Title

Determinants of generalized fatigue in individuals with symptomatic knee osteoarthritis: The MOST Study

Journal

International Journal of Rheumatic Diseases, 23(4)

ISSN

0219-0494

Authors

Fawole, Henrietta O
Riskowski, Jody L
Dell'Isola, Andrea
et al.

Publication Date

2020-04-01

DOI

10.1111/1756-185x.13797

Peer reviewed

HHS Public Access

Author manuscript

Int J Rheum Dis. Author manuscript; available in PMC 2021 April 01.

Published in final edited form as:

Int J Rheum Dis. 2020 April ; 23(4): 559–568. doi:10.1111/1756-185X.13797.

Determinants of Generalized Fatigue in Individuals with Symptomatic Knee Osteoarthritis: The MOST Study.

Henrietta O Fawole, MSc[1,2], **Jody L Riskowski, PhD**[1], **Andrea Dell'Isola, PhD**[3], **Martijn P Steultjens, PhD**[1], **Michael C Nevitt, PhD, MPH**[4], **James C Torner, PhD**[5], **Cora E Lewis, MD, MSPH**[6], **David T Felson, MD, MPH**[7], **Sebastien FM Chastin, PhD**[1,8]

[1]Centre for Living, School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, Scotland, UK.

[2]Department of Physiotherapy, College of Medical Sciences, University of Benin, Edo State, Nigeria.

[3]Department of Orthopaedics, Faculty of Medicine, Lund University, Sweden.

[4]University of San Francisco, San Francisco, CA, USA.

[5]University of Iowa, Iowa City, IA, USA.

[6]University of Alabama, Birmingham, AL, USA.

[7]Boston University School of Medicine, Boston, MA, USA.

[8]Department of Movement and Sports Science, Ghent University, Ghent, Belgium.

Abstract

Aim: The aim of the study was to identify sociodemographic, disease-related, physical and mental health-related determinants of fatigue at two-year follow-up in individuals with symptomatic knee osteoarthritis (OA).

Methods: A longitudinal analysis of participants with symptomatic knee OA from the Multicenter Osteoarthritis Study (MOST) was conducted to identify predictors of fatigue at two-year follow-up. Participants self-reported fatigue at baseline for the first time in the MOST cohort and at follow-up using a 0–10 visual analogue scale. At baseline, questionnaires on sociodemographics, disease-related symptoms, physical and mental health factors were completed. Data were analysed using linear regressions with a backwards elimination approach.

Results: Of the 2,330 individuals in the MOST cohort at baseline, 576 had symptomatic knee OA and of these, 449 with complete fatigue values at baseline and follow-up were included in this analysis. Minimally important fatigue change (i.e., worsening [≥1.13], no change [<0.82 or <1.13] and improvement [≥ −0.82]) from baseline to follow-up was unequal within the population

Corresponding Author: Henrietta O. Fawole, Centre for Living, School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, G4 0BA. Henrietta.Fawole@gcu.ac.uk.

AUTHOR CONTRIBUTION: HOF, JLR, AD, MSP and SFMC conceptualised and designed the study; MCN, JCT, CEL and DTF acquired the data; HOF performed the data analysis; HOF, JLR, AD, MSP, DFT and SFMC interpreted the data; HOF drafted the manuscript; all authors critically revised and approved of the final version of the manuscript. All authors take responsibility for the integrity of the work as a whole.

[34.5%, 26.9%, 38.5%; X^2(2, N=449) = 9.32, p=0.009]. The multiple linear regression showed that baseline fatigue (unstandardized coefficient (B)=0.435; 95% confidence interval [CI] [0.348, 0.523], p<0.001), slow gait speed (B=−1.124; 95% CI [−1.962, −0.285], p=0.009), depressive symptoms (B=0.049; 95% CI [0.024, 0.075], p<0.001) and higher numbers of comorbidities (B=0.242; 95% CI [0.045, 0.439], p=0.016) were significant predictors of greater fatigue at follow-up.

Conclusion: Fatigue is strongly associated with physical and mental related health factors. Individualised treatments that include combined psychological and physical function rehabilitation might be modalities for fatigue management.

Keywords

fatigue; knee osteoarthritis; risk factors; longitudinal

1 INTRODUCTION

Fatigue is a commonly reported symptom and a major contributor to substantial disability and decreased quality of life among individuals with knee osteoarthritis (OA).[1,2] Generalized fatigue affects almost half of adults with OA and its prevalence has been reported to be as high as 40%.[3,4] Individuals with OA describe fatigue as a symptom that considerably impacts daily functioning, social life and all aspect of daily living.[5] Despite the negative impact and the high prevalence of fatigue in this population, the aetiology is not well understood due to its complex and multifactorial nature. Further, fatigue in knee OA has received less research attention relative to other inflammatory rheumatic conditions such as rheumatoid arthritis (RA).[6]

In a recent narrative review of fatigue, factors such as female gender, age, comorbidities, depression, joint pain, poor sleep quality and disability were suggested as correlates of fatigue in the general OA population.[7] Similarly, other cross-sectional research on fatigue in chronic conditions have suggested that sleep disturbance, pain catastrophizing, impaired physical function and comorbidities may also influence feelings of fatigue.[3,4,8,9] These findings on correlates of fatigue, however, are mostly from cross-sectional studies[3,10–12] and conflict with studies reporting no associations.[10,12–14] The few available longitudinal studies of fatigue in those with lower limb OA either examined the pain-depression link whilst determining the influence of fatigue on this pathway, used subjective physical function measure and did not include sleep quality[15] or included just pain and subjective physical function as potential fatigue determinants and used a short (12 weeks) follow-up time.[13] Besides, prior studies evaluating fatigue in those with OA have included participants with other rheumatic conditions[3,11], combined multiple OA populations (e.g., hip, knee and/or hand)[3,13–16], and often used clinical populations[3,12,14,16] which constitutes only selected portion of individuals with OA.

To gain greater understanding of fatigue aetiology in the OA population, more longitudinal studies are warranted as well as well-defined populations, such as symptomatic knee OA; because in combining study populations, the results may not be as meaningful given that arthritic conditions have different symptoms and aetiologies. Therefore, the main aim of the

study was to identify important sociodemographic, disease-related, physical and mental determinants of generalized fatigue within a specific population of individuals with symptomatic knee OA starting from evidence based on fatigue studies in the general, chronic disease and OA populations. Additionally, a second aim was to determine whether symptomatic knee OA is associated with fatigue compared to those without symptomatic knee OA.

2 METHODS

2.1 Study design and sample

This is a secondary analysis of longitudinal data from Multicenter Osteoarthritis Study (MOST). MOST began in 2003 with the enrolment of 3,026 individuals from communities in Birmingham, Alabama and Iowa City, Iowa. MOST comprises a community-based sample of men and women aged 50–79 years with or at high risk of knee OA at study inception[17] with study details published elsewhere.[18] Participants were assessed at either of the two clinical centres (University of Alabama, Birmingham or University of Iowa) for baseline examination (i.e., 20-meter walk test, isokinetic concentric knee extensor/flexor strength and knee x-rays/MRIs) and questionnaire completion at study inception. [18] All surviving participants had follow-up telephone interview and clinic visit at 60 months (our study baseline). Exclusion criteria for MOST study included bilateral knee replacement, inability to give informed consent, intended movement out of the study area prior to follow-up, a life threatening illness that could make it unlikely to survive to follow up, diagnosis of rheumatoid or other inflammatory arthritis.[18]

In this study, we utilised data collected at 60-months (referred to here as baseline) because fatigue was assessed for the first time at 60-months and also at 84-months (referred to here as two-year follow-up). For this secondary analysis, inclusion criteria comprised baseline and follow-up fatigue data, and baseline symptomatic whole knee (WK) OA status. Exclusion criteria were similar to those in the MOST study. Radiographic whole knee OA status was considered as the presence of radiographic OA using either Kellgren Lawrence scores (KL) ≥2 for tibiofemoral (TF) joint or any osteophyte ≥2 or joint space narrowing ≥1 plus any osteophyte, sclerosis, or cyst >1 in the patellofemoral (PF) joint. The absence of osteophyte, joint space narrowing, sclerosis or cyst in the PF joint or KL<2 in TF joint was considered as no radiographic WK OA.[19] Study participants self-reported knee pain twice, once during a telephone interview and once at the clinic visit with a median of 33 days between the telephone interview and clinic visit. If participants reported frequent knee pain, aching and stiffness in either knee on most of past 30 days in both settings (i.e., telephone and clinic interviews) at baseline, they were defined as having frequent knee pain. Participants who did not report frequent knee pain, aching and stiffness in either knee on most days of the past 30 days in both settings at baseline were defined as not having frequent knee pain. For this analysis, definition of symptomatic knee OA included both the presence of radiographic whole knee OA and frequent knee pain in the same knee. Non-symptomatic knee OA was defined as having no frequent knee pain and no radiographic WK OA.

2.2 Ethical consideration

MOST was conducted in accordance with United States (US) Department of Health & Human Services Protection of Human Subjects regulations (45 CFR part 46) and the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996.[18] MOST sought and obtained ethical approval from local institutional review boards at the four MOST centres (FWA00000068 University of California, San Francisco; FWA00000301 Boston University; FWA00005960 University of Alabama, Birmingham & FWA00003007 University of Iowa), and all study participants gave informed consent prior to study participation according to the Declaration of Helsinki. We sought and obtained institutional ethical approval from Glasgow Caledonian University's School of Health and Life Sciences ethics committee to perform this secondary data analysis (HLS/PSWAHS/16/252).

2.3 Dependent measure

The outcome in this analysis was fatigue at follow-up assessment (2 years), and baseline fatigue was a predictor. Fatigue was defined in this study as 'generalized fatigue' that referred to the feelings of tiredness, weakness or feeling worn out or depleted over the course of several days. Participants self-reported their usual fatigue level over the past seven days at baseline and at two-year follow-up using a 0–10 visual analogue scale (VAS). A '0' on the fatigue VAS was defined as 'no fatigue' and '10' was defined as 'fatigue as bad as it can be' with higher values indicating greater fatigue severity. The VAS fatigue scale has been commonly used in OA research[4,16] and it is also a valid, reliable and responsive tool for subjective measurement such as fatigue.[6] Further, in rheumatic diseases, VAS fatigue strongly correlates with other fatigue measures such as the Multidimensional assessment of fatigue (MAF) at 0.80, short form 36 vitality subscale (SF-36 VT) at 0.71[20] and the Multi-dimensional fatigue inventory (MFI)-total and MFI-general fatigue at 0.62-.0.70.[21]

2.4 Independent measures

Study factors related to sociodemographics included age, gender (men vs. women), race/ethnicity (white and caucasian vs. black and /or others), living situation (living alone vs. living with significant others), and monthly bill payment (no difficulty vs. difficulty/unable to pay monthly bills). Disease-related variables as well as physical and mental health factors included sleep quality (poor vs. good), comorbidities, Western Ontario McMaster Universities Osteoarthritis index (WOMAC) pain, radiographic evidence of TF OA (KL score <2 vs. ≥2), Center for Epidemiologic Studies Depression Scale (CES-D), pain catastrophizing (<1 vs. ≥1), body mass index (BMI) and gait speed. Participants self-reported overall sleep quality using a single question from the Pittsburgh sleep quality index in the past 7 days as follows 'very good' 'fairly good' 'fairly bad' 'very bad'.[22] Poor sleep quality included 'fairly poor' or 'very bad' while good sleep included 'fairly good' and 'very good'. Overall comorbidity was assessed using modified Charlson comorbidity index.[23] The modified WOMAC pain subscale which ranged from 0–20 was used in reporting knee pain in 'the past 30 days'.[24] The limb, which corresponded with the symptomatic knee, was considered for this study. However, in cases with bilateral symptomatic knee OA, the more painful knee was used as index limb. Participants' KL score at 60 months was obtained from weight-bearing fixed-flexed posterior-anterior and semi flexed lateral positioning of knees.

The presence of radiographic TF OA was graded on 0 to 4 using the KL scale[25] by three expert readers (two rheumatologists and a musculoskeletal radiologist) blinded to the clinical data. Participants were defined as having no radiographic TF OA if they had KL score <2 or as having radiographic TF OA if they had KL score ≥2. Depressive symptoms were assessed using CES-D which ranged from 0–60 with increasing values signifying depressive symptoms.[26] Pain catastrophizing was assessed with a single question: 'When I feel pain, I feel it's terrible and that it's never going to get any better'. The question was rated on a scale of 0 (never do that) to 6 (always do that). This question represents catastrophizing, a subscale on the coping strategies questionnaire (CSQ), a valid instrument for measuring adjustment strategies to chronic pain.[27] Participants were considered as not pain catastrophizing if they answered zero (<1) and pain catastrophizing if the reported one or higher score (≥1). BMI (determined as kg/m^2) was assessed with standardised weight and height measurements. Gait speed was measured using the faster time (seconds) of two walking trials over a 20-meter distance (20m/faster time [s]).[28] The test was performed on an unobstructed walkway with timing commencing once the first foot crossed the start line and finishing after the last foot crossed the finish line. The 20-meter walk test is used in cohort studies of knee OA [29] and has high reliability for gait speed measurement.[30] Independent variables were assessed at baseline.

2.4 Statistical methods

Descriptive statistics included frequencies and percentages or mean and standard deviation (SD) as appropriate to determine sample's sociodemographic, disease-related and health factors. We used independent t-tests and Chi-square tests to examine the differences in baseline characteristics between participants with and without symptomatic knee OA with fatigue values at both baseline and follow-up, symptomatic knee OA subjects who were included and excluded. For those with symptomatic knee OA, the mean change in fatigue from baseline to follow-up was examined using paired-sample t-test and the distributions of minimally important changes in fatigue within the symptomatic knee OA population from baseline to follow-up were examined using one-sample Chi-square test. The distribution of relevant change in fatigue within the symptomatic knee OA population over the two years was based on minimally important fatigue change – a decrease of 0.82 for fatigue improvement and an increase of 1.13 or more for fatigue worsening.[31]

A separate multiple linear regression was used to determine if fatigue at two years follow-up was associated with either symptomatic knee OA or non-symptomatic knee OA while adjusting for baseline fatigue alone and further adjusting for age, gender, race and BMI. Bivariate linear regression was performed to test for association between each of the baseline independent variables and follow-up fatigue. Multiple linear regression models were used to determine which baseline factors were associated with fatigue at follow-up specifically within the subset of individuals with symptomatic knee OA. For these analyses, we included all independent variables in the first model.[32] To achieve a parsimonious model, manual backward elimination was performed by dropping variables that were not significant at $p>0.1$ one at a time in decreasing p-value order.[32] However, if the coefficient of any of the remaining variables changed by ≥10% when a variable was dropped, this variable was retained as a potential confounder.[33] Only variables with $p<0.05$ were retained in the final

model. As very few datasets were missing, we therefore handled missing values with pairwise deletion. Assumptions for multiple linear regressions including multicollinearity assumptions were checked and tested prior to statistical analysis. All tests of statistical significance were two-sided and considered significant at < 0.05 level and all analyses were conducted using SPSS software (version 23.0, SPSS, Chicago, IL, USA).

3 RESULTS

3.1 Subject characteristics

Of the 2,330 individuals available in the MOST cohorts at 60-months (this study's baseline), 1,627 had no symptomatic knee OA and 576 had symptomatic knee OA (Figure 1). Of these only 449 participants with symptomatic knee OA were included in the primary analysis as they had complete fatigue values at baseline and follow-up. The general characteristics of MOST participants with (n=449) and without (n=1,260) symptomatic knee OA with complete fatigue values at baseline and follow-up are shown in Table 1. There were generally statistically significant differences between those with and without symptomatic knee OA. The symptomatic knee OA individuals were more likely to be female, have worse health indicators (i.e., higher BMI, greater fatigue, greater pain, higher levels of depressive symptoms, and poorer sleep), and lower sociodemographic characteristics (i.e., being black/other, living alone, having difficulty paying monthly bills), but there were no statistically significant differences in age and gait speed between the two groups. In those with symptomatic knee OA, fatigue statistically decreased from baseline (3.91 [SD=2.45]) to follow-up (3.70 [SD=2.37]), t (448) =2.07, p=0.039. The distribution of relevant fatigue change within the symptomatic knee OA population (i.e., worsening [≥1.13], no change [<0.82 or <1.13] and improvement [≥ −0.82]) from baseline to follow-up were 34.5%, 26.9%, 38.5% respectively [X^2(2, N=449) = 9.32, p=0.009]. Generally, in the symptomatic knee OA, those who were excluded tended to be older, have more knee pain, have more comorbidities and lower gait speed relative to those included in this study. However, baseline and follow-up fatigue scores were similar in those included and excluded (results not shown).

3.2 Association between symptomatic knee OA and fatigue

Individuals with symptomatic knee OA had statistically significantly higher baseline fatigue (3.91±2.45; N=449) relative to those without symptomatic knee OA (2.96±2.23; N=1260), t(−7.25)=727.43; p<0.001 (Table 1). On average, participants with symptomatic knee OA had higher increase in fatigue at follow-up than individuals without symptomatic knee OA after adjusting for only baseline fatigue (unstandardized coefficient (B)=0.274; [95% confidence interval (CI) [0.082, 0.466], p=0.005). Further adjustment for age, gender, race and BMI revealed that individuals with symptomatic knee OA still had higher increase in fatigue compared to those without (B =0.228; CI [0.034, 0.422], p=0.021) [Data not shown].

3.3 Bivariate analysis between baseline factors and fatigue at follow-up in symptomatic knee OA

In the bivariate analysis, we found significant correlations between fatigue at follow-up and many of the independent baseline variables (Table 2). The following factors did not

significantly correlate with fatigue at follow-up in bivariate analysis: age (B= 0.005; CI [−0.023, 0.033], p=0.735), BMI (B=0.032; CI [−0.002, 0.065], p=0.066) and radiographic severity of knee OA (KL score ≥2) (B= −0.403; CI [−1.130, 0.324], p=0.277).

3.4 Multiple linear regression between baseline factors and fatigue at follow-up in symptomatic knee OA

In the first model with all variables included, only baseline fatigue, gait speed, depressive symptoms and comorbidities were significant predictors of fatigue at follow-up and this model accounted for 40.2% variance in fatigue at follow-up (Table 2). The final model, after backward elimination, accounted for 40.5% variance in fatigue at follow-up and fatigue at follow-up was statistically significantly associated with baseline fatigue (B= 0.435; CI [0.348, 0.523], p<0.001), slow gait speed (B= −1.124; CI [−1.962, −0.285], p=0.009), depressive symptoms (B= 0.049; CI [0.024, 0.075], p<0.001) and comorbidities (B= 0.242; CI [0.045, 0.439], p=0.016). Baseline fatigue had the largest standardised coefficient (β = 0.453), followed by depressive symptom (β = 0.177), gait speed (β = −0.103) while comorbidities had the smallest (β = 0.090). No variable was considered as a potential confounder based on our pre-definition of potential confounders.

4 DISCUSSION

The main goal of this analysis was to identify determinants of fatigue at two-year follow-up in a large population-based cohort of symptomatic knee OA and secondarily examined if the presence of symptomatic knee OA at baseline was associated with fatigue at follow-up. Those with symptomatic knee OA at baseline had greater levels of fatigue at follow-up relative to those with no symptomatic knee OA at baseline. In the 449 participants with symptomatic knee OA at baseline, fatigue at follow-up was significantly associated with baseline fatigue, poor physical function (i.e., low walking speed), depressive symptoms and comorbidities. These findings indicate that fatigue is a complex and multifactorial symptom which is associated with potentially modifiable physical and mental health-related factors, suggesting that treating these factors may lead to reduced risk of fatigue at follow-up in symptomatic knee OA population.

Our findings showed that individuals with symptomatic knee OA were more fatigued on average than those without symptomatic knee OA. Our study results were similar to those of Wolfe et al (1999), who found fatigue to be the strongest factor associated with WOMAC scores in the presence of other independent factors (symptom counts, low back pain and depression) in those with knee OA, hip OA, RA and fibromyalgia [11] and similarly to those of Grotle et al (2008) who reported OA to be strongly associated with fatigue in a Norwegian population.[34] This finding underscore fatigue as a key symptom which may require routine clinical assessment in individuals with symptomatic knee OA.

From the bivariate analysis, in those with symptomatic knee OA, several socio-demographic, health-related and disease-related factors were associated with fatigue at follow-up including potentially modifiable factors i.e., depression and physical function. Radiographic severity of knee OA was not associated with fatigue at follow-up, nor were age and BMI. However, most of these associations no longer remained significant after adjustments. The likely

explanation may be that other factors (likely baseline fatigue) were correlated with these factors and adjustment attenuated their associations with fatigue at follow-up. In the final regression analysis, pre-existing fatigue, slow gait speed, depressive symptoms and comorbidities were the only factors associated with prospective fatigue at two years. These finding support recent evidence signifying the presence of centrally-mediated symptoms such as fatigue in a subgroup of individuals with knee OA.[35]

Gait speed, an important indicator of functional mobility among older adults and those with lower extremity OA [36,37] was strongly associated with follow-up fatigue in the current study. This finding is consistent with prior research in older adult[38] and knee OA.[2] Although comparison should be with caution as both studies measured other constructs of fatigue (i.e., tiredness [38] and vitality [2] – opposite of fatigue). Besides, the van Dijk et al study used clinical knee OA patients receiving ongoing rehabilitation - which may have influenced the course of vitality and did not include depression in their analysis.[2] From our model a unit increase (1.0m/s) in baseline gait speed was associated with a reduction of 1.124 in follow-up fatigue, and this reduction is clinically relevant using the minimally important fatigue change (MCID) for 10cm VAS fatigue in RA which is ≥ - 0.82 for fatigue improvement.[31] We suggest that slow gait speed may indicate physical deconditioning that could lead to fatigue and vice versa. A potentially negative loop may ensue - where less engagement in or increased difficulty performing activities of daily living may continue to enhance deconditioning and thus escalate fatigue levels over time. In addition, the presence of other debilitating symptoms such as increasing comorbidities might further escalate fatigue by increasing knee muscles fatigability, thereby, resulting in a vicious cycle that negatively impact gait speed and fatigue levels [2,39]. Depressive symptoms arose as a key factor associated with future fatigue in this study confirming findings from previous works.[15,40] However, from the model, the effect size of 0.049 between baseline depression and follow-up fatigue was small and was not clinically relevant using the MCID for 10cm VAS of ≥ - 0.82 for fatigue improvement[31] in RA.

To make our results relevant in a clinical or similar setting, we used the model to estimate what change in the modifiable predictors would lead to minimally important fatigue change. An estimated change in gait speed that may predict relevant fatigue improvement (≥ - 0.82) in this population is ≥ 0.73m/s whilst an estimated change of ≥ 16 points in depression may possibly predict clinically relevant fatigue improvement. More so, minimising fatigue through a decrement of 16 points on 60-point depression (CES-D) scale may be difficult to achieve. Equally, improving fatigue by a change in gait speed of ≥ 0.73m/s may also not be feasible as this may be too large an increment in gait speed in this population. However, combining both gait speed and depression management might lead more easily to change in fatigue clinically. For example, improving gait speed with an increment of 0.4m/s in conjunction with a decrement of 10 point on depression (CES-D) scale may lead to effective fatigue management in this population. These estimations are obviously based on observational data rather than experimental - therefore should be interpreted with caution. Further, this study showed higher numbers of comorbidities were associated with future fatigue. As evidence indicates there is a high prevalence of comorbidities among individuals with knee OA[41], with rates as high as 66–85%[42–44], effectively managing comorbidities and their symptoms may be appropriate means for addressing fatigue over time. It maybe

hypothesised that the disease burden of comorbidities may influence fatigue by reducing physical functioning and favouring depressive mood, which in turn escalate fatigue preponderance among individuals with symptomatic knee OA. As such, it may be essential to include management of comorbidities when developing rehabilitation plans for addressing fatigue in symptomatic knee OA population. Baseline fatigue was a strong predictor of fatigue at two years follow-up. This finding suggests the need to consider fatigue measurement clinically and as part of the research agenda in symptomatic knee OA population. The American College of Rheumatology and the European League Against Rheumatism consensus panels have noted the need of fatigue assessment as essential in research[45], and these results of factors precipitating future fatigue suggest that fatigue is not likely to diminish without an effective management programme.

Pain and fatigue had a one-on-one correlation from our bivariate analysis; however, this association was attenuated in the multiple regression models. A potential reason may be due to inclusion of baseline fatigue in our model since it is likely that baseline fatigue is associated with pain. Similarly, this may be explained by high scores of fatigue at follow-up in some individuals with low baseline WOMAC pain. This finding is somewhat in concordance with a study by Snidjers et al (2011), who also found no significant association between change in Checklist Individual Strength (CIS) fatigue subscale and baseline WOMAC pain after 12 weeks.[13] Contrastingly, the same study found that change in CIS activity was independently associated with pain improvement after 12 weeks of conservative treatment. Contrary to our finding, Hawker et al (2011) reported WOMAC pain as a predictor of fatigue over two years. The difference between our study results and Hawker's may be due to the lower pain severity reported in our study (WOMAC average pain=6.78 ± 3.63 vs. 8.03 ± 4.22) and different fatigue scales used. Whilst there is indication of cross-sectional association between sleep quality and fatigue in OA studies [7]; however, there is a lack of longitudinal evidence on this relationship in symptomatic knee OA population. Our study found a bivariate correlation between fatigue and poor sleep but this relationship was not significant in the multivariable model. This may be due to the inclusion of other factors in our model (i.e., baseline fatigue, depressive symptoms,) or it may be possible that poor sleep rather acts as a mediator between depressive symptoms and fatigue longitudinally. More so, longitudinal evidence regarding the association between sleep quality with fatigue are contrasting [46–48] in rheumatic diseases such as RA. The conflicting results may be due to different sleep constructs, fatigue measurements and diverse follow-up times used in these studies. More longitudinal studies are warranted to determine the role of sleep to fatigue in symptomatic knee OA in addition to finding an appropriate sleep measure in this population. The use of an objective sleep measure such as polysomnograpy may enhance future evidence.

As one of the primary longitudinal studies that has comprehensively assessed sociodemographic, disease-related, physical and mental-related factors to future fatigue in a large cohort of symptomatic knee OA, the study findings must be interpreted within its limitations and with respect to its strengths. First, the use of retrospective unidimensional fatigue measure (VAS) limits the potential to address momentary fatigue and multiple fatigue domains which may provide more insights into fatigue aetiology in the symptomatic knee OA population.[1,5] Whilst there are currently many other multidimensional fatigue

measures, generally, the simple VAS fatigue and many of these complex measures yield similar results and are easier to use.[20,49] Also, the 0–10 VAS is commonly used in OA research[4,16,50] and clinical settings. Also, there could be possibility that some questions on CES-D might partially overlap with fatigue, however, no identified overlap of fatigue with these CES-D questions were found in a large OA population.[51] We, however suggest that future studies should include a comprehensive examination of the CES-D items such as "feeling everything was an effort" and "couldn't get going" with different fatigue constructs specifically in symptomatic knee OA population. Although there is strong evidence that depression and fatigue coexist in OA[15] nonetheless, there are indication that fatigue and depression are distinct and separate constructs.[52] Studies are thus warranted to determine the pathway of depression in fatigue aetiology. Another limitation of our study is the use of 10cm VAS MCID which has only been established in RA population but not yet determined in the knee OA population. Nonetheless, fatigue prevalence in RA and OA are comparable[3,14]; however caution is needed in interpreting our results. We did not examine the influence of knee extensor strength, a potential predictor of fatigue in post TKR patients.[4] Future studies should consider the assessment of knee extensors strength to enhance understanding of fatigue aetiology in symptomatic knee OA. Similarly, there are other potentially relevant factors that may be implicated in fatigue aetiology in symptomatic knee OA; these may include low-grade inflammation, tendon stiffness and physical deconditioning. Both low-grade inflammation[53] and tendon stiffness[54] have been hypothesised but not yet confirmed, thus more studies are needed to explore potential associations with fatigue in symptomatic knee OA population. Generalisation of our study findings may be limited to community-dwelling individuals with symptomatic knee OA, rather than more clinical population who may experience greater levels of pain and comorbidities. Although, we controlled for comorbidities and age in the backwards elimination models, increasing comorbidities was a significant predictor of fatigue at follow-up and age was not, suggesting that age is related to fatigue in large part because of increasing comorbidities with age. As this was an observational study, there is no means for ascertaining causality, and future longitudinal study designs should be undertaken to further explore fatigue causality. Lastly, the final model accounted for 40.5% in follow-up fatigue variance, suggesting there may be other factors (i.e., muscle fatigability, low grade inflammation, tendon stiffness, physical inactivity, medications, aerobic functioning, and self-efficacy) relevant to fatigue that were not examined in this study. Strengths of this study included its population based symptomatic knee OA cohort, the longitudinal design and evaluation of factors that addressed probable causes of fatigue such as sleep quality, pain catastrophizing, objective physical function and comorbidities which our large sample size permitted.

In conclusion, individuals with symptomatic knee OA are more likely to experience and report fatigue relative to those without symptomatic knee OA. Pre-existing fatigue, poor physical function (low gait speed), psychosocial factor (depressive symptoms) and comorbidities were associated with generalized fatigue at two-year follow-up in those with symptomatic knee OA. These results underline the complex and multifactorial nature of fatigue while providing account of factors associated with fatigue at follow-up. In the light of these results, individualised multi-interventions that incorporate both physical functional

and psychological rehabilitation such as cognitive behavioural therapies and functional activities may be considered in the treatment of generalized fatigue among patients with symptomatic knee OA.

ACKNOWLEDGEMENT:

MOST study was funded by the National Institutes of Health – National Institutes on Aging, grant numbers via institutions: Boston University (Felson): U01AG18820; University of Iowa (Torner) U01AG18832; University of Alabama at Birmingham (Lewis): U01AG18947 and University of California, San Francisco (Nevitt): U01AG19069. This work is part of a PhD studentship project (REG2016_SHLS3) funded by Glasgow Caledonian University, Scotland, United Kingdom.

REFERENCES

1. Murphy SL, Smith DM, Clauw DJ, Alexander NB. The impact of momentary pain and fatigue on physical activity in women with osteoarthritis. Arthritis Care Res 2008;59:849–856.
2. Van Dijk GM, Veenhof C, Lankhorst GJ, Van Den Ende CH, Dekker J. Vitality and the course of limitations in activities in osteoarthritis of the hip or knee. BMC Musculoskelet Disord 2011;12:269–278. [PubMed: 22111943]
3. Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol 1996;23:1407–1417. [PubMed: 8856621]
4. Hodges A, Harmer AR, Dennis S, Nairn L, March L, Crosbie J, et al. Prevalence and Determinants of Fatigue Following Total Knee Replacement: A Longitudinal Cohort Study. Arthritis Care Res (Hoboken) 2016;68:1434–1442. [PubMed: 26866417]
5. Power JD, Badley EM, French MR, Wall AJ, Hawker GA. Fatigue in osteoarthritis: a qualitative study. BMC Musculoskelet Disord 2008;9:63. [PubMed: 18452607]
6. Stebbings S, Treharne GJ. Fatigue in Rheumatic Disease: an overview. Int J Clin Rheumtol 2010;5:487–502.
7. Hackney AJ, Klinedinst NJ, Resnick B, Renn C, Fiskum G. A review and synthesis of correlates of fatigue in osteoarthritis. Int J Orthop Trauma Nurs 2019;33:4–10. [PubMed: 30808556]
8. van Hoogmoed D, Fransen J, Bleijenberg G, van Riel P. Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. Rheumatology 2010;49:1294–1302. [PubMed: 20353956]
9. Soares WJS, Lima CA, Bilton TL, Ferrioli E, Dias RC, Perracini MR. Association among measures of mobility-related disability and self-perceived fatigue among older people: A population-based study. Brazilian J Phys Ther 2015;19:194–200.
10. Stebbings S, Herbison P, Doyle TCH, Treharne GJ, Highton J. A comparison of fatigue correlates in rheumatoid arthritis and osteoarthritis: Disparity in associations with disability, anxiety and sleep disturbance. Rheumatology 2010;49:361–367. [PubMed: 20007746]
11. 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 1999;38:355–361. [PubMed: 10378714]
12. Creamer P, Lethbridge-Cejku M, Hochberg MC. Determinants of pain severity in knee osteoarthritis: Effect of demographic and psychosocial variables using 3 pain measures. J Rheumatol 1999;26:1785–1792. [PubMed: 10451078]
13. Snijders GF, van den Ende CHM, Fransen J, van Riel PLCM, Stukstette MJPM, Defoort KC, et al. Fatigue in knee and hip osteoarthritis: The role of pain and physical function. Rheumatology 2011;50:1894–1900. [PubMed: 21750001]
14. Zautra AJ, Fasman R, Parish BP, Davis MC. Daily fatigue in women with osteoarthritis, rheumatoid arthritis, and fibromyalgia. Pain 2007;128:128–135. [PubMed: 17055648]
15. Hawker GA, Gignac MAM, Badley E, Davis AM, French MR, Li Y, et al. A longitudinal study to explain the pain - Depression link in older adults with osteoarthritis. Arthritis Care Res 2011;63:1382–1390.

16. Wolfe F, Michaud K, Pincus T. Fatigue, rheumatoid arthritis, and anti-tumor necrosis factor therapy: An investigation in 24,831 patients. J Rheumatol 2004;31:2115–2120. [PubMed: 15517621]
17. Felson DT, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, et al. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. Arthritis Rheum 2007;56:2986–2992. [PubMed: 17763427]
18. Segal NA, Nevitt MC, Gross KD, Hietpas J, Glass NA, Lewis CE, et al. The Multicenter Osteoarthritis Study (MOST): Opportunities for Rehabilitation Research. Phys Med Rehabil 2013;5:987–994.
19. Felson DT, McAlindon TE, Anderson JJ, Naimark A, Weissman BW, Aliabadi P, et al. Defining radiographic osteoarthritis for the whole knee. Osteoarthr Cartil 1997;5:241–250. [PubMed: 9404469]
20. Wolfe F Fatigue assessments in rheumatoid arthritis: Comparative performance of visual analog scales and longer fatigue questionnaires in 7760 patients. J Rheumatol 2004;31:1896–1902. [PubMed: 15468350]
21. Ericsson A, Mannerkorpi K. Assessment of fatigue in patients with fibromyalgia and chronic widespread pain. Reliability and validity of the Swedish version of the MFI-20. Disabil Rehabil 2007;29:1665–1670. [PubMed: 17852297]
22. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. Psychiatry Res 1989;28(2):193–213. [PubMed: 2748771]
23. White DK, Tudor-Locke C, Zhang Y, Niu J, Felson DT, Gross KD, et al. Prospective change in daily walking over 2 years in older adults with or at risk of knee osteoarthritis: The MOST study. Osteoarthr Cartil 2016;24:246–253. [PubMed: 26318659]
24. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation Study of WOMAC: A Health Status Instrument for Measuring Clinically Important Patient Relevant Outcomes to Antirheumatic Drug Therapy in Patients with Osteoarthritis of the Hip or Knee. J Rheumatol 1988;15(12):1833–1840. [PubMed: 3068365]
25. Kellgren J, Lawrence J. Radiological assessment of osteoarthritis. Ann Rheum Dis 1957;16(4):494. [PubMed: 13498604]
26. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl Psychol Meas 1977;1(3):385–401.
27. Swartzman LC, Gwadry FG, Shapiro AP, Teasell RW. The factor structure of the Coping Strategies Questionnaire. Pain 1994;57(3):311–316. [PubMed: 7936709]
28. Cesari M, Kritchevsky SB, Penninx BWHJ, et al. Prognostic value of usual gait speed in well-functioning older people--results from the Health, Aging and Body Composition Study. J Am Geriatr Soc 2005;53(10):1675–1680. [PubMed: 16181165]
29. White DK, Zhang Y, Niu J, Keysor JJ, Nevitt MC, Lewis CE, et al. Do worsening knee radiographs mean greater chances of severe functional limitation? Arthritis Care Res 2010;62:1433–1439.
30. Stratford PW, Kennedy DM, Woodhouse LJ. Performance Measures Provide Assessments of Pain and Function in People With Advanced Osteoarthritis of the Hip or Knee. Phys Ther 2006;86(11):1489–1496. [PubMed: 17079748]
31. Khanna D, Pope JE, Khanna PP, Maloney M, Samedi N, Norrie D, et al. The minimally important difference for the fatigue visual analog scale in patients with rheumatoid arthritis followed in an academic clinical practice. J Rheumatol 2008;35:2339–2343. [PubMed: 19004044]
32. Hosmer DW, Lemeshow S. Applied Logistic Regression, New York, NY, John Wiley and Sons 2000.
33. Bowers D Medical Statistics from Scratch: An Introduction for Health Professionals. Med Stat From Scratch, West Sussex, John Wiley & Sons Ltd 2008.
34. Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Prevalence and burden of osteoarthritis: Results from a population survey in Norway. J Rheumatol 2008;35(4):677–684. [PubMed: 18278832]

35. Dell'Isola A, Allan R, Smith SL, Marreiros SSP, Steultjens M, Bierma-Zeinstra S, et al. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. BMC Musculoskelet Disord 2016;17:425. [PubMed: 27733199]
36. White DK, Niu J, Zhang Y. Is symptomatic knee osteoarthritis a risk factor for a trajectory of fast decline in gait speed? Results from a longitudinal cohort study. Arthritis Care Res 2013;65(2):187–194.
37. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. JAMA 2011;305:50–58. [PubMed: 21205966]
38. Avlund K, Sakari-Rantala R, Rantanen T, Pedersen AN, Frändin K, Schroll M. Tiredness and Onset of Walking Limitations in Older Adults. J Am Geriatr Soc 2004;52(11):1963–1965. [PubMed: 15507083]
39. Helbostad JL, Leirfall S, Moe-Nilssen R, Sletvold O. Physical fatigue affects gait characteristics in older persons. Journals Gerontol - Ser A Biol Sci Med Sci 2007;62(9):1010–1015.
40. Hewlett S, Nicklin J, Treharne GJ. Fatigue in musculoskeletal conditions. Arthritis Res UK Top Rev 2008; 6:1.
41. Reeuwijk KG, De Rooij M, Van Dijk GM, Veenhof C, Steultjens MP, Dekker J. Osteoarthritis of the hip or knee: Which coexisting disorders are disabling? Clin Rheumatol 2010;29(7):739–747. [PubMed: 20177725]
42. Caporali R, Cimmino MA, Sarzi-Puttini P, Scarpa R, Parazzini F, Zaninelli A, et al. Comorbid conditions in the AMICA study patients: Effects on the quality of life and drug prescriptions by general practitioners and specialists. Semin Arthritis Rheum 2005;35:31–37. [PubMed: 16084231]
43. Tuominen U, Blom M, Hirvonen J, Seitsalo S, Lehto M, Paavolainen P, et al. The effect of co-morbidities on health-related quality of life in patients placed on the waiting list for total joint replacement. Health Qual Life Outcomes 2007;5:16. [PubMed: 17362498]
44. Van Dijk GM, Veenhof C, Schellevis F, Hulsmans H, Bakker JPJ, Arwert H, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. BMC Musculoskelet Disord 2008;9:95. [PubMed: 18582362]
45. Lee YC, Cui J, Lu B, Frits ML, Iannaccone CK, Shadick NA, et al. Pain persists in DAS28 rheumatoid arthritis remission but not in ACR/EULAR remission: A longitudinal observational study. Arthritis Res Ther 2011;13:R83. [PubMed: 21651807]
46. Treharne GJ, Lyons AC, Hale ED, Goodchild CE, Booth DA, Kitas GD. Predictors of fatigue over 1 year among people with rheumatoid arthritis. Psychol Heal Med 2008;13:494–504.
47. Mancuso CA, Rincon M, Sayles W, Paget SA. Psychosocial variables and fatigue: A longitudinal study comparing individuals with rheumatoid arthritis and healthy controls. J Rheumatol 2006;33:1496–1502. [PubMed: 16783859]
48. Thyberg I, Dahlström Ö, Thyberg M. Factors related to fatigue in women and men with early rheumatoid arthritis: The swedish tira study. J Rehabil Med 2009;41:904–912. [PubMed: 19841842]
49. Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology 2006;45(7):885–889. [PubMed: 16449363]
50. Zullig LL, Bosworth HB, Jeffreys AS, Corsino L, Coffman CJ, Oddone EZ, et al. The association of comorbid conditions with patient-reported outcomes in Veterans with hip and knee osteoarthritis. Clin Rheumatol 2015;34:1435–1441. [PubMed: 24916605]
51. Power JD. The Role of Fatigue in Osteoarthritis and its Potential Overlap with Pain and Depression PhD Thesis. 2016.
52. Kirk KM, Hickie IB, Martin NG. Fatigue as related to anxiety and depression in a community-based sample of twins aged over 50. Soc Psychiatry Psychiatr Epidemiol 1999;34:85–90. [PubMed: 10189814]
53. Louati K, Berenbaum F. Fatigue in chronic inflammation - a link to pain pathways. Arthritis Res Ther 2015;17(1):254. [PubMed: 26435495]
54. Thorpe CT, Riley GP, Birch HL, Clegg PD, Screen HRC. Fascicles and the interfascicular matrix show decreased fatigue life with ageing in energy storing tendons. Acta Biomater 2017;56:58–64. [PubMed: 28323176]

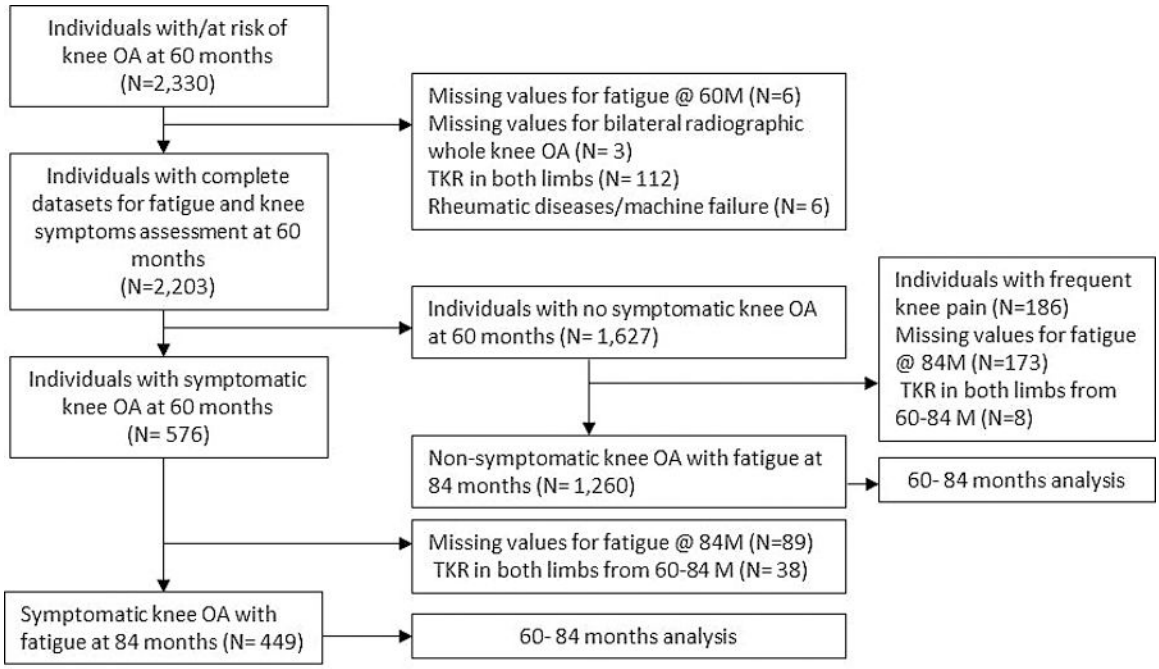

Figure 1.
Flowchart for symptomatic and non-symptomatic knee OA subjects (60-84 months)

Table 1:

Socio-demographic, disease-related and health characteristics of symptomatic and non-symptomatic knee OA participants with fatigue values at both baseline and follow-up

	All (n=1,709)	No symptomatic knee OA (n=1,260)	Symptomatic knee OA (n=449)	*P*-value
	N(%) or mean [SD]	N(%) or mean [SD]	N(%) or mean [SD]	
Age (per year)	66.89[7.70]	67.11[7.64]	66.27[7.85]	0.403
Gender				
Women	999 (59)	714 (57)	285 (64)	0.012*
Race/Ethnicity				
Black and/or others	259 (15)	162 (13)	97 (22)	<0.001*
Living situation lives alone missing	345 (20) 1	233 (19) 1	112 (25)	0.004*
Ability to pay monthly bills difficulty/ unable missing	270 (16) 1	171 (14) 5	99 (22) 1	<0.001*
BMI (kg/m^2) missing	30.66[5.99]	30.11[5.70]	32.25[6.48]	0.001*
Baseline fatigue (0–10 scale)	3.21[2.33]	2.96[2.23]	3.91[2.45]	<0.001*
Follow-up fatigue (0–10 scale)	3.08[2.25]	2.86[2.17]	3.70[2.37]	<0.001*
WOMAC pain (0–20 scale) missing	3.10[3.41] 4	1.96[2.43] 2	6.78[3.63] 2	<0.001*
Sleep quality poor sleep	281 (16)	172 (14)	109 (24)	<0.001*
Depressive symptoms (CES-D) (0–60 scale)	6.51[6.98]	5.87[6.18]	8.31[8.61]	<0.001*
Comorbidities (0–9 scale)	0.46[0.86]	0.43[0.85]	0.54[0.88]	0.013*
Pain catastrophizing ≥1	814 (48)	540(43)	274(61)	<0.001*
KL score ≥2 missing	957 (56) 49	580 (46) 23	396(88) 26	<0.001*
Gait speed (m/s) missing	1.25[0.21] 9	1.28[0.21] 6	1.18[0.22] 3	0.483

Statistical measure included chi-square and independent t-tests as appropriate with

*indicating $p<0.05$

SD = standard deviation; Knee OA = knee osteoarthritis; BMI = body mass index; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index; CES-D = Center for Epidemiologic Studies Depression Scale; KL score = Kellgren Lawrence score; kg/m^2 = kilogram per meter square; m/s = meters/seconds

Table 2:

Unadjusted and adjusted estimates of factors associated with fatigue at follow-up among individuals with symptomatic knee OA-The MOST Study

n=449	Bivariate B [95% CI]	β	*p*-value	Model 1 with † B [95% CI] Adj. R^2 = 40.2%	β	*p*-value	Final Model without‡ B [95% CI] Adj. R^2 = 40.5%	β	*p*-value
Baseline fatigue	**0.582 [0.511, 0.654]**	**0.604**	**<0.001** *	**0.423 [0.326, 0.520]**	**0.440**	**0.000** *	**0.435 [0.348, 0.523]**	**0.453**	**<0.001** *
Age	0.005 [−0.023, 0.033]	0.016	0.735	0.008 [−0.017, 0.034]	0.027	0.534	_____		
Gender									
Men	**Reference**			**Reference**					
Women	**0.740 [0.289, 1.191]**	**0.151**	**<0.001** *	0.008 [−0.392, 0.407]	0.002	0.969	_____		
Race/Ethnicity									
White	**Reference**			**Reference**					
Black and/or others	**0.657 [0.127, 1.187]**	**0.114**	**0.015** *	−0.115 [−0.622, 0.392]	−0.020	0.656	_____		
Living situation									
Lives with significant others	**Reference**			**Reference**					
Lives alone	**0.576 [0.071, 1.081]**	**0.105**	**0.025** *	−0.099 [−0.537, 0.339]	−0.018	0.656	_____		
Ability to pay monthly bills									
No difficulty	**Reference**			**Reference**					
Difficulty	**1.220 [0.702, 1.737]**	**0.214**	**<0.001** *	0.120 [−0.385, 0.625]	0.021	0.641	_____		
BMI (kg/m^2)	0.032 [−0.002, 0.065]	0.087	0.066	−0.016 [−0.047, 0.016]	−0.042	0.325	_____		
Gait speed (m/s)	**−3.370 [−4.334, −2.407]**	**−0.310**	**<0.001** *	**−1.078 [−2.082, −0.074]**	**−0.098**	**0.035** *	**−1.124 [−1.962, −0.285]**	**−0.103**	**0.009** *
Depressive symptoms (CES_D)	**0.138 [0.116, 0.160]**	**0.501**	**<0.001** *	**0.040 [0.011, 0.069]**	**0.145**	**0.008** *	**0.049 [0.024, 0.075]**	**0.177**	**<0.001** *
Pain catastrophizing									
<1	**Reference**			**Reference**					
≥1	**0.728 [0.283, 1.174]**	**0.150**	**0.001** *	−0.195 [−0.579, 0.189]	−0.040	0.318	_____		
WOMAC pain	**0.198 [0.141, 0.254]**	**0.309**	**<0.001** *	0.054 [−0.003, 0.112]	0.083	0.064	_____		
Comorbidity	**0.500 [0.254, 0.747]**	**0.185**	**<0.001** *	**0.256 [0.044, 0.469]**	**0.094**	**0.018** *	**0.242 [0.045, 0.439]**	**0.090**	**0.016** *
Sleep quality									
Good	**Reference**			**Reference**					
Poor	**1.727 [1.240, 2.213]**	**0.313**	**<0.001** *	0.247 [−0.221, 0.716]	0.045	0.300	_____		

n=449	Bivariate B [95% CI]	β	*p*-value	Model 1 with † B [95% CI] Adj. R^2 = 40.2%	β	*p*-value	Final Model without‡ B [95% CI] Adj. R^2 = 40.5%	β	*p*-value
Kellgren-Lawrence (KL) score									
KL <2	**Reference**			**Reference**					
KL ≥ 2	−0.403 [−1.130, 0.324]	−0.053	0.277	−0.238 [−0.824, 0.349]	−0.031	0.426	_____		

B= Unstandardized coefficient; β =Standardized coefficient; 95% CI= confidence interval; Adj R^2= adjusted R square; BMI = body mass index; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index; KL score = Kellgren Lawrence score; kg/m^2 = kilogram per meter square; m/s = meters/seconds; CI= confidence interval.

† = all variables

‡ = without gender, race, abilities to pay monthly bills, living situation, age, Kellgren-Lawrence (KL) score, sleep quality, BMI, pain catastrophizing and WOMAC pain

* indicating p<0.05