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Journal

ACR open rheumatology, 1(6)

ISSN

2578-5745

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Publication Date

2019-08-01

DOI

10.1002/acr2.11051

Peer reviewed

ACR Open Rheumatology
Vol. 1, No. 6, August 2019, pp 366–372
DOI 10.1002/acr2.11051

American College of Rheumatology
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The Impact of Frailty on Changes in Physical Function and Disease Activity Among Adults With Rheumatoid Arthritis

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Objective. Reduced physical function and frailty are common in rheumatoid arthritis (RA). However, relationships between frailty and changes in physical function and disease activity over time in RA are unknown. We tested whether frailty is a risk factor for worsening patient-reported physical function and disease activity in RA.

Methods. Adults from a longitudinal RA cohort (N = 124) participated. By using an established frailty definition, individuals with three or more of the following deficits were considered frail: 1) body mass index less than or equal to 18.5, 2) low grip strength, 3) severe fatigue, 4) slow 4-m walking speed, and 5) low physical activity. Individuals with one to two or zero deficits were considered "pre-frail" or "robust," respectively. Physical function and RA disease activity were assessed by the Health Assessment Questionnaire (HAQ) and Rheumatoid Arthritis Disease Activity Index (RADAI), respectively, at baseline and follow-up 2 years later. Regression analyses modeled associations of frailty status with change in HAQ and RADAI scores between baseline and follow-up with and without controlling for covariates. Associations of individual frailty components with change in HAQ and RADAI scores were also examined.

Results. Among adults with RA, baseline frailty status predicted significant increases, or worsening, in HAQ (β: 0.4; 95% confidence interval: 0.1-0.8; $P < 0.01$) but not RADAI scores (β: 0.5; 95% confidence interval: –0.4 to 1.5; $P > 0.05$) between baseline and follow-up in fully adjusted models. Fatigue was an important contributor to this effect.

Conclusion. Frailty may be an important risk factor for reduced physical function over time in RA. Future studies should address whether interventions to reduce frailty improve physical function in RA.

INTRODUCTION

Reduced physical function is common and is likely multifactorial among individuals with rheumatoid arthritis (RA) (1,2), and novel interventions are needed to improve physical function in these patients. Frailty, which is often defined as "a syndrome of decreased reserve and resistance to stressors…causing vulnerability to adverse outcomes" (3), may play an important role in the development of reduced physical function in RA. A validated phenotype of frailty, defined by sarcopenia, weakness, fatigue, slow gait, and low physical activity (3), is an important risk factor for reduced physical function, poor clinical outcomes, and death in the general population of older adults (3,4). In addition, this frailty phenotype is common among individuals with various chronic diseases, including congestive heart failure, chronic obstructive pulmonary disease, and chronic kidney disease, and is associated with reduced physical function and poor clinical outcomes in these populations (5–9).

Recent studies have suggested that this frailty phenotype likely represents an important clinical entity, associated with various poor clinical outcomes, among individuals with rheumatologic diseases. For example, this frailty phenotype is common among women with lupus and is associated with worse physical function and mortality over time (10). Among individuals with RA, frailty is also common and is correlated cross-sectionally with poorer patient-reported physical function (11). The direction of effect cannot be discerned from cross-sectional analyses, however, and the longitudinal relationship between baseline frailty status and change in physical function over time in RA has not been examined. In addition, the relationship between frailty status and change in RA disease activity over time has not been studied.

Supported by NIH National Institute on Aging grant 1-K23-AG-058756, NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases grant P60-AR-053308, NIH National Center for Research Resources, University of California, San Francisco Clinical and Translational Science Institute grant UL1-RR-024131, and the Rosalind Russell/Ephraim P. Engleman Rheumatology Research Center.

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

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Submitted for publication November 19, 2018; accepted in revised form June 14, 2019.

The aim of the current study is to address this gap in the literature by testing the hypothesis that baseline frailty status is an important risk factor for worsening patient-reported physical function and RA disease activity over time among individuals in a longitudinal RA cohort. Identifying frailty as a unique and potentially modifiable risk factor for reduced physical function and increased disease activity in RA would have the potential to facilitate the development of novel interventions targeting aspects of frailty to improve clinical outcomes for individuals with RA.

PATIENTS AND METHODS

Subjects. The sample for the present study is derived from a cohort developed at the University of California, San Francisco (UCSF) to study relationships between body composition and physical function in RA. Full details of this cohort have previously been published (11). Briefly, participants for the present cohort were drawn from a prior RA study, the UCSF RA panel study. Participants were recruited by telephone in 2009 and were eligible if they lived in the greater San Francisco Bay area and were willing to travel to UCSF. They were recruited for in-person assessments (including measurement of body composition) at the UCSF Clinical and Translational Science Institute Clinical Research Center. RA diagnoses using the American College of Rheumatology (ACR) criteria were verified by a medical record review (12). Exclusion criteria were non–English speaking, age less than 18 years, a current daily oral prednisone dose greater than 50 mg, current pregnancy, uncorrected vision problems that interfered with reading, and joint replacement within 1 year.

One hundred forty-one individuals completed baseline study visits, including assessments of body composition, components of the Fried Frailty Assessment (described below), and measures of functioning. Follow-up visits were intended to be approximately 2 years later. The actual mean time between the baseline and follow-up visit was 2.3 (range: 1.7-4.5) years; the median follow-up time was 2.2 (interquartile range: 2.0-2.4) years. Ninety percent of participants followed up within 2.9 years. Follow-up data were available for 122 individuals. The final sample for the present study was composed of those participants with complete grip strength data at baseline (N = 124). The study was approved by the UCSF Committee on Human Research (approval 11-05702).

Measures. *Frailty.* Frailty was assessed by using the method developed by Fried et al (3), which has been used previously in RA (11). Five physical deficits were assessed: 1) low body mass index (BMI), 2) low grip strength (adjusted for sex and BMI), 3) severe fatigue, 4) slow 4-m walking speed (adjusted for sex and height), and 5) low physical activity. Individuals with three or more deficits were classified as "frail," those with one or two deficits were classified as "pre-frail," and those with no deficits were classified as "robust." BMI was calculated as weight/height^2 (kg/m^2). A BMI greater than or equal to 18.5 was classified as low. Grip strength of the participant's dominant hand was measured by using a hand-held dynamometer (13). The fatigue severity subscale of the Multidimensional Assessment of Fatigue was used to assess fatigue; scores range from 0 to 10 (0 = no fatigue, and 10 = most-severe fatigue) (14). A score of 7 or more was classified as severe fatigue (10,11). Participants in the lowest quintile of 4-m walking speed (adjusted for sex and height) were classified as slow. Physical activity was assessed by self-report with the long form of the International Physical Activity Questionnaire (IPAQ) (15). The IPAQ has been used and validated in a number of populations (16,17). The scoring protocol provides a cut point by which individuals' weekly energy expenditure can be categorized as low, moderate, or high. Individuals who expended less than 600 metabolic equivalent task minutes per week were classified as having low physical activity (15,16,18).

Physical function. Self-reported physical function was assessed by using the Health Assessment Questionnaire (HAQ). Scores range from 0 to 3, with higher scores reflecting greater limitations (19).

RA disease activity. RA disease activity was assessed by using the Rheumatoid Arthritis Disease Activity Index (RADAI), a self-reported measure of disease activity in which scores range from 0 to 10, with higher scores reflecting greater RA disease activity (20).

Other variables. Age was obtained from the baseline RA panel telephone interview. High-sensitivity C-reactive protein (hsCRP) was analyzed by nephelometry, and cyclic citrullinated peptide (CCP) immunoglobulin G was analyzed by immunoassay at a regional clinical laboratory. Glucocorticoid and tumor necrosis factor inhibitor medication use was assessed at the time of the visit. Blood samples were collected during study visits.

Statistical analysis. *Primary analyses*. Linear regression analyses were used to model the effect of baseline frailty status on change in HAQ and RADAI scores between baseline and follow-up with and without adjusting for covariates (sex, age, baseline disease duration, hsCRP, CCP antibody level, and use of oral steroids). Because of skewedness, CRP values were logarithmically transformed to the normal distribution prior to inclusion in regression analyses. Regression models were not adjusted for baseline HAQ or RADAI score because doing so risks inaccurately inflating regression coefficient estimates (21). In addition, to evaluate the contribution of individual frailty components to the overall relationships of baseline frailty status with change in HAQ and RADAI scores between baseline and follow-up, linear regression models were conducted, in which each of the five components of frailty were included as individual terms in the same model.

Nineteen individuals were missing at least one outcome measure score at follow-up. Eleven individuals were missing follow-up HAQ scores, six were missing follow-up RADAI scores, and two were missing both scores. Differences in participant characteristics between those missing and those not missing HAQ and/or RADAI follow-up data were tested by using

either the *t* test, Kruskal-Wallis test, or χ^2 test. There were no statistically significant differences between participants missing versus participants not missing HAQ and/or RADAI scores at follow-up (Supplementary Table 1). To account for the impact of missing data due to loss to follow-up or lack of participation, we used multiple imputations with chained equations to model missing values, based on 10 replications (22–24), for the participants with complete baseline frailty data (N = 124). Here we report the results based on the use of multiple imputations, but in no instance were the results substantially different from those in the analyses in which missing values were not imputed.

Secondary analysis. To examine relationships of baseline frailty status with HAQ and RADAI scores at follow-up, linear regression analyses were used to model the effect of baseline frailty status on HAQ and RADAI scores at follow-up, rather than change in score between baseline and follow-up, with and without adjusting for covariates (baseline outcome score [HAQ or RADAI], sex, age, baseline disease duration, hsCRP, CCP antibody level, and use of oral steroids). HAQ and RADAI scores at follow-up are used to assess physical function and disease activity status at follow-up, which, like change over time, are also clinically relevant outcomes. Moreover, the relationships of baseline frailty status with HAQ and RADAI scores at follow-up are also unknown and may differ from those of baseline frailty with changes in HAQ or RADAI scores over time. For example, baseline frailty may not be associated with change the in HAQ or RADAI score over time, but it may nevertheless be associated with differences in HAQ or RADAI scores at follow-up.

Sensitivity analysis. To examine whether advanced age affects the primary relationships of interest, in preplanned sensitivity analyses, we examined whether the relationships of baseline frailty with change in HAQ and RADAI scores between baseline and follow-up were sensitive to limiting the analysis to participants age 64 years and younger. The number of participants age 64 years and younger did not permit analyzing frailty components individually in this subgroup. In addition, the relatively small number of participants age 65 years and older (n = 35) did not permit analyzing either frailty category or frailty components in this subgroup. All statistical analyses were conducted by using Stata version 13.1 (StataCorp).

RESULTS

Subject characteristics. Participant baseline characteristics are shown in Table 1. Overall, participants tended to be women in the sixth decade of life with long-standing CCP antibody–positive RA and relatively low disease activity. Frailty was common in our cohort, with 10% of participants categorized as frail and 71% categorized as pre-frail. Further details of the distribution of frailty components are reported elsewhere (11). The average change in score between baseline and follow-up for the entire cohort was 0.05 ± 0.4 and 0.1 ± 1.3 for the HAQ and RADAI measures, respectively.

Table 1. Participant baseline characteristics (N = 124)[a]

Variable	Result
Age, y	58.0 ± 10.8
Female sex, % (n)	87 (108)
Disease duration, y	19.1 ± 10.7
CCP Ab positivity, % (n)[b]	63 (78)
hsCRP, mg/l	4.3 ± 6.6
Daily prednisone use, % (n)	32 (40)
TNF-α inhibitor use, % (n)	45 (56)
HAQ score	0.9 ± 0.6
RADAI score	2.4 ± 1.7
Frailty category, % (n)	
Frail	10 (12)
Pre-frail	71 (88)
Robust	19 (24)
Frailty components, % (n)[c]	
Low BMI	2 (3)
Low grip strength	65 (81)
High fatigue	24 (30)
Slow gait speed	6 (7)
Low physical activity[d]	31 (38)

Abbreviation: BMI, body mass index; CCP Ab, cyclic citrullinated peptide autoantibody; HAQ, Health Assessment Questionnaire; hsCRP, high-sensitivity C-reactive protein; RADAI, Rheumatoid Arthritis Disease Activity Index; TNF-α, tumor necrosis factor α.
[a] Values are mean ± SD unless otherwise indicated.
[b] CCP Ab positivity is defined as a value of ≥ 20 units by enzyme-linked immunosorbent assay.
[c] Frailty components are defined per Fried LP et al (3).
[d] Low physical activity is based on International Physical Activity Questionnaire classification.

Effect of baseline frailty status on change in physical function and disease activity between baseline and follow-up. Baseline frailty status was significantly associated with change in HAQ but not RADAI scores between baseline and follow-up, even when adjusting for covariates (Table 2). Being frail, compared with being robust, was associated with an average 0.4-point increase in the HAQ score between baseline and follow-up, even when adjusting for covariates. In addition, being pre-frail, compared with being robust, was associated with an average 0.2-point increase in the HAQ score between baseline and follow-up in the fully adjusted model. When follow-up time (in years) was included as a covariate in the fully adjusted models, the overall trends remained the same (ie, baseline frailty status was associated with change in HAQ but not RADAI scores overt time) (data not shown).

Table 2. Complete model linear regression coefficients and 95% CIs for the effect of baseline frailty category on change in HAQ and RADAI scores between baseline and follow-up among individuals with RA (N = 124)[a]

	HAQ		RADAI	
	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
Frailty category				
Frail	0.4 (0.1 to 0.8)[b]	0.01[b]	0.5 (−0.4 to 1.5)	0.3
Pre-frail	0.2 (0.02 to 0.4)[b]	0.03[b]	−0.2 (−0.8 to 0.4)	0.4
Robust	Reference	...	Reference	...
Age (y)	−0.005 (−0.01 to 0.8)	0.2	−0.01 (−0.03 to 0.01)	0.4
Sex	0.05 (−0.2 to 0.3)	0.6	−0.02 (−0.7 to 0.7)	1.0
RA disease duration (y)	0.003 (−0.004 to 0.01)	0.4	0.007 (−0.02 to 0.03)	0.6
hsCRP (mg/l)[c]	−0.06 (−0.1 to −0.004)[b]	0.04[b]	−0.007 (−0.2 to 0.2)	0.9
Use of oral steroids (yes or no)	0.01 (−0.1 to 0.2)	0.8	−0.2 (−0.7 to 0.4)	0.5
CCP Ab titer (units)	−0.0002 (−0.0009 to 0.0005)	0.5	−0.0005 (−0.003 to 0.002)	0.3

Abbreviation: CCP Ab, cyclic citrullinated peptide auto-antibody; CI, confidence interval; HAQ, Health Assessment Questionnaire; hsCRP, high-sensitivity C-reactive protein; RA, rheumatoid arthritis; RADAI, Rheumatoid Arthritis Disease Activity Index.
[a] Increasing HAQ scores (0-3) and RADAI scores (0-10) reflect worse physical function and increased disease activity, respectively.
[b] $P < 0.05$.
[c] Natural log-adjusted hsCRP.

Effect of baseline frailty components on change in physical function and disease activity between baseline and follow-up. When the five frailty components were included in the same regression model as individual predictors of change in HAQ and RADAI scores between baseline and follow-up, the presence of high fatigue was statistically, significantly associated

Table 3. Complete model linear regression coefficients and 95% CIs for the effect of baseline frailty components on change in HAQ or RADAI scores between baseline and follow-up among individuals with RA (N = 124)[a]

	HAQ		RADAI	
	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
Frailty component				
Low BMI (yes or no)[b]	0.5 (−0.03 to 0.9)	0.06	0.4 (−1.1 to 2.0)	0.6
Low grip strength (yes or no)[b]	0.1 (−0.04 to 0.3)	0.1	−0.3 (−0.8 to 0.2)	0.3
High fatigue (yes or no)[b,c]	0.2 (0.03 to 0.4)[c]	0.02[c]	0.03 (−0.6 to 0.6)	0.9
Slow gait speed (yes or no)[b]	0.2 (−0.1 to 0.5)	0.3	−0.3 (−1.2 to 0.8)	0.6
Low physical activity (yes or no)[b,d]	−0.008 (−0.2 to 0.2)	0.9	0.2 (−0.3 to 0.8)	0.4
Age (y)	−0.003 (−0.01 to 0.004)	0.4	−0.006 (−0.03 to 0.02)	0.6
Sex	0.02 (−0.2 to 0.1)	0.8	0.04 (−0.7 to 0.7)	0.9
RA disease duration (y)	0.003 (−0.003 to 0.01)	0.4	0.01 (−0.01 to 0.04)	0.4
hsCRP (mg/l)[e]	−0.05 (−0.1 to 0.007)	0.08	0.05 (−0.1 to 0.3)	0.6
Use of oral steroids (yes or no)	0.04 (−0.1 to 0.2)	0.6	−0.2 (−0.7 to 0.4)	0.6
CCP Ab titer (units)	−0.000009 (−0.0007 to 0.0007)	1.0	−0.0006 (−0.003 to 0.002)	0.6

Abbreviation: BMI, body mass index; CCP Ab, cyclic citrullinated peptide auto-antibody; CI, confidence interval; HAQ, Health Assessment Questionnaire; hsCRP, high-sensitivity C-reactive protein; RA, rheumatoid arthritis; RADI, Rheumatoid Arthritis Disease Activity Index.
[a] Increasing HAQ scores (0-3) and RADAI scores (0-10) reflect worse physical function and increased disease activity, respectively.
[b] Frailty components are defined per Fried LP et al (3).
[c] $P < 0.05$.
[d] Low physical activity is based on International Physical Activity Questionnaire classification.
[e] Natural log-adjusted hsCRP.

with an increase in the HAQ but not the RADAI score between baseline and follow-up, even when adjusting for covariates (Table 3). The association between low grip strength and change in the HAQ score between baseline and follow-up approached but did not reach statistical significance.

Secondary analysis: effect of baseline frailty status on physical function and disease activity score at follow-up. Baseline frailty status was significantly associated with HAQ and RADAI scores at follow-up, even when adjusting for covariates (Supplementary Table 2). Being frail, compared with being robust, was associated with an average 0.5-point worse HAQ score and a 1.1-point worse RADAI score at follow-up, even when adjusting for covariates. In addition, being pre-frail, compared with being robust, was associated with an average 0.2-point worse HAQ score at follow-up in the fully adjusted model.

Sensitivity analyses: relationship of baseline frailty with change in physical function and disease activity between baseline and follow-up among those age 64 years and younger. Of the total cohort (N = 124), 89 (72%) were 64 years and younger. When the associations of baseline frailty status with changes in HAQ and RADAI scores between baseline and follow-up were assessed only in participants age 64 years and younger, the primary overall results remained unchanged (worse baseline frailty status was associated with an increase [ie, worsening] in HAQ but not RADAI scores between baseline and follow-up). In fully adjusted models, being frail, compared with being robust, at baseline was associated with an average 0.4-point increase (95% confidence interval: –0.0002 to 0.8; $P = 0.05$) in the HAQ score between baseline and follow-up. The association between baseline frailty status and change in RADAI score between baseline and follow-up among those age 64 years and younger was not statistically significant (data not shown).

DISCUSSION

In this cohort of men and women with established RA, we demonstrate significant effects of frailty on change in patient-reported physical function over time. Baseline frailty status predicted significant worsening in physical function, as measured by the HAQ, even when controlling for the effects of disease severity, disease duration, and medication use. These overall trends are unchanged when analyses are limited to participants age 64 years and younger, suggesting that effects of advanced age alone do not explain these relationships. In addition, fatigue appears to be a significant driver of the effect of baseline frailty status on change in physical function over time. These findings are, to our knowledge, among the first in the literature to demonstrate that baseline frailty is associated with worsening physical function over time in individuals with RA, and they suggest that frailty may be an important marker of individuals with RA who are at particular risk for increased physical disability over time.

The observed relationship of frailty status with change in physical function is likely to be clinically meaningful. The minimum clinically important difference (MCID), which represents the minimum change needed to be clinically relevant, for the HAQ is a change of 0.22 points (25,26). We demonstrate that being frail, compared with being robust, among individuals with RA is associated with an average 0.4-point increase in the HAQ score between baseline and follow-up, even when adjusting for covariates. Thus, the observed effect of frailty on change in the HAQ score over time exceeds by twofold, the threshold for a clinically important difference in the HAQ score.

The observed longitudinal relationship between frailty and change in patient-reported physical function in RA adds to recent studies that have implicated frailty as an important risk factor for reduced physical function and increased adverse outcomes in patients with rheumatologic disease. Among women with lupus, being frail, compared with being robust, at baseline was associated with a 0.3-point worse score on the Valued Life Activities (VLA) assessment, a patient-reported assessment of physical function that is scored 0-3, like the HAQ (27), and an approximately 7-point worse score on the physical functioning subscale of the 36-item Short Form Survey (MCID = 5) at the 2-year follow-up, even after adjusting for the effects of covariates, including age, lupus disease duration, lupus activity, and lupus damage (10). In that cohort, frailty was also associated with worse cognitive performance at the 2-year follow-up and increased all-cause mortality over an average follow-up time of 7 years.

Moreover, we have previously shown that in cross-sectional analyses of the same RA cohort as the present study, being frail, compared with being robust, was associated with a 0.44-point worse VLA score, even when adjusting for the effects of RA disease activity, medication use, and pain. The magnitude of the effect of baseline frailty on change over time in physical performance observed in the present study is comparable with that of these prior studies in lupus and RA. Thus, the observed relationship between baseline frailty status and differences in physical function appears consistent and reproducible across multiple studies of not only RA but also lupus.

We did not observe a statistically significant relationship of baseline frailty status with change in the RADAI score between baseline and follow-up. This finding suggests that the relationship of baseline frailty status with change over time in physical function may differ from the relationship with change over time in RA disease activity. Moreover, although we did not observe a significant relationship between frailty and change over time in the RADAI score, we did observe a significant relationship between frailty and the RADAI score at follow-up, even when adjusting for differences in baseline RADAI scores. Further studies are needed to explore and compare the relationships of baseline frailty status with change in the RADAI score over time and with the RADAI

score at follow-up, but our observations suggest that these relationships may differ. Although baseline frailty may not be associated with change in disease activity (eg, RADAI score) over time, baseline frailty may still be associated with differences in disease activity at follow-up in RA. Our findings may also reflect the overall relatively low RA disease activity present in our cohort, both at baseline and at follow-up, which could limit our ability to identify a significant relationship between frailty and change in the RADAI score over time. Additional studies among cohorts with a wider range of disease activity may help elucidate these relationships.

Fatigue appears to play an important role in explaining the relationship between frailty and changes over time in physical function among those with RA. In our cohort, baseline fatigue was associated with significant worsening in the HAQ score between baseline and follow-up. Fatigue is common among individuals with RA and often does not improve with RA-specific pharmacotherapy alone (28,29). By demonstrating that fatigue is an important contributor to the association between frailty and worse functional outcomes in RA, this study further underscores the clinical relevance of addressing fatigue symptoms in caring for patients with RA and suggests a potential role of interventions that target fatigue in improving physical function over time in RA.

Given these results, frailty may represent a measurable risk factor to identify individuals with RA at greatest risk of becoming disabled and may provide a unique opportunity to develop novel interventions aimed at improving clinical outcomes, such as physical performance, for individuals with RA. That baseline frailty status is associated with future physical performance in RA, even after adjusting for the effects of RA disease duration and severity, suggests that interventions specifically targeting aspects of frailty may help improve functional outcomes and prevent physical disability for patients with RA when added to standard clinical pharmacotherapies that are focused on RA disease activity. For example, a recent trial of a pedometer intervention to increase walking in individuals with RA significantly improved participants' physical activity and several patient-reported outcomes, including pain and fatigue, and trended toward improving disease activity, as assessed by the RADAI (30). Future studies will need to 1) further examine the ability of frailty status to identify patients with RA at increased risk of physical disability and poor RA-disease control over time and 2) determine which aspects of frailty may be targeted most effectively to prevent physical disability and improve disease control for these patients.

This study has potential limitations. The lack of a non-RA control group is a potential limitation. In addition, the lack of a disease activity index that includes physician-reported or laboratory data measures, such as the Clinical Disease Activity Index or the Disease Activity Score, to assess RA disease activity is another potential limitation, although the analyses were adjusted for C-reactive protein (CRP). As discussed previously (11), the 17 participants who did not complete the grip strength assessment represent a potential limitation, further underscoring the logistical challenges around studying muscle strength in a clinical cohort. The lack of information on medical comorbidities, such as cognitive impairment or chronic heart or lung disease, is also a potential limitation. Lastly, because our cohort had, on average, relatively long-standing and less symptomatic (as reflected in the RADAI score and CRP level) RA, it may limit generalizability to individuals with newly diagnosed or highly active RA.

There are also strengths of our study. The study is innovative in that it is one of the first to identify frailty and, in particular, fatigue as a component of frailty, as a significant risk factor for worse patient-reported physical function over time in RA. The study uses an established, validated measure of frailty that has been applied to various chronic disease populations. The men and women analyzed in the study compose a relatively large longitudinal cohort of individuals with physician-documented RA. The use of validated, practical patient-reported measures of physical function and disease activity is also a potential strength in that it facilitates conducting future studies by using these same measures in examining frailty and clinical outcomes in RA.

In conclusion, we observed that baseline frailty status is significantly associated with worse patient-reported physical function over time in individuals with RA. The observed effects of frailty on physical function persisted after adjustment for RA disease severity and duration, and the effects were clinically meaningful. Fatigue appears to be a primary contributor to the relationship between frailty and changes over time in physical function. These findings suggest that frailty may be an important and unique risk factor for physical disability in RA and that novel interventions targeting aspects of frailty may have the potential to improve functional outcomes for these patients.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual contact, and all authors approved the final version to be published and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Andrews, Trupin, Yelin, Katz.
Acquisition of data. Trupin, Katz.
Analysis and interpretation of data. Andrews, Trupin, Wysham, Hough, Yelin, Katz.

ACKNOWLEDGMENTS

The authors wish to acknowledge the study participants and their families.

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