.51)	0.07	0.91 (0.51)	0.07
Neighborhood estimates				
Neighborhood poverty	–	–	–0.11 (0.1)	0.27
Perceived neighborhood social cohesion	–	–	1.26 (0.77)	0.10
Perceived neighborhood access to physical activity and walking resources	–	–	0.41 (0.25)	0.11
Perceived neighborhood safety	–	–	–1.9 (1.3)	0.15

* Values are the regression coefficient (SE) unless indicated otherwise. OA = osteoarthritis.
† Results are adjusted for sex, race, age, body mass index, education, health insurance status, number of comorbidities, and physical activity.
‡ Statistically significant at $P < 0.05$.

$P = 0.04$), while increasing perceived neighborhood safety was associated with higher (better) reported knee impact scores (B = 2.59, $P = 0.03$).

Interaction of race/ethnicity with neighborhood context. We observed 2 significant interactions among the individualized estimates of neighborhood characteristics and race/ethnicity (Figure 1). First, we found that for both African American (B = –0.03, $P < 0.001$) and White adults (B = –0.01, $P = 0.001$), greater perceived neighborhood resources for physical activity and walking was associated with lower CES-D scores; however, the effect was stronger for African American versus White adults (P for interaction = 0.004).

Second, we observed an interaction among race, the individualized estimate of perceived neighborhood safety, and CES-D scores ($P = 0.009$). For White adults, greater perceived neighborhood safety was associated with lower CES-D scores (B = –0.04, $P = 0.003$), whereas no association was found for African American adults (B = 0.02, $P = 0.33$).

Sensitivity analyses findings. Additional tables with results from all sensitivity analyses are included in Supplementary Tables 4–7, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24125/abstract. Analyzing the data with multiple imputation did not change any conclusions; all significant parameters remained significant and the magnitude of estimates was similar. Analyzing the data while excluding individuals living in census block groups with <5 individuals (n = 37) also did not change any conclusions. The majority of main effects, with the exception of 2, remained significant.

DISCUSSION

In a sample of older adults with at least 1 chronic condition (radiographic knee OA), we found that neighborhood context matters, but in nuanced ways. Individualized estimates of neighborhood social cohesion and resources for physical activity and walking appeared to be important for depressive symptoms and knee impact scores, although we found few significant effects

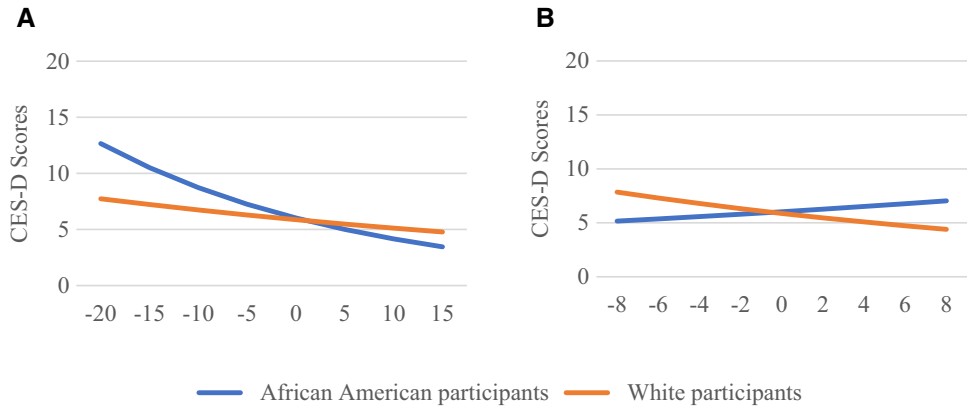

Figure 1. Interactions among race, neighborhood context, and Center for Epidemiologic Studies Depression Scale (CES-D) scores among adults with radiographic knee osteoarthritis (n = 656), from the Johnston County Osteoarthritis Project, Johnston County, North Carolina, 2006–2011. **A**, Individualized estimate of perceived neighborhood resources for physical activity and walking. The slopes for both African American participants and White participants are significant at $P < 0.05$, but the slope is stronger for African American participants. **B**, Individualized estimate of perceived neighborhood safety. Only the slope for White participants is significant at $P < 0.05$.

over time. We also found neighborhood characteristics to be differentially associated with outcomes for African American or White adults.

In contrast to a previous systematic review that found neighborhood SES to be the strongest and most consistent predictor of health outcomes among older adults compared to other neighborhood characteristics (45), we found no effect of neighborhood poverty on CES-D or knee impact scores. There are 3 possible reasons why this difference occurred. First, there was minimal clustering of health outcomes (i.e., CES-D scores and knee impact scores) by census block groups, and this lack of variation may have made it difficult to detect relevant associations between neighborhood poverty (only measured at the census block group level) and health outcomes. Second, using administrative boundaries to capture neighborhood characteristics (census block groups in this case) may not have accurately reflected what individuals think of as their neighborhoods (known as "spatial misclassification"). Finally, we found neighborhood poverty to be significantly correlated with other neighborhood characteristics in bivariate associations, namely social cohesion and perceived safety. Although poverty may not have had a direct effect on depression or knee impact, an indirect effect through other neighborhood characteristics could have occurred.

We also found more consistent effects of the individualized estimates of neighborhood characteristics than the neighborhood estimates of these variables. In other words, individuals who perceived their neighborhoods to be more cohesive or to have more built environment resources, relative to their neighbors' average scores, had better CES-D scores and/or knee impact scores. Notably, individualized estimates of neighborhood variables are not true measures of the "neighborhood" or "contextual neighborhood effects." Instead, they refer to individual-level perceptions of neighborhood conditions. Since neighborhoods are not necessarily internally homogeneous, possibly self-reported assessments of neighborhoods more closely represent individuals' own neighborhoods, how they interact with them, and how they are exposed to different neighborhood characteristics rather than area-level aggregated indicators of neighborhood conditions (46). However, our findings likely resulted from some of the reasons described above (e.g., minimal clustering of health outcomes) and individuals with a particular disposition (i.e., individuals with depressed moods) may have rated their environments as less satisfactory than individuals with a different disposition (i.e., individuals without depressed moods) (46).

In longitudinal analyses, we observed no consistent relationships among neighborhood characteristics and outcomes, which is consistent with previous research (47). Reduced power to observe significant associations longitudinally may explain these findings. Indeed, in longitudinal analyses, our sample size dropped by almost 35% due to participants' withdrawals or deaths. Possibly neighborhood characteristics changed between baseline and follow-up. Since we did not reassess these characteristics, our measures of neighborhood environment would have been insensitive to the effects of such changes. Finally, as other researchers have suggested, if neighborhood characteristics remain relatively stable over time, and if individuals have lived extended periods in those neighborhoods, then cross-sectional analyses are meaningful (47). Supporting this interpretation of the current findings, participants reported living at their current address for mean ± SD 45 ± 21.34 years in measures taken at the beginning of the parent study.

We also observed significant interactions among the neighborhood characteristics themselves, and we observed that race/ethnicity moderated the effects of neighborhood characteristics on CES-D and reported knee impact scores. These findings suggest that researchers should look holistically at neighborhoods when evaluating their influence on health (i.e., not examining 1 neighborhood characteristic, but examining a multitude of characteristics) and that some individual-level factors may buffer or change the relationships between neighborhoods and health.

We note that associations among neighborhood characteristics and our 2 outcomes, while significant, were small. However, we believe our findings remain worthy of attention for 4 reasons. First, this study only looked at 4 neighborhood characteristics, while in reality there are many other neighborhood characteristics that need to be considered before estimating a total effect size for how neighborhoods influence health. Second, there are likely indirect ways through which neighborhoods influence health (e.g., by affecting health behaviors, which then influence health outcomes) that were not measured by the current study. Third, neighborhood physical and social environments likely have aggregate effects on health (e.g., neighborhood safety and built environment can both affect physical activity above and beyond the influence of either one alone). Finally, results from this study could be used to effectively (and cost effectively) improve health. Indeed, there are innovative low-cost ways to encourage social interaction in neighborhoods (increasing vegetation and common spaces [48], designing homes with porches or stoops [49]), which might improve social cohesion and small improvements to neighborhood infrastructure (providing lighting or improving sidewalks) can increase physical activity (50) and consequently physical functioning. Thus, our findings, in conjunction with the growing body of literature on neighborhoods and arthritis (3–15), highlight the need for upstream interventions to improve OA outcomes.

Overall, our findings suggest the following questions for future research: 1) What is an important and meaningful effect size for how neighborhoods influence health? 2) What is the most appropriate way to measure neighborhood characteristics, and does that measurement change based on the neighborhood characteristic being measured? 3) How can we better model complex relationships between neighborhoods and health? and 4) How do genetic predispositions and other individual-level characteristics interact with neighborhood characteristics to influence health?

Several study limitations should be considered. First, we did not control for individual-level income data, which may have accounted for the observed effects. Second, this study relied on a specific population, older adults in Johnston County, North Carolina, which limits generalizability to other settings and populations. Third, participants included in these analyses were selected from a prospective cohort study and originally invited to participate between 1991 and 1997 (baseline of the parent study) or 2003 and 2004 (for cohort enrichment). By the baseline wave of data collection for this study (2006–2011), many individuals had died. Accordingly, results may not generalize to all community samples of older adults. Fourth, as discussed above, associations among neighborhood characteristics and outcomes, while significant, were modest. Finally, the lack of longitudinal findings reduces the validity of the cross-sectional findings.

In conclusion, in this sample of older adults with radiographic knee OA, we found that neighborhood context affected health outcomes in nuanced yet important ways. Interventions aiming to improve mental and physical functioning of older adults with radiographic knee OA can look to this study as evidence for the importance of neighborhood characteristics.

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. Kowitt 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. Kowitt, Aiello, Callahan, Fisher, Gottfredson, Jordan, Muessig.

Acquisition of data. Callahan, Jordan.

Analysis and interpretation of data. Kowitt, Aiello, Callahan, Fisher, Gottfredson, Jordan, Muessig.

REFERENCES

1. Gerteis J, Izrael D, Deitz D, LeRoy L, Ricciardi R, Miller T, et al. Multiple chronic conditions chartbook. Agency for Healthcare Research and Quality. Rockville (MD): AHRQ Publications; 2014.
2. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital Signs: Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation: United States, 2013–2015. MMWR Morb Mortal Wkly Rep 2017;66:246–53.
3. Brennan SL, Turrell G. Neighborhood disadvantage, individual-level socioeconomic position, and self-reported chronic arthritis: a cross-sectional multilevel study. Arthritis Care Res (Hoboken) 2012;64: 721–8.
4. Callahan LF, Shreffler J, Mielenz T, Schoster B, Kaufman JS, Xiao C, et al. Arthritis in the family practice setting: associations with education and community poverty. Arthritis Rheum 2008;59:1002–8.
5. Canizares M, Power JD, Perruccio AV, Badley EM. Association of regional racial/cultural context and socioeconomic status with arthritis in the population: a multilevel analysis. Arthritis Rheum 2008;59:399–407.
6. Cleveland RJ, Schwartz TA, Prizer LP, Randolph R, Schoster B, Renner JB, et al. Associations of educational attainment, occupation, and community poverty with hip osteoarthritis. Arthritis Care Res (Hoboken) 2013;65:954–61.
7. Callahan LF, Cleveland RJ, Shreffler J, Schwartz TA, Schoster B, Randolph R, et al. Associations of educational attainment, occupation and community poverty with knee osteoarthritis in the Johnston County (North Carolina) osteoarthritis project. Arthritis Res Ther 2011;13:R169.
8. Callahan LF, Shreffler J, Mielenz TJ, Kaufman JS, Schoster B, Randolph R, et al. Health-related quality of life in adults from 17 family practice clinics in North Carolina. Prev Chronic Dis 2009; 6:A05.
9. Cleveland RJ, Luong ML, Knight JB, Schoster B, Renner JB, Jordan JM, et al. Independent associations of socioeconomic factors with disability and pain in adults with knee osteoarthritis. BMC Musculoskelet Disord 2013;14:297.
10. Knight JB, Callahan LF, Luong ML, Shreffler J, Schoster B, Renner JB, et al. The association of disability and pain with individual and community socioeconomic status in people with hip osteoarthritis. Open Rheumatol J 2011;5:51–8.
11. White DK, Jette AM, Felson DT, Lavalley MP, Lewis CE, Torner JC, et al. Are features of the neighborhood environment associated with disability in older adults? Disabil Rehabil 2010;32:639–45.
12. Keysor JJ, Jette AM, LaValley MP, Lewis CE, Torner JC, Nevitt MC, et al. Community environmental factors are associated with disability in older adults with functional limitations: the MOST study. J Gerontol A Biol Sci Med Sci 2010;65:393–9.
13. Timmermans EJ, van der Pas S, Schaap LA, Cooper C, Edwards MH, Gale CR, et al. Associations between perceived neighbourhood problems and quality of life in older adults with and without osteoarthritis: results from the Hertfordshire Cohort Study. Health Place 2017;43:144–50.
14. Timmermans EJ, Schaap LA, Visser M, van der Ploeg HP, Wagtendonk AJ, van der Pas S, et al. The association of the neighbourhood built environment with objectively measured physical activity in older adults with and without lower limb osteoarthritis. BMC Public Health 2016;15:710.
15. Timmermans EJ, van der Pas S, Cooper C, Schaap LA, Edwards MH, Deeg DJ, et al. The neighbourhood environment and use of neighbourhood resources in older adults with and without lower limb osteoarthritis: results from the Hertfordshire Cohort Study. Clin Rheumatol 2016;35:2797–805.
16. Mingo CA, Martin KR, Shreffler J, Schoster B, Callahan LF. Individual and community socioeconomic status: impact on mental health in individuals with arthritis. Arthritis 2014;2014:256498.
17. Stubbs B, Aluko Y, Myint PK, Smith TO. Prevalence of depressive symptoms and anxiety in osteoarthritis: a systematic review and meta-analysis. Age Ageing 2016;45:228–35.
18. Lin EH. Depression and osteoarthritis. Am J Med 2008;121 Suppl S:16S–9S.
19. Kim KW, Han JW, Cho HJ, Chang CB, Park JH, Lee JJ, et al. Association between comorbid depression and osteoarthritis symptom severity in patients with knee osteoarthritis. J Bone Joint Surg Am 2011;93:556–63.
20. Rosemann T, Gensichen J, Sauer N, Laux G, Szecsenyi J. The impact of concomitant depression on quality of life and health service utilisation in patients with osteoarthritis. Rheumatol Int 2007;27:859–63.
21. Dieppe P, Basler HD, Chard J, Croft P, Dixon J, Hurley M, et al. Knee replacement surgery for osteoarthritis: effectiveness, practice variations, indications and possible determinants of utilization. Rheumatology (Oxford) 1999;38:73–83.
22. Allen KD, Helmick CG, Schwartz TA, DeVellis RF, Renner JB, Jordan JM. Racial differences in self-reported pain and function among individuals with radiographic hip and knee osteoarthritis: the Johnston County Osteoarthritis Project. Osteoarthritis Cartilage 2009;17:1132–6.

23. Allen KD, Chen JC, Callahan LF, Golightly YM, Helmick CG, Renner JB, et al. Racial differences in knee osteoarthritis pain: potential contribution of occupational and household tasks. J Rheumatol 2012;39:337–44.
24. Ibrahim SA, Siminoff LA, Burant CJ, Kwoh CK. Understanding ethnic differences in the utilization of joint replacement for osteoarthritis: the role of patient-level factors. Med Care 2002;40 Suppl S:I44S–51S.
25. Dominick KL, Bosworth HB, Dudley TK, Waters SJ, Campbell LC, Keefe FJ. Patterns of opioid analgesic prescription among patients with osteoarthritis. J Pain Palliat Care Pharmacother 2004;18:31–46.
26. Dominick KL, Bosworth HB, Jeffreys AS, Grambow SC, Oddone EZ, Horner RD. Racial/ethnic variations in non-steroidal anti-inflammatory drug (NSAID) use among patients with osteoarthritis. Pharmacoepidemiol Drug Saf 2004;13:683–94.
27. Diez Roux AV, Mair C. Neighborhoods and health. Ann N Y Acad Sci 2010;1186:125–45.
28. De Koning EJ, Timmermans EJ, van Schoor NM, Stubbs B, van den Kommer TN, Dennison EM, et al. Within-person pain variability and mental health in older adults with osteoarthritis: an analysis across 6 European cohorts. J Pain 2018;19:690–8.
29. Jordan JM. An ongoing assessment of osteoarthritis in African Americans and Caucasians in North Carolina: the Johnston County Osteoarthritis Project. Trans Am Clin Climatol Assoc 2015;126:77–86.
30. US Census Bureau. 2010 Census urban and rural classification and urban area criteria. 2015. URL: https://www.census.gov/programs-surveys/geography/guidance/geo-areas/urban-rural/2010-urban-rural.html.
31. Neogi T, Zhang Y. Epidemiology of osteoarthritis. Rheum Dis Clin North Am 2013;39:1–19.
32. Radloff LS. The use of the Center for Epidemiologic Studies Depression Scale in adolescents and young adults. J Youth Adolesc 1991;20:149–66.
33. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. J Clin Epidemiol 2010;63:1179–94.
34. Choi SW, Schalet B, Cook KF, Cella D. Establishing a common metric for depressive symptoms: linking the BDI-II, CES-D, and PHQ-9 to PROMIS depression. Psychol Assess 2014;26:513–27.
35. PROMIS. Depression: a brief guide to the PROMIS depression instrument. 2015. URL: http://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Depression_Scoring_Manual.pdf.
36. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes 2003;1:64.
37. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). Arthritis Care Res (Hoboken) 2011;63(Suppl 11):S208–28.
38. Vennu V, Bindawas SM. Relationship between falls, knee osteoarthritis, and health-related quality of life: data from the Osteoarthritis Initiative study. Clin Interv Aging 2014;9:793–800.
39. Hoogeboom TJ, den Broeder AA, de Bie RA, van den Ende CH. Longitudinal impact of joint pain comorbidity on quality of life and activity levels in knee osteoarthritis: data from the Osteoarthritis Initiative. Rheumatology (Oxford) 2013;52:543–6.
40. Sampson RJ, Raudenbush SW, Earls F. Neighborhoods and violent crime: a multilevel study of collective efficacy. Science 1997;277:918–24.
41. Echeverria SE, Diez-Roux AV, Link BG. Reliability of self-reported neighborhood characteristics. J Urban Health 2004;81:682–701.
42. Roffman CE, Buchanan J, Allison GT. Charlson comorbidities index. J Physiother 2016;62:171.
43. Preacher KJ, Zhang Z, Zyphur MJ. Alternative methods for assessing mediation in multilevel data: the advantages of multilevel SEM. Struct Equ Modeling 2011;18:161–82.
44. Lambert MT, Terrell JE, Copeland LA, Ronis DL, Duffy SA. Cigarettes, alcohol, and depression: characterizing head and neck cancer survivors in two systems of care. Nicotine Tob Res 2005;7:233–41.
45. Yen IH, Michael YL, Perdue L. Neighborhood environment in studies of health of older adults: a systematic review. Am J Prev Med 2009;37:455–63.
46. Weden MM, Carpiano RM, Robert SA. Subjective and objective neighborhood characteristics and adult health. Soc Sci Med 2008;66:1256–70.
47. Mair C, Diez Roux AV, Shen M, Shea S, Seeman T, Echeverria S, et al. Cross-sectional and longitudinal associations of neighborhood cohesion and stressors with depressive symptoms in the multiethnic study of atherosclerosis. Ann Epidemiol 2009;19:49–57.
48. Kweon BS, Sullivan WC, Wiley AR. Green common spaces and the social integration of inner-city older adults. Environmen Behav 1998;30:832–58.
49. Brown SC, Mason CA, Lombard JL, Martinez F, Plater-Zyberk E, Spokane AR, et al. The relationship of built environment to perceived social support and psychological distress in Hispanic elders: the role of "eyes on the street". J Gerontol B Psychol Sci Soc Sci 2009;64:234–46.
50. Hajna S, Ross NA, Joseph L, Harper S, Dasgupta K. Neighbourhood walkability and daily steps in adults with type 2 diabetes. PLoS One 2016;11:e0151544.

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Obesity Progression Between Young Adulthood and Midlife and Incident Arthritis: A Retrospective Cohort Study of US Adults

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Objective. To examine the association between weight change from young adulthood to midlife and the risk of incident arthritis.

Methods. Using data from the National Health and Nutrition Examination Survey, we categorized participants into weight-change categories based on their recalled weight during young adulthood and midlife. We estimated the association of weight change and developing an arthritis condition over 10 years using adjusted Cox models. Findings were extrapolated to the US population to determine the proportion of incident arthritis cases that could be averted if the entire population maintained a normal body mass index (BMI) in young adulthood and midlife.

Results. Among our sample of adults who were ages 40–69 years at their midlife weight measure (n = 13,669), 3,603 developed an arthritis condition. Compared with adults who maintained a normal–normal BMI, the normal–overweight, normal–obese, overweight–obese, and obese–obese groups had a significantly elevated risk of incident arthritis conditions. The obese–overweight group had a lower risk of incident arthritis conditions compared with the obese–obese group and a comparable risk to the overweight–overweight group. Nearly one-fourth of incident arthritis cases, corresponding to 2.7 million individuals, would have been averted under the hypothetical scenario where all individuals maintained normal weight from young adulthood to midlife.

Conclusion. Weight loss from young adulthood to midlife was associated with a substantially reduced risk of developing an arthritis condition. We found no evidence of residual risk from having been heavier earlier in life. Our findings highlight the critical need to expand obesity treatment and prevention to achieve meaningful reductions in the burden of arthritis.

INTRODUCTION

Collectively, rheumatic and musculoskeletal diseases result in substantial disability and diminished quality of life. Their prevalence has also been increasing, particularly for osteoarthritis (1), the most common form of arthritis (2). As of 2015, joint pain and arthropathies were the most common diagnosis for ambulatory care visits (3), and osteoarthritis was the second most common reason for nonpregnancy/non-neonatal hospitalization in the US (4).

The prevalence of obesity has also increased dramatically, from approximately 15% of US adults in 1980 to 40% in 2016 (5,6). Obesity is associated with an increased risk of developing rheumatic and musculoskeletal diseases, including osteoarthritis (7,8), rheumatoid arthritis (9,10), gout (11,12), and psoriatic arthritis (13,14). For inflammatory arthritis diseases, this relationship is likely related to adipose-derived inflammation (14,15). The obesity-osteoarthritis association may result from both increased joint loading and low-grade inflammation (14–18). Weight gain increases the risk of arthritis broadly (19), including osteoarthritis-

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SIGNIFICANCE & INNOVATIONS

- We used a novel application of a large, nationally representative cross-sectional survey to create a retrospective cohort design where change in recalled weight from 2 earlier stages of life was used to study the incidence of arthritis conditions.
- Weight loss from young adulthood to midlife was associated with a substantially reduced risk of developing an arthritis condition, and we found no evidence of residual risk from having been heavier earlier in life.
- Nearly one-fourth of incident arthritis cases, corresponding to 2.7 million individuals at the national level, would have been averted under the hypothetical scenario where all individuals maintained normal weight from young adulthood to midlife.

related hip and knee replacement (20,21) and gout (12). Additionally, prior studies have shown that weight loss is associated with a reduced risk of osteoarthritis (22,23) and gout (12).

In addition to increases in the overall prevalence of obesity, recent US birth cohorts are becoming obese earlier in life and are thus spending greater portions of their lives with excess weight. The effects of these weight shifts on the risk of arthritis are largely unknown. Using data from the Nurses' Health Study, 1 recent study estimated that weight gain from early to mid-adulthood of 2.5 to <10 kg, 10 to <20 kg, or ≥20 kg was associated with a 20%, 31%, and 40% increase in the likelihood of osteoarthritis-related total hip replacement (20). However, the study did not investigate the risk of other types of arthritis or the effects of weight loss. If the effects of obesity on arthritis conditions are cumulative, those who lose weight may experience residual risk due to irreversible pathologic processes from carrying excess weight earlier in life.

Additionally, although some studies have demonstrated how weight change modifies the risk of arthritis conditions at the individual-level (12,19–23), the aggregate effect of population-level weight loss or obesity prevention remains uncertain. Hence, additional empirical estimates derived from nationally representative data sources are needed to assess the population-level effect of weight change across the life-course on arthritis risk.

Our study used a novel application of the National Health and Nutrition Examination Survey (NHANES) data to test 2 hypotheses about the association between weight change from young adulthood to midlife and risk of incident arthritis. First, we hypothesized that individuals who lose weight are at a reduced risk of developing arthritis conditions relative to individuals who maintain a stable overweight or obese body mass index (BMI) ("risk reduction" hypothesis). Second, we hypothesized that individuals who are overweight or obese in young adulthood and lose weight are at a greater risk of arthritis conditions relative to individuals who started at a lower weight and maintained that weight ("residual risk" hypothesis). After testing these hypotheses, we extrapolated our findings to the population-level, estimating the percentage of incident arthritis cases that could be averted under hypothetical scenarios related to weight loss and comprehensive prevention of overweight/obesity across the life-course.

MATERIALS AND METHODS

Design. The NHANES is a nationally representative survey of US adults containing information on demographic characteristics, weight history, and health behaviors/conditions (24). We combined cross-sectional data from NHANES III (1988–1994) with repeat cross-sectional data from the NHANES continuous waves collected in 2-year cycles between 1999 and 2016, creating a sample that is representative of the US population during an average year of the combined survey period.

We used recall questions on weight history and age at arthritis diagnosis to create a retrospective cohort from the cross-sectional data. Specifically, we looked at recalled weight at age 25 years and at 10 years prior to the survey, to measure weight change between young adulthood and midlife. We investigated the association between weight change and the risk of incident arthritis over the 10-year period from the midlife measure to the time of the survey. Age at midlife and self-reported age at arthritis diagnosis were used to determine the timing of incident events. This study design, shown in Figure 1, was modified from a similar analysis of incident diabetes mellitus (25).

Sample. We included participants who were ages 50–79 years at the time of the NHANES survey so that their second recalled weight measure would correspond to midlife (ages 40–69 years). The sample was further restricted to participants with a BMI between 20 and 75 kg/m^2 at both time points. A lower bound of 20 kg/m^2 was chosen because people with lower BMIs may be experiencing weight loss related to illnesses such as chronic obstructive pulmonary diseases, heart failure, and cancer (26). Additionally, prior evidence suggests a j-shaped association between BMI and mortality, with a BMI of approximately 20 kg/m^2 having the lowest risk (27). Participants with missing information on weight, education level, or smoking status were excluded, as were those with unreliable BMI self-reports, defined as more than a 20% difference between BMI estimates calculated from self-reported weight and height and measured weight and height at the time of the survey. Adults who reported a diagnosis of arthritis >10 years prior to the survey were considered prevalent cases and were thus excluded from the analysis of incident arthritis (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24252/abstract).

Weight-change measures. We used recalled weights, which are strongly correlated with historically measured weight (28,29), to assess weight change between young adulthood and midlife. Respondents were asked to recall their weight at age

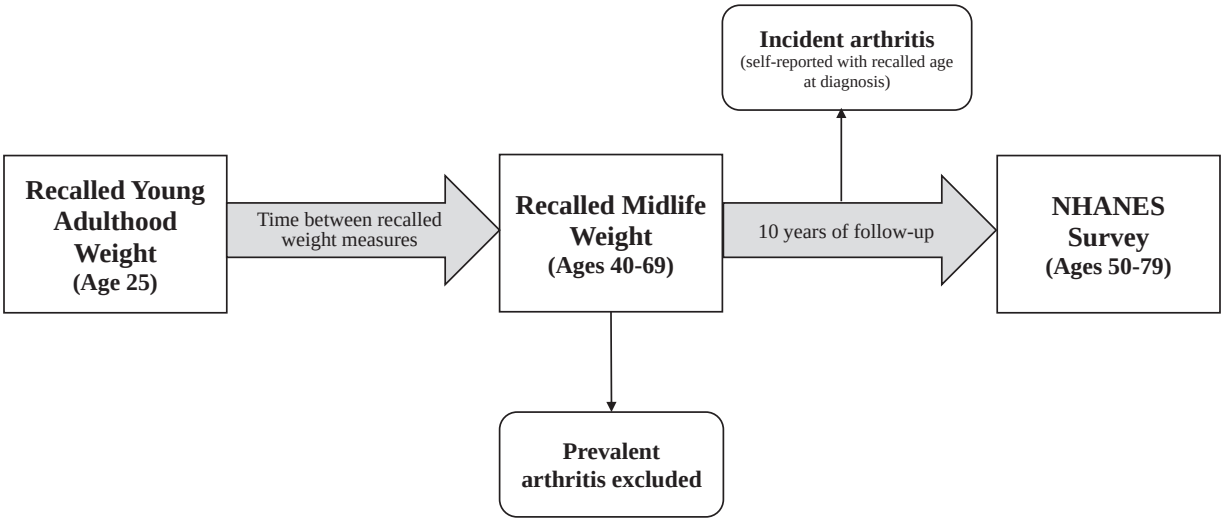

Figure 1. Study design for analysis of incident arthritis conditions (n = 13,669), showing how cross-sectional, recall questions on weight history and age at arthritis diagnosis were leveraged to create a retrospective cohort of US adults. We studied individuals who participated in the National Health and Nutrition Examination Survey (NHANES) III (1988–1994) or NHANES continuous (1999–2016) cross-sectional survey at ages 50–79 years. As part of the survey, individuals reported their recalled weight at age 25 years (young adulthood) and at 10 year prior to the survey (ages 40–69 years, midlife), which were used to create a measure of weight change between young adulthood and midlife. We then investigated the association between this weight change and a subsequent risk of developing an arthritis condition. Follow-up for incident arthritis began at the midlife weight measure, which was 10 years prior to the survey. Individuals who reported receiving a first diagnosis of arthritis >10 years prior to the survey were considered prevalent cases and thus were excluded from the analysis of incident arthritis. Individuals who reported receiving a first diagnosis of arthritis during the follow-up period between midlife and the time of the survey were considered to have experienced incident arthritis over follow-up.

25 years, which we considered young adulthood. For respondents in the NHANES continuous waves, we used recalled height and weight at age 25 to calculate BMI to account for the possibility of height decline with age. Because height at age 25 years was not recorded during NHANES III, we used measured height at the survey for these respondents.

Respondents were also asked to recall their weight from 10 years prior to the survey. Since participants' age 10 years prior to the survey ranged from 40 to 69 years, we considered this second time point to be a measure of midlife weight. We used measured height at the survey to calculate BMI at midlife. BMI values at both young adulthood and midlife were categorized into normal weight (20.0–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (30.0–74.9 kg/m^2).

We developed 9 weight-change categories: normal–normal, normal–overweight, normal–obese, overweight–normal, overweight–overweight, overweight–obese, obese–normal, obese–overweight, and obese–obese. For example, someone classified as normal–overweight had a normal BMI in young adulthood but an overweight BMI in midlife. We grouped the categories into weight loss, weight maintenance, and weight gain (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24252/abstract). For sensitivity analyses, we defined an alternative set of weight-change categories based on percent weight change: >10% weight loss, weight maintenance, and >10% weight gain.

Assessment of incident arthritis conditions. Arthritis conditions were defined based on the survey question, "Has a doctor or other health professional ever told you that you had arthritis?" Reported age at diagnosis was used to determine arthritis onset.

Statistical analysis. A Cox proportional hazards model was used to model incident arthritis conditions across the weight-change categories over 10 years of follow-up between midlife weight and the time of the survey, specifying the normal–normal category as the reference group. We adjusted for age at the midlife measure (40–44, 45–49, 50–54, 55–59, 60–64, 65–69 years), sex (male, female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Non-Hispanic other), education at survey (less than high school, high school or equivalent, some college, college or higher), smoking status at the midlife measure (never, former, current), and categorical survey year. In addition to its importance as a confounder, adjusting for age allowed us to account for the difference in length of time between young adulthood and midlife weight measures, which ranged from 15 to 44 years.

To better understand the differential risk between the weight-change categories, we tested 2 hypotheses. First, we investigated whether individuals who lost weight between young adulthood and midlife were at a reduced risk of developing an arthritis condition relative to those who remained overweight or obese. To test

this risk reduction hypothesis, we estimated the hazards of arthritis conditions for the overweight–normal group compared with the overweight–overweight group and the obese–overweight group relative to the obese–obese group.

Second, we investigated whether individuals with weight loss were at an increased risk of developing an arthritis condition relative to those who maintained a lower weight to determine whether there is any residual risk associated with having previously been heavier. To test this residual risk hypothesis, we compared the hazards of arthritis conditions for the obese–overweight group to the overweight–overweight group. We also estimated the hazards for the overweight–normal group relative to the normal–normal group.

Hypothetical scenarios. Using the formula for the population attributable fraction (PAF):

$$PAF = \sum_{i=0}^{k} pd_i \left(\frac{HR_i - 1}{HR_i} \right)$$

where pd_i is proportion of total incident cases observed in the i^{th} weight-change category and HR_i is the hazard ratio associated with that category, we estimated the fraction of cases that would be eliminated if a weight-change category were redistributed to another category. PAFs were then multiplied by the number of incident arthritis conditions in the overall population to determine the average number of cases that could be averted annually under 2 different hypothetical scenarios.

Under the obesity weight-loss scenario, we estimated what would have happened if those who were obese at age 25 years and during midlife instead lost down to an overweight BMI during midlife. This PAF calculation uses estimates from the primary Cox proportional hazards model, setting the obese–overweight group as the reference. Then, under the comprehensive prevention of overweight/obesity scenario, we examined the entire population who had a normal BMI at age 25 years and during midlife. Estimates for this calculation use the normal–normal group as the reference.

Sensitivity analysis. To test the impact of excluding participants with missing covariates, we used multiple imputation by chained equations (10 imputations) to account for missing data in education and smoking status and to refit our primary regression analysis using this imputed sample (30). Due to the wide range of ages at the midlife weight measure, we stratified our main results by age, comparing those who were ages 40–49 years at the midlife measure to those who were ages 50–69 years. We chose 50 years as the lower bound of the older age range because prior work has suggested weight gain levels off at approximately age 50 years (31). Additionally, we stratified by smoking status to assess the possibility of confounding by smoking that may affect the risk of arthritis.

We also tested the robustness of our risk reduction findings by modeling incident arthritis conditions as a function of percent weight-change categories among those who were obese at young adulthood. We tested the proportional hazards assumption for the Cox model using a time-varying coefficients model. The

Table 1. Sample characteristics, NHANES 1988–1994 and 1999–2016 (n = 13,669)*

Characteristic	Value†
Age at survey, years	
50–54	3,012 (28.4)
55–59	2,330 (21.9)
60–64	2,938 (17.9)
65–69	2,196 (14.0)
70–74	1,948 (11.0)
75–79	1,245 (6.9)
Sex	
Female	5,706 (43.3)
Male	7,963 (56.7)
Race/ethnicity	
Non-Hispanic White	6,549 (78.2)
Non-Hispanic Black	3,054 (9.5)
Hispanic	3,428 (8.4)
Non-Hispanic other	638 (3.8)
Education‡	
Less than high school	5,444 (26.1)
High school/equivalent	2,812 (22.1)
Some college	2,858 (24.8)
College or higher	2,555 (27.0)
Smoking status§	
Never	6,344 (46.8)
Former	3,537 (26.5)
Current	3,788 (26.6)
Weight-change category¶	
Normal–normal	3,634 (28.3)
Normal–overweight	4,191 (30.0)
Normal–obese	1,575 (10.6)
Overweight–normal	241 (1.6)
Overweight–overweight	1,587 (12.0)
Overweight–obese	1,592 (11.6)
Obese–normal	30 (0.2)
Obese–overweight	126 (0.8)
Obese–obese	693 (4.9)
Type of weight change#	
Weight loss	397 (2.5)
Weight maintenance	5,914 (45.3)
Weight gain	7,358 (52.2)
Incident arthritis conditions**	3,603 (25.8)

* Values are the number (%). NHANES = National Health and Nutrition Examination Survey.
† Percentages are sample weighted using NHANES examination weights. Counts are unweighted.
‡ Education was reported at the time of the NHANES survey.
§ Smoking status was reported from the midlife weight measure (10 years prior to the survey).
¶ Weight was recorded at age 25 years and also at 10 years prior to the survey to determine weight change between young adulthood and midlife.
# Weight loss includes overweight–normal, obese–normal, and obese–overweight. Weight maintenance includes normal–normal, overweight–overweight, and obese–obese. Weight gain includes normal–overweight, normal–obese, and overweight–obese.
** Incident arthritis conditions reflect the number of new arthritis conditions that occurred over the 10 years of follow-up from the recalled midlife weight measure to the time of the survey.

interaction term between years of follow-up and several weight-change categories was significant in this model, indicating a violation of proportionality. Therefore, we re-estimated PAF values using time-specific hazards at yearly intervals. The time-weighted PAF values were identical to the estimates derived from the primary models, suggesting we could proceed with the primary Cox models.

As the analyses used publicly available, de-identified data, institutional review board approval was not required. Stata 15 software was used for all analyses. Following NHANES analytic guidelines (32), all estimates were sample weighted using pooled NHANES examination sample weights to account for unequal probabilities of selection and nonresponse adjustments. As a result, estimates are representative of the US civilian, noninstitutionalized population during an average year of the combined survey period.

RESULTS

Our sample included 13,669 US adults ages 50–79 years at the time of the survey; 50.3% of the sample were age <60 years, 56.7% were male, and 78.2% were non-Hispanic White (Table 1). Additionally, 26.5% were former smokers and 26.6% were current smokers at midlife. Less than half of the sample (45.3%) maintained their BMI category; 28.3% were normal–normal, 12.0% were overweight–overweight, and 4.9% were obese–obese. Weight gain was common (52.2%); 30.0% were normal–overweight, 10.6% were normal–obese, and 11.6% were overweight–obese. Weight loss, on the other hand, was rare (2.5%); 1.6% were overweight–normal, 0.2% were obese–normal, and 0.8% were obese–overweight. Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24252/abstract, shows the average BMI during young adulthood and midlife across weight change categories.

Weight change and incident arthritis conditions. A total of 3,603 cases of incident arthritis conditions (25.8%) were reported over 123,412 years of person-time (29.2 cases per 1,000 person-years). The unadjusted incidence of arthritis conditions overall was similar among adults who maintained weight (25.0 cases per 1,000 person-years) and adults who lost weight (23.0 cases per 1,000 person-years). The unadjusted incidence of arthritis was higher among adults who gained weight (33.0 cases per 1,000 person-years).

Table 2 shows the hazard ratios (HRs) of developing an arthritis condition for each weight-change category compared with adults who maintained a normal BMI. Results were suppressed for the obese–normal weight group because there were <10 incident arthritis cases in this group. The normal–overweight, normal–obese, overweight–obese, and obese–obese groups had significantly elevated risks of incident arthritis conditions. Supplementary Figure 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24252/abstract, shows the cumulative hazard functions for each weight-change group.

Risk reduction hypothesis. Compared with adults who remained obese, those who lost weight to an overweight BMI had a lower risk of developing an arthritis condition (HR 0.54 [95% confidence interval (95% CI) 0.32–0.92]) (Table 3). However, adults

Table 2. Weight change from young adulthood to midlife and the risk of developing an arthritis condition, NHANES 1988–1994 and 1999–2016 (n = 13,669)*

Weight change†	Incident arthritis conditions, no.‡	Incidence (95% CI)§	HR (95% CI)¶	*P*
Normal–normal	783	23.3 (21.7–25.0)	Ref.	–
Normal–overweight	1,071	28.2 (26.6–30.0)	1.27 (1.10–1.46)	0.001
Normal–obese	554	40.6 (37.3–44.1)	1.73 (1.48–2.02)	<0.001
Overweight–normal	50	22.2 (16.8–29.3)	1.06 (0.76–1.47)	0.752
Overweight–overweight	333	22.8 (20.5–25.4)	1.12 (0.93–1.35)	0.229
Overweight–obese	539	38.8 (35.6–42.2)	2.00 (1.71–2.34)	<0.001
Obese–normal#	–	–	–	–
Obese–overweight	31	26.8 (18.9–38.2)	1.13 (0.68–1.87)	0.634
Obese–obese	238	40.0 (35.2–45.4)	2.08 (1.73–2.51)	<0.001

* 95% CI = 95% confidence interval; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; Ref. = reference.
† Weight-change categories based on body mass index (BMI) at age 25 years (young adulthood) and BMI 10 years prior to the survey (midlife). Weight-change categories are defined in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24252/abstract.
‡ Incident arthritis conditions reflect the number of new arthritis conditions that occurred over the 10 years of follow-up from the recalled midlife weight measure to the time of the survey.
§ Arthritis conditions incidence rate per 1,000 person-years, unadjusted.
¶ Hazard of developing an arthritis condition, using normal–normal as the reference group. The Cox proportional hazards model was sample weighted and adjusted for categorical age at the midlife measure, sex, race/ethnicity, education level at survey, smoking status at the midlife measure, and survey year.
# HR was suppressed because there were <10 incident cases in this group.

Table 3. Risk reduction and residual risk: HRs for weight change and incident arthritis conditions, NHANES 1988–1994 and 1999–2016 (n = 13,669)*

Weight change	HR (95% CI)†	*P*
Risk reduction hypothesis (weight loss vs. higher weight maintenance)		
Overweight–normal vs. overweight–overweight‡	0.94 (0.67–1.34)	0.739
Obese–overweight vs. obese–obese	0.54 (0.32–0.92)	0.023
Residual risk hypothesis (weight loss vs. lower weight maintenance)		
Overweight–normal vs. normal–normal	1.06 (0.76–1.47)	0.752
Obese–overweight vs. overweight–overweight	1.01 (0.61–1.68)	0.972

* Weight-change categories based on body mass index (BMI) at age 25 years (young adulthood) and BMI 10 years prior to the survey (midlife). Weight-change categories are defined in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24252/abstract. Incident arthritis conditions reflects new arthritis conditions that occurred over the 10 years of follow-up from the recalled midlife weight measure to the time of survey. 95% CI = 95% confidence interval; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey.
† HRs generated via post-estimation through the lincom command of the base model comparing all weight-change categories to the normal–normal reference group. All estimates were sample weighted and adjusted for categorical age at the midlife measure, sex, race/ethnicity, education level at survey, smoking status at the midlife measure, and survey year.
‡ This model presents the hazards of developing an arthritis condition for individuals who were overweight in young adulthood and lost to normal weight at midlife compared with individuals who were overweight and remained overweight. The other comparisons were constructed in the same fashion.

who lost from overweight to normal did not have a reduced risk of developing an arthritis condition (HR 0.94 [95% CI 0.67–1.34]) compared with adults who were overweight at both time points. Figures 2A and 2B show the difference in cumulative hazard functions for the 2 risk reduction comparisons.

Residual risk hypothesis. Compared with individuals who maintained a normal BMI, individuals who lost from overweight to normal (HR 1.06 [95% CI 0.76–1.47]) had a similar risk of developing an arthritis condition, suggesting there is little residual risk associated with having once had a higher BMI (Table 3). Adults who lost from obese to overweight also had a comparable risk to adults who were overweight at both time points (HR 1.01 [95% CI 0.61–1.68]). Figures 2C and 2D show the difference in cumulative hazard functions for the 2 residual risk comparisons.

Scenarios. If individuals who were obese in young adulthood and remained obese had instead lost weight and became overweight at midlife, 3.1% of incident arthritis conditions over the subsequent 10 years could have been averted (95% CI 1.0–5.2). Extrapolating these estimates to the population level, 335,276 cases (95% CI 108,154–562,398) on average per year of the study period, of a total of 10,815,354 incident cases, could have been averted under the hypothetical weight loss from obese scenario. If the total population had a normal BMI at both young adulthood and midlife, 24.7% (95% CI 17.6–31.2) of incident arthritis conditions may have been averted, corresponding to 2,671,392 cases on average per year at the population level (95% CI 1,903,502–3,374,390).

Analysis of sensitivity. Our sensitivity analysis using imputed data for missing covariates (see Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24252/abstract) was nearly identical to Table 2, suggesting that excluding participants without information on education or smoking status had no impact on our results. Supplementary Table 4, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24252/abstract, shows the associations between weight-change category and arthritis conditions stratified by midlife age. The overall patterns are broadly similar, but the younger age group (40–49 years) had a stronger risk in the weight gain categories. Additionally, being in the overweight–overweight group appears to increase risk for the younger age group but not for the older age group (50–69 years). Supplementary Table 5, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24252/abstract, shows the associations stratifying by smoking status, which are broadly similar to the main results. Using percent weight change to assess weight change, we found that obese adults who lost >10% had a reduced risk compared with those who maintained their weight, though the association was not statistically significant, likely reflecting a lack of precision, since few individuals achieved this degree of weight loss (see Supplementary Table 6, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24252/abstract).

DISCUSSION

This nationally representative study of the relation of weight change to the risk of incident arthritis had 4 principle findings. First, adults who lost weight from obese at age 25 years to overweight

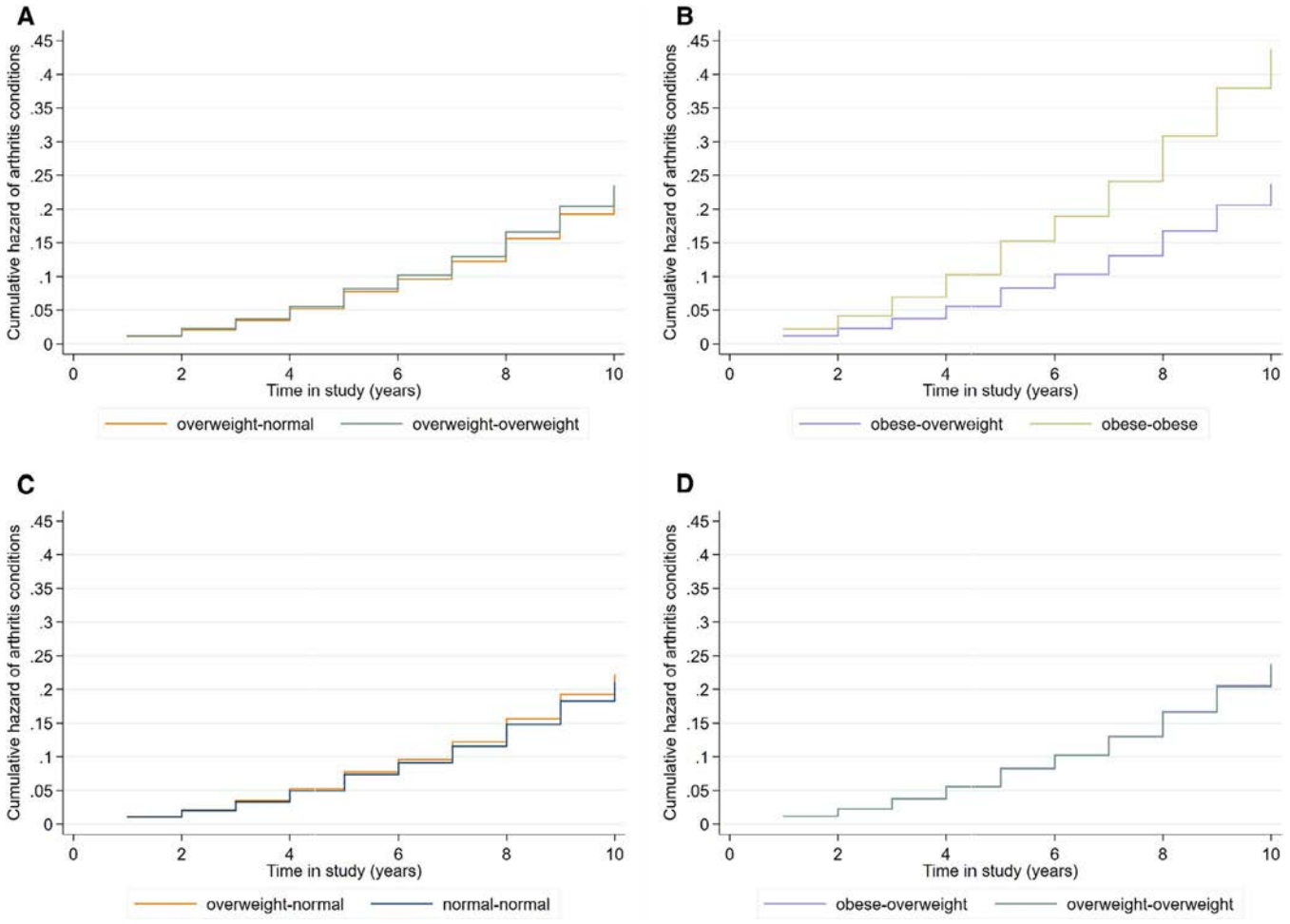

Figure 2. Cumulative hazards of arthritis conditions by weight-change category. **A**, Overweight–normal versus overweight–overweight; **B**, Obese–overweight versus obese–obese; **C**, Overweight–normal versus normal–normal; **D**, obese–overweight versus overweight–overweight. Graphs show results of testing the risk reduction hypothesis (**A** and **B**) and the residual risk hypothesis (**C** and **D**), from NHANES 1988–1994 and 1999–2016 (n = 13,669). Weight was recorded at age 25 years and at 10 years prior to the survey to determine weight change between young adulthood and midlife. The x-axis corresponds to years between the midlife BMI measure, when participants' ages were 40–69 years, and the time of the survey, when participants' ages were 50–79 years. Models were adjusted for age at the midlife measure, sex, race, education, smoking status at the midlife measure, and survey year.

at midlife had a reduced risk of developing an arthritis condition compared with those who remained obese. The same protective effect was not observed for individuals who lost from overweight to normal, suggesting weight loss is more beneficial for individuals with higher BMI. Second, individuals who lost weight had a similar level of risk as those who maintained a lower weight, suggesting there may not be residual risk associated with having been at a higher weight previously. Together, these results suggest that weight in midlife appears to be an important influencer of arthritis risk. Finally, we estimated that nearly one-fourth of incident arthritis cases at the national level, corresponding to 2.7 million individuals, would have been averted under the hypothetical scenario where all individuals were normal weight in young adulthood and midlife.

As in previous studies (12,19,20), we demonstrated an increase in arthritis risk associated with weight gain. Additionally, the risk reduction we observed was consistent with prior studies on osteoarthritis and gout (12,22,23). Weight loss may reduce arthritis risk through reduced joint loading and inflammation. Possibly the observed reduction in arthritis risk was because obese adults who lose to overweight started at lower weights than the obese adults who maintained their weight. However, Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24252/abstract, shows that the obese–overweight and obese–obese categories had similar average BMIs at age 25 years. Additionally, our sensitivity analysis using 10% weight change suggests that the findings are robust to different definitions of weight loss.

Prior evaluations of the residual risk hypothesis have been mixed. Analysis of an Australian cohort study concluded that childhood overweight measures were associated with adult knee pain independent of adult weight, but only among men (33). Conversely, an analysis of the 1946 British birth cohort study

concluded that there was no additional risk of knee osteoarthritis associated with adolescent BMI after accounting for adult BMI (34). Similarly, we found that those who lost weight had a comparable risk of developing an arthritis condition to participants who maintained a lower weight.

We also estimated the potential health implications of several weight-loss intervention and overweight/obesity prevention scenarios. We found that progressively more cases of incident arthritis conditions could be averted under more comprehensive intervention/prevention scenarios from 3.1% under the obesity weight-loss scenario to 24.7% under a comprehensive overweight/obesity prevention scenario (i.e., maintaining normal weight).

These findings underscore the importance of primary and secondary prevention of overweight/obesity in reducing arthritis incidence and its attendant substantial morbidity. In addition to reducing arthritis risk, lifestyle modification strategies associated with weight loss have been established as effective methods of improving outcomes and reducing pain and disability at the individual level among those with rheumatic and musculoskeletal diseases. Increasing physical activity has been shown to reduce the risk of disability in those with knee osteoarthritis (35). Exercise and diet interventions leading to weight loss have also been associated with reduction in knee pain (36,37). Bariatric surgery can reduce pain (38), improve joint function (39), increase overall functional health and wellbeing (38), and prevent gout and hyperuricemia (40).

Given the high cost of pharmacologic, including biologic, therapy for many rheumatic and musculoskeletal diseases and the lack of effective therapies for osteoarthritis beyond guidelines recommending weight loss and physical activity, a concerted effort to achieve and maintain a healthy weight is necessary to cost effectively manage arthritis conditions. However, we found that losing enough weight to drop BMI categories was rare (2.5%), potentially due to the set-point theory where the body calibrates its metabolic activity to a given weight and resists weight loss (41). Thus, the efficacy of individual-level behavioral change strategies encouraging weight loss/maintenance remain low. Instead, priority should be placed on developing policy interventions that reverse the upstream systemic and environmental drivers of the obesogenic environment, and as a result, reduce obesity at the population-level (42). Policy approaches, including taxes on unhealthy food and beverage, front-of-pack nutrition labeling, and reduction of junk food advertising to children, are generally more cost-effective than health promotion or clinical interventions that target patients who have already become overweight or obese (43).

Our study had several notable strengths. First, we used a novel application of a large, nationally representative cross-sectional survey to create a retrospective cohort design. As a result, our estimates are broadly generalizable to the US population. Second, in addition to evaluating weight loss in relation to weight maintenance, as most prior studies have done, we tested an additional hypothesis concerning the residual risk associated with having previously been at a higher weight. Third, since age-associated height loss can lead to spurious estimates of BMI (44), we used recalled height at age 25 years, which is strongly correlated with historically measured height (45,46), to calculate BMI at age 25.

Nonetheless, our study had several limitations. First, the definition of "arthritis" relied on self-reported doctor-diagnosed arthritis, which does not necessarily reflect the true incidence of arthritis conditions. Second, we investigated the association between weight change and the risk of arthritis conditions broadly, obscuring differences in types of arthritis. However, since self-reported doctor diagnosis of specific forms of arthritis in the NHANES is not validated, this broader approach is prone to less misclassification. Nonetheless, we acknowledge that the majority of these arthritis conditions are likely to be osteoarthritis, given its much higher prevalence (27 million in 2008 compared to 1.3 and 3 million cases of rheumatoid arthritis and gout, respectively) (47,48). Third, reliance on self-reported historic weight measures may have introduced error into our weight-change estimates. However, prior studies have shown that self-reports of both current weight (49) and past body weights are strongly correlated with measured weight (28,29). Fourth, our midlife BMI measure corresponds to an age range of 40–69 years, so our weight history period varies across individuals (between 15 and 44 years). However, analyses were adjusted for age at the midlife BMI measure to ensure that the associations of weight change with arthritis risk were made conditional on the length of the weight-change period. Additionally, our age-stratified results were broadly similar. Fifth, exclusions of prevalent arthritis cases were differential by weight-change category, with the largest exclusions in the normal–obese, overweight–obese, and obese–obese groups. However, the higher prevalence among these groups is consistent with the increased incidence we see in the present analysis. Finally, weight loss was rare (2.5%), affecting the precision of our estimates, and thus limiting our ability to make inferences regarding the effects of weight loss on arthritis risk.

In conclusion, in this nationally representative sample of US adults, we found strong associations between weight change from young adulthood to midlife and the risk of developing an arthritis condition. Weight gain was associated with an increased arthritis risk, whereas weight loss was associated with substantially reduced risk. Those who lost weight had a risk comparable to those who maintained a lower weight, suggesting that there may not be a residual risk associated with having previously been heavier. Extrapolating to the population-level, we estimated that a substantial portion of incident arthritis cases could be avoided through effective weight-loss strategies for individuals and population-level policies that encourage primary prevention of overweight/obesity. Our findings highlight the critical need to expand obesity treatment and prevention activities to achieve meaningful reductions in the burden of arthritis in the US 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. Stokes 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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ADDITIONAL DISCLOSURES

Authors Jason R. Waggoner and Chia-Wen Hsiao are employees of Ethicon Endo-Surgery, Inc. (a subsidiary of Johnson & Johnson, Inc.). Author Stephen S. Johnston is an employee of Johnson & Johnson.

REFERENCES

1. Park J, Mendy A, Vieira ER. Various types of arthritis in the United States: prevalence and age-related trends from 1999 to 2014. Am J Public Health 2018;108:256–8.
2. Martel-Pelletier J, Barr AJ, Cicuttini FM, Conaghan PG, Cooper C, Goldring MB, et al. Osteoarthritis. Nat Rev Dis Primers 2016;2:16072.
3. Rui P, Okeyode T. National ambulatory medical care survey: 2015 state and national summary tables. URL: https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2015_namcs_web_tables.pdf.
4. McDermott K, Elixhauser A, Sun R. Trends in hospital inpatient stays in the United States, 2005-2014. Vol. 225. Rockville, MD; 2017. URL: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb225-Inpatient-US-Stays-Trends.pdf.
5. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. JAMA 2012;307:483–90.
6. NCD Risk Factor Collaboration. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet 2017;390:2627–42.
7. Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology 1999;10:161–6.
8. Reyes C, Leyland KM, Peat G, Cooper C, Arden NK, Prieto-Alhambra D. Association between overweight and obesity and risk of clinically diagnosed knee, hip, and hand osteoarthritis: a population-based cohort sStudy. Arthritis Rheumatol 2016;68:1869–75.
9. Crowson CS, Matteson EL, Davis JM III, Gabriel SE. Contribution of obesity to the rise in incidence of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2013;65:71–7.
10. Linauskas A, Overvad K, Symmons D, Johansen MB, Stengaard-Pedersen K, de Thurah A. Body fat percentage, waist circumference, and obesity as risk factors for rheumatoid arthritis: a Danish cohort study. Arthritis Care Res (Hoboken) 2019;71:777–86.
11. Evans PL, Prior JA, Belcher J, Mallen CD, Hay CA, Roddy E. Obesity, hypertension and diuretic use as risk factors for incident gout: a systematic review and meta-analysis of cohort studies. Arthritis Res Ther 2018;20:1–15.
12. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men. Arch Intern Med 2005;165:742–8.
13. Jon Love T, Zhu Y, Zhang Y, Wall-Burns L, Ogdie A, Gelfand JM, et al. Obesity and the risk of psoriatic arthritis: a population-based study. Ann Rheum Dis 2012;71:1273–7.
14. Soltani-Arabshahi R, Wong B, Feng BJ, Goldgar DE, Duffin KC, Krueger GG. Obesity in early adulthood as a risk factor for psoriatic arthritis. Arch Dermatol 2010;146:721–6.
15. Gómez R, Conde J, Scotece M, Gómez-Reino JJ, Lago F, Gualillo O. What's new in our understanding of the role of adipokines in rheumatic diseases? Nat Rev Rheumatol 2011;7:528–36.
16. Thijssen E, Van Caam A, Van Der Kraan PM. Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. Rheumatology (Oxford) 2014;54:588–600.
17. Urban H, Little CB. The role of fat and inflammation in the pathogenesis and management of osteoarthritis. Rheumatology (Oxford) 2018;57:iv10–21.
18. Fowler-Brown A, Kim DH, Shi L, Marcantonio E, Wee CC, Shmerling RH, et al. The mediating effect of leptin on the relationship between body weight and knee osteoarthritis in older adults. Arthritis Rheumatol 2015;67:169–75.
19. Mo F, Morrison H, Neutel IC. Population attributable risk from obesity to arthritis in the Canadian Population Health Longitudinal Survey 1994-2006. Int J Rheum Dis 2014;17:628–34.
20. Zheng Y, Manson JE, Yuan C, Liang MH, Grodstein F, Stampfer MJ, et al. Associations of weight gain from early to middle adulthood with major health outcomes later in life. JAMA 2017;318:255–69.
21. Apold H, Meyer HE, Nordsletten L, Furnes O, Baste V, Flugsrud GB. Weight gain and the risk of knee replacement due to primary osteoarthritis: a population based, prospective cohort study of 225,908 individuals. Osteoarthritis Cartilage 2014;22:652–8.
22. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women: the Framingham Study. Ann Intern Med 1992;116:535–9.
23. Runhaar J, De Vos BC, van Middelkoop M, Vroegindeweij D, Oei EH, Bierma-Zeinstra SM. Prevention of incident knee osteoarthritis by moderate weight loss in overweight and obese females. Arthritis Care Res (Hoboken) 2016;68:1428–33.
24. National Center for Health Statistics. National Health and Nutrition Examination Survey: plan and Operations, 1999–2010. Vital Health Stat 2010;1:1999–2010.
25. Stokes A, Collins JM, Grant BF, Scamuffa RF, Hsiao CW, Johnson SS, et al. Obesity progression between young adulthood and midlife and incident diabetes: a retrospective cohort study of U.S. adults. Diabetes Care 2018;41:1025–31.
26. Stokes A, Preston SH. How dangerous is obesity? Issues in measurement and interpretation. Popul Dev Rev 2016;42:595–614.
27. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363:2211–9.
28. Casey VA, Dwyer JT, Berkey CS, Coleman KA, Gardner J, Valadian I. Long-term memory of body weight and past weight satisfaction: a longitudinal follow-up study. Am J Clin Nutr 1991;53:1493–8.
29. Perry GS, Byers TE, Mokdad AH, Serdula MK, Williamson DF. The validity of self-reports of past body weights by U.S. adults. Epidemiology 1995;6:61–6.
30. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res 2011;20:40–9.

31. Dutton GR, Kim Y, Jacobs DR Jr, Li X, Loria CM, Reis JP, et al. 25-year weight gain in a racially balanced sample of U.S. adults: the CARDIA study. Obesity (Silver Spring) 2016;24:1962–8.
32. Johnson C, Paulose-Ram R, Ogden C, Carroll MD, Kruszon-Moran D, Dohrmann SM, et al. National Health and Nutrition Examination Survey: analytic guidelines, 1999-2010. Vital Health Stat 2 2013;161: 1–24.
33. Antony B, Jones G, Venn A, Cicuttini F, March L, Blizzard L, et al. Association between childhood overweight measures and adulthood knee pain, stiffness and dysfunction: a 25-year cohort study. Ann Rheum Dis 2015;74:711–7.
34. Wills AK, Black S, Cooper R, Coppack RJ, Hardy R, Martin KR, et al. Life course body mass index and risk of knee osteoarthritis at the age of 53 years: evidence from the 1946 British birth cohort study. Ann Rheum Dis 2012;71:655–60.
35. Dunlop DD, Song J, Semanik PA, Sharma L, Bathon JM, Eaton CB, et al. Relation of physical activity time to incident disability in community dwelling adults with or at risk of knee arthritis: prospective cohort study. BMJ 2014;348:1–11.
36. Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA 2013;310:1263–73.
37. White DK, Neogi T, Rejeski WJ, Walkup MP, Lewis CE, Nevitt MC, et al. Can an intensive diet and exercise program prevent knee pain among overweight adults at high risk? Arthritis Care Res (Hoboken) 2015;67:965–71.
38. King WC, Chen J-Y, Belle SH, Courcoulas AP, Dakin GF, Elder KA, et al. Change in pain and physical function following bariatric surgery for severe obesity. JAMA 2016;315:1362–71.
39. Springer BD, Carter JT, McLawhorn AS, Scharf K, Roslin M, Kallies KJ, et al. Obesity and the role of bariatric surgery in the surgical management of osteoarthritis of the hip and knee: a review of the literature. Surg Obes Relat Dis 2017;13:111–8.
40. Maglio C, Peltonen M, Neovius M, Jacobson P, Jacobsson L, Rudin A, et al. Effects of bariatric surgery on gout incidence in the Swedish Obese Subjects study: a non-randomised, prospective, controlled intervention trial. Ann Rheum Dis 2017;76:688–93.
41. Fothergill E, Guo J, Howard L, Kerns JC, Knuth ND, Brychta R, et al. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. Obesity (Silver Spring) 2016;24:1612–9.
42. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie MK, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet 2011;378:804–14.
43. Gortmaker SL, Swinburn BA, Levy D, Carter R, Mabry PL, Finegood DT, et al. Changing the future of obesity: science, policy, and action. Lancet 2011;378:838–47.
44. Sorkin JD, Muller DC, Andres R. Longitudinal change in the heights of men and women: consequential effects on body mass index. Epidemiol Rev 1999;21:247–60.
45. Must A, Willett WC, Dietz WH. Remote recall of childhood height, weight, and body build by elderly subjects. Am J Epidemiol 1993;138:56–64.
46. Heaney R, Ryan R. Relation between measured and recalled body height. N Engl J Med 1988;319:795–6.
47. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I. Arthritis Rheum 2008;58:15–25.
48. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. Arthritis Rheum 2008;58:26–35.
49. Stokes A, Ni Y. Validating a summary measure of weight history for modeling the health consequences of obesity. Ann Epidemiol 2016;26:821–6.

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Low Back Pain as a Risk Factor for Recurrent Falls in People With Knee Osteoarthritis

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Objective. Knee osteoarthritis (OA) has been suggested to increase the risk of falls. Low back pain (LBP) is a potential risk factor for falls in people with knee OA, but this issue has not been addressed adequately in previous studies. The objective of this study was to investigate the relationship between LBP and falls in people with knee OA in a 12-month period.

Methods. Participants with knee OA (Kellgren/Lawrence [K/L] grade ≥1) completed questionnaires for LBP and falls that occurred in the preceding 12 months. Binary and ordinal logistic regression analyses were performed to assess the relationship between LBP or moderate-to-severe LBP (numeric rating scale ≥4 points) and any fall (≥1 fall) or recurrent falls (≥2 falls) after adjustment for age, sex, K/L grade, knee pain severity, and quadriceps strength. Sensitivity analyses were performed excluding people with sciatica, nonchronic LBP, K/L grade 1, and those receiving pain medications.

Results. We included 189 participants (ages 61–90 years, 78.3% women) in this study. Of these participants, 41 (21.6%) reported falls in the preceding 12 months. People with any LBP (n = 101) and those with moderate-to-severe LBP (n = 45) had 2.7- and 3.7-times higher odds of recurrent falls, respectively. Sensitivity analyses revealed a strong correlation between moderate-to-severe LBP and recurrent falls.

Conclusion. Thorough investigation of LBP as a risk factor for recurrent falls in people with knee OA may provide a novel insight into the pathomechanics of recurrent falls in this population.

INTRODUCTION

Knee osteoarthritis (OA), a leading cause of knee pain and disability, has been suggested to increase the risk of falls (1–3). Falls are the leading cause of unintentional injury in older adults (4), which could worsen mobility limitation and disability in patients with knee OA. In addition to disease prevention, the prevention of falls is necessary in these patients. A key component in the prevention of falls is the identification of factors that may increase the risk of falls (5). The potential risk factors for falls identified in patients with knee OA include poor balance, low muscle strength of the knee extensors and flexors, impaired proprioception, knee instability, and knee pain (6). Clear identification of the risk factors for falls in patients with knee OA can facilitate the development of multifactorial and multiple-component interventions for the prevention of falls (7).

A potential risk factor for falls in patients with knee OA that was not adequately addressed in earlier studies is low back pain (LBP). LBP, defined as pain in the lower back or buttocks, is a common comorbidity in 54.6–58.1% of patients with knee OA (8–10), which is much higher than that reported in older adults (11). In patients with knee OA, LBP increases the degree of disability (10) owing to its interaction with knee pain (8). Because LBP is a high-risk factor associated with falls in the preceding 12 months in older adults (12), it may also contribute, possibly in concert with knee pain, to falls in patients with knee OA. Patients with knee pain and LBP may have a higher probability of falls than those with knee pain or LBP alone. However, no study has directly investigated the relationship among LBP, knee pain, and falls in patients with knee OA. A clear understanding of the correlation between LBP and the risk of falls in patients with knee OA may help researchers in future clinical studies to establish effective programs for the prevention of falls in patients with knee OA.

This study investigated the correlation between LBP and falls in people with knee OA. Our hypotheses were that people with knee OA with LBP have a significantly higher prevalence of falls

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SIGNIFICANCE & INNOVATIONS

- Twenty-two percent of people with knee osteoarthritis (OA) experienced falls primarily caused by tripping/stumbling.
- Moderate-to-severe low back pain (LBP) was associated with recurrent falls in people with knee OA.
- The significant relationship between LBP and falls was independent of knee pain.

than do those without LBP, and that LBP has a stronger impact on falls in people with knee OA with severe knee pain than in those with mild knee pain.

MATERIALS AND METHODS

Participants. Community-dwelling elderly participants were identified through a mailed survey and invited to the Health and Welfare Center in Ayabe-shi, Kyoto, in September 2018 to participate in this study. The ethics committee of Kyoto University approved the study (approval E1923), and written informed consent was obtained from all the participants prior to enrollment. The inclusion criteria were age ≥45 years, knees with Kellgren/Lawrence (K/L) grade ≥1 based on the original version (13) in 1 or both knees in the medial tibiofemoral compartment, evaluated on weight-bearing anteroposterior radiographs, and ability to walk independently on a flat surface without an ambulatory assistive device. Participants with bilateral knee OA were not considered separately from those with unilateral knee OA. The exclusion criteria were a history of knee surgery, a history of rheumatoid arthritis, a history of periarticular fracture, the presence of neurologic problems such as hemiplegia, and administration of an intraarticular injection in the last month. Since knee pain and LBP are common in community-dwelling individuals age ≥45 years in Japan (14), the results could be generalized in this age group. We included people with K/L grade of ≥1 because preradiographically defined knee OA, particularly K/L grade 1, predicts radiographic OA progression to at least grade 2 within 3–5 years (15,16).

Measurements. LBP and self-reported assessment of falls were evaluated in all the participants. Demographic characteristics, radiographic OA severity, knee OA-related self-reported measures of knee pain and disability, and quadriceps muscle strength were also assessed as participant characteristics and/or covariates.

LBP. LBP was evaluated using the established self-report questionnaire in accordance with the consensus criteria for optimal definitions of LBP (17). This questionnaire was developed to standardize definitions of LBP for use in epidemiologic studies (17). The presence of LBP was determined by asking the question: "In the past 4 weeks, have you had pain in your lower back?" LBP was defined as pain in the lower back or buttocks and illustrated using a pain diagram (17). The presence of sciatica was identified by asking the question, "Have you had pain that goes down the leg?" LBP frequency (some days, most days, or daily), duration (<3 months, 3–7 months, 7 months to 3 years, or ≥3 years), and severity (0–10 points on a numeric rating scale [NRS]) in the past 4 weeks were also evaluated using the same questionnaire (17).

Assessment of falls. A fall was defined as unintentionally coming to rest on the ground or at some other lower level for causes other than a major intrinsic event (e.g., stroke) or an overwhelming external force (e.g., impact from a moving vehicle) (18). Falls in the previous 12 months were evaluated using the 4-point Hopkins Falls Grading Scale, which has established face validity, content validity, and excellent interrater reliability (19). Grade 1 indicates a near-fall; grade 2, a fall without injury; grade 3, a fall requiring medical attention; and grade 4, a fall requiring hospital admission. An individual was considered a faller if he or she had at least 1 fall (grades 2–4) in the preceding 12 months.

A customized survey was also completed by each subject to identify the cause of the fall (slip, trip/stumble, hit/bump, collapse of legs, incorrect shift of body weight, or others), activity at the time of the fall (walking, standing, turning, or others), and the initial direction of the fall (primarily forward, sideways, or backward). The survey was created by one author (HI) on the basis of clinical experience in the musculoskeletal field and a validated questionnaire for analyzing real-life falls captured on video (20).

Participant characteristics and covariates. Data on age, sex, and height were self-reported by the participants. Body mass was measured on a digital scale, with the participants dressed but not wearing shoes. Body mass index was calculated by dividing the body mass by the height (kg/m^2). Radiographic OA severity was assessed in the anteroposterior short view in the weight-bearing position as in an earlier study (21). Knee pain severity and the disability level were evaluated using the Japanese Knee Osteoarthritis Measure (JKOM) subcategories of "pain and stiffness" (8 questions, 0–32 points) and "activities of daily living" (10 questions, 0–40 points) (22). For each subcategory, higher scores indicate a worse condition. Self-reported pain medication for knee pain was also assessed. Gait velocity (in meters/second) was evaluated using the 10-meter walking test with self-selected speed, and a trained examiner (KS) measured the time taken to walk 10 meters with a stopwatch in accordance with a previously suggested method (23). The maximum isometric quadriceps strength (in Nm/kg) in both legs was measured using a hand-held dynamometer (μTas F-1, Anima) in accordance with a previously described method (24). The minimum detectable change (MDC_{95}) was 0.227 Nm/kg, and the intrarater reliability was excellent (intraclass correlation coefficient [$ICC_{1,1}$] 0.939 [95% confidence interval (95% CI) 0.921–0.954]) (24).

Statistical analysis. The sample size was calculated on the basis of the pilot data of multiple falls in people with (n = 13) and without LBP (n = 7) to find a significant relationship between LBP and multiple falls in an uncorrected chi-square test using the

Power and Sample Size Program, version 3.1.2 (Vanderbilt University Medical Center) (25). Earlier data showed that the probabilities of multiple falls in people with and without LBP were 0.231 and 0, respectively. To reject the null hypothesis that the multiple fall rates for people with and without LBP are equal to a probability (power) of 0.8, at least 68 people were needed in the study. The type I error probability associated with the test of this null hypothesis was 0.05. At least 75 participants were needed for this study, considering the potential 10% dropout rate due to the exclusion criteria and missing data. However, the maximum number of recruited participants was not limited because of the observational nature of the study.

To minimize any bias from similarities between the right and left knees of the same participant, only 1 knee per participant (index knee) was included in the statistical analysis of K/L grade and quadriceps strength. The index knee was defined as the more painful knee in the past or present. If the participants considered the pain in both knees to be equal, the index knee was randomly selected using a computer-generated permuted block randomization scheme (26).

Binary logistic regression analyses were performed to assess the relationship between LBP (0 = no, 1 = yes), which is the independent variable, and a fall (≥1 fall; 0 = no, 1 = yes) or multiple falls (≥2 falls; 0 = no, 1 = yes) in the preceding 12 months, which is the dependent variable. Because multiple (recurrent) falls may have different risk factors and have been associated with more physician contact and functional decline (27–30), this parameter (≥2 falls) was also included as a dependent variable in a separate binary logistic regression model. To investigate the possibility that LBP increases the number of falls, an ordinal logistic regression analysis was performed, with the number of falls included as an ordinal dependent variable (1 = no fall, 2 = 1 fall, 3 = ≥2 falls). Age (continuous), female sex, index knee tibiofemoral joint K/L grade (ordinal), JKOM pain score (continuous), and quadriceps muscle strength (continuous) were included as covariates. These covariates were chosen a priori based on clinical judgment and their

Table 1. Participants characteristics*

Characteristic	All participants (n = 189)	With LBP (n = 101)	Without LBP (n = 88)
Demographics			
Age, years	74.4 ± 5.70	74.6 ± 5.62	74.2 ± 5.8
Female, no. (%)	148 (78.0)	81 (80.2)	67 (76.1)
Height, meters	1.55 ± 0.08	1.55 ± 0.08	1.55 ± 0.08
Body mass, kg	52.4 ± 8.60	52.3 ± 8.54	52.5 ± 8.71
BMI, kg/m^2	21.8 ± 2.70	21.7 ± 2.85	21.9 ± 2.54
Disease characteristics, no. (%)			
Index knee K/L grade			
1	82 (43.4)	45 (44.6)	37 (42.1)
2	88 (46.6)	44 (43.6)	44 (50.0)
3	15 (7.9)	10 (9.9)	5 (5.7)
4	4 (2.1)	2 (2.0)	2 (2.3)
Bilateral disease	177 (93.7)	95 (94.1)	82 (93.2)
Functional characteristics			
Gait velocity, meters/second	1.56 ± 0.24	1.56 ± 0.27	1.57 ± 0.21
Quadriceps muscle strength, Nm/kg	1.22 ± 0.42	1.23 ± 0.48	1.21 ± 0.33
Knee pain characteristics			
JKOM			
Pain and stiffness, points†	4.48 ± 5.04, 3 [0–7]	5.34 ± 5.14, 5 [1–8]	3.49 ± 4.76, 1 [0–6]
Activities of daily living, points†	2.87 ± 4.04, 1 [0–5]	3.90 ± 4.63, 2 [0–6]	1.69 ± 2.83, 0 [0–2]
Pain medication for knee, no. (%)	1 (0.5)	0 (0.0)	1 (1.1)
LBP characteristics			
Presence of LBP, no. (%)	101 (53.4)	101 (100)	0 (0.0)
NRS score for LBP, points	2.05 ± 2.58	3.84 ± 2.35	–
Moderate-to-severe LBP, no. (%)	45 (23.8)	45 (44.6)	–
LBP frequency, no. (%)			
On some days	57 (30.1)	57 (56.4)	–
On most days	21 (11.1)	21 (20.8)	–
Daily	23 (12.2)	23 (22.8)	–
LBP duration, no. (%)			
<3	7 (3.7)	7 (6.9)	–
3–7 months	9 (4.8)	9 (8.9)	–
7 months to 3 years	25 (13.2)	25 (24.8)	–
≥3 years	60 (31.7)	60 (59.4)	–

* Values are the mean ± SD unless indicated otherwise. BMI = body mass index; JKOM = Japanese Knee Osteoarthritis Measure; K/L grade = Kellgren/Lawrence grade; LBP = low back pain; NRS = numeric rating scale.
† Higher scores indicate severe knee pain or severe disability. Median [interquartile range] is also provided because of the scattered distribution of the answered items.

Table 2. Characteristics of falls*

Characteristics	No fall (n = 148)	1 fall (n = 17)	≥2 falls (n = 24)
Mechanism of falls			
Slip	–	5 (29.4)	4 (16.7)
Trip/stumble	–	10 (58.8)	11 (45.8)
Hit/bump	–	0 (0.0)	0 (0.0)
Legs collapsed	–	0 (0.0)	0 (0.0)
Incorrect shift of body weight	–	0 (0.0)	3 (12.5)
Others	–	0 (0.0)	0 (0.0)
Combined	–	2 (11.8)	6 (25.0)
Activity at time of fall			
Walking	–	9 (52.9)	16 (66.7)
Standing	–	1 (5.9)	1 (4.2)
Turning	–	3 (17.7)	3 (12.5)
Other	–	4 (23.5)	2 (8.3)
Combined	–	0 (0.0)	2 (8.3)
Initial fall direction			
Primarily forward	–	11 (64.7)	16 (66.7)
Primarily sideways	–	3 (17.7)	2 (8.3)
Primarily backward	–	3 (17.7)	2 (8.3)
Combined	–	0 (0.0)	4 (16.7)
Hopkins Falls Grading Scale			
Grade 2	–	8 (47.1)	11 (45.8)
Grade 3	–	6 (35.3)	8 (33.3)
Grade 4	–	3 (17.7)	5 (20.8)

* Values are the number (%).

potential correlation with LBP and falls, and not on the causal relationship between LBP and falls (i.e., not an intermediate variable). Because LBP severity may have different functional implications (i.e., severe LBP may be strongly associated with falls), LBP was classified according to severity (0 = no, 1 = moderate-to-severe LBP [NRS ≥4 points]) and included as the independent variable in the separate binary logistic regression model. This judgment was made because at least moderate pain is suggested to correspond to a state with unacceptable symptoms and considered a clinically relevant treatment target (31,32). To test the hypothesis that a statistical interaction exists between the presence of LBP and knee pain severity, an interaction term of two variables (LBP × JKOM pain and stiffness) was further included in the binary and ordinal logistic regression analyses as the independent variable. Sensitivity analyses were performed to show the relationship between LBP and falls in specific subjects. The sensitivity analyses excluded people with sciatica, people taking oral pain medications, people with nonchronic LBP, and people with K/L grade 1.

Subgroup analyses were performed to investigate the effect of LBP frequency, duration, and intensity on falls in people with LBP. Here, logistic regression analyses were performed with LBP frequency (1 = on some days, 2 = on most days, and 3 = daily), duration (1 = <3 months, 2 = 3–7 months, 3 = 7 months to 3 years, and 4 = ≥3 years), and LBP intensity (continuous) as independent variables. Data analyses were performed using SAS JMP software, version 14.0. *P* values less than 0.05 were considered statistically significant.

RESULTS

Of the 206 participants evaluated, 10 (4.9%) with nonradiographic OA (K/L grade 0) and 7 (3.4%) who were receiving intraarticular injections were excluded. Thus, 189 participants (age 61–90 years, 78.3% women) were included in the study. Table 1 compares the characteristics of the participants with (n = 101 [53.4%]) and without LBP (n = 88 [46.6%]). Of the 101 participants with LBP, 45 (44.6%) and 94 (93.1%) had moderate-to-severe LBP and chronic (>3 months) LBP, respectively. The participants with LBP had more severe knee pain and disability than the participants without LBP.

Table 2 shows the number of single and multiple (≥2) falls that occurred in the preceding 12 months and their characteristics. Trip/stumble was the most frequent cause of falls, accounting for 58.8% and 45.8% of single and multiple falls, respectively. More than one-half of the falls occurred during walking and in a primarily forward direction in both single and multiple falls.

Table 3. Results of binary and ordinal logistic regression analyses showing the relationship between LBP and falls in people with knee osteoarthritis*

Variable	No. (%) of subjects			OR (95% CI)†		Proportional OR (95% CI)†
	No fall	1 fall	≥2 falls	≤1 fall	≥2 falls	
Any LBP						
Yes	75 (74.3)	8 (7.9)	18 (17.8)	1.56 (0.74–3.29)	2.74 (1.01–7.49)‡	1.72 (0.82–3.62)
No	73 (83.0)	9 (10.2)	6 (6.8)	–	–	–
Moderate-to-severe LBP§						
Yes	28 (62.2)	5 (11.1)	12 (26.7)	2.90 (1.31–6.43)‡	3.72 (1.45–9.58)‡	3.18 (1.46–6.93)‡
No	120 (83.3)	12 (8.3)	12 (8.3)	–	–	–

* 95% CI = 95% confidence interval; LBP = low back pain; OR = odds ratio.
† OR (95% CI) and proportional OR (95% CI) of mild-to-severe LBP (0 = no, 1 = yes) and moderate-to-severe LBP (0 = no, 1 = yes) were calculated to indicate their predictive ability for fall experience (≤1 fall or ≥2 falls) while simultaneously including (1-step model) age, female sex, index knee Kellgren/Lawrence grade, Japanese Knee Osteoarthritis Measure pain subscale score, and quadriceps muscle strength.
‡ Statistically significant.
§ Moderate-to-severe LBP indicates numeric rating scale ≥4 points. In the calculation of OR (95% CI) for moderate-to-severe LBP, people with mild LBP were treated as those without LBP.

Relationship between LBP and falls. Table 3 compares the prevalence of single and multiple falls in people with and without LBP. The people with LBP had a nonsignificantly higher prevalence of falls than the people without LBP (chi-square test $P = 0.065$). The binary logistic regression analysis revealed that people with LBP had multiple falls more frequently than those without LBP after adjustment for covariates (odds ratio [OR] 2.74 [95% CI 1.01–7.49]; $P = 0.04$).

The people with moderate-to-severe LBP had a significantly higher prevalence of falls than those without LBP (chi-square test $P = 0.007$). The binary logistic regression analyses revealed that the people with moderate-to-severe LBP had a significantly higher prevalence of any (OR 2.90 [95% CI 1.31–6.43]; $P = 0.010$) and multiple falls (OR 3.72 [95% CI 1.45–9.58]; $P = 0.007$) than those without LBP after adjustment for covariates. The ordinal logistic regression analysis also showed that the people with moderate-to-severe LBP had an increased probability of having any or multiple falls (proportional OR 3.18 [95% CI 1.46–6.9]; $P = 0.004$). No statistically significant interaction between LBP × JKOM pain and stiffness was confirmed in the binary and ordinal logistic regression analyses.

Table 4 shows the results of the sensitivity analyses. The results showed that the relationship between any LBP and multiple falls became nonsignificant after the exclusion of people with sciatica (n = 22) and people with K/L grade = 1 (n = 82). The results did not change considerably with the exclusion of people receiving medication (n = 1) or people with nonchronic LBP (n = 7). During the sensitivity analyses, the people with moderate-to-severe LBP were found to have a significantly higher prevalence of falls than those without LBP after adjustment for covariates.

Table 4. Sensitivity analysis for the relationship between LBP and falls in people with knee osteoarthritis*

Variable	No. (%) of subjects			OR (95% CI)†		Proportional OR (95% CI)†
	No fall	1 fall	≥2 falls	≤1 fall	≥2 falls	
Excluding sciatica (n = 22)						
Any LBP						
Yes	61 (77.2)	6 (7.6)	12 (15.2)	1.33 (0.60–2.92)	2.20 (0.77–6.35)	1.45 (0.66–3.17)
No	73 (83.0)	9 (10.2)	6 (6.8)	–	–	–
Moderate-to-severe LBP‡						
Yes	19 (65.5)	3 (10.3)	7 (24.1)	2.47 (0.99–6.20)	3.36 (1.13–9.95)§	2.71 (1.11–6.63)§
No	115 (83.3)	12 (8.7)	11 (8.0)	–	–	–
Excluding pain medication (n = 1)						
Any LBP						
Yes	75 (74.3)	8 (7.9)	18 (17.8)	1.52 (0.71–3.22)	3.60 (1.41–9.24)§	1.69 (0.80–3.54)
No	72 (82.8)	9 (10.3)	6 (6.9)	–	–	–
Moderate-to-severe LBP‡						
Yes	28 (62.2)	5 (11.1)	12 (26.7)	2.79 (1.26–6.15)§	3.60 (1.41–9.24)§	3.20 (1.48–6.93)§
No	119 (83.2)	12 (8.4)	12 (8.4)	–	–	–
Excluding nonchronic LBP (n = 7)						
Any LBP						
Yes	69 (73.4)	8 (8.5)	17 (18.1)	1.64 (0.77–3.49)	2.81 (1.01–7.79)§	1.80 (0.85–3.82)
No	73 (83.0)	9 (10.2)	6 (6.8)	–	–	–
Moderate-to-severe LBP‡						
Yes	28 (63.6)	5 (11.4)	11 (25.0)	2.45 (1.09–5.49)§	3.04 (1.16–7.98)§	2.66 (1.21–5.86)§
No	114 (82.6)	12 (8.7)	12 (8.7)	–	–	–
Excluding K/L grade 1 (n = 82)						
Any LBP						
Yes	43 (76.8)	4 (7.1)	9 (16.1)	1.18 (0.42–3.29)	2.87 (0.68–12.1)	1.38 (0.50–3.80)
No	42 (82.4)	6 (11.8)	3 (5.9)	–	–	–
Moderate-to-severe LBP‡						
Yes	16 (64.0)	3 (12.0)	6 (24.0)	2.81 (0.93–8.54)	4.09 (1.07–15.6)§	3.12 (1.07–9.14)§
No	69 (84.2)	7 (8.5)	6 (7.3)	–	–	–

* 95% CI = 95% confidence interval; LBP = low back pain; OR = odds ratio.
† OR (95% CI) and proportional OR (95% CI) of mild-to-severe LBP (0 = no, 1 = yes) and moderate-to-severe LBP (0 = no, 1 = yes) were calculated to indicate their predictive ability for fall experience (≤1 fall or ≥2 falls) while simultaneously including (1-step model) age, female sex, index knee Kellgren/Lawrence grade, Japanese Knee Osteoarthritis Measure pain subscale score, and quadriceps muscle strength.
‡ Moderate-to-severe LBP indicates numeric rating scale ≥4 points. In the calculation of OR (95% CI) for moderate-to-severe LBP, people with mild LBP were treated as those without LBP.
§ Statistically significant.

Table 5. Results of binary and ordinal logistic regression analyses showing the relationship between LBP frequency, duration, and intensity and fall in a knee osteoarthritis subpopulation with LBP (n = 101)*

Variable	No. (%) or mean ± SD			OR (95% CI)†		Proportional OR (95% CI)†
	No fall	1 fall	≥2 falls	≤1 fall	≥2 falls	
LBP frequency						
Daily	14 (18.7)	2 (25.0)	7 (38.9)	1.41 (0.81–2.46)	1.66 (0.89–3.12)	1.47 (0.85–2.53)
On most days	16 (21.3)	1 (12.5)	4 (22.2)	–	–	–
On some days	45 (60.0)	5 (62.5)	7 (38.9)	–	–	–
LBP duration						
≥3 years	45 (60.0)	6 (75.0)	9 (50.0)	1.13 (0.66–1.93)	0.88 (0.50–1.54)	1.07 (0.64–1.78)
7 months to 3 years	17 (22.7)	2 (25.0)	6 (33.3)	–	–	–
3–7 months	7 (9.3)	0 (0.0)	2 (11.1)	–	–	–
<3 months	6 (8.0)	0 (0.0)	1 (5.6)	–	–	–
LBP intensity	3.53 ± 2.23	4.13 ± 2.70	5.00 ± 2.47	1.19 (0.97–1.47)	1.25 (0.99–1.58)	1.20 (0.98–1.46)

* 95% CI = 95% confidence interval; LBP = low back pain; OR = odds ratio.
† OR (95% CI) and proportional OR (95% CI) of LBP frequency (1 = on some days, 2 = on most days, and 3 = daily), duration (1 = <3 months, 2 = 3–7 months, 3 = 7 months to 3 years, and 4 = ≥3 years), and LBP intensity (continuous) were calculated to indicate their predictive ability for fall experience (≤1 fall or ≥2 falls) while simultaneously including (1-step model) age, female sex, index knee Kellgren/Lawrence grade, Japanese Knee Osteoarthritis Measure pain subscale score, and quadriceps muscle strength.

Relationship between frequency, duration, and intensity of LBP and falls in people with LBP. Table 5 shows the subgroup analyses of the relationship between the frequency, duration, and intensity of LBP and falls in subpopulations of people with LBP. None of these variables were significantly associated with falls, although people with more severe LBP had a higher probability of falls than those with less severe LBP.

DISCUSSION

This study found that people with LBP, particularly those with moderate-to-severe LBP, had a higher prevalence of falls in the preceding 12 months, which supports our first hypothesis. Contrary to our second hypothesis, LBP significantly increased the probability of falls, regardless of knee pain severity. Figure 1 shows the graphic abstract. The findings show new potential risk factors for falls associated with knee OA, which may be beneficial knowledge in future clinical studies for the development of an effective strategy for the prevention of falls in people with knee OA.

The observed statistically significant relationship between LBP and falls, particularly multiple falls, in the preceding 12 months indicates that LBP may contribute to falls in people with knee OA or vice versa. Knee pain and quadriceps muscle strength are important confounders and have been associated with an increased probability of falls in patients with knee OA (33,34). However, this study included knee pain severity and quadriceps strength as covariates, which means that the observed relationship between LBP and falls cannot be attributed to severe knee pain or low muscle strength of the quadriceps.

People with moderate-to-severe LBP had an increased probability of multiple falls in the preceding 12 months. This result was consistent throughout the sensitivity analyses, which means that the observed relationship between moderate-to-severe LBP and multiple falls would be robust to change in particular features such as the presence of sciatica, LBP phase, and preradiographic OA (K/L grade 1). Considering that the relationship between any LBP and falls is weak, LBP severity may be a crucial factor for recurrent falls, which are indicative of poor health (27–30).

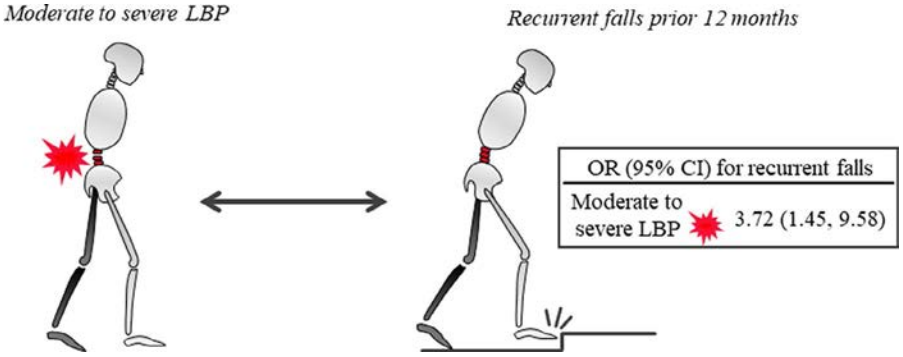

Figure 1. Graphical abstract. Moderate-to-severe low back pain (LBP) in people with knee osteoarthritis demonstrated a significantly higher prevalence of recurrent falls in the preceding 12 months (odds ratio [OR] 3.72 [95% confidence interval (95% CI) 1.45–9.58]) regardless of the presence of sciatica, use of pain medication, LBP duration, and Kellgren/Lawrence grade as shown in sensitivity analyses. Falls frequently occurred by tripping/stumbling during walking and primarily in the forward direction.

This study showed that trip/stumble was the primary cause of single (58.8%) and multiple falls (45.8%). This finding supports the results of an earlier study stating that ~40% of falls in people with severe knee OA were due to a trip/stumble (3). Notably, the correlation between moderate-to-severe LBP and an increased probability of multiple falls was consistent even when nontrip/nonstumble-related falls were excluded (data not shown). Moderate-to-severe LBP may have a correlation with trip/stumble-related multiple falls.

As highlighted in an earlier study, the relationship between LBP and falls caused by a trip/stumble may involve central mechanisms (35). Chronic pain may interfere with the cognitive activity necessary to prevent a fall. Successful avoidance or interruption of falls typically requires a cognitively mediated physical maneuver such as a quick reaction during ambulation. A systematic review of 25 studies revealed that adults with chronic pain had impaired executive functions compared with healthy controls (36). Furthermore, the ability of patients with knee OA to avoid obstacles is impaired (37), and pain relief partially restores this ability (38). An impaired response to physical hazards when attention is directed elsewhere can result in falls. Our findings show that the risk of falls caused by a trip/stumble is consistent with the cognitively mediated pathway.

This study included community-dwelling participants with relatively mild OA. All the participants had to walk independently of any assistive device, which may explain the low fall rate in the preceding 12 months (21.7%). Our study results should be interpreted with caution when considering more frail patients, such as elderly patients under long-term care, because an incorrect shift of body weight is the primary cause of falls in these patients (20).

LBP in people with knee OA is associated with a greater degree of disability (8,10). This study expands on this association by showing that people with coexisting knee OA and LBP have an increased risk of falls and disability. Our findings reinforce those of an earlier study that reported a significantly higher risk of multiple falls in adults with LBP in a preceding 12-month period (12).

The practical relevance of this study is in showing that LBP is an independent risk factor for falls in 54.6–58.1% of the patients with knee OA (8–10). Earlier studies have shown that patients with knee OA have an increased risk of falls (1–3). Our results suggest that the increased risk of falls in patients with knee OA may be due, at least in part, to LBP. A thorough investigation of LBP in patients with knee OA may provide novel insights into the pathomechanics of falls in these patients.

Even though the mechanism of LBP is still unclear, LBP can potentially be managed nonsurgically (39). Although the cross-sectional nature of this study limits our interpretation of the causality, this study highlights LBP as a potential therapeutic target to reduce the probability of falls in patients with knee OA. A prospective cohort study on falls in patients with LBP should be interesting.

This study has some limitations. First, the cross-sectional nature of the study limited our ability to identify causality between LBP and falls. LBP may be a consequence of previous falls, and our findings do not necessarily highlight intervention for LBP. Nevertheless, ~60% of the participants with LBP have had the condition for >3 years. The long history of LBP disproves the claim that LBP was caused by falls that occurred in the preceding 12 months. Second, the lack of information on pain in other joints limited our analysis. Concurrent musculoskeletal pain in other joints may contribute to falls (40). Finally, the self-reported questionnaire used for assessing falls experienced in the previous 12 months may have a recall bias. Because this study did not evaluate the presence of cognitive impairment, the survey of falls may have underestimated the experience of falls in people with cognitive impairment (41). Daily recordings of falls on a calendar, a gold-standard method, should be considered in future studies (42).

This study has several strengths that include: 1) a validated and reliable questionnaire used to assess LBP (17) and falls (19), 2) recruitment of people with knee OA from a community that may adequately represent the whole population, thereby limiting potential selection bias, and 3) performance of several sensitivity analyses that revealed the strong correlation between moderate-to-severe LBP and recurrent falls.

People with moderate-to-severe LBP have an increased likelihood of having recurrent falls in the preceding 12 months. A thorough investigation of LBP may provide a novel insight into the pathomechanics of recurrent falls. We need to determine the causality and ascertain the effectiveness of therapeutic interventions for LBP for the prevention of falls in people 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. Iijima had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Iijima, Aoyama, Takahashi.

REFERENCES

1. Khalaj N, Abu Osman NA, Mokhtar AH, Mehdikhani M, Wan Abas WA. Balance and risk of fall in individuals with bilateral mild and moderate knee osteoarthritis. PLoS One 2014;9:e92270.
2. Smith TO, Higson E, Pearson M, Mansfield M. Is there an increased risk of falls and fractures in people with early diagnosed hip and knee osteoarthritis? Data from the Osteoarthritis Initiative. Int J Rheum Dis 2018;21:1193–201.
3. Tsonga T, Michalopoulou M, Malliou P, Godolias G, Kapetanakis S, Gkasdaris G, et al. Analyzing the history of falls in patients with severe knee osteoarthritis. Clin Orthop Surg 2015;7:449–56.
4. Bergen G. Falls and fall injuries among adults aged ≥65 years: United States, 2014. MMWR Morb Mortal Wkly Rep 2016;65:993–8.

5. Rubenstein LZ, Josephson KR. Falls and their prevention in elderly people: what does the evidence show? Med Clin North Am 2006;90:807–24.
6. Manlapaz DG, Sole G, Jayakaran P, Chapple CM. Risk factors for falls in adults with knee osteoarthritis: a systematic review. PM R 2019;11:745–57.
7. Hopewell S, Adedire O, Copsey BJ, Boniface GJ, Sherrington C, Clemson L, et al. Multifactorial and multiple component interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2018;7:Cd012221.
8. Iijima H, Suzuki Y, Aoyama T, Takahashi M. Interaction between low back pain and knee pain contributes to disability level in individuals with knee osteoarthritis: a cross-sectional study. Osteoarthritis Cartilage 2018;26:1319–25.
9. Suri P, Morgenroth DC, Kwoh CK, Bean JF, Kalichman L, Hunter DJ. Low back pain and other musculoskeletal pain comorbidities in individuals with symptomatic osteoarthritis of the knee: data from the Osteoarthritis Initiative. Arthritis Care Res (Hoboken) 2010;62:1715–23.
10. Wolfe F. Determinants of WOMAC function, pain and stiffness scores: evidence for the role of low back pain, symptom counts, fatigue and depression in osteoarthritis, rheumatoid arthritis and fibromyalgia. Rheumatology (Oxford) 1999;38:355–61.
11. Meucci RD, Fassa AG, Faria NM. Prevalence of chronic low back pain: systematic review. Rev Saude Publica 2015;49:1.
12. Stubbs B, Binnekade T, Eggermont L, Sepehry AA, Patchay S, Schofield P. Pain and the risk for falls in community-dwelling older adults: systematic review and meta-analysis. Arch Phys Med Rehabil 2014;95:175–87.
13. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
14. Muraki S, Akune T, Oka H, En-Yo Y, Yoshida M, Saika A, et al. Impact of knee and low back pain on health-related quality of life in Japanese women: the Research on Osteoarthritis Against Disability (ROAD). Mod Rheumatol 2010;20:444–51.
15. Hart DJ, Spector TD. Kellgren & Lawrence grade 1 osteophytes in the knee: doubtful or definite? Osteoarthritis Cartilage 2003;11:149–50.
16. Cibere J, Sayre EC, Guermazi A, Nicolaou S, Kopec JA, Esdaile JM, et al. Natural history of cartilage damage and osteoarthritis progression on magnetic resonance imaging in a population-based cohort with knee pain. Osteoarthritis Cartilage 2011;19:683–8.
17. Dionne CE, Dunn KM, Croft PR, Nachemson AL, Buchbinder R, Walker BF, et al. A consensus approach toward the standardization of back pain definitions for use in prevalence studies. Spine (Phila Pa 1976) 2008;33:95–103.
18. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988;319:1701–7.
19. Davalos-Bichara M, Lin FR, Carey JP, Walston JD, Fairman JE, Schubert MC, et al. Development and validation of a falls-grading scale. J Geriatr Phys Ther 2013;36:63–7.
20. Yang Y, Schonnop R, Feldman F, Robinovitch SN. Development and validation of a questionnaire for analyzing real-life falls in long-term care captured on video. BMC Geriatr 2013;13:40.
21. Iijima H, Aoyama T, Nishitani K, Ito H, Fukutani N, Isho T, et al. Coexisting lateral tibiofemoral osteoarthritis is associated with worse knee pain in patients with mild medial osteoarthritis. Osteoarthritis Cartilage 2017;25:1274–81.
22. Akai M, Doi T, Fujino K, Iwaya T, Kurosawa H, Nasu T. An outcome measure for Japanese people with knee osteoarthritis. J Rheumatol 2005;32:1524–32.
23. Fritz S, Lusardi M. White paper: "walking speed: the sixth vital sign." J Geriatr Phys Ther 2009;32:46–9.
24. Iijima H, Eguchi R, Aoyama T, Takahashi M. Trunk movement asymmetry associated with pain, disability, and quadriceps strength asymmetry in individuals with knee osteoarthritis: a cross-sectional study. Osteoarthritis Cartilage 2019;27:248–56.
25. Dupont WD, Plummer WD Jr. Power and sample size calculations for studies involving linear regression. Control Clin Trials 1998;19:589–601.
26. Vickers AJ. How to randomize. J Soc Integr Oncol 2006;4:194–8.
27. Nevitt MC, Cummings SR, Kidd S, Black D. Risk factors for recurrent nonsyncopal falls: a prospective study. JAMA 1989;261:2663–8.
28. Kiel DP, O'Sullivan P, Teno JM, Mor V. Health care utilization and functional status in the aged following a fall. Med Care 1991; 29:221–8.
29. Wolinsky FD, Johnson RJ, Fitzgerald JF. Falling, health status, and the use of health services by older adults: a prospective study. Med Care 1992;30:587–97.
30. Tinetti ME, Williams CS. The effect of falls and fall injuries on functioning in community-dwelling older persons. J Gerontol A Biol Sci Med Sci 1998;53:M112–9.
31. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Ann Rheum Dis 2005;64:34–7.
32. Bodian CA, Freedman G, Hossain S, Eisenkraft JB, Beilin Y. The visual analog scale for pain: clinical significance in postoperative patients. Anesthesiology 2001;95:1356–61.
33. Foley SJ, Lord SR, Srikanth V, Cooley H, Jones G. Falls risk is associated with pain and dysfunction but not radiographic osteoarthritis in older adults: Tasmanian Older Adult Cohort study. Osteoarthritis Cartilage 2006;14:533–9.
34. De Zwart AH, van der Esch M, Pijnappels MA, Hoozemans MJ, van der Leeden M, Roorda LD, et al. Falls associated with muscle strength in patients with knee osteoarthritis and self-reported knee instability. J Rheumatol 2015;42:1218–23.
35. Leveille SG, Jones RN, Kiely DK, Hausdorff JM, Shmerling RH, Guralnik JM, et al. Chronic musculoskeletal pain and the occurrence of falls in an older population. JAMA 2009;302:2214–21.
36. Berryman C, Stanton TR, Bowering KJ, Tabor A, McFarlane A, Moseley GL. Do people with chronic pain have impaired executive function? A meta-analytical review. Clin Psychol Rev 2014;34:563–79.
37. Pandya NK, Draganich LF, Mauer A, Piotrowski GA, Pottenger L. Osteoarthritis of the knees increases the propensity to trip on an obstacle. Clin Orthop Relat Res 2005;431:150–6.
38. Pandya NK, Piotrowski GA, Pottenger L, Draganich LF. Pain relief in knee osteoarthritis reduces the propensity to trip on an obstacle. Gait Posture 2007;25:106–11.
39. Qaseem A, Wilt TJ, McLean RM, Forciea MA. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017;166:514–30.
40. Welsh VK, Clarson LE, Mallen CD, McBeth J. Multisite pain and self-reported falls in older people: systematic review and meta-analysis. Arthritis Res Ther 2019;21:67.
41. Ganz DA, Higashi T, Rubenstein LZ. Monitoring falls in cohort studies of community-dwelling older people: effect of the recall interval. J Am Geriatr Soc 2005;53:2190–4.
42. Hannan MT, Gagnon MM, Aneja J, Jones RN, Cupples LA, Lipsitz LA, et al. Optimizing the tracking of falls in studies of older participants: comparison of quarterly telephone recall with monthly falls calendars in the MOBILIZE Boston study. Am J Epidemiol 2010;171:1031–6.

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Impact of Thumb Carpometacarpal Joint Osteoarthritis: A Pragmatic Qualitative Study

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Objective. First carpometacarpal (CMC1) joint osteoarthritis (OA) is typically understood as part of the disease entity of hand OA. However, CMC1 joint OA often occurs in isolation or is a primary source of symptoms. The aim of the current study was to explore the experiences of New Zealanders with CMC1 joint OA to better understand the unique impact of this condition, ascertain outcomes of importance, and identify treatment targets.

Methods. In this pragmatic qualitative study, patients who either reported a history suggestive of CMC1 joint OA or had been diagnosed by a physician were recruited from health and community settings in 2 centers on the South Island of New Zealand. Thirty participants (11 men and 19 women, mean ± SD age 65.4 ± 11.36 years) took part in individual face-to-face interviews and kept diaries. The interviews were audio recorded, and along with the diaries, transcribed. Data were analyzed by thematic analysis using a primarily inductive approach. The Health Impact Model was employed to help with interpretation of the results.

Results. Five interrelated levels of health impact were identified: symptom status, functional limitations, restrictions in social activities and roles, negative thoughts and feelings, and an altered sense of self. Constant pain and pain at night were key symptoms that were associated with impact at the other levels.

Conclusion. Constant pain, pain at night, functional capacity, medication burden, emotional impact, and sense of self are important outcomes and treatment targets in people with CMC1 joint OA.

INTRODUCTION

Osteoarthritis (OA) involving the first carpometacarpal (CMC1) joint at the base of the thumb has a radiographic age-adjusted prevalence of 15% for women and 7% for men age ≥30 years (1), with a higher prevalence in older age. Symptomatic CMC1 joint OA is estimated to affect 22% of the general population age ≥50 years (2). An aging population accounts for an increasing prevalence.

The natural history can result in less symptomatic or stable end-stage disease (3) or progress to pain and functional limitations interfering with patients' quality of life (4–6). A range of conservative interventions is available, such as splints and exercise, but evidence for their effectiveness is sparse and of poor quality (7–11).

Studies of CMC1 joint OA face several challenges. First, there is no agreed-upon case definition, and CMC1 joint OA is usually considered part of hand OA. However, CMC1 joint OA often occurs in isolation and is arguably a distinct disease entity, possibly contributing to more pain and disability than other hand joint diseases and requiring specific treatment approaches (12).

At present there is no gold standard outcome measure. A core set of outcome domains for investigating interventions for hand OA has been recommended (pain, physical function, health-related quality of life, joint activity, and hand strength) (13,14). However, in studies investigating interventions (such as splinting) for CMC1 joint OA, there appears to be no consensus about which tools to use (7). The 2 instruments recommended to assess function in hand OA (Functional Index of Hand Osteoarthritis [FIHOA] and Australian/Canadian Hand Osteoarthritis Index [AUSCAN]) are clinician-centric in their development and face criticism for being outmoded (13–15). Further, access to the AUSCAN is restricted (13).

Previous research on CMC1 joint OA used survey and questionnaire methods and was conducted almost exclusively among northern-hemisphere Western European populations

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SIGNIFICANCE & INNOVATIONS

- Outcome measures and treatments tailored to the unique impact of first carpometacarpal (CMC1) joint osteoarthritis (OA) are likely to improve outcomes. This is the first study to explore CMC1 joint OA as a unique condition using qualitative methods other than surveys and questionnaires.
- Assessment of the specific effects that are important to patients with CMC1 joint OA is missing from recommended patient-reported outcome measures, including dropping objects, extra time to complete tasks, interaction with children/grandchildren, activities in which the hand takes impact or vibration, work and recreation activities, medication burden, emotional impact, and sense of self.
- Constant pain and pain at night are key symptoms of CMC1 joint OA and contribute to the impact of the condition at other levels.

(1,3–5,16–22). There is a need to understand how this condition manifests more broadly, including in the bicultural context of New Zealand. Although the prevalence of OA in New Zealand is not higher among indigenous Māori than non-Māori people, health care utilization for OA by Māori patients is poor (23), and OA research conducted in New Zealand must contribute to eliminating this inequity. The aim of the current study was to explore the experiences of New Zealanders with CMC1 joint OA to better understand the unique impact of this condition, ascertain outcomes of importance, and identify treatment targets.

MATERIALS AND METHODS

We undertook a qualitative study employing a pragmatic approach. Practical clinical questions of what should be measured and how patients should be treated were used to determine the study methods and design (24). Semistructured face-to-face interviews were conducted with 30 adults with CMC1 joint OA. The pilot-tested interview schedule covered 6 fields of interest. In lay terms these were: participants' story of their CMC1 joint OA, difficulties occurring because of CMC1 joint OA, pain experience, impact on health and life, experience of health services for their thumb OA, and what they would most like to change. Interview questions were generated from concepts included in current outcome measures, the clinical and qualitative research expertise of the research team (all authors are experienced clinicians and 3 are experienced qualitative researchers [CMC, SS, and KP-B]), and previous qualitative research exploring pain in OA (25). Within the interview schedule, the New Zealand Māori holistic health framework of Te Whare Tapa Whā (26), familiar to most New Zealanders, was adopted, inviting participants to reflect on 4 pillars of health: physical, spiritual, thoughts and feelings, and family/community.

Sample size was estimated based on previous qualitative studies (27–31). Participants were purposefully recruited from community and health settings, including general practices and hospital-based services in 2 centers in the South Island of New Zealand. The second center was included for its higher proportion of population identifying as Māori, and sampling was not restricted to those who had sought medical care. Included were those age ≥30 years with a history suggestive of CMC1 joint OA (25). Exclusion criteria were those who were asymptomatic, had previous surgery to the hand, or had inflammatory or autoimmune conditions (Table 1).

One researcher (MB), a physical therapist/hand therapist with 17 years of clinical experience and qualitative research training, conducted the 40–50-minute interviews in a health setting or participants' homes. In 2 cases a family member was present. Participants completed daily diaries for 1 week before the interview to record the impact in a natural setting and to enrich interview data (32). Interviews were audio recorded and field notes were made following each interview. The interviewing researcher (MB) transcribed diary entries, interviews, and field notes, entering

Table 1. Inclusion and exclusion criteria*

Inclusion criteria	Exclusion criteria
Age ≥30 years	Thumb nonsymptomatic for the past month
Physician diagnosis of CMC1 joint OA, OR an answer of "yes" to the question, "Have you experienced aching, discomfort, pain and/or stiffness in or around the joint at the base of either thumb on most days for at least 1 month (15 or more days of the month) during the past year?" and have no other specific diagnosis (25,30,31).	Previous surgery of the symptomatic joint
Give written informed consent	Concurrent rheumatoid arthritis or any other significant inflammatory or autoimmune conditions affecting the hand, such as scleroderma, systemic lupus erythematosus, and psoriatic arthritis, or another kind of chronic pain syndrome or metabolic disorder, such as fibromyalgia, diabetic neuropathy, or gout.
–	Unable to comprehend instructions and outcome measure instruments in English.

* CMC1 = first carpometacarpal; OA = osteoarthritis.

data in NVivo data management software. The same researcher analyzed interview and diary data primarily inductively, using a systematic method of thematic analysis (33). Coding and categorization were discussed from time-to-time and reflected on with a second (CMC) and third researcher (KP-B).

To aid practical application to the research and clinical setting, results were interpreted using the Health Impact Model of Wilson and Cleary (34). The model includes psychosocial alongside biologic aspects and assists in identifying outcomes that are significant to patients, understanding how outcomes and impact may vary, and planning patient-centered care. Parts of transcripts and analysis were then discussed with coauthors.

Demographic and disease characteristics were collected using a tailored questionnaire. Participants completed self-report outcome measures for function (FIHOA; score 0–30) and quality of life (EuroQol 5-domain instrument in 3 levels), and hand diagrams for pain and abnormal joints. Study findings were summarized and sent to participants. Permission was sought for use of individual quotes, and no comments or corrections were requested. Participants were reimbursed for expenses incurred in participating in the study with a $20 gas voucher. Ethics approval was obtained from the University of Otago Human Ethics Committee (Health), reference H17/032. For participant confidentiality, all names are pseudonyms.

RESULTS

Data were collected between June and September 2017. Participant characteristics are reported in Table 2. Current and previous vocations include a wide range of professional, manual, and care work, and retirees. Of note, several participants, both female and male, expressed offense at the gendered nature of question 7 of the FIHOA questionnaire, "For women: can you sew? For men: can you use a screwdriver?"

Thematic analysis. Five main themes representing 5 interrelated levels of health impact were identified: negative experience of symptoms, functional limitations, restrictions in social activities and roles, negative thoughts and feelings, and altered sense of self. Themes and subthemes along with sample quotes are given in Table 3. No new themes or subthemes were identified in the final 3 sets of interview data.

The 2 themes "symptom status" and "functional limitations" matched corresponding levels of the Health Impact Model, while the remaining 3 themes aligned to the model levels of General Health Perceptions and Overall Quality of Life (Figure 1). The impact at each level was found to be influenced by personal and environmental factors.

Symptom status. Participants described symptoms of pain, loss of dexterity, weakness, and stiffness. For nearly two-thirds of participants, pain was considered the biggest impact. The most common pain descriptors were "dull ache," followed closely by "sharp" or "knife-like"; less common but still frequent were "shooting," "stinging," and "spasm." Few participants described the pain as "burning," "throb," or "crunching." Pain intensity was often moderate to high and in some cases unbearable, causing participants to "change what I'm doing or just stop…sometimes tearful" (Hilary, age 59 years).

Table 2. Participant characteristics (n = 30)*

Characteristic	Value
Male:female	11:19
Age, mean ± SD years	64.5 ± 11.36
Descent	
New Zealand Māori	86.7
European/Pākehā	10
Indo-Australian	3.3
Employment status	
Part- or full-time	43.3
Retired	40
Disability pension	6.7
Student	3.3
Not working	3.3
Seeking work	3.3
Involved hand	
Dominant	70
Nondominant	80
OA at other joints	
Hand	16.7
Other location	40
CMC1 joint OA diagnosis	
Made by clinician	80
History suggestive	20
Duration of problem, mean ± SD years	5.74 ± 5.26
Previous treatments (non-oral drug)	
Splint	43.3
Physical therapy or hand therapy	36.7
Topical cream	33.3
Injection	20
Other†	23.3
Pain relief medication (for CMC1 joint OA or other condition)	
Paracetamol	50
Nonsteroidal antiinflammatories	26.7
Codeine	13.3
Gabapentin	3.3
Pain at base of thumb, mean ± SD (NRS, 0–10)	5.43 ± 2.1
Function, mean ± SD (FIHOA, 0–30)	7.7 ± 4.68
EQ-5D-3L dimension	
Mobility problem	26.7
Self-care problem	23.3
Usual activity problem	63.3
Pain/discomfort problem	90
Anxiety/depression problem	26.7
EQ-5D, mean ± SD (VAS, 0–100)	76.37 ± 14.83

* Values are the percentage unless indicated otherwise. CMC1 = first carpometacarpal; EQ-5D-3L = EuroQol 5-domain instrument in 3 levels; FIHOA = Functional Index of Hand Osteoarthritis questionnaire; NRS = numeric rating scale (pain); NSAIDs = nonsteroidal antiinflammatory drugs; OA = osteoarthritis.
† Other: contacted surgical consultant for appointment, glove for warmth, wheat bag (heat), stretches, self-massage.

Table 3. Themes, subthemes, and sample quotes relating to the impact of thumb carpometacarpal joint osteoarthritis

Theme 1: symptom status
Pain
Louise (52 years): "I think when it's, when I've got a lot of it, the fact that it never goes away. That it's always sitting there in the background. Once, it stopped sort of self-healing in the days I wasn't working, it was there constantly. Everything that I did caused pain, whether it was turning on a tap, or picking up the kettle, or even patting the cat. So, it was just the constancy of it."
Stuart (66 years): "…just a little less pain, and I would actually find that I would use my thumb more."
Loss of dexterity and fine (pincer) grip
Fabian (62 years): "See I'm a clock maker by trade, so all my work is done with fingertips and things, so you're pinching, holding, squeezing all the time, tools, whatever you're working on. You know, so, having something like that is an absolute pain."
Loss of power and torsional grip
Arthur (89 years): "I didn't realize I'd lost my grip. I used to have a very strong grip. And then I found that when I clench my fist like that, it gets, it's quite painful in there [base of thumb]."
Inability to grip wide objects
Craig (69 years): "That wide, wide grasp, yeah, is…grabbing things like turf and trying to pull, like that. I just haven't got the strength to do it."
Stiffness
Joanne (46 years): "I can't write for as long as I used to because it gets too sore and stiff and my handwriting gets worse and worse."
Lauren (74 years): "The span's limited…which stops you playing the piano."
Theme 2: functional limitations
Limited in everyday activities
Tracy (65 years): "Every single day my thumb problem impacts on my daily life: biking, driving, twisting tops off jars/bottles, sewing, pincer action between thumb and forefinger, knitting and crocheting, gardening, cleaning, wringing out cloths, housework in general (making beds is difficult)."
Fabian (62 years): "That's a bloody nuisance, that is [driving]."
Dropping things
Fiona (65 years): "I'd be quite happy if there was no pain, but I would be happier if I knew I wasn't going to drop stuff if I picked it up…I'll drop plates, I'll drop jars, anything that before I would feel…but now my grip is so weak in my right hand that I drop it."
Takes longer to do things
Lauren (74 years): "Showering has become more difficult, because your hands just won't do what you want them to do. And I'm longer in the shower, and I'm trying to be quick because I'm in other people's homes. So that, that is a stress actually. Trying to get through that quickly."
Theme 3: restrictions in social activities and roles
Restricted in participating in recreational activities and fulfilling family roles
Moira (63 years): "It's taken away my enjoyment of gardening. I used to love that but it's quite hard, now, with both hands like that. Because I can't pull out the roots. You know, I'll often break it off…so I just have to garden a bit differently…do it in smaller amounts."
Kate (48 years): "The biggest impact I think it has on me, is not being able to do stuff. I'd like to be able to go out bike riding with her [primary school age daughter] but, brakes, gears… We've got our bikes in the garage… I bought a coloring book cause she likes, she loves her arty stuff. I bought an adult's coloring book for me and one for her… I can't even sit down and do that with her."
Marie (50 years): "Yeah, kapa haka definitely, it's a huge part of my life and it's…I can still do it but I can't, I could never compete again or anything like that. Because I can't sustain that [wiri] with my hand."
Jennifer (64 years): "Well it's me! I've been a pianist since I was 8 years old. And I love it, and I feel cut off from it…the thumb is a big deal in playing."
Adele (78 years): "It's an inability to do things I could do in the past, because I am, I am a practical person. I do a lot of handcraft, and I had to reduce that activity, fairly drastically. So you just, you just have to give it up…that's past."
Aaron (74 years): "[She] loves having foot massages and shoulder massages. And I enjoy giving them to her. Jesus, it's painful! When she gets home eleven o'clock at night, really sore shoulders. Yes I can…it really stings!…really annoying that I can't do that without discomfort."
Lauren (74 years): "You find they [grandchildren] don't really understand. How could they? So, and you don't like saying, 'No, no, no, no, my thumbs are too sore for that'."
Moira (63 years): "…my 2-year-old grandson…I really struggle to pick him up, and because you have to spread around, you know, at their waist and lift them that way, and that's a really painful thing to do…the other thing I find really difficult is his harnesses, you know like in the pushchair and in the car seat. You know, squashing, pushing."
Restricted in work roles
Susan (59 years): "Just the writing really and shaking people's hands, that hurts. I sort of try and avoid that, well not so much avoid it but trying not to do it if I can get away with it."
Kate (48 years): "Some days I have taken days off because I've been too sore…I can't slow down, and take my time."
Amelia (66 years): "I've been retired for 4 years. I did relieving [childcare] until this year and I found that I couldn't lift the kids the same. I used to do nappies and whatever was going…but I can't now…just lifting the kids was just too much."
Theme 4: negative thoughts and feelings
Lost confidence in hand
Fabian (62 years): "I just don't trust my left at all. I know my left hand will fall open without even me knowing, knowing what's happened. The last thing I dropped was 5 kilos of oranges in the gateway. And guess where half them went!"
Charles (76 years): "I wouldn't risk lifting a big heavy pot or, with a handle in my left hand. So I've gotta make sure I use my right hand for those. Anything that…involves sort of strength I've, I've learnt to avoid."
Frustration
Joanne (46 years): "It's frustrating not being able to accomplish as much as I'd like to some days, but I'd rather not make my condition worse, so I try to rest it and not over use it as much as possible."
Aaron (74 years): "Just, frustration as much as anything else…it's bloody annoying at times."

(Continued)

Table 3. (*Cont'd*)

Anger
Paula (80 years): "Oh, I just get angry at it I think. Bugger old age, really. That's to be honest. You know, I just say, you know, 'Bugger this!' I'm really brassed off at it. Yes I am. Quite angry with it because you…you use this [thumb] all the time."
Robert (56 years): "And that's the irritating thing…that's when I start getting grumpy and then I just disappear out the family's way, because I'm a nasty swine. I don't intend to be and they say they understand it, but that's not the point."
Worry
Earle (66 years): "Just the fact that it's there. I know that it means that something's degrading."
Concern about the future
Moira (63 years): "When I first got diagnosed with it, I immediately thought, 'Right, gosh I'll have to shift house, you know, I obviously won't be able to manage on my own in this house.' You know it really upset me and depressed me, you know, for a while, because I was then having to go over in my mind, 'Oh, I won't be able to do that, and that…and I'd planned in retirement, and oh I won't be able to do that!'"
Robert (56 years): "I'm only 56, I'm not old, and these [thumbs]…will get worse as time goes on, cause age will make them worse, the wear will get worse, the bones, well most of it…I want to prolong that distance in time. I'm thinking in 5 years' time they're going to be buggered."
James (32 years): "Ahh, it troubles me…you know my livelihood depends on my fingers as well, because I know that I'm not super young, but at the same time I'm not, you know seventy or something. So I need to know what's going on so I can address them and manage them."
Mental burden
Fiona (65 years): "It's impacting on how I would normally live my life, I have to be more aware of what I'm going to do."
Fabian (62 years): "You just gotta be aware of it, you just gotta have it in your mind all the time."
Medication burden
Amelia (66 years): "Normally I'll just try and have 2 codeine through the day and then 2 when I go to sleep, at night. Some days it's really, really quite bad. But I try to stick to that because I don't wanna have too much…I'm on heart pills and other pills as well."
Kate (48 years): "I've been put on gabapentin. I used to be on tramadol and codeine and all of that. I took myself off them because it's got addictive tendencies and in my family there is addictive tendencies and I didn't want to get hooked on it. I don't want to be doped up driving round with her [primary school-age daughter] in the car or anything like that."
Theme 4(i): Not concerned about appearance
Sarah (73 years): "Well, I've noticed, you know if compared to this one there's a lot more knobbly bits. But it doesn't bother me, no."
Aaron (74 years): "No, couldn't care less. When you get my age everything looks different."
Hilary (59 years): "So long as there's no pain I don't care what it looks like."
Theme 5: Altered sense of self
Marker of aging
Fiona (65 years): "It is tied up with me getting older, I think. It's more than just the pain, it's the notification that I'm starting to get to be an older person…it's a kind of a holistic thing. It's the whole identify of myself…I'm turning into an older person."
Dispirited
Hilary (59 years): "I'm not prone to depression, but it's quite depressing when you know that it's not going to go away and there's nothing you can really do except stop everything you're doing, which isn't an option."
Robert (56 years): "The actual thing that gets rid of the pain better than anything, or makes me notice it less, is alcohol, which is not a good thing. Then I know if I want to go to sleep I actually need a couple of decent belts down…that's what I find the dispiriting side of it, the debilitating side."

Predictability of pain varied, with some participants reporting they "knew what they were in for" (Neil, age 70 years), while others reported that pain experiences were quite random. Pain was variably reported as both constant and intermittent or sudden onset, with constancy most often given as the worst thing about the pain. Delayed onset pain was common; pain at night was a problem for two-thirds of participants.

Weakness and loss of grip and dexterity were the biggest impact for approximately one-third of participants and bothered most participants to some degree. Clumsiness and trouble manipulating small things were often associated with pain. Limited power grip was associated with pain, stiffness, and perceived weakness, particularly with heavy lifting. Many participants had problems with torsional grip (gripping to turn) and wide grasp. Stiffness, either in the first web span or the whole thumb digit bothered just under half of the participants and contributed to problems with both fine and gross grips.

Functional limitations. Participants reported significant impact on their ability to carry out everyday tasks and self-cares, sleep, and increased time taken to do things. Difficulty undoing lids and dropping things were ubiquitous problems. Opening a variety of containers was problematic, including plastic packets, flip lids, and seals on milk bottles; child-proof lids caused particular difficulty.

Driving was a problem for half of the participants, "Especially in the new cars with the bigger, thicker steering wheels" (Tracy, age 65 years); in addition, participants had problems turning the key, operating seat belts and buckles, opening and closing doors, and changing gears (manual and automatic). One participant reported difficulty controlling the vehicle because her hand "just completely froze up" (Marie, age 50 years). Holding a media device or book was uncomfortable, but texting on a cell phone was not. For those who used computers, mouse use was more taxing than the keyboard. Writing was limited for all but 3 participants, for whom their dominant hand was involved.

Tasks involving impact or vibration were limited, e.g., using an axe and carrying heavy items such as the coal bucket or firewood. Operating tools, including pruning shears, frequently caused problems, as did turning taps and doorknobs, holding a cup, using scissors, cutting with a knife, peeling vegetables,

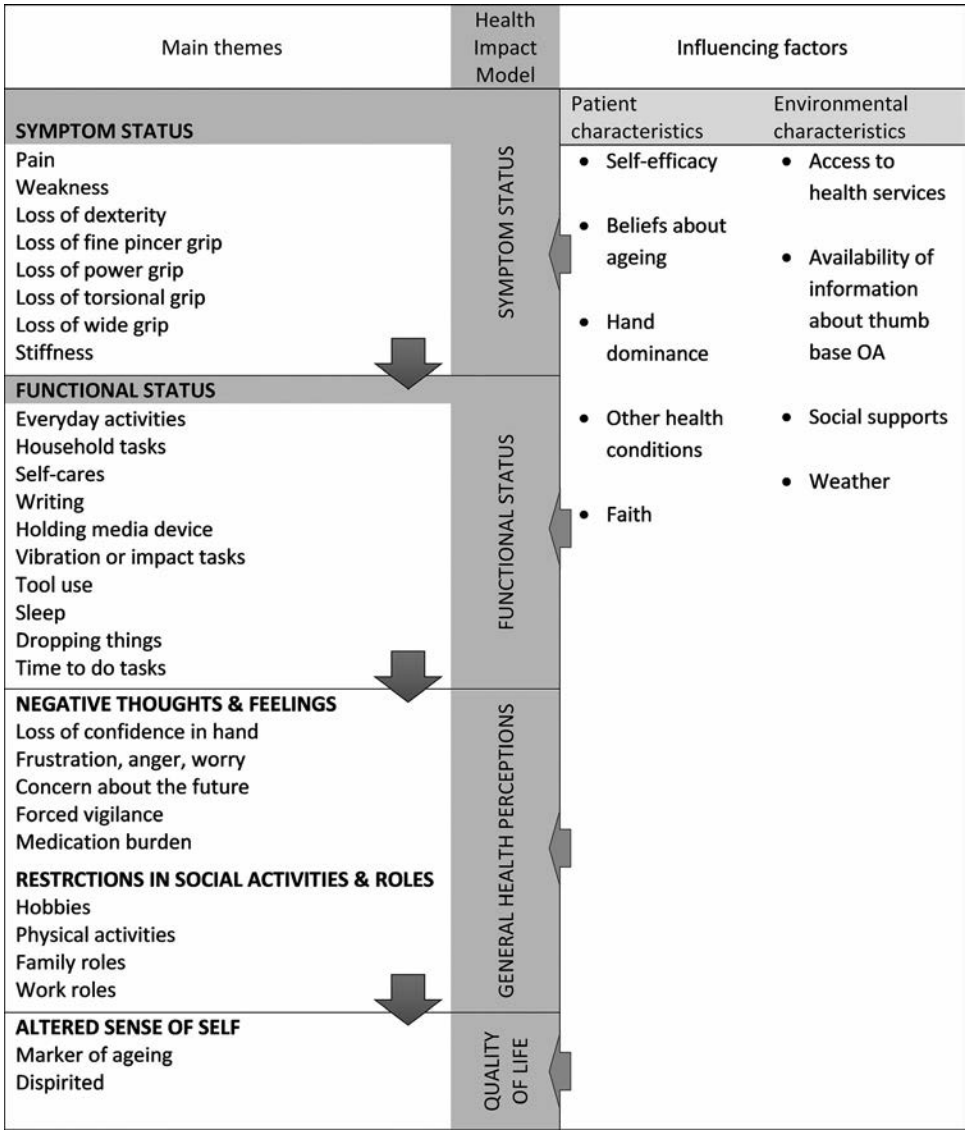

Figure 1. The 5 main themes representing 5 interrelated levels of health impact are aligned to the Health Impact Model, along with personal and environmental factors influencing the impact at each level. OA = osteoarthritis.

using a whisk, holding dishes to wash or dry, vacuuming, and ironing. Dressing (particularly trousers and socks), doing up buttons and bra, and tying shoelaces were the most frequently mentioned personal care tasks. Others included showering, doing hair, putting on jewelry, cleaning teeth, shaving, and wiping one's bottom.

Restrictions in social activities and roles. Participants described restrictions in social and recreational activities and restrictions in their life roles, including family and work. Commonly restricted physical activities were bike riding, going to the gym, and walking the dog. Pulling on tight clothing was a limiting factor in the gym and swimming. Problems were also reported with golf, tennis, paddling, and hiking (lifting a pack). Kapa haka (a cultural dance) was limited because of pain on performing the wiri (rapid hand motion). Similarly, flicking the hand, e.g., to shake off water, and clapping were painful. Gardening was an activity in which more than half the participants experienced difficulties.

Approximately one-fourth of participants had difficulty in or had stopped their arts and crafts, e.g., painting, jewelry making, crochet, knitting, and spinning. A smaller group were similarly impacted in playing musical instruments. Woodwork, photography, sewing (both on the machine or by hand), playing cards, and playing computer games were also limited.

Participants described limitations in fulfilling roles in the home, family, and community, including caring for children and grandchildren. Just over half of the participants said they were limited in their current, prospective, or previous paid or voluntary work roles or study because of their CMC1 joint OA, with some having to take frequent time off; for several it was the prompt to retirement.

Negative thoughts and feelings. Participants expressed negative thoughts and feelings associated with the impact of their thumb problem, including loss of confidence in their hands, frustration with their functional limitations, anger about the pain and restrictions in everyday roles and activities, worry about what was happening in their thumb, and concern about the future. Loss of confidence was associated with a tendency to drop things and often resulted in avoidance behavior. Feelings of frustration were closely linked to the pain and activities of everyday living becoming time-consuming and less enjoyable. The negative feelings contributed to negative mood, which impacted on family and those close to them. Concern about the future arose due to difficulty or pain with activities of independent daily living. The importance of thumb function was summed up by 1 participant who lived alone, "My thumb is the captain of the ship" (Paula, age 80 years).

Participants described the mental burden of always being aware of their thumb: an enforced vigilance required to respect functional limitations and manage pain, or "self-preservation" as 1 participant put it. Many participants were concerned about the impact of taking medications on their general health or other health conditions and on their mental state. For the most part, participants were not bothered by the appearance of their thumb/hand.

Altered sense of self. Participants described an altered sense of self; relating to how they perceived CMC1 joint OA as a marker of aging, and in response to the restrictions placed on them in fulfilling their important life roles. Some participants described being "dispirited" because of the pain, frustration, and seeming lack of options. On the other hand, some individuals had rationalized their problems and saw them as part of getting older, or relatively mild compared to other health conditions or the disability experienced by others.

Personal and environmental factors. Personal and environmental factors significantly influenced how CMC1 joint OA impacted each participant. Influencing factors along with sample quotes are given in Table 4. Availability of support from family, friends, or paid home help played a significant role in reducing the impact. Conversely, having no help increased the impact, although some participants took the "use it or lose it" approach. Cold weather worsened the problem.

Self-efficacy, evident as ingenuity in problem solving, often alleviated the impact, "You just gotta think of different ways to skin the cat, that's all" (Fabian, age 62 years). Many participants took a proactive approach to the care of their thumbs with self-help modalities, including massage, heat (including warm gloves), rest, topical creams, exercises and stretches, and simply avoiding painful tasks. Carrying on because the task needed to be completed, ignoring the pain or difficulty, was another way in which many participants demonstrated self-efficacy. Involvement of the dominant hand compounded the problem.

For some participants, the impact was perceived as less when other health conditions or life circumstances took priority, or where medication for other conditions masked the problem. For others, life events exacerbated CMC1 joint OA symptoms, or faith played a role in keeping well in the face of their thumb problems.

In some cases, participants did not seek care because they had rationalized their problem as part of aging, or their health provider held the same view and dismissed the problem. Accessing health care made a difference for several participants. However, access to care was sometimes limited by cost and/or geography, as was access to adaptive equipment and devices. Participants were motivated to access health care when their pain became unbearable or limited them in their most important activities or roles. While pain relief medication was often effective in managing pain, most participants were eager for nonpharmacologic interventions. However, nearly all participants had found it hard to come by information about the condition and self-management, even when they sought treatment.

DISCUSSION

The current study provides new insights into CMC1 joint OA as a unique disease entity and the impact of a hand OA condition. We identified 5 key interrelated levels of impact. We also identified personal and environmental factors that influence the impact of CMC1 joint OA, some of which are modifiable. Key concerns important to participants were constant pain and pain that interrupts sleep; limited performance of power grip and precision tasks; and limited participation in work, caregiving, recreational and physical activities, and activities of daily living. Negative thoughts and feelings included frustration, anger, worry, concern about the future, and the burden of medication. An altered sense of self was related to aging. Impact was greater where the dominant hand was involved.

Pain was found to be associated with impact at all levels and was a major concern for participants, similar to previous findings in general hand (35,36) and hip and knee OA (25,37). Like previous hand OA findings (38), constant aching pain was of greater concern to participants in the current study, contrasting with large joint OA where intense, unpredictable pain has been found to be more distressing (25). Hand weakness was frequently described in the current study, also matching previous findings in hand OA (17,36,39). Weakness and loss of dexterity were commonly accompanied by pain, suggesting these symptoms are closely linked.

While limitations in a wide variety of functional activities and life roles were reported in the current study, similar to previous hand OA studies (15,18,19,21,28,31,39–43), several differences were evident. Whereas cellphone use has been raised as a concern in general hand OA (15), this concern was not an issue for participants in the current study except for holding the device, possibly because many participants were "one-finger texters."

Table 4. Themes and sample quotes relating to factors influencing the impact of thumb carpometacarpal joint osteoarthritis*

Personal factors
Self-efficacy
Neil (70 years): "It doesn't impact on me at all because I've got that used to compensating, that it's just like favoring a sore, sore ankle if you had a sprain. You'll favor it till it comes right. I favor this to the extent that I don't get the pain."
Charles (76 years): "…to hold the bottles…sometimes I have to go and put them in the vice."
Fiona (65 years): "We cannot undo cans, or you know screw things, that's when we had to use the pipe-wrench."
Jennifer (64 years): "…peeling things…that's quite tricky. Now I just do as they say and just wash the carrots off and stick them straight in the oven."
Kate (48 years): "I tend to steer clear of buttons. I've got like, trackies…very rarely do I wear a pair of jeans that's got a button on it."
Sarah (73 years): "I was cleaning toilets at work, and it needed a new Janola thing…couldn't open it, couldn't find a pair of pliers, so I put it on the floor and put my foot on it, then gave it a twist and it worked."
Robert (56 years): "I like making pastry, I'm buggered if I'm not going to make it just cause they hurt, I've got to find a way of doing it."
Tracy (65 years): "If we do a long bike ride I think, 'Oh, and it's getting really sore.' But, you just do it! Nothing changes really, you just…you adjust."
Carry-on: use it or lose it approach
Clare (65 years): "Tops off bottles and that…I try not to give in and ask my husband because I know it's a strength thing you don't want to lose."
Sarah (73 years): "I tackle anything and everything. As long as I can do things myself I'll do it myself. I realize there'll be a time that I'll need to ask for help. But in the meantime, I'm still doing it."
Dominant hand not involved
Marie (50 years): "I'm actually glad it's my left hand as I wouldn't be able to do my job if it was the right."
Charles (76 years): "It would actually affect my life, really affect my life and what I can do. But because it's in the left hand, it's livable."
Role of other health conditions and life events
Marie (50 years): "Since then I have been dealing with other medical issues (I have COPD) and my hand has been an annoyance as opposed to an issue so I tend to ignore it, until it flares up like this week."
Celia (71 years): "I'm coping with…I've broken 2 ankles in 3 years, and I'm having a lot of pain with that. So this is nothing."
Lauren (74 years): "My focus in the last 2 years has just been survival. Just learning to live without your home, and everything you've got is in storage. And also I've struggled with other aspects of my health, apart from my thumb."
Paula (80 years): "Sometimes, if I'm going to bed and it's later at night I won't take Panadol, if I think I don't need it for my knee, and that's when I notice, that's really very bad [base of thumb]."
Amelia (66 years): "[My son-in-law] comes around…came to say he is going on the fishing boat tomorrow. Their baby is 2 weeks old. I am very stressed. My thumb started to ache. [Son-in-law] could be away for 3 months."
Faith
Jennifer (64 years): "I'm faithful and I believe that I'm given nothing to cope with that I won't be able to cope with. But it does really get to me sometimes."
Beliefs about aging
Tracy (65 years): "You just get on and do what you got to do. You just take it as you get older, you think, you know your joints are seizing up a bit."
Charles (76 years): "Nowadays it's something I can live with quite successfully…in old age, always something gets sore."
Lauren (74 years): "I feel quite grateful that I'm 74 and I'm not crippled with arthritis in other joints, so this is manageable."
Motivation to access health services
Robert (56 years): "And then it gets to the point, after 8, 9 months, when it's just unbearable and you don't get any break, and that's when I go back and get the injection in it."
Fabian (62 years): "If that played up with my sport [shooting], I'd be going somewhere pretty rapidly."
Sarah (73 years): "If I had mentioned this to my GP 2 years ago, or 3 years ago, I probably would have been into the system a lot earlier. But I didn't put much problem with it. I thought, 'Nah, it's just the garden and I'm not getting any younger and I'll…you got to expect it'."
Environmental factors
Social support
Moira (63 years): "Good team work…I'm managing quite well at work. My job's mainly hand work. But I'm hoping I'll be able to keep going."
Clare (65 years): "The worst thing was putting in earrings…my husband's retired and I'm working so he does most of it…lets me off the hook."
Lauren (74 years): "Gardening became more difficult…I got some help from WINZ to pay for 2 hours help once a fortnight."
Louise (52 years): "There is some stress in it because I know that I've still got to do. I live alone and I've still got to do the housework and I've still got to do the gardening and change the beds and all that and it doesn't matter whether my hand hurts or not. I don't have a choice in the matter."
Weather
Tracy (65 years): "Cold frosty days it seems to be worse. Sometimes when it's raining it seems to be worse. Go to Australia and I don't get any pain."
Access to health services
Sarah (73 years): "Previous to the support [splint], that was painful out in the garden. With the support I've got no trouble, it's great. When I take the support off, it's painful. But only for a wee short while, not for long."
Robert (56 years): "The night supports were marvelous. When I first got those, I had a night's sleep! And that was fabulous. It mightn't seem much but… you're just looking for incremental improvement. I'm not expecting, 'Boom, I'm cured.' I can mitigate the ache if I get the painkillers in…if I've been up for more than 2 hours and haven't taken them, I'm going to have problems for the day."
Susan (59 years): "I had that one X-rayed but it wasn't as bad. But you see it's dropped completely and even the GP said herself she was going to hurry them up…enquired into seeing a hand specialist but…he, she or whatever didn't think it was warranted. Otherwise I have to pay to see them. This is on the public system. Something like $400 or something or other to go and see this person [private hand therapist]."

(Continued)

Table 4. (*Cont'd*)

Access to health information
Adele (78 years): "If I can give things a name, I can control it better. It helps me to know, this is what's wrong, it's got a name, instead of being uncertain about things."
Marie (50 years): "And then I got antiinflammatories once off the doctor but then I didn't actually…I don't like taking pills…so is there other stuff I can be doing or is this just a part of getting old? Should I be using those little balls to strengthen it or is that aggravating it?"
Aaron (74 years): "I said to the doctor, 'I've got something wrong with my thumb, it's this, and this is how it affects me,' and he said, 'Oh, yeah, that'll be arthritis. Here's your prescription for your blood pressure. See you later.' So I thought, 'Oh yeah, tough!'"

* GP = general practitioner; WINZ = Work and Income New Zealand (New Zealand social welfare services).

Further, impact relating to computer use was specific to the computer mouse.

Although manual tasks were of primary concern for participants in the current study, there was also a pattern of reduced general physical activity due to limited hand function. A previous study of patients with hand OA found reduced levels of lower extremity as well as upper extremity functioning (44); that study's suggestion that hand OA impairments may contribute to reduced levels of general activity is supported by our study findings.

The mental and emotional impact identified in the current study concurs with previous studies in hand (15,28,29,44) and general OA (45–47). However, aesthetic appearance, previously identified as an area of impact in hand OA (15,28,29,40,42,48), was not a major concern in the current study. Perhaps the interphalangeal joints are more visible or prone to disfigurement, perhaps pain and function are bigger concerns for CMC1 joint, or perhaps aesthetic comfort is not a priority for people in the southern parts of New Zealand. We also found no embarrassment due to disability reported by previous authors (29), only high levels of frustration and anger. The negative impact on participants' sense of self, in that CMC1 joint OA was seen as a marker of aging, may be related to the view that one's dignity is jeopardized by aging (49). Negative perceptions of OA as an indicator of aging have previously been reported in general OA populations, with OA symptoms similarly often minimized or ignored (45).

Similar to the current study, environmental support and strategies to continue performing valued activities have previously been identified as important influencing factors in the impact of OA (27,29,31). Potential targets for intervention identified in this study are beliefs about aging, financial barriers to accessing services, lack of information about the condition and interventions that may halt progression and enable function, and emotional impact. The presence of other health conditions was identified as a barrier to accessing care for CMC1 joint OA. Where maintaining physical activity helps control comorbid conditions (e.g., heart disease or diabetes mellitus), untreated CMC1 joint OA may contribute to overall decline in health status.

That a substantial number of those who would benefit do not access health care has recently been confirmed in CMC1 joint OA (50) and previously in hand (40) and general OA (45). We endorse the findings of previous studies that there is a need, on the part of both patients and clinicians, to dispel the belief that OA problems are an inevitable part of aging (40,47). Development of a conceptual model of CMC1 joint OA that enables people to understand what is happening and to see how they can influence it would be helpful.

Although education and access to information is a core guideline recommendation (10), findings of the current study and those of a previous study in hand OA (30) indicate that this access is not readily available. In hand OA, this unmet need has been linked to clinical uncertainty and a lack of high-quality evidence for therapeutic options (30). Earlier access to evidence-based information, advice, and nonpharmacologic and nonsurgical interventions, in primary care or via public information platforms and agencies, would help address this gap (50).

Several functional limitations identified in this study, as well as impact at other levels found to be important to participants, are not assessed by the FIHOA or AUSCAN instruments (Table 5). Development of tools that better measure both the specific and broader impact of CMC1 joint OA is needed. The empirical evidence gathered in the current study may be used as the basis of a conceptual framework to underpin the development of valid patient-reported outcomes for CMC1 joint OA.

It is important to consider the impact of health conditions in different cultural contexts for treatment to be patient-centered (51). The current study contributes new information from the New Zealand context that will broaden and diversify knowledge about the specific needs of people with CMC1 joint OA globally. Although some of our findings may relate to local cultural and environmental

Table 5. Impact of thumb carpometacarpal osteoarthritis not included in recommended outcome instrument

Functional limitations
Dropping things
Time to do tasks
Vibration or impact tasks
Holding media device
Sleep interruption
Household tasks
Negative thoughts and feelings
Mental and emotional impact
Medication burden
Restrictions in social activities and roles
Interaction with children/grandchildren
Work roles
Recreational activities
Negative impact on sense of self

variations, many are comparable with previous studies of OA, with differences reflecting our specific focus on CMC1 joint OA versus hand or large joint OA. Most participants in the current study were New Zealanders of European descent (Table 2), many of whose social circumstances are not dissimilar to people living in Western European countries. Therefore, the findings will have relevance for people with this diagnosis generally.

A strength of this study is the use of qualitative methods to yield rich and varied data. The explanatory nature of findings is useful when little is known about the variables important to examine, as is the case for patients' perspectives of CMC1 joint OA. A second strength is our inclusion of participants who have not sought care, supporting knowledge generation that is inclusive of those who less often access health services.

Our study has some potential weaknesses. First, inclusion criteria were based on self-report of either clinician diagnosis or a history suggestive of CMC1 joint OA and did not include radiographic confirmation. However, a thorough screening process by a trained research assistant and application of inclusion criteria by an experienced physical therapist/hand therapist gives reasonable certainty that participants were symptomatic for CMC1 joint OA. The low mean FIHOA score of participants in the current study could suggest relatively low severity of CMC1 joint OA disease. However, the mean pain score and disease duration are comparable to those in a previous large qualitative study of hip and knee OA (25). Low FIHOA scores may instead reflect poor validity of the outcome measure for CMC1 joint OA.

It may be that findings in the current study are affected by the participants' experience of impact from OA at joints other than CMC1 joint. Although involvement of interphalangeal joints is known to exacerbate impact in the presence of CMC1 joint OA (50), only a small number of participants in the current study reported involvement of other hand joints (Table 2), and the interview schedule guided participants to focus on the impact relating specifically to CMC1 joint OA. Therefore, we are confident that the findings of our study substantially reflect the impact of CMC1 joint OA rather than that of other joints, including interphalangeal joints, although we accept that some impact is shared.

In conclusion, the current study indicates that CMC1 joint OA as a unique disease entity has a significant impact on many aspects of a person's health and well-being largely associated with pain. Key areas of impact were identified, which may serve as important treatment targets and assessment outcomes. There is a need for clinical practice and research to account for hand dominance, cold climate, financial and family/community resources, and attitudes to CMC1 joint OA. Availability and provision of high-quality information about self-management and effective treatments is a current gap needing to be addressed. Development of a CMC1 joint OA–specific instrument relevant to contemporary modes of living is also recommended. These findings from the New Zealand context hold relevance for populations with CMC1 joint OA generally.

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 Bühler 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. Bühler, Chapple, Stebbings, Pōtiki-Bryant, Baxter.

Acquisition of data. Bühler.

Analysis and interpretation of data. Bühler, Chapple, Pōtiki-Bryant, Baxter.

REFERENCES

1. Haara MM, Heliovaara M, Kroger H, Arokoski JP, Manninen P, Karkkainen A, et al. Osteoarthritis in the carpometacarpal joint of the thumb: prevalence and associations with disability and mortality. J Bone Joint Surg 2004;86A:1452–7.
2. Marshall M, van der Windt D, Nicholls E, Myers H, Dziedzic K. Radiographic thumb osteoarthritis: frequency, patterns and associations with pain and clinical assessment findings in a community-dwelling population. Rheumatology (Oxford) 2011;50:735–9.
3. Bijsterbosch J, Watt I, Meulenbelt I, Rosendaal FR, Huizinga TW, Kloppenburg M. Clinical and radiographic disease course of hand osteoarthritis and determinants of outcome after 6 years. Ann Rheum Dis 2011;70:68–73.
4. Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, Pols HA, Hazes JM, Koes BW. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). Ann Rheum Dis 2005;64:682–7.
5. Sonne-Holm S, Jacobsen S. Osteoarthritis of the first carpometacarpal joint: a study of radiology and clinical epidemiology. Results from the Copenhagen Osteoarthritis Study. Osteoarthritis Cartilage 2006;14:496–500.
6. Michon M, Maheu E, Berenbaum F. Assessing health-related quality of life in hand osteoarthritis: a literature review. Ann Rheum Dis 2011;70:921–8.
7. Buhler M, Chapple CM, Stebbings S, Sangelaji B, Baxter GD. Effectiveness of splinting for pain and function in people with thumb carpometacarpal osteoarthritis: a systematic review with meta-analysis. Osteoarthritis Cartilage 2019;27:547–59.
8. Osteras N, Kjeken I, Smedslund G, Moe RH, Slatkowsky-Christensen B, Uhlig T, et al. Exercise for hand osteoarthritis. Cochrane Database Syst Rev 2017;1:CD010388.
9. Spaans AJ, van Minnen LP, Kon M, Schuurman AH, Schreuders AR, Vermeulen GM. Conservative treatment of thumb base osteoarthritis: a systematic review. J Hand Surg Am 2015;40:16–21.
10. National Institute for Clinical Excellence. Osteoarthritis care and management in adults clinical guideline. URL: guidance.nice.org.uk/cg1772014.
11. Hamasaki T, Laprise S, Harris PG, Bureau NJ, Gaudreault N, Ziegler D, et al. Efficacy of non-surgical interventions for trapeziometacarpal (thumb base) osteoarthritis: a systematic review. Arthritis Care Res (Hoboken) 2020;72:1719–35.
12. Kloppenburg M, van Beest S, Kroon FP. Thumb base osteoarthritis: a hand osteoarthritis subset requiring a distinct approach. Best Pract Res Clin Rheumatol 2017;31:649–60.
13. Kloppenburg M, Maheu E, Kraus VB, Cicuttini F, Doherty M, Dreiser RL, et al. OARSI clinical trials recommendations: design and conduct of clinical trials for hand osteoarthritis. Osteoarthritis Cartilage 2015;23:772–86.
14. Wittoek R, Kroon FP, Kundakci B, Abhishek A, Haugen IK, Berenbaum F, et al. Report from the Hand Osteoarthritis Working

Group at OMERACT 2018: update on core instrument set development. J Rheumatol 2019;46:1183–7.
15. Stamm T, van der Giesen F, Thorstensson C, Steen E, Birrell F, Bauernfeind B, et al. Patient perspective of hand osteoarthritis in relation to concepts covered by instruments measuring functioning: a qualitative European multicentre study. Ann Rheum Dis 2009;68:1453–60.
16. Bijsterbosch J, Visser W, Kroon HM, Stamm T, Meulenbelt I, Huizinga TW, et al. Thumb base involvement in symptomatic hand osteoarthritis is associated with more pain and functional disability. Ann Rheum Dis 2010;69:585–7.
17. Lee HJ, Paik NJ, Lim JY, Kim KW, Gong HS. The impact of digit-related radiographic osteoarthritis of the hand on grip-strength and upper extremity disability. Clin Orthop Relat Res 2012;470:2202–8.
18. Calfee R, Chu J, Sorensen A, Martens E, Elfar J. What is the impact of comorbidities on self-rated hand function in patients with symptomatic trapeziometacarpal arthritis? Clin Orthop Relat Res 2015;473:3477–83.
19. Spacek E, Poiraudeau S, Fayad F, Lefevre-Colau MM, Beaudreuil J, Rannou F, et al. Disability induced by hand osteoarthritis: are patients with more symptoms at digits 2–5 interphalangeal joints different from those with more symptoms at the base of the thumb? Osteoarthritis Cartilage 2004;12:366–73.
20. Kwok WY, Kloppenburg M, Marshall M, Nicholls E, Rosendaal FR, Peat G. The prevalence of erosive osteoarthritis in carpometacarpal joints and its clinical burden in symptomatic community-dwelling adults. Osteoarthritis Cartilage 2014;22:756–63.
21. Slatkowsky-Christensen B, Haugen I, Kvien TK. Distribution of joint involvement in women with hand osteoarthritis and associations between joint counts and patient-reported outcome measures. Ann Rheum Dis 2010;69:198–201.
22. Hwang RW, Ring D. Pain and disability related to osteoarthrosis of the trapeziometacarpal joint. J Hand Microsurg 2011;3:63–5.
23. Loyola-Sanchez A, Hurd K, Barnabe C. Healthcare utilization for arthritis by indigenous populations of Australia, Canada, New Zealand, and the United States: a systematic review. Semin Arthritis Rheum 2017;46:665–74.
24. Shaw JA, Connelly DM, Zecevic AA. Pragmatism in practice: mixed methods research for physiotherapy. Physiother Theory Pract 2010;26:510–8.
25. Hawker GA, Stewart L, French MR, Cibere J, Jordan JM, March L, et al. Understanding the pain experience in hip and knee osteoarthritis: an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008;16:415–22.
26. Durie M. Whaiora: Māori health development. 2nd ed. Auckland (NZ): Oxford University Press; 1998.
27. Gooberman-Hill R, Woolhead G, Mackichan F, Ayis S, Williams S, Dieppe P. Assessing chronic joint pain: lessons from a focus group study. Arthritis Rheum 2007;57:666–71.
28. Leung YY, Li W, Thumboo J. Concerns important to elderly patients with hand osteoarthritis: a qualitative multi-ethnic Asian study. Osteoarthritis Cartilage 2015;23 Suppl 2:A335.
29. Hill S, Dziedzic KS, Ong BN. The functional and psychological impact of hand osteoarthritis. Chronic Illn 2010;6:101–10.
30. Hill S, Dziedzic KS, Ong BN. Patients' perceptions of the treatment and management of hand osteoarthritis: a focus group enquiry. Disabil Rehabil 2011;33:1866–72.
31. Bromann Bukhave E, la Cour K, Huniche L. The meaning of activity and participation in everyday life when living with hand osteoarthritis. Scand J Occup Ther 2014;21:24–30.
32. Creswell JW. Research design: qualitative, quantitative and mixed methods approaches. Los Angeles: Sage Publishing; 2009.
33. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77–101.
34. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes. JAMA 1995;273:59–65.
35. Siviero P, Zambon S, Limongi F, Castell MV, Cooper C, Deeg DJ, et al. How hand osteoarthritis, comorbidity, and pain interact to determine functional limitation in older people: observations from the European Project on OSteoArthritis Study. Arthritis Rheumatol 2016;68:2662–70.
36. MacDermid JC. The relationship between impairment, dexterity and self-reported disability of persons with osteoarthritis of the hand. J Hand Ther 2008;21:423–4.
37. Zambon S, Siviero P, Denkinger M, Limongi F, Victoria Castell M, van der Pas S, et al. Role of osteoarthritis, comorbidity, and pain in determining functional limitations in older populations: European Project on Osteoarthritis. Arthritis Care Res (Hoboken) 2016;68:801–10.
38. Marshall M, van der Windt D, Nicholls E, Myers H, Hay E, Dziedzic K. Radiographic hand osteoarthritis: patterns and associations with hand pain and function in a community-dwelling sample. Osteoarthritis Cartilage 2009;17:1440–7.
39. Zhang Y. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. Am J Epidemiol 2002;156:1021–7.
40. Dziedzic K, Thomas E, Hill S, Wilkie R, Peat G, Croft PR. The impact of musculoskeletal hand problems in older adults: findings from the North Staffordshire Osteoarthritis Project (NorStOP). Rheumatology (Oxford) 2007;46:963–7.
41. Bijsterbosch J, Haugen IK, Malines C, Maheu E, Rosendaal FR, Watt I, et al. Reliability, sensitivity to change and feasibility of three radiographic scoring methods for hand osteoarthritis. Ann Rheum Dis 2011;70:1465–7.
42. Leung YY, Li JC, Thumboo J. Patient rating of importance of domains of life impact for hand osteoarthritis. Osteoarthritis Cartilage 2017;25:S355–6.
43. Slatkowsky-Christensen B, Mowinckel P, Loge JH, Kvien TK. Health-related quality of life in women with symptomatic hand osteoarthritis: a comparison with rheumatoid arthritis patients, healthy controls, and normative data. Arthritis Rheum 2007;57:1404–9.
44. Moe RH, Grotle M, Kjeken I, Hagen KB, Kvien TK, Uhlig T. Disease impact of hand OA compared with hip, knee and generalized disease in specialist rheumatology health care. Rheumatology (Oxford) 2013;52:189–96.
45. Gignac MA, Davis AM, Hawker G, Wright JG, Mahomed N, Fortin PR, et al. "What do you expect? You're just getting older": a comparison of perceived osteoarthritis-related and aging-related health experiences in middle- and older-age adults. Arthritis Rheum 2006;55:905–12.
46. Baird CL. Living with hurting and difficulty doing: older women with osteoarthritis. Clin Excell Nurse Pract 2000;4:231–7.
47. Harris ML, Byles JE, Sibbritt D, Loxton D. "Just get on with it": qualitative insights of coming to terms with a deteriorating body for older women with osteoarthritis. PLoS One 2015;10:e0120507.
48. Hodkinson B, Maheu E, Michon M, Carrat F, Berenbaum F. Assessment and determinants of aesthetic discomfort in hand osteoarthritis. Ann Rheum Dis 2012;71:45–9.
49. Woolhead G, Calnan M, Dieppe P, Tadd W. Dignity in older age: what do older people in the United Kingdom think? Age Ageing 2004;33:165–70.
50. Gravas EM, Tveter AT, Nossum R, Eide RE, Klokkeide A, Matre KH, et al. Non-pharmacological treatment gap preceding surgical consultation in thumb carpometacarpal osteoarthritis: a cross-sectional study. BMC Musculoskelet Disord 2019;20:180.
51. Napier AD, Ancarno C, Butler B, Calabrese J, Chater A, Chatterjee H, et al. Culture and health. Lancet 2014;384:1607–39.

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Hand Examination, Ultrasound, and the Association With Hand Pain and Function in Community-Based Older Adults

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Objective. To describe cross-sectional associations between features observed on ultrasound (US) or clinical joint examination and hand symptoms among community-dwelling older adults (n = 519), and to determine whether such associations are independent of age, sex, body mass index, and other imaging features.

Methods. Hand pain, function, and stiffness were assessed using a visual analog scale (VAS) and the Australian/Canadian Hand Osteoarthritis (AUSCAN) index. Standardized clinical and US examinations were performed, and grip strength was assessed using a dynamometer. Data were analyzed using hurdle and linear models and adjusted for demographic factors and other features.

Results. Abnormal findings on joint examination and on US imaging are common in older adults with and without hand pain. Greater numbers of tender joints were associated with greater pain (VAS: β = 2.63 [95% confidence interval (95% CI) 1.88, 3.39]; AUSCAN pain: β = 10.57 [95% CI 4.00, 17.13]), poorer AUSCAN function (β = 4.07 [95% CI 1.28, 6.86]), and poorer grip strength (β = –0.15 [95% CI –0.27, –0.03]). Power Doppler imaging (PDI) synovitis was associated with greater pain (VAS: β = 2.61 [95% CI 1.03, 4.19]; AUSCAN pain: β = 13.07 [95% CI 3.82, 22.32]), but not function. Joint deformity was associated with poorer function (β = 4.51 [95% CI 1.75, 7.26]) and grip strength (β = –0.23 [95% CI –0.40, –0.05]), but not pain. Gray-scale synovitis was associated only with poorer grip strength (β = –0.22 [95% CI –0.41, –0.04]). Associations with function and grip strength were partially mediated by pain.

Conclusion. Joints that are tender on palpation or have US-identified PDI synovitis are potential treatment targets for hand pain. Treating tender joints and preventing hand deformity is required to improve hand function in community-dwelling older adults.

INTRODUCTION

Hand pain is common in older adults (1,2) and is associated with poorer hand function (3) and difficulty performing everyday tasks (4,5). Both clinical examination and imaging are routinely used to assess hand pain. Radiography is the usual imaging method, yet radiographic changes are weakly associated with pain and function (3,6–8). Ultrasonography is a promising technique for imaging hand joints because it assesses surface joints clearly and quickly, is often available in consultation rooms, and involves no radiation exposure; however, assessments of whether abnormal joints seen on ultrasound (US) are associated with pain and symptoms are needed (9).

Previous studies that used US imaging to examine hand joints have shown that osteophytes were associated with pain (10), but associations between synovitis and pain are inconsistent in patients with hand osteoarthritis (OA) (10–12). The sum of scores of gray-scale synovitis (a composite of synovial hypertrophy and effusion) was independently associated with Australian/Canadian Hand Osteoarthritis (AUSCAN) index pain scores in 1 study (10). Associations between power Doppler imaging (PDI) synovitis and pain are inconsistent either at the joint or patient

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SIGNIFICANCE & INNOVATIONS

- To our knowledge, this is the first study to report prevalence and severity of ultrasound-detected hand abnormalities in community-dwelling older adults.
- This study adds to existing evidence that inflammation assessment using ultrasound adds greater validity to assess hand abnormalities than clinical hand assessment alone.

level, with PDI synovitis associated with palpated pain in some studies (10,13) but not others at the joint (11) and patient level (12). All of these studies had small numbers of participants (25–55 participants) (10–14), and all of them were with patients with hand OA. Association between gray-scale synovitis and pain is independent of other US features (10), but whether PDI synovitis is also independent of other US features is unknown (13). Similarly, no studies have assessed whether associations between US features and physical function are independent of pain.

To our knowledge, only 2 studies have assessed associations between abnormal hand features on US and physical function limitation. One study showed that the sum of gray-scale synovitis scores was associated with a worse Short Form 36 physical component summary score (10); however, another study found no association between the sum of PDI synovitis scores, gray-scale synovitis, or osteophytes with AUSCAN function limitation (12).

Therefore, we aimed to describe cross-sectional associations between clinically evident swelling, tenderness, nodules, deformity, and US-detected osteophytes, gray-scale synovitis, and PDI synovitis with hand pain, stiffness, physical function limitation, and grip strength in a community-dwelling cohort made up of older adults. This study will enable us to assess whether associations are independent of age, sex, and other factors, and whether US findings add value to clinical assessment.

PATIENTS AND METHODS

Patients. The Tasmanian Older Adult Cohort (TASOAC) study is a prospective, population-based study that aimed to identify environmental, genetic, and biochemical factors associated with development and progression of OA at multiple sites (hand, knee, hip, and spine). Participants ages 50–80 years (n = 1,099) were recruited from the electoral roll in Southern Tasmania in 2002 using sex-stratified random sampling (the response rate was 57%). Participants were excluded if they were institutionalized or reported contraindications to magnetic resonance imaging (MRI). Data on hand OA features were collected only at the 10-year follow-up (phase 4, n = 519); therefore, analyses in this article consisted of cross-sectional data from phase 4. All research conducted was in compliance with the Declaration of Helsinki and was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee. All subjects gave informed written consent.

Outcomes in hand pain, stiffness, and physical function limitation. *Pain in target hand by visual analog scale (VAS).* Study participants were asked to assess pain in their target hand: "On this line, where would you rate your pain? Use the last 7 days as a time frame." This pain in the target hand was assessed using a single-item question of generic pain on a 100-mm VAS, a valid (15,16) and reliable (16) measure of hand pain in rheumatic conditions. The target hand was the participant's dominant hand unless they had contraindications to either MRI or high resolution peripheral quantitative computed tomography, in which case the contralateral hand was examined instead. This article uses only the US data.

Pain in both hands using the AUSCAN OA hand index VA3.1. Hand pain, stiffness, and difficulty performing daily activities in both hands was assessed using the AUSCAN index questionnaire VA3.1, which is a valid, reliable, and responsive measure for hand OA (17). The time horizon was the last 48 hours, and questions were assessed using a 100-mm VAS. AUSCAN consists of a total of 15 questions (5 for pain, 1 for [morning] stiffness, and 9 for physical function).

Clinical examination. Bilateral clinical joint examination of all 15 joints in each hand was performed by 1 trained assessor. The presence or absence of tenderness, soft tissue swelling, hard tissue enlargement (nodules), and deformity were assessed based on the American College of Rheumatology (ACR) criteria for hand OA (18). Briefly, tenderness was assessed by the examiner by exerting sufficient pressure on each joint using their thumb and index finger to produce whitening of the examiner's nail bed (19). Swollen joints were assessed visually and by palpation. Finger nodules were assessed by manual examination of each joint, and deformity was determined by the appearance of any deviation in the joint from the sagittal plane. Joint pain in the target hand was also determined by asking participants if they had pain (yes/no) in each individual joint in the preceding 7 days. Information from the clinical hand examination was used to diagnose clinically defined hand OA using ACR criteria (18). The intraobserver reliability of each of the abnormalities at the joint level was assessed with at least a 1-week interval between the readings, using a kappa statistic (20) in 10 participants. The results were fair to substantial: κ = 0.376 (95% confidence interval [95% CI] 0.061, 0.690) for left hand deformity, κ = 0.495 (0.211, 0.779) for left hand tenderness, κ = 0.606 (0.467, 0.746) for left hand nodules, κ = 0.668 (0.537, 0.799) for right hand nodules, and κ = 0.688 (0.431, 0.946) for right hand deformity. Swollen and tender joints in the right hand and swollen joints in the left hand had too little variability to enable kappa to be calculated.

US assessment. US assessments were completed by 1 experienced ultrasonographer (KS) using a GE LOCIQ e (GE Medical Systems) and an L8-18i hockey stick transducer using the methods of Keen et al (12). Power Doppler was assessed using a pulse repetition frequency of 0.8 kHz and medium wall filter (138 Hz) (21). Gain was adjusted until the background signal was eliminated. Each patient's target hand was examined with the patient seated at the scanning table.

Fifteen joints of the hand were assessed: the first carpometacarpal joint, the first to the fifth metacarpophalangeal joints, the first to the fifth proximal interphalangeal joints, and the second to the fifth distal interphalangeal joints. Following established protocols, the dorsal aspects of each joint were assessed by US for osteophytes, gray-scale synovitis, and PDI synovitis (22). Each joint was scanned in the longitudinal and transverse planes.

Imaging features were scored on a semiquantitative 0–3 scale for each joint. Osteophytes were defined as cortical protrusions seen in both the longitudinal and transverse planes, gray-scale synovitis was defined as a composite of both effusion and synovial hypertrophy, and PDI synovitis was defined as a power Doppler signal identified within the synovium of the area of gray-scale synovitis (22). For each of the gray-scale synovitis and osteophytes, joints were classified as 0 = no pathology, 1 = mild pathology, 2 = moderate pathology, and 3 = severe pathology (21,22). Similarly, PDI synovitis was scored as 0 = no PDI signal within the synovium adjacent to the joint, 1 = minimal PDI signal, 2 = moderate signal, and 3 = marked evidence of PDI signal (22). Intrarater reliability for US measures at the joint level was determined by reimaging a subgroup of 20 participants on the same day as their original assessment. Reliability was assessed using weighted kappa. Reliability for all measures was substantial, with $\kappa_{(w)}$ = 0.753 (95% CI 0.730, 0.760) for osteophytes, $\kappa_{(w)}$ = 0.661 (0.586, 0.719) for gray-scale synovitis, and $\kappa_{(w)}$ = 0.689 (0.525, 0.780) for PDI synovitis.

All of the participants had at least 1 joint with osteophyte and gray-scale synovitis; therefore, we collapsed categories for analysis, dichotomizing osteophytes and gray-scale synovitis as ≥2 (due to the high prevalence) and PDI synovitis score ≥1, measured on US as present or absent on each of the 15 joints, and we summed the number of joints with abnormalities.

Other factors. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$ with weight measured to the nearest 0.1 kg using a single set of calibrated electronic scales (Seca Delta Model 707), and height measured to the nearest 0.1 cm using a stadiometer, minus shoes, socks, and headwear. Grip strength was measured by North Coast Bulb Dynamometer, adult 0–30 psi, model no. 70154, with the participant sitting with the shoulder in a neutral position and 90-degree flexed elbow. The best performance of 2 attempts was recorded for each hand. In this study, we used measurements of the target hand. Any of the pain medications that were used were recorded in a self-reported questionnaire from the list of medications patients were taking (medication name, dose, and frequency).

Statistical analyses. The primary exposure for all analyses was the number of joints with features on clinical assessment (tenderness, swelling, nodules, and deformity; both hands for AUSCAN scales and target hand only for association with target hand VAS pain score and grip strength) and US assessment (osteophytes, gray-scale synovitis, and PDI synovitis).

We used exponential hurdle models to estimate associations between the number of joints with clinical and US features and the outcomes; target hand VAS pain score, AUSCAN subscales, and total AUSCAN scores were bounded by 0 and nonnormally distributed with a large number of zeros. The distribution of the outcomes (bimodal, given the large number of people with no pain) meant that the data were difficult to model and simpler methods (e.g., linear regression) were not suitable. The hurdle models had 2 components: presence and absence of pain and pain severity, which were modeled separately. Model coefficients estimated the average marginal effects (predicted changes in pain) for a 1-unit increase in the number of joints with abnormalities (Tables 1 and 2). Linear regression was used to assess the association between the number of joints with target hand clinical and US features and target hand grip strength. all models were adjusted for age, sex, and BMI and further adjusted for pain (for function limitation and grip strength), and then all other clinical or US variables.

We conducted a sensitivity analysis to examine whether pain medication use was a confounder. All statistical analyses were performed using Stata 15 SE software. *P* values less than or equal to 0.05 (2-tailed) were considered statistically significant.

Table 1. Associations between the number of joints with target hand clinical and US features of osteoarthritis and target hand pain by VAS (mm) during the last 7 days*

	Adjusted for age, sex, BMI	Adjusted for clinical/US features†
No. of joints, clinical		
Swollen	7.73 (3.15, 12.32)‡	3.55 (−0.04, 7.14)
Tender	2.84 (2.07, 3.61)‡	2.63 (1.88, 3.39)‡
Nodules	0.29 (−0.15, 0.73)	0.14 (−0.26, 0.54)
Deformity	1.88 (0.70, 3.06)‡	0.44 (−0.62, 1.49)
No. of joints, US		
Osteophytes	0.78 (0.23, 1.32)‡	0.42 (−0.15, 1.00)
Gray-scale synovitis	1.69 (0.62, 2.77)‡	0.44 (−0.79, 1.66)
PDI synovitis	3.17 (1.69, 4.64)‡	2.61 (1.03, 4.19)‡

* Values are the β (95% confidence interval). Presence of osteophytes and gray-scale synovitis at the joint level was dichotomized to ≥2; other clinical and US features were dichotomized at ≥1. Associations were assessed using a hurdle model. BMI = body mass index; PDI = power Doppler imaging; US = ultrasound; VAS = visual analog scale.
† Further adjusted for other clinical features (for clinical exposures) or other US features (for US exposures).
‡ Statistically significant.

Table 2. Associations of the number of joints with clinical and US osteoarthritis features and AUSCAN scales*

	Pain score, mm		Physical function limitation score, mm			Stiffness score, mm		
	Adjusted for age, sex, BMI	Adjusted for clinical/US features†	Adjusted for age, sex, BMI	Adjusted for AUSCAN pain	Adjusted for clinical/US features†	Adjusted for age, sex, BMI	Adjusted for AUSCAN pain	Adjusted for clinical/US features†
No. of joints, clinical								
Swollen	16.69 (5.55, 27.83)‡	1.08 (–6.26, 8.42)	35.53 (11.44, 59.63)‡	7.97 (–1.27, 17.22)	6.26 (–3.18, 15.71)	2.70 (0.66, 4.75)‡	0.53 (–0.91, 1.97)	0.68 (–0.82, 2.19)
Tender	10.95 (4.20, 17.69)‡	10.57 (4.00, 17.13)‡	25.97 (18.78, 33.15)‡	4.81 (1.97, 7.64)‡	4.07 (1.28, 6.86)‡	1.83 (1.35, 2.30)‡	0.37 (0.04, 0.71)‡	0.31 (–0.02, 0.65)
Nodules	0.83 (–0.30, 1.96)	0.23 (–0.65, 1.10)	2.30 (–0.06, 4.67)	0.91 (–0.18, 2.01)	0.49 (–0.64, 1.61)	0.38 (0.14, 0.62)‡	0.25 (0.07, 0.43)‡	0.27 (0.08, 0.46)‡
Deformity	6.64 (3.05, 10.24)‡	2.13 (–0.15, 4.42)	15.56 (7.92, 23.20)‡	5.41 (2.74, 8.08)‡	4.51 (1.75, 7.26)‡	1.29 (0.60, 1.97)‡	0.25 (–0.14, 0.64)	0.06 (–0.46, 0.57)
No. of joints, US								
Osteophytes	3.96 (1.12, 6.80)‡	2.64 (–0.45, 5.73)	8.27 (2.44, 14.10)‡	2.11 (–2.89, 7.12)	–0.38 (–6.11, 5.35)	1.09 (0.52, 1.67)‡	0.53 (0.10, 0.96)‡	0.51 (0.03, 0.99)‡
Gray-scale synovitis	7.42 (1.67, 13.16)‡	1.27 (–5.37, 7.92)	21.46 (8.91, 34.01)‡	11.23 (–0.02, 22.47)	9.94 (–3.08, 22.97)	1.63 (0.50, 2.75)‡	0.52 (–0.32, 1.35)	–0.20 (–1.19, 0.80)
PDI synovitis	15.76 (7.22, 24.29)‡	13.07 (3.82, 22.32)‡	35.99 (17.5, 54.49)‡	11.43 (–3.99, 26.86)	6.20 (–10.70, 23.10)	3.49 (1.80, 5.18)‡	1.15 (–0.08, 2.37)	0.92 (–0.42, 2.27)

* Values are the β (95% confidence interval). Associations were assessed using a hurdle model. Presence of osteophytes and gray-scale synovitis at the joint level was dichotomized to ≥2; other clinical and ultrasound (US) features were dichotomized at ≥1. AUSCAN = Australian/Canadian Hand Osteoarthritis; BMI = body mass index; PDI = power Doppler imaging.
† Further adjusted for other clinical features (for clinical exposures) or other US features (for US exposures).
‡ Statistically significant.

RESULTS

Study participants. The study included participants who attended the 10-year TASOAC follow-up, a subset of the original cohort. Compared to those lost at follow-up, participants were younger at baseline (mean ± SD age 61.4 ± 6.6 years versus 64.0 ± 7.9 years, n = 519; $P < 0.001$) and had greater steps per day (mean ± SD 9,150 ± 3,314 versus 8,115 ± 3,318; $P < 0.001$). There was a similar proportion of women (49% versus 53%; $P = 0.30$), mean ± SD BMI (27.6 ± 4.4 versus 28.2 ± 5.0 kg/m^2; $P = 0.05$), and proportion of current smokers (11% versus 13%; $P = 0.18$) compared to those who were lost to follow-up.

Table 3 shows the characteristics of study participants stratified by the presence or absence of hand pain, assessed by the AUSCAN pain score. Participants with hand pain were of similar age and BMI to those with no pain, but more were women, and a higher proportion of them met ACR hand OA criteria and had clinical and US features (except where features were ubiquitous, i.e., nodules). All of the participants had a score ≥1 for osteophytes and gray-scale synovitis; therefore, we dichotomized them (above or below 2, at the joint level). In all, 92% of joints had osteophytes, 41% had gray-scale synovitis, and 3.5% had PDI synovitis (Table 3).

Hand pain. Greater numbers of clinically swollen, tender, or deformed joints and joints with US-detected osteophytes, gray-scale synovitis, or PDI synovitis were associated with more intense pain in the target hand (Table 1) and AUSCAN pain score (Table 2), after adjustment for age, sex, and BMI. However, these associations persisted only for the target hand's number of tender joints and PDI synovitis after further adjustment for other clinical or US features. The number of joints with nodules was not associated with either VAS or AUSCAN hand pain (Tables 1 and 2).

Hand physical function limitation. Greater numbers of clinically swollen, tender, or deformed joints and US-detected osteophytes, gray-scale synovitis, and PDI synovitis were all associated with increased function limitation scores after adjustment for age, sex, and BMI (Table 2). After further adjustment for the AUSCAN pain score, effect sizes reduced and remained statistically significant only for the number of tender and deformed joints. These effect sizes reduced slightly after further adjustment for all other clinical assessment features but remained statistically significant. The number of clinically swollen and nodulous joints, US-detected osteophytes, gray-scale synovitis, and PDI synovitis was not associated with function limitation scores after adjustment of the AUSCAN pain score and all other US features (Table 2).

Hand stiffness. The number of joints with clinical swelling, tenderness, nodules, or deformity and US-detected osteophytes, gray-scale synovitis, and PDI synovitis was associated with a greater stiffness score, after adjustment for demographic factors (Table 2). After further adjustment for AUSCAN pain score, associations remained statistically significant for the number of joints with tenderness, nodules, and osteophytes. These associations only persisted for nodules and osteophytes after adjustment for other clinical or US features.

Total AUSCAN score. Greater numbers of joints with swollen, tender, or deformed joints, osteophytes, gray-scale synovitis, or PDI synovitis were associated with a greater total AUSCAN score, after adjustment for demographic factors (see Supplementary Table 1 available on the *Arthritis Care & Research* website

Table 3. Characteristics of study participants, by presence or absence of hand pain on AUSCAN*

	Whole sample (n = 519)	No hand pain, AUSCAN pain = 0 (n = 210)	Hand pain, AUSCAN pain >0 (n = 309)
Age, years	72.05 ± 6.41	72.11 ± 6.01	72.01 ± 6.67
Female, %	50	42	54
BMI, kg/m^2	28.03 ± 4.88	27.91 ± 4.75	28.11 ± 4.97
Met ACR HOA criteria, %	67	41	84
Grip strength	10.96 ± 3.77	11.76 ± 3.45	10.41 ± 3.88
Clinical assessment, (%) mean ± SD†			
Swollen	(48) 0.1 ± 0.8	(22) 0.1 ± 0.4	(65) 0.2 ± 1.0
Tender	(5) 2.0 ± 4.1	(2) 0.4 ± 1.0	(7) 3.1 ± 4.9
Nodules	(100) 22.3 ± 7.3	(100) 21.7 ± 6.8	(100) 22.7 ± 7.6
Deformity	(66) 2.1 ± 2.5	(60) 1.7 ± 2.3	(70) 2.3 ± 2.6
US features, (%) mean ± SD‡			
Osteophytes	(97) 5.93 ± 3.28	(96) 5.38 ± 3.18	(97) 6.29 ± 3.29
Gray-scale synovitis	(53) 1.05 ± 1.41	(42) 0.75 ± 1.17	(60) 1.25 ± 1.51
PDI synovitis	(33) 0.52 ± 0.9	(23) 0.34 ± 0.72	(40) 0.65 ± 1.08

* Values are the mean ± SD unless indicated otherwise. Presence of osteophytes and gray-scale synovitis at the joint level was dichotomized to ≥2; other clinical and ultrasound (US) features were dichotomized at ≥1. ACR HOA = American College of Rheumatology criteria for hand osteoarthritis; AUSCAN = Australian/Canadian hand osteoarthritis index; BMI = body mass index; PDI = power Doppler imaging; VAS = visual analog scale.
† No. of joints 0–30.
‡ No. of joints 0–15.

Table 4. Associations of number of joints with target hand clinical and US features and grip strength of target hand (psi)*

	Adjusted for age, sex, BMI	Adjusted for AUSCAN pain	Adjusted for clinical/US features†
No. of joints, clinical			
Swollen	−0.46 (−0.89, −0.03)‡	−0.19 (−0.62, 0.23)	−0.10 (−0.53, 0.33)
Tender	−0.32 (−0.42, −0.23)‡	−0.18 (−0.3, −0.07)‡	−0.15 (−0.27, −0.03)‡
Nodules	−0.09 (−0.16, −0.03)‡	−0.08 (−0.14, −0.02)‡	−0.06 (−0.12, 0.005)
Deformity	−0.40 (−0.58, −0.23)‡	−0.31 (−0.48, −0.14)‡	−0.23 (−0.40, −0.05)‡
No. of joints, US			
Osteophytes	−0.14 (−0.20, −0.07)‡	−0.10 (−0.17, −0.04)‡	−0.08 (−0.16, 0.004)
Gray-scale synovitis	−0.33 (−0.47, −0.20)‡	−0.27 (−0.40, −0.13)‡	−0.22 (−0.41, −0.04)‡
PDI synovitis	−0.31 (−0.51, −0.11)‡	−0.14 (−0.34, 0.06)	0.10 (−0.15, 0.347)

* Values are the β (95% confidence interval). Presence of osteophytes and gray-scale synovitis at the joint level was dichotomized to ≥2; other clinical and ultrasound (US) features were dichotomized at ≥1. Associations were assessed using linear regression. AUSCAN = Australian/Canadian Hand Osteoarthritis; BMI = body mass index; PDI = power Doppler imaging.
† Further adjusted for other clinical features (for clinical exposures) or other US features (for US exposures).
‡ Statistically significant.

at http://onlinelibrary.wiley.com/doi/10.1002/acr.24128/abstract). Associations remained significant for the number of joints with tenderness, deformity, and PDI synovitis after further adjustment for other clinical or US features.

Hand grip strength. Greater numbers of joints with tenderness, nodules, or deformities on the target hand, and abnormalities in all US features were associated with weaker grip strength for all abnormal features after adjustment for age, sex, and BMI (Table 4). With the exception of associations with PDI synovitis, effect sizes reduced slightly after further adjustment for AUSCAN pain score but remained statistically significant. Associations between tender and deformed joints and joints with gray-scale synovitis remained statistically significant after further adjustment for other clinical or US features, with only small reductions in effect size. (Table 4). We further adjusted all of our models for any use of pain medication. This adjustment did not change the effect sizes by >10% (data not shown).

DISCUSSION

To our knowledge, this study is the first to report the prevalence and severity of US-detected hand OA abnormalities in community-dwelling older adults. A greater number of joints that were tender on palpation or had PDI synovitis on US was associated with hand pain and independent of other findings on clinical examination or US. A greater number of joints that were tender or deformed on clinical examination or with gray-scale synovitis on US was associated with function limitation or lower grip strength. Associations between these abnormalities and function limitation, grip strength, and stiffness were predominantly mediated through pain; however, tenderness and deformity affected function even after taking pain into account.

Prevalence estimates for abnormal imaging features were similar to those reported in cohorts of people with hand OA: 41% of joints had gray-scale synovitis, compared to 25–46% in other studies (10,12,13); similarly, 3.5% of joints had PDI synovitis, compared to literature estimates of 2–9% (10,12,23–25). However, the prevalence of US-detected osteophytes in our study was higher than literature estimates (range 41–85%) (14,26,27), which may be explained by differences in average ages of the cohort (ours was >10 years older). We expected the abnormalities prevalence to be smaller than estimates from hand OA cohorts, but our study suggests that these abnormalities are common in the general population of older people.

These results suggest that the most important aspect of the clinical examination is identifying people with tender joints on palpation, a specific type of pain present in only a small proportion (7%) of people with hand pain and with joint deformity. The former is important for both pain and function, the latter only for function. Similarly, the most important US finding is PDI synovitis.

Associations between tender joints and PDI synovitis with hand pain (both pain in the target hand and AUSCAN pain score) were in contrast to 2 studies that found no associations between the number of joints with US features and hand pain (12,28). However, both of these studies were likely underpowered to detect an association due to a small number of participants (<20 participants), suggesting that our findings are real associations, and that the negative finding in the literature may be false negatives.

Associations between a greater number of tender and deformed joints (but not nodules) and physical function limitation (assessed by AUSCAN function and grip strength) was consistent with 2 previous studies (28,29), although we are the first to demonstrate that these associations are independent of other clinical features, as well as partially mediated by pain. Meanwhile, the latter differs from other studies, where Jones et al (3) and Bagis et al (29) reported that Heberden's nodes were associated with physical function (but were not independent of pain). Our result suggests that improving joint tenderness may improve hand function, and that preventing deformity may also improve hand function.

Associations between a greater number of joints with nodules and osteophytes and a greater AUSCAN stiffness score in our study were consistent with a cross-sectional study of 190 women

with hand OA (30), but not a case–control study of 55 adults with and without hand OA (12), although the reason for the different findings is unclear. Kortekaas et al (10) showed weak associations between gray-scale synovitis and stiffness, but they did not adjust for pain or other US features. In our study, associations between gray-scale synovitis and stiffness were not independent of pain or other features. This dependence of stiffness on pain suggests that improving hand stiffness will require improvements in hand pain.

We demonstrated that a US-detected PDI synovitis signal was independently correlated with pain, while combined synovial hypertrophy and effusion (gray-scale synovitis) were not. Therefore, successfully treating PDI synovitis may improve hand pain, but treating gray-scale synovitis may not. Additionally, since PDI synovitis is associated with radiographic damage and reduced cartilage thickness in hand OA at the joint level cross-sectionally (11,24,31), our results support PDI synovitis as an important correlate of structural abnormalities in hand pain, and thereby represent a treatment target for reducing hand pain and the progression of hand OA.

Strengths of this study include the standardized clinical assessment and US data from examinations conducted by a single experienced assessor, as well as the population-based source of the data, which enable findings to be generalized to older adults in the community. A limitation from this study was the loss to follow-up within the TASOAC cohort. Data used for this study are a subset of the original cohort (with 53% lost to follow-up over 10.7 years). However, the cohort retained is largely representative of the original cohort. Therefore, the risk of bias from participants lost to follow-up is low, and the results remain generalizable to older people. While the generalizable cohort is a strength, a generalizable cohort also means that the study includes people with other rheumatic conditions common in older adults, meaning that abnormalities observed could be due to a range of underlying conditions. The US assessment scoring system does not include erosion assessment (12) because US is less sensitive to the presence of erosions than conventional radiography (32). Other limitations include a limited field of view for the US, with US examination performed on the dorsal side of each finger joint only. This procedure is in line with established protocols within the field (12,14). While the limited field of view for US might underestimate the prevalence of US abnormalities, this limitation is unlikely because US abnormalities were extremely common. Additionally, the study is cross-sectional, and therefore inferences regarding causality are limited.

In conclusion, joints that were tender on palpation and had PDI synovitis on US were independently associated with hand pain and are potential treatment targets for hand pain. Joints that were tender or deformed, or had gray-scale synovitis, were associated with reduced function or grip strength cross-sectionally. Associations with function were predominantly mediated through pain, but tenderness and deformity remained associated with function even after adjusting for pain. Therefore, treating tender joints and preventing hand deformity are required to improve hand function in community-dwelling older adults.

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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. Jones 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. Mattap, Laslett, Aitken, Keen, Cicuttini, Winzenberg, Jones.

Acquisition of data. Squibb, Winzenberg, Jones.

Analysis and interpretation of data. Mattap, Laslett, Wills, Otahal, Pan, Aitken, Cicuttini, Winzenberg, Jones.

REFERENCES

1. Dahaghin S, Bierma-Zeinstra SM, Reijman M, Pols HA, Hazes JM, Koes BW. Prevalence and determinants of one month hand pain and hand related disability in the elderly (Rotterdam study). Ann Rheum Dis 2005;64:99–104.
2. Keenan AM, Tennant A, Fear J, Emery P, Conaghan PG. Impact of multiple joint problems on daily living tasks in people in the community over age fifty-five. Arthritis Rheum 2006;55:757–64.
3. Jones G, Cooley HM, Bellamy N. A cross-sectional study of the association between Heberden's nodes, radiographic osteoarthritis of the hands, grip strength, disability and pain. Osteoarthritis Cartilage 2001;9:606–11.
4. Kalichman L, Hernández-Molina G. Hand osteoarthritis: an epidemiological perspective. Semin Arthritis Rheum 2010;39:465–76.
5. Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. Br Med Bull 2013;105:185–99.
6. Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, Pols HA, Hazes JM, Koes BW. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). Ann Rheum Dis 2005;64:682–7.
7. Hart D, Spector T, Egger P, Coggon D, Cooper C. Defining osteoarthritis of the hand for epidemiological studies: the Chingford Study. Ann Rheum Dis 1994;53:220–3.
8. Haugen IK, Slatkowsky-Christensen B, Bøyesen P, van der Heijde D, Kvien TK. Cross-sectional and longitudinal associations between radiographic features and measures of pain and physical function in hand osteoarthritis. Osteoarthritis Cartilage 2013;21:1191–8.
9. Haugen IK, Hammer HB. Role of modern imaging techniques in hand osteoarthritis research and clinical practice. Curr Rheumatol Rep 2013;16:399.
10. Kortekaas MC, Kwok WY, Reijnierse M, Watt I, Huizinga TW, Kloppenburg M. Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound. Ann Rheum Dis 2010;69:1367–9.
11. Arrestier S, Rosenberg C, Etchepare F, Rozenberg S, Foltz V, Fautrel B, et al. Ultrasound features of nonstructural lesions of the proximal and distal interphalangeal joints of the hands in patients with finger osteoarthritis. Joint Bone Spine 2011;78:65–9.
12. Keen HI, Wakefield RJ, Grainger AJ, Hensor EM, Emery P, Conaghan PG. An ultrasonographic study of osteoarthritis of the hand: synovitis and its relationship to structural pathology and symptoms. Arthritis Rheum 2008;59:1756–63.

13. Kortekaas MC, Kwok WY, Reijnierse M, Huizinga TW, Kloppenburg M. Follow-up study of inflammatory ultrasound features in hand osteoarthritis over a period of 3 months: variable as well as constant. Osteoarthritis Cartilage 2014;22:40–3.
14. Kortekaas MC, Kwok WY, Reijnierse M, Huizinga TW, Kloppenburg M. Osteophytes and joint space narrowing are independently associated with pain in finger joints in hand osteoarthritis. Ann Rheum Dis 2011;70:1835–7.
15. Joyce CR, Zutshi DW, Hrubes V, Mason RM. Comparison of fixed interval and visual analogue scales for rating chronic pain. Eur J Clin Pharmacol 1975;8:415–20.
16. Ferraz MB, Quaresma MR, Aquino LR, Atra E, Tugwell P, Goldsmith CH. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. J Rheumatol 1990;17:1022–4.
17. Bellamy N, Campbell J, Haraoui B, Gerecz-Simon E, Buchbinder R, Hobby K, et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. Osteoarthritis Cartilage 2002;10:863–9.
18. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatolgy criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33:1601–10.
19. Van Riel P, Van Gestel A, Scott D. EULAR handbook of clinical assessments in rheumatoid arthritis. Nijmegen: Van Zuiden; 2000.
20. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.
21. Keen HI, Wakefield RJ, Grainger AJ, Hensor EM, Emery P, Conaghan PG. An ultrasonographic study of osteoarthritis of the hand: synovitis and its relationship to structural pathology and symptoms. Arthritis Rheum 2008;59:1756–63.
22. Keen HI, Lavie F, Wakefield RJ, D'Agostino MA, Hammer HB, Hensor EM, et al. The development of a preliminary ultrasonographic scoring system for features of hand osteoarthritis. Ann Rheum Dis 2008;67:651–5.
23. Vlychou M, Koutroumpas A, Malizos K, Sakkas LI. Ultrasonographic evidence of inflammation is frequent in hands of patients with erosive osteoarthritis. Osteoarthritis Cartilage 2009;17:1283–7.
24. Kortekaas MC, Kwok WY, Reijnierse M, Kloppenburg M. Inflammatory ultrasound features show independent associations with progression of structural damage after over 2 years of follow-up in patients with hand osteoarthritis. Ann Rheum Dis 2015;74:1720–4.
25. De Olivia Spolidoro Paschoal N, Natour J, Machado FS, Alcântara Veiga de Oliveira H, Vilar Furtado RN. Interphalangeal joint sonography of symptomatic hand osteoarthritis: clinical and functional correlation. J Ultrasound Med 2017;36:311–9.
26. Keen HI, Wakefield RJ, Grainger AJ, Hensor EM, Emery P, Conaghan PG. Can ultrasonography improve on radiographic assessment in osteoarthritis of the hands? A comparison between radiographic and ultrasonographic detected pathology. Ann Rheum Dis 2008;67:1116–20.
27. Mathiessen A, Haugen IK, Slatkowsky-Christensen B, Bøyesen P, Kvien TK, Hammer HB. Ultrasonographic assessment of osteophytes in 127 patients with hand osteoarthritis: exploring reliability and associations with MRI, radiographs and clinical joint findings. Ann Rheum Dis 2013;72:51–6.
28. Koutroumpas AC, Alexiou IS, Vlychou M, Sakkas LI. Comparison between clinical and ultrasonographic assessment in patients with erosive osteoarthritis of the hands. Clin Rheumatol 2010; 29:511–6.
29. Bagis S, Sahin G, Yapici Y, Cimen OB, Erdogan C. The effect of hand osteoarthritis on grip and pinch strength and hand function in postmenopausal women. Clin Rheumatol 2003;22:420–4.
30. Slatkowsky-Christensen B, Haugen IK, Kvien TK. Distribution of joint involvement in women with hand osteoarthritis and associations between joint counts and patient-reported outcome measures. Ann Rheum Dis 2010;69:198–201.
31. Mancarella L, Magnani M, Addimanda O, Pignotti E, Galletti S, Meliconi R. Ultrasound-detected synovitis with power Doppler signal is associated with severe radiographic damage and reduced cartilage thickness in hand osteoarthritis. Osteoarthritis Cartilage 2010;18:1263–8.
32. Iagnocco A, Filippucci E, Ossandon A, Ciapetti A, Salaffi F, Basili S, et al. High resolution ultrasonography in detection of bone erosions in patients with hand osteoarthritis. J Rheumatol 2005;32:2381–3.

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Association of Low Muscle Density With Deteriorations in Muscle Strength and Physical Functioning in Rheumatoid Arthritis

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Objective. Rheumatoid arthritis (RA) is associated with low muscle density due to the accumulation of intramuscular fat. The present study was undertaken to identify predictors of changes in muscle density and to determine whether low muscle density predicted changes in strength and physical function.

Methods. Patients with RA, ages 18–70 years, completed whole-body dual-energy x-ray absorptiometry and peripheral quantitative computed tomography to quantify lean and fat mass indices and muscle density. Dynamometry was used to measure strength at the hand, knee, and lower leg. Disability and physical function were measured with the Health Assessment Questionnaire (HAQ) and the Short Physical Performance Battery (SPPB). Assessments were performed at baseline and at follow-up. Regression analyses assessed associations between patient characteristics, muscle density, and deteriorations in strength and function.

Results. Muscle density was assessed at baseline in 107 patients with RA. Seventy-nine of these patients (74%) returned for a follow-up assessment at a median follow-up time of 2.71 years (interquartile range 2.35–3.57). Factors associated with declines in muscle density included female sex, higher disease activity, smoking, and lower insulin-like growth factor 1 (IGF-1) levels. Greater muscle density Z score at baseline (per 1 SD) was associated with less worsening per year according to HAQ, SPPB, and 4-meter walk time scores and a lower risk of a clinically important worsening in HAQ score (odds ratio [OR] 1.90 [95% confidence interval (95% CI) 1.06, 3.42]; $P = 0.03$) and walking speed (OR 2.87 [95% CI 1.05, 7.89]; $P = 0.04$).

Conclusion. Worsening of skeletal muscle density occurred in patients with higher disease activity, in smokers, and in those with lower IGF-1. Low muscle density was associated with worsening of physical function. Interventions addressing reductions in muscle quality might prevent functional decline.

INTRODUCTION

Intramuscular fat accumulation resulting in low muscle density is an adverse feature of aging and is associated with excess adiposity and insulin resistance (1–5). In the general population, it has been linked to low muscle strength, poor physical function, fracture, cardiovascular disease, and early mortality (2,3,6–11).

In rheumatoid arthritis (RA), adverse changes to body composition, including obesity, excess adiposity, and low muscle mass, have been linked to poor physical function in cross-sectional studies (12–15). Low muscle density has also recently been observed in patients with RA and is independently associated with greater disease activity, high interleukin-6 (IL-6) levels, and worse physical function in several cross-sectional studies (16–19).

While prior cross-sectional studies may suggest a relationship between muscle density (muscle quality), disease activity, and physical functioning, they do not establish temporal relationships and might be related to reverse causality. In other words, an apparent association between low muscle density and poor physical function could conceivably result from the presence of

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SIGNIFICANCE & INNOVATIONS

- Declines in muscle density among patients with rheumatoid arthritis (RA) are associated with greater disease activity, smoking, and low insulin-like growth factor 1 levels.
- Low muscle density at baseline independently predicts worsening of physical function.
- The temporal associations help to support the hypothesis that low muscle density is a risk factor for worsening of function in patients with RA.

common risk factors. Longitudinal studies can help define temporal relationships (e.g., Does low muscle density independently predict the development of functional decline?).

We hypothesized that higher disease activity at baseline would be associated with long-term declines in muscle density, and that lower muscle density at baseline would be associated with greater decline in physical functioning independent of other factors including body composition. We aimed to define factors that were predictive of long-term changes in muscle density in order to help define areas of potential intervention. We also aimed to determine whether greater muscle density at baseline was protective against subsequent declines in physical functioning.

PATIENTS AND METHODS

Study setting. Patients with RA, ages 18–70 years, with rheumatologist-confirmed RA and who met the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for RA (20), were recruited from the University of Pennsylvania and Philadelphia VA Medical Center Rheumatology practices. Subjects with juvenile idiopathic arthritis (or an inflammatory arthritis other than RA), active cancer, a history of chronic diseases known to affect bone health (e.g., chronic kidney disease, liver disease, or malabsorption syndromes), pregnancy, or who were unable to perform the muscle density or body composition assessments due to physical limitations, excess weight (>300 pounds), or a calf size that would not fit in the scanner were excluded. The original study was expanded to include a follow-up visit that, for most participants, occurred between 2 and 3 years from baseline. Unless otherwise noted, all study procedures were performed both at baseline and at follow-up.

The protocols were approved by the Institutional Review Board at the University of Pennsylvania and the Philadelphia Veterans Affairs Medical Center. Informed consent was obtained from all participants.

Assessment of anthropometrics and race. Weight and height were measured with patients in light clothing and with shoes removed using a digital scale (Scaltronix) and stadiometer (Holtain), respectively. Body mass index (BMI) was also calculated (kg/m^2). The participants self-identified their race according to National Institutes of Health categories, and this information was used in the analyses.

Body composition assessments. Subjects underwent whole-body dual x-ray absorptiometry assessment using a Delphi/Discovery Systems densitometer (Hologic) to measure appendicular lean mass, as well as total and regional fat mass. Similar to the adjustment of weight for height to estimate BMI, body composition estimates were adjusted for $height^2$ to generate Appendicular Lean Mass Index (ALMI, kg/m^2) and fat mass index (FMI, kg/m^2). The in vitro coefficient of variation (CV) for measurement of lean mass was <0.6%, and the in vivo CV in adults was <1% (21). We utilized a previously validated method to quantify visceral adipose tissue area (22).

Muscle density assessment. Muscle, fat, and bone measures in the left lower leg were obtained with the patient in a seated position by a Stratec XCT2000 12-detector peripheral quantitative computed tomography (QCT) unit (Orthometrix) with a voxel size of 0.4 mm, slice thickness of 2.3 mm, and scan speed of 25 mm/second. All scans were analyzed with Stratec software, version 6.00. Calf muscle and subcutaneous fat cross-sectional area (mm^2) were assessed at 66% proximal to the distal physis using a threshold of 40 mg/cm^3 for fat/lean separation and 711 mg/cm^3 for lean/bone separation. The peripheral quantitative computed tomography (peripheral QCT) measure of muscle density (mg/cm^3) was used as a composite index of intra- and extramyocellular fat content, as previously described (23,24). Edge-detection and threshold techniques were used to separate tissues based on attenuation characteristics that are directly related to tissue composition and density (1,4). Images were filtered prior to being analyzed using contour mode 3 (–101 mg/cm^3) to find skin, and peel mode 2 (40 mg/cm^3) to separate adipose and muscle/bone, respectively. Images were filtered subsequently with a combination 3 × 3 and double 5 × 5 kernel image filter that clearly defined the edge of the muscle using contour mode 31 (40 mg/cm^3). All bone was identified using a threshold of 150 mg/cm^3 and mathematically removed to generate results for muscle density. Quality control was monitored daily using a phantom. In our laboratory, the CV for short-term precision has ranged from 0.5% to 1.6% for peripheral QCT outcomes.

Dynamometric measurement of muscle strength. Muscle strength was assessed in several ways. Using the Multi-Joint System 3 Pro Dynamometer (Biodex), peak torque (foot-pounds) was measured in triplicate (with no practice trial) at the knee and lower leg (ankle) with visual feedback. For the lower leg (ankle), we report strength as peak isometric torque (foot-pounds) in dorsiflexion (with the foot placed in 20 degrees of plantarflexion), as previously described (25). Peak isokinetic torque (highest of 3 attempts; 60 degrees per second) in flexion

and extension at the knee was also reported (foot-pounds), with the knee at 90 degrees and the participant in a seated position. High intrarater (0.97 to 0.99) and interrater (0.93 to 0.96) intraclass correlation coefficients have been reported (26). Hand grip strength (kg) was measured using a hand-grip dynamometer adjusted to the size of the hand (Takei Scientific Instruments). A clinically important decrease in hand grip strength has been previously defined as 6.5 kg (27).

Assessments of physical function and disability. Disability was assessed using the Health Assessment Questionnaire (HAQ), a widely used tool in RA. Physical function was assessed using the Short Physical Performance Battery (SPPB). The SPPB is a simple test to measure lower extremity function using tasks that mimic daily activities. It examines static balance, gait speed, and timed chair stands (28,29). SPPB testing was initiated later and was therefore measured in a smaller sample of participants (n = 63). The time needed for the participant to walk 4 meters was also recorded. Clinically important changes in HAQ, SPPB, and walking speed scores have been previously defined (30,31). Based on these prior data, this study defined an important worsening of HAQ score as an increase of ≥0.2, an important worsening of SPPB score as a decrease of ≥1, and an important decrease in walk speed as a decrease of ≥0.05 meters per second.

Physical activity questionnaire. Physical activity was assessed over a typical week in the last month using a detailed and validated questionnaire developed for the Multi-Ethnic Study of Atherosclerosis (32,33). We used a definition of intentional exercise (the sum of walking for exercise, sports/dancing, and conditioning metabolic equivalent hours/week) as previously defined (34,35). The total number of reported sedentary hours per week was also recorded.

Disease measures, inflammatory markers. Erythrocyte sedimentation rate was measured using the Westergren method. C-reactive protein (CRP) level was measured using a fixed-point immunoassay. Medication use was determined by self-report and confirmed in the medical record. Disease activity was quantified using the Modified Disease Activity Score (M-DAS) (36). This assessment of disease activity is a composite measure that includes the CRP level, swollen joint count, and evaluator global score. It has been validated to correlate more strongly with synovitis on magnetic resonance imaging and radiographic damage progression, and it was used to avoid bias related to incorporation of the patient global score, which is closely correlated with physical functioning scores (e.g., HAQ score). Cytokine assays were performed using a V-Plex Plus Proinflammatory Panel 1 kit (Meso Scale Diagnostics). Insulin-like growth factor 1 (IGF-1) levels (ng/ml) were measured by an Immulite 1000 kit (Siemens). Radiographs of the hands and feet were performed, and Sharp/van der Heijde scores were determined by a trained radiologist (ET).

Statistical analysis. Measures of muscle density were converted to age-, sex-, and race-specific Z scores based on distributions among a reference population (13,17,37,38). Z scores represent the number of SDs above or below the predicted value for a healthy control of the same age, sex, and race. Body composition measures (ALMI and FMI) were converted to Z scores relative to a national reference population (using the National Health and Nutrition Examination Survey).

Factors associated with changes in muscle density over time. Changes in muscle density Z score over time were compared to disease characteristics, demographic information, inflammatory cytokines, adipokines, hormones, and body composition in univariate and multivariate linear regression models incorporating generalized estimating equations (GEEs) with robust estimators and exchangeable correlation matrices. Independent associations between baseline factors (e.g., disease activity) and changes in muscle density were assessed in multivariable models by interpreting multiplicative interaction terms with time (in years). Thus, the regression coefficients presented in the tables represent the difference in the change in muscle density Z score per year among individuals with that exposure compared to those without that exposure. Multivariable models incorporated only predictors that were modestly associated in univariate analyses to avoid overfitting ($P < 0.10$).

Associations between baseline muscle density and changes in physical functioning. Changes in physical functioning and strength outcomes per year were quantified in similar regression models that incorporated GEEs. We evaluated the impact of prehypothesized confounders identified in prior analyses, including baseline age, sex, race, baseline ALMI and FMI Z scores, disease activity, and smoking status (39). Height was included in regression models when evaluating muscle strength outcomes.

To assess the clinical importance of these relationships, we also performed logistic regression models to explore the difference in the odds of clinically important worsening in function and strength outcomes from baseline, adjusting for age, sex, race, baseline value, ALMI and FMI Z scores, smoking, and disease activity among those with follow-up data. We performed sensitivity analyses with a combined outcome of worsening or death for each outcome.

Sample size was originally determined based on detecting moderate effect sizes for the difference in the change in Z scores between equal groups. Analyses were performed with Stata, version 14.2 software.

RESULTS

Basic characteristics and description of cohort. Of 149 patients approached, a total of 107 patients with RA were eligible and enrolled in the study. Seventy-nine (74%) of these participants returned for a follow-up assessment at a median follow-up time

Table 1. Basic characteristics of study participants (n = 107)*

Characteristic	Value
Age, years	55.5 ± 12.7
Female, no. (%)	55 (51)
African American, no. (%)	32 (31)
Body mass index, kg/m^2	28.2 ± 6.8
ALMI Z score	−0.27 ± 0.99
FMI Z score	−0.23 ± 1.16
Muscle density Z score	−0.79 ± 1.12
RA disease characteristics	
M-DAS-CRP score	2.29 ± 1.15
DAS28-CRP score	3.10 ± 1.17
HAQ score	0.75 ± 0.61
SPPB score, median (IQR)	11 (9–12)
ACPA positive, no. (%)	86 (80)
SHS, median (IQR) (n = 92)	13.5 (3–60)
Disease duration, median (IQR) years	8.3 (2.6–18.6)
Current methotrexate, no. (%)	71 (66)
Current biologic therapy, no. (%)	56 (52)
Current prednisone, no. (%)	49 (46)

* Values are the mean ± SD unless indicated otherwise. Mean and SD of all Z scores in controls are 0 ± 1, by definition. ACPA = anti–citrullinated protein antibody; ALMI = Appendicular Lean Mass Index; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; FMI = fat mass index; HAQ = Health Assessment Questionnaire; IQR = interquartile range; M-DAS-CRP = Modified Disease Activity Score using the CRP; RA = rheumatoid arthritis; SHS = Sharp/van der Heijde score; SPPB = Short Physical Performance Battery.

of 2.71 years (interquartile range 2.35–3.57), with 6 participants following up between 4 and 5 years, and 6 participants following up after 5 years. Seven patients (7%) died prior to follow-up. Other reasons for loss to follow-up included moving away from the area (n = 7), declining the visit due to health reasons (n = 5), declining the follow-up visit for other reasons (e.g., lack of transportation) (n = 3), and inability to contact the participant (n = 6). Participants who died had numerically lower muscle density Z scores at baseline (mean ± SD –1.40 ± 1.41 versus –0.74 ± 1.09; P = 0.14). Baseline muscle density Z scores and baseline HAQ scores were similar among patients who were lost to follow-up compared to those who completed follow-up assessments (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24126/abstract). The baseline characteristics of the overall study population are shown in Table 1.

Changes in muscle density over time. Changes in muscle density were observed in association with baseline patient factors. There were significant declines in muscle density per year of follow-up (β = –0.11 [95% confidence interval (95% CI) –0.21, –0.006], P = 0.04). However, muscle density Z score did not decline significantly (β = –0.000 [95% CI –0.044, 0.044], P = 0.99), suggesting that changes in muscle density, on average, were consistent with age-related declines. Factors associated with declines in muscle density Z score per year in univariate analyses included female sex, higher M-DAS score, higher baseline HAQ score, and current smoking status (Table 2). Use of methotrexate at baseline was associated with lower rates of decline. In multivariable models, only female sex,

Table 2. Factors associated with changes in muscle density Z score per year*

	Adjusted for baseline muscle density only†		Multivariable model (n = 106)†	
	β (95% CI)	*P*	β (95% CI)	*P*
Age, per year	0.000 (–0.003, 0.004)	0.83	–	–
Female	–0.085 (–0.17, 0.002)	0.05	–0.079 (–0.14, –0.014)	0.02
African American race	–0.041 (–0.15, 0.062)	0.43	–	–
BMI, kg/m^2	0.005 (–0.003, 0.012)	0.20		
ALMI Z score	0.039 (–0.004, 0.082)	0.08	0.023 (–0.016, 0.63)	0.25
FMI Z score	0.035 (–0.009, 0.080)	0.12	–	–
Waist circumference, per cm	0.002 (–0.001, 0.005)	0.18	–	–
Current smoking	–0.12 (–0.22, –0.016)	0.02	–0.098 (–0.17, –0.022)	0.01
Exercise, MET hours/week	0.000 (–0.001, 0.001)	0.52	–	–
Sedentary, hours/week	0.000 (–0.003, 0.003)	0.79	–	–
M-DAS28-CRP score	–0.047 (–0.069, –0.024)	<0.001	–0.027 (–0.052, –0.003)	0.03
HAQ score	–0.076 (–0.14, –0.016)	0.01	–0.020 (–0.089, 0.048)	0.56
Disease duration, per year	–0.001 (–0.005, 0.002)	0.47	–	–
ACPA positive	0.061 (–0.058, 0.18)	0.32	–	–
Current prednisone	–0.034 (–0.12, 0.055)	0.46	–	–
Current methotrexate	0.11 (0.029, 0.20)	0.009	0.10 (–0.012, 0.22)	0.08
Current biologic	–0.012 (–0.10, 0.079)	0.80	–	–
SHS, per unit	0.000 (–0.001, 0.001)	0.80	–	–

* Regression coefficients represent the difference in change per year among individuals with the exposure. 95% CI = 95% confidence interval; ACPA = anti–citrullinated protein antibody; ALMI = Appendicular Lean Mass Index; BMI = body mass index; FMI = fat mass index; HAQ = Health Assessment Questionnaire; M-DAS28-CRP = Modified Disease Activity Score in 28 joints using the C-reactive protein level; MET = metabolic equivalent; RA = rheumatoid arthritis; SHS = Sharp/van der Heijde score.
† Adjusted for baseline muscle density Z score.

Table 3. Associations between insulin-like growth factor 1 (IGF-1) levels, inflammatory cytokines, and adipokines and changes in muscle density per year, adjusting for demographics and muscle density at baseline*

	Change in muscle density Z score	
	β (95% CI)	*P*
IGF-1, per 10 ng/ml	0.011 (0.002, 0.019)	0.01
CRP, per 1 mg/dl	−0.015 (−0.062, 0.031)	0.52
IL-6, per 1 pg/ml	−0.009 (−0.022, 0.005)	0.21
IL-1, per 1 pg/ml	−0.06 (−0.26, 0.13)	0.55
TNF, per 10 pg/ml	0.000 (−0.001, 0.002)	0.81
Adiponectin, per 1 pg/ml	−0.003 (−0.009, 0.003)	0.31
Leptin, per ng/ml	−0.0003 (−0.002, 0.001)	0.72

* Adjusted for age, sex, race, and baseline muscle density Z score. 95% CI = 95% confidence interval; CRP = C-reactive protein (level); IL-1 = interleukin-1; TNF = tumor necrosis factor.

greater M-DAS score, and active smoking status were independently associated with declines in muscle density Z score.

After adjustment for age, sex, race, and baseline muscle density Z score, higher IGF-1 levels at baseline (per 10 ng/ml) were associated with significantly less decline per year in muscle density Z score (β = 0.011 [95% CI 0.002, 0.019], *P* = 0.01) (Table 3). Associations between IGF-1 and change in muscle density per year were independent of ALMI Z score, M-DAS score, smoking status, female sex, and baseline methotrexate use (β = –0.008 [95% CI 0.001, 0.014], *P* = 0.02) (full model not shown). Inflammatory cytokines (IL-6, IL-1, and tumor necrosis factor) and adipokines (leptin, adiponectin) were not associated with changes in muscle density (Table 3).

Baseline muscle density and changes in physical functioning. As has been previously described, muscle density Z score was associated with baseline HAQ score, SPPB score, and muscle strength at baseline (39). Higher muscle density Z score was not significantly correlated with shorter 4-meter walk time at baseline (ρ = –0.13, *P* = 0.32). Participants who reported being disabled from working had lower baseline muscle density Z scores (mean ± SD –1.10 ± 1.01 versus –0.62 ± 1.15; *P* = 0.04).

Low muscle density was associated with declines in physical function. On average, there were not significant changes per year in physical functioning during follow-up for HAQ score (β = –0.018 [95% CI –0.044, 0.008], *P* = 0.18); SPPB score (β = –0.059 [95% CI –0.24, 0.12], *P* = 0.52), and 4-meter walk time (β = –0.001 [95% CI –0.22, 0.19], *P* = 0.90). Similarly, in the total sample, there were not statistically significant changes per year in muscle strength measured by knee flexion (β = –0.10 [95% CI –1.31, 1.10], *P* = 0.87), knee extension (β = –0.78 [95% CI –0.17, 0.61], *P* = 0.27), hand grip (β = –0.24 [95% CI –0.68, 0.20], *P* = 0.28), or ankle dorsiflexion (β = –0.34 [95% CI –0.59, 0.52], *P* = 0.90). There was clinically important worsening in HAQ score in 20 of 79 participants (25%), worsening in SPPB score in 10 of 45 (22%), worsening of 4-meter walk speed in 19 of 45 (42%), and worsening in hand grip strength in 12 of 78 (15%).

Associations between muscle density at baseline and changes in physical function outcomes and muscle strength per year are shown in Tables 4 and 5 and in Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24126/abstract. In models adjusting for age, sex, race, M-DAS score, smoking status, and baseline values for each outcome, a greater muscle density Z score at baseline was associated with less worsening per year in physical function as measured by HAQ score, SPPB score, and 4-meter walk speed. In models that were further adjusted for body composition, significant associations remained for HAQ score and 4-meter walk speed.

A greater FMI Z score was independently associated with greater reductions in SPPB score and 4-meter walk speed per year (Table 5). In these analyses, greater M-DAS score at baseline tended toward an association with reductions in HAQ score at follow-up (β = –0.022 [95% CI –0.044, 0.006], *P* = 0.06) but was not associated with changes in SPPB score.

There was no association between muscle density Z score at baseline and changes in strength outcomes such as leg extension, ankle dorsiflexion, or hand grip strength in basic models or after adjusting for body composition, M-DAS score, and smoking status (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24126/abstract). A greater FMI Z score was associated with reductions in strength with leg flexion and ankle dorsiflexion. In these models, smoking status tended to be associated with

Table 4. Association with per-year change in physical functioning as measured by the Health Assessment Questionnaire (HAQ)*

	Adjusted model (n = 107)†		Further adjusted for body composition (n = 106)†	
	β (95% CI)	*P*	β (95% CI)	*P*
Muscle density Z score	−0.024 (−0.048, −0.000)	0.048	−0.032 (−0.060, −0.005)	0.02
ALMI Z score	–		0.010 (−0.027, 0.047)	0.60
FMI Z score	–		−0.028 (−0.069, 0.012)	0.17

* Coefficients presented are the value for the interaction term with year and represent the difference in change per year in the outcome among those with the exposure. 95% CI = 95% confidence interval; ALMI = Appendicular Lean Mass Index; FMI = fat mass index.
† Adjusted for age, sex, race, baseline Health Assessment Questionnaire score, Modified Disease Activity Score in 28 joints using the C-reactive protein level, and current smoking.

Table 5. Associations between muscle density, body composition, and per-year changes in Short Physical Performance Battery (SPPB) score and 4-meter walk speed*

	Adjusted model (n = 63)†		Further adjusted for body composition (n = 63)	
	β (95% CI)	*P*	β (95% CI)	*P*
SPPB score (n = 63)				
Muscle density Z score	0.18 (0.007, 0.36)	0.04	0.12 (–0.012, 0.26)	0.07
ALMI Z score	–		0.24 (–0.11, 0.58)	0.18
FMI Z score	–		–0.32 (–0.60, –0.044)	0.02
4-meter walk speed (meters/second)‡				
Muscle density Z score	0.028 (0.011, 0.046)	0.002	0.024 (0.005, 0.042)	0.01
ALMI Z score	–		0.010 (–0.024, 0.044)	0.58
FMI Z score	–		–0.021 (–0.042, 0.001)	0.06
5× chair stand time (log-adjusted)‡				
Muscle density Z score	–0.004 (–0.030, 0.022)	0.78	–0.000 (–0.024, 0.023)	0.98
ALMI Z score	–		0.043 (–0.020, 0.11)	0.18
FMI Z score	–		0.027 (–0.32, 0.086)	0.37

* 95% CI = 95% confidence interval; ALMI = Appendicular Lean Mass Index; FMI = fat mass index; HAQ = Health Assessment Questionnaire.
† Adjusted for age, sex, race, baseline Health Assessment Questionnaire score, Modified Disease Activity Score in 28 joints using the C-reactive protein level, and current smoking.
‡ N = 63.

declines in knee flexion muscle strength (β = –2.63 [95% CI –5.4, 0.13], *P* = 0.06). Higher M-DAS score at baseline was associated with greater reductions in hand grip strength per year (β = –0.50 [95% CI –0.83, 0.18], *P* = 0.002) and increases in ankle dorsiflexion per year (β = 0.35 [95% CI 0.005, 0.71], *P* = 0.05) (full data not shown).

A lower muscle density Z score at baseline (per 1 SD) was associated with a greater odds of significant worsening in HAQ score (odds ratio [OR] 1.90 [95% CI 1.06, 3.42], *P* = 0.03) and walk speed (OR 2.87 [95% CI 1.05, 7.89], *P* = 0.04) and tended toward an association with a greater risk of significant worsening of SPPB score (OR 2.64 [95% CI 0.90, 7.74], *P* = 0.08) and hand grip strength (OR 1.79 [95% CI 0.95, 3.37], *P* = 0.07) after adjusting for baseline age, sex, race, and baseline values. The predicted probability of worsening was greater for all outcomes among those with the lowest muscle density Z scores (Figure 1). Results were similar and statistically significant in sensitivity analyses with the outcome of worsening function or death (see Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24126/abstract).

DISCUSSION

To our knowledge, this is the first study to identify factors associated with changes in muscle density over a relatively long-term follow-up period. Greater disease activity and active smoking status were the most important predictors of declines

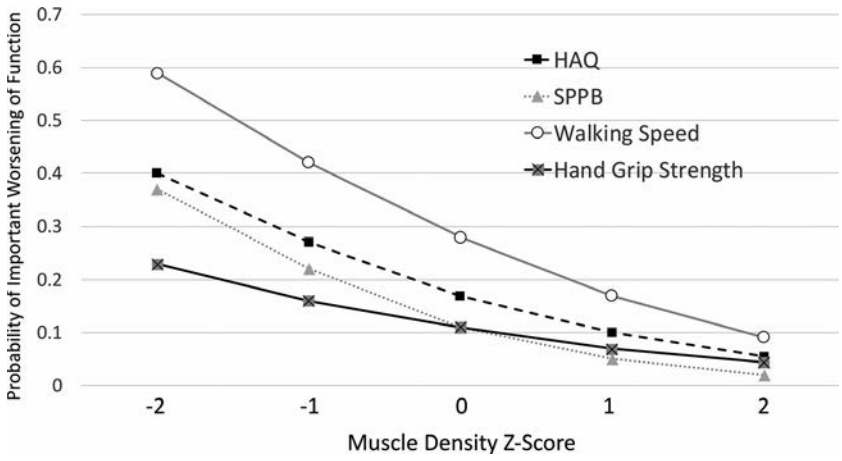

Figure 1. Probability of significant worsening of strength or function by muscle density Z score at baseline based on regression models adjusting for age, sex, race, fat mass index Z score, and baseline value. HAQ = Health Assessment Questionnaire; SPPB = Short Physical Performance Battery.

in muscle density, largely supporting prior cross-sectional studies. This study also found that lower muscle density (related to intramuscular fat accumulation) is predictive of declines in physical functioning among patients with RA. Study participants with lower muscle density had greater worsening in several measures of physical functioning, both patient-reported and performance-based. Greater adiposity was also significantly and independently associated with declines in physical functioning, walking speed, and muscle strength. These longitudinal data support the hypothesis that muscle quality and excess adiposity are important contributors to long-term changes in physical functioning in this population (12,15,19,39).

Overall, we observed significant reductions in muscle density over time that were consistent with what might be expected with aging. However, participants who had greater disease activity and who were actively smoking demonstrated the greatest declines in muscle density with time. Prior studies have observed cross-sectional associations between higher IL-6 levels and low muscle density (18). In this study, specific inflammatory cytokines were not significantly associated with changes in muscle density (18). Overall, however, these longitudinal data support the hypothesis that greater inflammatory disease activity is likely to contribute to intramuscular fat infiltration over time independent of other factors. Loss of skeletal muscle in the context of systemic inflammation from a number of mechanisms may lead to the replacement of muscle with adipose tissue, resulting in low muscle density (40). In this study, physical activity, excess adiposity, and active prednisone use were not significantly associated with declines in muscle density.

Prior studies also identified cross-sectional associations between IGF-1 and low muscle density (41). In the current study, we observed that lower baseline IGF-1 levels were a predictor of declines in muscle density, further emphasizing a potential relationship. There is evidence that IGF-1 plays an important role in skeletal muscle metabolism and growth (42,43). Furthermore, dynamic exercise has been shown to increase IGF-1 levels in patients with inflammatory arthritis (44). The observations from the current study are important, as they support a potential role of IGF-1 therapy in the prevention and treatment of skeletal muscle deficits in this setting. However, further study is necessary to determine whether low IGF-1 levels mediate intramuscular fat accumulation or are simply a marker of processes that are themselves adverse to skeletal muscle health.

Very few longitudinal studies in any population have evaluated relationships between muscle density and long-term physical functioning (3,45,46). These studies suggested that low muscle density predicts incident disability and mobility limitation in the elderly and among patients with peripheral vascular disease. The current study is the first to evaluate these associations in a rheumatic disease. While the observations described here might not be specific to patients with RA, the implications are particularly relevant in this population that is at high risk of intramuscular fat accumulation and resulting low muscle density. The observation that reductions in muscle density predict subsequent long-term changes in physical functioning suggests that accumulation of intramuscular fat precedes the development of clinically important changes in physical functioning. This observation is important because it supports prior cross-sectional studies and provides a much-needed temporal understanding of the relationship that is not possible to extrapolate from cross-sectional data.

Despite evident associations between muscle density and changes in physical function, there were no consistent associations with change in direct measures of muscle strength. We previously published data from this study cohort demonstrating positive associations between muscle density and muscle strength at baseline and hypothesized that low muscle density would also predict declines in strength over time (47). The current study was inadequately powered to detect small changes in strength. However, the lack of association might suggest that relationships between muscle density and worsening of physical functioning are not explained by measurable changes in muscle strength. Other measures of muscle performance may be relevant, such as fatigability and balance (47). Alternatively, low muscle density may represent a marker of other aspects of health that impact physical functioning in other ways that are not related to muscle performance.

The current study demonstrated that low muscle density and adiposity predicted changes in physical functioning, while disease activity was not associated with declines in physical functioning. While we should expect that uncontrolled disease activity would eventually lead to worsening in physical functioning, the current study suggests that the effect of disease activity may be overshadowed by more notable effects of poor skeletal muscle health and excess adiposity. Those participants with greater disease activity at baseline also had the greatest opportunity to see their disease activity and related joint symptoms improve with management of the arthritis, at least in the short term.

Exercise and resistance training have been shown to have beneficial effects on muscle density in older adults (48,49). This may represent a valuable approach in patients with RA who are able to participate in an exercise program. Other interventions that have been less promising include whole-body vibration (50). Pharmacologic approaches to address skeletal muscle deficits are largely unavailable.

This was the largest longitudinal study performed to look at muscle quality in patients with RA, but the sample size was not large enough to define weaker relationships between skeletal muscle parameters and outcome or to characterize all of the contributors to changes in muscle quality over time. Power calculations at study design were not performed with this secondary analysis in mind. While long-term follow-up was an important strength in this type of study, some participants died, and some were lost to follow-up. Because loss to follow-up may occur in association with clinical factors, these factors may introduce bias into the study. For example, patients who become ill during

follow-up might be unable to return for study visits. In addition, we did not adjust for multiple comparisons given the relatedness of the outcomes studied. Therefore, some findings may have occurred by chance. Finally, even though analytic models included adjustment for a number of previously identified confounders, residual confounding may still be present.

The strengths of this study include the detailed assessments of disease activity, muscle quality, body composition, and the longitudinal assessments of strength and function over a relatively long-term follow-up period. These longitudinal data also provide an opportunity to characterize temporal relationships between exposures and outcomes that are critical in advancing our understanding of the relevance of previously identified cross-sectional associations.

In conclusion, this study supports the hypothesis that active disease, smoking, and reductions in IGF-1 contribute to intramuscular fat accumulation in patients with RA. Patients with low muscle density are at greater risk for declines in physical functioning over time. Overall, these longitudinal data support prior cross-sectional observations in this population. Reductions in skeletal muscle quality may have important implications for long-term outcomes that are among the most important to patients with arthritis.

AUTHOR CONTRIBUTIONS

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

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Acquisition of data. Baker, Long, Taratuta, Zemel.
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REFERENCES

1. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. J Appl Physiol 1985;2000(89):104–10.
2. Cawthon PM, Fox KM, Gandra SR, Delmonico MJ, Chiou CF, Anthony MS, et al. Do muscle mass, muscle density, strength, and physical function similarly influence risk of hospitalization in older adults? J Am Geriatr Soc 2009;5:1411–9.
3. Malkov S, Cawthon PM, Peters KW, Cauley JA, Murphy RA, Visser M, et al. Hip fractures risk in older men and women associated with DXA-derived measures of thigh subcutaneous fat thickness, cross-sectional muscle area, and muscle density. J Bone Miner Res 2015;30:1414–21.
4. Kelley DE, Slasky BS, Janosky J. Skeletal muscle density: effects of obesity and non-insulin-dependent diabetes mellitus. Am J Clin Nutr 1991;54:509–15.
5. Therkelsen KE, Pedley A, Speliotes EK, Massaro JM, Murabito J, Hoffmann U, et al. Intramuscular fat and associations with metabolic risk factors in the Framingham Heart Study. Arterioscler Thromb Vasc Biol 2013;33:863–70.
6. Reinders I, Murphy RA, Brouwer IA, Visser M, Launer L, Siggeirsdottir K, et al. Muscle quality and myosteatosis: novel associations with mortality risk: the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study. Am J Epidemiol 2016;183:53–60.
7. Zhao Q, Zmuda JM, Kuipers AL, Jonnalagadda P, Bunker CH, Patrick AL, et al. Greater skeletal muscle fat infiltration is associated with higher all-cause mortality among men of African ancestry. Age Ageing 2016;45:529–34.
8. Miljkovic I, Kuipers AL, Cauley JA, Prasad T, Lee CG, Ensrud KE, et al. Greater skeletal muscle fat infiltration is associated with higher all-cause and cardiovascular mortality in older men. J Gerontol A Biol Sci Med Sci 2015;70:1133–40.
9. Akazawa N, Okawa N, Tamura K, Moriyama H. Relationships between intramuscular fat, muscle strength and gait independence in older women: a cross-sectional study. Geriatr Gerontol Int 2017;17:1683–8.
10. Baker JF, Davis M, Alexander R, Zemel BS, Mostoufi-Moab S, Shults J, et al. Associations between body composition and bone density and structure in men and women across the adult age spectrum. Bone 2013;53:34–41.
11. Therkelsen KE, Pedley A, Hoffmann U, Fox CS, Murabito JM. Intramuscular fat and physical performance at the Framingham Heart Study. Age (Dordr) 2016;38:31.
12. Baker JF, England BR, Mikuls TR, Sayles H, Cannon GW, Sauer BC, et al. Obesity, weight loss, and progression of disability in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2018;70:1740–7.
13. Baker JF, Giles JT, Weber D, Leonard MB, Zemel BS, Long J, et al. Assessment of muscle mass relative to fat mass and associations with physical functioning in rheumatoid arthritis. Rheumatology (Oxford) 2017;56:981–8.
14. Santanasto AJ, Newman AB, Strotmeyer ES, Boudreau RM, Goodpaster BH, Glynn NW. Effects of changes in regional body composition on physical function in older adults: a pilot randomized controlled trial. J Nutr Health Aging 2015;19:913–21.
15. Baker JF, Long J, Leonard MB, Harris T, Delmonico MJ, Santanasto A, et al. Estimation of skeletal muscle mass relative to adiposity improves prediction of physical performance and incident disability. J Gerontol A Biol Sci Med Sci 2018;73:946–52.
16. Baker JF, Long J, Mostoufi-Moab S, Denburg M, Jorgenson E, Sharma P, et al. Muscle deficits in rheumatoid arthritis contribute to inferior cortical bone structure and trabecular bone mineral density. J Rheumatol 2017;44:1777–85.
17. Baker JF, Von Feldt J, Mostoufi-Moab S, Noaiseh G, Taratuta E, Kim W, et al. Deficits in muscle mass, muscle density, and modified associations with fat in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2014;66:1612–8.
18. Kramer HR, Fontaine KR, Bathon JM, Giles JT. Muscle density in rheumatoid arthritis: associations with disease features and functional outcomes. Arthritis Rheum 2012;64:2438–50.
19. Khoja SS, Moore CG, Goodpaster BH, Delitto A, Piva SR. Skeletal muscle fat and its association with physical function in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2018;70:333–42.
20. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.
21. Leonard MB, Shults J, Elliott DM, Stallings VA, Zemel BS. Interpretation of whole body dual energy X-ray absorptiometry measures in children: comparison with peripheral quantitative computed tomography. Bone 2004;34:1044–52.
22. Rothney MP, Xia Y, Wacker WK, Martin FP, Beaumont M, Rezzi S, et al. Precision of a new tool to measure visceral adipose tissue (VAT) using dual-energy X-Ray absorptiometry (DXA). Obesity (Silver Spring) 2013;21:E134–6.

23. Farr JN, Funk JL, Chen Z, Lisse JR, Blew RM, Lee VR, et al. Skeletal muscle fat content is inversely associated with bone strength in young girls. J Bone Miner Res 2011;26:2217–25.
24. Lang T, Cauley JA, Tylavsky F, Bauer D, Cummings S, Harris TB. Computed tomographic measurements of thigh muscle cross-sectional area and attenuation coefficient predict hip fracture: the health, aging, and body composition study. J Bone Miner Res 2010;25:513–9.
25. Wetzsteon RJ, Kalkwarf HJ, Shults J, Zemel BS, Foster BJ, Griffin L, et al. Volumetric bone mineral density and bone structure in childhood chronic kidney disease. J Bone Miner Res 2011;26:2235–44.
26. Leggin BG, Neuman RM, Iannotti JP, Williams GR, Thompson EC. Intrarater and interrater reliability of three isometric dynamometers in assessing shoulder strength. J Shoulder Elbow Surg 1996;5:18–24.
27. Kim JK, Park MG, Shin SJ. What is the minimum clinically important difference in grip strength? Clin Orthop Relat Res 2014;472:2536–41.
28. Mihalko SL, Wickley KL, Sharpe BL. Promoting physical activity in independent living communities. Med Sci Sports Exerc 2006;38:112–5.
29. Corsonello A, Lattanzio F, Pedone C, Garasto S, Laino I, Bustacchini S, et al. Prognostic significance of the short physical performance battery in older patients discharged from acute care hospitals. Rejuvenation Res 2012;15:41–8.
30. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc 2006;54:743–9.
31. Pope JE, Khanna D, Norrie D, Ouimet JM. The minimally important difference for the health assessment questionnaire in rheumatoid arthritis clinical practice is smaller than in randomized controlled trials. J Rheumatol 2009;36:254–9.
32. Ainsworth BE, Irwin ML, Addy CL, Whitt MC, Stolarczyk LM. Moderate physical activity patterns of minority women: the Cross-Cultural Activity Participation Study. J Womens Health Gend Based Med 1999;8:805–13.
33. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.
34. Baker JF, Davis M, Alexander R, Zemel BS, Mostoufi-Moab S, Shults J, et al. Associations between body composition and bone density and structure in men and women across the adult age spectrum. Bone 2013;53:34–41.
35. Bertoni AG, Whitt-Glover MC, Chung H, Le KY, Barr RG, Mahesh M, et al. The association between physical activity and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 2009;169:444–54.
36. Baker JF, Conaghan PG, Smolen JS, Aletaha D, Shults J, Emery P, et al. Development and validation of modified disease activity scores in rheumatoid arthritis: superior correlation with magnetic resonance imaging–detected synovitis and radiographic progression. Arthritis Rheum 2014;66:794–802.
37. Weber D, Long J, Leonard MB, Zemel B, Baker JF. Development of novel methods to define deficits in appendicular lean mass relative to fat mass. PLoS One 2016;11:e0164385.
38. Kelly TL, Wilson KE, Heymsfield SB. Dual energy X-Ray absorptiometry body composition reference values from NHANES. PLoS One 2009;4:e7038.
39. Baker JF, Mostoufi-Moab S, Long J, Zemel B, Ibrahim S, Taratuta E, et al. Intramuscular fat accumulation and associations with body composition, strength, and physical functioning in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2018;70:1727–34.
40. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cachexia and sarcopenia: mechanisms and potential targets for intervention. Curr Opin Pharmacol 2015;22:100–6.
41. Baker JF, Von Feldt JM, Mostoufi-Moab S, Kim W, Taratuta E, Leonard MB. Insulin-like growth factor 1 and adiponectin and associations with muscle deficits, disease characteristics, and treatments in rheumatoid arthritis. J Rheumatol 2015;42:2038–45.
42. Hamarneh SR, Murphy CA, Shih CW, Frontera W, Torriani M, Irazoqui JE, et al. Relationship between serum IGF-1 and skeletal muscle IGF-1 mRNA expression to phosphocreatine recovery after exercise in obese men with reduced GH. J Clin Endocrinol Metab 2015;100:617–25.
43. Schmidt K, von Haehling S, Doehner W, Palus S, Anker SD, Springer J. IGF-1 treatment reduces weight loss and improves outcome in a rat model of cancer cachexia. J Cachexia Sarcopenia Muscle 2011;2:105–9.
44. Karatay S, Yildirim K, Melikoglu MA, Akcay F, Senel K. Effects of dynamic exercise on circulating IGF-1 and IGFBP-3 levels in patients with rheumatoid arthritis or ankylosing spondylitis. Clin Rheumatol 2007;26:1635–9.
45. McDermott MM, Ferrucci L, Guralnik J, Tian L, Liu K, Hoff F, et al. Pathophysiological changes in calf muscle predict mobility loss at 2-year follow-up in men and women with peripheral arterial disease. Circulation 2009;120:1048–55.
46. Baker JF, Newman AB, Kanaya A, Leonard MB, Zemel B, Miljkovic I, et al. The adiponectin paradox in the elderly: associations with body composition, physical functioning, and mortality. J Gerontol A Biol Sci Med Sci 2019;74:247–53.
47. Scott D, Trbojevic T, Skinner E, Clark RA, Levinger P, Haines TP, et al. Associations of calf inter- and intra-muscular adipose tissue with cardiometabolic health and physical function in community-dwelling older adults. J Musculoskelet Neuronal Interact 2015;15:350–7.
48. Duff WR, Chilibeck PD, Candow DG, Gordon JJ, Mason RS, Taylor-Gjevre R, et al. Effects of ibuprofen and resistance training on bone and muscle: a randomized controlled trial in older women. Med Sci Sports Exerc 2017;49:633–40.
49. Englund DA, Kirn DR, Koochek A, Zhu H, Travison TG, Reid KF, et al. Nutritional supplementation with physical activity improves muscle composition in mobility-limited older adults, the VIVE2 study: a randomized, double-blind, placebo-controlled trial. J Gerontol A Biol Sci Med Sci 2017;73:95–101.
50. Masani K, Alizadeh-Meghrazi M, Sayenko DG, Zariffa J, Moore C, Giangregorio L, et al. Muscle activity, cross-sectional area, and density following passive standing and whole body vibration: a case series. J Spinal Cord Med 2014;37:575–81.

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Are Health Care Professionals' Implicit and Explicit Attitudes Toward Conventional Disease-Modifying Antirheumatic Drugs Associated With Those of Their Patients?

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Objective. It is generally unknown how the attitudes and beliefs of health care professionals (HCPs) might affect the attitudes, beliefs, and medication-taking behavior of patients with rheumatoid arthritis (RA). This study aims 1) to examine the attitudes, health-related associations (both implicit and explicit), and beliefs of HCPs about conventional disease-modifying antirheumatic drugs, and 2) to assess whether these attitudes, health-related associations, and beliefs of HCPs are associated with those of their patients, with their patients' medication-taking behavior, and disease activity.

Methods. HCPs were recruited from 2 centers that specialized in rheumatology across The Netherlands, and patient recruitment followed. In this observational study, implicit outcomes were measured with single-category implicit association tests, whereas explicit outcomes were measured with a bipolar evaluative adjective scale and the Beliefs About Medicines Questionnaire–Specific. Spearman's rank correlations were used to describe correlations between implicit and explicit measures of the attitudes of HCPs. Multilevel, mixed-effects linear models were used to examine the association of HCP-related characteristics, including the implicit and explicit outcomes of HCPs, with those of their patients, their medication-taking behaviors, and disease activity.

Results. Of the 1,659 initially invited patients, 254 patients with RA (mean age 62.8 years, mean disease duration 11.8 years, and 68.1% of the patients were female) who were treated by 26 different HCPs agreed to participate in this study. The characteristics, attitudes, health-related associations, and beliefs about medicines of HCPs were not significantly associated with those of their patients, nor with their medication-taking behaviors or disease activity scores.

Conclusion. This study demonstrated that the attitudes, health-related associations (as measured both implicitly and explicitly), and beliefs of HCPs were not significantly associated with the attitudes, beliefs, medication-taking behavior, and disease activity of patients with RA.

INTRODUCTION

Disease-modifying antirheumatic drugs (DMARDs) are recommended to patients with rheumatoid arthritis (RA) to suppress the inflammatory response, and consequently, to decrease disease activity and reduce radiologic damage (1,2). Despite the beneficial effects of DMARDs, previous studies have reported major issues regarding medication-taking behavior of RA patients, with adherence rates varying from 30% to 107% depending on the measurement method used (3–5). Nonadherence to medication can lead to worsening of clinical outcomes (i.e., high disease activity, radiologic progression, and a decrease in physical functioning and

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

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SIGNIFICANCE & INNOVATIONS

- It is unknown whether the attitudes and beliefs of health care professionals (HCPs) might affect attitudes, beliefs, and medication-taking behavior of patients with rheumatoid arthritis (RA).
- This study demonstrated that sociodemographic characteristics, implicit and explicit attitudes and health-related associations, and the beliefs of HCPs about medicines were not associated with those of their patients with RA nor with patients' medication-taking behavior and disease activity scores.
- These findings provide some first insights into the potential (and the lack thereof) of implicit and explicit perceptions of medication of HCPs in relation to patients' medication adherence and disease activity.

quality of life) and increased health care expenditures (6–8). There have been several attempts to explore effective intervention strategies and targets for improving medication-taking behavior in this population (9). However, so far, adherence-improving interventions were only partly effective in changing medication-taking behavior.

An explanation for the ineffectiveness of adherence-improving interventions might be that previous studies have largely focused on the perspective of patients rather than the perspective of health care professionals (HCPs) (9–12). Several studies suggest that the attitudes and beliefs of HCPs might be associated with the attitudes and beliefs of their patients (Zwikker et al, submitted for publication) (13–15). It can, therefore, be assumed that during clinic visits, the attitudes and beliefs of HCPs might affect patients' medication-taking behavior as well. However, targeting the concerns of patients and their beliefs about the need for medication (16), and making HCPs aware of patients' suboptimal medication intake (17), does not improve patients' medication-taking behavior. New insights into processes that may underlie patients' nonadherent medication-taking behavior, or that may influence the patient–provider interaction, are therefore required.

Theoretical and empirical contributions in the field of psychology provide abundant evidence that only a small part of behavior originates from conscious or reflective thought processes and largely depends on subconscious or automatic processes (18–21). These dual process theories assume that subconscious or automatic processes explain a unique part of behavior that cannot be explained by conscious thought (18–21). By extending these findings to adherence research, these dual process theories provide a plausible explanation as to why the often-measured and explicitly reported attitudes and beliefs about medicines may give insufficient insight into the processes underlying adherence. These theories also pinpoint automatic processes, and specifically, implicit attitudes, as potentially essential elements in understanding the communication of HCPs and patients' medication-intake behavior (18–21). In this study, we define implicit attitudes as automatically activated associations, which are based on past experiences and mediate favorable or unfavorable feelings that individuals might not be aware of, whereas explicit attitudes are defined as deliberate or conscious evaluations of medication (19–21). Few studies have investigated patients' implicit attitudes and their association with medication-taking behavior in rheumatic diseases (22,23). However, studies on the implicit attitudes of HCPs toward medication in the field of rheumatology are lacking. The implicit attitudes of HCPs might be involved in the patient–provider interaction (e.g., communication between HCPs and patients), which then might affect patients' attitudes as well as patients' medication-taking behavior. It is unknown whether the implicit attitudes and beliefs of HCPs about medication might be associated with patients' implicit attitudes and beliefs about medication, patients' medication-taking behavior, and patients' disease activity in the field of rheumatic diseases (15,22).

Therefore, the aim of this study is 1) to examine the implicit and explicit attitudes of HCPs and the health-related associations with conventional DMARD use, together with HCPs' explicitly reported beliefs about medicines, and 2) to assess whether these attitudes are associated with those of their patients, patients' medication-taking behavior, and patients' disease activity scores.

SUBJECTS AND METHODS

Study design and setting. An observational study was performed in 2 of the largest centers that specialize in rheumatology across The Netherlands (i.e., covering ~20% of all patients with RA): Sint Maartenskliniek (Nijmegen) and Reade (Amsterdam). Rheumatologists and physician assistants (PAs) were recruited between July 5, 2016 and January 23, 2017, and patients were recruited between July 5, 2016 and November 30, 2017. This project resulted in a large data set, including measures of implicit and explicit attitudes and beliefs toward medication of both patients and HCPs. Van Heuckelum et al focused on the patient data only (a detailed description on the measurement of patients' implicit and explicit attitudes, medication-taking behavior, and clinical variables published previously) (23). The current study focuses on the implicit and explicit attitudes of HCPs and explores their associations with patient data. An overview of the study is presented in Table 1. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies and the ESPACOMP Medication Adherence Reporting Guideline (EMERGE) were used as guidance for adequate reporting in this study (24,25).

Ethics approval and patient and public involvement. This study was conducted according to the Ethical Principles for Medical Research as stated in the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) and was approved by the Medical Research Ethics Committee of Arnhem-Nijmegen (File 2016–2410). Two patient

Table 1. Study overview and measurements of health care professionals and rheumatoid arthritis patients at baseline and follow-up*

Baseline	Follow-up
Health care professionals Implicit attitudes and health-related associations Sociodemographics Explicit attitudes and health-related associations Beliefs about medicines (i.e., necessity and concern beliefs about cDMARDs)	Not applicable
Patients Implicit attitudes and health-related associations Sociodemographics Explicit attitudes and health-related associations Beliefs about medicines (i.e., necessity and concern beliefs about cDMARDs) Self-reported medication-taking behavior Disease activity score (i.e., DAS28-CRP)	Medication-taking behavior measured with Medication Event Monitoring System (Aardex) for a minimum period of 3 months.

* Inclusion and performing baseline measurements of health care professionals were completed before inclusion and performing baseline measurements of patients with rheumatoid arthritis. The maximum follow-up period for patients was 9 months. cDMARDs = conventional disease-modifying antirheumatic drugs; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level.

research partners were involved in the design phase of this study. The patient research partners pretested the Single-Category Implicit Association Tests (SC-IATs) and assessed the comprehensibility of the hardcopy questionnaire for patients with RA.

Eligibility criteria and selection procedures. All rheumatologists, residents, and PAs working in the rheumatology departments at Sint Maartenskliniek and Reade with a minimum employment contract period of 9 months were asked to participate in this study. Written information about the study protocol (an adapted version for patients was used) and an informed consent form were attached to an email sent to all rheumatologists and PAs. After the rheumatologists and PAs agreed to the study via email, a research appointment was made to sign the informed consent form. Subsequently, patients were assessed for eligibility. All consecutive adult patients (age ≥18 years) with a clinical diagnosis of RA and treated with at least 1 conventional DMARD (cDMARD) for a minimum period of 1 year were invited to participate in this study. No additional inclusion and exclusion criteria were defined for patient selection. Written information about the study protocol and an informed consent form were sent by mail to all consecutive patients 4 weeks before the planned regular consultation with their treating clinician. After the patient's agreement to participate, the researcher made a research appointment before the planned regular consultation in order to sign the informed consent form.

Procedures of data collection. At baseline, the implicit and explicit attitudes and health-related associations of HCPs, combined with sociodemographic data (i.e., age, sex, current position, years of working experience, and mean hours of patient contact per week) and explicit beliefs about medicines, were assessed. Implicit data were collected prior to completing the hardcopy questionnaires in order to prevent contamination effects of explicit measures with implicit measures. The same procedures were applied to patients at baseline, supplemented with a hardcopy questionnaire to assess self-reported medication-taking behavior. Electronic monitoring of medication-taking behavior was continued for a minimum period of 3 months after the patient's inclusion in the study. At the patient's follow-up visit, Medication Event Monitoring System (MEMS) read-outs were used to assess medication-taking behavior over the previous months. The patient's disease activity score (measured by the Disease Activity Score in 28 joints using the C-reactive protein level [DAS28-CRP]) was assessed in conformity with treatment protocols as part of the standard care.

Measurement instruments. *SC-IATs.* SC-IATs were used to measure 2 concepts of automatic associations in this study: implicit attitudes (i.e., positive versus negative), and implicit health-related associations (i.e., health versus sickness) with medication. The SC-IAT is considered a reliable and valid instrument to measure implicit associations with a single attitude object (i.e., antirheumatic drugs) (26). Each concept was assessed in 3 rounds: 1 practice round of 20 trials, followed by 2 experimental rounds of 40 trials each. Trials displayed various positive/health-related, negative/sickness-related, and medicine-related words and pictures in a computerized categorization task in which automatic associations were measured based on the response times of HCPs and patients. The response times in the experimental rounds served as a proxy for association strength, where faster responses represented stronger associations. In other words, if HCPs were on average faster in categorizing trials coupling drug stimuli and negative (versus positive) stimuli, then this reflects a relatively negative (versus positive) automatic association with cDMARDs. SC-IATs for rheumatologists/PAs included 5 generic pictures of cDMARDs (i.e., methotrexate,

leflunomide, hydroxychloroquine, sulfasalazine, and azathioprine), whereas SC-IATs for patients were personalized based on their personal cDMARD treatment. Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24186/abstract, provides a more detailed description of the SC-IAT procedures used in this study.

Bipolar evaluative adjective scale. For both HCPs and patients, a bipolar evaluative adjective scale was used to assess explicit medication attitudes (10 semantic differential scaled items, e.g., "I think [name of cDMARD(s)] is 1 negative–5 positive") and explicit health-related associations (8 semantic differential scaled items, e.g., "To what extent do you associate [cDMARD] with the following terms, 1 dead–5 alive"). Items in this questionnaire represented the same associations with cDMARDs as measured with the SC-IATs (see Supplementary Appendix B, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24186/abstract).

Beliefs About Medicines Questionnaire–Specific (BMQ-Specific). HCPs filled out the BMQ-Specific (10 Likert-scaled items) adapted to the perspective of HCPs (e.g., "Without the medicines my patients would be very ill"), whereas patients filled out the original validated BMQ-Specific (e.g., "Without the medicines I would be very ill"). Item scores varied from 1 (strongly disagree) to 5 (strongly agree), which resulted in sum scale scores of 5 to 25 for each subscale (necessity beliefs versus concern beliefs) (12,27).

Compliance Questionnaire on Rheumatology (CQR) and MEMS. Self-reported medication-taking behavior of patients was measured with the validated CQR (19 Likert-scaled items, ranging from 1 to 4). MEMS (Aardex) were used as electronic monitors to measure medication-taking behavior based on device usage. A diary was given to patients to register unintended openings of the MEMS. Medication-taking behavior was operationalized as correct dosing, which is defined as the percentage of days in which the correct number of doses was taken.

Clinical (laboratory) outcomes. Clinical characteristics (i.e., serology, disease duration, type and current number of DMARD(s), and disease activity scores [i.e., the DAS28-CRP]) were extracted from patients' medical files by the local researchers.

Study size. Assuming a sample size requirement of 10 patients per variable, a study sample of 240 patients is sufficient to build a reliable linear model including a maximum of 8 independent variables. Taking into account a 15% loss to follow-up, a sample size of 275 patients was required.

Statistical analysis. Statistical analyses were performed with Stata, version 13.1. Descriptive statistics were used for describing the characteristics of HCPs and patients. Data were presented as percentages in case of proportions. *P* values less than or equal to 0.05 were considered statistically significant.

Data obtained from the SC-IATs were expressed as response times in milliseconds (ms). The improved IAT scoring algorithm described by Greenwald and Nosek was used to calculate the *D* measure for strength of automatic associations (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24186/abstract, for a detailed description on calculating *D* measures) (28). *D* measures above zero indicated that HCPs or patients had relatively faster responses on the positive categorization rounds than on negative categorization rounds and were interpreted as a relatively more positive than negative implicit attitude toward cDMARDs, or a relatively more health-related association than a sickness-related association, and vice versa.

For explicit medication attitudes and associations, mean scale scores with SDs were calculated. Beliefs about medicines were operationalized as sum scale scores for necessity beliefs, sum scale scores for concern beliefs, and necessity–concerns differential (NCD) scores. NCD scores were calculated by subtracting the sum of the item scores for concerns from the sum of item scores for necessity beliefs. A positive NCD indicated that necessity beliefs dominate concern beliefs, and vice versa (27,29). Medication-taking behavior was operationalized as correct dosing (i.e., proportion of days with the correct number of doses taken). Self-reported, medication-taking behavior was calculated with the discriminant function for CQR items as described by de Klerk et al (30,31). Correct dosing measured with MEMS was calculated over a period of 3 months follow-up based on device usage.

Depending on the distribution and type of variables, independent samples *t*-tests, Pearson's chi-square tests, Fisher's exact tests, and proportion tests were performed to test for significant differences in the characteristics of HCPs between study sites. Spearman's rank correlations were used to describe the correlation between implicit and explicit HCP outcomes. Because of the explorative (rather than the hypothesis-testing) character of this study, no multiple testing corrections were performed over the separate correlational analyses.

Due to the hierarchical structure of data (i.e., patients were nested in the sample of HCPs), linear multilevel regression models were built to assess the association of the characteristics, implicit and explicit attitudes and health-related associations of HCPs, and beliefs about medicines with the following: patients' implicit attitudes and health-related associations, patients' explicit attitudes and health-related associations, patients' necessity and concern beliefs, correct dosing measured with both self-report and MEMS, and disease activity scores. Bivariate analyses were performed to select the most important predictors to prevent overfitting of the model due to the large number of variables measured in this study. Determinants with *P* values <0.2 were entered in the final models. These final models were adjusted for the following patient-related variables: age, sex, level of education, household situation (i.e., living alone versus living together with at least 1 person), disease duration, anti–cyclic citrullinated peptide status, hospital, and biologic DMARD use. Final models for correct

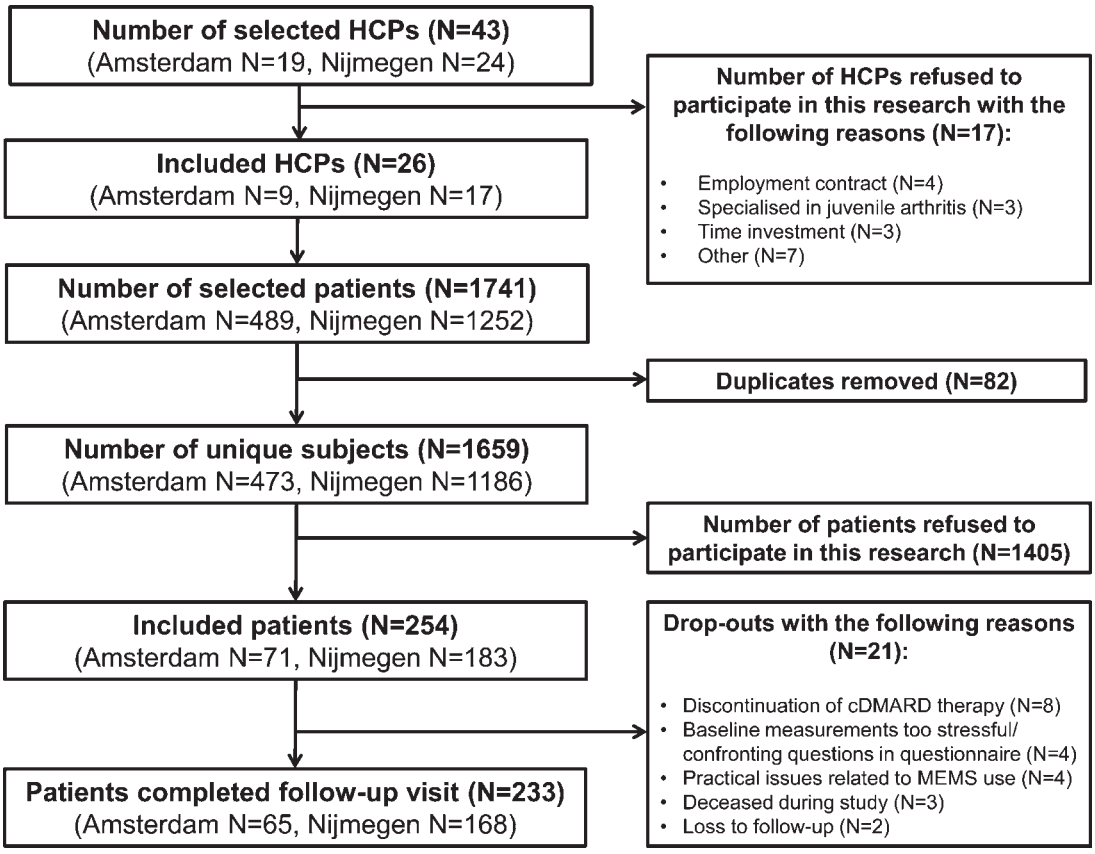

Figure 1. Flow chart of health care professionals (HCPs) and their patients with rheumatoid arthritis. cDMARDs = conventional disease-modifying antirheumatic drugs; MEMS = Medication Event Monitoring System.

dosing and disease activity scores were additionally adjusted for the patient's necessity and concern beliefs.

RESULTS

Study sample characteristics. Of the 43 initially invited rheumatologists and PAs, 26 HCPs agreed to participate in this study (overall response rate 60.5%; Amsterdam response rate 47.4%; and Nijmegen response rate 70.8%) (Figure 1). The majority of participants (92.3%) had a current position as a rheumatologist and were male (69.2%). Participating HCPs had a mean ± SD age of 49.7 ± 8.3 years with an average of 16.4 ± 9.4 years of working experience. See Table 2 for a complete overview of HCP characteristics. Of the nonparticipating HCPs, 30.8% were male, and 71.4% had a current position as a rheumatologist. A total of 254 patients treated by these 26 different HCPs (overall response rate 15.3%; Amsterdam response rate 15.0%; and Nijmegen response rate 15.4%) agreed to participate in this study, which resulted in several patients per HCP, varying from 3 to 19 patients. Patients had a mean age of 62.8 ± 11.2 years, 68.1% were female, 32.7% of the patients was highly educated, and 22.0% were living alone. Biologic DMARDs were prescribed to 32.7% of the patients, and the mean ± SD disease duration of patients was 11.8 ± 9.0 years. A more detailed description of all patient

Table 2. Characteristics of health care professionals in the field of rheumatology participating in the study*

Characteristics of health care professionals	Nijmegen (n = 17)	Amsterdam (n = 9)	Overall (n = 26)	*P*
Age, mean ± SD years	48.5 ± 8.7	52.1 ± 7.4	49.7 ± 8.3	0.31
Female	7 (41.2)	1 (11.1)	8 (30.8)	0.11
Current position				0.28
Rheumatologist	15 (88.2)	9 (100)	24 (92.3)	
Physician assistant	2 (11.8)	0 (0.0)	2 (7.7)	
Working experience, mean ± SD years	14.9 ± 9.6	19.2 ± 8.7	16.4 ± 9.4	0.27
Patient contact per week, mean ± SD hours	18.4 ± 8.0	25.3 ± 10.7	20.8 ± 9.4	0.07
Right-handed	15 (88.2)	5 (55.6)	20 (76.9)	0.06

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

characteristics can be found in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24186/abstract.

HCPs' attitudes, health-related associations, and beliefs. The mean ± SD *D* measure for implicit attitudes of HCPs was 0.045 ± 0.41, whereas the mean ± SD *D* measure for implicit health-related associations was –0.037 ± 0.36. The mean ± SD scale score for explicit attitudes (i.e., positive–negative) was similar to the mean ± SD scale score for explicit health-related associations (3.8 ± 0.45 and 3.9 ± 0.34, respectively). Regarding beliefs about medicines (necessity and concern beliefs), the mean sum scale score for the necessity beliefs of HCPs (20.9 ± 1.77) was higher than the mean sum scale for concern beliefs (11.5 ± 2.19). This resulted in a mean NCD-score for HCPs of 9.4 ± 3.35, which indicates that necessity beliefs outweigh concern beliefs about cDMARDs.

No significant correlation was found between the implicit attitudes and implicit health-related associations of HCPs nor between the implicit and explicit attitudes and health-related associations of HCPs. The same applied for implicit attitudes/associations and NCD scores (ρ = –0.10, $P = 0.63$, and ρ = 0.22, $P = 0.29$, respectively). This lack of association is illustrated in Figure 2. However, a significant correlation was found between the explicit attitudes of HCPs toward cDMARDs and their explicit health-related associations (ρ = 0.48, $P = 0.01$).

Association of the attitudes and beliefs of HCPs about medicines with attitudes and beliefs of their patients. Table 3 provides an overview of the final multilevel linear regression models with patients' implicit and explicit outcomes as dependent variables. HCP-related factors, including sociodemographic characteristics, implicit and explicit attitudes, and health-related associations combined with explicit beliefs about medicines were not significantly associated with patients' implicit and explicit outcomes. Only a few patient-related factors were significantly associated with patients' implicit and explicit outcomes. A high level of education of patients was significantly associated with more positive implicit attitudes toward cDMARDs, compared to patients with a low to medium level of education (coefficient 0.11 [95% confidence interval (95% CI) 0.001, 0.22]). The patient's age was significantly associated with their explicitly reported attitudes and health-related associations (coefficient 0.01 [95% CI 0.002, 0.02] and coefficient 0.01 [95% CI 0.001, 0.02], respectively), where older patients reported explicitly more positive attitudes and health-related associations than younger patients. Biologic DMARD users reported significantly higher sum scale scores for necessity beliefs than patients who were currently not treated with biologic DMARDs (coefficient 1.25 [95% CI 0.30, 2.20]). Patients who were living alone (coefficient –1.25 [95% CI –2.40, –0.11]) or with a longer mean disease duration (coefficient –0.07 [95% CI –0.12, –0.02]) reported significantly fewer concern beliefs than patients who were living together or who had a short mean disease duration.

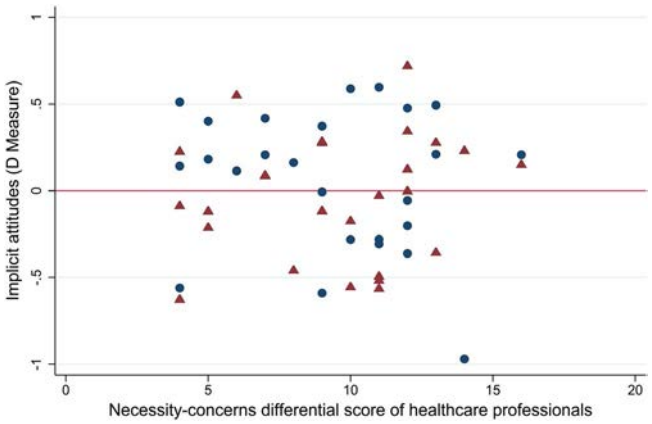

Figure 2. Lack of association between implicit measures (i.e., single-category implicit association test [SC-IAT] concept for attitudes and health-related associations) and differential scores of health care professionals' necessity concerns. Circles represent SC-IAT concept attitudes (positive–negative). Triangles represent SC-IAT concept associations (health–sickness).

Association of the attitudes, associations, and beliefs of HCPs with medication adherence and disease activity scores. HCP-related factors, including sociodemographic characteristics, implicit and explicit attitudes, and health-related associations combined with beliefs about medicines were not significantly associated with correct dosing and disease activity scores (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24186/abstract). However, the patients' age, necessity beliefs, and concern beliefs were significantly associated with self-reported correct dosing (coefficient 0.02 [95% CI 0.01, 0.04], coefficient 0.10 [95% CI 0.06, 0.15], and coefficient –0.05 [95% CI –0.09, –0.002], respectively). Higher age and higher necessity beliefs were associated with higher scores for self-reported correct dosing, whereas higher concern beliefs were associated with lower scores for self-reported correct dosing. Patients' disease duration and necessity beliefs were significantly associated with correct dosing measured with MEMS (coefficient –0.26 [95% CI –0.48, –0.04] and coefficient 0.61 [95% CI 0.04, 1.17], respectively). A relatively longer disease duration was associated with lower scores for MEMS correct dosing, whereas higher necessity beliefs were associated with higher scores for MEMS correct dosing. Sum scale scores for patients' concern beliefs were significantly associated with disease activity scores (coefficient 0.04 [95% CI 0.003, 0.09]), where more concerns were associated with higher disease activity scores.

DISCUSSION

This study demonstrated that HCP-related factors, including sociodemographic characteristics, implicit and explicit attitudes, and health-related associations combined with explicit

Table 3. Results of the multivariate, multilevel, linear regression models and predictors for patient's implicit and explicit attitudes, health-related associations, and beliefs about medicines*

	Patient's implicit attitudes	Patient's implicit health-related associations	Patient's explicit attitudes	Patient's explicit health-related associations	Patient's necessity beliefs about medicines	Patient's concern beliefs about medicines
HCP-related factors						
Age, years	†	†	†	†	†	†
Sex, female (yes/no)	†	†	†	†	†	†
Current position rheumatologist (yes/no)	†	†	−0.13 (−0.54, 0.29)	0.19 (−0.32, 0.71)	†	−0.55 (−2.27, 1.17)
Working experience, years	†	†	−0.005 (−0.015, 0.006)	†	†	†
Mean hours of patient contact per week	†	†	†	†	0.04 (−0.01, 0.10)	†
HCP's implicit and explicit attitudes and health-related associations						
Implicit attitudes, mean *D* measure	†	†	†	†	†	†
Implicit health-related associations, mean *D* measure	†	†	−0.19 (−0.46, 0.07)	−0.01 (−0.34, 0.32)	†	†
Explicit attitudes, mean scale score	†	†	0.09 (−0.20, 0.38)	0.24 (−0.12, 0.60)	0.34 (−0.86, 1.33)	−0.55 (−1.78, 0.69)
Explicit health-related associations, mean scale score	†	−0.09 (−0.21, 0.03)	0.12 (−0.20, 0.43)	0.11 (−0.29, 0.50)	1.02 (−0.31, 2.34)	†
HCP's beliefs about medicines						
Necessity beliefs, sum scale scores	†	†	−0.05 (−0.10, 0.007)	−0.02 (−0.09, 0.04)	0.10 (−0.16, 0.36)	†
Concern beliefs, sum scale scores	†	†	†	†	†	†
Patient-related factors						
Age, years	†	0.004 (−0.0004, 0.008)	0.01 (0.002, 0.02)‡	0.01 (0.001, 0.02)‡	†	†
Sex, female (yes/no)	†	†	†	†	†	†
High level of education (yes/no)	0.11 (0.001, 0.22)‡	0.08 (−0.02, 0.18)	†	†	†	†
Household situation, alone (yes/no)	†	0.08 (−0.03, 0.19)	†	†	†	−1.25 (−2.40, −0.11)‡
Disease duration, years	†	†	†	†	0.04 (−0.01, 0.09)	−0.07 (−0.12, −0.02)‡
Anti-CCP positive (yes/no)	†	†	†	†	†	†
Biologic DMARD (yes/no)	−0.06 (−0.17, 0.05)	†	−0.06 (−0.25, 0.14)	−0.14 (−0.38, 0.09)	1.25 (0.30, 2.20)‡	†
Hospital Nijmegen (yes/no)	†	†	†	†	†	−0.87 (−2.05, 0.31)

* Values are the coefficient (95% confidence interval). Reference level was "no" for predictors with "yes/no" categories. Anti-CCP = anti–cyclic citrullinated peptide; DMARD = disease-modifying antirheumatic drug; HCP = health care professional.
† Covariate not included in the final multivariate model due to the level of significance of this covariate in bivariate analysis ($P \geq 0.2$).
‡ Predictor remained significant in the multivariate, multilevel, regression models.

beliefs about medicines were not significantly associated with patients' implicit and explicit attitudes and associations, as well as patients' medication-taking behavior and disease activity scores. Only a few patient-related factors were significantly associated with the outcome measures in this study: the patient's age (outcome measures: self-reported correct dosing and the patient's explicit attitudes and health-related associations), level of education (outcome measure: the patient's implicit attitudes), household situation (outcome measure: the patient's concern beliefs about medicines), disease duration (outcome measures: MEMS correct dosing and the patient's concern beliefs about medicines), biologic DMARD use (outcome measure: the patient's necessity beliefs about medicines), sum scale scores for the patient's necessity beliefs (outcome measure: MEMS correct dosing and self-reported correct dosing), and concern beliefs (outcome measures: self-reported correct dosing and the patient's disease activity scores). Regarding medication-taking behavior and disease activity scores, the patient's necessity beliefs and concern beliefs were the only modifiable variables as possible targets for improving medication-taking behavior and disease activity in patients with RA.

To our knowledge, this is the first study that investigates the implicit and explicit associations of HCPs with medication in the field of rheumatology. Although some research has been carried out on implicit attitudes of HCPs, previous studies have predominantly focused on implicit attitudes toward other concepts rather than medication or medication-taking behavior (e.g., mental illness, sex, racial bias, and sexuality) (32–35). This makes it challenging to compare our findings with previous work.

Contrary to our expectations, the attitudes, health-related associations, and beliefs of HCPs were not significantly associated with those of their patients, indicating that the perception of HCPs regarding medication seems independent from patients' perceptions and subsequent medication-taking behavior. An explanation for this result might be that patients' attitudes, health-related associations, and beliefs about medicines rely more on previous experiences with medication, whereas the attitudes, health-related associations, and beliefs about medicines of HCPs might rely more on recommendations based on scientific evidence. Another explanation is that if an HCP has a particularly negative implicit or explicit attitude against certain medication it might influence other components of the patient–provider interaction rather than the outcomes measured in this study (e.g., style of communication, trust in the HCP, and patient satisfaction). However, it is possible that the implicit and explicit attitudes and health-related associations or beliefs about medication of HCPs are associated with those of their patients but were not detected in this study due to methodologic limitations. This thought is in line with the study of Fitzgerald et al, which recognized the complexity in studying the involvement of implicit outcomes in the patient–provider interaction due to methodologic issues and the diversity in characteristics of both patients and HCPs (36).

One of the key strengths of this study is HCP and patient recruitment in 2 of the largest centers that specialize in rheumatology across The Netherlands, combined with the large sample size of patients treated by these HCPs. Another strength is the use of electronic drug monitors to measure medication-taking behavior of patients over a 3-month period in addition to self-reported medication-taking behavior. The use of multiple measurement instruments might, however, have contributed to an overestimation of adherence levels due to the patient's awareness of being monitored and the small amount of variance in adherence measures. Together, with the small amount of variance in explicit measures and the extensive working experience at the level of HCPs, this might have limited the possibility of detecting potential influences of HCPs. The validity of the SC-IATs, used for both study groups, might be questioned because patients might have had limited hand function in contrast with HCPs. This might provide an insufficient contrast between the experimental rounds in the SC-IATs at the patient level and a large contrast between study groups. Also, the design of the SC-IATs (i.e., words and pictures used as stimuli) might have influenced implicit outcomes because it is unclear if those words and pictures are optimally related to the patient's medication use and the prescription of cDMARDs by HCPs. However, pictures were created based on pharmacy records at participating study sites (i.e., manufacturer of the drugs, type of packaging, and appearance of the drug) to increase the ability of patients and HCPs to recognize the cDMARDs at a glance.

All HCPs who participated in this study were working in hospitals that specialized in rheumatology and reported extensive years of work experience. Therefore, caution must be applied for extrapolating our findings to HCPs who were working in more general hospitals or who recently specialized in the field of rheumatology. We have also focused on cDMARDs exclusively. It is, however, conceivable that the implicit and explicit attitudes of HCPs toward biologic DMARDs and recently introduced JAK inhibitors may differ from attitudes toward cDMARDs. On the level of patients, it is assumed that selection bias has occurred due to the large proportion of adherent patients, the small variety in ethnic background, the high percentage of patients who had a high level of education, and a long disease duration. In adherence research, the difficulty of recruiting patients who represent the general population is well recognized and often challenging (37,38).

In conclusion, the implicit and explicit attitudes and health-related associations of HCPs were not significantly associated with each other. Also, the sociodemographic characteristics and the implicit and explicit attitudes, associations, and beliefs about medicines of HCPs were not associated with those of their patients nor with correct dosing and patients' disease activity

scores. These findings provide some first insights into the potential (and the lack thereof) of the implicit and explicit perceptions of medication of HCPs in relation to patients' medication adherence and disease activity.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Ms van Heuckelum 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. van Heuckelum, Hebing, Vandeberg, Linn, Flendrie, Nurmohamed, van Dulmen, van den Ende, van den Bemt.

Acquisition of data. van Heuckelum, Hebing, Vandeberg, Linn, Flendrie, Nurmohamed, van Dulmen, van den Ende, van den Bemt.

Analysis and interpretation of data. van Heuckelum, Vandeberg, van Dulmen, van den Ende, van den Bemt.

REFERENCES

1. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.
2. Lindqvist E, Jonsson K, Saxne T, Eberhardt K. Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. Ann Rheum Dis 2003;62:611–6.
3. Pasma A, den Boer E, van Spijker A, Timman R, van den Bemt B, Busschbach J, et al. Nonadherence to disease modifying antirheumatic drugs in the first year after diagnosis: comparing three adherence measures in early arthritis patients. Rheumatology (Oxford) 2016;55:1812–9.
4. Van den Bemt BJ, van den Hoogen FH, Benraad B, Hekster Y, van Riel PL, van Lankveld W. Adherence rates and associations with nonadherence in patients with rheumatoid arthritis using disease modifying antirheumatic drugs. J Rheumatol 2009;36:2164–70.
5. Salt E, Frazier S. Adherence to disease modifying anti-rheumatic drugs in rheumatoid arthritis patients: a narrative review of the literature. Orthop Nurse 2010;29:260–75.
6. Waimann CA, Marengo MF, de Achaval S, Cox VL, Garcia-Gonzalez A, Reveille JD, et al. Electronic monitoring of oral therapies in ethnically diverse and economically disadvantaged patients with rheumatoid arthritis: consequences of low adherence. Arthritis Rheum 2013;65:1421–9.
7. Harrold L, Briesacher B, Peterson D, Beard A, Madden J, Zhang F, et al. Cost-related medication nonadherence in older rheumatoid arthritis patients. J Rheumatol 2013;40:1–14.
8. Pasma A, Schenk C, Timman R, van't Spijker A, Appels C, van der Laan WH, et al. Does non-adherence to DMARDs influence hospital-related healthcare costs for early arthritis in the first year of treatment? PLoS One 2017;12:1–14.
9. Galo JS, Mehat P, Rai SK, Avina-Zubieta A, de Vera MA. What are the effects of medication adherence interventions in rheumatic diseases: a systematic review. Ann Rheum Dis 2016;21:667–73.
10. Demonceau J, Ruppar T, Kristanto P, Hughes DA, Farger E, Kardas P, et al. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. Drugs 2013;73:545–62.
11. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence [review]. Cochrane Database Syst Rev 2014;CD000011.
12. Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the necessity-concerns framework. PLoS One 2013;8:1–24.
13. Mårdby AC, Akerlind I, Hedenrud T. General beliefs about medicines among doctors and nurses in out-patient care: a cross-sectional study. BMC Fam Pract 2009;10:35.
14. Darlow B, Fullen BM, Dean S, Hurley DA, Baxter GD, Dowell A. The association between health care professional attitudes and beliefs and the attitudes and beliefs, clinical management, and outcomes of patients with low back pain: a systematic review. Eur J Pain 2011;16:3–17.
15. Rand LZ, Berger Z. Disentangling evidence and preference in patient-clinician concordance discussions. AMA J Ethics 2019;21:E505–12.
16. Zwikker H, van den Bemt B, van den Ende CH, van Lankveld W, den Broeder A, van den Hoogen F, et al. Development and content of a group-based intervention to improve medication adherence in non-adherent patients with rheumatoid arthritis. Patient Educ Couns 2012;89:143–51.
17. Van den Bemt B, den Broeder A, van den Hoogen F, Benraad B, Hekster Y, van Riel P, et al. Making the rheumatologist aware of patients' non-adherence does not improve medication adherence in patients with rheumatoid arthritis. Scan J Rheumatol 2011;40:192–6.
18. Ackermann CL, Mathieu JP. Implicit attitudes and their measurement: theoretical foundations and use in consumer behavior research. Rech Appl Mark 2016;30:55–77.
19. Greenwald AG, Banaji MR. Implicit social cognition: attitudes, self-esteem, and stereotypes. Psychol Rev 1995;102:4–27.
20. Wilson TD, Lindsey S, Schooler TY, Damiani M, Fazio R, Giner-Soroua R, et al. A model of dual attitudes. Psychol Rev 2000;107:101–26.
21. Jaccard J, Blanton H. A theory of implicit reasoned action: the role of implicit and explicit attitudes in the prediction of behavior. In: Ajzen I, Albarracin D, Hornik R, editors. Prediction and change of health behavior: applying the reasoned action approach. Mahwah (NJ): Psychology Press; 2007. p. 69–93.
22. Linn AJ, Vandeberg L, Wennekers AM, Vervloet M, van Dijk L, van den Bemt BJ. Disentangling rheumatoid arthritis patients ' implicit and explicit attitudes toward methotrexate. Front Pharmacol 2016;7:1–7.
23. Van Heuckelum M, Linn A, Vandeberg L, Hebing R, van Dijk L, Vervloet M, et al. Implicit and explicit attitudes towards disease-modifying antirheumatic drugs as possible target for improving medication adherence. PLoS One 2019;14:e0221290.
24. De Geest S, Zullig LL, Dunbar-Jacob J, Helmy R, Hughes DA, Wilson IB, et al. ESPACOMP Medication Adherence Reporting Guideline (EMERGE). Ann Intern Med 2018;169:30–6.
25. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9.
26. Karpinski A, Steinman RB. The single category implicit association test as a measure of implicit social cognition. J Pers Soc Psychol 2006;91:16–32.
27. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for

assessing the cognitive representation of medication. Psychol Heal 1999;14:1–24.

28. Greenwald AG, Nosek BA. Understanding and using the implicit association test: I. An improved scoring algorithm. J Pers Soc Psychol 2003;85:197–216.
29. Zwikker HE, van Dulmen S, van den Bemt BJ, van den Ende C. Perceived need to take medication is associated with medication non-adherence in patients with rheumatoid arthritis. Patient Prefer Adherence 2014;8:1635–45.
30. De Klerk E, van der Heijde D, van der Tempel H, van der Linden S. Development of a questionnaire to investigate patient compliance with antirheumatic drug therapy. J Rheumatol 1999;26:2635–41.
31. De Klerk E, van der Heijde D, Landewé R, van der Tempel H, van der Linden S. The Compliance-Questionnaire-Rheumatology compared with electronic medication event monitoring: a validation study. J Rheumatol 2003;30:2469–75.
32. Dabby L, Tranulis C, Kirmayer LJ. Explicit and implicit attitudes of Canadian psychiatrists toward people with mental illness. Can J Psychiatry 2015;60:451–9.
33. Blair IV, Steiner JF, Fairclough DL, Hanratty R, Price DW, Hirsh HK, et al. Clinicians' implicit ethnic/racial bias and perceptions of care among Black and Latino patients. Ann Fam Med 2013;11:43–52.
34. Kopera M, Suszek H, Bonar E, Myszka M, Gmaj B, Ilgen M, et al. Evaluating explicit and implicit stigma of mental illness in mental health professionals and medical students. Community Ment Health J 2015;51:628–34.
35. Sabin J, Nosek BA, Greenwald A, Rivara FP. Physicians' implicit and explicit attitudes about race by MD race, ethnicity, and gender. J Health Care Poor Underserved 2009;20:896–913.
36. FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. BMC Med Ethics 2017;18:19.
37. Bender B, Milgrom H, Apter A. Adherence intervention research: what have we learned and what do we do next? J Allergy Clin Immunol 2003;112:489–94.
38. Shemesh E, Mitchell J, Neighbors K, Feist S, Hawkins A, Brown A, et al. Recruiting a representative sample in adherence research: the MALT multisite prospective cohort study experience. Pediatr Transplant 2017;21:1–14.

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Making Decisions About Stopping Medicines for Well-Controlled Juvenile Idiopathic Arthritis: A Mixed-Methods Study of Patients and Caregivers

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Objective. Improved treatments for juvenile idiopathic arthritis (JIA) have increased remission rates. We conducted this study to investigate how patients and caregivers make decisions about stopping medications when JIA is inactive.

Methods. We performed a mixed-methods study of caregivers and patients affected by JIA, recruited through social media and flyers, and selected by purposive sampling. Participants discussed their experiences with JIA, medications, and decision-making through recorded telephone interviews. Of 44 interviewees, 20 were patients (50% ages <18 years), and 24 were caregivers (50% caring for children ages ≤10 years). We evaluated characteristics associated with high levels of reported concerns about JIA or medicines using Fisher's exact testing.

Results. Decisions about stopping medicines were informed by competing risks between disease activity and treatment. Participants who expressed more concerns about JIA were more likely to report disease-related complications ($P = 0.002$) and more motivated to continue treatment. However, participants expressing more concern about medicines were more likely to report treatment-related complications ($P = 0.04$) and felt more compelled to stop treatment. Additionally, participants considered how JIA or treatments facilitated or interfered with their sense of normalcy and safety, expressed feelings of guilt and regret about previous or potential adverse events, and reflected on uncertainty and unpredictability of future harms. Decision-making was also informed by trust in rheumatologists and other information sources (e.g., family and online support groups).

Conclusion. When deciding whether to stop medicines whenever JIA is inactive, patients and caregivers weigh competing risks between disease activity and treatment. Based on our results, we suggest specific approaches for clinicians to perform shared decision-making regarding stopping medicines for JIA.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) contributes to numerous short- and long-term physical and psychosocial sequelae, including chronic pain, disability, depression, and impaired quality of life (1,2). Approximately one-half of patients with JIA have persistently active disease into adulthood (3,4). However, with increasing availability of effective antirheumatic medicines, health outcomes in children with JIA have improved considerably in recent years. Many patients are able to achieve inactive disease, a state that may persist after stopping JIA drugs altogether (5). These improvements in treatments and outcomes for patients with JIA

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SIGNIFICANCE & INNOVATIONS

- To our knowledge, this is the first study to jointly examine patients' and caregivers' perspectives on stopping medicines for inactive juvenile idiopathic arthritis (JIA) or any other chronic pediatric disease.
- Decisions about stopping JIA medicines involve a trade-off between competing risks and fears of disease activity and risks and fears of the medicines; the magnitude of these reported fears is associated with prior complications from the disease and treatments, respectively.
- Unlike prior research on decisions to stop medicines for rheumatoid arthritis, the current study highlights the influence of guilt and regret on decision-making, the financial costs of treatment, the perspectives of family members, impacts of disease activity and treatment on family dynamics, and other pediatric-specific issues.
- These considerations can inform shared decision-making with clinicians regarding stopping medicines for JIA.

have not been without challenges. Conventional and biologic disease-modifying antirheumatic drugs (DMARDs) have a range of potential harms, from mild side effects to more serious and uncertain complications, including serious infections and potential malignancy (6–11). JIA treatments, particularly biologics, can cause substantial financial burdens on families resulting from the high medicine costs and missed school and work for office visits, infusions, and hospitalizations (12,13).

Decisions about stopping effective medications are challenging and complex. A widely used and validated definition of inactive disease does not include patient-/parent-reported measures and may not account for factors most important to patients and families in decision-making (14,15). Additionally, clinical definitions of inactive disease and remission do not reflect the complex biology that predisposes some children to experience a disease flare after withdrawing treatment (16). Biomarkers for guiding decisions on treatment withdrawal have been tested (17) but not sufficiently validated for routine clinical use (18). Choices about stopping treatment are further complicated by insufficient data on effective withdrawal strategies (19,20).

Given the substantial uncertainty about how to manage inactive JIA, decisions about withdrawing treatment generally involve discussions between clinicians, patients, and families, each party with potentially different experiences, values, and priorities. Previous studies have examined clinicians' motivations and priorities regarding stopping JIA medicines (19,21). Some studies have explored patients' and parents' perspectives on starting and adhering to JIA medicines (22,23). Other research has examined decision-making regarding stopping treatment for rheumatoid arthritis (RA) (24,25) and other pediatric conditions (e.g., attention deficit hyperactivity disorder [ADHD], and epilepsy) (26,27). No study, however (to our knowledge), has formally examined how patients with JIA and caregivers approach decision-making for well-controlled disease. We conducted a mixed-methods study of adolescents and young adults with JIA and caregivers to identify important factors and priorities when deciding whether to stop medications for inactive JIA. We hypothesized that caregivers would prioritize long-term impacts (e.g., damage prevention and long-term drug toxicities) and that patients would prioritize short-term impacts (e.g., symptoms, side effects).

PATIENTS AND METHODS

Study design and population. We performed a mixed-methods study based on semistructured telephone interviews with patients with JIA and caregivers (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24129/abstract). Eligible participants were required to live in the US, be age ≥13 years, and report having either a JIA/juvenile rheumatoid arthritis (JRA) diagnosis or a child with JIA/JRA. We recruited participants via social media and flyers in pediatric rheumatology clinics. Interested caregivers and adults with JIA were asked to complete a preliminary online survey. Caregivers were asked for their permission to allow children with JIA ages 13–17 years to participate. We purposively selected participants for interviews based on demographic and disease variables to ensure a broad range of participants (Table 1).

Interviews. After obtaining verbal consent, research staff conducted telephone interviews that were ~30–45 minutes long using a semistructured interview guide. This guide included open-ended questions followed by prompts to probe specific ideas and elicit additional thoughts and opinions (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24129/abstract). Questions explored participants' experiences with JIA, treatment, and factors that might influence treatment-related decisions, focusing on inactive disease and treatment withdrawal. Parallel interview scripts for caregivers and patients shared the same structure with age-appropriate questions. Interview scripts were developed through iterative revisions based on extensive feedback from study investigators (pediatric rheumatologists, 2 parents of children with JIA, a medical sociologist, and sociology trainees), prior literature on JIA (28,29), RA (30), and patients' perspectives on taking medicines (31), and input from social and behavioral scientists, patients, and parents not involved with the study. We also used software (Health Literacy Advisor) to ensure that the script was suitable for general understanding. Interviews were digitally recorded, professionally transcribed, and deidentified for analysis.

Table 1. Self-reported characteristics of interview participants*

Characteristic	No. (%)
Demographics and geography	
Group	
Patient, 13–17 years	10 (23)
Patient, ≥18 years (range 18–38 years)	10 (23)
Mother, child ≤10 years and younger	11 (25)
Mother, child >10 years	13 (30)
Patient sex, female	35 (80)
Hispanic/Latino ethnicity	10 (23)
Nonwhite race	6 (14)
Public insurance	10 (23)
Maximum level of parental education (any parent or guardian)	
High school	4 (9)
College	21 (47)
Graduate school	19 (43)
Region of US	
Midwest	9 (20)
Northeast	8 (18)
South	19 (43)
West	8 (18)
Disease and drug experience	
JIA category	
Oligoarticular	11 (25)
Polyarticular	18 (41)
Psoriatic	4 (9)
Enthesitis-related arthritis	5 (11)
Systemic	5 (11)
Other	1 (2)
Years since JIA diagnosis	
<4	10 (23)
4–8	19 (43)
>8	15 (34)
Uveitis	9 (20)
Methotrexate use	
None	7 (16)
Prior	17 (39)
Current	20 (45)
Biologic use	
None	7 (16)
Prior	5 (11)
Current	32 (73)
History of inactive JIA, drug discontinuation	
Never inactive	10 (23)
Never stopped, inactive before	2 (5)
Never stopped, inactive now	11 (25)
Stopped, now active	12 (27)
Stopped, now inactive	9 (20)

* JIA = juvenile idiopathic arthritis.

Analysis. We performed qualitative coding of transcripts using Dedoose, a cloud-based platform for storing and analyzing textual data with qualitative and mixed-methods approaches (32). A hierarchical list of codes was developed based on the study questions using the Common Sense Model of Self-Regulation (CSM) (33). The CSM focuses on patients' understanding of their illness to assess how perceptions of illness can shape actions. Understanding of illness includes the name and symptoms of a disease, its expected duration, perceived cause(s), the ways that disease can be controlled or cured, and its impact and consequences on health and lifestyle. The CSM is used to understand how experience-based beliefs affect treatment adherence and outcomes (34,35).

Two research staff (JS and AW), including the interviewer, coded each transcript (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24129/abstract). Investigators (DBH and MR) met with research staff monthly to review recently coded transcripts, resolve questions or discrepancies in coding and interpretation, discuss emerging themes, and determine when thematic saturation was reached. Upon completion of transcript coding and review, the team developed a conceptual model, matching codes to themes and identifying illustrative quotes for each theme. Differences and similarities were identified between responses from caregivers, adult patients, and adolescent patients.

Additionally, we assessed the level of concern or fear that participants expressed regarding future effects of JIA and medicines, respectively. We compared characteristics of subjects who did and did not express high levels of concern or fear by Fisher's exact testing (see Supplementary Appendix, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24129/abstract).

RESULTS

We interviewed a varied group of 20 patients (50% ages <18 years) and 24 caregivers (all mothers, 46% caring for children ages ≤10 years) (Table 1). Participants came from different demographic and educational backgrounds and different US regions. Participants represented different JIA categories, most commonly polyarticular JIA. Most participants reported past or ongoing use of conventional (84%) or biologic (84%) DMARDs. Most reported having inactive disease (77%), either in the past (32%) or currently (45%). Approximately one-half of participants (47%) had stopped all medicines due to having inactive disease, 43% of whom remained off medication (Table 1).

Balance of competing risks, fears, and adverse experiences from JIA and from JIA medicines. Decision-making about decreasing or stopping medicines generally hinged on a perceived balance between risks and fears from the disease and corresponding risks and fears from the medicines (Figure 1 and Table 2). Participants reported numerous concerns about JIA, including flares and symptoms (e.g., pain, fatigue, vision loss, fevers), long-term damage of joints, eyes, or other organs, limited participation in activities, work, or school, loss of functional capacity through JIA-related joint or eye damage, and various psychosocial consequences, including mood disorders (e.g., depression, anxiety), behavioral problems, social isolation, bullying, and family disruption. Reported concerns about medicines closely paralleled concerns about JIA: toxicities and side effects (e.g., pain, fatigue, nausea, and brain fog) analogous to JIA symptoms; long-term risks to health (e.g., cancer, immunosuppression)

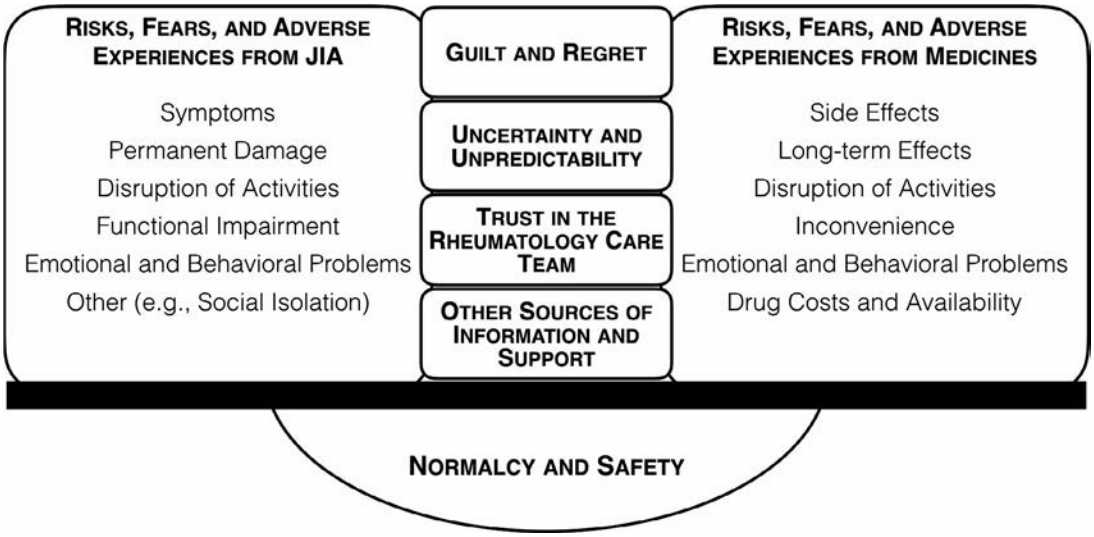

Figure 1. Conceptual diagram of factors influencing decisions to stop or continue medicines for well-controlled juvenile idiopathic arthritis (JIA). The diagram illustrates the balancing that takes place between competing sets of risks, fears, and adverse experiences from JIA and from medicines when patients and caregivers are deciding whether to stop medicines. Each set contains analogous considerations. This balance is influenced by feelings of guilt and regret, and by the uncertainty and unpredictability of future disease or treatment effects, and is informed by trust in the rheumatology care team, as well as other sources of information and support. Patients' and caregivers' decisions about stopping JIA treatment are often aimed at achieving or preserving a sense of normalcy and safety.

analogous to JIA-related damage; interference with school, work, and activities analogous to JIA-related functional and activity limitations; and various corresponding psychosocial consequences (e.g., anxiety around injections). Participants also reported concerns about the cost of JIA medicines and access to treatment.

Participants with past or ongoing adverse experiences from JIA or JIA medicines were more likely to express salient concerns and fears related to those experiences (Table 3). Adolescents, adults with JIA, and caregivers reflected on such adverse experiences to a similar degree. Nonetheless, many concerns focused on possible future complications that might result from decisions to either continue or stop medicines. These fears of future complications sometimes, but not always, reflected past experiences and were more commonly reported by adults with JIA or caregivers than by adolescents.

Several individuals articulated explicit trade-offs between these competing sets of concerns, reflecting on the tension between the risks of continuing unnecessary treatment that relate to future complications (e.g., cancer) and the risks of premature treatment discontinuation that lead to future disease complications (e.g., pain, disability, damage, and adverse impacts on school or work). Decisions about withdrawing treatment often related to whether individuals perceived that disease activity or medicines represent the greater risk and threat to health. Those who worried more about what JIA had done or could do in the future expressed more motivation to continue treatment. On the other hand, participants who viewed medicines as noxious, toxic, disruptive, or otherwise dangerous to present or future health expressed more motivation to stop medicines sooner. Individuals with stronger beliefs about one set of risks being greater than the other expressed stronger preferences about either undergoing treatment for a long time or stopping treatment quickly. For others, whose views about the trade-off were more balanced or uncertain, decisions about withdrawing medicines seemed to be more fluid and dependent on context and external input, such as from rheumatologists, family, friends, and others affected by JIA (see sections below on trust in the rheumatology care team and other sources of information and support).

Among other demographic, disease-related, and treatment-related factors examined, publicly insured participants were more likely than privately insured individuals to report high levels of fear of JIA and of medicines (Table 3). Other numeric differences in reported fears were observed across other domains (e.g., sex, region, and JIA type) that, nonetheless, did not achieve traditional statistical significance (Table 3).

Normalcy and safety. In reflecting positively on the competing concerns about JIA and medicines, participants discussed striving to achieve and maintain good health and wellness free from ill effects (Table 4). Participants reflected on the importance of feeling normal and safe, for example, to grow and develop like other children, to participate fully and without limitations in school, work, or sports, and to be considered equal to and not different from siblings or peers. For some participants, medicines were the means of maintaining freedom from adversity and living more normal lives by controlling flares and preventing future disabilities and/or complications from the disease. These participants perceived stopping medicine as a threat to that sense of normalcy and safety. Other participants who felt that they or their children

Table 2. Representative quotes regarding risks, fears, adverse experiences, and trade-offs in decisions about stopping juvenile idiopathic arthritis (JIA) medicines*

Concept and participant	Quote
Risks, fears, and adverse experiences from JIA	
Patient with JIA, age 38, F	"I'm in pain from the moment I open my eyes till I fall asleep at night, until whenever the flare goes away. And sometimes it's not horrific pain. And sometimes it's just being uncomfortable, but uncomfortable over a lot of hours wears on you."
Patient with JIA, age 13, F	"Well, I can't do PE most of the time. I can't do a lot of things with other girls in PE. But I also sometimes – my sister has to help me out – just get up and get my dinner kinda thing because I can't get off the couch because my legs hurt or open my water bottles and cans – things like that."
Mother of child (age 4, F) with JIA	"… especially when she's in more pain than usual, she just doesn't deal well with even…little disappointments. She'll just go into a full-fledged tantrum – crying, screaming, throwing herself on the floor. Where the normal child would be upset or disappointed, but she just takes it to a whole new level."
Risks, fears, and adverse experiences from medicines	
Patient with JIA, age 22, F	"I was on [medicine] a month ago, and [it] was giving me stomach ulcers. And I was so desperate because I was in so much pain that I was taking [it] anyway…but it was giving me so many side effects that I was almost like, 'maybe I should just deal with the pain and stop taking the NSAID because I'm so miserable. I have the worst heartburn of my life. I can't deal with this every day'."
Mother of child (age 3, F) with JIA	"…it was not good for her because it could stunt her growth and damage her organs. And that's what I was scared about. And now once we had her at the doctor's appointment, we found out the [medicine] was stunting her growth, so we had to stop that."
Patient with JIA, age 19, F	"I worry about with all the medications I'm taking affecting my fertility…now going on 20…I worry about if my medications will affect my chances of that. How will it affect me being a mom?"
Patient with JIA, age 13, F	"I think about that a lot. Especially when I'm like watching TV and some commercials come on for the medicine that I take and the side effects. I get really worried and scared because there's some severe side effects…my mom has been putting it off for giving it to me for years because it's hard core. It's very – I don't know the word. Risky I guess."
Patient with JIA, age 13, M	"Usually the day I take the medicine, I can't – I mean I go to school but I don't really function that much because I don't feel that great and usually if I take my medicine and I'm feeling nauseated that day, I'll get checked out after my fourth period."
Trade-off between competing risks	
Patient with JIA, age 13, F	"I think that if it's so painful or there's just a lot of side effects, is it really worth it? If it's getting my arthritis better, but it's putting me through so much pain, then it's not really taking away the pain. So then I don't see any point on going on that specific medicine."
Mother of child (age 14, F) with JIA	"The thing is always in the back of your mind. How long can she do it before the side effects in the future – it's – you're playing with fire and with fate. You just don't know how it's going to affect [your child] in the future and what's the magic number? When do you stop so that you don't have a reaction in the future? So that's why we stopped, because there was so much uncertainty. And do the risks outweigh the benefits?"
Mother of child (age 10, F) with JIA	"I mean, there's always worries about all of the horrible side effects with all of the drugs that are used to treat it. So I mean, there's always those worries, like those things. But I always try to put them in the back of my head because it's way worse to leave her arthritis untreated than it is to worry about side effects that may or not happen when we know what is currently happening."
Mother of child (age 4, F) with JIA	"So it's kind of – again, benefit versus risk. Right now, the benefit of the medications currently is going to be protecting her future as far as keeping her from being permanently disabled versus well, okay, there might be a risk of something that we don't know in the future. I'm not gonna let a possibility of some unknown thing happening prevent me from protecting her now."

* F = female; M = male; NSAID = nonsteroidal antiinflammatory drug; PE = physical education.

were particularly threatened or endangered by medicines, including the possibility of developing severe treatment-related harms or disruption of daily activities because of side effects, viewed stopping medicines as a necessary means to achieving more normal and safer lives.

Guilt and regret. Some participants expressed feelings of guilt and regret about their perceived involvement in or responsibility for past events (Table 4). These prior events included the diagnosis of JIA (a common source of guilt among parents), severe flares occurring after prior treatment discontinuation, and severe reactions to medicines. This sense of guilt and regret was projected forward in anticipation of future complications from the disease and/or medicines related to perceived actions (e.g., giving or stopping medicines) or inactions (e.g., not stopping or not giving medicines). A heightened sense of guilt or regret over what the disease had done or could do if poorly controlled in the future (e.g., damage to the joints or eyes) motivated participants to continue treatments. In contrast, guilt or regret over experiencing harms from treatment led to preferences to stop treating sooner. For example, caregivers were concerned with allergic reactions or side effects that severely limited patients' ability to achieve

Table 3. Relationship between participant characteristics and high reported levels of fear of juvenile idiopathic arthritis (JIA) or medicines*

Characteristic	High level of concern or fear of JIA†		High level of concern or fear of medicines‡	
	No. (%)	*P*§	No. (%)	*P*§
All participants	20 (45)	–	9 (20)	–
Demographics and geography				
Group		0.65		0.46
Patient, ages 13–17 years	4 (40)		3 (30)	
Patient, ages ≥18 (range 18–38 years)	3 (30)		1 (10)	
Mother, child 10 years and younger	6 (55)		1 (9)	
Mother, child older than 10 years	7 (54)		4 (31)	
Patient sex		0.48		0.17
Female	17 (49)		9 (26)	
Male	3 (33)		0	
Race/ethnicity		0.62		0.99
White, non-Hispanic/Latino	12 (43)		6 (21)	
Hispanic/Latino	4 (40)		2 (20)	
Other	4 (67)		1 (17)	
Insurance		0.002		0.02
Private	11 (32)		4 (12)	
Public	9 (90)		5 (50)	
Maximum level of parental education (any parent or guardian)		0.76		0.70
No bachelor's degree	8 (50)		4 (25)	
Bachelor's degree	12 (43)		5 (18)	
Region of US		0.24		0.05
Midwest	5 (56)		4 (44)	
Northeast	1 (13)		0	
South	10 (53)		5 (26)	
West	4 (50)		0	
Disease and drug experience				
JIA category		0.58		0.84
Oligoarticular	3 (27)		3 (27)	
Polyarticular	9 (50)		4 (22)	
Spondyloarthritis	4 (44)		2 (22)	
Systemic	3 (60)		0	
Other	1 (100)		0	
Years since JIA diagnosis		0.79		0.31
<4	4 (40)		2 (20)	
4–8	8 (42)		2 (11)	
>8	8 (53)		5 (33)	
Uveitis		0.99		0.36
No	16 (46)		6 (17)	
Yes	4 (44)		3 (33)	
Methotrexate use		0.66		0.47
None	2 (29)		0	
Prior	8 (47)		4 (24)	
Current	10 (50)		4 (25)	
Biologic use		0.70		0.50
None	2 (29)		1 (14)	
Prior	2 (40)		2 (40)	
Current	16 (50)		6 (19)	
History of inactive JIA, drug discontinuation		0.37		0.33
Never inactive	5 (50)		1 (10)	
Never stopped, inactive before	2 (100)		0	
Never stopped, inactive now	5 (45)		1 (9)	
Stopped, now active	6 (50)		5 (42)	
Stopped, now inactive	2 (22)		2 (22)	
Complications from JIA¶		0.002		0.72
No	3 (16)		3 (17)	
Yes	17 (65)		6 (23)	

(Continued)

Table 3. (*Cont'd*)

Characteristic	High level of concern or fear of JIA†		High level of concern or fear of medicines‡	
	No. (%)	*P*§	No. (%)	*P*§
Complications from medicines#		0.53		0.04
No	12 (41)		3 (10)	
Yes	8 (53)		6 (40)	

* JIA = juvenile idiopathic arthritis.
† Quantitated in response to the question, "Are there any particular fears or concerns about the disease that are especially important in this decision (whether to stop medicines)?"
‡ Quantitated in response to the question, "Are there any particular fears or concerns about the treatment that are especially important in this decision (whether to stop medicines)?"
§ *P* value calculated from Fisher's exact tests.
¶ Reported history of systemic JIA with macrophage activation syndrome, permanent damage to the joints, eyes, or other organs, severe flare, physical disability, or severe comorbidities.
# Reported history of severe side effects or other harms from medicines or aversion to medicines.

normalcy. Caregivers were generally more likely to express guilt and regret for past or future actions or inactions than patients, although the attribution of these feelings to JIA or medicines did not differ between caregivers and patients.

Uncertainty and unpredictability. Participants discussed coping with the uncertainty and unpredictability of having JIA and treating it with potentially harmful medicines, using words such as "terrifying," "scary," and "worried" (Table 4). Uncertainty was expressed as not knowing how likely events were to occur, such as eye damage or cancer. Unpredictability was expressed as not knowing whether or when events, such as flares, might occur. Some individuals felt more concern about the potential for harm from JIA, including harm that was not readily detected (e.g., clinically silent damage). Several participants were concerned about whether the same medicine that controlled their or their child's disease would still work if restarted after flares. Some participants expressed distress from uncertainty and unpredictability about the disease when discussing preferences to continue treatment. Others expressed more concerns about the possibility of future adverse effects from medicines, however likely or unlikely those outcomes were; these individuals preferred stopping treatment sooner. The sense of uncertainty or unpredictability sometimes was linked by participants to doctors' inability to give detailed or accurate assessments of risks or to predict how a patient might respond to a particular treatment.

Trust in the rheumatology care team. Participants commonly reflected on the importance of trusting the rheumatologists and staff when making decisions about whether to stop medicines (Table 5). This trust encompassed a sense of interacting well with informed, knowledgeable clinicians who listened, cared, and included patients and caregivers in the decision-making process. Some participants expressed high levels of trust in rheumatologists, which often corresponded to support for following the rheumatologists' recommendations about continuing or stopping medicine. In contrast, other individuals recounted experiences that led them to lose trust in the rheumatologist, such as feeling unheard, disregarded, or judged for their health beliefs. These feelings motivated some to find new clinicians and others to avoid returning to the rheumatology clinic for treatment, managing symptoms on their own, or in some cases, turning to alternate care providers. Lower levels of trust in rheumatologists were associated with expressing greater fears about medicines and less willingness to continue them. Some participants expressed frustration about variations in medical care and about differences in doctors' professional opinions and treatment recommendations. Levels of trust in rheumatologists did not appreciably differ between patients and caregivers.

Other sources of information and support. When making decisions about stopping, patients and caregivers turned to various sources of information and support besides the treating rheumatologists, including family members, friends, websites, social media, others with arthritis, and the medical literature (Table 5). Participants reported feeling empowered and more in control by having access to greater knowledge and understanding about JIA and medicines. Many reflected on the importance of camaraderie, community, and having support from others who have gone through similar experiences and could offer both advice and validation. Online groups were important sources of community for young patients with JIA. Several individuals also commented on the diversity of information and opinions online and the need to remain skeptical. Many reported a preference for reading peer-reviewed articles or reports by foundations or nonprofit organizations. Some acknowledged the diversity of individual experiences, and that what worked for some people (e.g., stopping treatment) might not work for others in similar situations.

DISCUSSION

This study represents the first mixed-methods study focused on the perspectives of patients and caregivers on stopping JIA medicines. Patients and caregivers described their decisions

Table 4. Representative quotes regarding safety and normalcy, guilt and regret, and uncertainty and unpredictability in decisions about stopping juvenile idiopathic arthritis (JIA) medicines

Concept and participant	Quote
Safety and normalcy	
Mother of child (age 9, F) with JIA	"…she's a child and you want them to be happy and you want them to play and you want them to run and you want them to be as normal as – live as normal of a life as they can while they're still living an abnormal life because it's not normal to get poked 2 or 3 times a day. But it's just that's what's most important to me is to keep her healthy and keep her active."
Patient with JIA, age 16, F	"I feel that stopping medication obviously is going to make you feel more quote, unquote normal than you were before with all the medication."
Mother of child (age 3, F) with JIA	"…that's for me to stop medicine for my child is just have the naturals in her body without the chemicals – medicines that's infecting her body where it's gonna – who knows if it's gonna affect her in the long run. It may help her now, but I don't know."
Patient with JIA, age 14, F	"I don't want anything else to be put at risk of getting worse or happening. I feel a lot more safe on the medicine. I know I'm okay right now, and that's good to know."
Mother of child (age 15, F) with JIA	"If you read one of those god-awful 8,000-page packets that come with your prescription about the potential side effects, that's enough to scare anybody out of that…I don't mind as long as it's gonna work, but none of this stuff said yes, we can cure her. It was just a Band-Aid. And I wasn't willing to gamble those side effects for a Band-Aid…"
Guilt and regret	
Mother of child (age 12, F) with JIA	"So the worst part for her was the pain, and for us it was the pain and the feeling we couldn't – for the first time in our lives as parents, we couldn't fix what we were supposed to fix for her."
Mother of child (age 7, F) with JIA	"She didn't know how she would feel without the medications. She didn't know how life would be different without the medications. So by stopping them and restarting them, that's when we saw the biggest changes in her behaviors and attitudes…And she did have some damage to her eyesight because of the recurrence and the uveitis. So perhaps that may not have occurred. It's a lot of what-ifs because you can't turn back the clock."
Patient with JIA, age 38, F	"I mentioned something before about believing that there was a genetic factor. And I wish I would have known that sooner…And then as an adult, it was at my daughter's rheumatology appointment that the suggestion made that I have genetic testing done for myself. And I wish that would have happened differently."
Mother of child (age 10, F) with JIA	"I hate it. Every time – for the first year, every time I'd give her her shot I would feel like I was gonna be physically ill after. But I always have to rationalize in my brain that this is way better than her having damage from untreated arthritis…"
Uncertainty and unpredictability	
Patient with JIA, age 14, F	"I think I feel more comfortable knowing what [the disease is] doing. I feel like if I were in remission, it would make me a little nervous because I wouldn't know when it would come up again. I'd like to know what's going on with it. I don't like things being up to chance."
Mother of child (age 12, F) with JIA	"And so it was – it was terrifying because you'd have no control. At first we didn't know what it was. Then we knew it was arthritis, but it was uncontrolled with the [medicine]. And so you don't know is your kid going to be disabled for life? Are you ever going to be able to get them out of pain?"
Patient with JIA, age 28, F	"I know that there's a lot of research out there about how varied it is between physicians and their opinions. As a patient, I am leery of stopping medications because I know how quickly antibodies can build up and make the medication stop working. So you wouldn't necessarily be able to go on the same medication again when you restart if you needed to."
Mother of child (age 9, F) with JIA	"It can be scary too because you don't know what the long-term effects could be from these medications. So they're helping them right now but in the years to come is this gonna cause other issues…Because these are some pretty high-powered medications these kids take."
Patient with JIA, age 14, F	"I'm a little worried because this is a newer medicine, and not many people have weaned off of it. So I'm a little worried because they don't really know anything. I kind of feel like a guinea pig, so that's a little strange."
Patient with JIA, age 24, F	"Then I think also there's the medical piece to it which is not knowing or being a little concerned about what it may mean to take immune-suppressants in the long term. And so I think the sooner I can get off of it, the less I have to be concerned about that."

regarding stopping treatments based on a key trade-off: risks and fears of the disease itself compared to risks and fears of medicines for the disease. For many participants, this requires weighing parallel risks: symptoms versus side effects; disease-related damage versus long-term treatment-related toxicities; limitations in participation and function from disease sequelae versus disruptions in life and activities from treatments; and the emotional toll of having JIA or experiencing treatment-related harms. These judgments are based on both prior personal experiences and concerns about future consequences of treatment-related decisions. Other factors that appeared important in balancing these competing risks included the following: optimizing a sense of normalcy and safety (having well-controlled JIA versus not taking medicines); distress from uncertainty and unpredictability of JIA-related or treatment-related complications; feelings of guilt and regret about taking or not taking action; levels of trust in physicians; and reliance on other sources of information and support, including family, friends, and various online venues.

Stopping antirheumatic medicines appropriately is important, given their toxicities, inconvenience, and costs to society (36). However, stopping treatment also poses risks of subsequent disease flares, which may or may not respond to the same

Table 5. Representative quotes regarding trust in rheumatology team, other sources of information, and support in decisions about stopping juvenile idiopathic arthritis (JIA) medicines*

Concept and participant	Quote
Trust in the rheumatology care team	
Patient with JIA, age 19, F	"I tell my rheumatologist everything. We're very close. I'm very blessed to have that kind of relationship with my doctor, like I said. She's known me since before I could even remember – at 14 months old when she first met me. And while I was seeing a different rheumatologist at the beginning, she's always been there…And actually, most of the time, if I have any sort of medical issue, I go to them instead of my primary care doctor because I trust them more than my PCP because they know me better."
Patient with JIA, age 13, F	"I think I get an input exactly. Like they would like to ask me, how does this make you feel, and would you be okay with this or would this make you uncomfortable. I don't get to decide completely. I don't get to say like 'Okay. We're going to start this', because I am only 13 and I only know so much. Yeah, my doctor is very – he's very – he cares a lot about what I say and how I feel about it."
Mother of child (age 10, F) with JIA	"…I trust my rheumatologist to make the best decision. So I would say it's probably an 80/20 type scenario. I leave 80 percent of it up to him and then I just ask questions to make sure that we're making the best decision … I trust him and I would leave the decision up to him, even though sometimes I have doubts and I ask lots of questions, but he's managed her this far."
Patient with JIA, age 15, F	"My last rheumatologist, he wanted to do all those infusions and all those shots and every single day get an infusion. That was a lot. But I don't think that was a great idea … when we started the different diet and that helped me a lot and he wasn't about that. He wasn't about diet because he wanted to do all the [medications] and stuff. But we didn't wanna do that…"
Mother of child (age 8, M) with JIA	"…well, listening to my doctor who I trust which is strange because I don't trust most doctors. We've had a lot of doctors in our family with the different things, and half of them contradict each other. Or they say one thing and another doctor says another. So I don't trust them as a whole. But I really like this doctor and he knows his research, and so I would trust him."
Mother of child (age 4, F) with JIA	"But we're lucky to have a really wonderful rheumatologist who will take the time to sit and explain and give me options and allow me to say, well, okay, this is what I want for her or let's try something different. So we have a really good team…I feel like I'm a member of that team decision, not just a parent being told, okay, well, this is what we're doing for your kid and I don't have a say."
Other sources of information and support	
Patient with JIA, age 16, F	"I have friends that I met at the arthritis convention. And I usually talk to them about it because I just don't think other people understand…And we listen to each other and how each of us are doing. And we talk about medicines and stuff. And we talk about other things too, but like mostly – that's what we talk about with our arthritis."
Patient with JIA, age 28, F	"I am connected with a lot of other people who have the same or similar diseases. And so I try whenever I am on the fence about a medical decision or just trying to kind of toss around some ideas to myself, I do try to reach out to some of them and see what their thoughts are. Because a lot of them have been on medications I haven't been on yet or have been through kind of this whole process of stopping meds and then waiting and then having to come back on and those kinds of things. So I really value the opinions of my friends who have been in the same or similar positions as well."
Mother of child (age 14, M) with JIA	"There's a good Facebook group, and so it's always interesting to see what other people with similar situations, what advice they're getting from their physicians. And so it's information that I read and I digest and it might help prompt questions I need to be asking."
Patient with JIA, age 22, F	"So for me, a very important part of making decisions about medication is being informed about it. And so I personally read a lot of studies of things that have been published. I don't think it's good to just Google something and read anything on the Internet. I want to read something that's like gone through a peer review process. So something that's on Google Scholar, or PubMed or something like that. I think it's important to know things like that to see what response rates are, what different types of JIA have been seen to respond better to different types of medications, what side effects there are."

* PCP = primary care provider.

regimens that once kept the disease well-controlled. Decisions about when to stop effective medicines are particularly challenging given the lack of high-quality evidence on individual risks of flare after treatment withdrawal, reliable strategies for withdrawing treatment, and the likelihood of regaining disease control (i.e., recapture) after treatment reinitiation (20). Clinicians may have different priorities (e.g., maintaining remission) from patients and families (e.g., achieving a sense of normalcy, eliminating ongoing side effects or costs, or avoiding long-term treatment-related harms). We hypothesized that patients and caregivers would worry differently about long-term versus short-term risks. Instead, we found a divide between age lines, with adolescents tending to consider short-term risks to well-being, as previously reported (37,38), while adults with JIA, like caregivers, were often more future oriented. We did not observe any significant age-related differences in perceived levels of fear toward JIA or medicines more broadly. Notably, publicly insured participants were more likely to express high levels of fear about both JIA and JIA medicines compared to privately insured participants, another unexpected finding that bears confirmation in future

research. We did not find parallel differences based on level of parental education.

An existing body of research has described the attitudes and behaviors of patients who take or choose not to take medication for conditions other than JIA (31). Many studies, including an older study on the use of nonsteroidal medications for RA, have focused on adherence and reasons why people stop medications despite ongoing disease activity (e.g., for lack of efficacy) (31,39). In pediatric rheumatology, more qualitative research has focused on decisions about starting DMARDs, including studies on the perspectives of patients and families (21,23). Prior research about stopping JIA medications has focused on clinicians' perspectives through interviews and surveys (19,21). Research examining the perspectives of adults with RA on stopping antirheumatic medicines has also highlighted similar tensions between risks of arthritis and risks of treatments, the role of uncertainty and unpredictability, the importance of achieving normalcy, and impacts of prior disease experiences (24,25). However, these studies have not touched on other themes identified in our study, including the perspectives of family members, impacts of disease and treatment on family dynamics, the financial costs of treatment, the influence of guilt and regret on decision-making, and other issues specific to pediatrics, including growth, development, and bullying.

Research examining decision-making around treatment withdrawal for other pediatric diseases has mainly focused on neuropsychiatric conditions, including ADHD and epilepsy, citing adverse side effects and decreased efficacy as main factors for withdrawal (26,27,40,41). None of these studies has elicited or compared the perspectives of both patients and caregivers. Furthermore, clinical differences distinguish JIA medicines from those for neuropsychiatric diseases, including concerns and uncertainties about long-term drug toxicities (e.g., malignancy), as well as unpredictability of treatment response to future disease flares. Additionally, no prior study in RA or other pediatric diseases has quantified the impact of participants' characteristics or experiences on reported fears of disease and treatment.

Previous studies have explored topics of general importance in the experiences of children with JIA and their families, including the importance of understanding medications and their potential toxicities and their impact on everyday life (28,29). Other research has also discussed issues mentioned by participants in this study, including impacts of JIA on physical and psychosocial function, disruption of activities, striving for normality, social isolation, and uncertainty (42,43). Other studies have also demonstrated the importance of different sources for information and support, including rheumatologists, support groups, and trusted internet sources, all of which have a role in decision-making more broadly for JIA (44,45). This study helps illustrate the complex interplay of these and other themes in the decision-making process that patients and families commonly confront when managing JIA. In particular, the roles of guilt and regret have not been well described in research on decision-making in JIA. Among participants in our study, these feelings appeared more prominent among caregivers than patients. Guilt and regret have been reported in other pediatric research on health care decisions, including decision-making regarding end-of-life care for children and adolescents (46,47).

Our conceptual model of competing risks and fears raised by our participants, along with their goals of achieving normalcy and safety, echoes the traditional balance of benefits and risks that applies to medical decision-making. Many participants we interviewed were risk averse and stated preferences to avoid negative consequences through their decisions, whether those consequences related to JIA, medicines, or both. This risk aversion was reflected in associations between reported complications from JIA or treatment and higher levels of fear regarding future effects of disease activity or medicines, respectively. Not surprisingly, severe consequences such as irreversible joint damage from relapse after treatment withdrawal, or development of cancer, appeared particularly influential in participants' stated preferences, even if such consequences were rare or of uncertain connection to treatment (11). These concepts of loss aversion and overweighting of low-probability events have been well described (48).

In the face of medical uncertainty and an unpredictable future, trust in the treatment team, having access to trustworthy information, and having agency in the decision-making process were key moderating influences that helped participants make difficult decisions. Patients and parents alike valued relationships with trusted, caring clinicians to help them weigh these competing risks, relying on their clinical experience and knowledge to guide the decision-making process (49,50).

Our study had certain limitations. While we purposefully selected and analyzed responses from a diverse group of participants affected by JIA, participants may not have fully represented the greater population of individuals making decisions about stopping JIA medicines. For example, compared to nonparticipants, participants in our study may have been affected by more severe forms of JIA and may have been more motivated and proactive (e.g., in advocacy and reading primary medical literature). Furthermore, all disease and treatment history was self-reported. Finally, quantitative comparisons were limited by small sample sizes and their exploratory nature, thus warranting replication in larger, more representative samples.

In conclusion, decisions regarding the withdrawal of medicines for inactive JIA emerge from trade-offs between sets of competing risks and fears from the disease and the treatment, with the goal to attain and preserve a sense of normalcy and safety. Individuals weigh these risks differently based on past experiences, how they cope with uncertainty and unpredictability, and feelings of guilt and regret. Trusting relationships with the rheumatology care team and other sources of information and support inform, enable, and empower individuals to make these decisions. Future research should better quantify these considerations and priorities for decision-making in larger populations. When discussing the benefits and risks of JIA treatment

withdrawal, medical professionals may ask patients and families about what they fear most about the disease and treatment and whether they would feel more normal and safer by continuing medicines or by stopping them. Clinicians might also ask about what patients and families would regret more in scenarios of future outcomes (e.g., flares or treatment-associated toxicities) and what other information would help with decision-making. Greater awareness of the trade-offs that patients and caregivers face, along with their concerns and priorities, will help improve shared decision-making regarding JIA treatment withdrawal.

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

1. Adam V, St-Pierre Y, Fautrel B, Clarke AE, Duffy CM, Penrod JR. What is the impact of adolescent arthritis and rheumatism? Evidence from a national sample of Canadians. J Rheumatol 2005;32:354–61.
2. Peterson LS, Mason T, Nelson AM, O'Fallon WM, Gabriel SE. Psychosocial outcomes and health status of adults who have had juvenile rheumatoid arthritis: a controlled, population-based study. Arthritis Rheum 1997;40:2235–40.
3. Nordal E, Zak M, Aalto K, Berntson L, Fasth A, Herlin T, et al. Ongoing disease activity and changing categories in a long-term Nordic cohort study of juvenile idiopathic arthritis. Arthritis Rheum 2011;63:2809–18.
4. Bertilsson L, Andersson-Gare B, Fasth A, Petersson IF, Forsblad-D'elia H. Disease course, outcome, and predictors of outcome in a population-based juvenile chronic arthritis cohort followed for 17 years. J Rheumatol 2013;40:715–24.
5. Guzman J, Oen K, Tucker LB, Huber AM, Shiff N, Boire G, et al. The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort. Ann Rheum Dis 2015;74:1854–60.
6. Diak P, Siegel J, La Grenade L, Choi L, Lemery S, McMahon A. Tumor necrosis factor α blockers and malignancy in children: forty-eight cases reported to the Food and Drug Administration. Arthritis Rheum 2010;62:2517–24.
7. Bulatović M, Heijstek M, Verkaaik M, van Dijkhuizen EH, Armbrust W, Hoppenreijs EP, et al. High prevalence of methotrexate intolerance in juvenile idiopathic arthritis: development and validation of a methotrexate intolerance severity score. Arthritis Rheum 2011;63:2007–13.
8. Beukelman T, Xie F, Chen L, Baddley JW, Delzell E, Grijalva CG, et al. Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum 2012;64:2773–80.
9. Beukelman T, Xie F, Baddley JW, Chen L, Delzell E, Grijalva CG, et al. Incidence of selected opportunistic infections among children with juvenile idiopathic arthritis. Arthritis Rheum 2013;65:1384–9.
10. Beukelman T, Xie F, Baddley JW, Chen L, Mannion ML, Saag KG, et al. The risk of hospitalized infection following initiation of biologic agents versus methotrexate in the treatment of juvenile idiopathic arthritis. Arthritis Res Ther 2016;18:210.
11. Beukelman T, Xie F, Chen L, Horton DB, Lewis JD, Mamtani R, et al. Risk of malignancy associated with paediatric use of tumour necrosis factor inhibitors. Ann Rheum Dis 2018;77:1012–6.
12. Minden K, Niewerth M, Listing J, Mobius D, Thon A, Ganser G, et al. The economic burden of juvenile idiopathic arthritis-results from the German Paediatric Rheumatologic database. Clin Exp Rheumatol 2009;27:863–9.
13. Ungar WJ, Costa V, Hancock-Howard R, Feldman BM, Laxer RM. Cost-effectiveness of biologics in polyarticular-course juvenile idiopathic arthritis patients unresponsive to disease-modifying antirheumatic drugs. Arthritis Care Res (Hoboken) 2011;63:111–9.
14. Wallace CA, Giannini EH, Huang B, Itert L, Ruperto N, for the Childhood Arthritis and Rheumatology Research Alliance (CARRA), the Pediatric Rheumatology Collaborative Study Group (PRCSG), and the Paediatric Rheumatology International Trials Organisation (PRINTO). American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2011;63:929–36.
15. Morgan EM, Munro JE, Horonjeff J, Horgan B, Shea B, Feldman BM, et al. Establishing an updated core domain set for studies in juvenile idiopathic arthritis: a report from the OMERACT 2018 JIA workshop. J Rheumatol 2019;46:1006–13.
16. Knowlton N, Jiang K, Frank M, Aggarwal A, Wallace C, McKee R, et al. The meaning of clinical remission in polyarticular juvenile idiopathic arthritis: gene expression profiling in peripheral blood mononuclear cells identifies distinct disease states. Arthritis Rheum 2009; 60:892–900.
17. Rothmund F, Gerss J, Ruperto N, Däbritz J, Wittkowski H, Frosch M, et al. Validation of relapse risk biomarkers for routine use in patients with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2014;66:949–55.
18. Hinze CH, Foell D, Johnson AL, Spalding SJ, Gottlieb BS, Morris PW, et al. Serum S100A8/A9 and S100A12 levels in children with polyarticular forms of juvenile idiopathic arthritis: relationship to maintenance of clinically inactive disease during anti–tumor necrosis factor therapy and occurrence of disease flare after discontinuation of therapy. Arthritis Rheumatol 2019;71:451–9.
19. Horton DB, Onel KB, Beukelman T, Ringold S. Attitudes and approaches for withdrawing drugs for children with clinically inactive nonsystemic JIA: a survey of the Childhood Arthritis and Rheumatology Research Alliance. J Rheumatol 2017;44:352–60.
20. Halyabar O, Mehta J, Ringold S, Rumsey DG, Horton DB. Treatment withdrawal following remission in juvenile idiopathic arthritis: a systematic review of the literature. Paediatr Drugs 2019;21:469–92.
21. Lipstein EA, Brinkman WB, Sage J, Lannon CM, Morgan Dewitt E. Understanding treatment decision making in juvenile idiopathic arthritis: a qualitative assessment. Pediatr Rheumatol Online J 2013;11:34.

22. Gomez-Ramirez O, Gibbon M, Berard R, Jurencak R, Green J, Tucker L, et al. A recurring rollercoaster ride: a qualitative study of the emotional experiences of parents of children with juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2016;14:13.
23. Lipstein EA, Muething KA, Dodds CM, Britto MT. "I'm the one taking it": adolescent participation in chronic disease treatment decisions. J Adolesc Health 2013;53:253–9.
24. Markusse IM, Akdemir G, Huizinga TW, Allaart CF. Drug-free holiday in patients with rheumatoid arthritis: a qualitative study to explore patients' opinion. Clin Rheumatol 2014;33:1155–9.
25. Baker KF, Isaacs JD, Thompson B. "Living a normal life": a qualitative study of patients' views of medication withdrawal in rheumatoid arthritis. BMC Rheumatol 2019;3:2.
26. Wong IC, Asherson P, Bilbow A, Clifford S, Coghill D, DeSoysa R, et al. Cessation of attention deficit hyperactivity disorder drugs in the young (CADDY): a pharmacoepidemiological and qualitative study. Health Technol Assess 2009;13:1–120.
27. Chiu YP, Lee TY, Lin KL, Laadt VL. Adjusting to a seizure-free "new normal" life following discontinuation of antiepileptic drugs during adolescence. Epilepsy Behav 2014;33:54–8.
28. Tong A, Jones J, Craig JC, Singh-Grewal D. Children's experiences of living with juvenile idiopathic arthritis: a thematic synthesis of qualitative studies. Arthritis Care Res (Hoboken) 2012;64: 1392–404.
29. Guzman J, Gomez-Ramirez O, Jurencak R, Shiff NJ, Berard RA, Duffy CM, et al. What matters most for patients, parents, and clinicians in the course of juvenile idiopathic arthritis? A qualitative study. J Rheumatol 2014;41:2260–9.
30. Van Tuyl LH, Hewlett S, Sadlonova M, Davis B, Flurey C, Hoogland W, et al. The patient perspective on remission in rheumatoid arthritis: 'You've got limits, but you're back to being you again'. Ann Rheum Dis 2015;74:1004–10.
31. Pound P, Britten N, Morgan M, Yardley L, Pope C, Daker-White G, et al. Resisting medicines: a synthesis of qualitative studies of medicine taking. Soc Sci Med 2005;61:133–55.
32. SocioCultural Research Consultants. Dedoose, version 8.0.35: web application for managing, analyzing, and presenting qualitative and mixed method research data. 2018. URL: dedoose.com.
33. Cameron LD, Leventhal H. The self-regulation of health and illness behaviour. London: Psychology Press; 2003.
34. Toupin April K, Higgins J, Ehrmann Feldman D. Application of Rasch analysis to the parent adherence report questionnaire in juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2016;14:45.
35. April K, Feldman D, Zunzunegui M, Duffy C. Association between perceived treatment adherence and health-related quality of life in children with juvenile idiopathic arthritis: perspectives of both parents and children. Patient Prefer Adherence 2008;2:121–8.
36. Gidman W, Meacock R, Symmons D. The humanistic and economic burden of juvenile idiopathic arthritis in the era of biologic medication. Curr Rheumatol Rep 2015;17:31.
37. Grootens-Wiegers P, Hein IM, van den Broek JM, de Vries MC. Medical decision-making in children and adolescents: developmental and neuroscientific aspects. BMC Pediatr 2017;17:120.
38. Lipstein E, Dodds C, Lovell D, Denson L, Britto M. Making decisions about chronic disease treatment: a comparison of parents and their adolescent children. Health Expect 2016;19:716–26.
39. Donovan JL, Blake DR. Patient non-compliance: deviance or reasoned decision-making? Soc Sci Med 1992;34:507–13.
40. Brinkman WB, Sherman SN, Zmitrovich AR, Visscher MO, Crosby LE, Phelan KJ, et al. Parental angst making and revisiting decisions about treatment of attention-deficit/hyperactivity disorder. Pediatrics 2009;124:580–9.
41. Cuenca J, Glazebrook C, Kendall T, Hedderly T, Heyman I, Jackson G, et al. Perceptions of treatment for tics among young people with Tourette syndrome and their parents: a mixed methods study. BMC Psychiatry 2015;15:46.
42. Cartwright T, Fraser E, Edmunds S, Wilkinson N, Jacobs K. Journeys of adjustment: the experiences of adolescents living with juvenile idiopathic arthritis. Child Care Health Dev 2015;41:734–43.
43. Tong A, Jones J, Craig JC, Singh-Grewal D. Children's experiences of living with juvenile idiopathic arthritis: a thematic synthesis of qualitative studies. Arthritis Care Res (Hoboken) 2012;64:1392–404.
44. Condon C, O'Regan D, MacDermott E, Killeen O. Self-management needs of children with JIA in Ireland: a qualitative survey of families. Euro J Physiother 2017;19:237–42.
45. Cai RA, Beste D, Chaplin H, Varakliotis S, Suffield L, Josephs F, et al. Developing and evaluating JIApp: acceptability and usability of a smartphone app system to improve self-management in young people with juvenile idiopathic arthritis. JMIR Mhealth Uhealth 2017;5:e121.
46. Liu SM, Lin HR, Lu FL, Lee TY. Taiwanese parents' experience of making a "do not resuscitate" decision for their child in pediatric intensive care unit. Asian Nurs Res (Korean Soc Nurs Sci) 2014;8:29–35.
47. Himelstein B. Palliative care for infants, children, adolescents, and their families. J Palliative Med 2006;9:163–81.
48. Kahneman D, Tversky A. Prospect theory: an analysis of decision under risk. Econometrica 1979;47:263–91.
49. Konstantynowicz J, Marcinowicz L, Abramowicz P, Abramowicz M. What do children with chronic diseases and their parents think about pediatricians? A qualitative interview study. Matern Child Health J 2016;20:1745–52.
50. Anyfantakis D, Symvoulakis E. Medical decision and patient's preference: 'much ethics' and more trust always needed. Int J Med Sci 2011;8:351–2.

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Using Clinical Characteristics and Patient-Reported Outcome Measures to Categorize Systemic Lupus Erythematosus Subtypes

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Objective. The type 1 and type 2 systemic lupus erythematosus (SLE) categorization system was recently proposed to validate the patients' perspective of disease and to capture a more comprehensive spectrum of symptoms. The objective of this study was to characterize the clinical manifestations of SLE subtypes and to determine the correlation between the patient- and physician-reported measures used in the model.

Methods. This was a cross-sectional study of patients with SLE in a university clinic. Patients completed the Systemic Lupus Activity Questionnaire (SLAQ) and 2011 American College of Rheumatology fibromyalgia (FM) criteria. Active SLE was defined as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score ≥6, clinical SLEDAI score ≥4, or active lupus nephritis. We identified 4 groups: type 1 SLE (active SLE without FM), type 2 SLE (inactive SLE with FM), mixed SLE (active SLE with FM), and minimal SLE (inactive SLE without FM).

Results. In this cohort of 212 patients (92% female, mean age 45 years), 30% had type 1 SLE, 8% had type 2 SLE, 13% had mixed SLE, and 49% had minimal SLE. Regardless of SLE disease activity, patients with FM (21%), reported higher SLAQ scores, patient global assessment scores, and self-reported lupus flare that resulted in discordance between patient- and physician-reported measures.

Conclusion. Fatigue, widespread pain, sleep dysfunction, and mood disorders are common symptoms in SLE. Identifying these symptoms as type 2 SLE may be a method to improve patient communication and understanding. The level of type 2 SLE impacts patients' perception of disease and self-reported symptoms. The SLAQ may need to be reinterpreted based on the FM severity scale.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease characterized by diverse clinical manifestations that vary in intensity and severity (1). Along with symptoms directly related to inflammation, individuals with this condition commonly report symptoms of widespread pain, fatigue, cognitive dysfunction, and depression (2–5). Despite improved survival rates and short-term outcomes over the last 50 years (6), patients with SLE continue to have lower health care–related quality of life and increased rates of disability, largely driven by the symptoms of chronic pain, fatigue, cognitive dysfunction, and depression (7,8). Currently, the mechanisms underlying these features remain elusive; thus, they remain challenging to manage, complicate disease assessment, and potentially confound the conduct of clinical trials and interpretation of results.

While not included in the classification criteria for SLE, fatigue and generalized pain represent the most common symptoms reported by patients with SLE (5,9,10). Patients often describe these symptoms as the most bothersome features of their disease (11,12), and importantly, may not readily differentiate chronic pain and fatigue from inflammatory lupus manifestations such as nephritis or arthritis. The etiology of myalgia, fatigue, and related symptoms is often multifactorial and can be driven by both immunologic and nonimmunologic factors. These symptoms usually do not respond to conventional immunosuppression and can be difficult to quantify, monitor, and relate to disease activity. As a result, these symptoms may not receive adequate attention by physi-

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SIGNIFICANCE & INNOVATIONS

- Patient- and physician-reported measures can be used to categorize systemic lupus erythematosus (SLE) subtypes.
- Type 1 SLE symptoms include the classic inflammatory features of SLE, while type 2 SLE symptoms encompass fatigue, impaired sleep, widespread pain, mood disorders, and cognitive dysfunction.
- Patients with type 2 SLE symptoms report more symptoms and greater disease activity, which may differ from the physician's assessment. Implementing division of SLE into subtypes in clinical practice encourages the provider to address these important symptoms.

cians, contributing to the well-described discordance between patient and physician perceptions of disease activity and severity (13–15). This discordance in perception can hinder communication between patients and physicians, thereby impairing patient–physician relationships and contributing to poor treatment adherence and increased risk of lupus flares (16).

To incorporate patient symptomatology more fully into clinical assessment, validate patient perceptions about disease activity and severity, and close the gap between physician and patient concerns, Pisetsky et al (17) have recently proposed a novel conceptual model of SLE to categorize SLE manifestations. In this model, symptomatology can be divided into 2 main categories: type 1 and type 2. Type 1 SLE includes active inflammatory manifestations, such as nephritis, arthritis, serositis, and rash; these manifestations can respond to conventional immunosuppression. Type 1 symptoms can be assessed by measures such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Type 2 SLE symptoms include fatigue, widespread pain, cognitive dysfunction, sleep disturbance, and depression; these symptoms typically do not respond to conventional immunosuppression. Type 2 symptoms can be assessed by measures such as the 2016 American College of Rheumatology (ACR) fibromyalgia criteria, as well as other validated indices of fatigue or depression (18). The mixed SLE subtype includes features of both active type 1 and active type 2 SLE, while patients with inactive disease and no type 2 symptoms can be categorized as having minimal SLE.

The goal of this study was to determine, using patient- and physician-reported lupus disease activity measures in a tertiary care population of patients with SLE, the prevalence of each lupus subtype according to the type 1 and type 2 categorization system. Furthermore, this study examined the impact of type 2 SLE symptoms on patient-reported measures of disease activity for patients with and without active type 1 SLE. Additional analyses evaluating the correlation between patient and physician disease activity measures were conducted to understand the impact of type 2 symptoms on these assessments. Finally, we investigated the management of type 2 SLE symptoms in routine clinical care.

MATERIALS AND METHODS

This was a cross-sectional study of consecutive patients with SLE seen in the Duke University Lupus Clinic from January to May 2018. All patients met ACR 1997 or Systemic Lupus International Collaborating Clinics 2012 criteria for SLE (10,19). This study was determined by the Duke Health Institutional Review Board to be exempt (Pro00093208), because it was a quality improvement project to improve care of fatigue, depression, and fibromyalgia in the Duke Lupus Clinic.

At each clinic visit, patients completed a series of questionnaires: Systemic Lupus Activity Questionnaire (SLAQ) (20) and 2011 ACR fibromyalgia criteria (21), self-reported medication adherence, and self-reported emergency department and hospitalization visits. The SLAQ is a patient-reported survey of lupus-related symptoms derived from the Systemic Lupus Activity Measure (SLAM). SLAQ items are weighted and scored similarly to the SLAM, ranging from 0 to 33. The SLAQ also includes a 10-point patient global assessment and a self-assessment of lupus flare severity in the previous month. In this study, the SLAQ was modified to include 6 additional lupus-related items, including questions about sicca symptoms, anxiety, edema, hypertension, foamy urine/elevated urine protein, and dysuria. These items were added to evaluate for anxiety and sicca symptoms, to exclude urinary tract infections found in routine urinalysis, and to both capture and educate patients on symptoms related to lupus nephritis (i.e., hypertension, edema, elevated urine protein), but were not included in the SLAQ score. Patient-reported symptoms rated as "moderate" or "severe" on the SLAQ were considered to be present. Physician measures of disease activity collected at each visit included SLEDAI and physician global assessment of disease activity (22–25). Additional lupus laboratory measures, including anti–double stranded DNA (anti-dsDNA; measured using a multiplex, fluorescent bead assay, positive values >120 IU/ml), C3, C4, complete blood count, and urinalysis, were collected as part of routine clinical care. Demographics were limited to age and sex, due to the quality improvement nature of the study.

Active SLE was defined as a SLEDAI score ≥6, clinical SLEDAI score ≥4, or active lupus nephritis as defined by proteinuria >0.5 grams or glomerular hematuria >5 red blood cells or casts not due to other causes. For this study, fibromyalgia was studied as an example of type 2 symptoms and was determined using the 2011 ACR fibromyalgia diagnostic criteria. Fibromyalgia was considered present when the following criteria were met: 1) widespread pain score ≥7 and symptom severity score ≥5, or 2) widespread pain score ≥3 and symptom severity score ≥9 (21).

For the purpose of this analysis, we identified 4 groups of patients based on SLE activity and fibromyalgia criteria: type 1 SLE (active SLE without meeting fibromyalgia diagnostic criteria), type 2 SLE (inactive SLE meeting fibromyalgia diagnostic criteria), mixed SLE (active SLE meeting fibromyalgia diagnostic

criteria), and minimal SLE (inactive SLE without meeting fibromyalgia diagnostic criteria).

The clinic note of each patient in this study was reviewed to determine whether fibromyalgia symptoms were addressed during the visit and to determine the type of interventions recommended. For inclusion, interventions had to be specifically documented in the note to address symptoms of fibromyalgia, depression, fatigue, or chronic pain. In addition to assessing a recommendation of fibromyalgia counseling, the chart review also determined whether there was an escalation in immunosuppressant therapy at each visit, defined as an increase in a current medication dose or the addition of a new immunosuppressant medication.

In the statistical analysis, we compared demographics, patient-reported symptoms, and clinical characteristics, with differences estimated by Wilcoxon's rank sum test or Fisher's exact test. To evaluate the effect of active type 2 SLE on patient- and physician-reported measures, we made comparisons between those patients with inactive type 1 SLE (minimal SLE and type 2 SLE) and active type 1 SLE (type 1 SLE and mixed SLE). A stepwise linear regression analysis analyzed predictors of treatment for fibromyalgia. To determine the correlation between continuous patient- and physician-reported measures, we calculated Pearson's correlations stratified by SLE subtype. Correlations were defined as weak (r = 0–0.3), moderate (0.4–0.6), and strong (0.7–1.0) (31). All analyses were performed in SAS software, version 9.4.

RESULTS

The analysis included 212 patients with SLE (92% female, mean age 45 years). In this cohort, 30% had active SLE without meeting fibromyalgia diagnostic criteria (type 1 SLE), 8% had inactive SLE while meeting fibromyalgia diagnostic criteria (type 2 SLE), 13% had active SLE and met fibromyalgia diagnostic criteria (mixed SLE), and 49% had inactive SLE without meeting fibromyalgia diagnostic criteria (minimal SLE).

The frequency of patient-reported flares, severity of patient global assessment, SLAQ scores, and the number of modified SLAQ symptoms were all increased in patients with SLE with fibromyalgia (type 2 and mixed SLE) compared to patients without fibromyalgia (Table 1). Among patients with fibromyalgia, 81% of patients with type 2 SLE and 100% of patients with mixed SLE reported a flare in the previous month, compared to 63% of patients with type 1 SLE and 40% of patients with minimal SLE ($P < 0.0001$). When the analysis was limited to patients with active type 1 SLE (type 1 and mixed SLE patients), patients with fibromyalgia had higher patient global assessment and SLAQ scores. There was no difference in the number of all-cause emergency department/hospitalizations and self-reported medication compliance in patients with fibromyalgia, regardless of type 1 activity.

Physician assessment of clinical manifestations revealed few differences between patients with and without fibromyalgia

Table 1. Differences in patient- and physician-reported disease activity*

	Inactive type 1 SLE			Active type 1 SLE		
	Minimal SLE (n = 103)	Type 2 SLE (n = 17)	*P*	Type 1 SLE (n = 64)	Mixed SLE (n = 28)	*P*
Patient-reported SLE activity						
PtGA (0–10)	3 (1–5)	6 (5–8)	<0.0001	4 (2–6)	7 (5.5–8.5)	0.0002
SLAQ (0–44)	8 (4–13)	17 (15–22)	<0.0001	11 (7–13)	19 (13.5–25)	<0.0001
Patient-reported flare, no. (%)	36 (40)	13 (81)	0.003	38 (63)	26 (100)	0.0001
Emergency room/hospitalization, no. (%)	16 (16)	5 (29)	0.2	16 (28)	6 (25)	1
Correlation between patient-reported measures						
PtGA and SLAQ	0.6†	0.6‡	–	0.6†	0.3	–
Physician-reported SLE activity						
PhGA (0–3)	0 (0–0.25)	0 (0–0.5)	0.4	0.8 (0.5–1.0)	1 (1–1.5)	0.03
SELENA-SLEDAI	2 (0–2)	0 (0–2)	0.2	6 (6–10)	6 (4–8)	0.1
Correlation between physician-reported measures						
PhGA and SLEDAI	0.2	0.6§	–	0.3‡	0.4‡	–
Correlation between patient-reported and physician reported measures						
PtGA and PhGA	0.2‡	0	–	0.6†	0.3	–
PtGA and SLEDAI	−0.1	−0.02	–	0.03	0.3	–
SLAQ and PhGA	0.04	0.5	–	0.5†	0.4‡	–
SLAQ and SLEDAI	−0.1	0.3	–	0.06	0.2	–

* Values are the median (interquartile range) unless indicated otherwise. PhGA = physician global assessment; PtGA = patient global assessment; SELENA = Safety of Estrogens in Lupus Erythematosus National Assessment; SLAQ = Systemic Lupus Activity Questionnaire; SLE = systemic lupus erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.
† $P < 0.0001$.
‡ $P < 0.05$.
§ $P < 0.01$.

(Table 1). There was no significant difference in SLEDAI or physician global assessment scores. Additionally, frequencies of the clinical components of the SLEDAI, including inflammatory arthritis, rash, alopecia and mucosal ulcers and serositis, were similar between active type 1 SLE with and without fibromyalgia and inactive type 1 SLE with and without fibromyalgia (data not shown). There were serologic differences between groups. The key serologic differences between patients with type 1 SLE and mixed SLE were the higher frequency of anti-dsDNA positivity (54.7% versus 32.1%; $P = 0.07$) and low complement (32.8% versus 14.3%; $P = 0.08$) in type 1 SLE patients. Minimal SLE patients demonstrated a higher frequency of anti-dsDNA positivity at the time of the visit compared to type 2 SLE patients (30.1% versus 5.9%; $P = 0.04$).

As expected, patients with type 2 and mixed SLE reported a higher frequency of symptoms on the SLAQ that are common among patients with fibromyalgia, including muscle weakness, muscle pain, fatigue, forgetfulness, depression, headaches, numbness, and stomach pain (Table 2). However, these patients also reported a higher frequency of symptoms often considered attributable to SLE, including dry eyes, oral/nasal ulcers, shortness of breath, and chest pain. Swollen joints were most commonly reported in patients with mixed SLE (79%); interestingly, although patients with type 2 SLE by definition did not meet SLEDAI criteria for inflammatory arthritis, the frequency of swollen joints reported by patients with type 1 SLE and type 2 SLE was similar (44% and 47%, respectively).

According to documentation in the clinic note, type 2 symptoms were addressed at 33% of all patient visits. Counseling included exercise or physical therapy recommendations (46%), pharmacologic interventions (37%), advice on sleep hygiene (23%), referral to psychology or psychiatry (20%), or other diagnostic and therapeutic procedures (7%). In regression models, the frequency of counseling for fibromyalgia increased with increasing SLAQ scores (odds ratio [OR] 1.10 [95% confidence interval (95% CI) 1.03–1.16]) or for patients who self-reported a lupus flare of any severity (OR 2.64 [95% CI 1.08–6.49]). In contrast, fibromyalgia counseling decreased with increasing physician global assessment score (OR 0.23 [95% CI 0.10–0.55]).

Patient- and physician-reported measures of disease activity did not correlate well in patients with fibromyalgia (Table 1). Pearson's correlation coefficients between patient- and physician-reported measures of disease activity showed differences across the 4 groups. For patients with fibromyalgia, there was a poor correlation between patient and physician assessments of disease activity. In both type 2 and mixed SLE groups, there was no correlation between the physician-reported measures (physician global assessment and SLEDAI scores) with the patient-reported measures (patient global assessment and SLAQ). In contrast, both

Table 2. Differences in patient-reported symptoms by type 1 systemic lupus erythematosus (SLE) and fibromyalgia*

	Inactive type 1 SLE			Active type 1 SLE		
	Minimal SLE (n = 103)	Type 2 SLE (n = 17)	*P*	Type 1 SLE (n = 64)	Mixed SLE (n = 28)	*P*
Muscle pain	37 (37)	14 (82)	0.0009	23 (37)	22 (79)	0.0005
Muscle weakness	27 (27)	10 (59)	0.01	18 (29)	20 (71)	0.0002
Swollen joints	24 (24)	8 (47)	0.07	27 (44)	22 (79)	0.003
Stiff joints	42 (41)	10 (59)	0.2	35 (56)	24 (86)	0.008
Dry eyes	25 (25)	11 (65)	0.003	10 (16)	12 (43)	0.02
Oral/nasal ulcers	8 (8)	5 (29)	0.02	5 (8)	6 (21)	0.09
Alopecia	8 (8)	3 (18)	0.2	6 (10)	8 (29)	0.03
Rash after sun	8 (8)	3 (18)	0.2	6 (10)	5 (18)	0.3
Rash on cheeks	10 (10)	0 (0)	0.4	10 (16)	3 (11)	0.7
Other skin rash	9 (9)	3 (18)	0.4	12 (19)	6 (21)	0.8
Dark spots	7 (7)	1 (6)	1.0	5 (8)	2 (7)	1.0
Fatigue	43 (42)	15 (88)	0.0004	39 (64)	25 (89)	0.02
Swollen glands	5 (5)	1 (6)	1.0	5 (8)	7 (25)	0.04
Raynaud's phenomenon	24 (24)	3 (18)	0.8	19 (30)	14 (50)	0.1
Chest pain	7 (7)	4 (24)	0.05	8 (13)	11 (39)	0.01
Stomach pain	9 (9)	4 (24)	0.09	9 (15)	12 (43)	0.006
Shortness of breath	10 (10)	4 (24)	0.1	7 (11)	12 (43)	0.002
Depression	13 (13)	6 (35)	0.03	9 (15)	8 (29)	0.1
Forgetfulness	25 (25)	8 (47)	0.08	14 (23)	14 (50)	0.01
Anxiety	15 (15)	2 (12)	1.0	9 (15)	10 (36)	0.05
Numbness	8 (8)	8 (47)	0.0002	5 (8)	11 (39)	0.0008
Headaches	12 (12)	6 (35)	0.02	7 (11)	16 (57)	<0.0001
Stroke	1 (1)	1 (6)	0.3	1 (2)	0 (0)	1.0
Seizures	0 (0)	0 (0)	–	1 (2)	1 (4)	0.5
Edema	8 (8)	3 (18)	0.2	13 (22)	8 (29)	0.6
Hypertension	11 (11)	0 (0)	0.4	4 (6)	4 (14)	0.2
Foamy urine or elevated urine protein	5 (5)	1 (6)	1.0	4 (7)	4 (14)	0.3

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

patient- and physician-reported measures of disease activity performed well in type 1 SLE, with a positive correlation between the patient global assessment and the SLEDAI, physician global assessment, and SLAQ, as well as with the SLAQ and physician global assessment.

DISCUSSION

In the current study, we have used patient-reported outcomes and measures of lupus disease activity to assess patient symptoms according to a recently proposed categorization system for lupus (17). This system uses classically defined measures of disease activity, such as the SLEDAI, along with measures of symptoms such as the 2011 ACR fibromyalgia criteria to categorize patients as having type 1, type 2, mixed SLE, or minimal SLE. We examined the clinical manifestations reported in each subgroup. In this study of patients with SLE, those who met fibromyalgia criteria had higher SLAQ scores, greater self-reported lupus severity, and more frequent self-reported flares, and they more commonly reported a range of SLE-related symptoms, from fatigue to chest pain, compared to patients with SLE without fibromyalgia.

Our findings indicate that individuals with SLE consider the symptoms of fatigue, widespread pain, myalgia, and cognitive dysfunction as part of their lupus and not as separate entities. Attribution of these symptoms to SLE can be difficult because the underlying pathophysiology and the interplay between these symptoms is not completely understood. Although patient education is an important aspect of patient care, explaining the etiology of these symptoms to patients can be challenging. Our approach is to use a nomenclature and provide patient education in a manner that is congruent with the patients' lived experience (26). Thus, a categorization system based on types of SLE symptomatology can validate patients' concerns, reduce the tendency of providers to dismiss type 2 symptoms, and encourage providers to manage these symptoms more comprehensively. Together these approaches can enhance the therapeutic relationship.

In this study, the rate of emergency department visits and hospitalization did not differ between SLE groups. Patients with inactive and minimal SLE symptoms had high rates of hospitalization that were similar to those reported for patients with SLE nationally (27). While the reasons for emergency department visits and hospitalization were not collected in this study, possibly even when lupus activity is controlled, patients continue to have increased complications, including infection, cardiovascular disease, and/or chronic pain that may drive emergency department and hospital admissions. In our population, these visits do not appear to be due to differences in medication compliance, because the rate of self-reported medication compliance was similar across all groups. Alternatively, patients may seek care in emergency rooms for symptoms that may not reflect inflammatory disease activity. Similarly, physicians who are less experienced in the management of SLE may recommend hospitalization because of concerns about certain symptoms, even if the relationship to inflammation is uncertain.

Fibromyalgia symptoms, including fatigue, widespread pain, sleep disturbance, cognitive dysfunction and depression, are common in patients with SLE. The frequency of fibromyalgia in our study (i.e., the proportion of subjects manifesting type 2 SLE and mixed SLE) was similar to the reported frequency of fibromyalgia from many large American centers (i.e., approximately 20%) (28,29); the rates of fibromyalgia in SLE cohorts, however, vary more widely in other countries, ranging from 5% to 65% (30–32). The rate of fibromyalgia in SLE is significantly greater than the 2–6% rate reported in the general population (26,33,34) and is similar to a recent pooled meta-analysis in rheumatoid arthritis (35); the rate for lupus is also greater than that in other rheumatic diseases such as psoriatic arthritis or axial spondyloarthritis (36). The significantly higher rate of fibromyalgia in our SLE cohort compared to the general public suggests that type 2 SLE may be distinct from primary fibromyalgia and that the biology of SLE contributes to the development of fibromyalgia symptoms.

As expected, our study demonstrated increased rates of fatigue, arthralgia, myalgia, cognitive dysfunction, and waking unrefreshed in patients with SLE with fibromyalgia (type 2 and mixed SLE) compared to those patients without fibromyalgia (type 1 and minimal SLE); these symptoms are inherent in the diagnosis of fibromyalgia. Interestingly, in our study, patients with SLE with fibromyalgia also self-reported a greater frequency of symptoms that could be characterized as inflammatory or autoimmune in nature, including sicca, mucocutaneous ulcers, alopecia, chest pain, shortness of breath, numbness, and headache compared to patients without fibromyalgia. This increase in self-reported symptoms in patients with fibromyalgia suggests that these patients have heightened sensitivity to a variety of stimuli and exemplifies the challenge that the presence of fibromyalgia poses in the evaluation and management of SLE. Accordingly, we found discordance between the patients' assessment of disease activity (the SLAQ, patient-reported flares, and severity of patient global assessment) and the physician measures of activity (SLEDAI and physician global assessment) in patients with fibromyalgia.

Although not demonstrated in our study, the overreporting of inflammatory symptoms by patients with fibromyalgia could influence the physician's assessment of lupus disease activity as well as diagnosis of SLE in terms of scoring historical pleurisy, oral ulcers, alopecia, or sun sensitivity, for example. If recorded on a SLEDAI score by a physician, these symptoms could result in inappropriate scoring of lupus activity. In the clinical trial setting, scoring these symptoms as evidence of disease activity could allow patients with otherwise inactive disease to meet entry criteria into clinical trials; as a trial proceeds, reports of these symptoms could also be confused as evidence of a flare. In the setting of a clinical trial, occurrence of these symptoms could contribute to

negative results if these symptoms reflect heightened sensitivity or abnormal pain processing rather than ongoing SLE inflammation.

The reasons for the heightened sensitivity to physical symptoms and abnormal pain processing for patients with fibromyalgia remain unclear. In trying to understand the etiology of fibromyalgia, some investigators have suggested that this condition results from a maladaptive reaction to chronic illness, possibly in patients with a genetic predisposition exacerbated by environmental or social stressors (37,38). Other researchers propose that fibromyalgia may have a unique inflammatory or neuroinflammatory etiology based on heightened levels of substance P, interleukin (IL)-8, IL-6, and tumor necrosis factor, and based on the identification of unique gene signatures, including those associated with immune system regulation and with glutamine, purinergic, nociception, and mitochondrial domains (39–42). Further studies are needed, specifically in patients with SLE with fibromyalgia to better understand the underlying pathobiology in this subgroup.

Irrespective of the origin of the symptoms, current treatment recommendations for fibromyalgia in SLE are similar to those of primary fibromyalgia and include graded exercise, improvement in restorative sleep, cognitive and behavioral therapy for underlying mood disorders, and pharmacologic therapies directed at depression and neuropathic pain (43–46). Aerobic exercise has demonstrated safety and efficacy for alleviating fatigue and depression in patients with SLE (47–49). Nonetheless, our study suggests a need to improve the treatment of type 2 SLE symptoms in practice, since in this study, fewer than half of the patients with SLE with type 2 symptoms received specific treatment interventions (as documented in the medical record). Fibromyalgia counseling was increased in those with depression and self-reported lupus flare. The incorporation of the type 1/type 2 categorization system in patient education could reinforce the importance of these symptoms and their burden on patients in the minds of the physician, thus prompting the physician to address them more actively.

Our study demonstrates that the use of patient-reported outcomes in routine clinical practice can be successfully employed to capture patient-specific information and augment providers' diagnostic assessments. The clinical utility of patient-reported outcomes in rheumatic diseases has been well described in the literature, but not in SLE due to the wide discrepancy between patient and physician assessments of disease activity. Our current model uses both patient- and physician-reported measures to categorize lupus symptoms into 2 distinct but often overlapping groups. Castrejón et al developed RheuMetric, a physician checklist to evaluate rheumatologic-related symptoms using a scale for 3 variables: activity due to inflammation, symptoms due to damage, and symptoms related to distress (50). The RheuMetric system similarly integrates both patient- and physician-reported measures to quantitatively document these symptoms and aid in the diagnostic decision-making process for complex rheumatic diseases.

This pilot study has several limitations. Complete demographic and medication information was not available due to the quality improvement nature of the project. Active lupus was defined using the SLEDAI, a validated and widely used metric of SLE disease activity. However, the SLEDAI is limited in its sensitivity to small changes in disease activity and does not capture all manifestations of active lupus. Future studies using type 1 and 2 categorization could include the physician global assessment as a second assessment of lupus disease activity, which captures the physician's overall assessment of disease activity. Given the limitations of serologic assays and the uncertain relationship of SLE activity and serology results, we included the clinical SLEDAI and the presence of nephritis as additional criteria for type 1 activity to capture patients without serologic activity in terms of complement and anti-dsDNA. Another potential limitation of this study relates to the definition of type 2 SLE based on the 2011 ACR fibromyalgia criteria cutoff points. Because type 2 SLE may be clinically distinct from primary fibromyalgia, patients with SLE may exhibit meaningful fibromyalgia symptoms at different levels than those defined by the 2011 ACR criteria.

In the use of this categorization system in the real-world setting, all patients considered for type 1 or 2 SLE definitely must meet diagnostic criteria for SLE. Type 2 SLE should not be assigned to patients with fibromyalgia and a positive antinuclear antibody, with or without a few symptoms that would not otherwise diagnose SLE. Such overdiagnosis could lead to overtreatment with immunosuppressants and steroids. On the other hand, the type 1 and 2 nomenclature may be particularly helpful for clinicians who do not see large numbers of patients with SLE by assisting them in determining appropriate therapy. For example, with a good assessment tool, we envision primary care and emergency physicians better able to determine when a patient with SLE does and does not require steroids.

In summary, the findings of this study indicate the utility of a categorization system that incorporates patient-reported outcomes to encompass inflammatory and noninflammatory lupus symptoms in overall patient assessment. This model, while congruent with patients' perception and understanding of their disease symptoms, represents a departure from the traditional medical view of fatigue, chronic pain, unrefreshed sleep, and mood disorders in patients with SLE as separate or coincidental. The use of outcome measures incorporating the differing perceptions of patients and physicians could improve communication, trust, and connectedness between patients and physicians. Indeed, preliminary use of this categorization system in communication with patients in the Duke Lupus Clinic appears to be an effective way to partner with patients and explain why their type 2 symptoms are not being addressed with increased immunosuppression. Furthermore, narrowing the conceptual gap using a slightly altered nomenclature for fibromyalgia symptoms could lead to improved patient understanding and buy-in for nonimmunosuppressing therapy, potentially improving patient care and quality of life. Finally, using this model in clinical research and clinical trials could further our understanding of the pathophysiology of type 2 symptoms and lead to therapies that

target these symptoms specifically and thus improve outcomes for patients with SLE. Future studies are in progress to explore these issues and develop biomarkers for symptom categorization.

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. Rogers 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. Rogers, Eudy, Pisetsky, Clowse.

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Analysis and interpretation of data. Rogers, Eudy, Pisetsky, Criscione-Schreiber, Sun, Doss, Clowse.

REFERENCES

1. Lisnevskaia L, Murphy G, Isenberg D. Systemic lupus erythematosus. Lancet 2014;384:1878–88.
2. Ceccarelli F, Perricone C, Pirone C, Massaro L, Alessandri C, Mina C, et al. Cognitive dysfunction improves in systemic lupus erythematosus: results of a 10 years prospective study. PLoS One 2018;13:e0196103.
3. Kozora E, Ellison MC, West S. Depression, fatigue, and pain in systemic lupus erythematosus (SLE): relationship to the American College of Rheumatology SLE neuropsychological battery. Arthritis Rheum 2006;55:628–35.
4. Sutanto B, Singh-Grewal D, McNeil HP, O'Neill S, Craig JC, Jones J, et al. Experiences and perspectives of adults living with systemic lupus erythematosus: thematic synthesis of qualitative studies. Arthritis Care Res (Hoboken) 2013;65:1752–65.
5. Pettersson S, Lövgren M, Eriksson LE, Moberg C, Svenungsson E, Gunnarsson I, et al. An exploration of patient-reported symptoms in systemic lupus erythematosus and the relationship to health-related quality of life. Scand J Rheumatol 2012;41:383–90.
6. Tektonidou MG, Lewandowski LB, Hu J, Dasgupta A, Ward MM. Survival in adults and children with systemic lupus erythematosus: a systematic review and Bayesian meta-analysis of studies from 1950 to 2016. Ann Rheum Dis 2017;76:2009–16.
7. Baker K, Pope J. Employment and work disability in systemic lupus erythematosus: a systematic review. Rheumatology (Oxford) 2009;48:281–4.
8. Kuriya B, Gladman DD, Ibañez D, Urowitz MB. Quality of life over time in patients with systemic lupus erythematosus. Arthritis Rheum 2008;59:181–5.
9. Bruce IN, Mak VC, Hallett DC, Gladman DD, Urowitz MB. Factors associated with fatigue in patients with systemic lupus erythematosus. Ann Rheum Dis 1999;58:379–81.
10. Petri M, Orbai AM, Alarcõn GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.
11. Tench CM, McCurdie I, White PD, D'Cruz DP. The prevalence and associations of fatigue in systemic lupus erythematosus. Rheumatology (Oxford) 2000;39:1249–54.
12. Morgan C, Bland AR, Maker C, Dunnage J, Bruce IN. Individuals living with lupus: findings from the LUPUS UK Members Survey 2014. Lupus 2018;27:681–7.
13. Alarcón GS, McGwin G, Brooks K, Roseman JM, Fessler BJ, Sanchez ML, et al. Systemic lupus erythematosus in three ethnic groups. XI. Sources of discrepancy in perception of disease activity: a comparison of physician and patient visual analog scale scores. Arthritis Rheum 2002;47:408–13.
14. Neville C, Clarke AE, Joseph L, Belisle P, Ferland D, Fortin PR. Learning from discordance in patient and physician global assessments of systemic lupus erythematosus disease activity. J Rheumatol 2000;27:675–9.
15. Golder V, Ooi JY, Antony AS, Ko T, Morton S, Kandane-Rathnayake R, et al. Discordance of patient and physician health status concerns in systemic lupus erythematosus. Lupus 2018;27:501–6.
16. Ward MM, Sundaramurthy S, Lotstein D, Bush TM, Neuwelt CM, Street RL. Participatory patient-physician communication and morbidity in patients with systemic lupus erythematosus. Arthritis Rheum 2003;49:810–8.
17. Pisetsky DS, Clowse ME, Criscione-Schreiber LG, Rogers JL. A novel system to categorize the symptoms of systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2019;71:735–41.
18. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, et al. 2016 revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016;46:319–329.
19. Hochberg MC, for the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
20. Karlson EW, Daltroy LH, Rivest C, Ramsey-Goldman R, Wright EA, Partridge AJ, et al. Validation of a systemic lupus activity questionnaire (SLAQ) for population studies. Lupus 2003;12:280–6.
21. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010;62:600–10.
22. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288–91.
23. Petri M, Hellmann D, Hochberg M. Validity and reliability of lupus activity measures in the routine clinic setting. J Rheumatol 1992; 19:53–9.
24. Dancey C, Reidy J. Statistics without maths for psychology. Upper Saddle River (NJ): Prentice-Hall; 2004.
25. Nelson W, Katz P, Daly RP, Topf L, Connolly-Strong E, Reed M, et al. Lupus flare activity from the patient perspective [abstract]. Arthritis Rheumatol 2018;70 Suppl 10.
26. Jones GT, Atzeni F, Beasley M, Flüß E, Sarzi-Puttini P, Macfarlane GJ. The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. Arthritis Rheumatol 2015;67:568–75.
27. Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. Arthritis Rheum 2007;56:2092–4.
28. Middleton GD, Mcfarlin JE, Lipsky PE. The prevalence and clinical impact of fibromyalgia in systemic lupus erythematosus. Arthritis Rheum 1994;37:1181–8.
29. Wolfe F, Petri M, Alarcón GS, Goldman J, Chakravarty Ece F, Katz RS, et al. Fibromyalgia, systemic lupus erythematosus (SLE), and evaluation of SLE activity. J Rheumatol 2009;36:82–8.
30. Friedman AW, Tew MB, Ahn C, McGwin G, Fessler BJ, Bastian HM, et al. Systemic lupus erythematosus in three ethnic groups. XV: prevalence and correlates of fibromyalgia. Lupus 2003;12:274–9.
31. Neumann L, Buskila D. Epidemiology of fibromyalgia. Curr Pain Headache Rep 2003;7:362–8.
32. Valencia-Flores M, Cardiel MH, Santiago V, Resendiz M, Castaño VA, Negrete O, et al. Prevalence and factors associated with fibromyalgia in Mexican patients with systemic lupus erythematosus. Lupus 2004;13:4–10.

33. Vincent A, Lahr BD, Wolfe F, Clauw DJ, Whipple MO, Oh TH, et al. Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. Arthritis Care Res (Hoboken) 2013;65:786–92.
34. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19–28.
35. Duffield SJ, Miller N, Zhao S, Goodson NJ. Concomitant fibromyalgia complicating chronic inflammatory arthritis: a systematic review and meta-analysis. Rheumatology (Oxford) 2018;57:1453–60.
36. Haliloglu S, Carlioglu A, Akdeniz D, Karaaslan Y, Kosar A. Fibromyalgia in patients with other rheumatic diseases: prevalence and relationship with disease activity. Rheumatol Int 2014;34:1275–80.
37. Bradley LA. Pathophysiologic mechanisms of fibromyalgia and its related disorders. J Clin Psychiatry 2008;69 Suppl 2:6–13.
38. Wolfe F, Rasker JJ. The Symptom Intensity Scale, fibromyalgia, and the meaning of fibromyalgia-like symptoms. J Rheumatol 2006;33:2291–9.
39. Lukkahatai N, Majors B, Reddy S, Walitt B, Saligan LN. Gene expression profiles of fatigued fibromyalgia patients with different categories of pain and catastrophizing: a preliminary report. Nurs Outlook 2013;61:216–24.
40. Jones KD, Gelbart T, Whisenant TC, Waalen J, Mondala TS, Iklé DN, et al. Genome-wide expression profiling in the peripheral blood of patients with fibromyalgia. Clin Exp Rheumatol 2016;34:89–98.
41. Iacob E, Light AR, Donaldson GW, Okifuji A, Hughen RW, White AT, et al. Gene expression factor analysis to differentiate pathways linked to fibromyalgia, chronic fatigue syndrome, and depression in a diverse patient sample. Arthritis Care Res (Hoboken) 2016;68:132–40.
42. Mendieta D, Cruz-Aguilera DL, Barrera-Villalpando MI, Becerril-Villanueva E, Arreola R, Hernández-Ferreira E, et al. IL-8 and IL-6 primarily mediate the inflammatory response in fibromyalgia patients. J Neuroimmunol 2016;290:22–5.
43. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Flub E, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 2017;76:318–28.
44. Navarrete-Navarrete N, Peralta-Ramírez MI, Sabio-Sánchez JM, Coín MA, Robles-Ortega H, Hidalgo-Tenorio C, et al. Efficacy of cognitive behavioural therapy for the treatment of chronic stress in patients with lupus erythematosus: a randomized controlled trial. Psychother Psychosom 2010;79:107–15.
45. Conceição CT, Meinão IM, Bombana JA, Sato EI. Psychoanalytic psychotherapy improves quality of life, depression, anxiety and coping in patients with systemic lupus erythematosus: a controlled randomized clinical trial. Adv Rheumatol 2019;59:4.
46. Lillis TA, Tirone V, Gandhi N, Weinberg S, Nika A, Sequeira W, et al. Sleep disturbance and depression symptoms mediate the relationship between pain and cognitive dysfunction in lupus patients. Arthritis Care Res (Hoboken) 2019;71:406–12.
47. Abrahão M, Gomiero A, Peccin M, Grande A, Trevisani V. Cardiovascular training vs. resistance training for improving quality of life and physical function in patients with systemic lupus erythematosus: a randomized controlled trial. Scand J Rheumatol 2016;45:197–201.
48. Tench CM, McCarthy J, McCurdie I, White PD, D'Cruz DP. Fatigue in systemic lupus erythematosus: a randomized controlled trial of exercise. Rheumatology (Oxford) 2003;42:1050–4.
49. O'Dwyer T, Durcan L, Wilson F. Exercise and physical activity in systemic lupus erythematosus: a systematic review with meta-analyses. Semin Arthritis Rheum 2017;47:204–15.
50. Castrejón I, Chua JR, Pincus T. A RheuMetric physician checklist to quantitate levels of inflammation, damage and distress on 0–10 visual analogue scales. Clin Exp Rheumatol 2017;35 Suppl 107:21–25.

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High Burden of Premature Arteriosclerosis on Renal Biopsy Results in Incident Lupus Nephritis

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Objective. Cardiovascular disease (CVD) is accelerated in patients with systemic lupus erythematosus and lupus nephritis (LN). Despite the literature suggesting that renal arteriosclerosis predicts CVD in other glomerulonephritis diseases, arteriosclerosis grading and reporting might be particularly overlooked in LN biopsies. Our objective was to examine the burden of renal arteriosclerosis in LN and to assess whether arteriosclerosis is underreported in LN biopsies.

Methods. We identified all patients with LN undergoing kidney biopsy between 1994 and 2017 at an academic center. We interpreted LN biopsy reports to classify the Banff categories of absent, mild, moderate, or severe renal arteriosclerosis. The prevalence of renal arteriosclerosis was compared with the prevalence published for age-matched healthy peers, and predictors of arteriosclerosis were examined. We overread biopsies for Banff renal arteriosclerosis grading and compared to pathology reports.

Results. Among 189 incident patients with LN, renal arteriosclerosis prevalence was 2 decades earlier compared to their healthy peers, affecting 40% of patients ages 31–39 years with LN compared to 44% of healthy peers ages 50–59 years. A multivariable analysis showed a 3-fold higher odds of renal arteriosclerosis in patients ages ≥30 years with LN. LN chronicity on biopsy results predicted a 4-fold higher odds of renal arteriosclerosis. The overreads determined that 50% of standard LN biopsy reports missed reporting the presence or absence of renal arteriosclerosis.

Conclusion. Renal arteriosclerosis is accelerated by 2 decades in patients with LN compared to their healthy peers and is overlooked by pathologists in half of the routine biopsy reports. We propose incorporating Banff renal arteriosclerosis grading in all LN biopsy reports.

INTRODUCTION

Premature cardiovascular disease (CVD) in patients with systemic lupus erythematosus (SLE) has been recently attributed to the interplay between inflammatory and immune mechanisms of atherosclerosis (1,2). Further, lupus nephritis (LN) is an independent risk factor for CVD, conferring a 9-fold higher risk of CVD events compared to healthy peers (3) and a 6-fold higher risk compared to patients with SLE without LN (4).

Methods to identify and prevent CVD early in patients with LN have not been determined, aside from managing CVD risk factors such as hypertension, tobacco use, and hyperlipidemia. There is limited information on early indicators of CVD in patients with LN. Hence, health care teams cannot implement timely preventive strategies to reduce the CVD burden in patients with LN (1,3,4). Clinicians urgently need early predictors of CVD in patients with LN to prevent related morbidity and mortality.

The classification system of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) for LN primarily focuses on glomerular pathology and places no emphasis on standard or systematic grading of vascular lesions (5,6). Other renal pathology classification systems, such as the Banff classification system used in renal transplantation, apply quantitative assessment across all renal structures, including the vasculature (7). Therefore, nonglomerular biopsy findings, including renal arterial changes, may have been overlooked as a method to identify CVD risk in patients with LN (8). A few contradicting studies have evaluated the burden of renal arterial changes in LN (8–13), but only 2 studies examined the association between CVD events and renal arterial changes (9,10). Both studies found a poor association

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SIGNIFICANCE & INNOVATIONS

- Renal arteriosclerosis is accelerated and premature in patients with lupus nephritis (LN) by 2 decades in comparison with their healthy peers.
- Despite the high specificity of renal arteriosclerosis reporting in current biopsy reports, we found significant sensitivity gaps (>50%) in routine pathology reporting on renal arteriosclerosis in LN biopsy results.
- Our study underscores a need for universal use of systematic Banff renal arteriosclerosis grading criteria in all LN biopsy results, similar to transplant pathology reporting standards.
- Clinicians urgently need early predictors of cardiovascular disease (CVD) in patients with LN to prevent related morbidity and mortality, and renal arteriosclerosis on pathology reports could be an early predictor of CVD in patients with LN.

between graded renal arterial changes and CVD events (9,10). However, none of these LN studies used standard systematic grading for renal arterial changes, such as Banff criteria that are universally used to grade renal arteriosclerosis in all transplant and donor biopsy results (8–13).

Among patients with IgA nephropathy and renal transplant patients and donors, researchers use Banff scoring to grade renal arterial changes (14–16). They report that severe renal arteriosclerosis is an early predictor of CVD in both IgA nephropathy and transplant patients (14,16). Other studies report a similar correlation between renal arteriosclerosis and coronary atherosclerosis, suggesting that renal arteriosclerosis is an initial step associated with accelerated atherosclerosis and CVD (14,16,17).

We hypothesized that a similar correlation exists in patients with LN but is often missed due to the absence of systematic reporting of renal arterial changes. The underreporting of renal arteriosclerosis may explain contradicting results in prior LN studies, and systematic reporting could offer new methods to target CVD prevention.

In our current study, our objective was to examine the burden of renal arteriosclerosis in kidney biopsy reports of patients with LN and to compare the prevalence rates of renal arteriosclerosis in patients with LN to the prevalence in healthy kidney donors by age group. We also aimed to use systematic Banff criteria on a subsample of LN biopsy reports to assess whether arteriosclerosis and its severity are underreported in pathology reports. We hypothesized that renal arteriosclerosis burden would occur at a younger age in patients with LN, compared to healthy donors. We also hypothesized that arteriosclerosis is underreported on routine LN pathology reports, indicating a need for standard use of systematic Banff criteria to grade arteriosclerosis in all LN biopsy reports.

PATIENTS AND METHODS

Cohort. We identified all consecutive patients with LN who underwent native renal biopsy between 1994 and 2017 at the University of Wisconsin Hospital and Clinics. We abstracted data on patient and disease characteristics from a comprehensive renal biopsy database and electronic health records. We used the 1997 updated American College of Rheumatology and Systemic Lupus International Collaborating Clinics 2012 criteria to validate the SLE diagnoses (18,19). We included the first native LN biopsy reports for all validated patients with SLE in our cohort. We excluded subsequent pathology reports after incident LN diagnosis, patients with transplant kidneys, and those who did not meet SLE diagnostic criteria and the ISN/RPS 2004 classification for LN (6). The study was approved by the University of Wisconsin Human Subjects Committee with a waiver of informed consent (number 2016-1260).

Covariates: sociodemographics and comorbidity. Using electronic health record and database information, we recorded sociodemographic and comorbidity information at the time of biopsy. Patient and disease characteristics included age, sex, race, smoking status, and comorbidities. Hypertension, hyperlipidemia, and diabetes mellitus were assessed using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes, a problem list diagnosis, or medication use. CVD events before LN diagnosis were assessed according to American Heart Association guidelines (20–22). Chronic kidney disease stage was assessed using the glomerular filtration rate at the time of biopsy (23). A modified CVD risk count was calculated by summing 7 risk factors used in arteriosclerotic cardiovascular disease (ASCVD) scoring: age, sex, race, smoking history, hyperlipidemia (high total cholesterol or low high-density lipoprotein cholesterol), hypertension, and diabetes mellitus, plus chronic kidney disease stage ≥3 and previous CVD events (24). We categorized the modified ASCVD risk to be present for patients with >1 risk factor based on studies reporting CVD events in patients with >1 traditional CVD risk factor (25). Patients with 0 or 1 risk factor on a modified ASCVD count were categorized as having a negative ASCVD score.

Renal histopathology. Renal biopsy was performed for clinical indication (increase in serum creatinine, hematuria, and/or proteinuria). Fixed sections of kidney tissue were stained with hematoxylin and eosin, periodic acid–Schiff, and Masson's trichrome stain for pathologic analysis. Immunofluorescent staining was performed on frozen sections. Electron microscopic analysis was performed on ultrathin sections. Pathologic assessment of all kidney biopsy reports was performed by clinical renal pathologists according to ISN/RPS guidelines (6). Using a comprehensive database, we abstracted the following data from renal pathology reports: class of LN, the presence or absence of chronic lesions on

biopsy, and the degree of arteriosclerosis. We abstracted the LN class (I–VI), categorized as proliferative or nonproliferative, and LN chronicity (present/absent) according to ISN/RPS guidelines (6). Per the 2003 ISN/RPS guidelines, renal pathologists are required to report the number of glomeruli with active or chronic lesions, but reporting the chronicity index (scores) in all LN pathology reports is not mandatory (6). The LN chronicity index (scores) was not uniformly reported in all LN biopsy reports. Hence, consistent with the 2003 ISN/RPS guidelines, we defined LN chronicity as the presence of any chronic lesions on pathology reports, which were uniformly reported in all LN biopsy reports. The primary outcome of renal arteriosclerosis was graded using pathology reports, in which details were classified into Banff categories. Consistent with Banff, the renal arteriosclerosis biopsy report findings were categorized as none (0% luminal narrowing or not reported or no reporting on arteriosclerosis present/absent), mild (≤25% narrowing or reported as mild), moderate (26–50% narrowing or reported as moderate), and severe (>50% narrowing or reported as severe) (Table 1) (7).

Overread using Banff criteria. Next, a blinded study pathologist (YH) overread a 25% convenience sample (n = 43 biopsy reports). This sample was randomly selected for overread, including approximately 50% with and without reported renal arteriosclerosis with oversampling of recent biopsy reports (2014–2017), which could have improved with new standards in transplant biopsy grading. Light microscopy biopsy slides were analyzed to grade renal arteriosclerosis and other renal arterial changes, using the standard Banff criteria for grading renal arterial changes. According to the Banff criteria, renal arteriosclerosis was directly interpreted from the slides as none, mild (<25%), moderate (26–50%), and severe (>50%) luminal narrowing (7). For control comparison, we used the published rates of renal arteriosclerosis in kidney donors, graded using the standard Banff criteria and reported by age group (26).

Statistical analysis. Descriptive data were expressed as the mean ± SD (for normally distributed data) or median and range (for data that were not normally distributed). We compared the prevalence of arteriosclerosis present and moderate or severe renal arteriosclerosis between our cohort and published controls by age group using a chi-square test.

We used a chi-square test and univariable logistic regression models to examine the association between the presence of renal arteriosclerosis, testing 10-year and 15-year age groups, modified ASCVD count, LN proliferative class, LN chronicity, and 1-year, 2-year, and 5-year SLE duration before LN diagnosis periods. Based on the findings of the univariable analysis, we found a significant association between patients ages ≥30 years with LN and the presence of renal arteriosclerosis. Further, we noted an accelerated risk of arteriosclerosis in patients ages ≥30 years with LN in comparison with age-matched healthy donors. Therefore, for multivariable logistic regression models, we categorized patients with LN by age into 2 groups: age <30 years and ≥30 years. Further, SLE duration at the time of LN diagnosis was categorized in 2 periods: LN diagnosis within 2 years of SLE and LN diagnosis after 2 years of SLE for multivariable analysis. This decision was based on the recent studies emphasizing the accelerated risk of CVD or related arterial changes earlier, within the first 2 years of the SLE disease course (27,28). Variables with a *P* value less than 0.1 in univariable models and LN proliferative class were included in multivariable analyses. For patients with reports lacking information on the presence or absence of arteriosclerosis, we supplemented with available overread Banff grade classification. We used univariable and multivariable logistic regression to analyze associations between supplemented renal arteriosclerosis and covariables. We calculated kappa agreement and predictive values for establishing the diagnostic accuracy of biopsy reports in comparison with the overread Banff arteriosclerosis grade. Statistical software R, version 3.4.1, was used for the analysis (29).

RESULTS

Patient and disease characteristics. Patient and disease characteristics of the cohort are summarized in Table 2. A total of 189 patients with incident LN met the inclusion criteria for the study. The median patient age at the time of kidney biopsy was 25 years (range 2–79 years). Of the 189 patients, 78% were female, 73% were White, 17% were from other minority races, and 10% had missing race data. At the time of biopsy, 23% were ever smokers, and 34% had >1 risk factor of the modified ASCVD count. Regarding LN disease characteristics, 41% of patients were classified as proliferative, LN chronicity was present in 38%, and 49% of patients were diagnosed with LN within 2 years of SLE diagnosis. In biopsy reports, we found that 41% of patients with LN had renal arterial changes. In total, 31% had renal arteriosclerosis and 12% had hyaline arteriolosclerosis.

Table 1. Interpretations of biopsy-reported renal arteriosclerosis using the Banff scoring system

Grade	Banff criteria for renal arteriosclerosis scoring	Biopsy interpretation using the Banff categories
None	0% luminal narrowing	0% narrowing or reported as not present or not reported
Mild	<25% luminal narrowing	<25% narrowing or reported as mild
Moderate	26–50% luminal narrowing	26–50% narrowing or reported as moderate
Severe	>50% luminal narrowing	>50% narrowing or reported as severe

Table 2. Lupus nephritis cohort characteristics (n = 189)*

Characteristic	Value
Age, median (range) years	25 (2–79)
Female	148 (78)
Race	
White	138 (73)
African American	17 (9)
Asian/other	15 (8)
Missing	19 (10)
Smoker, ever	44 (23)
Modified ASCVD count, >1 risk factor	64 (34)
Lupus duration	
<2 years	93 (49)
≥2 years	44 (23)
Missing	52 (28)
LN class	
Proliferative	78 (41)
Nonproliferative	91 (48)
Missing LN class	20 (11)
LN chronicity present	72 (38)
Renal arteriosclerosis	
Mild	43 (24)
Moderate	13 (6)
Severe	2 (1)
Arteriolar hyalinosis present	23 (12)

* Values are the number (%) unless indicated otherwise. ASCVD = arteriosclerotic cardiovascular disease; LN = lupus nephritis.

Burden of renal arteriosclerosis by age group and published comparisons. We found that 40% of our patients with LN age ≥30 years had renal arteriosclerosis and >10% of patients had moderate-to-severe arteriosclerosis on biopsy reports. More strikingly, >50% of patients with LN age ≥30 years had renal arteriosclerosis when biopsy reports were overread using the standard Banff criteria to grade renal arteriosclerosis. We found that the prevalence of renal arteriosclerosis increased with age. Among the age group 60–69 years, the burden of moderate-to-severe arteriosclerosis (by routine pathology reports or supplemented with overread renal arteriosclerosis grade) was 1 in 3.

The onset of any arteriosclerosis in patients with LN was 2 decades earlier compared to the published prevalence in healthy kidney donors (Figure 1). Our LN cohort's prevalence of 41% of any renal arteriosclerosis at ages 30–39 years was comparable to healthy kidney donors ages 50–59 years (41% versus 44%; P = 0.9). Likewise, patients with LN ages 40–49 years had a comparable prevalence to controls age 60–69 years (52% versus 51%; P = 0.95). Moreover, the burden of moderately severe arteriosclerosis in patients with LN for the age group 60–69 years was 5-fold higher than reported in age-matched healthy donors (33% versus 6%) (Figure 2).

Predictors of renal arteriosclerosis. Using the full LN cohort, we found that patients with LN age ≥30 years (OR 6.9 [95% confidence interval (95% CI) 3.5–14]), and LN chronicity (OR 3.0 [95% CI 1.5–5.7]) were predictors of renal arteriosclerosis on univariable analysis. Modified ASCVD count and LN diagnosis within 2 years of SLE were kept in the model as possible predictors of renal arteriosclerosis (P < 0.1). In multivariable analyses,

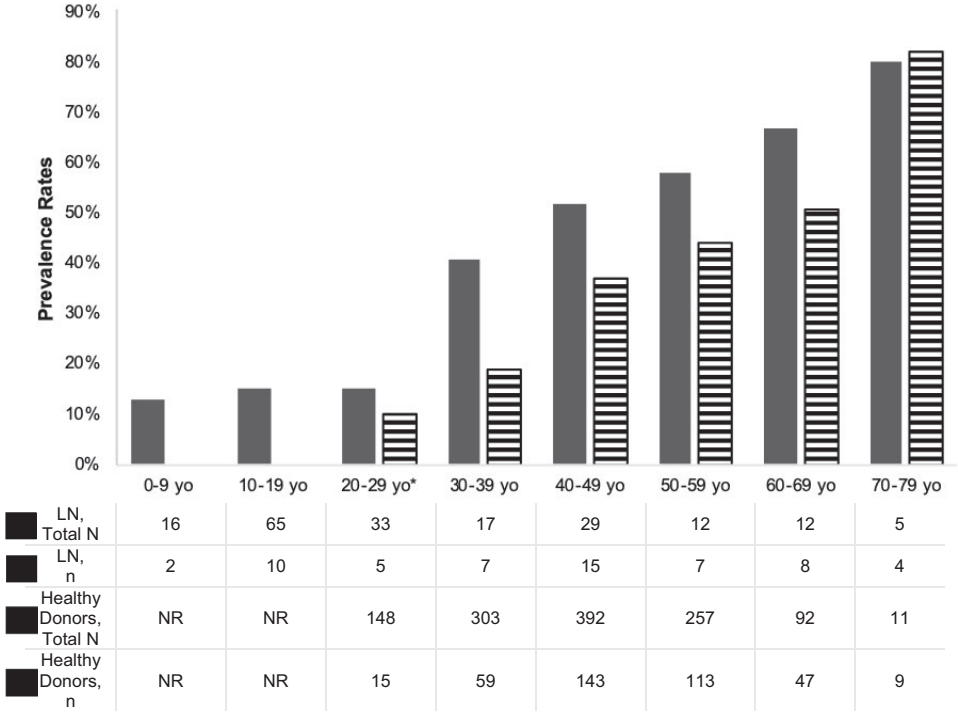

Figure 1. Prevalence of any renal arteriosclerosis by age group in patients with lupus nephritis (LN) on biopsy reports (black bars) compared to the published prevalence of any arteriosclerosis in healthy donors by age groups. NR = not reported; * = the comparator group started at age 18–29 years (yo) (26).

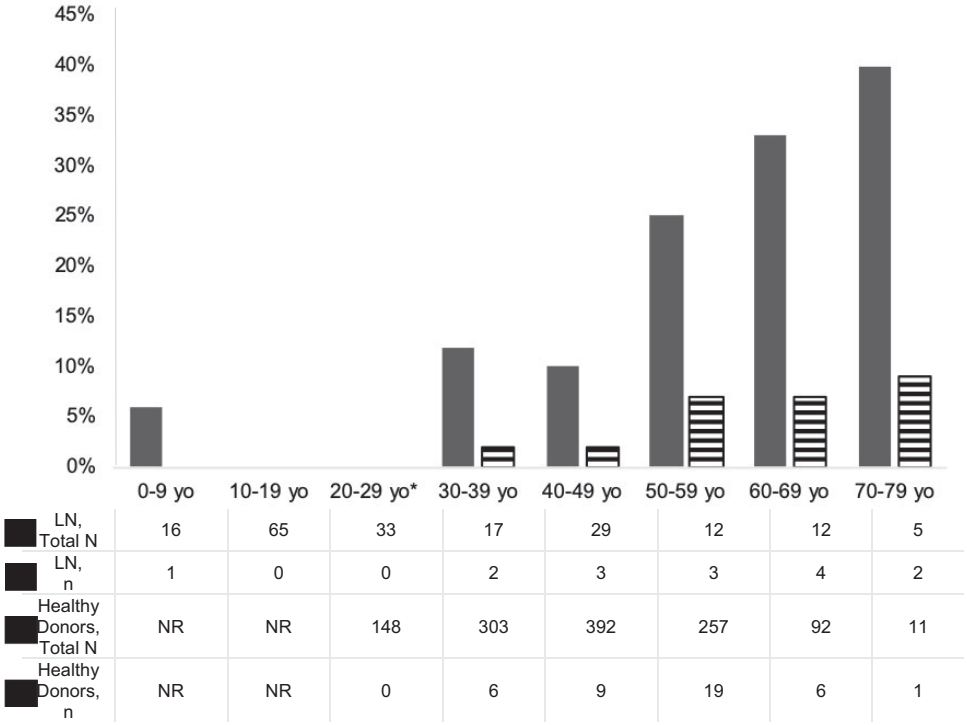

Figure 2. Prevalence of moderate-to-severe renal arteriosclerosis in patients with lupus nephritis (LN) on biopsy reports (black bars) compared to the published prevalence of moderate-to-severe arteriosclerosis in healthy donors by age group. NR = not reported; * = the comparator group started at age 18–29 years (yo) (26).

we found a 3-fold higher odds of renal arteriosclerosis in patients with LN ages ≥30 years versus patients with LN ages <30 years (odds ratio [OR] 3.3 [95% CI 1.3–9.1], P = 0.02). Further, LN chronicity predicted a 4-fold greater odds of renal arteriosclerosis (OR 4.0 [95% CI 1.5–11.6], P = 0.01) (Table 3). LN proliferative class, modified ASCVD count, and SLE disease duration were not associated with the presence of renal arteriosclerosis on the multivariable analysis. Using supplemented arteriosclerosis grades that added available information from the overread Banff analysis, we found a similar odds of an increase in the age group ≥30 years compared with patients with LN age <30 years (Table 3).

Diagnostic accuracy of reports compared to Banff renal arteriosclerosis overread. For a 25% convenience sample (n = 43 patients), we overread renal biopsy slides using the Banff criteria to grade renal arteriosclerosis. The sociodemographic and disease characteristics of the patients in our convenience sample included a mean age of 31 years at the time of LN diagnosis,

Table 3. Predictors of reported and supplemented renal arteriosclerosis in lupus nephritis patients*

	Reported renal arteriosclerosis		Supplemented renal arteriosclerosis†	
Variable	Unadjusted	Adjusted	Unadjusted	Adjusted
Age <30 years	Ref.	Ref.	Ref.	Ref.
Age ≥30 years	6.9 (3.5–14)‡	3.3 (1.3–9.1)‡	5.3 (2.8–10)‡	3.2 (1.3–8.1)‡
ASCVD count ≤1	Ref.	Ref.	Ref.	Ref.
ASCVD count >1	1.8 (0.9–3.7)	1.3 (0.5–3.4)	2.5 (1.3–4.7)	2.0 (0.8–4.9)
SLE duration<2 years	Ref.	Ref.	Ref.	Ref.
SLE duration ≥2 years	2.0 (0.9–4.5)	1.3 (0.5–3.7)	1.8 (0.8–3.6)	0.8 (0.3–2.1)
LN chronicity absent	Ref.	Ref.	Ref.	Ref.
LN chronicity present	3.0 (1.5–5.7)‡	4.0 (1.5–11.6)‡	2.7 (1.5–5)‡	2.9 (1.1–7.7)‡
LN nonproliferative	Ref.	Ref.	Ref.	Ref.
LN proliferative	1.2 (0.6–2.5)	0.9 (0.3–2.5)	1.0 (0.6–1.9)	0.8 (0.3–1.9)

* Values are the odds ratio (95% confidence interval). ASCVD = arteriosclerotic cardiovascular disease; LN = lupus nephritis; Ref. = reference; SLE = systemic lupus erythematosus.
† Supplemented renal arteriosclerosis: reported renal arteriosclerosis with none or not reported was supplemented with overread grades.
‡ Statistically significant.

25% African American patients, and 72% female patients, and 49% of patients had LN chronicity on their pathology reports (all $P > 0.05$). We found a poor agreement between overread grades using the Banff criteria for renal arteriosclerosis and the original pathology reports ($\kappa = 0.25$). More than 50% of the original pathology reports missed renal arteriosclerosis (negative predictive value 49%), and nearly 40% of all reports lacked details on arterial changes or arteriosclerosis, whereas the positive predictive value of reported renal arteriosclerosis was 80%. The specificity of the biopsy reports for reported renal arteriosclerosis in comparison to overread arteriosclerosis, using the Banff criteria, was 84%.

DISCUSSION

To our knowledge, this is one of the first studies examining the burden of renal arteriosclerosis in incident patients with LN using the standard Banff interpretation and comparing the prevalence of renal arteriosclerosis to healthy donors. Our study found that renal arteriosclerosis is common and accelerated in patients with LN compared to age-matched healthy controls. Specifically, we found that renal arteriosclerosis appeared 2 decades earlier in LN in comparison to healthy donors (26). We found that patients with LN who were ages ≥30 years and LN chronicity predicted the presence of renal arteriosclerosis. We also found that renal arteriosclerosis reporting and grading in LN biopsy reports were missed or overlooked in more than one-half of the routine pathology reports, because of the lack of standard guidelines on reporting renal arterial changes, although when the presence of renal arteriosclerosis was reported on routine pathology reports, it was an accurate report. Our study highlights the prevalence of renal arteriosclerosis in patients with LN along with gaps in current pathology reports, suggesting a need to standardize reporting and grading of renal arteriosclerosis in all LN biopsies by using universal Banff arteriosclerosis grading.

Historically, renal arteriosclerosis has been overlooked in patients with LN. The first report on renal involvement in SLE by Appel et al in 1978 (8) graded renal arteriosclerosis in all kidney biopsy reports, among many other factors, but few comments on this finding were mentioned. In their report, approximately 60% of the cohort ages 10–57 years who had any renal arteriosclerosis was similar to our rate of 51%. A few other studies have globally reviewed renal arterial changes. Two studies reported a <20% burden of arteriosclerosis, suggesting risk in "older hypertensive adults" with LN (11,12). Barber et al (9) and Huang et al (10) reported a 57% prevalence of any renal arterial changes in patients with LN at younger ages. None of these studies used systematic grading for renal arteriosclerosis, such as Banff criteria to report renal arteriosclerosis, which could explain such contradictory findings (8–13). Unlike prior reports, we found no correlation between renal arteriosclerosis and traditional risk factors, including hypertension, other ASCVD risk factors, or proliferative LN (8,9,11,13).

Renal arteriosclerosis is now established as an early predictor of incident CVD events in IgA nephropathy (14,15). In IgA nephropathy, Myllamäki et al (14,15) scored renal arteriosclerosis using the standard Banff criteria and found severe arteriosclerosis to be significantly associated with CVD events (37% severe arteriosclerosis with CVD events versus 17% severe arteriosclerosis without CVD events; $P < 0.05$). Similarly, in renal transplant recipients, antibody-mediated severe arteriosclerosis was a strong predictor of major cardiovascular events (OR 4.1 [95% CI 2.4–7.1], $P < 0.0001$) (16). These studies have emphasized a common mechanistic pathway leading to both renal arteriosclerosis and atherosclerosis. But a similar relationship in patients with LN, who are at a 9-fold higher risk of CVD compared to their healthy peers, is yet to be elucidated. Therefore, we plan to perform future studies to grade renal arteriosclerosis in all LN biopsy reports, using a systematic renal arteriosclerosis grading criterion, such as Banff, and examine its role as an early predictor of CVD events in patients with LN.

Despite the solid positive predictive value of routine pathology reporting on the presence of arteriosclerosis (80%), overall renal arteriosclerosis was underreported in the routine LN pathology reports. Unlike in transplant biopsy reports that routinely use the Banff criteria to grade renal arteriosclerosis, in LN biopsies, >50% of the pathology reports did not comment on the presence of renal arteriosclerosis. The current ISN/RPS guidelines for LN biopsies do not provide recommendations on the standard use of systematic criteria to grade renal arteriosclerosis, such as the Banff criteria, in all LN biopsy reports. Recently, the ISN/RPS committee acknowledged the importance of renal arterial changes in LN, yet a standard systematic grading system to grade renal arteriosclerosis in all LN biopsies is still lacking (5,6). The presence of renal arteriosclerosis could be used as an early predictor of CVD events that will help clinicians to implement timely CVD preventive strategies and reduce CVD-related morbidity and mortality in patients with LN. Therefore, our study underscores the need for a universal standard to systematically report renal arteriosclerosis as an actionable precursor of CVD in patients with LN. This study supports the standard use of systematic Banff criteria to grade renal arteriosclerosis in all LN biopsies and calls for future prospective studies to explore the role of arteriosclerosis as an early predictor of CVD in patients with LN.

Despite the strengths of this study, including the inclusion of a validated incident LN cohort and using the systematic Banff criteria for renal arteriosclerosis grading, we also acknowledge a few limitations. First, our midwestern center had 73% White patients and may not fully represent the LN population in the US. Likewise, renal biopsies were not a standard procedure in all patients with LN. For example, our cohort may be missing patients with LN who received empiric treatment for LN without a biopsy. However, we believe that this limitation reflects real-life practice. Unlike prior reports, we found no correlation between renal arteriosclerosis and hypertension, >1 ASCVD risk factor, or proliferative LN, likely due to sample size limitations. Moreover, in

the absence of standard guidelines for reporting arteriosclerosis in LN biopsies, nearly 50% of biopsy reports did not comment on the presence or absence of arteriosclerosis. Therefore, our prevalence estimates for renal arteriosclerosis are conservative and might underreport the true burden of renal arteriosclerosis in patients with LN. We also acknowledge that the published data on the prevalence of renal arteriosclerosis in healthy donors could underrepresent the true prevalence of renal arteriosclerosis in the healthy population. Further, because renal arteriosclerosis grading in LN biopsies and healthy donors was performed by different pathologists, there could have been an interobserver bias in renal arteriosclerosis grading. We attempted to overcome the limitation that renal arteriosclerosis is underreported in LN biopsy reports by overreading 25% of the LN biopsy reports, and applying overread arteriosclerosis grades, using standard Banff criteria, when routine pathology reports lacked details on the presence or absence of renal arteriosclerosis. In supplemented regression models, results were unchanged, and we again reported a good association between patients ages ≥30 years with LN and the presence of LN chronicity, and the presence of renal arteriosclerosis (Table 3). While overreading was not feasible in this study, in future studies we plan to overread all biopsy reports to grade renal arteriosclerosis, using the standard Banff criteria, and to collaborate with other diverse LN centers to examine the association between Banff renal arteriosclerosis grades and CVD events in patients with LN.

To conclude, we found that renal arteriosclerosis appeared in patients with LN 2 decades before their healthy peers. Despite the high specificity of renal arteriosclerosis in current biopsy reports, we found significant sensitivity gaps (>50%) in routine pathology reporting on renal arteriosclerosis in LN biopsy reports. Hence, our study underscores a need for universal use of systematic Banff renal arteriosclerosis grading criteria in all LN biopsies, similar to transplant pathology reporting standards.

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. Garg 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. Garg, Bartels, Hansen, Panzer.

Acquisition of data. Garg, Bartels, Hansen, Zhong, Huang, Semanik, Panzer.

Analysis and interpretation of data. Garg, Bartels, Hansen, Smith, Panzer.

REFERENCES

1. Salmon JE, Roman MJ. Accelerated atherosclerosis in systemic lupus erythematosus: implications for patient management. Curr Opin Rheumatol 2001;13:341–4.
2. Abusamieh M, Ash J. Atherosclerosis and systemic lupus erythematosus. Cardiol Rev 2004;12:267–75.
3. Hermansen ML, Lindhardsen J, Torp-Pedersen C, Faurschou M, Jacobsen S. The risk of cardiovascular morbidity and cardiovascular mortality in systemic lupus erythematosus and lupus nephritis: a Danish nationwide population-based cohort study. Rheumatology (Oxford) 2017;56:709–15.
4. Garg S, Bao G, Niyibizi M, Drenkard C, Lim SS. Differences between early and late cardiovascular disease in a population-based cohort of systemic lupus erythematosus patients [abstract]. Arthritis Rheumatol 2016;68 Suppl 10.
5. Bajema IM, Wilhelmus S, Alpers CE, Bruijn JA, Colvin RB, Cook HT, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney Int 2018;93:789–96.
6. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 2004;65:521–30.
7. Liapis H, Gaut JP, Klein C, Bagnasco S, Kraus E, Farris AB III, et al. Banff histopathological consensus criteria for preimplantation kidney biopsies. Am J Transplant 2017;17:140–50.
8. Appel GB, Silva FG, Pirani CL, Meltzer JI, Estes D. Renal involvement in systemic lupus erythematosus (SLE): a study of 56 patients emphasizing histologic classification. Medicine (Baltimore) 1978;57:371–410.
9. Barber C, Herzenberg A, Aghdassi E, Su J, Lou W, Qian G, et al. Evaluation of clinical outcomes and renal vascular pathology among patients with lupus. Clin J Am Soc Nephrol 2012;7:757–64.
10. Huang J, Han SS, Qin DD, Wu LH, Song Y, Yu F, et al. Renal interstitial arteriosclerotic lesions in lupus nephritis patients: a cohort study from China. PLoS One 2015;10:e0141547.
11. Banfi G, Bertani T, Boeri V, Faraggiana T, Mazzucco G, Monga G, et al. Renal vascular lesions as a marker of poor prognosis in patients with lupus nephritis. Gruppo Italiano per lo Studio della Nefrite Lupica (GISNEL). Am J Kidney Dis 1991;18:240–8.
12. Descombes E, Droz D, Drouet L, Grunfeld JP, Lesavre P. Renal vascular lesions in lupus nephritis. Medicine (Baltimore) 1997;76: 355–68.
13. Grishman E, Venkataseshan VS. Vascular lesions in lupus nephritis. Mod Pathol 1988;1:235–41.
14. Myllamäki J, Syrjanen J, Helin H, Pasternack A, Kattainen A, Mustonen J. Vascular diseases and their risk factors in IgA nephropathy. Nephrol Dial Transplant 2006;21:1876–82.
15. Myllamäki J, Honkanen T, Syrjanen J, Helin H, Rantala I, Pasternack A, et al. Uric acid correlates with the severity of histopathological parameters in IgA nephropathy. Nephrol Dial Transplant 2005;20:89–95.
16. Loupy A, Vernerey D, Viglietti D, Aubert O, Duong Van Huyen JP, Empana JP, et al. Determinants and outcomes of accelerated arteriosclerosis: major impact of circulating antibodies. Circ Res 2015;117:470–82.
17. Tracy RE. Histologic characteristics of coronary artery in relation to the renovasculopathies of hypertension. Ann Diagn Pathol 1998;2:159–66.
18. Hochberg MC, for the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
19. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.
20. Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, Gardin JM, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

(Committee on Management of Patients with Chronic Stable Angina). Circulation 1999;99:2829–48.

21. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:2064–89.
22. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary. Vasc Med 2017;22:NP1–43.
23. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro III AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
24. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285–350.
25. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling Jr JW, Garcia FA, et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. JAMA 2016;316:1997–2007.
26. Rule AD, Amer H, Cornell LD, Taler SJ, Cosio FG, Kremers WK, et al. The association between age and nephrosclerosis on renal biopsy among healthy adults. Ann Intern Med 2010;152:561–7.
27. Bartels CM, Buhr KA, Goldberg JW, Bell CL, Visekruna M, Nekkanti S, et al. Mortality and cardiovascular burden of systemic lupus erythematosus in a US population-based cohort. J Rheumatol 2014;41:680–7.
28. Urowitz MB, Gladman DD, Anderson NM, Su J, Romero-Diaz J, Bae SC, et al. Cardiovascular events prior to or early after diagnosis of systemic lupus erythematosus in the systemic lupus international collaborating clinics cohort. Lupus Sci Med 2016;3:e000143.
29. R: a language and environment for statistical computing. Vienna (Austria): R Foundation for Statistical Computing; 2017.

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Association Between Specimen Length and Number of Sections and Diagnostic Yield of Temporal Artery Biopsy for Giant Cell Arteritis

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Objective. To investigate the association between specimen length and number of sections evaluated and the diagnostic yield of temporal artery biopsy (TAB) for giant cell arteritis (GCA).

Methods. A pathologist reviewed all TABs performed for suspected GCA between January 1991 and December 2012. The blocks of all the inadequate and negative biopsy specimens were recut, and further slides at deeper levels were stained with hematoxylin and eosin in order to avoid missing inflammatory changes.

Results. In total, findings from 662 TABs were included in the study (71% female; mean age 73.2 years). A total of 427 TAB specimens (65%) were classified as negative, and 235 (35%) were classified as positive for GCA. Compared to those with negative TAB results, patients with positive TAB results were older and more frequently female. There was no difference in postfixation TAB specimen length between TAB specimens negative and positive for GCA (mean 6.5 mm versus 6.9 mm; $P = 0.068$). Cuts of additional biopsy sections revealed inflammation at deeper levels in 26 of 408 TAB specimens (6.4%) originally reported as uninflamed. The inflamed section was the second in 14 TAB specimens, the third in 9 specimens, and the fourth in 3 specimens. Piecewise logistic regression identified 5 mm as the TAB specimen length change point for diagnostic sensitivity. Compared to a TAB specimen length of <5 mm, the age- and sex-adjusted odds ratio for positive TAB results in samples ≥5 mm long was 1.5 (95% confidence interval 1.0–2.0), $P = 0.032$.

Conclusion. A postfixation TAB specimen length of at least 5 mm should be sufficient to make a histologic diagnosis of GCA. In order not to miss inflammatory changes, at least 3 further sections at deeper levels should be evaluated in all negative TAB specimens.

INTRODUCTION

Giant cell arteritis (GCA) is the most common vasculitis in Western countries in individuals >50 years of age. It mainly involves the large and medium-sized arteries and may produce a wide spectrum of clinical symptoms. Temporal artery biopsy (TAB) showing transmural inflammation (TMI) is considered the gold standard for the diagnosis of GCA (1,2). However, a negative TAB result does not rule out GCA, and a diagnosis of biopsy-negative GCA has been reported in up to 40% of patients (3). Furthermore, inflammation that is more limited and restricted to the adventitial or periadventitial tissue without medial involvement may also be associated with GCA (4–6). The sensitivity of TAB varies depending on the prevalence of GCA in the evaluated population, the clinical threshold for considering the procedure, and the clinical phenotype of GCA (large-vessel GCA versus cranial GCA) (7). The diagnostic sensitivity of TAB can be affected by the discontinuous character of the histopathologic changes, with skip lesions reported in 0–28% of patients with GCA, by the bilaterality of the biopsy procedure, by the length of specimens, and by the number of sections evaluated (3,8–11). The optimal postfixation biopsy length associated with increased diagnostic yield varies between studies from >0.5 cm to ≥1.5 cm (12–15). To date, only a few studies have investigated the presence of skip lesions in TAB specimens from patients with GCA and the number of sections that need to be evaluated in order not to miss these skip lesions.

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SIGNIFICANCE & INNOVATIONS

- Temporal artery biopsy (TAB) specimen length is potentially less important when patients are accurately selected and the TAB specimen is carefully examined.
- A postfixation TAB specimen length of 5 mm should be sufficient to make a diagnosis of giant cell arteritis.
- In order not to miss inflammatory changes, 3 further sections should be evaluated in all negative TAB specimens.

Recently, European League Against Rheumatism recommendations for the management of large vessel vasculitis suggested a biopsy specimen length of at least 1 cm, which corresponds to a postfixation length of at least 0.7 cm (16). The length of the TAB specimen seems crucial to maximize its diagnostic performance, but the optimal TAB specimen length and the optimal number of sections that need to be evaluated in order to avoid missing skip lesions are still undefined. The aim of the current study was to investigate the association between specimen length and number of sections evaluated and the diagnostic yield of TAB for GCA.

PATIENTS AND METHODS

Patients and pathologic assessment. Using a computerized pathology laboratory's register, which keeps a record of all TABs performed at our institution, we identified all consecutive patients with suspected GCA who underwent TAB from January 1991 to December 2012. Santa Maria Nuova Hospital is the only referral center for a population of 519,480 people living in the Reggio Emilia area. All patients referred by medical practitioners and community-based specialists for suspected GCA are usually assessed in the Rheumatology Department at Reggio Emilia Hospital within 24 hours, while TAB is routinely performed within 5 days of the first referral in all patients for whom the clinical suspicion of GCA is confirmed. TAB procedures in Reggio Emilia are detailed elsewhere (5,6). The same protocol for histologic evaluation of TAB findings was followed throughout the entire study period. The biopsy specimens were transversally sectioned into pieces of 3–4 mm in length, fixed in formalin, and embedded in paraffin. Technicians were instructed to embed the TAB specimen transversally. Sections 4 μm thick were cut from paraffin blocks and stained with hematoxylin and eosin. The selected TAB reports were printed out, and 2 researchers (FM and GT) reviewed them. The abstracted information included sex, patient's age at biopsy, and postfixation TAB specimen length. All the biopsy findings were reviewed by a single pathologist (AC), who had no access to the clinical data. According to a recent article by our group, TAB findings were classified into 4 categories: 1) inadequate, when the biopsy did not sample the muscular artery; 2) uninflamed, when the temporal artery was devoid of inflammation; 3) periadventitial and/or adventitial inflammation (PA/AI), when inflammation was limited to small PA vessels devoid of muscular coat and/or to the adventitia without extension to the media; and 4) TMI, when the temporal artery showed TMI with external elastic lamina disruption and extension of the inflammation to the media (5). The blocks of all the inadequate and uninflamed biopsy specimens were retrieved from the pathologic archive, and additional slides at deeper levels were cut and stained with hematoxylin and eosin in order to avoid missing arterial tissue or skip lesions. Additional slides at deeper levels were cut in all TAB specimens showing PA/AI in order to avoid missing TMI.

For the purpose of the current study, uninflamed TAB specimens and TAB specimens showing PA/AI were considered negative for GCA, while TAB specimens showing TMI were considered positive for GCA. The study was approved by the Reggio Emilia Provincial Ethics Committee.

Statistical analysis. Continuous data were represented as mean ± SD or median and interquartile range (IQR), and categorical variables were represented as absolute frequencies and percentages. A Kolmogorov-Smirnov test was used to assess whether data were normally distributed. Continuous variables were compared using Student's *t* test, and categorical variables by chi-square test. Receiver operating characteristic (ROC) analysis was used to identify the minimum arterial specimen length associated with the highest sensitivity and specificity for a TAB specimen positive for GCA. To identify a potential change point in the risk of obtaining a TAB specimen positive for GCA, we used the piecewise linear approach suggested by Mahr et al (13). Univariate and multivariate logistic regression models were used to evaluate potential predictors of obtaining a positive TAB result. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were computed for each predictor in the univariate analysis and in the multivariate model using the entry method. All tests were 2-sided, and *P* values less than 0.05 were considered significant. Statistical analysis was performed using SPSS, version 22.0.

RESULTS

A total of 694 TABs were performed in the study period and subsequently reviewed. All patients underwent unilateral TAB. In total, 32 of 694 TAB findings (4.6%) were classified as inadequate and were excluded from the analysis. The remaining 662 TAB findings were classified as adequate and represent the object of this study. Table 1 shows demographic and biopsy characteristics of included patients and comparisons between patients with positive and those with negative TAB results for GCA. Mean ± SD age at TAB was 73.2 ± 8.8 years; 470 of 662 (71%) were female. The mean ± SD postfixation TAB specimen length was 6.6 ± 4.4 mm (median [IQR] 5 [3–9 mm]; range 1–40 mm), and the median (IQR) number of sections evaluated was 3 (1–4); range 1–33. The distribution of the TAB specimen lengths is shown in Figure 1.

Table 1. Demographic and biopsy characteristics of all patients and comparisons between patients with positive and those with negative temporal artery biopsy (TAB) findings*

Variables	All TAB (n = 662)	Positive TAB (n = 235)	Negative TAB (n = 427)	*P*
Age, years	73.2 ± 8.8	74.4 ± 7.3	72.5 ± 9.5	0.031
Female, no. (%)	470 (71)	187 (80)	283 (66)	<0.0001
Postfixation length of specimen, mm	6.6 ± 4.4	6.9 ± 4.2	6.5 ± 4.5	0.068
No. of sections evaluated, median (IQR)	3 (1–4)	1 (1–3)	4 (3–5)	<0.0001

* Values are the mean ± SD unless indicated otherwise. IQR = interquartile range.

In total, 427 (65%) adequate TAB findings were negative for GCA (382 uninflamed and 45 PA/AI), while the remaining 235 (35%) were positive (TMI). Compared to those with a negative TAB result, patients with positive TAB findings were older ($P = 0.031$) and more frequently female ($P < 0.0001$). There was no difference in postfixation TAB specimen length ($P = 0.068$), but positive TAB specimens had a lower number of sections evaluated compared with negative TABs ($P < 0.0001$).

There was no difference in the mean TAB specimen length between PA/AI and uninflamed TAB specimens (mean ± SD length 7.6 ± 6.4 mm versus 6.4 ± 4.3 mm; $P = 0.207$) and between PA/AI and TMI (mean ± SD length 7.6 ± 6.4 mm versus 6.9 ± 4.2 mm; $P = 0.804$).

Cuts of additional biopsy sections revealed TMI at deeper levels only in 3 of 430 (0.7%) TAB specimens originally reported as negative for GCA. However, PA/AI without extension to the media was found at deeper levels in 23 of 408 (5.6%) TAB specimens originally reported as uninflamed. Therefore, inflamed sections (TMI or PA/AI) were found after cuts of additional biopsy sections at deeper levels in 26 of 408 (6.4%) TAB specimens originally reported as uninflamed. The inflamed section was the second in 14 TAB specimens, the third in 9 specimens, and the fourth in 3 specimens. Negative sections were found in 23 of 45 cases of PA/AI (51%), and in 3 of 235 (1%) cases of TMI.

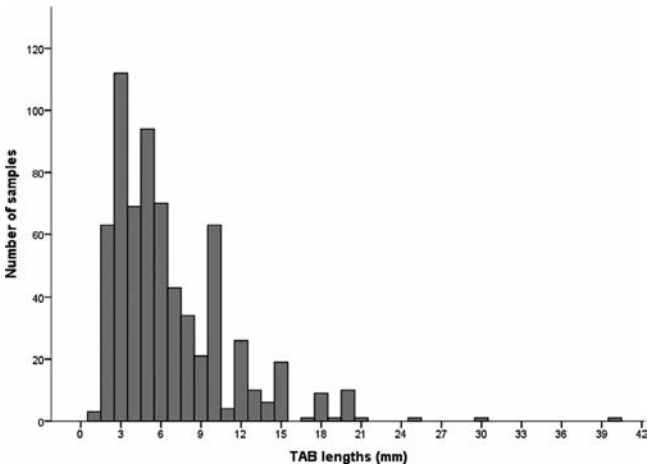

Figure 1. Distribution of temporal artery biopsy (TAB) specimen lengths.

ROC analysis identified a postfixation specimen length of at least 5 mm as the cutoff with the highest predictive value for a positive TAB result (area under the ROC curve 0.543), and piecewise logistic regression confirmed 5 mm as the TAB specimen length change point for diagnostic sensitivity (13). Table 2 shows the predictive variables of obtaining a positive TAB result. At univariate analysis, age (OR 1.025 [95% CI 1.006–1.045]), female sex (OR 1.982 [95% CI 1.362–2.885]), and TAB specimen length >5 mm (OR 1.397 [95% CI 1.000–1.953]) were significant predictors of obtaining a positive TAB result. Multivariate analysis confirmed age (OR 1.023 [95% CI 1.003–1.043]), female sex (OR 1.978 [95% CI 1.353–2.892]), and TAB specimen length >5 mm (OR 1.453 [95% CI 1.033–2.043]) as significant predictors of obtaining a positive TAB result. The rate of positive TAB results was 30.8% when postfixation specimen length was <5 mm, and 38.3% when TAB specimen length was ≥5 mm. Beyond the cutoff of 5 mm, the rate of biopsy positivity did not increase with increasing TAB specimen length and was similar among all ranges of biopsy specimen length evaluated. Finally, samples ≥5 mm long had a significantly higher number of sections evaluated compared to those <5 mm (median [IQR] 3 [1–5] versus 3 [1–4], $P < 0.0001$).

DISCUSSION

Accurate and prompt GCA diagnosis remains challenging. TAB findings showing TMI are considered the gold standard for the diagnosis of GCA (1). A negative biopsy result can protect the patient from prolonged, unnecessary glucocorticoid treatment. On the other hand, a negative TAB result does not rule out GCA, and a diagnosis of biopsy-negative GCA has been reported in up to 40% of patients (3). False-negative biopsy results are usually attributed to the patchy involvement of the temporal artery, where areas of inflamed artery may alternate with areas of normal artery. Such skip lesions have been found to be 0.29–1.0 mm long and have been reported to be present in up to 28% of TAB results positive for GCA (8–11). It has been suggested that longer temporal artery segments should be excised to reduce the probability of falsely negative TAB results. Older studies from the late 1980s and 1990s recommended to biopsy a long segment (4–6 cm) of temporal artery. However, the trend in recent years has been to reduce the size of biopsy specimens as a push toward minimally invasive diagnostic procedures. The issue of TAB specimen length has been discussed

Table 2. Predictive variables of obtaining a positive temporal artery biopsy (TAB) result*

Variable	No. positive TABs/no. total (%)	Univariate		Multivariate	
		OR (95% CI)	*P*	OR (95% CI)	*P*
TAB specimen length change point					
<5 mm (ref.)	76/247 (30.8)	1	–	1	–
≥5 mm	159/415 (38.3)	1.397 (1.000–1.953)	0.050	1.453 (1.033–2.043)	0.032
Age, years	–	1.025 (1.006–1.045)	0.011	1.023 (1.003–1.043)	0.025
Sex, female	–	1.982 (1.362–2.885)	<0.0001	1.978 (1.353–2.892)	<0.0001
TAB specimen length class					
<5 mm (ref.)	76/247 (30.8)	1	–	1	–
5–9 mm	102/262 (38.9)	1.434 (0.994–2.070)	0.054	1.506 (1.037–2.188)	0.032
10–14 mm	38/109 (34.9)	1.204 (0.747–1.942)	0.446	1.263 (0.777–2.054)	0.346
15–19 mm	15/30 (50)	2.250 (1.047–4.835)	0.038	2.081 (0.958–4.521)	0.064
≥20 mm	4/14 (28.6)	0.900 (0.274–2.960)	0.862	0.911 (0.273–3.040)	0.879
Age, years	–	1.025 (1.006–1.045)	0.011	1.022 (1.002–1.043)	0.028
Sex, female	–	1.982 (1.362–2.885)	<0.0001	1.963 (1.342–2.873)	0.001

* 95% CI = 95% confidence interval; OR = odds ratio; ref. = reference.

extensively in the literature, but the optimal TAB specimen length and the optimal number of sections that need to be evaluated in order to avoid missing skip lesions remain controversial.

Findings from 662 consecutive TABs were included in the current study, with a mean postfixation TAB specimen length of 6.6 mm. In total, 35% of TAB specimens showed the classical transmural pattern of inflammation and were considered positive for GCA. There was no difference in postfixation TAB specimen length between TAB specimens positive and negative for GCA. Our data are concordant with 3 previous studies that reported comparable biopsy sample lengths in positive and negative TAB specimens (13,17,18). However, 4 other studies reported longer biopsy sample lengths in TAB specimens positive for GCA compared with negative TAB specimens (Table 3) (12,14,15,19). All these studies, including the present one, compared TAB specimen length between patients with a positive TAB result and those with a negative TAB result. However, some authors suggested that the comparison of TAB specimen length between patients with biopsy-proven and biopsy-negative GCA would more accurately reflect the association between biopsy specimen length and the result of the biopsy. In this regard, 2 studies from Israel compared TAB specimen length between biopsy-positive and biopsy-negative GCA, excluding patients with negative TAB results but without GCA, and had conflicting results (Table 3) (20,21).

The mean postfixation TAB specimen length observed in our study was lower than most of the mean or median TAB specimen lengths reported in other studies. Nevertheless, 35% of our TAB specimens were positive for GCA, a proportion higher than that observed in most of the previous studies, indicating a more accurate clinical suspicion in our population of patients and a higher accuracy in the pathologic examination. In this regard, our study design is unique. All the TABs performed for suspected GCA during the study period at our center were reviewed by a single pathologist (AC) with expertise in vasculitides, and additional slides were cut at deeper levels in all inadequate and uninflamed TAB specimens, as well as in all the TAB specimens showing PA/AI, in order not to miss inflammatory changes. In most other studies, only the pathologic records were reviewed, and only few studies reviewed the original slides of the TAB without additional cuts (Table 3). Our findings suggest that TAB specimen length is potentially less important than has previously been considered. Even considering a length of <5 mm, 30.8% of our TAB specimens (76 of 247) were positive for GCA, a proportion still higher than that reported in most other studies, confirming that samples of short length might not substantially account for negative TAB findings. Regional variation in the prevalence of the disease, different indications for requesting a TAB, different degrees of accuracy in clinical suspicion, and different methodology in performing and analyzing TAB findings all could have contributed to the different results reported in the literature.

False-negative biopsy results are usually attributed to the patchy involvement of the temporal artery, with areas of inflamed artery alternating with areas of normal artery. Such skip lesions have been found to be 0.29–1.0 mm long and are reported to be present in up to 28% of TAB specimens positive for GCA. However, the existence of skip lesions in GCA has not been confirmed by all histologic studies (8–11). All 4 studies that looked for the presence of skip lesions evaluated multiple sections from TAB specimens originally classified as positive for GCA, while negative TAB specimens were not included. Furthermore, all these studies considered as negative the sections showing nontransmural inflammation. Skip lesions were not found in any of the 42 positive TAB findings evaluated by Cohen et al (11), in 3 of the 35 (8.5%) positive TAB findings evaluated by Poller et al (9), in 2 of the 10 (20%) positive TAB findings evaluated by Albert et al (10), and in 17 of 60 (28%) positive TAB findings evaluated by Klein et al (8).

In the current study, inflamed sections were found after cuts of additional biopsy sections at deeper levels in 26 of 408 (6.4%) TAB specimens originally reported as uninflamed. The inflamed section was the second in 14 TAB specimens, the third in 9 specimens, and the fourth in 3 specimens. In 88% of cases,

Table 3. Main findings of the studies comparing specimen length between temporal artery biopsy (TAB) positive and TAB negative for giant cell arteritis (GCA)*

Author, year (ref.)	Country	No. of TABs included	Single or multicenter study	Positive TAB, %	Revision of the original slides	Postfixation TAB specimen length, mm	Positive TAB specimen length, mm	Negative TAB specimen length, mm	*P*	Cutoff length, mm
Current study	Italy	662	Single	35	Yes	6.6	6.9	6.5	0.068	5
Ypsilantis et al, 2011 (13)	England	966	Multi	21	No	10	12	10	0.001	7
Oh et al, 2018 (14)	Australia	538	Single	23	Only in uncertain cases	17.6	19.9	16.8	0.0009	15
Sudlow, 1997 (18)	Scotland	185	Single	27	No	10	10.6	8.6	0.02	NE
Taylor-Gjevere et al, 2005 (11)	Canada	141	Single	27	Yes	17.6	20.7	16.9	0.058	10
Mahr et al, 2006 (12)	France	1,520	Multi	15	No	13.3	13.4	13.3	0.79	5
Kaptanis et al, 2014 (16)	England	151	Single	13	No	6.4	7	6.5	0.43	NE
Papadakis et al, 2018 (17)	Germany	116	Single	55	No	9.4	9.6	9.1	0.581	NE
Breuer et al, 2009 (20)†	Israel	305	Single	35	Yes	NR	12.7	10.1	0.008	NE
Grossman et al, 2017 (19)†	Israel	240	Single	26	No	10.7	11.3	11.5	0.928	NE

* NE = not evaluated; NR = not reported; ref. = reference.
† These 2 studies compared TAB specimen length between biopsy-positive and biopsy-negative GCA.

inflammation found at deeper levels was restricted to periadventitial and/or adventitial tissue without extension to the media. Our data are in keeping with those of Chakrabarty et al (22), who found negative sections alternating with inflamed sections in 16 of 132 (12%) TAB specimens originally reported as negative. In 94% of these 16 cases, inflammation found at deeper levels was restricted to adventitial/periadventitial tissue without extension to the media (22).

The different design of these studies has allowed us to reach some conclusions. The results reported by the 4 studies that looked for skip lesions in TAB specimens positive for GCA confirmed the patchy involvement of the temporal artery in a variable proportion of patients with biopsy-proven GCA (between 0 and 28% of cases). The study by Chakrabarty et al (22) and the current study looked for inflamed sections from TAB specimens originally reported as negative. In these 2 studies, additional examination of TAB specimens at multiple levels determined only a small increase in the diagnostic yield of TAB for the diagnosis of GCA, while a more relevant number of cases with inflammation restricted to adventitial/periadventitial tissue without extension to the media were observed in TAB specimens originally reported as negative (~10%). According to the economic model built by Chakrabarty et al (22), the cost–benefit of evaluating additional sections in all negative TAB specimens depends on the value that is ascribed to the presence of this restricted inflammation in terms of potential contribution to clinical and therapeutic decision-making. To date, the significance of this more limited inflammation is controversial. Some authors, including our group, consider it part of the pathologic spectrum of GCA and/or polymyalgia rheumatica, while others consider it a finding associated with aging not indicative of an inflammatory process or as a sign of a systemic small vessel vasculitis (4–6). However, the predictive value of this restricted inflammation at TAB for the diagnosis of GCA is still unclear. A recent study by our group showed that a large portion of patients with restricted inflammation at TAB have GCA or polymyalgia rheumatica. However, the diagnostic value of restricted inflammation for GCA diagnosis was not relevant (positive likelihood ratio 0.88 [95% CI 0.61–1.27]) (23).

Few studies have determined a specific cutoff length as a change point for higher diagnostic sensitivity. Our search for an optimal cutoff suggested that the best diagnostic sensitivity might be achieved with a postfixation TAB specimen length of ≥5 mm. Compared with TAB specimen length of <5 mm, the age- and sex-adjusted OR for obtaining a positive TAB result for longer samples was 1.5. We did not find a clear-cut linear relation between increasing TAB specimen length and positivity for GCA, indicating that increasing TAB specimen length beyond the cutoff of 5 mm does not increase the sensitivity of TAB for GCA. Also in the study by Mahr et al (13), a fixed TAB specimen length of at least 5 mm was sufficient to make a histologic diagnosis of GCA, and the best diagnostic sensitivity was observed for this cutoff. Compared with TAB specimen length of <0.5 cm, the reported OR for positive TAB results in samples ≥0.5 cm in length was 5.7 (13). Ypsilantis et al (14) identified postfixation specimen length of at least 0.7 cm as the cutoff length with highest positive predictive value for a positive biopsy (14). Compared with TAB specimen length <0.7 cm, the reported OR for positive TAB results in samples ≥0.7 cm in length was 2.2 (14). Taylor-Gjevere et al (12) identified a cutoff point of 1.0 cm as the point at which the relationship between TAB specimen length and cumulative percentage of positive biopsy results took a steeper slope. Biopsy specimens ≥1.0 cm in length were more likely to be positive than those <1.0 cm. Raising the threshold length above 1.0 cm did not increase the frequency of a positive result (12). Finally, using the Youden index, Oh et al (15) estimated that the optimal threshold predicting a positive biopsy result was 15 mm. Compared with a TAB specimen length of <15 mm, the reported OR for positive TAB results in samples ≥15 mm in length was 3.7 (15).

Our data confirm that a postfixation TAB specimen length of at least 5 mm should be sufficient to make a histologic diagnosis of GCA. As the arterial specimen contracts after removal by 15–20% of its original length, both before and after formalin fixation (24), the present findings indicate that surgeons should aim for a prefixation surgical specimen length of 7–10 mm in order to maximize the diagnostic accuracy of TAB.

Our study has some limitations. We did not differentiate between biopsy-positive and biopsy-negative GCA, and we did not assess whether patients were treated with glucocorticoids at the time of biopsy. However, in our hospital, patients with suspected GCA are usually assessed by a rheumatologist within 24 hours, and TAB is routinely performed within 5 days from the first referral in all patients in whom the clinical suspicion of GCA is confirmed. Different studies have shown that there are no changes in the sensitivity of TAB for the diagnosis of GCA until after 2 to 4 weeks of steroid treatment (3). Therefore, we believe that previous steroid treatment is unlikely to have influenced the results of our study. The proportion of 4.6% of inadequate TAB specimens found in our study is concordant with other studies that reported similar rates. Our study has a number of strengths, including the large number of consecutive TAB specimens included, which is the largest number of TAB specimens with a postfixation length of <5 mm reported in the literature, the monocentric design, and the review of all TAB specimens by a single pathologist with expertise in vasculitides, who evaluated additional slides cut at deeper levels in all inadequate and negative TAB specimens in order not to miss inflammatory changes.

In conclusion, our findings suggest that TAB specimen length is potentially less important than has been thought when patients are accurately selected and TAB specimens are carefully examined. A postfixation TAB specimen length of at least 5 mm should be sufficient to make a histologic diagnosis of GCA. As the arterial specimen contracts after removal, surgeons should aim for a prefixation surgical specimen length of 7–10 mm in order to maximize the diagnostic accuracy of TAB. In order not to miss inflammation

limited to adventitial and/or periadventitial small vessels, at least 3 further sections at deeper levels should be evaluated in all uninflamed TAB specimens.

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. Salvarani 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. Muratore, Boiardi, Cavazza, Pipitone, Croci, Salvarani.

Acquisition of data. Muratore, Boiardi, Cavazza, Tiengo, Galli, Cimino, Bonacini, Salvarani.

Analysis and interpretation of data. Muratore, Boiardi, Cavazza, Aldigeri, Croci, Salvarani.

REFERENCES

1. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet 2008;372:234–45.
2. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, Miranda-Filloy JA, Gonzalez-Juanatey C, Martin J, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum 2009;61:1454–61.
3. Muratore F, Cavazza A, Boiardi L, Gullo AL, Pipitone N, Germanò G, et al. Histopathologic findings of patients with biopsy-negative giant cell arteritis compared to those without arteritis: a population-based study. Arthritis Care Res (Hoboken) 2016;68:865–70.
4. Restuccia G, Cavazza A, Boiardi L, Pipitone N, Macchioni P, Bajocchi G, et al. Small-vessel vasculitis surrounding an uninflamed temporal artery and isolated vasa vasorum vasculitis of the temporal artery: two subsets of giant cell arteritis. Arthritis Rheum 2012;64:549–56.
5. Cavazza A, Muratore F, Boiardi L, Restuccia G, Pipitone N, Pazzola G, et al. Inflamed temporal artery: histologic findings in 354 biopsies, with clinical correlations. Am J Surg Pathol 2014;38:1360–70.
6. Muratore F, Boiardi L, Cavazza A, Aldigeri R, Pipitone N, Restuccia G, et al. Correlations between histopathological findings and clinical manifestations in biopsy-proven giant cell arteritis. J Autoimmun 2016;69:94–101.
7. Muratore F, Kermani TA, Crowson CS, Green AB, Salvarani C, Matteson EL, et al. Large-vessel giant cell arteritis: a cohort study. Rheumatology (Oxford) 2015;54:463–70.
8. Klein RG, Campbell RJ, Hunder GG, Carney JA. Skip lesions in temporal arteritis. Mayo Clin Proc 1976;51:504–10.
9. Poller DN, van Wyk Q, Jeffrey MJ. The importance of skip lesions in temporal arteritis. J Clin Pathol 2000;53:137–9.
10. Albert DM, Ruchman MC, Keltner JL. Skip areas in temporal arteritis. Arch Ophthalmol 1976;94:2072–7.
11. Cohen DN, Smith TR. Skip areas in temporal arteritis: myth versus fact. Trans Am Acad Ophthalmol Otolaryngol 1974;78:772–83.
12. Taylor-Gjevre R, Vo M, Shukla D, Resch L. Temporal artery biopsy for giant cell arteritis. J Rheumatol 2005;32:1279–82.
13. Mahr A, Saba M, Kambouchner M, Polivka M, Baudrimont M, Brochériou I, et al. Temporal artery biopsy for diagnosing giant cell arteritis: the longer, the better? Ann Rheum Dis 2006;65:826–8.
14. Ypsilantis E, Courtney ED, Chopra N, Karthikesalingam A, Eltayab M, Katsoulas N, et al. Importance of specimen length during temporal artery biopsy. Br J Surg 2011;98:1556–60.
15. Oh LJ, Wong E, Gill AJ, McCluskey P, Smith JE. Value of temporal artery biopsy length in diagnosing giant cell arteritis. ANZ J Surg 2018; 88:191–5.
16. Hellmich B, Agueda A, Monti S, Buttgereit F, De Boysson H, Brouwer E, et al. 2018 update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19–30.
17. Kaptanis S, Perera JK, Halkias C, Caton N, Alarcon L, Vig S. Temporal artery biopsy size does not matter. Vascular 2014;22:406–10.
18. Papadakis M, Kaptanis S, Kokkori-Steinbrecher A, Floros N, Schuster F, Hübner G. Temporal artery biopsy in the diagnosis of giant cell arteritis: bigger is not always better. Am J Surg 2018;215:647–50.
19. Sudlow C. Diagnosing and managing polymyalgia rheumatica and temporal arteritis: sensitivity of temporal artery biopsy varies with biopsy length and sectioning strategy. BMJ 1997;315:549.
20. Grossman C, Ben-Zvi I, Barshack I, Bornstein G. Association between specimen length and diagnostic yield of temporal artery biopsy. Scand J Rheumatol 2017;46:222–5.
21. Breuer GS, Nesher R, Nesher G. Effect of biopsy length on the rate of positive temporal artery biopsies. Clin Exp Rheumatol 2009;27 Suppl 52:S10–3.
22. Chakrabarty A, Franks AJ. Temporal artery biopsy: is there any value in examining biopsies at multiple levels? J Clin Pathol 2000;53:131–6.
23. Galli E, Muratore F, Boiardi L, Restuccia G, Cavazza A, Catanoso M, et al. Significance of inflammation restricted to adventitial/periadventitial tissue on temporal artery biopsy. Semin Arthritis Rheum 2020;50:1064–72.
24. Su GW, Foroozan R, Yen MT. Quantitative analysis of temporal artery contraction after biopsy for evaluation of giant cell arteritis. Can J Ophthalmol 2006;41:500–3.

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Incidence Trends and Mortality of Giant Cell Arteritis in Southern Norway

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Objective. Southern Norway consists of a homogeneous population of nearly 300,000 inhabitants and is an ideal epidemiologic setting. We aimed to explore potential changes in incidence of giant cell arteritis (GCA) in Southern Norway from 2000–2013, with comparisons of previous reports from the same population cohort from 1987–1994 and 1992–1996, and to investigate the mortality rates of GCA over a period of 14 years.

Methods. All patients diagnosed with GCA during January 1, 2000 to December 31, 2013 were identified through the electronic health records and biopsy findings databases at our clinic. The diagnosis of GCA and information about death was confirmed by reviewing the patients' hospital records. Inclusion criteria were: 1) fulfillment of the American College of Rheumatology 1990 criteria for GCA, or 2) histologically proven GCA, or 3) confirmed arteritis of the large or medium-sized vessels by imaging.

Results. A total of 206 patients were included, and 147 (72%) were females. The annual incidence rate of GCA per 100,000 inhabitants age ≥50 years was 16.8 (95% confidence interval [95% CI] 14.6–19.2), 24.5 for females (95% CI 19.2–26.5), and 10.2 for males (95% CI 7.9–13.2). Forty-six patients (22%) died (24 women, 22 men). The overall standardized mortality ratio was 1.05 (95% CI 0.77–1.38), 0.92 for females (95% CI 0.61–1.35), and 1.38 for males (95% CI 0.88–2.05). Overall survival rate was significantly higher in females compared to males ($P < 0.001$).

Conclusion. GCA incidence is not increasing. We did not find excess mortality; however, males seem to have a worse survival rate compared to females.

INTRODUCTION

Giant cell arteritis (GCA) is the most common form of systemic vasculitis involving the medium and/or large-sized arteries. The disorder is more common in women and rarely seen before the age of 50 years. The highest incidence is reported among Scandinavians, with a peak rate of 43.6 per 100,000 inhabitants ages ≥50 years from Iceland (1).

The etiology of GCA is still unknown, and epidemiologic studies are essential in identifying potential etiologic clues. Southern Norway consists of a homogeneous population with low rates of migration and is thus ideal as an epidemiologic setting. With an aging population and improved diagnostic tools, the number of cases with GCA might be expected to increase. In some studies, the annual incidences of GCA seem to fluctuate (2,3), whereas in others, the incidence seem to be stable (4,5) or decreasing (6). With 2 notable exceptions (6,7), studies on GCA mortality in large cohorts are lacking. Furthermore, the evidence is somewhat conflicting (6–10), although overall mortality does not seem to be increased (11). Long-term observation studies are therefore highly warranted, as they may reveal the outcome of the disease.

Our primary aim was to look for potential changes in incidence in Southern Norway from 2000–2013, with a comparison of previous reports from the same population cohort from 1987–1994 and 1992–1996 (12,13). Secondly, we aimed to investigate the mortality rates of GCA in a stable, homogeneous population cohort over a period of 14 years.

MATERIALS AND METHODS

The Hospital of Southern Norway serves the population of the 2 counties, Vest-Agder and Aust-Agder, with a total of 292,225 inhabitants (January 1, 2014). The study period was from January 1, 2000 to December 31, 2013. During this period,

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

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SIGNIFICANCE & INNOVATIONS

- This is a comprehensive longitudinal report on mortality and incidence trends of giant cell arteritis (GCA), covering the same population cohort over 3 different periods of time.
- The study provides evidence that incidence of GCA is not increasing, and that there is no excess mortality of GCA compared to the general population.
- These results are consistent with previous epidemiologic reports on GCA in populations of Scandinavian ancestry. However, there seems to be a sex bias in survival rate.

the mean population of inhabitants age ≥50 years in these 2 counties was 87,821. All patients with a diagnosis of GCA in this period were identified through the clinical electronic hospital databases using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision coding system with the following codes M31.5 (GCA) or M31.6 (GCA with polymyalgia rheumatica). Additionally, a search for temporal biopsies in the electronic biopsy database in the department of pathology was performed. The diagnosis was confirmed by reviewing clinical information from patients' hospital records and the histopathologic reports.

All patients who either: 1) fulfilled the American College of Rheumatology (ACR) 1990 criteria for GCA (14), or, 2) had histologically proven GCA, or, 3) had arteritis of the large or medium-sized vessels confirmed by color Doppler ultrasonography (CDUS), magnetic resonance imaging, computed tomography (CT) angiography, or positron emission tomography CT were included. In our department, CDUS has been routinely applied in the diagnosis of GCA since 2010, and the fast-track outpatient GCA ultrasound clinic was fully implemented in 2012 (15). Only 1 experienced specialist in rheumatology (APD) in our department performed the CDUS examinations of all suspected GCA cases since 2010 until the end of the study period.

Differences between groups were assessed using the chi-square test for categorical variables and nonparametric Mann-Whitney U test for continuous variables. Two-sided *P* values less than 0.05 were considered statistically significant. The mean population age ≥50 years during the study period was used as the denominator population when estimating incidence. Ninety-five percent confidence intervals (95% CIs) were calculated assuming a Poisson distribution. Survival analyses were based on the overall mortality and were performed by the Kaplan-Meier method using the log rank test for group comparison. Period-specific person-years of follow-up with the corresponding rates for the entire Norwegian population, matched for age, sex, and year-specific mortality rates, were used to calculate the expected number of deaths. Standardized mortality ratios (SMRs) with 95% CIs were then calculated in Openepi (http://www.openepi.com) using the Mid-P exact test. Statistical analyses were performed in SPSS Statistics for Windows, version 20.0.

RESULTS

A total of 206 patients met the inclusion criteria, 147 (72%) females, 59 (28%) males, with the female-to-male ratio being 2.5:1. Mean ± SD age was 73.2 ± 8.6 years, with no difference between females (73.1 ± 8.5 years) and males (73.4 ± 9.0 years). Of these, 152 (74%) had a biopsy-proven GCA diagnosis (Table 1). In 13 patients (6%), a biopsy was not performed. ACR 1990 criteria were fulfilled in 198 patients (96%) (14). Patients who did not fulfill the ACR criteria (4%) had either a positive biopsy and/or vessel inflammation by imaging. Vision disturbances were reported in 73 patients (35%) and vision loss in 33 patients (16%).

The annual incidence rate of GCA per 100,000 inhabitants age ≥50 years was 16.8 (95% CI 14.6–19.2) (Table 2). Furthermore,

Table 1. Characteristics of patients with giant cell arteritis in Southern Norway, 2000–2013*

Characteristic	Total (n = 206, 100%)	Female (n = 147, 72%)	Male (n = 59, 28%)
Age at onset, mean ± SD years	73.2 ± 8.6	73.1 ± 8.5	73.4 ± 9.0
Biopsy			
Positives	152 (74)	110 (53)	42 (20)
Negatives	41 (20)	27 (13)	14 (7)
Not performed	13 (6)	10 (5)	3 (2)
CDUS			
Positives	49 (62)	35 (44)	14 (18)
Vision			
Disturbances	73 (35)	53 (26)	20 (10)
Loss	33 (16)	22 (11)	11 (5)
Death			
Overall deaths	46 (22)	24 (12)	22 (11)

* Values are the number (%) unless indicated otherwise. Values for color Doppler ultrasonography (CDUS) positives were calculated from the total number of patients included after year 2010 (n = 79). Some numbers were rounded.

Table 2. Mean annual incidence rates for giant cell arteritis (GCA) according to age groups and sex, age ≥50 years, 2000–2013*

Age groups, years	GCA patients, no.			Mean population			Incidence rate (95% CI)		
	F	M	All	F	M	All	F	M	All
50–59	7	6	13	16,806	17,233	34,039	3.0 (1.4–6.2)	2.5 (1.1–5.5)	2.7 (1.6–4.7)
60–69	40	11	51	12,644	12,302	24,946	22.6 (16.6–30.8)	6.4 (3.5–11.5)	14.6 (11.1–19.2)
70–79	61	25	86	9,269	7,573	16,842	47.0 (36.6–60.4)	23.6 (15.9–34.9)	36.5 (29.5–45.1)
≥80	39	17	56	7,882	4,112	11,994	35.3 (25.8–48.4)	29.5 (18.4–47.5)	33.4 (25.7–43.3)

* Rates are per 100,000 inhabitants. 95% CI = 95% confidence interval; F = female; M = male.

the incidence rate for females was 24.5 (95% CI 19.2–26.5) and for males 10.2 (95% CI 7.9–13.2). Peak age of incidence was 70–79 years. The incidence of biopsy-proven GCA was 12.4 per 100,000 inhabitants age ≥50 years (95% CI 10.5–14.5). The lowest incidence rate was found in year 2001 and was 7.5 per 100,000 inhabitants age ≥50 years (95% CI 3.4–16.6), while the highest rate was found in year 2010 and was 24.8 per 100,000 inhabitants age ≥50 years (95% CI 16.5–37.3). Comparisons of GCA incidence rates in Norway are shown in Figure 1 (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/art.24133/abstract). There were no differences in the yearly incidence rates during the study period, Figure 2 (see Supplementary Table 2, online at http://onlinelibrary.wiley.com/doi/10.1002/art.24133/abstract).

Mean ± SD observation time from diagnosis to the end of the study period (December 31, 2013) or death was 5.4 ± 3.8 years, with no differences in sex (P = 0.6). Females were followed for a mean ± SD of 5.5 ± 3.8 years and males for 5.2 ± 3.8 years. In total, 46 patients (22%) died during the study period (24 women, 22 men). Eleven patients (5%) died within 1 year of diagnosis (4 women, 7 men), 17 (8%) within 5 years of diagnosis (7 women, 10 men), 14 within 10 years (9 women, 5 men), and 4 (all women) within ≥10 years of follow-up. The overall SMR (Table 3) was 1.05 (95% CI 0.77–1.38), 0.92 (95% CI 0.61–1.35) for females, and 1.38 (95% CI 0.88–2.05) for males. Overall survival was significantly higher in female GCA patients compared to males (P < 0.001) (Figure 3).

DISCUSSION

In this study, we present epidemiologic characteristics of patients with GCA in a large, stable population over a period of 14 years. Our incidence rate of 16.8 is among the highest reported worldwide and in line with the most recent, large epidemiologic hospital-based report from Western Norway (incidence rate 16.7) and Scandinavia (2,16–21), but lower than previous reports from Southern Norway (incidence rates 29.0 and 32.8) (12,13). Differences in observation periods (14 years versus 8 and 5 years, respectively) and study designs might have contributed to these discrepancies. Also, small samples and short observation periods risk overestimating the true incidence of a disease (22–24). The confidence intervals lend some support to this, as the current study and the study from Western Norway, both with long observation periods and large samples, have narrow confidence intervals compared to the study from 1992–1996 (95% CIs were not available for the study from 1987–1994). Moreover, when restricting incident cases to those found in the period 1992–1996 in Western Norway, Brekke et al calculated a higher mean annual incidence than for the entire observation period (26.7 versus 16.7) (2). Cyclic fluctuations in incidence might also explain the observed differences, e.g., annual incidence rates in Western Norway ranged 2.1–32.8 during the study period of 41 years, while the current study ranged 7.5–24.8 over a period of 14 years. However, the Swedish study did not confirm this trend (6). Indeed, evidence suggests that

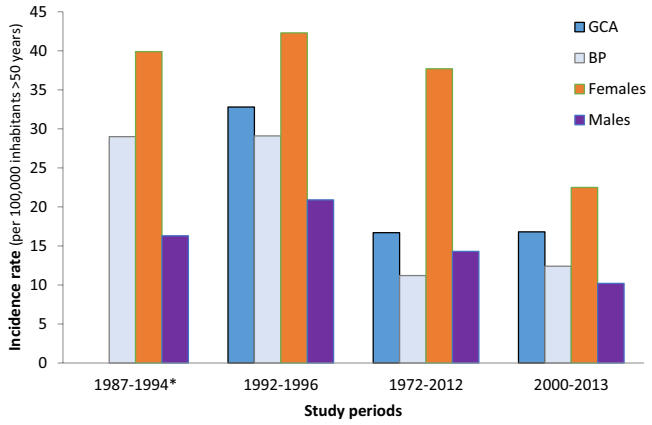

Figure 1. Comparison of giant cell arteritis (GCA) incidence rates in Norway, 1987–2013. * = only biopsy positive (BP) cases were included.

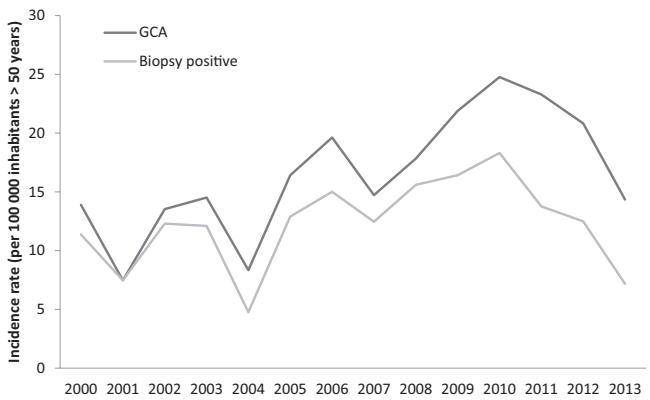

Figure 2. Annual incidence rates of giant cell arteritis (GCA) patients age ≥50 years and biopsy positives, 2000–2013.

Table 3. Standardized mortality ratios of giant cell arteritis (GCA) patients, 2000–2013*

Age groups, years	Population, no.	Population, deaths, no.	Death rate	Expected deaths	GCA person-year	GCA, no.	GCA, death, no.	SMR (95% CI)
Male								
50–59	303,811	1,508	0.005	0.164	33	6	1	
60–69	215,526	2,826	0.013	0.682	52	11	0	
70–79	134,137	5,077	0.038	5.034	133	25	11	
80–89	65,325	7,233	0.111	10.076	91	17	10	
≥90	7,992	2,237	0.280	0.000	0	0	0	
Total				15.955	309	59	22	1.38 (0.88–2.05)
Female								
50–59	293,645	959	0.003	0.121	37	7	0	
60–69	220,710	1,740	0.008	1.995	253	40	5	
70–79	164,980	3,760	0.023	7.566	332	61	6	
80–89	114,892	8,889	0.077	13.926	180	37	11	
≥90	24,104	5,544	0.230	2.300	10	2	2	
Total				25.907	812	147	24	0.92 (0.61–1.35)
All								
50–59	597,456	2,466	0.004	0.289	70	13	1	
60–69	436,235	4,566	0.010	3.192	305	51	5	
70–79	299,114	8,837	0.030	13.737	465	86	17	
80–89	180,217	16,122	0.089	24.243	271	54	21	
≥90	32,096	7,782	0.242	2.424	10	2	2	
Total				43.886	1,121	206	46	1.05 (0.77–1.38)

* Population data and numbers of death in the population are retrieved from Statistics Norway and calculated as the mean for the study period. SMR = standardized mortality ratio.

incidence rates of GCA are decreasing or stabilizing worldwide (3–6,20). In Sweden, a significant decrease in incidence over a period of 14 years compared to a previous study from the same area was observed (6). In Western Norway, the incidence increased over the first 14 years of the study but remained stable until the end of the study period (2). When comparing the incidence of GCA in different regions of Norway to Southern Norway during the period 1992–1996, no differences were observed (25). These findings indicate that the incidence rates from the current study confirm the trend of decreasing incidence for the last 2 decades, as this is an extension of 2 previous studies of the same population (Figure 1).

In 7% of the patients in our study, a biopsy was not performed, as the diagnosis was confirmed by imaging. This might explain the low incidence rate of the biopsy-proven cases in our study of 12.4 per 100,000 inhabitants age ≥50 years compared to the rest of Scandinavia. Still, this rate is higher than elsewhere in the world (26).

Overall mortality in GCA patients was not increased compared to the Norwegian population, which is in line with other recent Norwegian studies (27,28). Nevertheless, the survival

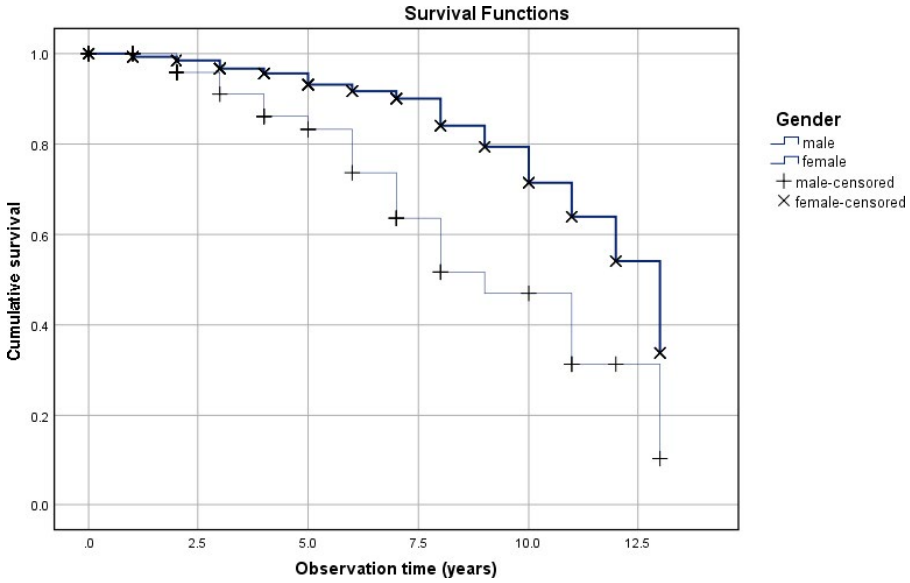

Figure 3. Survival of male and female giant cell arteritis patients 2000–2013. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24133/abstract.

rate was lower in male patients compared to female patients. One young (age <60 years) male patient died during the study period. When removing this individual from the mortality calculations, the mortality ratio for males was not significantly altered (from 1.38 to 1.32). Few studies have explored potential sex differences in survival, and the results are conflicting (29,30). Recently, mortality of GCA patients recruited through hospital settings was, however, shown in a meta-analysis to be increased (11). Prognostic factors include comorbid conditions and high-maintenance doses of glucocorticoids. We did not have information about comorbidity or therapy. A study from the same area for the period 1987–1997 did not confirm the association between use of glucocorticoids and disease activity and death, nor was mortality increased (31).

Excess mortality in the initial period after the diagnosis has been reported in different parts of the world, including Denmark and Sweden (6–9,32). The latter 2 countries are comparable to Norway regarding GCA incidence, ethnicity, access to health care, and life expectancy. The Swedish authors demonstrated that the excess mortality was present in the first 2 years after the diagnosis, but that after 5 years of follow-up, there was no difference in the mortality between GCA patients and the general population. Due to small samples, subgroup analysis of mortality and time of follow-up was not calculated for our cohort.

The strength of this study is the population-based setting with a homogeneous, stable population. Health care in Norway is free and universal, and risk of selection bias in this setting is small. Potential limitations were differences in the study design, which made direct comparisons between studies challenging. Furthermore, due to the nature of the retrospective design of our study, some patients might have been lost to follow-up, thus underestimating the true incidence (19). GCA is considered an emergency due to possible loss of vision, and we therefore believe that most patients would be referred to a specialist. There are 2 publicly funded private rheumatologists in the area, but all suspected cases of GCA would be referred to the department of rheumatology (at the hospital). Some patients may have been referred to other departments, e.g., internal medicine, ophthalmology, geriatrics, or neurology. However, as this is a hospital-based study, any patients who were given a GCA diagnosis would be included in our material. Therefore, in our opinion, only a few cases would have been missed.

In conclusion, in this cohort study from a region with high incidence of GCA, the mortality rate does not seem to be increased, but males seem to have a poorer survival rate than females. Furthermore, this study confirms high incidence of GCA in Norway and shows a probable trend of decreasing incidence. Our findings suggest, despite modern imaging techniques, changing demographic characteristics with an aging population, and better availability of and awareness among physicians, that the incidence of GCA is not rising. Further studies are warranted to explore why mortality seems to differ between sexes.

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. Andersen 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. Andersen, Pripp, Diamantopoulos.
Acquisition of data. Myklebust, Haugeberg, Diamantopoulos.
Analysis and interpretation of data. Andersen, Myklebust, Haugeberg, Pripp, Diamantopoulos.

REFERENCES

1. Tomasson G, Bjornsson J, Zhang Y, Gudnason V, Merkel PA. Cardiovascular risk factors and incident giant cell arteritis: a population-based cohort study. Scand J Rheumatol 2018:1–5.
2. Brekke LK, Diamantopoulos AP, Fevang BT, Abetamus J, Espero E, Gjesdal CG. Incidence of giant cell arteritis in Western Norway 1972–2012: a retrospective cohort study. Arthritis Res Ther 2017;19:278.
3. Gonzalez-Gay MA, Miranda-Filloy JA, Lopez-Diaz MJ, Perez-Alvarez R, Gonzalez-Juanatey C, Sanchez-Andrade A, et al. Giant cell arteritis in northwestern Spain: a 25-year epidemiologic study. Medicine (Baltimore) 2007;86:61–8.
4. Catanoso M, Macchioni P, Boiardi L, Muratore F, Restuccia G, Cavazza A, et al. Incidence, prevalence, and survival of biopsy-proven giant cell arteritis in Northern Italy during a 26-year period. Arthritis Care Res (Hoboken) 2017;69:430–8.
5. Chandran AK, Udayakumar PD, Crowson CS, Warrington KJ, Matteson EL. The incidence of giant cell arteritis in Olmsted County, Minnesota, over a 60-year period 1950–2009. Scand J Rheumatol 2015;44:215–8.
6. Mohammad AJ, Nilsson JA, Jacobsson LT, Merkel PA, Turesson C. Incidence and mortality rates of biopsy-proven giant cell arteritis in southern Sweden. Ann Rheum Dis 2015;74:993–7.
7. Baslund B, Helleberg M, Faurschou M, Obel N. Mortality in patients with giant cell arteritis. Rheumatology (Oxford) 2015;54:139–43.
8. Crow RW, Katz BJ, Warner JE, Alder SC, Zhang K, Schulman S, et al. Giant cell arteritis and mortality. J Gerontol A Biol Sci Med Sci 2009;64:365–9.
9. Li L, Neogi T, Jick S. Mortality in patients with giant cell arteritis: a cohort study in UK primary care. Arthritis Care Res (Hoboken) 2018;70:1251–6.
10. Ninan J, Nguyen AM, Cole A, Rischmueller M, Dodd T, Roberts-Thomson P, et al. Mortality in patients with biopsy-proven giant cell arteritis: a South Australian population-based study. J Rheumatol 2011;38:2215–7.
11. Hill CL, Black RJ, Nossent JC, Ruediger C, Nguyen L, Ninan JV, et al. Risk of mortality in patients with giant cell arteritis: a systematic review and meta-analysis. Semin Arthritis Rheum 2017;46:513–9.
12. Gran JT, Myklebust G. The incidence of polymyalgia rheumatica and temporal arteritis in the county of Aust Agder, South Norway: a prospective study 1987–94. J Rheumatol 1997;24:1739–43.
13. Haugeberg G, Paulsen PQ, Bie RB. Temporal arteritis in Vest Agder County in southern Norway: incidence and clinical findings. J Rheumatol 2000;27:2624–7.
14. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122–8.
15. Diamantopoulos AP, Haugeberg G, Lindland A, Myklebust G. The fast-track ultrasound clinic for early diagnosis of giant cell arteritis significantly reduces permanent visual impairment: towards a more effective strategy to improve clinical outcome in giant cell arteritis? Rheumatology (Oxford) 2016;55:66–70.

16. Noltorp S, Svensson B. High incidence of polymyalgia rheumatica and giant cell arteritis in a Swedish community. Clin Exp Rheumatol 1991;9:351–5.
17. Bengtsson BÅ, Malmvall BE. The epidemiology of giant cell arteritis including temporal arteritis and polymyalgia rheumatica: incidences of different clinical presentations and eye complications. Arthritis Rheum 1981;24:899–904.
18. Elling P, Olsson AT, Elling H. Synchronous variations of the incidence of temporal arteritis and polymyalgia rheumatica in different regions of Denmark; association with epidemics of Mycoplasma pneumoniae infection. J Rheumatol 1996;23:112–9.
19. Franzen P, Sutinen S, von Knorring J. Giant cell arteritis and polymyalgia rheumatica in a region of Finland: an epidemiologic, clinical and pathologic study, 1984–1988. J Rheumatol 1992;19:273–6.
20. Petursdottir V, Johansson H, Nordborg E, Nordborg C. The epidemiology of biopsy-positive giant cell arteritis: special reference to cyclic fluctuations. Rheumatology (Oxford) 1999;38:1208–12.
21. Baldursson O, Steinsson K, Björnsson J, Lie JT. Giant cell arteritis in Iceland: an epidemiologic and histopathologic analysis. Arthritis Rheum 1994;37:1007–12.
22. Ward MM. Estimating disease prevalence and incidence using administrative data: some assembly required. J Rheumatol 2013;40:1241–3.
23. Ng R, Bernatsky S, Rahme E. Observation period effects on estimation of systemic lupus erythematosus incidence and prevalence in Quebec. J Rheumatol 2013;40:1334–6.
24. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2008.
25. Haugeberg G, Irgens KA, Thomsen RS. No major differences in incidence of temporal arteritis in Northern and Western Norway compared with reports from Southern Norway. Scand J Rheumatol 2003;32:318–9.
26. Koster MJ, Warrington KJ, Kermani TA. Update on the epidemiology and treatment of giant cell arteritis. Curr Treat Options in Rheum 2016;2:138–52.
27. Garen T, Lerang K, Hoffmann-Vold AM, Andersson H, Midtvedt O, Brunborg C, et al. Mortality and causes of death across the systemic connective tissue diseases and the primary systemic vasculitides. Rheumatology (Oxford) 2019;58:313–20.
28. Brekke LK, Fevang BS, Diamantopoulos AP, Assmus J, Espero E, Gjesdal CG. Survival and death causes of patients with giant cell arteritis in Western Norway 1972–2012: a retrospective cohort study. Arthritis Res Ther 2019;21:154.
29. Uddhammar A, Eriksson AL, Nystrom L, Stenling R, Rantapaa-Dahlqvist S. Increased mortality due to cardiovascular disease in patients with giant cell arteritis in northern Sweden. J Rheumatol 2002;29:737–42.
30. Graham E, Holland A, Avery A, Russell RW. Prognosis in giant-cell arteritis. Br Med J (Clin Res Ed) 1981;282:269–71.
31. Gran JT, Myklebust G, Wilsgaard T, Jacobsen BK. Survival in polymyalgia rheumatica and temporal arteritis: a study of 398 cases and matched population controls. Rheumatology (Oxford) 2001;40:1238–42.
32. Nesher G, Sonnenblick M, Friedlander Y. Analysis of steroid related complications and mortality in temporal arteritis: a 15-year survey of 43 patients. J Rheumatol 1994;21:1283–6.

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Fatigue and Its Association With Social Participation, Functioning, and Quality of Life in Systemic Sclerosis

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Objective. Fatigue is consistently ranked as one of the most problematic symptoms of systemic sclerosis (SSc), but the impact of fatigue on daily life is not well characterized. The purpose of this study was to examine the contribution of fatigue to deficits in social participation, functioning, and quality of life.

Methods. Baseline data from a sample undertaking a clinical trial were utilized (n = 267). Fatigue, pain interference, depressive symptoms, physical function, and social participation were assessed by measures from the Patient-Reported Outcomes Measurement Information System. Hierarchical linear regressions were performed to determine the unique contribution of fatigue to social participation, physical function, and quality of life above and beyond the effects of demographic and clinical variables, pain interference, and depressive symptoms.

Results. The sample was predominantly female (91%), with an average age of 53.7 years, average disease duration of 9 years, and a mean fatigue T score of 58.7. Of all outcomes, fatigue was most strongly associated with deficits in social participation, explaining 48% of the variance beyond demographic and clinical factors, which is similar to the amount of variance contributed by pain interference and depressive symptoms combined (49%). Fatigue also accounted for significant amounts of variance in physical function and quality of life (R^2 = 0.27 and 0.33, respectively) above and beyond the effects of demographic and clinical factors.

Conclusion. Fatigue is an important clinical problem in SSc and is strongly associated with decreased participation in social roles and activities. Rehabilitation interventions that focus on fatigue management may be necessary to maximize participation.

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune disease associated with vascular damage and tissue fibrosis that affects the skin and internal organs (1–3). In the US, it affects between 13.5 and 39.9 per 100,000 people (4). In addition to the classic skin hardening that restricts movement, a major complaint of individuals with SSc is the substantial symptom burden. Symptoms such as fatigue, pain, and depressive symptoms are common, and because SSc is diagnosed in early to middle age and has no cure, individuals with SSc face many years of managing the manifestations of a complex and progressive condition (5).

Symptoms of SSc significantly disrupt daily activities and diminish quality of life (6–9). Of the symptoms experienced, fatigue has been consistently ranked as one of the most problematic (6,7,10–12). Fatigue in SSc is significantly greater than what is experienced by the general population, which is similar to other rheumatologic conditions and those who are actively receiving cancer treatment (8,9,12). Fatigue affects many facets of life, diminishing the ability to perform usual tasks (7,13), engage in meaningful activities (7,14), perform work duties (15,16), and fulfill family responsibilities (14,17,18). The debilitating nature of fatigue has prompted a call for research to better understand fatigue and its correlates (6,7,9,14) in order

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SIGNIFICANCE & INNOVATIONS

- Fatigue is associated with physical function, quality of life, and social participation. Individuals with systemic sclerosis and higher levels of fatigue had reduced ability to participate in social roles and activities.
- Fatigue explains the same amount of variance in social participation as pain and depressive symptoms combined. With pain and depressive symptoms included in the model, fatigue explains an additional 9% of variance in social participation.
- Fatigue was a significant predictor of physical function and quality of life, although pain interference and depressive symptoms accounted for more variability, suggesting that different symptoms have variable effects depending on the functional domain.

to better address this symptom, reduce disability, and improve quality of life.

To better understand the contribution of fatigue to functioning and quality of life in SSc, we examined baseline data from a sample of participants in a clinical trial investigating the effectiveness of an internet-based, self-management program (19). The purpose of this study was to examine the contribution of fatigue to deficits in social participation, functioning, and quality of life in individuals with SSc. We hypothesized that fatigue would be the strongest unique contributor to each of these outcomes in multivariable models that included other symptoms (pain interference and depressive symptoms), clinical variables, and demographics.

PATIENTS AND METHODS

Procedure. Adults with SSc were recruited to participate in a randomized controlled trial designed to evaluate the efficacy of an internet-based, chronic disease self-management program (19). Participants were recruited from 2 universities (in the Midwest and Southeast US) as well as from websites and social media from national SSc foundations. To be included in the trial, participants needed to be US residents, report a diagnosis of SSc, be age 18 years or older, have basic computer literacy and access to a computer with internet and email capabilities, be able to communicate in English, and be willing to complete the study procedures. All participants provided informed consent. After informed consent was obtained, participants were sent a Qualtrics survey to complete baseline assessments examined in this secondary data analysis. The study was approved by institutional human subjects review boards at the University of New Mexico, University of Michigan, and the Medical University of South Carolina.

Measures. Fatigue was measured using the 4 items from the fatigue subscale of the Patient-Reported Outcomes Measurement Information System (PROMIS)–29, version 2.0. The PROMIS-29 contains several scales used in this analysis that have been validated in a large international sample of individuals with SSc (20). Referenced for the past 7 days and rated on a scale from 1 (not at all) to 5 (very much), the 4 items are as follows: 1) I feel fatigued; 2) I have trouble starting things because I am tired; 3) How rundown did you feel on average?; and 4) How fatigued were you on average? Ratings were converted to a T score metric that standardized the ratings to the US population, in which the mean ± SD ages were 50 ± 10 years. A higher score indicates worse fatigue.

Outcomes. *Social participation.* The Ability to Participate in Social Roles and Activities scale was part of the PROMIS-29 and consists of 4 items. On a scale of 5 (never) to 1 (always), participants were asked to rate the following: 1) I have trouble doing all of my regular leisure activities with others; 2) I have trouble doing all of the family activities that I want to do; 3) I have trouble doing all of my usual work (including work at home); and 4) I have trouble doing all of the activities with friends that I want to do. Scores were converted to T scores for analysis. A higher score indicates better ability.

Physical function. The PROMIS-29 has a physical function scale with 4 items. On a scale of 5 (without any difficulty) to 1 (unable to do), participants were asked to rate the following: 1) Are you able to do chores such as vacuuming or yard work?; 2) Are you able to go up and down stairs at a normal pace?; 3) Are you able to go for a walk of at least 15 minutes?; and 4) Are you able to run errands and shop? A higher score indicates better physical function.

Quality of life. The 5-level EuroQol 5-domain instrument is a generic health-related, quality of life assessment commonly used in populations with various chronic conditions (21,22). It has domains of mobility, self-care, activity, pain, and anxiety. Participants are asked to rate their health state on a scale of no problems, slight problems, moderate problems, severe problems, and extreme problems. Responses are then transformed to a metric of health utility using an algorithm in which scores range from 0.0 (death) to 1.0 (full/optimal health).

Demographic and clinical characteristics. Demographic information included age, race, ethnicity, sex, education level, marital status, and employment status. Clinical characteristics included scleroderma type (limited/CREST syndrome [calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias]/sine, diffuse, or overlap) and disease duration (measured as the year diagnosed). Self-rated health was ascertained using 1 question, in which participants rated their overall health as excellent, very good, good, fair, or poor.

Other symptoms. *Pain interference and depressive symptoms.* Both of these symptoms were assessed from the PROMIS scales of the PROMIS-29. Pain interference was assessed by 4 items. For the previous 7 days, participants rated pain interference on a scale of 1 (not at all) to 5 (very much) for the following questions: 1) How much did pain interfere with your day to day activities?; 2) How much did pain interfere with work

Table 1. Sample-reported symptoms, functioning, and quality of life (n = 267 participants)*

Measures	Overall sample	Diffuse cutaneous SSc (n = 115)	Limited cutaneous SSc (n = 120)	Overlap SSc (n = 31)
Fatigue†	58.7 ± 10.4	57.5 ± 10.1	58.4 ± 10.4	63.7 ± 10.1
Pain interference	58.0 ± 9.3	56.9 ± 9.7	58.0 ± 8.8	61.4 ± 8.9
Pain intensity (0–10 NRS)	4.2 ± 2.2	3.9 ± 2.3	4.2 ± 2.1	4.9 ± 2.2
Depressive symptoms	51.3 ± 9.8	51.3 ± 10.1	51.3 ± 10.0	51.6 ± 8.7
Anxiety	54.0 ± 10.0	53.4 ± 9.9	54.4 ± 10.1	54.7 ± 10.5
Sleep disturbance†	53.7 ± 6.5	53.9 ± 6.5	52.5 ± 5.7	57.0 ± 8.2
Social participation	45.0 ± 8.2	44.9 ± 8.0	45.8 ± 8.5	43.3 ± 7.2
Quality of life, EQ-5D-5L	0.78 ± 0.08	0.78 ± 0.08	0.79 ± 0.08	0.77 ± 0.07
Self-rated health, no. (%)†				
Excellent	3 (1.1)	3 (2.6)	0 (0)	0 (0)
Very good	33 (12.4)	16 (13.9)	15 (12.5)	1 (3.2)
Good	114 (42.7)	38 (33.0)	62 (51.7)	14 (45.2)
Fair	100 (37.5)	51 (44.4)	36 (30.0)	13 (41.9)

* Values are the mean ± SD unless indicated otherwise. We used the Patient-Reported Outcomes Measurement Information System–29, version 2, which comprises scales for fatigue, pain interference, pain intensity, depressive symptoms, anxiety, sleep disturbance, ability to participate in social roles (social participation), and physical function. EQ-5D-5L = 5-level EuroQol 5-domain instrument; NRS = numerical rating scale; SSc = systemic sclerosis.
† $P \leq 0.05$ difference among SSc subtypes.

around the home?; 3) How much did pain interfere with your ability to participate in social activities?; and 4) How much did pain interfere with your household chores? Depressive symptoms were also assessed for the past 7 days. On a scale of 1 (never) to 5 (always), participants rated the following: 1) I felt worthless; 2) I felt helpless; 3) I felt depressed; and 4) I felt hopeless. Higher scores on these scales indicated worse symptoms.

Statistical analysis. Descriptive statistics were used to characterize the sample. We used frequency and proportion for categorical variables, means and SDs for normally distributed continuous data, and median and interquartile ranges for nonnormally distributed continuous data. The association between fatigue (T score from the PROMIS measure) and 3 outcome variables was investigated in 3 separate, hierarchical, multivariable linear regression analyses with the following outcome variables: social participation, physical function, and quality of life. For each outcome, 3 models were constructed to examine the relative contributions of fatigue and other symptoms (pain interference and depressive symptoms) above and beyond demographic and clinical variables. This method allowed us to examine the unique contribution of fatigue and the set of other symptoms, respectively, to the model variance without the influence of each other. It also allowed for comparison across models given the difference in order of entry. In Model 1, demographic and clinical variables (age, sex, race, scleroderma subtype, and years since scleroderma diagnosis) were entered in block 1, and fatigue was entered in block 2. In Model 2, demographic and clinical variables were entered in block 1, fatigue in block 2, and pain interference and depressive symptoms in block 3. Model 2 was performed to examine how much the symptom of fatigue explained the variance in each outcome above and beyond clinical factors, and how much unique variance is then explained by pain interference and depressive symptoms. In Model 3, the order of entry of the pain interference and depressive symptoms block and the fatigue block were reversed. Model 3 was performed to examine how much unique variance fatigue adds to the model above and beyond demographic and clinical variables and symptoms of pain interference and depressive symptoms. R^2 values indicated the amount of variance in the outcomes attributable to the variable blocks entered into the models. To depict the unadjusted relationship between fatigue and social participation, a scatter plot with overlaid best-fitting lines was constructed, estimated using ordinary least squares piecewise regression. We prespecified a cut point of 1 SD below the sample fatigue T score mean.

RESULTS

The characteristics of the sample have been reported in detail elsewhere (19). Briefly, the sample was predominantly female (91%), the mean ± SD age was 53.7 ± 11.7 years, and the sample consisted of 17% racial/ethnic minorities (nonwhite). Approximately three-fourths of the sample (74%) had academic degrees or professional qualifications, with a mean of 16 years of education; 64% were married, and 42% reported working part or full time. For the scleroderma subtype reported by participants, 45% had limited cutaneous SSc or sine scleroderma; 43% had diffuse cutaneous SSc; 12% had scleroderma overlapping with another rheumatic disease, and 0.4% (n = 1) did not know the subtype. Time since diagnosis was a median of 9 years, with an interquartile range of 5–16 years.

Table 1 shows the values for reported functioning, health, and symptom measures. In total, 43.9% of the sample rated their overall health to be fair or poor. Fatigue was the symptom rated to be worst (mean T score 58.7 or 0.87 SD above the US population), followed

Table 2. Association of fatigue with ability to participate in social roles*

	Model 1			Model 2			Model 3		
	Block	β	ΔR^2	Block	β	ΔR^2	Block	β	ΔR^2
Constant		82.83†			94.93†			94.93†	
Demographic/clinical factors	1		0.02	1		0.02	1		0.02
Age		−0.10†			−0.12†			−0.12†	
Female		1.62			1.51			1.51	
Minority		1.03			1.51			1.51	
Diffuse SSc‡		−1.49†			−1.65†			−1.65†	
Overlap SSc‡		0.10			−0.19			−0.19	
Diagnosis year		−0.04			−0.03			−0.03	
Fatigue	2	−0.56†	0.48†	2	−0.32†	0.48†	3	−0.28†	0.09†
Pain interference				3	−0.28†	0.11†	2	−0.16†	0.49†
Depressive symptoms					−0.16†			0.32†	
Total model R^2			0.50			0.61			0.60

***** Fatigue, ability to participate in social roles and activities, pain interference, and depressive symptoms are scales from the Patient-Reported Outcomes Measurement Information System–29, version 2. Hierarchical regression models were constructed with variable(s) entered in blocks. Beta coefficients are from full models. ΔR^2 is shown for pain interference and depressive symptoms in combination, as they were entered together in a block. N = 266 in all models (1 participant had missing data for systemic sclerosis [SSc] type).
† $P \leq 0.05$.
‡ Reference group: limited or sine scleroderma.

by pain interference (mean T score 58.0). Mean anxiety, sleep disturbance, and depressive symptoms scores were all within 0.5 SDs of the normative sample mean (T score 50). Using 1-way analyses of variance or chi-square tests to examine differences across SSc subtype, only fatigue, sleep disturbance, and self-rated health were significantly different ($P \leq 0.05$). Participants with overlap SSc had the highest levels of fatigue and sleep disturbance and comprised the highest proportion of those who rated their health as fair or poor (51.6%). Participants with diffuse cutaneous SSc also comprised a high proportion of individuals who rated their health as fair or poor (50.5%), but their mean fatigue and sleep disturbance levels were similar to those with limited cutaneous SSc or sine scleroderma.

Fatigue and social participation. Table 2 shows results from hierarchical regression models in which fatigue and other variables were examined as predictors of social participation. In Model 1, 50% of the variance in social participation was explained by demographic and clinical factors, which contributed a negligible

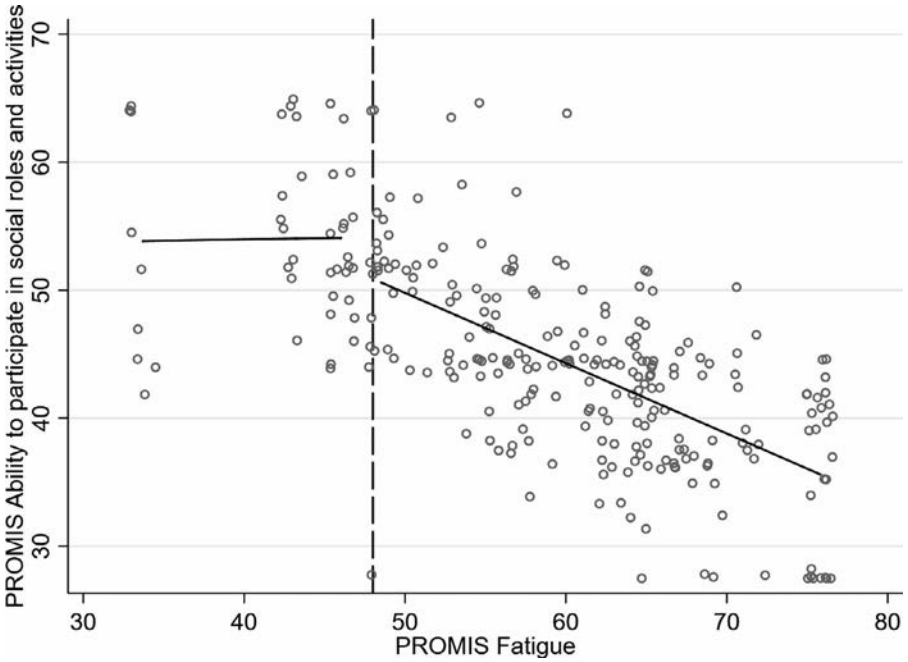

Figure 1. Unadjusted relationship between fatigue and social participation. Social participation is measured by the Patient-Reported Outcomes Measurement Information System (PROMIS), using the Ability to Participate in Social Roles and Activities subscale. Both axes depict T scores. The cut point used (dotted line) is 1 SD below the sample mean for the PROMIS fatigue subscale (T score 48). Solid lines depict the best-fit (ordinary least squares regression) lines above and below the cut point. Symbols show data points for individual participants.

Table 3. Association of fatigue with physical function*

	Model 1			Model 2			Model 3		
	Block	β	ΔR^2	Block	β	ΔR^2	Block	β	ΔR^2
Constant		66.41†			76.51†			76.51†	
Demographic/clinical factors	1		0.03	1		0.03	1		0.03
Age		−0.07†			−0.09†			−0.09†	
Female		0.84			1.13			1.13	
Minority		0.47			1.00			1.00	
Diffuse SSc‡		−1.84†			−2.05†			−2.05†	
Overlap SSc‡		−1.23			−1.15			−1.15	
Diagnosis year		−0.07			−0.06			−0.06	
Fatigue	2	−0.36†	0.27†	2	−0.16†	0.27†	3	−0.16†	0.03†
Pain interference				3	−0.35†	0.13†	2	−0.35†	0.37†
Depressive symptoms					−0.03			−0.03	
Total model R^2			0.30			0.43			0.43

* Fatigue, physical function, pain interference, and depressive symptoms are scales from the Patient-Reported Outcomes Measurement Information System–29, version 2. Hierarchical regression models were constructed with variable(s) entered in blocks. Beta coefficients included in the table are from full models. ΔR^2 is shown for pain interference and depressive symptoms in combination, as they were entered together in a block. N = 266 in all models (1 participant had missing data for systemic sclerosis [SSc] type).
† $P \leq 0.05$.
‡ Reference group: limited or sine scleroderma.

amount (2%) of variance, and by fatigue, which accounted for nearly one-half (48%) of the variance. Of the demographic and clinical factors, age and the diffuse cutaneous SSc subtype demonstrated significant independent negative associations with social participation. When pain interference and depressive symptoms were added in a block after fatigue (Model 2), a further increase of 11% of variance in the outcome was explained by these symptoms. In Model 3, fatigue accounted for a significant amount of variance (9%) above and beyond the effects of pain interference and depressive symptoms combined (49% of variance). Regardless of the order of entry, the models accounted for ~60% of the variance in social participation.

Figure 1 shows the unadjusted association between fatigue and social participation, with the best-fit line segmented at 1 SD below the sample mean (fatigue mean T score 48). In this graph, the negative association between fatigue and social participation is only seen when patients have fatigue that is approximately at the mean or greater (T score of 48 or higher). Fatigue was not associated with social participation for individuals with low fatigue.

Fatigue and physical function. Table 3 shows the results from the hierarchical regression models in which physical function was the outcome. In Model 1, 30% of the variance in physical function was explained by demographic and clinical factors (3% combined) and fatigue (27% of the variance). Age and diffuse cutaneous SSc were significantly negatively associated with physical function and depressive symptoms. In Model 2, fatigue accounted for a significant and substantial amount of variance in physical function (27%); pain and depressive symptoms added a significant amount of variance above and beyond the effect of fatigue on physical function. In Model 3, pain interference and depressive symptoms accounted for a substantial and significant amount of variance in physical function (37%); fatigue added a statistically significant, although small amount of variance in physical functioning when added in the third step. The models accounted for 43% of the variance in self-reported physical function.

Fatigue and quality of life. Table 4 shows the results from the hierarchical regression models in which quality of life was the outcome. In Model 1, 35% of the variance in quality of life was explained by demographic and clinical factors and fatigue; as in prior models, demographic and clinical variables accounted for very small amounts of the variance in quality of life (2%), whereas fatigue accounted for 33% of the variance. Of the demographic factors, diffuse cutaneous SSc was significantly associated with lower quality of life. In Model 2, pain interference and depressive symptoms contributed an additional 21% variance in quality of life above and beyond the effects of fatigue. In contrast, in Model 3, fatigue only contributed an additional 1% variance in quality of life above the variance explained by pain interference and depressive symptoms, which accounted for 53% of the variance in quality of life. These models explained 56% of the variance in quality of life and depressive symptoms.

DISCUSSION

Fatigue is a symptom often described in the literature as debilitating by individuals with SSc (6,10,11), but it is not yet clear what aspects of functioning and quality of life are most affected by fatigue and other symptoms. In this study, our objective was to examine the contribution of fatigue to deficits in social participation, functioning, and quality of life. To accomplish this, we examined the relative contributions of fatigue above and beyond demographics and clinical factors and other symptoms (pain interference and depression).

Table 4. Association of fatigue with quality of life*

	Model 1			Model 2			Model 3		
	Block	β	ΔR^2	Block	β	ΔR^2	Block	β	ΔR^2
Constant		1.05†			1.22†			1.22†	
Demographic/clinical factors	1		0.02	1		0.02	1		0.02
Age		−0.0001			−0.0004			−0.0004	
Female		0.02			0.02			0.02	
Minority		−0.004			0.002			0.002	
Diffuse SSc‡		−0.01			−0.02†			−0.02†	
Overlap SSc‡		−0.004			−0.008			−0.008	
Diagnosis year		−0.0004			−0.0003			−0.0003	
Fatigue	2	−0.005†	0.33†	2	−0.001†	0.33†	3	−0.001†	0.01†
Pain interference				3	−0.004†	0.21†	2	−0.004†	0.53†
Depressive symptoms					−0.002†			−0.002†	
Total model R^2			0.35			0.56			0.56

* Quality of life was measured using the 5-level EuroQol 5-domain instrument. Fatigue, pain interference, and depressive symptoms are scales from the Patient-Reported Outcomes Measurement Information System–29, version 2. Hierarchical regression models were constructed with variable(s) entered in blocks. Beta coefficients included in the table are from full models. ΔR^2 is shown for pain interference and depressive symptoms in combination, as they were entered together in a block. N = 266 in all models (1 participant had missing data for systemic sclerosis [SSc] type).
† $P \leq 0.05$.
‡ Reference group: limited or sine scleroderma.

There are 3 main findings of this study. First, of all outcomes assessed, fatigue was most strongly associated with decreased ability to participate in social roles and activities. Fatigue alone accounted for nearly the same amount of variance in social participation ($R^2 = 0.48$) (Table 2) as pain interference and depressive symptoms combined ($R^2 = 0.49$) (Table 2). Furthermore, the substantial amount of unique variance that fatigue explained over and above symptoms of pain interference and depressive symptoms suggests that fatigue is particularly influential with regard to reduced social participation. These findings are in contrast to those of Sandusky et al, who reported that fatigue was not a significant correlate for social participation after controlling for depressive symptoms (7), and Poole et al (23), who used a single visual analog scale measure for fatigue and reported no difference in social participation with higher levels of fatigue. However, there are several key differences in the measurement of social participation between the current study and those studies. Sandusky et al measured social participation via social networks and relationships as opposed to participation in particular activities, and Poole et al measured social participation by ascertaining frequency of performance of activities, such as gardening, household maintenance, and shopping, and also counted higher frequency as better participation.

In the current study, social participation was measured using the PROMIS social participation scale, which assesses difficulty in usual activities and whether participation is above or below what the individual wants to do. In addition, the PROMIS social participation scale has been validated and has stronger psychometric properties compared to the instruments used in the prior studies. Last, differences between this study's sample and the samples in those studies may also affect the comparisons. For instance, in the study by Sandusky et al, a higher proportion of individuals reported having a high school education or less (32%) in relation to the current sample (20%).

One reason why fatigue may have a strong negative association with social participation is because work limitations are included in the social participation measure. In SSc, fatigue is a strong correlate of work disability (24,25), and baseline fatigue severity was a main predictor of work disability in a longitudinal study (16). This study's findings, showing a strong negative association between fatigue and social participation, are similar to those of studies of another chronic condition: multiple sclerosis (26,27). In those studies, pain and depressive symptoms are also important factors in decreased physical function and quality of life.

Our findings have implications for both assessment and intervention development. While clinical assessment often includes measures of physical function, it appears important to include measures of social participation when assessing patients with SSc, especially if they report high fatigue. In addition, the assessment used to measure fatigue is an important consideration, as some assessments, such as the Multidimensional Fatigue Inventory and Multidimensional Assessment of Fatigue Scale, include items asking about the impact of fatigue on participation. Assessment of social participation may reveal areas for intervention that would be appropriate for rehabilitation professionals to address, such as workplace adaptation, and also supports the idea that fatigue management is necessary in this population, which is similar to the recommendations in other studies (6,7,9,12,14).

Second, although fatigue accounted for approximately one-third of the variance in physical function and quality of life outcomes when entered in the models prior to the addition of pain interference and depressive symptoms, fatigue did not significantly contribute to the variance in physical function and quality of life after these symptoms were included in the models (only 1% and 3%, respectively). The findings suggest that interventions to impact physical function and quality of life need to be multifaceted

and include strategies to reduce pain and depressive symptoms in addition to fatigue management. Indeed, other studies have confirmed this relationship between fatigue, pain, depressive symptoms, and function (7,12,28).

Third, this finding extends the understanding of how demographic and clinical factors relate to symptoms, functioning, and quality of life in SSc. Neither age nor disease subtype was associated with the outcomes measured. Interestingly, individuals with SSc all have relatively high symptom severity compared to normative populations, and individuals with the 2 main subtypes of SSc (diffuse and limited) have somewhat similar fatigue levels (T scores 57 and 58, respectively). This is similar to a previous study that showed no significant differences in fatigue by subtype (7). Although fatigue severity was similar in these groups, individuals with diffuse cutaneous SSc have greater deficits in their ability to participate in social roles and activities, suggesting that fatigue management is particularly important in this group. Moreover, lung, gastrointestinal, and muscle involvement, more common with diffuse cutaneous SSc, have been reported to be predictors of fatigue (12).

In regard to limitations, this study utilized cross-sectional data, so causality between fatigue and outcomes cannot be assumed. Furthermore, participants comprised a national sample and self-reported all measures via survey, so clinical variables could not be corroborated by medical records. In addition, other measures of health status, such as number and types of comorbidities, were not collected, and this information could have further explained variance in the functioning and quality of life outcomes. Future studies should examine longitudinal associations between fatigue and social participation.

In conclusion, this study showed that fatigue related strongly to deficits in the ability to participate in social roles and activities. Intervention development for fatigue management may be particularly needed to maximize social participation in this 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. Murphy had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Murphy, Kratz, Whibley, Poole, Khanna.
Acquisition of data. Murphy, Poole, Khanna.
Analysis and interpretation of data. Murphy, Kratz, Whibley, Poole, Khanna.

REFERENCES

1. Johnson SR, Chung L, Fransen J, van den Hoogen FH. Evolving concepts of diagnosis and classification. In: Varga J, Denton CP, Wigley FM, Allanore Y, Kuwana M, editors. Scleroderma: from pathogenesis to comprehensive management. Cham: Springer International; 2017. p. 49–64.
2. Bolster M, Silver R. Clinical features of systemic sclerosis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. 5th ed. Philadelphia: Mosby, Elsevier; 2011. p. 1373–86.
3. Denton C, Khanna D. Systemic sclerosis. Lancet 2017;390:1685–99.
4. Bergamasco A, Hartmann N, Wallace L, Verpillat P. Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease. Clin Epidemiol 2019;11:257–73.
5. Schnitzer M, Hudson M, Baron M, Steele R. Disability in systemic sclerosis-a longitudinal observational study. J Rheumatol 2010;38: 685–92.
6. Bassel M, Hudson M, Taillefer SS, Schieir O, Baron M, Thombs BD. Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a Canadian national survey. Rheumatology (Oxford) 2011;50:762–7.
7. Sandusky SB, McGuire L, Smith MT, Wigley FM, Haythornthwaite JA. Fatigue: an overlooked determinant of physical function in scleroderma. Rheumatology (Oxford) 2009;48:165–9.
8. Thombs BD, Hudson M, Bassel M, Taillefer SS, Baron M, Markland J, et al. Sociodemographic, disease, and symptom correlates of fatigue in systemic sclerosis: evidence from a sample of 659 Canadian Scleroderma Research Group Registry patients. Arthritis Rheum 2009;61:966–73.
9. Thombs BD, van Lankveld W, Bassel M, Baron M, Buzza R, Haslam S, et al. Psychological health and well-being in systemic sclerosis: state of the science and consensus research agenda. Arthritis Care Res (Hoboken) 2010;62:1181–9.
10. Richards HL, Herrick AL, Griffin K, Gwilliam PD, Loukes J, Fortune DG. Systemic sclerosis: patients' perceptions of their condition. Arthritis Rheum 2003;49:689–96.
11. Van Lankveld WG, Vonk MC, Teunissen H, van den Hoogen FH. Appearance self-esteem in systemic sclerosis: subjective experience of skin deformity and its relationship with physician-assessed skin involvement, disease status and psychological variables. Rheumatology (Oxford) 2007;46:872–6.
12. Basta F, Afeltra A, Margiotta D. Fatigue in systemic sclerosis: a systematic review. Clin Exp Rheumatol 2018;36:150–60.
13. Peytrignet S, Denton CP, Lunt M, Hesselstrand R, Mouthon L, Silman A, et al. Disability, fatigue, pain and their associates in early diffuse cutaneous systemic sclerosis: the European scleroderma observational study. Rheumatology (Oxford) 2018;57:370–81.
14. Nakayama A, Tunnicliffe DJ, Thakkar V, Singh-Grewal D, O'Neill S, Craig JC, et al. Patients' perspectives and experiences living with systemic sclerosis: a systematic review and thematic synthesis of qualitative studies. J Rheumatol 2016;43:1363–75.
15. Sandqvist G, Scheja A, Hesselstrand R. Pain, fatigue and hand function closely correlated to work ability and employment status in systemic sclerosis. Rheumatology (Oxford) 2010;49:1739–46.
16. Sharif R, Mayes MD, Nicassio PM, Gonzalez EB, Draeger H, McNearney TA, et al. Determinants of work disability in patients with systemic sclerosis: a longitudinal study of the GENISOS cohort. Semin Arthritis Rheum 2011;41:38–47.
17. Poole JL, Wilier K, Mendelson C. Occupation of motherhood: challenges for mothers with scleroderma. Am J Occup Ther 2009;63:214–9.
18. Poole JL, Willer K, Mendelson C, Sanders M, Skipper B. Perceived parenting ability and systemic sclerosis. Musculoskeletal Care 2011;9:32–40.
19. Khanna D, Serrano J, Berrocal VJ, Silver RM, Cuencas P, Newbill SL, et al. Randomized controlled trial to evaluate an internet-based self-management program in systemic sclerosis. Arthritis Care Res (Hoboken) 2019;71:435–47.
20. Kwakkenbos L, Thombs BD, Khanna D, Carrier ME, Baron M, Furst DE, et al. Performance of the patient-reported outcomes measurement information system-29 in scleroderma: a scleroderma

patient-centered intervention network cohort study. Rheumatology (Oxford) 2017;56:1302–11.
21. Rabin R, de Charro F. EQ-SD: a measure of health status from the EuroQol group. Ann Med 2001;33:337–43.
22. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.
23. Poole JL, Chandrasekaran A, Hildebrand K, Skipper B. Participation in life situations by persons with systemic sclerosis. Disabil Rehabil 2015;37:842–5.
24. Hudson M, Steele R, Lu Y, Thombs BD, Baron M. Work disability in systemic sclerosis. J Rheumatol 2009;36:2481–6.
25. Sandqvist G, Scheja A, Eklund M. Working ability in relation to disease severity, everyday occupations and well-being in women with limited systemic sclerosis. Rheumatology (Oxford) 2008;47:1708–11.
26. Kratz AL, Braley TJ, Foxen-Craft E, Scott E, Murphy JF III, Murphy SL. How do pain, fatigue, depressive, and cognitive symptoms relate to well-being and social and physical functioning in the daily lives of individuals with multiple sclerosis? Arch Phys Med Rehabil 2017;98:2160–6.
27. Salter A, Fox RJ, Tyry T, Cutter G, Marrie RA. The association of fatigue and social participation in multiple sclerosis as assessed using two different instruments. Mult Scler Relat Disord 2019;31:165–72.
28. Yacoub Y, Amine B, Bensabbah R, Hajjaj-Hassouni N. Assessment of fatigue and its relationships with disease-related parameters in patients with systemic sclerosis. Clin Rheumatol 2012;31:655–60.

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Unmet Workplace Support Needs and Lost Productivity of Workers With Systemic Sclerosis: A Path Analysis Study

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Objective. Few studies have examined how workplace support can address work productivity loss among individuals with systemic sclerosis (SSc). The objective was to 1) examine the relationship between unmet workplace support needs and work productivity loss among workers with SSc, and 2) determine whether SSc symptom severity, fatigue, active disease periods, and workplace activity limitations mediate the relationship between unmet workplace support needs and work productivity loss.

Methods. A cross-sectional survey was conducted of employed individuals with SSc who were recruited through rheumatology clinics. Information on work productivity loss (i.e., absenteeism, presenteeism, job disruptions) and the need, availability, and use of workplace supports was collected. SSc symptom severity (e.g., workplace activity limitations, active disease periods, fatigue, and overall SSc symptom severity) and demographic, health, and work context characteristics were collected. Three Bayesian path models examined the association between unmet workplace support needs and each work productivity loss outcome. SSc symptom severity variables were examined as mediators in each model.

Results. A total of 110 employed participants were recruited (mean ± SD ages 49 ± 12.9 years). More than three-fourths of participants were female (77%) and worked full-time (77%). The most needed workplace supports included extended health benefits (84%), special equipment (63%), and flextime (59%). Additionally, 61% reported unmet workplace support needs. Path models indicated that indirect relationships between unmet workplace support needs and work productivity loss were significant. For all models, workplace activity limitations mediated the relationship between unmet workplace support needs and productivity loss.

Conclusion. To foster productive employment of individuals with SSc, interventions need to address symptom severity and meet workplace support needs.

INTRODUCTION

For workers with rare rheumatic conditions like systemic sclerosis (SSc; scleroderma), the workplace has the potential to play a critical role in helping to sustain employment and minimize lost productivity. To date, research has mostly focused on the work experiences of more prevalent rheumatic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus) (1–4). These studies indicate that a rheumatic disease contributes to absenteeism (i.e., health-related missed work days), presenteeism (i.e., working while unwell), and job disruptions (e.g., interruptions to work) (2,5–7). These studies also indicate that the management of symptom severity and modifications to the work context can mitigate productivity loss (3,4,8–11). A paucity of evidence currently exists on the relationship between SSc and work productivity. Moreover, there are few studies across any rheumatic disease that examine the relationship between workplace supports and employment outcomes. We present findings from a survey of workers with SSc that examined whether meeting or not meeting workplace support needs is related to SSc symptoms and workplace activity limitations, as well as to employment outcomes. Findings will inform the development of workplace policies and practices that could foster the employment of people with SSc.

SSc is a rare and complex multisystem autoimmune disease that involves a tightening or hardening of the skin or

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

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SIGNIFICANCE & INNOVATIONS

- Few studies have examined the at-work experiences of people with systemic sclerosis (SSc) and the role of workplace supports in addressing lost productivity.
- The identification of unmet workplace support needs among nearly two-thirds of study participants points to new areas where intervention efforts should be focused.
- Meeting workplace support needs for people living with SSc has the potential to address lost productivity, especially for those with greater workplace activity limitations.

other connective tissues (12,13). Like other rheumatic diseases, SSc is characterized by a range of symptoms (e.g., fatigue, pain, and joint stiffness, as well as gastrointestinal, pulmonary, and vascular manifestations, and renal or cardiac involvement) that can be intermittent in severity and associated with functional limitations and participation restrictions (12,14–16). SSc more commonly affects females than males (4.7:1), and the prevalence of SSc ranges from 13.3 (male) to 74.4 (female) cases per 100,000 (17,18). Despite the relatively low prevalence, SSc can have a considerable impact on employment, in part because it is most likely to be diagnosed between ages 18 and 50 years, which are typically considered prime career years (19). A small body of research has examined the relationship between SSc and employment participation. These studies indicate that SSc is associated with work disability, including not participating in employment (14,15,20) and absenteeism (21,22). More severe SSc symptoms (e.g., greater fatigue and functional limitations) are associated with greater work disability (14,15). Limited research has examined the employment experiences of those who are trying to work with SSc, and its association with presenteeism or job disruptions. In addition, a few studies have examined the role of work context factors and workplace supports and their potential to mitigate the impact of the disease.

Biopsychosocial models of disability suggest that health factors are rarely the only explanatory variable related to labor market activity and provide a limited understanding of person–job fit needs and impact (23–25). Work context factors are key aspects of disability and employment. A body of research from the rheumatic diseases literature indicates that work context factors, such as unpredictable work scheduling, more physical and psychosocial job demands, or less supervisor social support are significantly associated with not participating in employment and with greater absenteeism, presenteeism, and job disruptions (1,26). This research suggests that the provision of supports within the workplace has the potential to ameliorate the impact of rheumatic disease in ways that strengthen person–job fit and minimize productivity loss. The workplace supports that are in the highest demand as reported by people with rheumatic disease include scheduling accommodations, extended medical/drug benefits, adaptations to the physical work environment, modified job duties, and workplace social support (8,10,11,27,28).

What has been less studied is whether these workplace support needs have been met. A recent study of 681 older workers (ages 50–67 years) with inflammatory arthritis and osteoarthritis found that close to one-fourth of participants (23.5%) indicated unmet workplace support needs (8). Findings from the study also highlight an interrelationship between unmet workplace support needs, symptom severity, and work productivity. That is, unmet workplace support needs were associated both with more severe disease and with greater work productivity losses (8). However, the study did not disentangle these relationships. To our knowledge, no studies have examined the workplace support needs of people living with SSc.

This study adopted a biopsychosocial perspective to examine the workplace support needs of people with SSc. We examined the interrelationships among unmet workplace support needs, symptom severity (e.g., pain and fatigue, workplace activity limitations, and active disease periods), and work productivity loss (e.g., absenteeism, presenteeism, and job disruptions) using a path modeling analytical approach. We addressed 2 research questions in this study. The first question was: Do greater unmet support needs directly relate to greater work productivity loss? The second question addressed whether the relationship between workplace support and productivity loss is mediated by more severe SSc symptoms and limitations (i.e., greater fatigue, workplace activity limitations, and the number of active disease periods). Specifically, is having unmet support needs associated with greater SSc symptoms and limitations, and in turn, related to productivity loss?

PATIENTS AND METHODS

To test the study hypotheses, we conducted a cross-sectional survey of employed individuals with SSc. Surveys were administered over the phone by a trained interviewer and lasted ~25 minutes. Participants received a $10 gift card for their participation. All study procedures were reviewed by the Research Ethics Board of the University Health Network (REB# 14–7848) in Toronto, Canada.

Recruitment and eligibility. Participants were recruited primarily through the Toronto Scleroderma Program, a health care network comprised of 3 academic, hospital-based SSc specialty clinics, which are all affiliated with the University of Toronto. During an appointment with their rheumatologist, eligible participants were provided with information about the study, and if interested, were asked to consent to being contacted by a research coordinator. The research coordinator contacted potential participants to provide detailed information about the study, confirm eligibility, obtain consent, and schedule a telephone interview.

Participants were eligible to complete the survey if they met the American College of Rheumatology/European League Against Rheumatism SSc classification criteria (29), had SSc disease duration of >1 year, were working age (18–70 years), were currently employed or employed in the last 5 years, and were fluent in the English language. Exclusion criteria included diagnosis of any other physical or mental health condition that limited work or recovery from surgery in the past 6 months.

Measures. A questionnaire was administered to all participants to collect information on demographic and health characteristics, work experiences, and work context factors. Items and measures were selected based on evidence of precision, validity, feasibility, and responsiveness to change.

Outcome: work productivity loss. Three measures were administered to examine lost productivity. For presenteeism, a global item from the Work Productivity and Activity Impairment Questionnaire (30) was administered to participants to rate the extent to which their health affected productivity while working in the past month (0 = no effect, 10 = prevented working). For absenteeism, the number of days participants were absent from work due to health problems in the past 3 months was also collected (31). For job disruptions, 7 items asked whether a participant had experienced a disruption to their employment (e.g., arriving late, leaving early, or missing meetings) in the past 6 months (yes/no). The items were summed for a total score ranging 0–7 (6).

Primary independent variable: unmet workplace support needs. A list of 9 job accommodations, (e.g., special equipment), modifications (e.g., modified job tasks), or benefits (e.g., wellness programs) were presented to participants. The list of job accommodations, modifications, and benefits was designed from previous studies of accommodation practices for people with rheumatic diseases (8,10). Participants were asked whether a particular job accommodation, modification, or benefit was available (yes/no/don't know), needed (yes/no), and used (yes/no). Unmet workplace support need, the primary study independent variable, was calculated by the frequency of workplace supports where need was greater than or equal to usage (8).

Mediators: SSc symptom severity. Three measures that reflected SSc symptom severity and limitations were assessed and examined as mediators in the relationship between unmet workplace support needs and productivity loss. For active disease periods, respondents were asked, "How many flares or times of more severe overall scleroderma disease difficulty have you had in the past 3 months?" Participants could select from the following options: 0 active disease periods, 1–2 disease periods, or ≥3 periods. Difficulties with workplace activities and tasks were measured using the Workplace Activity Limitation Scale. Twelve questions asked about problems with lower mobility, upper mobility, concentration, and the pace and schedule of work (0 = no difficulty/not applicable to job, 3 = unable to do). Items were summed to produce a score ranging 0–36 (32,33). To asses fatigue, 8 items from the Profile of Mood States fatigue subscale (e.g., worn out, fatigued) were administered. Responses were collected on a 4-point, Likert-type scale (0 = not at all, 4 = extremely). A total fatigue score was produced (34). To asses overall SSc severity, information was drawn from the Scleroderma Heath Assessment Questionnaire (SHAQ), where 1 item asked about overall disease severity considering pain, discomfort, activity limitations, and bodily and life changes (0 = no disease, 100 = very severe limitation) (35,36).

Covariates. Information on demographic, health-related, and work context factors was collected for descriptive purposes and was examined in bivariate and multivariable models. Demographic information collected included age (in years), sex, educational attainment, and marital status. Health factors measured included self-reported health (1 = poor, 5 = excellent) and years living with SSc and variability of SSc symptoms (1 = not at all, 5 = a great deal). Using items from the SHAQ, information on activity limitations attributed to SSc symptoms (e.g., intestinal problems, breathing problems, Raynaud's phenomenon, and finger ulcers) was assessed (0 = does not limit activities, 100 = very severe limitations) (35,36). Work context factors were job sector, hours worked/week, self-employment, job tenure at current organization (years), and firm size (≤100 employees, >100 employees).

Statistical analysis. A path analysis modeling approach was conducted to test study hypotheses. Means ± SDs and percentages were produced to describe demographic, health, and work context covariates, SSc symptom severity, work productivity outcomes, and workplace support needs. Distributions of all variables were examined for normality. Bivariate analyses (chi-square and *t*-tests) were conducted to examine significant differences between those with met and unmet workplace support needs. Additional bivariate analyses were conducted (Pearson's,

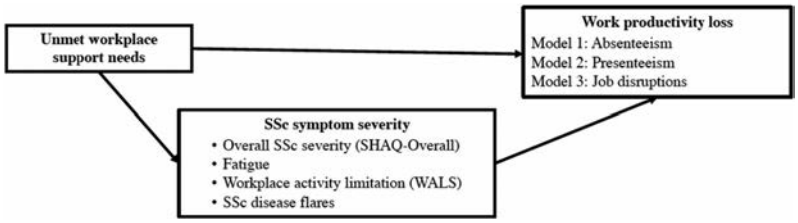

Figure 1. Path models examining the direct and indirect relationship between unmet workplace support needs and work productivity loss. SHAQ = Scleroderma Heath Assessment Questionnaire; SSc = systemic sclerosis; WALS = Workplace Activity Limitations Scale.

tetrachoric, and biserial correlations) to examine the interrelationship between work productivity outcome measures, the independent variable, mediator variables, and covariates. Covariates that were associated with mediator and work outcome variables were retained in the multivariable path models.

Bayesian path analysis models examined the direct association between unmet workplace support needs and work productivity loss outcomes. The path analysis models also examined whether the relationship between unmet workplace support needs and work productivity was indirect and mediated by SSc symptom severity (i.e., fatigue, active disease periods, workplace activity limitations) (37). Activity limitations attributed to specific SSc symptoms, with the exception of Raynaud's phenomenon, did not significantly differ between participants with and without unmet workplace support needs. Accordingly, we chose to examine how overall SSc severity mediated the relationship between unmet workplace support needs and work productivity. Separate path models were conducted for each work productivity outcome measure (i.e., absenteeism, presenteeism, and job disruptions). A summary of the path models is shown in Figure 1. A notable feature of path models is that they provide fit indices that allow us to determine how well our model fits the data. To examine model fit, default priors

Table 1. Sample description of employed participants with systemic sclerosis (SSc), with descriptive characteristics compared by those reporting workplace support needs met and unmet (n = 110)*

Characteristic	Total sample	Workplace support needs		*P*†
		Met	Unmet	
Demographic factors				
Age, years	48.4 ± 12.9	47.2 ± 13.0	49.2 ± 12.8	0.4168
Female, no. (%)	85 (77.3)	31 (36.5)	54 (63.5)	0.2990
Married/living as if married, no. (%)	70 (64.2)	11 (47.8)	12 (52.2)	0.5631
Education, no. (%)				
Less than postsecondary	25 (22.7)	10 (40.0)	15 (60.0)	0.9156
More than postsecondary	85 (77.3)	33 (38.8)	52 (61.2)	–
Health factors/SSc symptom severity				
Disease duration, years	9.3 ± 7.2	10.9 ± 8.7	8.3 ± 5.8	0.0871
Self-rated health (1–5)	3.0 ± 0.9	3.4 ± 0.8	2.7 ± 0.8	0.0001‡
Disease variability (1–5)	2.4 ± 1.0	2.1 ± 0.9	2.6 ± 1.0	0.0319‡
Intestinal problems interfered with daily activities (0–100)	28.0 ± 29.8	21.4 ± 30.4	32.2 ± 28.9	0.0623
Breathing problems interfered with daily activities (0–100)	20.1 ± 27.7	15.5 ± 26.5	23.1 ± 28.3	0.1621
Raynaud's phenomenon interfered with daily activities (0–100)	35.4 ± 33.9	22.1 ± 31.1	43.9 ± 33.1	0.0008‡
Finger ulcers interfered with daily activities (0–100)	18.3 ± 31.1	12.5 ± 25.5	22.1 ± 34.0	0.0990
Overall SSc severity (0–100)	36.9 ± 26.6	24.1 ± 21.4	45.1 ± 26.4	<0.0001‡
Active disease periods, no. (%)				
None	45 (41.7)	24 (53.3)	21 (46.7)	0.0093‡
≥1	63 (58.3)	18 (28.6)	45 (71.4)	–
Workplace activity limitations (WALS: 0–36)	8.1 ± 5.7	5.0 ± 3.9	10.1 ± 5.7	<0.0001‡
Fatigue (0–32)	17.2 ± 6.4	14.6 ± 6.6	18.8 ± 5.8	0.0006‡
Work context factors				
Full-time employment (≥35 hours/week), no. (%)	84 (77.1)	40 (47.6)	44 (52.4)	0.0014‡
Job tenure, years	11.3 ± 9.7	14.1 ± 10.5	9.6 ± 8.8)	0.0167‡
Self-employed, no. (%)	23 (20.9)	8 (34.8)	15 (65.2)	0.6340
Employer size, no. (%)				
<100 employees	37 (41.1)	13 (35.1)	24 (64.9)	0.3357
≥100 employees	53 (58.9)	24 (45.3)	29 (54.7)	–
Industry, no. (%)				
Professional services/education/health/nonprofit	43 (41.3)	–	–	0.6272
Sales/retail	16 (15.4)	18 (41.9)	25 (58.1)	–
Utilities/construction/agriculture/mining	15 (14.4)	5 (31.3)	11 (68.7)	–
Bank/insurance/government	30 (28.9)	4 (26.7)	11 (73.3)	–
Perceived work stress (1–5)	3.2 ± 1.0	13 ± 43.3	17 ± 56.7	–
Work productivity outcomes				
Absenteeism, no. (%)				
<1 day	54 (49.5)	15 (27.8)	39 (72.2)	0.0223‡
≥1 day	55 (50.5)	27 (49.1)	28 (50.9)	–
Presenteeism (WPAI: 0–10)	2.8 ± 2.7	1.6 ± 1.8	3.6 ± 3.0	<0.0001‡
Job disruptions (0–7)	1.6 ± 1.7	0.9 ± 1.2	2.1 ± 1.8	0.0001‡
Unmet workplace support needs, no. (%)	67 (60.9)	–	–	–

* Values are the mean ± SD unless indicated otherwise. Sample size may vary due to missing data. WALS = Workplace Activity Limitations Scale; WPAI = Work Productivity and Activity Impairment Questionnaire.
† *P* values were calculated using chi-square (categorical variables) and *t*-test (continuous variables).
‡ Significant at $P < 0.05$.

were used for all estimated parameters (38,39). Two chains were estimated with 50,000 iterations each. Convergence was reached (potential scale reduction convergence criterion value of 1.00), and all 3 models had a positive predictivity ($P < 0.50$). After checking trace plots and autocorrelation plots of estimated parameters, we found that some parameters showed high autocorrelation. Accordingly, analyses were repeated with thinning of 20 and 2 chains with 100,000 iterations each. All diagnostic plots showed good model fit. Analyses were conducted using SAS software, version 9.3 (40) and Mplus, version 8.1 (41).

RESULTS

A total of 140 respondents with SSc completed the survey, of which 110 (79%) were participating in paid employment. The analyses will focus only on employed participants. Sample characteristics are summarized in Table 1. The mean ± SD age of participants was 48 ± 12.9 years, 77% were female, 64% were married/living as if married, and more than three-fourths had a postsecondary education (85%). Participants indicated living with their condition for mean ± SD 9.3 ± 7.2 years and reported moderate self-rated health (mean ± SD 3.0 ± 1.0) and disease variability (mean ± SD 2.4 ± 1.0). Participants indicated a mean ± SD fatigue score of 17.2 ± 6.4. More than half reported an active disease period in the past month (58%) and a mean ± SD overall SSc severity score of 36.9 ± 26.6. Among SSc symptoms, Raynaud's phenomenon (SSc severity score 35.4 ± 33.9) and intestinal problems (SSc severity score 28.0 ± 29.8) that interfered with daily activity limitations were most frequently reported.

A mean ± SD Workplace Activity Limitations Scale score of 8.1 ± 5.7 was reported. The most difficult workplace activities and tasks included working with hands, crouching, bending or kneeling, and lifting, carrying, or moving objects (Table 2). With the exception of sitting for long periods and getting to and from work, participants with unmet workplace support needs reported significantly greater difficulty with workplace activities and tasks when compared to those reporting that their workplace support needs were met.

A majority of participants worked full-time (77%), 41% worked for a small company (≤100 employees), and 1 in 5 were self-employed (21%). Participants reported a mean ± SD job tenure of 11.3 ± 9.7 years, and close to one-third (29%) worked in the bank/insurance/government sector. Participants reported a mean ± SD work stress score of 3.2 ± 1.0. In terms of work productivity outcome measures, close to one-half of participants reported >1 day of absence related to their health, and a mean ± SD presenteeism score of 2.8 ± 2.7. In addition, respondents indicated a mean ± SD of 1.6 ± 1.7 job disruptions of a possible 7 disruptions (Table 1).

Overall, 61% of participants reported that their workplace support needs were unmet. Table 1 compares sample characteristics between participants who reported that workplace support needs were met and unmet. Participants reporting unmet support needs indicated significantly greater SSc symptom severity (i.e., more active disease periods, greater workplace activity limitation, greater fatigue) and more work productivity losses (e.g., greater absenteeism, presenteeism, and job disruptions).

A description of the most needed, available, and used workplace support needs reported by study participants is given in Figure 2. The most needed workplace supports included extended health benefits (84%), special equipment for work (63%), and flextime (59%). The most available workplace supports reported by participants included special equipment for work (88%), short-term leave (83%), and rest periods (82%). The most used workplace supports included special equipment for work (88%), flextime (54%), and extended health benefits (53%).

The interrelationship between study variables was also examined through bivariate analyses (Table 3). SSc symptom

Table 2. Limitations reported by study respondents to specific workplace acts and tasks using the Workplace Activity Limitations Scale (n = 110)*

		Workplace support needs		
	Total sample	Met	Unmet	P†
Working with hands	1.13 ± 0.83	0.79 ± 0.71	1.34 ± 0.83	0.0005
Crouching, bending, kneeling	0.96 ± 0.92	0.62 ± 0.66	1.18 ± 0.99	0.0006
Lifting, carrying, or moving objects	0.94 ± 0.86	0.72 ± 0.77	1.09 ± 0.89	0.0273
Standing for long periods of time	0.66 ± 0.75	0.56 ± 0.67	0.73 ± 0.79	0.2361
Concentrating on your work	0.64 ± 0.67	0.35 ± 0.53	0.82 ± 0.69	0.0001
Reaching	0.61 ± 0.73	0.29 ± 0.55	0.81 ± 0.76	0.0001
Sitting for long periods of time	0.60 ± 0.71	0.48 ± 0.63	0.68 ± 0.75	0.1429
Meeting job demands	0.60 ± 0.69	0.26 ± 0.44	0.87 ± 0.72	0.0001
Pace of work	0.58 ± 0.70	0.24 ± 0.48	0.80 ± 0.73	0.0001
Getting around the workplace	0.49 ± 0.63	0.23 ± 0.43	0.65 ± 0.69	0.0002
Work schedule	0.46 ± 0.70	0.21 ± 0.41	0.63 ± 0.79	0.0005
Getting to and from work	0.36 ± 0.64	0.24 ± 0.58	0.44 ± 0.66	0.1223

* Values are the mean ± SD unless indicated otherwise. Each item on the table was rated on a 4-point scale (0 = no difficulty/not applicable to job; 3 = unable to do).
† *P* value for testing equality of means across needs met/unmet groups.

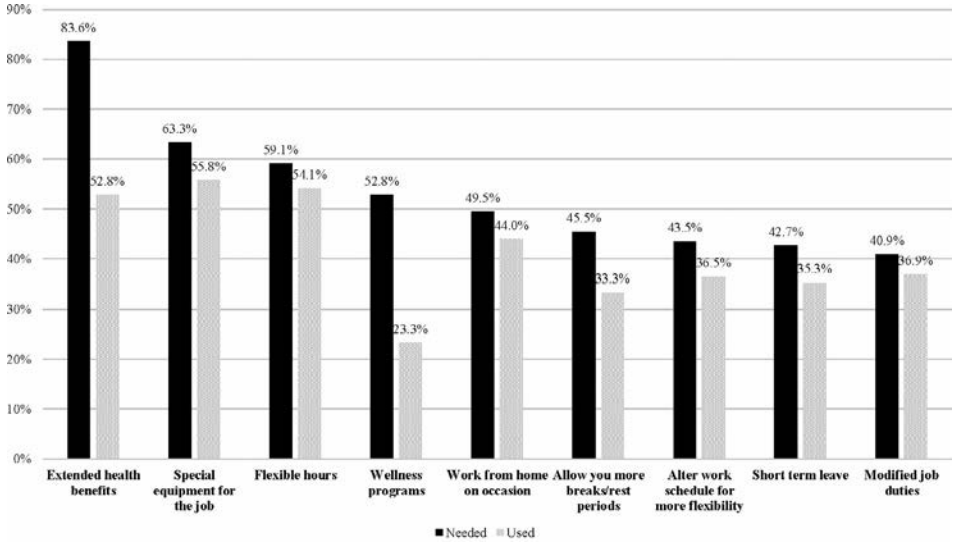

Figure 2. Frequency of workplace supports needed and used by study participants living with systemic sclerosis (SSc).

severity variables (mediators) were significantly associated with work productivity outcomes as well as with unmet workplace support needs ($P < 0.05$). Bivariate analyses indicated that other covariates were not significantly associated with either independent, mediator, or work outcome variables and were not retained in final path models. However, drawing from previous research, age and sex were carried forward as covariates in the path models (10,42).

Direct and indirect estimates from path models for each work productivity outcome are shown in Table 4. In all models, the direct relationship between unmet workplace support needs and work productivity loss was not significant. That is, having unmet support needs was not directly related to work productivity losses. Instead, in all 3 path models, unmet support needs were related to more workplace activity limitations, which in turn was also associated with productivity losses (i.e., greater absenteeism, presenteeism, and job disruptions). Additionally, path models indicated that the relationship between unmet workplace support needs and presenteeism was mediated by overall SSc severity when a total score was created.

DISCUSSION

This survey is one of the largest of its kind to examine the at-work experiences and the workplace support needs of people living with SSc a rare rheumatic disease. Findings indicated that many participants living with SSc reported unmet workplace support needs and had lost productivity related to their health. The potential value of meeting workplace support needs may be mostly in having the potential to reduce workplace activity limitations, which in turn may ultimately help improve productivity. These findings align with a growing body of research that highlights the role of work context and health factors in addressing rheumatic disease–related work disability (8,10,11). The results can also inform workplace strategies that promote productive employment of people living SSc by highlighting supports that are often needed but are less available.

Table 3. Correlation matrix of study variables*

	1	2	3	4	5	6	7	8	9	10
1. Age	–	–	–	–	–	–	–	–	–	–
2. Female	−0.059	–	–	–	–	–	–	–	–	–
3. Workplace support needs unmet	0.099	0.171	–	–	–	–	–	–	–	–
4. WALS score	0.052	0.094	0.585†	–	–	–	–	–	–	–
5. Fatigue	0.198†	0.240	0.402†	0.431†	–	–	–	–	–	–
6. Overall SSc severity	0.117	0.172	0.498†	0.653†	0.527†	–	–	–	–	–
7. Active disease periods	−0.129	0.271	0.388†	0.505†	0.500†	0.657†	–	–	–	–
8. Absenteeism	−0.115	0.529†	0.343†	0.497†	0.182†	0.381†	0.454†	–	–	–
9. Presenteeism	0.002	0.153	0.489†	0.700†	0.474†	0.684†	0.523†	0.520†	–	–
10. Job disruptions	−0.145	0.204	0.468†	0.700†	0.392†	0.542†	0.416†	0.657†	0.616†	–

* Pearson, tetrachoric, and biserial correlations were calculated based on the distribution of the variables. SSc = systemic sclerosis; WALS = Workplace Activity Limitations Scale.
† Correlations significant at $P < 0.05$.

Notably, the most needed workplace supports to sustain employment included extended health benefits, special equipment, and flextime. These workplace supports have the potential to address both disease symptoms and workplace limitations, and align with the needs identified in previous studies of people living with more prevalent rheumatic diseases (8,10). However, despite their support needs, many participants reported not using many workplace supports, and close to two-thirds indicated having their workplace support needs unmet. Unmet workplace support needs were often related to a lack of availability. For example, nearly one-fourth of study participants worked part-time, which is often related to less availability of workplace supports and benefits. Previous research of people with other rheumatic diseases found that job characteristics (e.g., industry, job demands, and job tenure) or psychosocial factors (e.g., workplace social support and job control) can also relate to the decision to use supports within the workplace (11,26,32). More research is needed to identify and understand the barriers and facilitators to accessing workplace supports among individuals with rare conditions like scleroderma.

Having SSc was associated with greater absenteeism, presenteeism, and job disruptions. A novel feature of this study was the use of path models to address research questions related to the interrelationships among workplace supports, disease symptoms and limitations, and employment outcomes. A point of interest was that workplace support was not directly related to work productivity. Instead, a mediated model was significant, with unmet workplace support needs being associated with greater workplace activity limitations, which in turn was related to poorer productivity. Notably, these data were cross-sectional, and we cannot establish causality or the direction of the relationships with certainty. Nonetheless, findings align with a body of research that indicates the importance of both health and work context factors in shaping the employment experiences of individuals with rheumatic diseases (3,32,43,44). Results are relevant to employers, who can promote productivity of workers with SSc through the provision of job modifications, accommodations, and workplace benefits. Similarly, as a way of addressing work-related concerns among patients, health care providers may treat SSc symptoms and encourage the identification and use of available workplace supports.

As noted, workplace activity limitations were identified as the prime mediator in the relationship between unmet workplace support needs and lost productivity, more so than other SSc symptom severity variables. The operationalization and measurement of workplace activity limitations captures a broader range of physical and psychosocial difficulties attributed to SSc and as a result may relate to both employment experiences and workplace support needs (32). Results may highlight the importance of workplace supports in minimizing workplace activity limitations and enhancing productivity for people with rheumatic diseases (10). Conversely, given the cross-sectional study design, findings from our path model could also suggest that for those with greater workplace activity limitations, unmet workplace support needs may arise as a result of lost productivity. Additional longitudinal research of patients with SSc is needed to further unpack the relationships among workplace activity limitations and other factors.

Study strengths include our recruitment of a clinic-based sample of individuals with SSc and the use of a survey that enabled us to collect specific details on productivity loss, workplace support needs, and a range of demographic, health, and work context covariates. Our analytical approach also represented a study strength. Using a path model, we examined the direct and indirect association of unmet workplace support needs on work productivity. There are also study limitations to acknowledge. As noted, our survey was cross-sectional, and we could not establish causation in our models. Moreover, although our study is one of the first to examine work productivity of people with SSc, our sample size limited more robust analyses. Additionally, while recruitment through specialty clinics enabled us to

Table 4. Summary of path models for each work productivity outcome, with standardized direct, indirect, and total effects estimates examining the interrelationship between unmet workplace needs and work productivity loss*

	Model 1: absenteeism	Model 2: presenteeism	Model 3: job disruptions
Direct effect	0.114 (–0.328, 0.544)	0.001 (–0.281, 0.283)	0.100 (–0.199, 0.396)
Indirect effect via fatigue	–0.143 (–0.354, 0.023)	0.074 (–0.030, 0.202)	0.077 (–0.033, 0.210)
Indirect effect via WALS score	0.366 (0.121, 0.646)†	0.360 (0.179, 0.564)†	0.495 (0.273, 0.735)†
Indirect effect via overall SSc severity	–0.044 (–0.337, 0.234)	0.258 (0.077, 0.474)†	0.107 (0.072, 0.307)
Indirect effect via active disease periods	0.225 (–0.057, 0.599)	0.017 (–0.154, 0.210)	–0.040 (–0.237, 0.137)
Total indirect effect	0.404 (0.111, 0.702)†	0.709 (0.452, 0.956)†	0.638 (0.392, 0.878)†
Total effect	0.518 (0.093, 0.897)†	0.710 (0.364, 1.01)†	0.738 (0.399, 1.04)†
Observations used, no.	110	110	110
Parameters estimated, no.	27	27	27
Difference between observed and replicated chi-square values	–25.26, 21.31	–23.83, 22.99	–23.62, 22.88
Posterior predictive *P* value	0.561	0.512	0.507
R^2	51.7%	58.6%	56.0%

* Values are the standardized estimate (95% credibility intervals) unless indicated otherwise. Estimates are standardized only with respect to the outcomes and mediating variables; to calculate percent mediated when there is negative mediation, we used absolute values to calculate total mediation (ref. 37). WALS = Workplace Activity Limitations Scale.
† Significant at $P < 0.05$.

reach participants living with SSc, our sample may have limited generalizability outside of clinic settings. Efforts should be taken to recruit patients with SSc within the broader community to further understand workplace experiences and support needs across a sample with varied socioeconomic and health characteristics. Lastly, details on disease severity and SSc symptoms relied on the participant's self-report. Future research that collects clinical health information could supplement our study findings and enable us to better understand how clinical characteristics of SSc are related to working experiences and the requirement for workplace supports.

In conclusion, workplace supports offer a mechanism to foster productive employment for people with SSc, especially insofar as such supports may minimize workplace activity limitations and improve workplace productivity. This study highlights the importance of work disability prevention interventions that target both health and work context factors. To promote long-term participation in the labor market of people with SSc, lost productivity should be addressed within the workplace and clinical environments.

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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. Jetha 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. Jetha, Johnson, Gignac.
Acquisition of data. Jetha, Gignac.
Analysis and interpretation of data. Jetha.

REFERENCES

1. Backman CL. Employment and work disability in rheumatoid arthritis. Curr Opin Rheumatol 2004;16:148–52.
2. Escorpizo R, Bombardier C, Boonen A, Hazes JM, Lacaille D, Strand V, et al. Worker productivity outcome measures in arthritis. J Rheumatol 2007;34:1372–80.
3. Burton W, Morrison A, Maclean R, Ruderman E. Systematic review of studies of productivity loss due to rheumatoid arthritis. Occup Med (Lond) 2005;56:18–27.
4. Dhanhani AM, Gignac MA, Su J, Fortin PR. Work disability in systemic lupus erythematosus. Arthritis Rheum 2009;61:378–85.
5. Jetha A, Badley E, Beaton D, Fortin PR, Shiff NJ, Gignac MA. Unpacking early work experiences of young adults with rheumatic disease: an examination of absenteeism, job disruptions, and productivity loss. Arthritis Care Res (Hoboken) 2015;67:1246–54.
6. Gignac MA, Cao X, Lacaille D, Anis AH, Badley EM. Arthritis-related work transitions: a prospective analysis of reported productivity losses, work changes, and leaving the labor force. Arthritis Rheum 2008;59:1805–13.
7. Jetha A, Chen C, Mustard C, Ibrahim S, Bielecky A, Beaton D, et al. Longitudinal examination of temporality in the association between chronic disease diagnosis and changes in work status and hours worked. Occup Environ Med 2017;74:184–91.
8. Gignac MA, Cao X, McAlpine J. Availability, need for, and use of work accommodations and benefits: are they related to employment outcomes in people with arthritis? Arthritis Care Res (Hoboken) 2015;67:855–64.
9. Allaire SH. What work changes do people with arthritis make to preserve employment, and are such changes effective? Arthritis Rheum 2004;51:871–3.
10. Jetha A, Gignac MA, Bowring J, Tucker S, Connelly CE, Proulx L, et al. Supporting arthritis and employment across the life course: a qualitative study. Arthritis Care Res (Hoboken) 2018;70:1461–8.
11. Lacaille D, Sheps S, Spinelli JJ, Chalmers A, Esdaile JM. Identification of modifiable work-related factors that influence the risk of work disability in rheumatoid arthritis. Arthritis Rheum 2004;51:843–52.
12. Bassel M, Hudson M, Taillefer SS, Schieir O, Baron M, Thombs BD. Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a Canadian National Survey. Rheumatology (Oxford) 2010;50:762–7.
13. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685–99.
14. Allaire SJ, Keysor JJ, Alheresh R. Effect of arthritis and other rheumatic conditions on employment. Work 2013;45:417–20.
15. Hudson M, Steele R, Lu Y, Thombs BD, Baron M. Work disability in systemic sclerosis. J Rheumatol 2009;36:2481–6.
16. Johnson S, Gladman D, Schentag C, Lee P. Quality of life and function status in systemic sclerosis compared to patients with other rheumatic diseases. J Rheumatol 2006;33:1117–22.
17. Bernatsky S, Joseph L, Pineau C, Belisle P, Hudson M, Clarke AE. Scleroderma prevalence: demographic variations in a population-based sample. Arthritis Rheum 2009;61:400–4.
18. Hussein H, Lee P, Chau C, Johnson S. The effect of male sex on survival in systemic sclerosis. J Rheumatol 2014;41:2193–200.
19. Charles C, Clements P, Furst DE. Systemic sclerosis: hypothesis-driven treatment strategies. Lancet 2006;367:1683–91.
20. Mau W, Listing J, Huscher D, Zeidler H, Zink A. Employment across chronic inflammatory rheumatic diseases and comparison with the general population. J Rheumatol 2005;32:721–8.
21. Morrisroe K, Sudararajan V, Stevens W, Sahhar J, Zochling J, Roddy J, et al. Work productivity in systemic sclerosis, its economic burden and association with health-related quality of life. Rheumatology (Oxford) 2017;57:73–83.
22. Singh MK, Clements PJ, Furst DE, Maranian P, Khanna D. Work productivity in scleroderma: analysis from the University of California, Los Angeles scleroderma quality of life study. Arthritis Care Res (Hoboken) 2012;64:176–83.
23. Sandqvist JL, Henriksson CM. Work functioning: a conceptual framework. Work 2004;23:147–57.
24. World Health Organization. International Classification of Functioning, Disability and Health: ICF. Geneva (Switzerland): World Health Organization; 2001.
25. Loisel P, Durand P, Abenhaim L, Gosselin L, Simard R, Turcotte J, et al. Management of occupational back pain: the Sherbrooke model. Results of a pilot and feasibility study. Occup Environ Med (Lond) 1994;51:597–602.
26. Allaire SH, Li W, LaValley MP. Work barriers experienced and job accommodations used by persons with arthritis and other rheumatic diseases. Rehabil Couns Bull 2003;46:147–56.
27. Wang PP, Badley EM, Gignac MA. Perceived need for workplace accommodation and labor-force participation in Canadian adults with activity limitations. Am J Public Health 2004;94:1515–8.

28. Gignac MA, Kristman V, Smith PM, Beaton DE, Badley EM, Ibrahim S, et al. Are there differences in workplace accommodation needs, use and unmet needs among older workers with arthritis, diabetes and no chronic conditions? Examining the role of health and work context. Work Aging Retire 2018;4:381–98.
29. Van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737–47.
30. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353–65.
31. Mattke S, Balakrishnan A, Bergamo G, Newberry SJ. A review of methods to measure health-related productivity loss. Am J Manag Care 2007;13:211–7.
32. Gignac MA. Arthritis and employment: an examination of behavioral coping efforts to manage workplace activity limitations. Arthritis Rheum 2005;53:328–36.
33. Beaton DE, Tang K, Gignac MA, Lacaille D, Badley EM, Anis AH, et al. Reliability, validity, and responsiveness of five at-work productivity measures in patients with rheumatoid arthritis or osteoarthritis. Arthritis Care Res (Hoboken) 2010;62:28–37.
34. Shacham S. A shortened version of the Profile of Mood States. J Pers Assess 1983;47:305–6.
35. Johnson S, Hawker G, Davis A. The Health Assessment Questionnaire disability index and Scleroderma Health Assessment Questionnaire in scleroderma trials: an evaluation of their measurement properties. Arthritis Rheum 2005;53:256–62.
36. Steen VD, Medsger TA Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997;40:1984–91.
37. MacKinnon DP. Introduction to statistical mediation analysis. Mahwah (NJ): Lawrence Erlbaum Associates; 2008.
38. Muthén B, Asparouhov T. Bayesian structural equation modeling: a more flexible representation of substantive theory. Psychol Methods 2012;17:313–15.
39. Van Erp S, Mulder J, Oberski DL. Prior sensitivity analysis in default Bayesian structural equation modeling. Psychol Methods 2018;23:363–88.
40. SAS software: release 9.3. Cary (NC): SAS Institute; 2015.
41. Muthén LK, Muthén BO. Mplus user's guide. 8th ed. Muthen and Muthen: Los Angeles; 2017.
42. Kaptein SA, Gignac MA, Badley EM. Differences in the workforce experiences of women and men with arthritis disability: a population health perspective. Arthritis Rheum 2009;61:605–13.
43. Mancuso CA, Paget SA, Charlson ME. Adaptations made by rheumatoid arthritis patients to continue working: a pilot study of workplace challenges and successful adaptations. Arthritis Care Res (Hoboken) 2000;13:89–99.
44. Lacaille D. Work loss in rheumatoid arthritis: can we prevent it? Adv Rheumatol 2009;7:107–13.

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Adiposity and Physical Activity as Risk Factors for Developing Psoriatic Arthritis: Longitudinal Data From a Population-Based Study in Norway

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Objective. Adiposity is prevalent among patients with psoriatic arthritis (PsA). However, the temporal relation is unclear. The present study was undertaken to investigate whether adiposity and body fat distribution are related to the risk of developing PsA, and whether physical activity could modify the possible risk.

Methods. We included 36,626 women and men from the Norwegian Nord-Trøndelag Health Study without diagnosed PsA at baseline from 1995 to 1997. Cox regression analysis was used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) of incident PsA at follow-up from 2006 to 2008.

Results. During follow-up, 185 new cases of PsA were reported. Increases of 1 SD in body mass index (BMI) (4.2 and 3.5 kg/m^2 for women and men, respectively) and waist circumference (10.8 and 8.6 cm, respectively) were associated with HRs of 1.40 (95% CI 1.24, 1.58) and 1.48 (95% CI 1.31, 1.68), respectively. Compared to individuals of normal weight, obese individuals had an HR of 2.46 (95% CI 1.65, 3.68), and overweight individuals had an HR of 1.41 (95% CI 1.00, 1.99). Comparing extreme quartiles of waist circumference yielded an HR of 2.63 (95% CI 1.73, 3.99). In analyses of combined effects using a BMI of <25 kg/m^2 and high physical activity as reference, a BMI of ≥25 kg/m^2 was associated with HRs of 2.06 (95% CI 1.18, 3.58) and 1.53 (95% CI 0.80, 2.91) among those with low and high physical activity levels, respectively. Corresponding HRs for high waist circumference and physical activity were 2.25 (95% CI 1.40, 1.63) and 1.85 (95% CI 0.95, 3.50).

Conclusion. The results suggest that adiposity, particularly central obesity, is associated with increased risk of incident PsA. Although there was no clear modifying effect of physical activity, high levels of physical activity reduced the risk of PsA, regardless of BMI.

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory joint disease associated with psoriasis. The observed prevalence varies from <0.01% to 0.67% in different countries (1–3), with the highest prevalence found in Norway (3). PsA is associated with obesity, dyslipidemia, and insulin resistance, all part of metabolic syndrome, and which significantly increase patients' risk of cardiovascular disease (CVD) and mortality (4–8). In addition, obesity can reduce the treatment effect of disease-modifying medication (9). Compared to patients with psoriasis alone, the body fat percentage seems to be even higher in patients with PsA (10,11). Some authors claim that obesity is a consequence of psoriasis and PsA because of social isolation, depression, physical inactivity, high-fat diet, and alcohol consumption (11). Conversely, other studies indicate that high body mass index (BMI) is a cause of PsA rather than a consequence (12–14), and that even at a young age, obesity seems to increase the risk of PsA (15).

Adiposity might be an environmental trigger of PsA in genetically susceptible individuals (13,16). The adipose tissue is an

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SIGNIFICANCE & INNOVATIONS

- Adiposity is prevalent among patients with psoriatic arthritis (PsA); however, the nature of the temporal relation is unclear.
- Adiposity, and particularly central obesity, was found to be associated with increased risk of incident PsA.
- There was no clear modifying effect of physical activity (PA) on adiposity and risk of PsA. However, individuals performing high-level PA had a somewhat reduced risk of PsA, regardless of body mass index.
- The results support evidence suggesting that the risk of PsA is modifiable, highlighting the importance of preventive work against obesity, including encouragement to engage in PA to reduce the incidence of PsA.

endocrine organ producing inflammatory mediators, such as several different adipokines, which influence the pathophysiology of both CVD and inflammatory conditions, as seen in psoriatic diseases (17,18).

There is evidence that physical activity has the ability to modify the detrimental effects of adiposity on CVD and metabolic diseases (19–22). Moreover, high physical activity level can reduce body fat (23) and increase cardiorespiratory fitness (24), and both these factors are associated with a reduced risk of CVD (25). It is unknown whether physical activity can affect the ultimate development of PsA in genetically susceptible individuals. A potential concern is that physical trauma from vigorous exercise causing mechanical stress could potentially trigger an inflammatory response, such as enthesitis, thereby contributing to the development of PsA. There is some evidence that such local inflammatory responses may be of etiologic relevance to PsA, which has led to PsA being considered more of an autoinflammatory condition rather than a strictly autoimmune disease (26–28).

The aim of this longitudinal, population-based study was to investigate the association of adiposity and body fat distribution with the risk of developing PsA. Further, we examined whether a high physical activity level could modify the possible adverse effect of high BMI and waist circumference on the risk of incident PsA.

MATERIALS AND METHODS

Study population. This is a prospective study using data from the Nord-Trøndelag Health Study (HUNT); a population-based, longitudinal study conducted in Norway. HUNT consists of 3 consecutive surveys: HUNT1 (1986–1988), HUNT2 (1995–1997), and HUNT3 (2006–2008). All individuals ≥20 years of age were invited to participate, completing a comprehensive questionnaire and undergoing a clinical examination (29).

This study utilizes data from HUNT2 and HUNT3; the participation rate of the invited individuals was 70% of 93,898 in HUNT2, and 54% of 93,860 in HUNT3. Of 116,043 participants, 37,070 individuals participated in both surveys and were selected for this study.

For the purpose of the current study, we excluded 94 participants with onset of PsA before participation in HUNT2, 151 with missing information on BMI, as well as 200 participants with a BMI of <18.5 kg/m^2. The latter group was excluded due to small numbers of patients as well as the possibility that the low weight might relate to some intercurrent comorbidity. This left 36,626 participants available for analyses of BMI (Figure 1). Analyses of waist circumference and physical activity included 36,595 and 34,834 individuals due to some missing data on these respective factors.

All participants signed written informed consent, and the study was approved by the Regional Committee for Ethics in Medical Research (REC 2010/2661). The study was conducted according to the Declaration of Helsinki.

Outcome. At follow-up in HUNT3 (2006–2008), all participants received a first questionnaire with the invitation. Based on answers to this questionnaire, individuals reporting psoriasis or 6 other specific disorders (e.g., CVD, diabetes mellitus [DM], or cancer) were also given a more detailed questionnaire for the specific disease. Each participant could only fill in 2 additional questionnaires, and CVD and DM were prioritized (3). In 2012, an experienced rheumatologist (MH) validated possible cases of PsA by assessing hospital medical records using the Classification of Psoriatic Arthritis (CASPAR) criteria. A total of 1,238 possible cases were included in the validation study based on their questionnaire response: 1) self-reported psoriasis and rheumatoid arthritis or ankylosing spondylitis; 2) self-reported psoriasis and CVD; and 3) self-reported psoriasis and answering "yes" or "I do not know" to the question about PsA (3). A total of 338 validated cases of PsA were identified in the records.

In addition to cases of PsA occurring between baseline (HUNT2) and follow-up in HUNT3, new cases of PsA diagnosed according to the hospital records between the follow-up survey in 2006–2008 and 2012 were also included in the current study. Additional details of the validation study have been previously presented (3).

Exposures. *BMI, waist circumference, and waist-to-hip ratio.* Standardized measures of body height (to the nearest cm) and weight (to the nearest one-half kg) obtained at the clinical examination in HUNT2 were used to calculate BMI (kg/m^2) (30). Participants were then classified into 1 of 3 BMI categories according to the cutoff points suggested by the World Health Organization (WHO): normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), or obese (BMI ≥30.0 kg/m^2) (31).

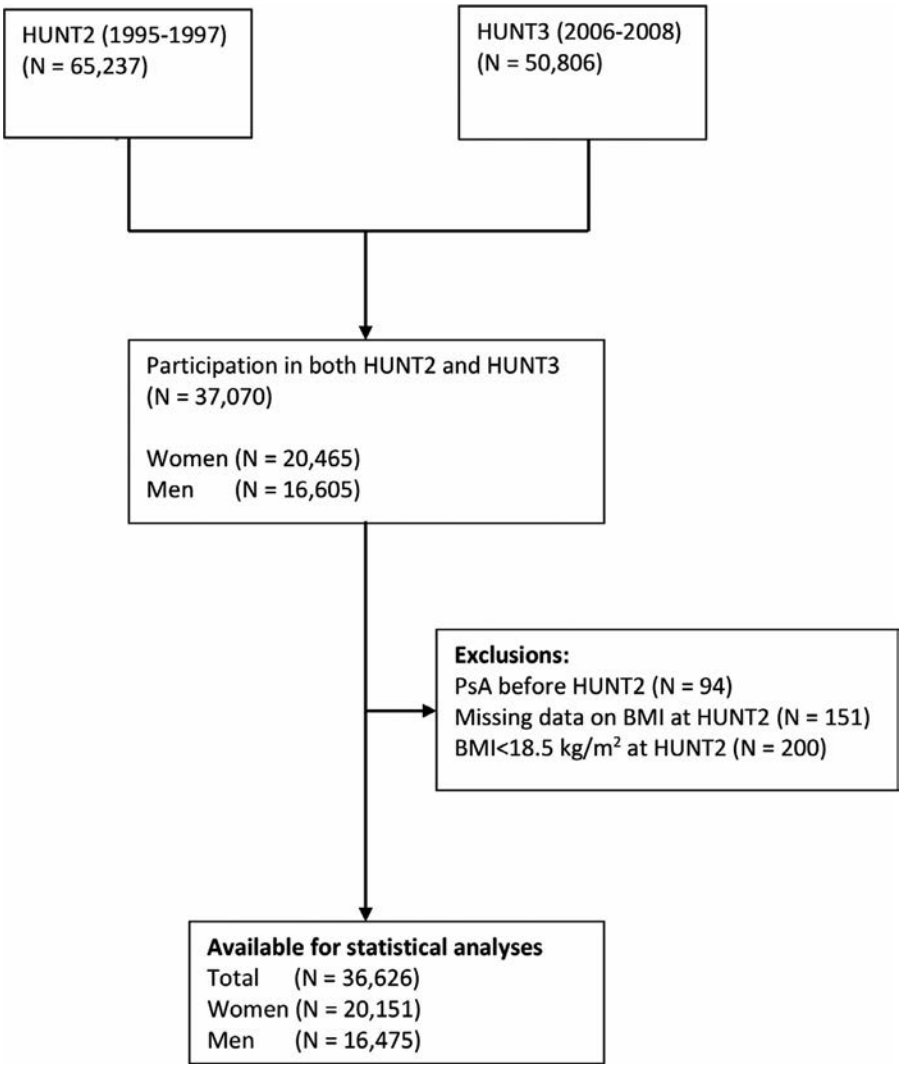

Figure 1. Flow chart of selection of study participants. BMI = body mass index; HUNT = Nord-Trøndelag Health Study; PsA = psoriatic arthritis.

For analysis of the combined effect of BMI, overweight and obesity were collapsed into 1 category (i.e., ±25 kg/m^2).

Waist circumference was measured with a steel band to the nearest cm at the level of the umbilicus (30). Based on the distribution of the measures, participants were classified into 4 categories using the sex-specific quartiles as cutoffs (<74, 74–79, 80–87, and >87 cm in women; <87, 87–90, 91–96, and >96 cm in men). For analysis of the combined effect of waist circumference and BMI, waist circumference was split in 2 categories (± median value).

Participants were also classified into 2 categories of waist circumference according to the sex-specific cutoff points suggested by the WHO: 1 = low (<81 cm in women, <95 cm in men), and 2 = high (≥81 cm in women, ≥95 cm in men) (32). This latter classification was used for the analyses of the combined effect of waist circumference and physical activity.

Hip circumference was measured with a steel band to the nearest cm at the thickest part of the hip. Waist-to-hip ratio was calculated as waist circumference (cm) divided by hip circumference (cm). Based on the distribution of the measures, participants were classified into 4 categories using the sex-specific quartiles as cutoffs (<0.75, 0.75–0.79, 0.80–0.82, and >0.82 cm in women; <0.86, 0.86–0.89, 0.90–0.92, and >0.92 cm in men). In addition, sex-specific SD scores (Z scores) were calculated for BMI, waist circumference, and waist-to-hip ratio as the observed value minus the sex-specific mean value, divided by the sex-specific SD. For individuals with information on body weight from HUNT1, the 10-year change in body weight from HUNT1 to HUNT2 was calculated by subtracting the weight at HUNT1 from the weight at HUNT2 and categorized into 4 groups.

Physical activity. Leisure-time physical activity was assessed using the following question: "How much of your leisure time have you been physically active during the last year? (Think of a weekly average for the year. Your commute to work counts as leisure time)." The participants were then asked to specify number of hours per week of light (no sweating or heavy breathing) and/or hard (sweating and heavy breathing) physical activity with the

response options: "none," "less than 1 hour," "1–2 hours," and "3 or more hours" for both light and hard activity (33). Based on this information, a new variable with 4 categories was constructed combining information on light and hard activity: inactive (no light or no hard activity); low activity (<3 hours of light and no hard activity); moderate activity (≥3 hours of light and/or <1 hour of hard activity); and high activity (any light and ≥1 hour of hard activity) (34). For the analyses of the combined effect, the 3 first categories (inactive, low activity, and moderate activity) were collapsed into 1 category.

Statistical analysis. Descriptive data are given as mean ± SD for continuous data and number (%) for categorical data. Cox regression analysis was used to calculate hazard ratios (HRs) of incident PsA associated with categories of baseline BMI, waist circumference, waist-to-hip ratio, and physical activity, as well as with continuous measures of these factors using both the original scale and sex-specific normalized values (Z score). Precision of the estimated associations was assessed with a 95% confidence interval (95% CI). Potential confounders were selected a priori based on knowledge about factors that could be associated with both the outcome and the exposures. All estimates were adjusted for possible confounding by age (as the time scale in the model), sex (female, male), smoking (current, former, never, unknown [3.9%]), and education (<10 years [elementary school], 10–12 years [high school], ≥13 years [college/university], and unknown [1.4%]). Due to uncertainty about the direction of possible confounding effects between BMI and physical activity, as well as waist circumference and physical activity, these factors were mutually adjusted in a supplementary analysis.

Similarly, the combined effects of BMI and physical activity, of waist circumference and physical activity, and of BMI and waist circumference on risk of PsA were estimated. In the first combined analysis, normal BMI and high physical activity level constituted the reference group. In the second analysis, low waist circumference according to WHO cutoffs and high physical activity level constituted the reference group. In the third analysis, normal BMI and waist circumference below median was the reference group. The within-category median value of BMI and/or waist circumference was calculated for all the combined analyses.

Potential effect modification between the variables was assessed both as departure from additive effects, calculating the relative excess risk due to interaction (RERI), and as departure from multiplicative effects in a likelihood ratio test of a product term in the regression model. RERI estimates were calculated with 95% CIs using the following equation: RERI = RR11 – RR10 – RR01 + 1 (35), i.e., RERI >0 indicates a synergistic effect beyond additivity.

In a sensitivity analysis, participants with a new onset of PsA within the first 3 years after HUNT2 were excluded to reduce possible reverse causality due to existing undiagnosed disease

Table 1. Characteristics of the population according to the 4 categories of physical activity at baseline*

	Inactivity (n = 2,007)	Low activity (n = 10,742)	Moderate activity (n = 12,000)	High activity (n = 10,085)
Female	965 (48.1)	6,802 (63.3)	6,743 (56.2)	4,442 (44.0)
Age, mean ± SD years	47.7 ± 13.7	48.3 ± 12.7	46.8 ± 13.4	43.1 ± 12.6
BMI, mean ± SD kg/m^2				
Women	27.3 ± 5.1	26.4 ± 4.4	25.8 ± 4.1	25.1 ± 3.8
Men	27.0 ± 3.9	26.8 ± 3.4	26.5 ± 3.2	26.1 ± 3.0
BMI, kg/m^2				
18.5–24.9	712 (36.1)	3,960 (37.2)	4,925 (41.4)	4,640 (46.4)
25.0–29.9	817 (41.5)	4,856 (45.6)	5,375 (45.2)	4,322 (43.2)
≥30.0	441 (22.4)	1,828 (17.2)	1,596 (13.4)	1,048 (10.5)
Waist circumference, mean ± SD cm				
Women	84.1 ± 12.6	81.7 ± 10.9	79.7 ± 10.3	77.3 ± 9.7
Men	93.2 ± 10.1	92.7 ± 8.8	91.6 ± 8.4	89.6 ± 8.1
Waist-to-hip ratio, mean ± SD				
Women	0.81 ± 0.06	0.80 ± 0.06	0.79 ± 0.06	0.78 ± 0.05
Men	0.91 ± 0.06	0.90 ± 0.05	0.89 ± 0.05	0.88 ± 0.05
Education, years				
<10	858 (42.8)	3,888 (36.2)	3,354 (28.0)	1,886 (18.7)
10–12	911 (45.4)	4,833 (45.0)	5,573 (46.4)	4,987 (49.5)
≥13	180 (9.0)	1,832 (17.1)	2,912 (24.3)	3,128 (31.0)
Smoking status				
Never	697 (34.7)	4,319 (40.2)	5,139 (42.8)	4,902 (48.6)
Former	540 (26.9)	2,897 (26.0)	3,383 (28.2)	2,741 (27.2)
Current	708 (35.3)	3,092 (28.8)	3,031 (25.3)	2,025 (20.1)
Pain†				
Yes	1,082 (54.2)	5,542 (51.8)	5,481 (45.9)	3,967 (39.5)

* Values are the number (%) unless indicated otherwise. BMI = body mass index.
† Pain and/or stiffness in muscle/skeleton in the last year.

at baseline. Assuming that the estimated associations reflect causal effects of high BMI and waist circumference on PsA risk, we estimated the population attributable fraction to quantify the proportion of PsA that potentially could be prevented by avoiding overweight and obesity.

Departure from the proportional hazards assumption was evaluated by tests of Schoenfeld residuals and by graphical inspection of log–log plots. All analyses were conducted using Stata for Windows, version 14.2.

RESULTS

A total of 36,626 participants were included in the study; 55% were women. A total of 185 incident cases (59% women) of PsA were diagnosed during follow-up; 164 between HUNT2 (1995–1997) and HUNT3 (2006–2008), and 21 between HUNT3 and 2012. The incidence proportion for 14 years was 0.5%. Table 1 displays baseline characteristics of the study population stratified by physical activity. There was no evidence of violation of the proportional hazards assumption for any of the results presented below.

Effect of BMI, waist circumference, and waist-to-hip ratio. An increase of 1 SD in BMI (4.2 kg/m^2 in women, and 3.5 kg/m^2 in men), waist circumference (10.8 cm in women, and 8.6 cm in men), and waist-to-hip ratio (0.06 in women, and 0.05 in men) was associated with adjusted HRs of 1.40 (95% CI 1.24, 1.58), 1.48 (95% CI 1.31, 1.68), and 1.39 (95% CI 1.24, 1.57) (Table 2). Individuals with a BMI of ≥30 kg/m^2 had an HR of 2.46 (95% CI 1.65, 3.68) compared to individuals of normal weight (BMI 18.5–24.9 kg/m^2). Those in the highest quartile of waist circumference

Table 2. Risk of incident psoriatic arthritis (PsA) during 14 years of follow-up associated with body mass index (BMI), waist circumference, waist-to-hip ratio, and leisure-time physical activity*

	Person-years	No. of cases of incident PsA	Rate†	Crude HR (95% CI)‡	Adjusted HR (95% CI)§
BMI, kg/m^2					
18.5–24.9	230,376	59	2.6	1.00 (Ref.)	1.00 (Ref.)
25.0–29.9	252,561	79	3.1	1.33 (0.95, 1.87)	1.41 (1.00, 1.99)
≥30.0	82,884	43	5.2	2.33 (1.57, 3.47)	2.46 (1.65, 3.68)
BMI per SD, kg/m^2¶	565,820	181	3.2	1.39 (1.23, 1.57)	1.40 (1.24, 1.58)
BMI per kg/m^2	565,820	181	3.2	1.09 (1.05, 1.12)	1.09 (1.06, 1.12)
Waist circumference quartiles, cm#					
First	164,171	36	2.2	1.00 (Ref.)	1.00 (Ref.)
Second	126,933	36	2.8	1.36 (0.85, 2.16)	1.35 (0.85, 2.14)
Third	139,045	48	3.5	1.76 (1.14, 2.72)	1.78 (1.15, 2.75)
Fourth	135,176	63	4.7	2.60 (1.72, 3.95)	2.63 (1.73, 3.99)
Waist circumference (WHO cutoffs)					
Women <81 cm; men <95 cm	351,084	94	2.7	1.00 (Ref.)	1.00 (Ref.)
Women >80 cm; men >94 cm	214,241	89	4.2	1.78 (1.33, 2.39)	1.75 (1.30, 2.35)
Waist circumference per SD, cm**	565,325	183	3.2	1.48 (1.31, 1.68)	1.48 (1.31, 1.68)
Waist circumference, per cm	565,325	183	3.2	1.03 (1.02, 1.04)	1.04 (1.03, 1.05)
Waist-to-hip ratio, quartiles††					
First	143,180	27	1.9	1.00 (Ref.)	1.00 (Ref.)
Second	140,277	44	3.1	1.70 (1.05, 2.75)	1.64 (1.01, 2.65)
Third	142,221	48	3.4	1.96 (1.22, 3.15)	1.87 (1.16, 3.01)
Fourth	139,648	64	4.6	2.95 (1.87, 4.66)	2.74 (1.73, 4.34)
Waist-to-hip ratio, per SD‡‡	565,325	183	3.2	1.42 (1.26, 1.60)	1.39 (1.24, 1.57)
Waist-to-hip ratio, per 0.1 unit	565,325	183	3.2	1.36 (1.12, 1.65)	1.78 (1.45, 2.19)
Physical activity					
High	155,892	41	2.6	1.00 (Ref.)	1.00 (Ref.)
Moderate	185,127	70	3.8	1.54 (1.05, 2.26)	1.45 (0.98, 2.13)
Low	165,915	54	3.3	1.33 (0.89, 2.01)	1.22 (0.80, 1.84)
Inactive	31,019	11	3.5	1.48 (0.76, 2.88)	1.30 (0.66, 2.54)

* 95% CI = 95% confidence interval; HR = hazard ratio; Ref. = reference; WHO = World Health Organization.
† Incidence of PsA per 10,000 person-years.
‡ Adjusted for age (as the time scale in the model).
§ Adjusted for sex, age, education level, and smoking status.
¶ Sex-specific SD: women, SD 4.2 kg/m^2; men, SD 3.5 kg/m^2.
# Waist circumference quartiles: women (first ≤73 cm; second 74–79 cm; third 80–87 cm; fourth ≥88 cm); men (first ≤86 cm; second 87–90 cm; third 91–96 cm; fourth ≥97).
** Sex-specific SD: women, SD 10.8 cm; men, SD 8.6 cm.
†† Waist-to-hip ratio quartiles: women (first <0.75; second 0.75–0.79; third 0.80–0.82; fourth >0.82); men (first <0.86; second 0.86–0.89; third 0.90–0.92; fourth >0.92).
‡‡ Sex-specific SD: women, SD 0.06; men, SD 0.05.

Table 3. The combined effect of body mass index (BMI) and waist circumference (WC) on risk of incident psoriatic arthritis (PsA)*

	Normal weight, BMI 18.5–24.9 kg/m^2				Overweight/obese, BMI ≥25 kg/m^2			
	Person-years	Cases	Rate†	HR (95% CI)‡	Person-years	Cases	Rate†	HR (95% CI)‡
WC ≤ median§	200,273	45	2.2	–	87,675	25	2.9	1.43 (0.87, 2.35)
WC > median§	28,667	14	4.9	2.30 (1.26, 4.20)	245,182	97	4.0	2.13 (1.49, 3.07)

* 95% CI = 95% confidence interval; HR = hazard ratio.
† Incidence of PsA per 10,000 person-years.
‡ HR adjusted for age, sex, smoking status, and education status.
§ Median: women, 79 cm; men, 90 cm.

had an HR of 2.63 (95% CI 1.73, 3.99) compared to those in the first quartile. Using WHO cutoffs, individuals with a high waist circumference (≥81 cm in women, ≥95 cm in men) had an HR of 1.75 (95% CI 1.30, 2.35) compared to those with a low waist circumference (WHO cutoffs: <81 cm in women, <95 cm in men). Correspondingly, individuals in the fourth sex-specific quartile of waist-to-hip ratio had an HR 2.74 (95% CI 1.73, 4.34) compared to the first quartile. In supplementary analysis of ~10 years weight change (data not shown), those who increased ≥10 kg had an HR of 1.41 (95% CI 0.86, 2.30) compared to those who were weight stable (±2.5 kg).

In analyses of the joint categories of waist circumference and BMI, individuals with a waist circumference greater than median had an HR of 2.13 (95% CI 1.49, 3.07) if BMI was ≥25 kg/m^2 and an HR of 2.30 (95% CI 1.26, 4.20) if BMI was <25 kg/m^2, compared to those with waist circumference less than or equal to median and BMI was <25 kg/m^2 (Table 3). Waist circumference less than or equal to median and a BMI of ≥25 kg/m^2 yielded an HR of 1.43 (95% CI 0.87, 2.35).

Additional adjustment for physical activity did not change the results (data not shown). Attributable fractions calculated from the estimated associations suggest that 20.8% of PsA cases in the study population can be attributed to either overweight (8.8%) or obesity (12%).

Effect of physical activity. Overall, lower levels of physical activity were associated with a slightly higher risk of PsA than the highest physical activity level, although the precision of the estimates was low (Table 2). HRs among moderate, low, and inactive individuals were 1.45 (95% CI 0.98, 2.13), 1.22 (95% CI 0.80, 1.84), and 1.30 (95% CI 0.66, 2.54), respectively. Adjusting for BMI or waist circumference as possible confounders did not change the results.

Combined effect of physical activity and BMI/waist circumference. Compared to the reference category (BMI <25 kg/m^2 and high physical activity level), a BMI of ≥25 kg/m^2 and physical activity at any lower level was associated with a 2-fold increased risk (HR 2.06 [95% CI 1.18, 3.58]), whereas those with a BMI of ≥25 kg/m^2 and high physical activity level had an HR of 1.53 (95% CI 0.80, 2.91) (Table 4). A BMI of <25 kg/m^2 and low physical activity level resulted in an HR of 1.27 (95% CI 0.70, 2.30) compared to the reference category. The within-category median value of BMI was similar in the 2 categories of BMI <25 kg/m^2, as well as in the 2 categories of BMI ≥25 kg/m^2 (data not shown). There was no evidence of a synergistic effect of overweight/obesity and low physical activity, with a RERI of 0.26 (95% CI –0.65, 1.17). Furthermore, no evidence of interaction was found on a multiplicative scale (P = 0.71).

Table 4. The combined effect of body mass index (BMI) and level of physical activity (PA) on risk of incident psoriatic arthritis (PsA)*

	Normal weight, BMI 18.5–24.9 kg/m^2				Overweight/obese, BMI ≥25 kg/m^2			
	Person-years	No. of cases	Rate†	HR (95% CI)‡	Person-years	No. of cases	Rate†	HR (95% CI)‡
PA high§	71,771	15	2.1	1.00 (Ref.)	82,961	25	3.0	1.53 (0.80, 2.91)
PA low¶	148,270	42	2.8	1.27 (0.70, 2.30)	230,097	90	3.9	2.06 (1.18, 3.58)

* 95% CI = 95% confidence interval; HR = hazard ratio; Ref. = reference.
† Incidence of PsA per 10,000 person-years.
‡ HR adjusted for age, sex, smoking status, and education status.
§ High PA level.
¶ PA at moderate/low level or inactivity.

Table 5. The combined effect of World Health Organization categories of waist circumference and level of physical activity (PA) on risk of incident psoriatic arthritis (PsA)*

	Normal waist circumference†				High waist circumference‡			
	Person-years	No. of cases	Rate§	HR (95% CI)¶	Person-years	No. of cases	Rate§	HR (95% CI)¶
PA high#	113,518	24	2.1	1.00 (Ref.)	41,026	16	3.9	1.84 (0.97, 3.47)
PA low**	222,761	68	3.1	1.38 (0.86, 2.21)	155,144	66	4.3	2.22 (1.37, 3.58)

* 95% CI = 95% confidence interval; HR = hazard ratio; Ref. = reference.
† Normal waist circumference: <81 cm for women, <95 cm for men.
‡ High waist circumference: ≥81 cm for women, ≥95 cm for men.
§ Incidence of PsA per 10,000 person-years.
¶ HR adjusted for age, sex, smoking status, and education status.
# High PA level.
** PA at moderate/low level or inactivity.

Individuals with a high waist circumference (WHO cutoffs: ≥81 cm in women, ≥95 cm in men) and low physical activity had a >2-fold higher risk of developing PsA (HR 2.22 [95% CI 1.37, 3.58]), whereas a high waist circumference and high physical activity level were associated with an HR of 1.84 (95% CI 0.97, 3.47) (Table 5), both compared to the reference category of low waist circumference and high physical activity. The within-category median value of waist circumference was similar in the 2 categories of low waist circumference, as well as in the 2 categories of high waist circumference (data not shown). The RERI estimate for these associations was 0.00 (95% CI –1.17, 1.17), indicating no synergistic effect above additivity for high waist circumference and low physical activity. Similarly, there was no evidence of interaction on a multiplicative scale (P = 0.85). Sensitivity analyses excluding those with new onset of PsA within the first 3 years after inclusion did not change the above associations (data not shown).

DISCUSSION

In this population-based longitudinal study, adiposity, and in particular central obesity, was associated with increased risk of PsA. Individuals reporting low levels of physical activity had a somewhat higher risk of PsA than the most physically active. Although there was no clear evidence of a synergistic effect of physical activity and adiposity on PsA risk, the results suggest that the adverse effect of adiposity was somewhat lower among the most physically active participants. Our data also indicate an increased risk of PsA associated with weight gain, although the precision of these estimates was low.

To our knowledge, this is the first study showing the effect of leisure-time physical activity on risk of developing PsA. However, the results for BMI are in line with previous studies indicating a higher risk of developing PsA in overweight and obese individuals (12,13,36–38). A recent study suggested that the risk of incident PsA among patients with psoriasis can be modified by weight reduction (39). Approximately one-fifth of cases of incident PsA could be attributed to overweight or obesity if the estimated associations reflect causal relations. It has been indicated that excess body weight has a cumulative effect, as obesity in young age increases the risk of PsA (13). Biomechanical factors have been suggested as contributing factors in the development of PsA, and a high BMI results in greater mechanical stress for musculoskeletal structures (40). In the current study, the positive association between adiposity and risk of PsA was stronger for waist circumference than for BMI. Waist circumference may be a more accurate measure of visceral fat than BMI (41), as the latter is influenced by muscle mass. In addition, measure of waist circumference may be a better indicator of metabolic abnormalities and CVD risk (32). In light of the observed results, it is also conceivable that visceral fat plays an important role in the development of PsA. It has been described how complex interactions between the metabolic systems and cells of the immune system have pivotal roles in the pathogenesis of obesity-associated disease. The number of macrophages in adipose tissue in the obese state are triple those in lean adipose tissue, and adipose tissue–activated macrophages secrete high concentrations of proinflammatory cytokines and play a central role in promoting obesity-associated inflammation (42). The proinflammatory cytokines can trigger the interleukin-23/Th17 pathway that plays a pivotal role in the pathogenesis of PsA (43). There is also evidence that obesity can trigger autoinflammation (42), and PsA is partially considered an autoinflammatory disease (44).

In this study, physical activity at high levels seemed to modify the risk of PsA in overweight/obese individuals. However, individuals of normal weight doing low level of physical activity had a slightly increased risk as well. In addition, there was no evidence of a modifying effect of high physical activity level on the association between waist circumference and PsA risk. Thus, excessive fat seemed to be of greater importance than low levels of physical activity. A recent study on CVD risk reported that obesity combined with inactivity was associated with the highest risk of myocardial infarction (MI); however, physical activity seemed to attenuate but

not eliminate the risk of MI associated with excess body weight (20). Other studies indicate that high-level physical activity reduces abdominal/visceral fat that could lead to a reduction in low-grade inflammation, regardless of BMI (23,45). This could explain the protective effect of physical activity on the risk of both PsA and CVD.

According to the biomechanical stress theory (26,27), high-level physical activity could potentially contribute to the development of PsA due to the mechanical wear in load-bearing joints and in entheses, similar to the effect of a high body mass. However, in our study, high-level physical activity did not increase the risk of PsA, regardless of BMI.

Psoriasis is a major risk factor for PsA, and overweight/obesity is reported to increase the risk of psoriasis (11). A Mendelian randomization study suggested a causal effect of increased BMI on psoriasis (46). A recent meta-analysis also reported increased risk of psoriasis with higher BMI, waist circumference, and weight gain (47). A study conducted in the same population as that in the current study reported increased risk of psoriasis in individuals with high BMI and waist circumference (48), although the associations were somewhat weaker than those observed for PsA. Our results support previous data suggesting that obesity could be a stronger risk factor for development of PsA than for skin psoriasis alone (36).

Strengths of this study include the large sample and population-based, longitudinal design. Furthermore, the diagnoses of PsA have been validated according to patients' medical records (3). Also, the level of leisure-time physical activity from the questionnaire in HUNT2 has been validated against measured maximum oxygen uptake, and the term "hard leisure time physical activity" performed well (33). This suggests that our category of high-level physical activity represents vigorous activity. However, it is not possible to calculate metabolic equivalent of task hours from the questionnaire data because no information on type of activity was obtained.

Our study has some limitations. Individuals included in the study had to participate in both HUNT2 and HUNT3, and selection bias could have influenced the results if participation in HUNT3 was dependent on physical activity and adiposity status or PsA risk. However, such bias would most likely underestimate the associations under study.

Furthermore, validation of the diagnosis of PsA was accomplished according to stricter criteria than the CASPAR criteria because all validated cases had to include psoriasis to establish a diagnosis of PsA (3). Approximately 15% of all incident PsA patients develop arthritis and psoriasis simultaneously, or PsA precedes psoriasis (49), and thus a few cases of PsA may not have been identified. However, whether this leads to underestimation or overestimation of the associations under study is not clear, and this possibility would require that adiposity and physical activity be associated with these undetected cases in a different way than with the observed cases. Furthermore, based on the selection criteria for the validation study, it is conceivable that some cases of PsA that occurred among individuals with DM were not detected because they did not receive the psoriasis questionnaire. Since DM could be caused by adiposity and inactivity, this could bias the observed association toward the null.

PsA is believed to have a long preclinical phase, and delay between the onset of joint symptoms and diagnosis of PsA could be on average 5 years (50). The prevalence of pain at baseline was higher among inactive participants compared to those with high-level physical activity, which could indicate reverse causality by undiagnosed PsA. However, sensitivity analyses excluding the cases with disease onset within the first 3 years did not change the association of obesity and physical activity with risk of PsA. Last, because there were only a few individuals and cases of PsA in some of the categories, particularly when examining combined effects, the precision of the estimated associations for these categories was low.

In conclusion, the results from this population-based, longitudinal study indicate a positive association of adiposity, and in particular central obesity, with the risk of incident PsA. Although there was no clear modifying effect of physical activity on adiposity, individuals performing high-level physical activity had a reduced risk of PsA, regardless of BMI. Thus, our study adds to the growing evidence that the risk of PsA is modifiable and highlights the importance of preventive work against obesity, as well as the importance of encouraging individuals to engage in physical activity to reduce the incidence of PsA.

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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. Thomsen 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. Thomsen, Nilsen, Hoff.

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REFERENCES

1. Gelfand JM, Gladman DD, Mease PJ, Smith N, Margolis DJ, Nijsten T, et al. Epidemiology of psoriatic arthritis in the population of the United States. J Am Acad Dermatol 2005;53:573.
2. Tam LS, Leung YY, Li EK. Psoriatic arthritis in Asia. Rheumatology (Oxford) 2009;48:1473–7.
3. Hoff M, Gulati AM, Romundstad PR, Kavanaugh A, Haugeberg G. Prevalence and incidence rates of psoriatic arthritis in central Norway: data from the Nord-Trondelag health study (HUNT). Ann Rheum Dis 2015;74:60–4.
4. Gladman DD, Ang M, Su L, Tom BD, Schentag CT, Farewell VT. Cardiovascular morbidity in psoriatic arthritis. Ann Rheum Dis 2009;68:1131–5.
5. Jamnitski A, Symmons D, Peters MJ, Sattar N, McInnes I, Nurmohamed MT. Cardiovascular comorbidities in patients with psoriatic arthritis: a systematic review. Ann Rheum Dis 2013;72:211–6.

6. Eder L, Wu Y, Chandran V, Cook R, Gladman DD. Incidence and predictors for cardiovascular events in patients with psoriatic arthritis. Ann Rheum Dis 2016;75:1680–6.
7. Gulati AM, Semb AG, Rollefstad S, Romundstad PR, Kavanaugh A, Gulati S, et al. On the HUNT for cardiovascular risk factors and disease in patients with psoriatic arthritis: population-based data from the Nord-Trondelag Health Study. Ann Rheum Dis 2016;75:819–24.
8. Polachek A, Touma Z, Anderson M, Eder L. Risk of cardiovascular morbidity in patients with psoriatic arthritis: a meta-analysis of observational studies. Arthritis Care Res (Hoboken) 2017;69:67–74.
9. Lupoli R, Pizzicato P, Scalera A, Ambrosino P, Amato M, Peluso R, et al. Impact of body weight on the achievement of minimal disease activity in patients with rheumatic diseases: a systematic review and meta-analysis. Arthritis Res Ther 2016;18:297.
10. Pedreira PG, Pinheiro MM, Szejnfeld VL. Bone mineral density and body composition in postmenopausal women with psoriasis and psoriatic arthritis. Arthritis Res Ther 2011;13:R16.
11. Daien CI, Sellam J. Obesity and inflammatory arthritis: impact on occurrence, disease characteristics and therapeutic response. RMD Open 2015;1:e000012.
12. Ogdie A, Gelfand JM. Clinical risk factors for the development of psoriatic arthritis among patients with psoriasis: a review of available evidence. Curr Rheumatol Rep 2015;17:64.
13. Russolillo A, Iervolino S, Peluso R, Lupoli R, Di Minno A, Pappone N, et al. Obesity and psoriatic arthritis: from pathogenesis to clinical outcome and management. Rheumatology (Oxford) 2013;52:62–7.
14. Gulati AM, Salvesen O, Thomsen RS, Kavanaugh A, Semb AG, Rollefstad S, et al. Change in cardiovascular risk factors in patients who develop psoriatic arthritis: longitudinal data from the Nord-Trondelag Health Study (HUNT). RMD Open 2018;4:e000630.
15. Soltani-Arabshahi R, Wong B, Feng BJ, Goldgar DE, Duffin KC, Krueger GG. Obesity in early adulthood as a risk factor for psoriatic arthritis. Arch Dermatol 2010;146:721–6.
16. Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet 2018;391:2273–84.
17. Gerdes S, Rostami-Yazdi M, Mrowietz U. Adipokines and psoriasis. Exp Dermatol 2011;20:81–7.
18. Scotece M, Conde J, Gomez R, Lopez V, Pino J, Gonzalez A, et al. Role of adipokines in atherosclerosis: interferences with cardiovascular complications in rheumatic diseases. Mediators Inflamm 2012;2012:125458.
19. Ouerghi N, Fradj MK, Bezrati I, Khammassi M, Feki M, Kaabachi N, et al. Effects of high-intensity interval training on body composition, aerobic and anaerobic performance and plasma lipids in overweight/obese and normal-weight young men. Biol Sport 2017;34:385–92.
20. Renninger M, Lochen ML, Ekelund U, Hopstock LA, Jorgensen L, Mathiesen EB, et al. The independent and joint associations of physical activity and body mass index with myocardial infarction: the Tromso Study. Prev Med 2018;116:94–8.
21. Rocha-Rodrigues S, Rodriguez A, Goncalves IO, Moreira A, Maciel E, Santos S, et al. Impact of physical exercise on visceral adipose tissue fatty acid profile and inflammation in response to a high-fat diet regimen. Int J Biochem Cell Biol 2017;87:114–24.
22. Wedell-Neergaard AS, Krogh-Madsen R, Petersen GL, Hansen AM, Pedersen BK, Lund R, et al. Cardiorespiratory fitness and the metabolic syndrome: roles of inflammation and abdominal obesity. PLoS One 2018;13:e0194991.
23. Maillard F, Pereira B, Boisseau N. Effect of high-intensity interval training on total, abdominal and visceral fat mass: a meta-analysis. Sports Med 2018;48:269–88.
24. Helgerud J, Hoydal K, Wang E, Karlsen T, Berg P, Bjerkaas M, et al. Aerobic high-intensity intervals improve VO2max more than moderate training. Med Sci Sports Exerc 2007;39:665–71.
25. Aspenes ST, Nilsen TI, Skaug EA, Bertheussen GF, Ellingsen O, Vatten L, et al. Peak oxygen uptake and cardiovascular risk factors in 4,631 healthy women and men. Med Sci Sports Exerc 2011;43:1465–73.
26. Jacques P, Lambrecht S, Verheugen E, Pauwels E, Kollias G, Armaka M, et al. Proof of concept: enthesitis and new bone formation in spondyloarthritis are driven by mechanical strain and stromal cells. Ann Rheum Dis 2014;73:437–45.
27. McGonagle DG, Helliwell P, Veale D. Enthesitis in psoriatic disease. Dermatology 2012;225:100–9.
28. Schett G, Lories RJ, D'Agostino MA, Elewaut D, Kirkham B, Soriano ER, et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13:731–41.
29. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, et al. Cohort profile: the HUNT Study, Norway. Int J Epidemiol 2013;42:968–77.
30. Holmen J. The Nord-Trøndelag Health Study 1995–97 (HUNT 2): objectives, contents, methods and participation. Norsk Epidmiologi 2003;13:19–32.
31. World Health Organization. Obesity: preventing and managing the global epidemic. 2000. URL: https://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/.
32. World Health Organization. Waist circumference and waist-hip ratio. 2008. URL: https://www.who.int/nutrition/publications/obesity/WHO_report_waistcircumference_and_waisthip_ratio/en/.
33. Kurtze N, Rangul V, Hustvedt BE, Flanders WD. Reliability and validity of self-reported physical activity in the Nord-Trondelag Health Study (HUNT 2). Eur J Epidemiol 2007;22:379–87.
34. Skarpsno ES, Nilsen TI, Sand T, Hagen K, Mork PJ. Do physical activity and body mass index modify the association between chronic musculoskeletal pain and insomnia? Longitudinal data from the HUNT study, Norway. J Sleep Res 2018;27:32–9.
35. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol 2005;20:575–9.
36. Li W, Han J, Qureshi AA. Obesity and risk of incident psoriatic arthritis in US women. Ann Rheum Dis 2012;71:1267–72.
37. Love TJ, Zhu Y, Zhang Y, Wall-Burns L, Ogdie A, Gelfand JM, et al. Obesity and the risk of psoriatic arthritis: a population-based study. Ann Rheum Dis 2012;71:1273–7.
38. Scher JU, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. Nat Rev Rheumatol 2019;15:153–66.
39. Green A, Shaddick G, Charlton R, Snowball J, Nightingale A, Smith C, et al. Modifiable risk factors and the development of psoriatic arthritis in people with psoriasis. Br J Dermatol 2020;182:714–20.
40. Tonuk SB, Ramadan B, Yorgancioglu ZR. Kinetic factors may trigger lesion development in the patients with psoriatic arthritis. Int J Rheum Dis 2016;19:1032–4.
41. Lee WS. Body fatness charts based on BMI and waist circumference. Obesity (Silver Spring) 2016;24:245–9.
42. Kanneganti TD, Dixit VD. Immunological complications of obesity. Nat Immunol 2012;13:707–12.
43. Marinoni B, Ceribelli A, Massarotti MS, Selmi C. The Th17 axis in psoriatic disease: pathogenetic and therapeutic implications. Auto Immun Highlights 2014;5:9–19.
44. McGonagle D. Enthesitis: an autoinflammatory lesion linking nail and joint involvement in psoriatic disease. J Eur Acad Dermatol Venereol 2009;23 Suppl S:9S–13S.
45. Wedell-Neergaard AS, Eriksen L, Gronbaek M, Pedersen BK, Krogh-Madsen R, Tolstrup J. Low fitness is associated with

abdominal adiposity and low-grade inflammation independent of BMI. PLoS One 2018;13:e0190645.

46. Budu-Aggrey A, Brumpton B, Tyrrell J, Watkins S, Modalsli EH, Celis-Morales C, et al. Evidence of a causal relationship between body mass index and psoriasis: a Mendelian randomization study. PLoS Med 2019;16:e1002739.
47. Aune D, Snekvik I, Schlesinger S, Norat T, Riboli E, Vatten LJ. Body mass index, abdominal fatness, weight gain and the risk of psoriasis: a systematic review and dose-response meta-analysis of prospective studies. Eur J Epidemiol 2018;33:1163–78.
48. Snekvik I, Smith CH, Nilsen TI, Langan SM, Modalsli EH, Romundstad PR, et al. Obesity, waist circumference, weight change, and risk of incident psoriasis: prospective data from the HUNT Study. J Invest Dermatol 2017;137:2484–90.
49. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med 2017;376:2095–6.
50. Kavanaugh A. Psoriatic arthritis and burden of disease: patient perspectives from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey. Rheumatol Ther 2016;3:91–102.

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Classifying Pseudogout Using Machine Learning Approaches With Electronic Health Record Data

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Objective. Identifying pseudogout in large data sets is difficult due to its episodic nature and a lack of billing codes specific to this acute subtype of calcium pyrophosphate (CPP) deposition disease. The objective of this study was to evaluate a novel machine learning approach for classifying pseudogout using electronic health record (EHR) data.

Methods. We created an EHR data mart of patients with ≥1 relevant billing code or ≥2 natural language processing (NLP) mentions of pseudogout or chondrocalcinosis, 1991–2017. We selected 900 subjects for gold standard chart review for definite pseudogout (synovitis + synovial fluid CPP crystals), probable pseudogout (synovitis + chondrocalcinosis), or not pseudogout. We applied a topic modeling approach to identify definite/probable pseudogout. A combined algorithm included topic modeling plus manually reviewed CPP crystal results. We compared algorithm performance and cohorts identified by billing codes, the presence of CPP crystals, topic modeling, and a combined algorithm.

Results. Among 900 subjects, 123 (13.7%) had pseudogout by chart review (68 definite, 55 probable). Billing codes had a sensitivity of 65% and a positive predictive value (PPV) of 22% for pseudogout. The presence of CPP crystals had a sensitivity of 29% and a PPV of 92%. Without using CPP crystal results, topic modeling had a sensitivity of 29% and a PPV of 79%. The combined algorithm yielded a sensitivity of 42% and a PPV of 81%. The combined algorithm identified 50% more patients than the presence of CPP crystals; the latter captured a portion of definite pseudogout and missed probable pseudogout.

Conclusion. For pseudogout, an episodic disease with no specific billing code, combining NLP, machine learning methods, and synovial fluid laboratory results yielded an algorithm that significantly boosted the PPV compared to billing codes.

INTRODUCTION

Pseudogout, also called acute calcium pyrophosphate (CPP) crystal arthritis, represents the acute inflammatory subtype of calcium pyrophosphate deposition disease (CPPD) (1). The incidence of pseudogout has not been well characterized, even among the 8–10 million adults in the US with CPPD (2). While pseudogout was first recognized in 1962, nearly 60 years later our understanding of risk factors for and long-term outcomes of this inflammatory arthritis remain limited. One of the main challenges in studying pseudogout epidemiology is accurately identifying pseudogout in large data sets. The lack of specific billing codes for this acute subtype of CPPD poses a major challenge to identifying the disease in large administrative data sets. We previously reported that a published billing code algorithm for CPPD had a very low positive predictive value (PPV) of 18% for the pseudogout phenotype in an academic medical center electronic health record (EHR) data set (3).

Machine learning approaches that incorporate information from narrative EHR notes provide an opportunity to more accurately classify patients with rare or episodic diseases for which

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SIGNIFICANCE & INNOVATIONS

- Limited methods exist to identify patients with pseudogout for large epidemiologic studies, particularly due to its episodic nature, and thus intermittent documentation in the electronic health record (EHR), and lack of specific billing codes.
- To address this need, we tested a novel topic modeling–based method that draws on a wide variety of EHR data to predict pseudogout, rather than using a traditional method of manually creating a small list of potentially predictive features to predict pseudogout.
- We developed an approach to identify patients with pseudogout using EHR data with a positive predictive value of 81% and identified 2,490 patients with definite or probable pseudogout.
- The proposed approach allows for the development of a pseudogout cohort and will enable much needed epidemiologic studies of pseudogout, the acute inflammatory subtype of calcium pyrophosphate crystal deposition disease.

billing codes may not exist or are not accurate. Rich clinical data documented in narrative notes can be transformed into a structured format using natural language processing (NLP) techniques. Counts of pertinent clinical "concepts" or term mentions (e.g., "pseudogout") can then be included in machine learning algorithms together with other structured data, such as billing codes, laboratory data, and prescriptions.

Previous studies have validated several machine learning approaches for phenotyping chronic conditions (4). Pseudogout poses unique challenges due to its lack of specific billing codes as well as its episodic nature, which means that documentation about pseudogout in the EHR is sparse. We hypothesized that leveraging the semantic structure of the data (i.e., the interconnectedness of pseudogout-related words in narrative notes) may help to optimize an algorithm for identifying pseudogout. Topic modeling is a type of statistical modeling that can be used to identify structure, or "topics," in a data set (5). Traditionally used to discover topics in bodies of text, such as "politics" in a set of newspaper articles, here we used it to identify discussion of pseudogout in narrative notes. We integrated topic modeling with our published machine learning approaches for phenotyping to identify a cohort of definite/probable pseudogout cases from EHR data and to compare this approach to using billing codes or manually reviewed laboratory data.

MATERIALS AND METHODS

Overview. Our approach (Figure 1) includes 1) applying an initial filter containing billing codes relevant to pseudogout to create a preliminary data mart enriched for pseudogout cases and obtaining gold standard labels by medical record review, 2) curating EHR data and applying NLP techniques to extract features from narrative notes for patients in the data mart, 3) applying a second filter to further enrich the data mart for pseudogout cases, 4) identifying additional gold standard labels for patients in the final data mart, 5) applying a topic modeling approach to predict the probability of pseudogout, and 6) evaluating algorithm performance and comparing cohorts.

Data source. We developed our algorithm using the Partners HealthCare Research Patient Data Repository (RPDR), 1991–2017. Partners RPDR includes EHR data for 5.5 million patients from 2 large academic medical centers, Brigham and Women's Hospital and Massachusetts General Hospital, and their affiliated community hospitals, community health centers, and primary care practices (6). In an initial attempt to increase the prevalence of pseudogout in our data mart, which improves algorithm performance (7,8), we identified patients with ≥1 relevant billing code (e.g., 712.x for chondrocalcinosis) or a simple text search of narrative notes to form a preliminary data mart (Figure 1).

EHR data extraction. Among 50,062 patients in the preliminary data mart, we obtained all narrative notes (such as clinic visits, discharge summaries, radiology reports, and pathology reports), selected laboratory data (e.g., synovial fluid crystal analysis, parathyroid hormone, magnesium), and prescriptions for relevant medications (e.g., nonsteroidal antiinflammatory drugs [NSAIDs], oral steroids, colchicine). Synovial fluid crystal analysis performed by the hospital laboratory was provided as structured data (ever/never performed). Among >10,000 patients with synovial fluid crystal analysis performed by the laboratory, the presence or absence of synovial fluid CPP crystals was determined by manual review of laboratory data because these results were recorded as free text rather than in structured data fields.

NLP to extract information from narrative notes. To transform information from narrative notes into structured data, we applied NLP. The National Library of Medicine maintains a database of medical concepts, the Unified Medical Language System (UMLS) (9). We first identified a list of 73 UMLS medical concepts relevant to pseudogout from online knowledge sources such as Medline and Wikipedia, using an automated method; see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24132/abstract, for a complete list of these concepts (10). NILE software for NLP was applied to 9,756,936 narrative notes among all patients in the preliminary data mart to count mentions of relevant NLP concepts for each patient (11). Forty-one NLP concepts appeared in >5% of notes containing the NLP concept "pseudogout" and were included in subsequent steps.

Creation of the final data mart. We randomly selected 600 patients from the preliminary data mart for EHR review to estimate pseudogout prevalence in the data mart. The prevalence

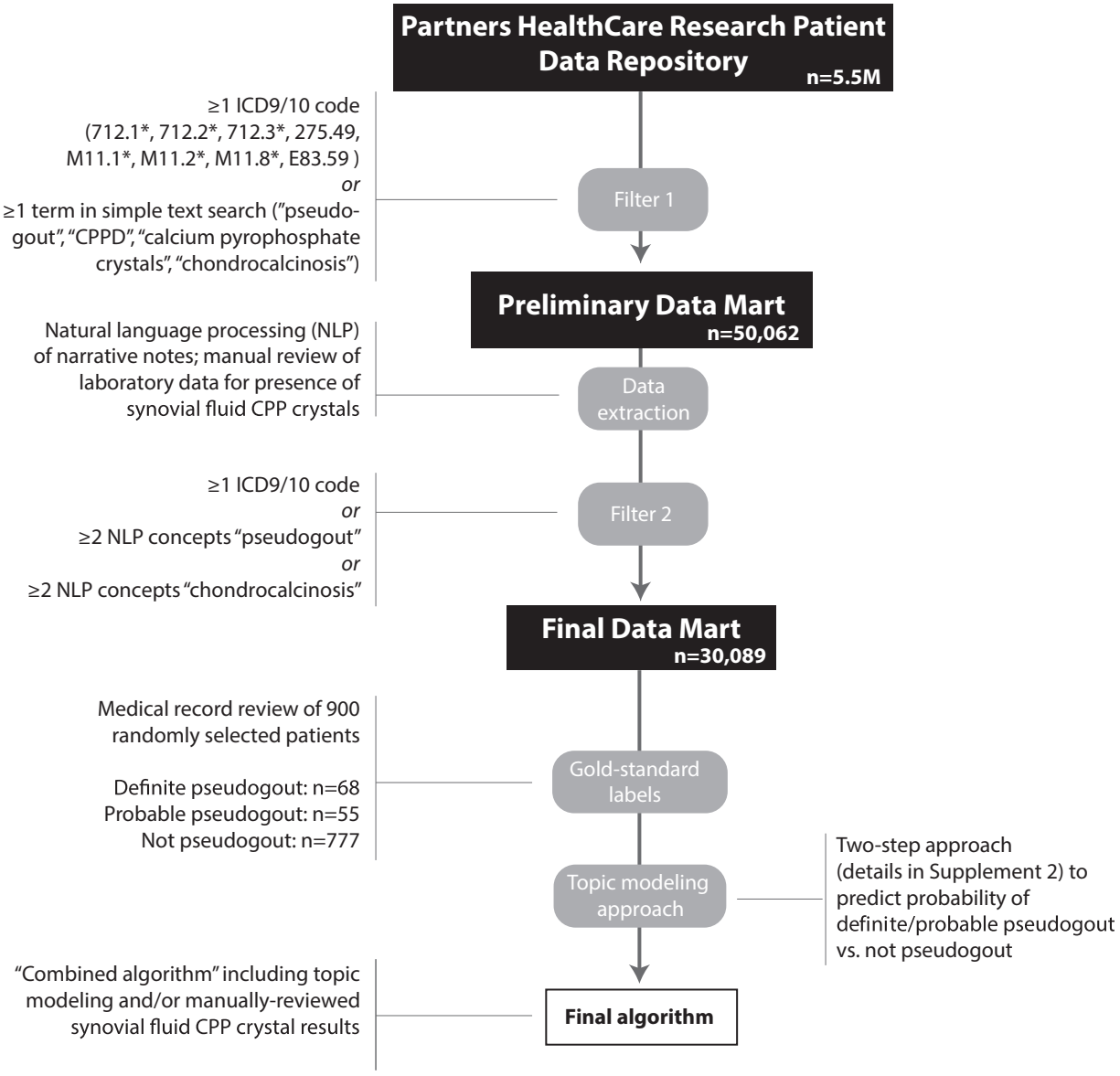

Figure 1. Novel machine learning approach to classifying definite/probable pseudogout in an electronic health record data set. CPP = calcium pyrophosphate; CPPD = calcium pyrophosphate deposition disease; ICD-9/10 = International Classification of Diseases, Ninth Revision/Tenth Revision.

was 5.5%, which is suboptimal for developing any algorithm, because low prevalence limits the PPV of an algorithm. To further increase pseudogout prevalence, we used data from this randomly selected group to create a second filter including billing codes and NLP concepts (Figure 1). Our final data mart included 30,089 patients passing the second filter; pseudogout prevalence was 13.7% (see Results below).

Pseudogout gold standard labels. We then randomly selected 900 patients from the final data mart for gold standard chart review by 1 of 2 reviewers (SKT and KAY) to label as definite pseudogout, probable pseudogout, or not pseudogout (see Table 1 for definitions). Pseudogout definitions were based on Ryan and McCarty's proposed diagnostic criteria for CPPD and the 2011 European League Against Rheumatism (EULAR) recommendations for CPPD terminology and diagnosis (1,12); we required synovitis for both definite and probable pseudogout. Due to the random selection, some of the 900 patients overlapped with the initial 600 patients; only those passing both the first and second filters were included in the 900. All cases of definite or probable pseudogout were confirmed by a board-certified rheumatologist (SKT).

Topic modeling approach. To identify definite/probable pseudogout versus not, we applied a novel approach that employs topic modeling followed by penalized regression (4). We herein refer to the topic modeling method followed by regression as the "topic modeling approach."

Table 1. Pseudogout definitions for gold standard medical record review*

Definite pseudogout	1) Synovitis (joint pain, swelling, tenderness, ± warmth) and 2) synovial fluid crystal analysis positive for calcium pyrophosphate crystals as documented in laboratory results and/or narrative notes
Probable pseudogout	Synovitis (joint pain, swelling, tenderness, ± warmth) and 1) acute onset in the wrist, knee, or ankle, and chondrocalcinosis in the affected joint, or 2) a rheumatologist or orthopedist opinion that pseudogout was the most likely diagnosis

* Definitions were based on Ryan and McCarty's proposed diagnostic criteria for calcium pyrophosphate deposition disease (CPPD) and the 2011 European League Against Rheumatism recommendations for CPPD terminology and diagnosis (1,12).

For common conditions such as diabetes mellitus, including the primary International Classification of Diseases, Ninth Revision or Tenth Revision (ICD-9/10) billing code for the condition (e.g., 250.00 for diabetes mellitus without mention of complications) and primary NLP concept alone (e.g., "diabetes") in an algorithm can achieve relatively high PPVs (13). However, for episodic or uncommon conditions that may be discussed at only a handful of visits, such as pseudogout, additional features related to the condition may be useful. Topic modeling provides a method for identifying discussion of pseudogout in the EHR by combining information from a wide variety of features, including symptoms (e.g., joint swelling), laboratory tests (e.g., synovial fluid crystal analysis), and medications. We employed a novel topic modeling method, called sureLDA, because this method has recently been shown to work well for phenotyping a host of both acute and chronic diseases from EHR data (14). This method predicts a pseudogout propensity score (sureLDA score) for each of the 30,089 patients. See Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24132/abstract, for further details on our topic modeling approach.

To optimize pseudogout prediction combining the unsupervised sureLDA method and gold standard labels, we subsequently developed a supervised regression model including the sureLDA score, counts of the NLP concept "pseudogout," and indication of whether synovial fluid crystal analysis had been performed by the hospital laboratory (ever/never). We used the coefficients from the model to obtain the predicted probability of definite/probable pseudogout (range 0–1) for all 30,089 patients in the final data mart. We defined the probability threshold for classifying a patient as definite/probable pseudogout by setting the specificity at 98%. We used 10-fold cross validation to correct for overfitting.

The topic modeling approach only included EHR features that were available as structured data or via NLP. Thus, information regarding the presence of synovial fluid CPP crystals, which required manual review of laboratory data, was not included in the topic modeling approach. By contrast, whether synovial fluid crystal analysis had ever been performed by the laboratory (regardless of result) was available as structured data and could be included in this approach.

Performance assessment. For comparison, we computed the accuracy of 5 alternative phenotyping methods for pseudogout: 1) ≥1 relevant ICD-9/10 billing code, 2) ≥3 relevant ICD-9/10 billing codes, 3) the presence of synovial fluid CPP crystals, 4) the topic modeling approach (described above), and 5) a combined algorithm (topic modeling approach and/or the presence of synovial fluid CPP crystals). We calculated sensitivity, specificity, PPV, and area under the curve for each of the 5 algorithms based on the 900 gold standard labels. We used 10-fold cross-validation to correct performance metrics for overfitting bias for algorithms 4 and 5. The F-score, a metric jointly representing the sensitivity and PPV of the algorithm, was calculated as the harmonic mean of sensitivity and PPV. We applied each of the 5 algorithms to the final data mart (n = 30,089) to identify the resultant cohorts and examined similarities and differences across the cohorts.

RESULTS

Among the 900 randomly selected subjects from the final data mart of 30,089 patients passing both filters (Figure 1), 123 (13.7%) had pseudogout by chart review (68 definite, 55 probable). The presence of ≥1 billing code for chondrocalcinosis and/or other disorders of calcium metabolism, previously used to identify pseudogout patients, had a sensitivity of 65%, a specificity of 63%, a PPV of 22%, and F-score of 32% for definite/probable pseudogout (Table 2). Requiring ≥3 billing codes had a lower sensitivity of 46% and a higher specificity of 79%, and marginally improved the PPV to 26%. The presence of CPP crystals by manual review of laboratory results had a sensitivity of 29%, a PPV of 92%, and F-score of 44%; as expected, the assessment was 100% specific because definite pseudogout was defined by the presence of CPP crystals. Without using CPP crystal results, the topic modeling approach had a sensitivity of 29%, a specificity of 98%, a PPV of 79%, and F-score of 42%. The combined algorithm yielded a higher sensitivity of 42% with similar specificity of 98%, PPV of 81%, and F-score of 55%.

When we applied the 5 algorithms to our final data mart of 30,089 patients, ≥1 billing code alone yielded the largest cohort (n = 12,035). However, the low PPV of 22% for ≥1 billing code alone raises concerns about misclassification of many nonpseudogout patients as having pseudogout. On the other hand, classifying all subjects with CPP crystals in synovial fluid as having pseudogout yielded a high PPV of 92% but missed 71% of chart review–confirmed cases of definite or probable pseudogout.

Table 3 illustrates important differences between the cohort classified by ≥1 billing code versus cohorts classified by the

Table 2. Performance of algorithms to identify definite or probable pseudogout in an electronic health record (EHR) data set*

Algorithm	Performance among gold standard labels (n = 900)					Cases in EHR data set (n = 30,089)
	Sensitivity	Specificity	PPV	AUC	F-score	
≥1 billing code†	0.65	0.63	0.22	0.64	0.32	12,035
≥3 billing codes†	0.46	0.79	0.26	0.63	0.32	7,213
Presence of CPP crystals‡	0.29	1.00	0.92	0.64	0.44	1,630
Topic modeling approach§	0.29	0.98	0.79	0.86	0.42	1,870
Combined: topic modeling approach and/or presence of CPP crystals	0.42	0.98	0.81	0.70	0.55	2,490

* AUC = area under the curve; CPP = calcium pyrophosphate; PPV = positive predictive value.
† Among International Classification of Diseases, Ninth Revision (ICD-9) or ICD-10 billing codes for chondrocalcinosis or calcium metabolism disorder: ICD-9 712.1*, 712.2*, 712.3*, 275.49; ICD-10 M11.1*, M11.2*, M11.8*, E83.59. Adapted from Bartels et al (17), which only included ICD-9 codes, by also including ICD-10 codes.
‡ The presence of synovial fluid CPP crystals was ascertained via manual review of laboratory results recorded as free text in the EHR.
§ Topic modeling approach includes: score for propensity of pseudogout from a topic modeling method (sureLDA) including all relevant features, counts of the NLP concept "pseudogout," and whether synovial fluid crystal analysis was performed (regardless of result).

presence of CPP crystals or by the combined algorithm. The billing code cohort was slightly younger, had a higher percentage of females, and a lower percentage of African Americans. Mentions of "pseudogout" in narrative notes, a history of synovial fluid crystal analysis, and prescriptions for colchicine, NSAIDs, and oral glucocorticoids were much less common in the billing code cohort than in the other 2 cohorts.

The combined algorithm identified 50% more patients than the presence of CPP crystals, because the latter captured most but not all cases of definite pseudogout and missed all cases of probable pseudogout, which by definition did not have synovial fluid CPP crystals in laboratory results. The cohorts identified by the presence of CPP crystals and the combined algorithm were remarkably similar, even though the combined algorithm contained both definite and probable pseudogout patients, while the CPP crystal cohort only included definite pseudogout. Mean age, sex, race, the presence of pertinent billing codes, mentions of "pseudogout" in narrative notes, and prescriptions for NSAIDs and oral glucocorticoids were similar between these 2 cohorts. Synovial fluid crystal analysis was very common (86%) in the combined algorithm cohort and was required by definition for the CPP crystal cohort. Colchicine prescriptions were slightly more common in the combined algorithm cohort compared to the CPP crystal cohort.

DISCUSSION

For pseudogout, an episodic disease without a specific billing code, adding information derived from a topic modeling approach to an existing approach for phenotyping using NLP and machine learning yielded an algorithm with a signif-

Table 3. Comparison of cohorts identified by algorithms for definite or probable pseudogout applied to the final data mart of 30,089 patients*

	≥1 billing code	CPP crystals present	Combined: topic modeling approach and/or CPP crystals present
Patients, no.	12,035	1,630	2,490
Age at last medical visit, mean ± SD years	72.8 ± 15.6	76.4 ± 13.0	76.3 ± 12.8
Female	55.6	50.6	50.8
Race			
White	84.7	79.5	81.0
African American	4.8	8.8	7.8
Other	10.5	11.7	11.2
≥1 pertinent billing code	100.0	72.6	74.1
≥1 NLP concept "pseudogout"	34.3	86.1	90.8
Synovial fluid crystal analysis performed, regardless of result	18.9	100.0	86.0
Synovial fluid CPP crystals present	9.8	100.0	65.5
Prescription medications in EHR			
Colchicine	17.3	35.1	43.4
NSAID	59.1	69.1	72.7
Oral glucocorticoids	44.4	62.9	67.4

* Values are the percentage unless indicated otherwise. CPP = calcium pyrophosphate; EHR = electronic health record; NLP = natural language processing; NSAID = nonsteroidal antiinflammatory drug.

icantly improved PPV compared to billing codes alone. The combined algorithm, incorporating a topic modeling approach and/or the presence of synovial fluid CPP crystals, yielded a large cohort of patients with a high likelihood for definite or probable pseudogout that can be employed for epidemiologic studies of this crystalline arthritis. Similarities between the cohorts identified by the presence of CPP crystals and by the combined algorithm are reassuring and suggest that the cohort identified by the combined algorithm accurately represents pseudogout.

We compared 5 algorithms for classifying pseudogout and identified tradeoffs of each approach. For an investigator who wishes to identify pseudogout with 100% specificity and is willing to accept the tradeoff of missing the majority of cases, reviewing laboratory results for the presence of synovial fluid CPP crystals may be sufficient. In our EHR, the major downside to obtaining synovial fluid CPP crystals results is that a time-consuming manual review was required, because the laboratory recorded these results as free text with a variety of labels (e.g., "1+ intracellular CPP," "CPP crystals present," "2+ calcium pyrrophosphate [sic] crystals"). Additionally, synovial fluid crystal analyses performed by rheumatologists in the clinic were documented in narrative notes but were not recorded in laboratory results; this absence explains why the algorithm defined by the presence of CPP crystals in laboratory data missed some cases of definite pseudogout. A topic modeling approach, which used data extracted via NLP and other structured EHR data, achieved a high PPV (79%) with moderate sensitivity (29%) and did not require manual review of synovial fluid laboratory data.

Since the goal of this project was to construct a large pseudogout cohort for future epidemiologic studies, the combined algorithm will be used due to its high PPV (81%) plus improved sensitivity (42%) that provides a larger cohort than the presence of CPP crystals or the topic modeling approach alone. We manually reviewed 100 randomly selected cases among the 2,490 pseudogout cases identified by our combined algorithm and found that 85 fulfilled the study definition of definite or probable pseudogout. This result signifies a PPV of 85% in this small randomly selected sample, consistent with the PPV in our derivation set of gold standard labels. The large cohort identified by the combined algorithm will provide improved power for epidemiologic association studies and improved generalizability compared to a smaller cohort constructed among subjects who necessarily had both synovial fluid crystal analysis performed at a Partners HealthCare laboratory and a positive result for CPP crystals.

The sensitivity achieved by our combined algorithm (42%) is slightly lower than the sensitivity of machine learning algorithms for other rheumatic diseases such as rheumatoid arthritis (sensitivity 63%) (8) and systemic lupus erythematosus (SLE) (sensitivity 47% for definite/probable SLE) (6). Nonetheless, our combined algorithm provides a more robust PPV of 81% compared to ≥1 billing code alone (PPV 22%), while achieving a modest sensitivity of 42%.

Several case–control studies that focused on risk factors for pseudogout defined pseudogout using 1 diagnosis code for pseudogout (Read code N02.14) recorded by general practitioners in the UK (15,16). To our knowledge, the accuracy of 1 Read code for pseudogout has not been validated against medical record review and might represent a broader definition of CPPD, pseudogout, or a combination of these and other conditions. A published billing code algorithm for CPPD, developed using Veterans' Administration data, had a very low PPV for pseudogout (18%) in our EHR (3). In the current study, we identified the fact that increasing the number of billing codes (e.g., ≥3) increased the specificity but did not substantially increase the PPV for pseudogout, providing motivation for identification using approaches that incorporate a broader set of information, such as NLP. Our method for identifying pseudogout using data from narrative notes via NLP and machine learning methods combined with synovial fluid laboratory data provides a blueprint for identifying pseudogout cohorts in other EHR systems. Our approach may also prove useful for phenotyping other episodic or rare rheumatic diseases for which documentation may be sparse and/or specific billing codes do not exist.

Our study has several limitations, including the exclusive use of EHR data from an academic medical center, which may limit the generalizability of the combined algorithm to nonacademic settings. Synovial fluid crystal analysis results were not available as structured data, so time-consuming manual review was required and may not be feasible for other data sets. Notably, the topic modeling approach produced an algorithm with a PPV close to 80%, even without including synovial fluid CPP crystal results, though with a lower sensitivity and thus a smaller cohort size. Validation in an external EHR data set will be required to determine reproducibility of the algorithm performance. Our machine learning algorithm was designed to classify definite or probable pseudogout rather than just definite pseudogout, because definite pseudogout requires synovial fluid crystal analysis, which is underutilized in clinical practice and may produce false-negative results due to challenges with identifying small, weakly birefringent CPP crystals (17–19). Classification criteria for pseudogout have not yet been developed. Thus, we defined definite and probable pseudogout based on Ryan and McCarty's proposed diagnostic criteria for CPPD and the 2011 EULAR CPPD terminology and diagnosis recommendations.

Pseudogout epidemiology research hinges on the ability to accurately identify pseudogout patients in large data sets. We provide a method for classifying definite or probable pseudogout using EHR data among 5.5 million subjects, though further testing in an external data set is needed prior to widespread application.

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. Tedeschi 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. Tedeschi, Tianxi Cai, Liao.

Acquisition of data. Tedeschi, Tianrun Cai, Yates, Dahal, Xu.

Analysis and interpretation of data. Tedeschi, He, Ahuja, Hong, Lyu, Yoshida, Solomon, Tianxi Cai, Liao.

REFERENCES

1. Zhang W, Doherty M, Bardin T, Barskova V, Guerne PA, Jansen TL, et al. European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. Ann Rheum Dis 2011;70:563–70.
2. Abhishek A, Neogi T, Choi H, Doherty M, Rosenthal AK, Terkeltaub R. Unmet needs and the path forward in joint disease associated with calcium pyrophosphate crystal deposition [review]. Arthritis Rheumatol 2018;70:1182–91.
3. Tedeschi SK, Solomon DH, Liao KP. Pseudogout among patients fulfilling a billing code algorithm for calcium pyrophosphate deposition disease. Rheumatol Int 2018;38:1083–8.
4. Zhang Y, Cai T, Yu S, Cho K, Hong C, Sun J, et al. Methods for high-throughput phenotyping with electronic medical record data using a common semi-supervised approach (PheCAP). Nat Protoc 2019;14:3426–44.
5. Liu L, Tang L, Dong W, Yao S, Zhou W. An overview of topic modeling and its current applications in bioinformatics. Springerplus 2016;5:1608.
6. Jorge A, Castro VM, Barnado A, Gainer V, Hong C, Cai T, et al. Identifying lupus patients in electronic health records: development and validation of machine learning algorithms and application of rule-based algorithms. Semin Arthritis Rheum 2019;49:84–90.
7. Liao KP, Cai T, Savova GK, Murphy SN, Karlson EW, Ananthakrishnan AN, et al. Development of phenotype algorithms using electronic medical records and incorporating natural language processing. BMJ 2015;350:h1885.
8. Liao KP, Cai T, Gainer V, Goryachev S, Zeng-treitler Q, Raychaudhuri S, et al. Electronic medical records for discovery research in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2010;62:1120–7.
9. Unified Medical Language System Terminology Services. 2017. URL: https://uts.nlm.nih.gov/home.html.
10. Yu S, Chakrabortty A, Liao KP, Cai T, Ananthakrishnan AN, Gainer VS, et al. Surrogate-assisted feature extraction for high-throughput phenotyping. J Am Med Inform Assoc 2017;24:e143–9.
11. Yu S, Cai T, Cai T. NILE: Fast natural language processing for electronic health records. 2013.
12. Ryan L, McCarty D. Calcium pyrophosphate crystal deposition disease; pseudogout; articular chondrocalcinosis. In: McCarty D, editor. Arthritis and allied conditions. 10th ed. Philadelphia: Lea and Febiger; 1985. p. 1515–46.
13. Liao KP, Sun J, Cai TA, Link N, Hong C, Huang J, et al. High-throughput multimodal automated phenotyping (MAP) with application to PheWAS. J Am Med Inform Assoc 2019;26:1255–62.
14. Ahuja Y, Zhou D, He Z, Sun J, Castro VM, Gainer V, et al. sureLDA: a multidisease automated phenotyping method for the electronic health record. J Am Med Inform Assoc 2020;27:1235–43.
15. Rho YH, Zhu Y, Zhang Y, Reginato AM, Choi HK. Risk factors for pseudogout in the general population. Rheumatology (Oxford) 2012; 51:2070–4.
16. Roddy E, Muller S, Paskins Z, Hider SL, Blagojevic-Bucknall M, Mallen CD. Incident acute pseudogout and prior bisphosphonate use: matched case-control study in the UK-Clinical Practice Research Datalink. Medicine (Baltimore) 2017;96:e6177.
17. Bartels CM, Singh JA, Parperis K, Huber K, Rosenthal AK. Validation of administrative codes for calcium pyrophosphate deposition: a Veterans Administration study. J Clin Rheumatol 2015;21:189–92.
18. Berendsen D, Neogi T, Taylor WJ, Dalbeth N, Jansen TL. Crystal identification of synovial fluid aspiration by polarized light microscopy: an online test suggesting that our traditional rheumatologic competence needs renewed attention and training. Clin Rheumatol 2017;36:641–7.
19. Swan A, Amer H, Dieppe P. The value of synovial fluid assays in the diagnosis of joint disease: a literature survey. Ann Rheum Dis 2002;61:493–8.

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Effects of Repetitive Transcranial Magnetic Stimulation and Multicomponent Therapy in Patients With Fibromyalgia: A Randomized Controlled Trial

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Objective. Fibromyalgia (FM) is a chronic painful condition partly due to alterations in pain modulation by the central nervous system. Multicomponent therapy (MT) and repetitive transcranial magnetic stimulation (rTMS) have both been reported as pain modulators in patients with FM. The aim of this study was to compare the effects of rTMS on pain with a combination of MT and rTMS versus MT alone.

Methods. Thirty-nine FM patients with visual analog scale (VAS) results for pain of ≥40 mm were randomized to active or sham rTMS (high-frequency, primary motor cortex M1) plus 12 weeks of MT (3 sessions per week combining aerobic training, pool-based exercises, and relaxation). Repetitive TMS was started 2 weeks prior to MT and maintained until the end of the program (week 14). Assessments were achieved at baseline, at week 14, and at 6 months (week 40) after completion of the program. The main criterion was pain reduction, as assessed by the weekly mean self-reported level of pain (reported daily). Secondary outcomes were cardiorespiratory fitness (graded maximal exercise test), cardiac autonomic adaptations, and FM impact (using scales for FM impact, depression, sleep efficiency, and pain catastrophizing).

Results. The reduction of the weekly mean of pain reported daily did not differ significantly between groups (using repeated measures of analysis of variance [ANOVA]). Two-way ANOVAs showed that pain VAS results, as well as cardiorespiratory fitness, quality of life, depression, and catastrophizing, improved significantly at week 14 and remained stable until week 40. Neither cardiac autonomic adaptations nor sleep efficiency changed significantly.

Conclusion. Repetitive TMS did not reduce pain in patients with FM who followed the MT program.

INTRODUCTION

Fibromyalgia (FM) is a chronic disabling condition characterized by generalized pain, sleep disturbances, and widespread sensory disturbances that predominantly affect women (1–3). Although its pathophysiology remains incompletely understood, sensitization of the central nervous system, and control of pain pathways in particular, is recognized as a key mechanism and explains the diversity of FM symptoms and the difficulties in treating patients with FM (2–5).

Although both pharmacologic and nonpharmacologic interventions follow evidence-based recommendations (6,7), their clinical relevance or the magnitude of their benefits are questionable or limited (8). Tailored multidisciplinary, nonpharmacologic approaches are now advocated by several research groups and guidelines. More specifically, interventions combining patient education, cognitive behavioral therapy, and/or exercise, in particular, pool-based therapy and aerobic reconditioning, are increasingly being used (3,6–11). These multicomponent therapies (MTs) have been shown to produce substantial improvements in quality of life (QoL) and to have mild-to-moderate effects on FM outcomes (6–8,10,12). These effects cannot be explained merely by improvements in muscular and cardiorespiratory fitness but may also be due to alterations in central pain processing (13–15).

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SIGNIFICANCE & INNOVATIONS

- Repetitive transcranial magnetic stimulation (rTMS) does not reduce pain in patients with fibromyalgia (FM) who undergo multicomponent therapy (MT).
- MT alone seems sufficient to modulate pain and to improve quality of life and secondary outcomes in patients with FM.
- Neither MT nor rTMS improved cardiac autonomic system adaptations in patients with FM.

Repetitive transcranial magnetic stimulation (rTMS), a noninvasive brain stimulation technique, has been used for various neurologic and psychiatric conditions and is approved for the treatment of depression (16–18). In particular, rTMS modulates the excitability of cortical and deep brain areas through an electromagnetic field applied on the scalp (17). In FM patients, it has been suggested that rTMS produces analgesic effects through the modulation of descending pain pathways (19,20) and of the right limbic area involved in the socioemotional dimension of pain (21). Recent meta-analyses showed that rTMS significantly reduced pain in patients with chronic pain syndrome or FM (20,22). Moreover, pain reduction was greater when primary motor (M1) rather than prefrontal cortex stimulation was applied (20). Nevertheless, this improvement (12%) was lower than the minimum clinically important difference threshold (20,22).

Since both rTMS and MT (exercise in particular) are reported to partly exert pain attenuation through neuroplastic alterations (13,17), we hypothesized that their combination may lead to additional clinically relevant pain reduction. We further hypothesized that rTMS could also improve cardiovascular and hormonal adaptations during exercise in patients with FM through beneficial action on the autonomic nervous system (23). We thus designed a double-blind randomized controlled study to investigate the effects of active rTMS (ArTMS) versus sham rTMS (SrTMS) applied over the M1 cortex and combined with MT using a visual analog scale (VAS) score for pain at 30 days as the primary outcome.

PATIENTS AND METHODS

Eligibility criteria. This study was conducted in the Pain and Rheumatology departments and the Sports Pathologies medical unit of Grenoble Alpes University Hospital. In total, 450 consecutive patients who were secondary- or tertiary-care outpatients were recruited from the pain or rheumatology centers. Patients' eligibility criteria were checked during monthly multidisciplinary meetings.

Inclusion criteria were as follows: 1) diagnosis of FM (using American College of Rheumatology criteria [1]); 2) VAS pain score of ≥40 mm (24); 3) patients naive for rTMS; 4) >18 years of age; and 5) no antidepressants, pain killers, corticosteroids, or nonsteroidal antiinflammatory drugs added 3 months before screening.

Exclusion criteria were as follows: 1) FM associated with chronic inflammatory or autoimmune disease; 2) neuromuscular disease; 3) a severe psychiatric condition (posttraumatic stress syndrome [using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition] or depression); 4) patients unable to exercise on a cycle ergometer, those having cardiac or pulmonary disease, or those having undergone physical reconditioning within 2 years prior to enrollment; 5) a body mass index of >35 kg · meter^{-2}; 6) contraindication to rTMS, including a history of seizures; 7) patients with restless legs syndrome or sleep apnea syndrome; 8) pregnant women or those who were breastfeeding; and 9) patients living too far from the hospital (driving time >45 minutes).

Ethics. This study conformed to the Declaration of Helsinki and was approved by the local ethics committee (CPP Sud-Est V, IRB 6705) and the French Drug and Device Regulation Agency (EudraCT database no. 20010-A00865-34). All patients

Time frame	Week -1 to Week 0		Week1	Week2	Week 3	Week 4	Week 5 and 6	Week 7 to 9	Week 10 to 14	Week 15 //	Week 40
			Induction phase of rTMS		Maintenance phase of rTMS					Post intervention phase	
Treatments	Inclusion and allocation treatment	Sham rTMS or	5 sessions	5 sessions	2 sessions	1 session	1 session	1 session	1 session		
		Active rTMS	5 sessions	5 sessions	2 sessions	1 session	1 session	1 session	1 session		
					Multicompnent therapy Aerobic training + pool based therapy + relaxation: 3 sessions a week each Educational therapy: 1-hour monthly session						
Outcomes assessments	x									x	x
Mean weekly pain VAS	x		x	x	x	x	x	x	x	x	x

Figure 1. Diagram of the treatment course. rTMS = repetitive transcranial magnetic stimulation; VAS = visual analog scale (pain).

gave written informed consent. The study was registered on the ClinicalTrials.gov website under identifier NCT01308801.

Study design. Study design is shown in Figure 1. This was a prospective, randomized, controlled, double-blind and monocentric study. Patients were randomly assigned to either ArTMS or SrTMS. Repetitive TMS started 2 weeks before and lasted throughout the MT program (Figure 1). Randomization was performed from a computer-generated list so that all investigators (excepting the rTMS operator) and physical therapists were unaware of the allocated arm. Randomization was stratified according to mean pain intensity over the 3 days before the time of inclusion (VAS score <70 mm versus VAS score ≥70 mm).

rTMS protocol. The rTMS protocol comprised a 2-week induction phase (5 sessions per week) (25), followed by a 12-week, gradually decreasing maintenance phase, 2 sessions for week 3 (the first week of exercise training), and then 1 session per week for weeks 4, 6, 9, and 13, as previously described (19). Repetitive TMS was performed using a MagPro device (MagVenture, Alpine Biomed). One session delivered 2,000 impulsions at 10 Hz for 20 minutes on the M1 cortex (dominant thenar area). The intensity was set at 80% of the resting motor threshold (RMT) as determined prior to the first session by measuring motor evoked potentials with a monitor linked to the rTMS device (26). A navigation-assisted TMS Navigator stimulation device (Localite) was used to precisely and individually determine the position of the coil based on the patients' anatomic magnetic resonance imaging data set. Sham stimulations were carried out with a sham coil of identical size, color, and shape that emitted the same sound as the active coil.

MT program. Patients attended a 12-week multicomponent program comprised of 3 sessions weekly (weeks 3 to 14) (Figure 1). Sessions were performed in groups of 5 patients at the Institut de rééducation de rhumatologie. Each session started with 45-minute aerobic training on an ergocycle, and then 45 minutes of pool-based exercises followed by 45 minutes of relaxation supervised by a physical therapist. Moreover, 3 individual sessions (1 hour per month) of educational

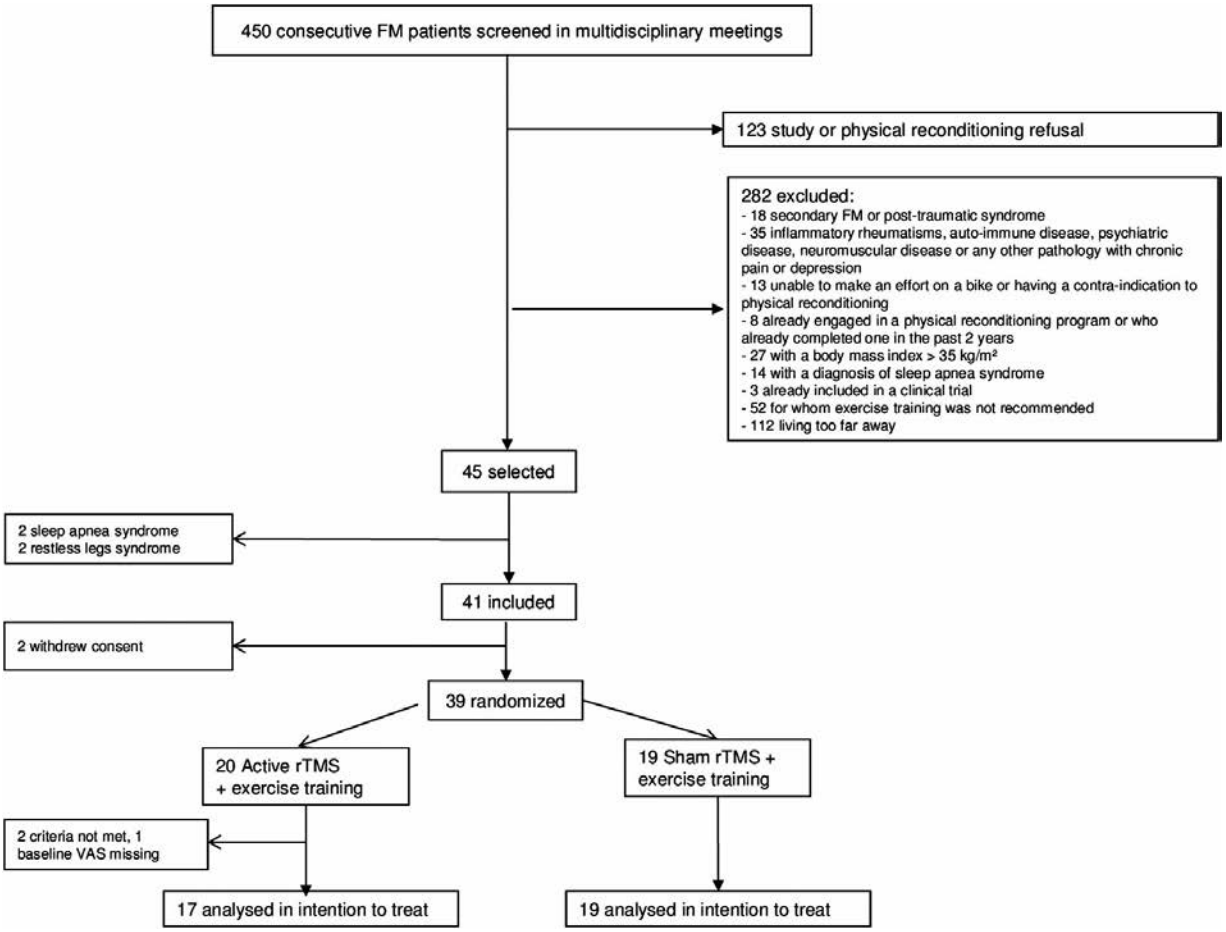

Figure 2. Flow chart of selected patients with fibromyalgia (FM). rTMS = repetitive transcranial magnetic stimulation; VAS = visual analog scale (pain).

therapy aimed at practicing physical activity were provided by a trained physical therapist. Training was performed on an ergocycle, and the first session comprised three 10-minute stints of continuous exercise at the target intensity (see below), interspersed by 5 minutes of active recovery (free push–pull). The duration of stints was progressively increased every week according to the patient's tolerance, for up to 45 minutes at the target intensity. The target intensity was determined at inclusion and defined as the heart rate (HR) at the first lactate threshold (LT1) assessed during an incremental cardiopulmonary exercise test (CPET). This intensity is considered sufficient to produce a significant improvement in fitness (27). HR was continuously monitored during the session to control exercise intensity. Pool-based exercises included progressive and tailored balance and posture work groups while sitting or standing. Relaxation was based on sophronization aimed at its use in daily life activities.

Evaluation of outcomes. Evaluation was performed by a physician (MG) at baseline (week 0 [W0]), immediately after patients completed the program (W14), and at 6 months (W40) (Figure 1). The primary end point was the difference in VAS pain between baseline and W14. Pain, assessed using the mean of daily values from a self-reported VAS over 7 days, was recorded weekly (24). Secondary end points were FM-related outcomes, cardiorespiratory fitness, and cardiac autonomic nervous system adaptations. FM-related outcomes were assessed using self-administered questionnaires. The functional impact of FM was assessed using the French version of the Fibromyalgia Impact Questionnaire (FIQ) (range 0–100) (28). Depression was assessed using the Beck Depression Inventory (BDI) (range 0–63) (29). The subjective quality of sleep was measured using the Pittsburgh Sleep Quality Inventory (PSQI; range 0–21) (30). Pain catastrophism was evaluated using the Pain Catastrophism Scale (PCS; range 0–52) (31). Response to training was assessed using the Patient Global Improvement of Change (PGIC) and a 7-point Likert scale, with scores of <3 indicating a good response to interventions (32).

Cardiac autonomic nervous system adaptations. A head-up tilt test was completed before every CPET (between 2:00 PM and 2:30 PM). Patients were asked to avoid smoking, alcohol, and food consumption at least 2 hours before the test. HR and blood pressure (BP) were continuously monitored for 10 minutes with the patient in supine position, and for 10 minutes with the patient in a standing position (70°). BP was measured with a fingertip photo-plethysmograph, and HR was measured using a 4-lead electrocardiogram (Nexfin). R-R intervals and pulse wave signals were extracted and analyzed according to international recommendations (33) using free Kubios heart rate variability (HRV) analysis software, version 2.0 (University of Kuopio). The temporal parameters (mean HR, mean systolic BP, diastolic and mean BP, and the root mean square of successive differences [RMSSD] of R-R [34]) and spectral parameters (normalized units of low-frequency [LF_{R-R}] and high-frequency density [HF_{R-R}], and total power spectral density [PSD_{R-R}]) of R-R intervals were retained for analysis. The baroreflex sensitivity index (α_{LF}) was calculated as follows (35):

$$\alpha_{LF} = \sqrt{(LF_{R-R}/LF_{BP})}$$

Table 1. Patient characteristics at baseline*

	ArTMS (n = 18)	SrTMS (n = 19)
Female, no. (%)	18 (100)	15 (79)
Age, years	46.5 ± 10.4	42.8 ± 8.8
BMI, kg · meter^{-2}	26.7 ± 4.8	25.1 ± 4.5
Employment, no. (%)	8 (44.4)	12 (63.2)
Education level, no. (%)		
College	9 (50.0)	12 (63.2)
High school	9 (50.0)	7 (36.8)
FM characteristics		
Symptom duration, years	11.2 ± 10.9	9.2 ± 9.6
Pain VAS score, mm	60.9 ± 14.9	57.3 ± 16.1
FIQ score (of 100)	65.4 ± 11.8	64.0 ± 9.4
BDI score (of 63)	25.6 ± 11.2	23.5 ± 11.1
PCS score (of 52)	25.4 ± 11.2	23.7 ± 13.0
PSQI score (of 21)	13.9 ± 4.0	12.2 ± 3.5
Treatments, no. (%)		
Analgesics, level I	12 (66.7)	11 (57.9)
Analgesics, level II	12 (66.7)	12 (63.2)
Analgesics, level III	1 (5.6)	1 (5.3)
Antidepressants	8 (44.4)	9 (47.4)
Benzodiazepines	1 (5.6)	2 (10.5)
NSAIDs	1 (5.6)	2 (10.5)
Others	10 (55.6)	6 (31.6)
Peak exercise values		
VO_2, ml · minute^{-1} · kilogram^{-1}	17.5 ± 3.1‡	22.9 ± 6.4
Predicted VO_{2max}, %	72.8 ± 14.9	82.2 ± 22.4
HR, beats per minute	162 ± 23	159 ± 16
Blood lactate, mmoles · liter^{-1}	7.09 ± 2.10	7.61 ± 2.49
Submaximal (LT1) exercise values		
VO_2, ml · minute^{-1} · kilogram^{-1}	12.0 ± 1.9	13.3 ± 3.0
% VO_{2peak}	70.1 ± 13.5†	60.0 ± 10.7
HR, beats per minute	130 ± 15‡	117 ± 12
Lactate, mmoles · liter^{-1}	2.47 ± 0.75	2.27 ± 0.51
Supine cardiac autonomic values		
HR, beats per minute	80.6 ± 11.2	74.8 ± 9.5
Systolic BP, mm Hg	117 ± 20	116 ± 17
Diastolic BP, mm Hg	67 ± 12	64 ± 11
RMSSD, msec	20.6 ± 9.3†	32.4 ± 20.8
LF_{HR}, normalized units	59.2 ± 13.4†	49.7 ± 13.9
HF_{HR}, normalized units	40.9 ± 13.5†	50.3 ± 13.9
LF_{BP}, mm Hg^2	12.2 ± 9.7	13.2 ± 15.8
BRS index, msec · mm Hg^{-1}	5.45 ± 3.23	8.78 ± 7.15

* Values are the means ± SD unless indicated otherwise. ArTMS = active repetitive transcranial magnetic stimulation; BDI = Beck Depression Inventory; BMI = body mass index; BP = blood pressure; BRS = baroreflex sensitivity; FIQ: Fibromyalgia Impact Questionnaire; FM = fibromyalgia; HF = high frequency; HR = heart rate; LF = low frequency; LT1 = first lactate threshold; NSAIDs = nonsteroidal antiinflammatory drugs; PCS = Pain Catastrophizing Scale; PSQI = Pittsburg Sleep Quality Inventory; RMSSD = root mean square of successive differences; SrTMS = sham repetitive transcranial magnetic stimulation; VAS = visual analog scale; VO_2 = oxygen consumption.
† ArTMS versus SrTMS significantly different at $P < 0.05$.
‡ ArTMS versus SrTMS significantly different at $P < 0.01$.

CPET. A CPET was performed on an Ergoselect 150P cycle ergometer (Ergoline). Power output was increased every 2 minutes until exhaustion or the appearance of intolerable symptoms according to the exercise limitations of FM patients. HR and gas exchanges were continuously monitored using a 12-lead electrocardiogram and an automated Ergocard ergospirometer (Medisoft), allowing the measurement of oxygen uptake (VO_2), carbon dioxide output, and ventilation. Lactate kinetics were measured by sampling a fingertip drop of blood (0.7 μl) during the last 30 seconds of each 2-minute incremental stage of the CPET, and at 2 and 4 minutes of the recovery phase. Blood lactate was measured with a hand-held Lactate Plus lactate oxidase biosensor (Nova Biomedical). LT1 was determined based on a graphical method, as recommended (36). In order to assess exercise tolerance, predicted values of VO_{2max} were calculated using a validated formula based on activity and age- and sex-matched data (37).

Statistical analysis. *Main criterion.* The primary end point was the difference in the magnitude of the diminution of weekly self-reported pain intensity levels between groups (ArTMS versus SrTMS). In a previous study, significant changes had been found in pain evolution between ArTMS and SrTMS (25). These results were used in the computation of sample size. Eighteen patients were necessary in each treatment group to detect a difference of 20 mm on a 100-mm VAS between weeks 0 and 14, with a power of 80% and an α risk of 5% (using nQuery Advisor, version 7.0 [Statistical Solutions]). With a dropout rate estimated at 20%, 20 patients needed to be included in each group.

Mean daily pain evolution was analyzed over 2 periods: first, the treatment period (weeks 0 to 14) comparing absolute difference from baseline; and secondly, between weeks 14 and 40 to assess the continuity of any effect. Changes were compared using a bilateral Student's *t*-test when variables followed a normal distribution. Otherwise, a nonparametric Mann-Whitney U test was used. The integrated change in pain from baseline was analyzed with an analysis of covariance, with group and pain at week 0 as covariates. A 2-way analysis of variance (ANOVA) with repeated measures was also performed to investigate a potential group effect (ArTMS versus SrTMS), time effect (weeks 0, 14, and 40), and time × group interaction. Pain analyses were performed on a modified intent-to-treat basis for all randomized patients who had a baseline measurement and received at least 1 session of ArTMS. We used multivariate imputation by chained equations to replace missing data.

Secondary criteria. The same analyses were performed to compare the effects of rTMS on secondary outcomes (using the FIQ, BDI, PSQI, and PCS) and on physiologic parameters (using CPET and autonomic nervous system parameters, as previously detailed). A log transformation was completed to normalize autonomic nervous system variables (LF_{R-R}, HF_{R-R}, PSD_{R-R}, and LF_{BP}). *P* values less than 0.05 were considered significant. Statistical analyses were performed using Stata software, version 13.1. The plan for the statistical analysis was developed in collaboration with the Grenoble Clinical Research Center (CIC 1406).

RESULTS

Participants. A total of 39 patients with FM were randomized, 19 to the SrTMS group, and 20 to the ArTMS group (Figure 2). Two patients were excluded from the active group because inclusion criteria were not fulfilled. One had a VAS pain score of <40 mm. One additional patient (in the ArTMS group) was excluded from analysis for the main criterion because pain VAS data were not available during the entire study. Finally, data from 36 patients were analyzed using a modified intent-to-treat analysis for the main criterion, and data from 37 patients were analyzed for the other variables. Baseline results are shown in Table 1. All patients completed the initiation phase of rTMS, but 5 withdrew during the MT program (2 in the SrTMS group, 3 in the ArTMS group), and 1 was lost to follow-up before week 40 (in the ArTMS group). The reasons for discontinuation were pregnancy (n = 1), moving (n = 1), worsening of FM (n = 1), and personal reasons (n = 2). No adverse effects were recorded during the phases of the study.

Effects on pain and secondary FM outcomes. Effects on pain and secondary FM outcomes are shown in Figure 3 and Table 2, respectively. There was neither time × group interaction for VAS pain nor for the FIQ, BDI, PCS, and PSQI scores. Taking into account the characteristics of the study sample, 52 patients would have been required in each group to show a significant time × treatment interaction on pain VAS (with an α risk of 0.05 and a power of 80%). The power of this study was 32%, and the effect size 0.24.

There was no group effect on VAS pain or on FIQ, BDI, PCS, and PSQI scores. There was a time effect in both groups on VAS pain ($P < 0.05$) and on results from the FIQ ($P < 0.001$), the BDI ($P < 0.001$), the Hospital Anxiety and Depression Scale ($P < 0.05$), and the PCS ($P < 0.05$) at W14 versus W0, which persisted until W40. Neither a group nor a time effect was shown for results from the PSQI.

Effects on the cardiorespiratory system. Effects on the cardiorespiratory system are shown in Table 2. The ArTMS group displayed smaller improvements in cardiorespiratory fitness than the SrTMS group regarding specific VO_2 at both maximal and submaximal exercise levels ($P < 0.01$). This difference disappeared when VO_2 was expressed according to its predicted (pred) value ($P = 0.123$). There was no significant group effect for lactate and HR_{max}.

Cardiorespiratory fitness significantly improved in both groups at maximal and submaximal levels. As for VO_{2max}, VO_{2LT1} significantly increased between baseline and the end of MT ($P < 0.005$ and $P < 0.0001$, respectively). This effect persisted at W40. There was no time × group interaction for VO_{2max}, $VO_{2maxpred}$, or VO_{2LT1}.

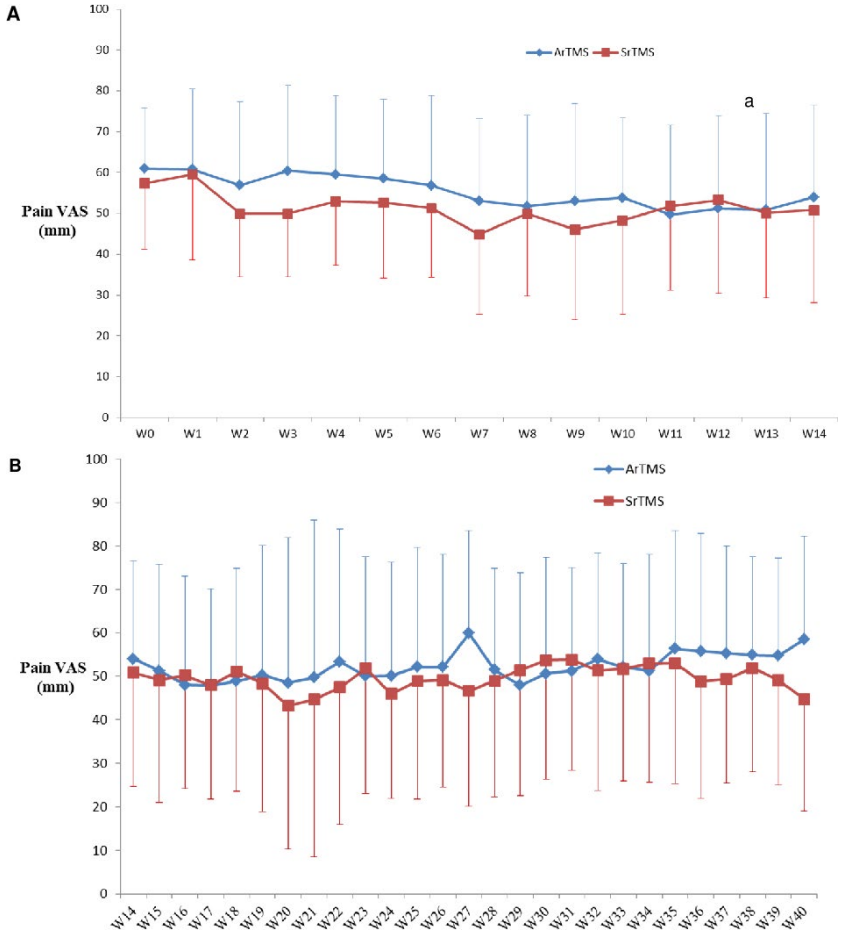

Figure 3. Mean weekly pain evolution. **A**, 14 weeks during the repetitive transcranial magnetic stimulation (rTMS) and reconditioning program. A 2-way analysis of variance showed a time effect (a) at week 14 versus week 0 in both groups ($P < 0.05$) but neither a group interaction nor a time × group interaction. **B**, 26 weeks after rTMS and the training program. ArTMS = active repetitive TMS; SrTMS = sham repetitive TMS; W = week. Bars show the mean ± SD.

Effects on the cardiac autonomic nervous system. There were neither time × group nor time interactions between both resting (Table 3) and head-up tilt test or cardiac autonomic parameters. Supine HR, RMSSD, and HF normalized unit (HFnu) were significantly reduced in the SrTMS group ($P < 0.05$, $P < 0.01$, and $P < 0.01$, respectively) compared to the ArTMS group at baseline and at W14. The RMSSD only differed significantly at W40. Supine LF normalized unit (LFnu) was significantly higher in the SrTMS group than in the ArTMS group at baseline and W14.

DISCUSSION

This randomized sham-controlled study showed that ArTMS had no additional effects on self-reported pain in patients with severe FM (32) over and above the effect of the exercise training program being followed. Pain intensity decreased in both groups during the 14-week intervention phase, and this reduction was maintained 6 months after the end of the intervention (Figure 3).

Previous systematic reviews of the literature (20,22,38) have shown that rTMS significantly reduced pain in FM or in chronic pain syndrome, while another study reported a significant effect only on QoL (39). We have provided an updated meta-analysis (data not shown) showing that ArTMS had no superior effect on VAS pain at 30 days compared to SrTMS. The discrepancies concerning the analgesic effect of rTMS in FM could be due to modalities (high- versus low-frequency), locations used in these studies, or the treatment courses of rTMS, while an operator effect cannot be excluded (20). Although there is no recommendation for FM (17), the intensity of magnetic stimulations was set at 80% of the RMT, as previously published in similar studies of FM patients (19,25) and patients with chronic pain (17). Indeed, intensities at 80% or 90% of the RMT are usually used on the motor cortex for patients with chronic pain (see review in ref. 17). The reason for this subliminal intensity was to generate cortical excitation without muscular contractions and to reduce the risk of seizure. Actually, higher intensities are used (110% or 120% of the RMT) when the dorsolateral prefrontal cortex is stimulated, in particular in depression and sometimes in chronic pain syndromes (17).

Table 2. Evolution of fibromyalgia secondary outcomes and graded maximal exercise test values*

	ArTMS			SrTMS		
	W0	W14	W40	W0	W14	W40
FIQ score (of 100)†	64.3 ± 12.0	53.3 ± 17.9	52.8 ± 12.8	62.9 ± 9.9	51.6 ± 18.7	51.1 ± 17.2
BDI score (of 63)†	25.4 ± 10.5	18.3 ± 10.3	20.5 ± 5.8	23.5 ± 10.8	17.5 ± 8.5	17.2 ± 10.0
PSQI score (of 21)	13.3 ± 2.7	11.5 ± 3.5	12.5 ± 2.9	12.2 ± 3.5	13.2 ± 6.5	11.1 ± 3.5
PCS score (of 52)†	25.9 ± 11.0	17.4 ± 10.8	18.8 ± 10.8	23.7 ± 13.0	20.9 ± 12.0	20.8 ± 13.2
PGIC score <3, no. (%)	NA	8 (44)	6 (32)	NA	7 (39)	3 (16)
Graded maximal exercise test						
VO_{2max}, ml · minute^{-1} · kilogram^{-1}‡	17.5 ± 3.0	20.6 ± 4.0	20.9 ± 3.5	22.9 ± 6.2	24.2 ± 5.4	23.9 ± 4.4
%Pred VO_{2max}†	73.5 ± 13.9	86.3 ± 17.4	86.2 ± 21.9	83.3 ± 22.4	88.0 ± 20.9	86.5 ± 18.6
HR_{max}, beats per minute	162 ± 22	167 ± 17	170 ± 14	159 ± 16	157 ± 18	162 ± 12
La_{max}, mmoles · liter^{-1}	7.09 ± 2.04	7.70 ± 2.59	7.27 ± 1.71	7.61 ± 2.42	7.55 ± 2.99	8.62 ± 2.28
VO_{2LT1}, ml · minute^{-1} · kilogram^{-1}†	12.0 ± 1.8	13.6 ± 1.8	13.7 ± 3.1	13.3 ± 3.1	15.4 ± 4.0¶	14.0 ± 3.3§
HR_{LT1}, beats per minute#	130 ± 15	130 ± 16	133 ± 19	117 ± 12**	117 ± 12**	115 ± 13**
%VO_{2max}	70.1 ± 13.1	68.3 ± 13.7	65.8 ± 11.0	59.6 ± 11.1	64.2 ± 12.9	58.6 ± 8.5

* Values are the means ± SD unless indicated otherwise. Two-way analysis of variance with repeated measures showed no group × time interactions. BDI = Beck Depression Inventory; FIQ = Fibromyalgia Impact Questionnaire; HR = heart rate; La = blood lactate; LT1 = first lactate threshold; Max = peak exercise; NA = not available; PCS = Pain Catastrophizing Scale; PGIC = personal global improvement of change; Pred = predicted; PSQI = Pittsburg Sleep Quality Inventory; VO_2 = oxygen consumption; W0 = week 0 (baseline).
† Time effect: $P < 0.001$.
‡ Time effect: $P < 0.001$; group effect (ArTMS vs. SrTMS): $P < 0.05$ and $P < 0.01$.
§ W14 and W40 differed significantly from baseline ($P < 0.05$).
¶ W14 and W40 differed significantly from baseline ($P < 0.01$).
# Group effect (ArTMS vs. SrTMS): $P < 0.01$.
** SrTMS differed significantly from ArTMS ($P < 0.01$).

The present rTMS protocol reproduced the protocol of Mhalla et al (19), with high-frequency stimulation on the M1 cortex, which seems to be more efficient than prefrontal cortex stimulation (20). It is also possible that of the analgesic effect of rTMS was concealed because the induction phase of our study might not have lasted long enough. Indeed, 4 to 6 weeks (a 5-week session) are recommended for depression, while antidepressant effects of rTMS usually appear as soon as 2 or 3 weeks (18). Nevertheless, in most of these studies, pain improvement did not reach the minimum clinically significant change (15%) (20,22), suggesting that rTMS had low efficiency in FM pain modulation. Our study thus suggests that MT was the main pain modulator, although it was not designed to assess the superiority of MT versus rTMS. In particular, pain intensity did not decrease during the 2-week initiation phase of rTMS, but only after the beginning of MT (Figure 3). Taken together, these results suggest MT-induced effects on pain, QoL, depression, and cardiorespiratory fitness, as previously reported (8,10), with no additive effect of rTMS.

In regard to the effects on cardiorespiratory fitness and secondary outcomes in FM, a 2-way ANOVA with repeated measures showed that there was a significant improvement in cardiorespiratory fitness in both groups between baseline and the end of the program. Interestingly, this effect persisted 6 months after

Table 3. Evolution of resting heart rate (HR) and blood pressure variability*

	ArTMS			SrTMS		
	W0	W14	W40	W0	W14	W40
HR sup, beats per minute†	81 ± 12	80 ± 12	83 ± 13	75 ± 9	73 ± 10	75 ± 11
Delta HR, beats per minute	17 ± 9	15 ± 8	13 ± 5	13 ± 9	14 ± 7	13 ± 8
MBP sup, mm Hg	87 ± 15	86 ± 11	86 ± 18	85 ± 13	88 ± 15	83 ± 14
MBP st, mm Hg	95 ± 15	95 ± 13	101 ± 26	93 ± 12	95 ± 15	93 ± 10
RMSSD sup, msec‡	20.6 ± 9.6	22.7 ± 12.0	20.0 ± 9.9	32.4 ± 20.7	36.6 ± 20.7	33.2 ± 17.5
LF sup, normalized units†	59.2 ± 13.0	65.0 ± 13.8	65.9 ± 12.6	49.7 ± 13.5	47.3 ± 12.9	56.0 ± 14.9
HF sup, normalized units§	40.9 ± 13.1	35.3 ± 13.7	34.1 ± 12.6	50.3 ± 13.5	52.7 ± 12.9	43.4 ± 15.7
LF_{SBP} sup, mm Hg^2	11.6 ± 9.3	7.8 ± 6.0	14.5 ± 22.7	13.2 ± 15.4	12.1 ± 10.5	12.3 ± 8.4
BRS index sup, ms · mm Hg^{-1}	5.33 ± 3.06	7.32 ± 3.42	6.72 ± 3.90	8.78 ± 6.96	7.79 ± 5.32	8.19 ± 9.27

* Values are the means ± SD. Two-way analysis of variance with repeated measures showed no group × time interactions. BRS = baroreflex sensitivity; Delta HR = difference between HR standing, HR during orthostatic stress, and supine HR; HF = high-frequency (wave); LF = low-frequency (wave); MBP = mean blood pressure; NA = not available; NU = normalized units; RMSSD = root mean square of successive differences; SBP = systolic blood pressure; St = standing; Sup = supine; W0 = week 0 (baseline).
† Group effect (ArTMS vs. SrTMS): $P < 0.05$ but no time interaction.
‡ Group effect (ArTMS vs. SrTMS): $P < 0.01$ but no time interaction.
§ Group effect (ArTMS vs. SrTMS): $P < 0.001$ but no time interaction.

the end of the intervention (Table 2). It is likely that this improvement in cardiorespiratory fitness was mainly due to the aerobic training, as previously shown (40), but a placebo effect of the intervention cannot be excluded.

Secondary FM outcomes (as measured by the FIQ, BDI, and PCS) improved (Table 2). Indeed, mean FIQ score decreased by ~11 points (17%) in both groups between baseline and W14 and was long lasting. Thus, the impact of FM on QoL in these patients diminished more than that reported previously (40) and was greater than the minimum clinically important difference (i.e., the intervention was efficient for this outcome and lasted at least 6 months) (32). A similar analysis was conducted for depression (using the BDI), which decreased (~27%) in both groups at W14, again by more than the minimum clinically important difference (41). This is in line with the literature, which describes mood improvements after programs involving aerobic exercises (8,40). Significant decreases in PCS scores were also seen at W14 in both groups, suggesting that FM patients increased their ability to cope with pain after the intervention. Decreased catastrophizing is an important issue because it is an indicator of poor outcomes of chronic pain, and in particular of severe physical disability (42).

In regard to the effects on HR and BP variability, no significant effect over time was shown in either group for any of the variables studied, including those not shown in Table 3 (mainly standing values). It is thus implied that neither rTMS nor MT altered cardiac autonomic system adaptations despite pain and fitness improvements. This suggests that different mechanisms are involved in regulatory pathways of pain and the cardiovascular autonomic system in FM, particularly after aerobic training (43,44). These results contrast with those of previous studies that showed that aerobic training had significant effects both on resting HR and HF power and sympathetic drive in healthy subjects and patients (see reviews in refs. 44 and 45). The effects of MT on the cardiac autonomic system in FM have been poorly investigated, although at-rest modifications are well described (43). To our knowledge, only 1 study has been published that showed improvements in HRV after aerobic training (34). In the current study, we cannot exclude the possibility that the exercise intensity or duration were not sufficient to provoke alterations in HRV. Nevertheless, patients underwent aerobic training sessions at higher intensity and more frequently than in the study of Sanudo et al (34).

There was a group effect at baseline that persisted throughout the study; the SrTMS group showing better vagal tone (lower resting HR, and higher RMSSD and HF components) (33). This could be related to the sex distribution between the groups (all men were allocated to the SrTMS group and had better cardiorespiratory fitness), which may influence HRV (46).

Tolerance and efficiency of rTMS and reconditioning were as follows: 34 of 39 randomized patients finished the 12-week intervention, corresponding to an attrition rate of 12.9%. This percentage was below the range in the literature (~20%) for programs consisting of aerobic training (40,47). Tolerance was good, as only 1 patient dropped out after a flare of FM symptoms. The initiation phase of rTMS was well tolerated, as all the patients finished this session. Fifteen patients (38.4%) were good responders (PGIC score <3), with no significant difference between groups. This rate seems substantial in FM, although we found no data in the literature analyzing PGIC results after reconditioning.

In terms of study limitations and strengths, first, this trial was designed to demonstrate that rTMS plus MT is more effective than MT alone in reducing pain. Thus, a placebo effect of rTMS could not be excluded. We used a sham coil with size, color, and shape identical to the active coil. Both coils emitted the same sound, so patients could not distinguish between the sham and the active device.

Second, this study might be underpowered because we calculated a power of 32% and an effect size of 0.24 from the pain VAS of the sample. The original calculation of sample size was based on prior studies (19,25), with an hypothesis of 20% pain reduction with rTMS. This hypothesis was likely overestimated regarding the effect size of this study. Accordingly, 52 patients per group would have been needed to show a significant time × treatment interaction on a VAS for pain.

Third, one cannot exclude that another study design (e.g., one with a longer initiation phase, or one that started MT at a different time) might have been more efficient. Finally, only 10% of the patients who were screened were included in the study. It is possible that a selection bias occurred because some patients had difficulty joining the study due to its duration and time-related constraints. This also reflects the difficulty in combining MT and rTMS sessions over the same timeframe for patients experiencing pain and exhaustion.

In conclusion, this study showed that rTMS associated with MT did not induce greater reduction in pain than MT alone in patients with severe FM. The updated meta-analysis strengthens the results of this study, suggesting that rTMS is not effective in improving either pain or QoL in patients with severe FM.

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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. Guinot 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. Guinot, Maindet, H. Hodaj, Bachasson, Cracowski, Launois.

Acquisition of data. Guinot, Maindet, Bachasson, Baillieul.

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REFERENCES

1. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010;62:600–10.
2. Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. J Rheumatol Suppl 2005;75:6–21.
3. Clauw DJ. Fibromyalgia: a clinical review. JAMA 2014;311:1547–55.
4. Kuner R. Central mechanisms of pathological pain. Nat Med 2010;16:1258–66.
5. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152 Suppl S:2S–15S.
6. Ablin J, Fitzcharles MA, Buskila D, Shir Y, Sommer C, Hauser W. Treatment of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines with special emphasis on complementary and alternative therapies [review]. Evid Based Complement Alternat Med 2013;2013:485272.
7. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Hauser W, Fluss E, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 2017;76:318–28.
8. Nuesch E, Hauser W, Bernardy K, Barth J, Juni P. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. Ann Rheum Dis 2013;72:955–62.
9. Fitzcharles MA, Ste-Marie PA, Goldenberg DL, Pereira JX, Abbey S, Choiniere M, et al. 2012 Canadian guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary. Pain Res Manag 2013;18:119–26.
10. Häuser W, Bernardy K, Arnold B, Offenbächer M, Schiltenwolf M. Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. Arthritis Rheum 2009;61:216–24.
11. Van Koulil S, van Lankveld W, Kraaimaat FW, van Helmond T, Vedder A, van Hoorn H, et al. Tailored cognitive-behavioural therapy and exercise training improves the physical fitness of patients with fibromyalgia. Ann Rheum Dis 2011;70:2131–3.
12. Bourgault P, Lacasse A, Marchand S, Courtemanche-Harel R, Charest J, Gaumond I, et al. Multicomponent interdisciplinary group intervention for self-management of fibromyalgia: a mixed-methods randomized controlled trial. PLoS One 2015;10:e0126324.
13. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 2008;9:58–65.
14. Koltyn KF. Analgesia following exercise: a review. Sports Med 2000;29:85–98.
15. Flodin P, Martinsen S, Mannerkorpi K, Lofgren M, Bileviciute-Ljungar I, Kosek E, et al. Normalization of aberrant resting state functional connectivity in fibromyalgia patients following a three month physical exercise therapy. Neuroimage Clin 2015;9:134–9.
16. Cruccu G, Garcia-Larrea L, Hansson P, Keindl M, Lefaucheur JP, Paulus W, et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. Eur J Neurol 2016;23:1489–99.
17. Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014;125:2150–206.
18. McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J Clin Psychiatry 2018;79;16cs10905.
19. Mhalla A, Baudic S, Ciampi de Andrade D, Gautron M, Perrot S, Teixeira MJ, et al. Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. Pain 2011;152: 1478–85.
20. O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev 2018;3:CD008208.
21. Boyer L, Dousset A, Roussel P, Dossetto N, Cammilleri S, Piano V, et al. rTMS in fibromyalgia: a randomized trial evaluating QoL and its brain metabolic substrate. Neurology 2014;82:1231–8.
22. Saltychev M, Laimi K. Effectiveness of repetitive transcranial magnetic stimulation in patients with fibromyalgia: a meta-analysis. Int J Rehabil Res 2017;40:11–8.
23. Christensen NJ, Galbo H. Sympathetic nervous activity during exercise. Annu Rev Physiol 1983;45:139–53.
24. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983;17:45–56.
25. Passard A, Attal N, Benadhira R, Brasseur L, Saba G, Sichere P, et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain 2007;130:2661–70.
26. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015;126:1071–107.
27. American College of Sports Medicine. ACSM guidelines for exercise testing and prescription. 7th ed. Baltimore: Lippincott; 2006.
28. Perrot S, Dumont D, Guillemin F, Pouchot J, Coste J. Quality of life in women with fibromyalgia syndrome: validation of the QIF, the French version of the fibromyalgia impact questionnaire. J Rheumatol 2003;30:1054–9.
29. Beck AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. J Clin Psychol 1984;40:1365–7.
30. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
31. Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychol Assess 1995;7:524–32.
32. Bennett RM, Bushmakin AG, Cappelleri JC, Zlateva G, Sadosky AB. Minimal clinically important difference in the fibromyalgia impact questionnaire. J Rheumatol 2009;36:1304–11.
33. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043–65.
34. Sanudo B, Carrasco L, de Hoyo M, Figueroa A, Saxton JM. Vagal modulation and symptomatology following a 6-month aerobic exercise program for women with fibromyalgia. Clin Exp Rheumatol 2015;33 Suppl S:41S–5S.
35. Barbieri R, Parati G, Saul JP. Closed- versus open-loop assessment of heart rate baroreflex. IEEE Eng Med Biol Mag 2001;20:33–42.
36. Vallier J, Bigard A, Carré F, Eclache J, Mercier J. Determination of lactic and ventilatory thresholds: position of the French Medicine Sports Society. Sci Sports 2000;15:133–40.
37. Wasserman K, Hansen J, Sue D, Casaburi R, Whipp B. Principles of exercise testing and interpretation. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2004.
38. Marlow NM, Bonilha HS, Short EB. Efficacy of transcranial direct current stimulation and repetitive transcranial magnetic stimulation

for treating fibromyalgia syndrome: a systematic review. Pain Pract 2013;13:131–45.
39. Knijnik LM, Dussan-Sarria JA, Rozisky JR, Torres IL, Brunoni AR, Fregni F, et al. Repetitive transcranial magnetic stimulation for fibromyalgia: systematic review and meta-analysis. Pain Pract 2016;16:294–304.
40. Bidonde J, Busch AJ, Schachter CL, Overend TJ, Kim SY, Goes SM, et al. Aerobic exercise training for adults with fibromyalgia. Cochrane Database Syst Rev 2017;6:CD012700.
41. Button KS, Kounali D, Thomas L, Wiles NJ, Peters TJ, Welton NJ, et al. Minimal clinically important difference on the Beck Depression Inventory – II according to the patient's perspective. Psychol Med 2015;45:3269–79.
42. Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol 2011;7:216–24.
43. Sarzi-Puttini P, Atzeni F, Diana A, Doria A, Furlan R. Increased neural sympathetic activation in fibromyalgia syndrome. Ann N Y Acad Sci 2006;1069:109–17.
44. Sandercock GR, Bromley PD, Brodie DA. Effects of exercise on heart rate variability: inferences from meta-analysis. Med Sci Sports Exerc 2005;37:433–9.
45. Routledge FS, Campbell TS, McFetridge-Durdle JA, Bacon SL. Improvements in heart rate variability with exercise therapy. Can J Cardiol 2010;26:303–12.
46. Sammito S, Bockelmann I. New reference values of heart rate variability during ordinary daily activity. Heart Rhythm 2017;14: 304–7.
47. Busch AJ, Schachter CL, Overend TJ, Peloso PM, Barber KA. Exercise for fibromyalgia: a systematic review. J Rheumatol 2008;35: 1130–44.

Erratum

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In the article by Fitzgerald et al in the June 2020 issue of *Arthritis Care & Research* (2020 American College of Rheumatology Guideline for the Management of Gout [pages 744–760]), under the section "High-fructose corn syrup" on page 754, the following sentence was incorrect: "In the National Health and Nutrition Examination Survey, artificially sweetened carbonated beverage consumption was associated with higher SU levels (101)." The correct sentence should be: "In the National Health and Nutrition Examination Survey, sugar-sweetened carbonated beverage consumption was associated with higher SU levels (101)."

We regret the error.