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Authors

Fawole, HO
Felson, DT
Frey-Law, LA
et al.

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Is the association between physical activity and fatigue mediated by physical function or depressive symptoms in symptomatic knee osteoarthritis?: The Multicenter Osteoarthritis Study

Henrietta O Fawole^{1,2}, David T Felson³, Laura A Frey-Law⁴, S Reza Jafarzadeh³, Andrea Dell'Isola⁵, Martijn P Steultjens², Michael C Nevitt⁶, Cora E Lewis⁷, Jody L Riskowski², Sebastien FM Chastin^{2,8}

¹Department of Physiotherapy, College of Medical Sciences, University of Benin, Edo State, Nigeria.

²Centre for Living, School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, Scotland, UK.

³School of Medicine, Boston University School of Medicine, Boston, MA, USA.

⁴Department of Physical Therapy and Rehabilitation Science, University of Iowa, Iowa City, IA, USA.

⁵Department of Clinical Sciences Lund, Orthopaedics, Clinical Epidemiology Unit, Faculty of Medicine, Lund University, Lund, Sweden.

⁶Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA.

⁷Department of Epidemiology, School of Public Health, University of Alabama, Birmingham, AL, USA.

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

Abstract

Objectives.—To examine whether physical activity (PA) was associated with fatigue and quantify the extent of potential mediation through depressive symptoms or physical function (PF) on PA and fatigue relationship in symptomatic knee osteoarthritis (KOA).

Method.—This longitudinal study used data from the Multicenter Osteoarthritis Study (n=484) which comprised subjects aged 50 years. Baseline PA was quantified via ankle-worn accelerometer. Outcome was fatigue measurement using a 0–10 rating scale at two years follow-up. Mediators included gait speed as a measure of PF and depressive symptoms at two years

Correspondence to: Henrietta O. Fawole, Department of Physiotherapy, College of Medical Sciences, University of Benin, P.M.B.1154, Edo State, Nigeria. henrietta.fawole@uniben.edu.

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follow-up. Mediation analyses was carried out after adjustment for baseline confounders. Further, stratified analysis by baseline fatigue status [no/low (<4) and high fatigue (4)] was performed.

Results.—A significant direct association was found between PA and fatigue at 2 years (unstandardized coefficient (B)= -0.054; 95% confidence interval [CI] -0.107, -0.002, $p=0.041$). PA and fatigue relationship was not mediated by gait speed (B= -0.006; 95% CI -0.018, 0.001) nor depressive symptoms (B= 0.009; 95% CI 0.009, 0.028). In the subgroup with high baseline fatigue, direct associations were found between PA and fatigue (gait speed model; B= -0.107; 95%CI -0.212, -0.002, $p=0.046$; depressive symptoms model; B= -0.110; 95% CI -0.120, -0.020, $p=0.017$); but in the no/low baseline fatigue group, no significant association was found between PA and fatigue.

Conclusions.—In the symptomatic KOA population, higher baseline PA was directly associated with reduced fatigue two years later especially in those with high baseline fatigue. However, this relationship was not mediated by depressive symptoms or PF.

Keywords

Symptomatic knee osteoarthritis; Physical activity; Fatigue; Depressive symptoms; Gait speed; Mediation analysis

Introduction

Knee osteoarthritis (KOA) is a significant cause of functional loss and physical disability which, in turn, drives excessive medical costs (1). A prevalent and clinically-important symptom among individuals with KOA is fatigue (2,3). Fatigue substantially affects all aspects of daily life in people with KOA (4), exacerbating disability levels and reducing quality of life (5). Aetiology of fatigue remains unclear due to its complexity and multifactorial nature; however, factors such as depression, pain, poor physical function and low physical activity levels have been suggested as fatigue correlates in KOA (6,7).

In the absence of curative treatments for KOA, treatment frequently aims to alleviate symptoms and enhance quality of life (8). The use of strategies such as increasing physical activity for symptom management have been well documented in populations with KOA (9,10). More so, physical activity is relatively low-cost, feasible and readily available (11). Despite the benefits of physical activity as an intervention, evidence has shown that individuals with KOA have reduced physical activity levels compared to their healthy age-matched counterparts (12). Nonetheless, recent studies indicate that even small improvements in physical activity below recommended guidelines (13,14), can produce substantive health improvements in chronic and KOA populations (15,16). Besides, physical activity has been suggested as a non-pharmacological intervention which may help reduce fatigue in the general and chronic disease populations (17,18). Whilst studies have examined real-time and short-term associations between fatigue and physical activity in KOA (6), there are no studies that have examined whether longitudinal association between physical activity and fatigue exists in persons with KOA. Further, it is unclear whether this longitudinal association might be mediated by effects of measurable intermediates in the KOA population.

Our recent work on fatigue determinants in individuals with symptomatic KOA demonstrated that both physical and mental health-related factors were associated with fatigue two years later. Specifically, higher levels of depressive symptoms and poorer physical function, noted as slower gait speed, emerged as potentially modifiable predictors of worse fatigue over two years (7). However, other studies have shown that both depression and physical function are improved by or related to physical activity in the general population (19,20), and to varying degrees in those with KOA (21–23). Therefore, probable paths through which physical activity and fatigue may be indirectly related could be through depressive symptoms or physical function.

Thus, the purposes of this study were to evaluate whether physical activity was a factor associated with later fatigue in persons with symptomatic KOA, including those with high and low levels of fatigue at baseline and to examine whether depressive symptoms or physical function mediated the physical activity-fatigue relationship. Establishing these relationships may help clinicians devise effective targeted treatment for fatigue that may decrease fatigue-associated disability among persons with symptomatic KOA. We hypothesised that physical function or depressive symptoms would mediate the relationship between physical activity and fatigue. Furthermore, we explored several related questions: a. whether there was an unmediated, direct relationship between physical activity and fatigue; b. whether mediation effects depend on levels of initial fatigue, and c. whether the potential mediating roles of depressive symptoms or physical function differ.

Method

Study Design

We used longitudinal data from the Multicenter Osteoarthritis Study (MOST) cohort collected at the 60-month exam (considered baseline for these analyses) and the 84-month follow-up exam (referred to as two-year follow-up). Objective physical activity and fatigue were assessed for the first time at the 60-month visit, thus the reason for using this exam period as baseline for this study.

Original study subjects and data collection

Detailed description of the Multicenter Osteoarthritis Study (MOST) have been published elsewhere (24). Briefly, MOST is a longitudinal cohort study funded by the National Institute of Health (NIH); the study included a community-based sample of men and women aged 50–79 years with or at high risk of knee OA (24). MOST began with the enrolment of 3,026 adults from communities in and surrounding Birmingham, Alabama and Iowa City, Iowa in 2003. Participants' clinical examinations and completed questionnaires were assessed at University of Alabama, Birmingham (UAB) or University of Iowa, Iowa (UIOWA), with data for this study based on telephone interviews and clinic visits at two time points: 60-months (collected between May 2009 and January 2011) and 84-months (between September 2011 and January 2013) exams. MOST study protocol was approved by institutional review boards at the four MOST centers (University of California, San Francisco; Boston University; University of Alabama, Birmingham & University of Iowa)

and all study participants provided written informed consent prior to study participation (25).

Study Sample: Present Study—This study used a subset of the MOST participants (n=484; age ranged from 55–84 years), who met these additional inclusion criteria for this analysis: symptomatic KOA at baseline, data availability for physical activity as measured by accelerometry at baseline, and data on fatigue at baseline and follow-up. We excluded participants if they had bilateral total knee replacement and/or self reported diagnosis of rheumatic conditions (e.g., rheumatoid arthritis [RA]) at baseline and those who received total knee replacement between baseline and follow-up visits. Local institutional ethics approval was obtained from Glasgow Caledonian University’s School of Health and Life Sciences ethics committee prior to performing this secondary analysis (HLS/PSWAHS/16/252).

For this study, we defined symptomatic KOA as having frequent knee pain (i.e., pain, aching or stiffness in either knee on most of the past 30 days) at either clinic or telephone interview and whole knee radiographic evidence of OA in either tibiofemoral or patellofemoral joints. Radiographic whole KOA status was operationally defined as having at least one of the following signs: a Kellgren and Lawrence grade 2 at the tibiofemoral joint or for the patellofemoral joint, an osteophyte 2 or any joint space narrowing 1 plus any osteophyte, sclerosis, or cyst 1 (26).

Measures

Physical activity.—Participants’ physical activity levels were objectively measured over a 9-day period using an ankle-worn StepWatch Activity Monitor at baseline (Orthocare Innovations, LLC, Oklahoma City, OK) (27), with resulting data calculated into average steps/day using software available through StepWatch. The StepWatch activity monitor is a small (70 × 50 × 20 mm; 38g) waterproof, self-contained uniaxial accelerometer-based device which records the number of strides taken every minute without provision of feedback to its user. Steps were calculated by doubling strides. Study participants were fitted with the StepWatch and given written and verbal instructions for affixing the monitor each morning and removing it at bedtime for seven consecutive days (excluding days when device was given and returned). A valid day of accelerometer wear was considered a minimum of 10-hour of monitoring time (28), determined from the first step recorded in the morning to the last step recorded in the evening. The 10-hour requirement represents more than 66% of waking hours and has been used as a threshold in physical activity studies among general adult and KOA populations (28,29). Finally we included only those who wore the StepWatch for at least three valid days since this is considered a minimum standard to establish a reliable physical activity estimate with high test-retest reliability (intraclass correlation coefficient [ICC] = 0.90) (30). We calculated average steps/day by summing up the number of steps taken each valid day of physical activity monitoring divided by the number of valid days.

Depressive symptoms.—Participants’ depressive symptoms at baseline and follow-up were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-

item measurement tool designed to assess depressive symptoms in community populations (31). The CES-D is a valid measure of depressive symptoms in people with arthritis and has moderate to high [ICC = 0.45–0.70] test-retest reliability (32). Scores range from 0–60 with increasing values indicating more depressive symptoms (31). Depressive symptoms at follow-up was used as a mediator; the baseline measure was used as a covariate.

Physical function.—Participants' physical function was measured with a 20-meter walk test at baseline and two-year follow-up. Gait speed was used as a surrogate of physical function and was calculated using the faster time (seconds) of two walking trials over a 20-meter distance (20m/faster time [s])(33). The test was performed on an unobstructed walkway with timing commencing once the first foot crossed the start line and ending after the last foot crossed the finish line. The 20-meter walk test is used in cohort studies of KOA (34) and has high test-retest reliability (ICC = 0.91) for gait speed measurement (35). We used gait speed assessed at follow-up as mediator in this study and baseline gait speed as a covariate.

Fatigue.—Fatigue was defined as 'a feeling of being worn out, pooped, sluggish, run down, tired, or lacking energy'. Participants were asked to mark on a written line their usual fatigue level during the past 7 days, using a 0–10 numeric rating scale (NRS). A zero (0) would mean 'no fatigue' and ten (10) would mean 'fatigue as bad as it can be'. A 0–10 NRS is commonly used in OA research (36,37) and has been shown to provide valid measurement of subjective feelings such as fatigue (38) with high test-retest reliability [ICC = 0.79] (39). Fatigue at the two-year follow-up was considered the study outcome and baseline fatigue was used as a covariate. We defined *a priori* fatigue subgroups using baseline fatigue status cut-off points of no/low fatigue (<4 on 0–10 NRS) and moderate to high fatigue (≥ 4 on 0–10 NRS) based on prior research (37).

Statistical Analyses

Descriptive statistics for continuous variables are represented by means and standard deviations [SD] and for categorical variables as proportions (%). To assess sample bias, characteristics of included and excluded participants were compared using independent sample t-test or Chi-square test of independence as appropriate. To determine the variations in fatigue, depressive symptoms and gait speed from baseline to follow-up, we examined the overall mean change using paired t-tests. However, for the mediation analyses, values of fatigue, depressive symptoms and gait speed at follow-up were used. To examine the extent to which either depressive symptoms or physical function at follow-up mediated or did not mediate the relationship between physical activity and fatigue (Fig. 1), we conducted mediation analyses and controlled for baseline fatigue, mediators, age, sex (male or female), body mass index (kg/m²) and study sites (40). We used the modern mediation analysis methodology that is based on counterfactual framework described by Lange et al. (40) rather than the traditional Baron and Kenny approach (41). Subsequently, we used a bootstrapping method (with n=5000 bootstrap resamples) to calculate the bias corrected confidence intervals around the mediated (indirect) and direct effects using PROCESS in SPSS 23 (42). We used continuous values for baseline physical activity, follow-up fatigue, gait speed and depressive symptoms throughout the mediation analyses, adjusting

for baseline fatigue, depressive symptoms and gait speed as covariates. We repeated these calculations in subgroup analyses defined (i.e., stratified) by baseline fatigue status as a secondary hypothesis.

Results

Sample Characteristics

From the 2330 individuals available at baseline, 591 participants had symptomatic KOA and physical activity data (Fig. 2). Of these individuals, 107 were excluded due to total knee replacement or missing data for fatigue at two-year follow-up (Fig. 2), yielding 484 participants for this analysis. Participants who were excluded were more likely to be older and white, with poorer health indicators (e.g., lower average steps/day and slower gait speed) in comparison to those included in the analysis (Table 1). The mean age of included study participants was 67.28 ± 7.91 years, 60% were women and majority were white (86%; Table 1). Average baseline physical activity of participants was $8,044 \pm 3,034$ steps/day; baseline and follow-up fatigue scores were 3.54 ± 2.36 and 3.43 ± 2.29 respectively which did not differ significantly ($t=1.16$; $p=0.243$). At the two-year follow-up, no change from baseline was noted for depressive symptoms (7.04 ± 7.59 to 7.00 ± 7.36 ; $t=0.14$; $p=0.889$). Gait speed declined significantly from baseline to two-year follow-up (1.20 ± 0.21 to 1.18 ± 0.23 ; $t=2.85$; $p=0.005$), but the effect size was quite small (Cohen's $d = 0.09$) [table not shown].

Mediation analysis

We found a statistically significant direct negative relationship between baseline physical activity and fatigue two-years later (Unstandardised coefficient (B) = -0.054 ; 95% confidence interval [CI]: -0.107 ; -0.002 , $p=0.041$). However, this physical activity-fatigue relationship was not significantly mediated by gait speed (mediating effect, B= -0.006 ; 95% CI: -0.018 ; 0.001) or depressive symptoms at follow-up (mediating effect, B= 0.009 ; 95% CI: -0.009 ; 0.028). Baseline physical activity had no association with either gait speed or depressive symptoms at two-year follow-up (Table 2, path a). There was a significant negative association between gait speed and fatigue at follow-up (Table 2, path b), where faster gait speed was associated with less fatigue. Further, a positive association between depressive symptoms at follow-up and fatigue at follow-up was observed (Table 2, path b), where higher levels of depressive symptoms were associated with greater fatigue.

Subgroup mediation analysis by baseline fatigue

When stratifying by fatigue sub-groups, only those with moderate to high fatigue at baseline demonstrated a significant direct relationship between baseline physical activity and fatigue 2 years later (B = -0.107 ; 95% CI: -0.212 ; -0.002 , $p=0.046$), where higher physical activity was related to reduced fatigue. Again, gait speed (mediating effect, B= -0.003 ; 95% CI: -0.025 ; 0.011) and depressive symptoms (mediating effect, B= 0.030 ; 95% CI: -0.007 ; 0.073) at follow-up had no significant mediating effect on the baseline physical activity-fatigue relationship. Baseline physical activity was not related to gait speed at follow-up (path a) and similarly no relationship between gait speed and fatigue at follow-up (path b) was identified in those with pre-existing high fatigue. Baseline physical activity showed

no relationship with depressive symptoms at follow-up (path a), but a significant positive association existed between depressive symptoms and fatigue at follow-up (path b), where at follow-up, higher level of depressive symptoms was associated with higher fatigue.

Conversely, in those with little to no fatigue at baseline, baseline physical activity did not relate to fatigue at the two-year follow-up ($B = -0.022$; 95% CI: -0.097 ; 0.053 , $p = 0.565$). However, the relationship between baseline physical activity–fatigue at follow-up was partially mediated by gait speed (mediating effect, $B = -0.013$; 95% CI: -0.033 ; -0.000) in this group. Higher levels of baseline physical activity was associated with faster gait speed at follow-up (path a) and likewise faster gait speed at follow-up was also associated with reduced fatigue at follow-up (path b). Depressive symptoms did not mediate the relationship between baseline physical activity and fatigue two years later (mediating effect, $B = -0.010$; 95% CI: -0.031 ; 0.010). Further, baseline physical activity was not related to depressive symptoms at two years (path a); however, higher levels of depressive symptoms at follow-up were associated with greater fatigue at follow-up (path b).

Discussion

Our results suggested that higher levels of physical activity are related to lower levels of later fatigue especially in persons with high levels of fatigue at baseline. Neither depressive symptoms nor physical function, as measured by gait speed, mediated the relationship between baseline physical activity and fatigue after two years in the overall symptomatic KOA population, contrary to our initial hypotheses. Surprisingly, subgroup analysis revealed that physical function partially mediated the relationship between physical activity and fatigue only in those with little to no fatigue at baseline, while physical activity was directly related to fatigue two-years later in those with moderate to high pre-existing fatigue. These findings suggest that physical function may be more important than depressive symptoms in the causal links between physical activity and subsequent fatigue in those with little to no pre-existing fatigue symptoms. Whereas, in individuals with high baseline fatigue, baseline physical activity levels predict the development of fatigue over time. That is, in those with moderate or greater fatigue, higher levels of physical activity is associated with improved fatigue, whereas lower levels of physical activity is associated with worsening fatigue, even two years later. These findings may indicate that different approaches may be required when treating fatigue in the symptomatic KOA population, depending on initial fatigue complaints.

Independently, depressive symptoms did not mediate physical activity and fatigue relations in our study nor was there an association between baseline physical activity and depressive symptoms at follow-up in this population. Prior studies have reported conflicting evidence on the association between physical activity and depressive symptoms in osteoarthritis population (21,43), however few have considered a two-year predictive interval.

Our findings suggested that baseline physical activity levels were inversely associated with fatigue two years later. This result highlights the significance of higher physical activity levels as a potential prevention for fatigue in the symptomatic KOA population, particularly in those with significant pre-existing feelings of fatigue. Our finding of physical

activity's direct influence on fatigue, even in the presence of previous and significant feelings of fatigue, extends the positive role of physical activity as a potential element for influencing beneficial health effects (i.e., sustaining strength, flexibility and balance), that may consequently have a reductive effect on fatigue (44,45). Subsequently, this effect may also influence abilities to engage in more physical activity and eventually result in reduced levels of dependence and disability (46). Thus, we suggest that engagement in physical activity, such as aerobic exercise, including walking may be one approach for reducing subsequent feelings of fatigue in the symptomatic KOA population with pre-existing high fatigue. We caution that this finding should be interpreted within the limit of this study as the effect size was small. Besides, the direct effect of physical activity on fatigue may suggest that other causal paths (i.e., self-efficacy, sleep quality or quadriceps muscle weakness) could play a role in the beneficial association between physical activity and fatigue in this subgroup. Further, more studies are warranted to examine the influence of physical activity types, duration, frequency and intensities on different fatigue dimensions given that physical activity thresholds may be different for populations who have lower-limb disability. Further, different types of physical activity and intensities may have distinct effects on fatigue and its dimensions. In addition, because fatigue is multidimensional and can also be quite unstable across time, traditional longitudinal approach which takes measurement years apart may be insufficient in capturing fatigue variability.

In those with no to low pre-existing fatigue, high levels of baseline physical activity was found to be associated with faster gait speed at follow-up while faster gait speed was associated with less fatigue at follow-up. These findings may provide preliminary evidence on the partial mediating effect of physical function, using the surrogate of gait speed, on physical activity and fatigue relations in individuals with symptomatic KOA with low pre-existing fatigue. Thus, the directionality of the relationship between physical activity and fatigue may inherently be related to some extent to measures of physical functioning in this group.

Study limitations and strengths

There are several important strengths and limitations in the study. Limitations include the use of only two potential mediators; however, physical function and depressive symptoms were included because both emerged as modifiable determinants of fatigue in our recent analysis (7). Similarly the effect sizes observed in this study were relatively small, although longitudinal effects are always smaller and more difficult to detect relative to cross-sectional ones (47). Nonetheless, our results provide a basis for future studies to evaluate the mediating roles of physical function and other factors on physical activity and fatigue relations in populations with KOA. Also, other aspects of physical function such as walking endurance, balance and functional lower extremity strength may also have a role in the physical activity-fatigue relationship. Similarly, unobserved/uncontrolled confounding may be present in these analyses as we could not perfectly determine if potential mediator-outcome confounding, exposure-mediator interaction, or mediator-outcome confounding affected by the exposure introduced bias into our data (48), which maybe unavoidable in observational studies where designs are not randomised (49). Equally, the half-longitudinal approach used in this study may have limited temporal precedence given that the mediator(s)

and outcome were assessed at the same time points. Future research with a randomised controlled experimental design that includes multiple measures (3) of variables over time is needed to confirm potential causal effects. The use of a retrospective fatigue measure (NRS) limits the ability to address different fatigue dimensions (e.g., mental, physical and emotional fatigue) (4). Nevertheless, in general the NRS and many of the multidimensional fatigue instruments yield similar results (50). Also the stratification approach employed in this study may be simplistic, yet it balances the complexity of statistical analysis with the evaluation of a clinically relevant question. Generalisation of our findings may not be applicable to those with severe cases of KOA. The strengths of the study comprise its prospective design, inclusion of large numbers of individuals with symptomatic KOA from a population-based cohort, and the use of validated subjective relevant measurement tools (31,39). Using objective assessments of physical activity (steps/day) and physical function (i.e., gait speed) (27,33) decrease recall bias, yielding greater validity of the data compared to subjective measures. Recognizing these strengths and limitations, this study's results provide an important first step in determining a modifiable factor (physical activity) to limit the effect of fatigue for those with symptomatic KOA and higher fatigue (4).

Conclusion

Physical activity is directly related to reduced fatigue two years later, but this relationship was not mediated through physical function or depressive symptoms in the overall symptomatic KOA population or in those with high pre-existing fatigue. However, in those with low levels of pre-existing fatigue, improvement in physical function may partly contribute to the positive effects of physical activity on fatigue. In contrast, while depression was previously identified as a predictor of subsequent fatigue, it was not a mediator in the physical activity–fatigue relationship in those with symptomatic KOA. In conclusion, general physical activity increment may have the potential to reduce fatigue over time for those with symptomatic KOA and higher perceptions of fatigue.

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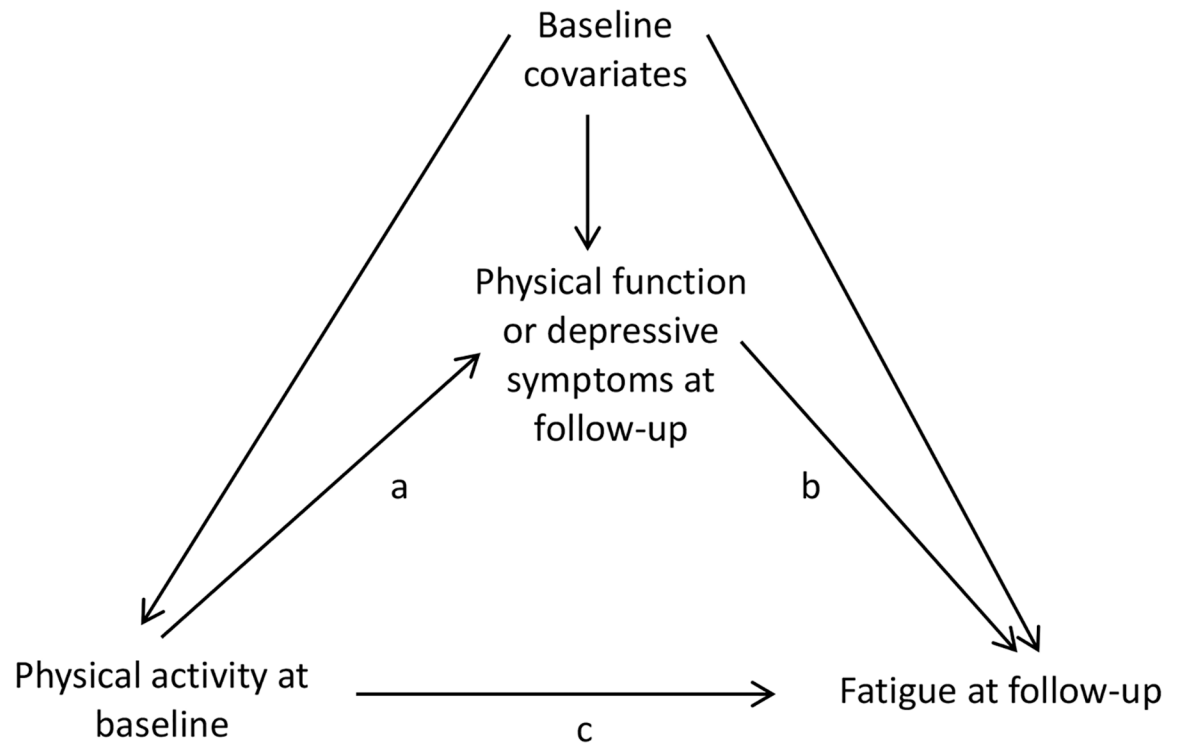
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**Fig 1:**

Physical function or depressive symptoms mediating the association between physical activity and fatigue.

$a+b$ = indirect/mediated effect

c = direct effect.

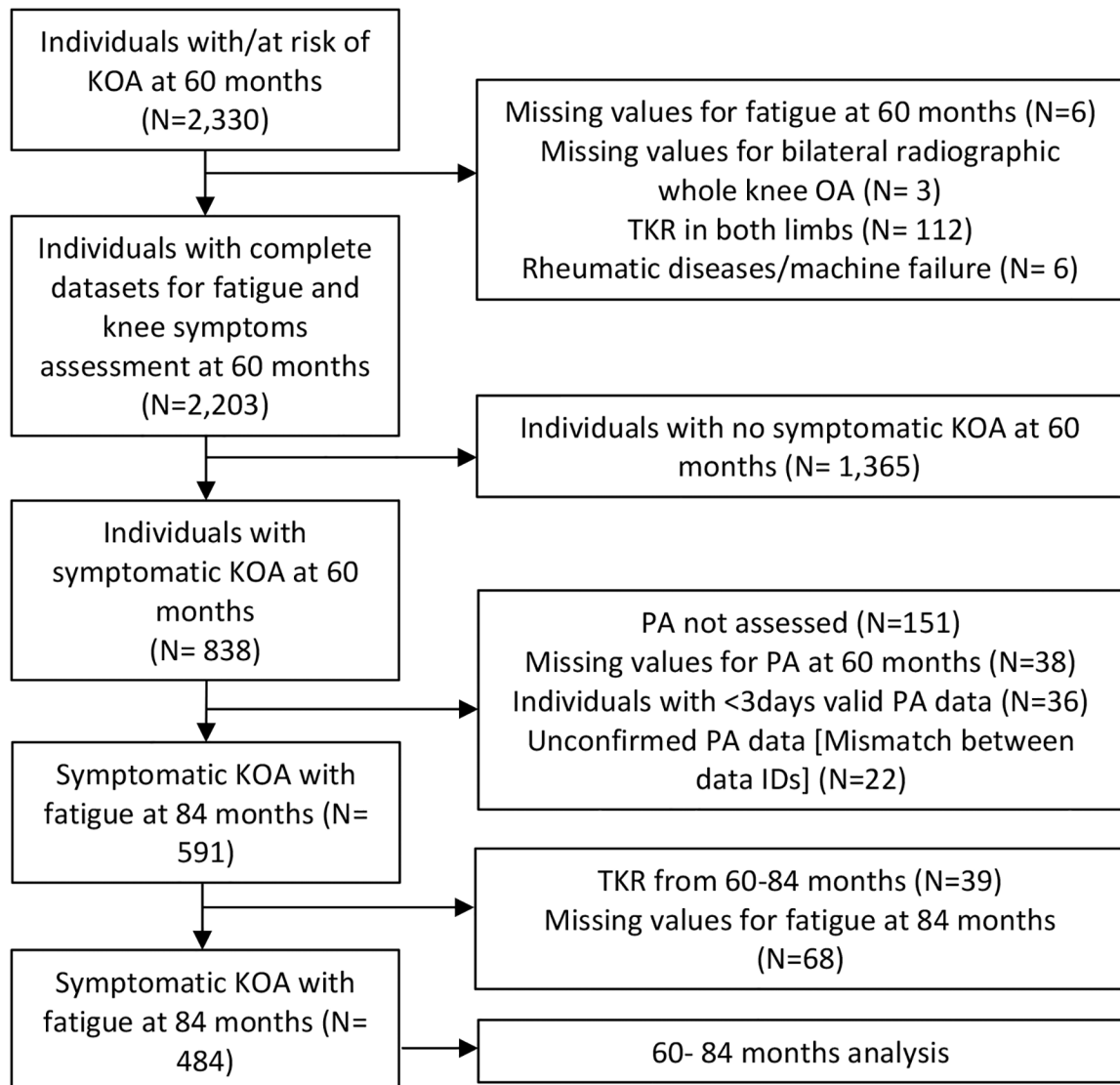


Fig. 2: Prospective analyses flowchart of physical activity (PA) at baseline (60-months) and fatigue at two-year follow-up (84 months). KOA, knee osteoarthritis; OA, osteoarthritis, TKR, total knee replacement; PA, physical activity.

Table 1:

Characteristics of MOST participants

	All n=591	Excluded; [‡] n=107	Included; n=484	p-value
Age, years	67.88±7.97	70.57±7.71	67.28±7.91	<0.001*
Gender				
Men	228 (39)	35 (33)	193 (40)	
Women	363 (61)	72 (67)	291 (60)	0.168
Race/Ethnicity				
White and Caucasians	520 (88)	104 (97)	416 (86)	
Black and others	71 (12)	3 (3)	68 (14)	0.001*
BMI (kg/m ²)	31.77±6.34	31.47±6.58	31.83±6.29	0.594
Study Sites				
UAB	228 (39)	39 (36)	189 (39)	
UIOWA	363 (61)	68 (64)	295 (61)	0.590
Fatigue (0–10)				
Baseline	3.64±2.36	4.13±2.28	3.54±2.36	0.018*
Follow-up	-	-	3.43±2.29	
Missing data at follow-up	68			
Depressive symptoms (0–60)				
Baseline	7.18±7.52	7.83±7.19	7.04±7.59	0.324
Follow-up	7.12±7.49	8.54±8.97	7.00±7.36	0.219
Physical Function (m/s)				
Baseline	1.17±0.22	1.10±0.23	1.20±0.21	<0.001*
Follow-up	1.17±0.23	1.10±0.23	1.18±0.23	0.028*
Missing data at follow-up			1	
Average step counts/day (in 1000)				
Baseline	8.28±3.33	7.56±3.24	8.44±3.34	0.013*

Data are shown as number (percentage) or mean ± sd.

Abbreviations: SD = standard deviation; kg/m² = kilogram per meter square; m/s = meter per second; BMI = body mass index; UAB = University of Alabama; UIOWA = University of Iowa; 60 months = baseline; 84 months = two years follow-up

* indicates $p < 0.05$

NB:

[‡]: 107 participants were excluded due to missing fatigue data at two years follow-up [n=68] and having total knee replacement (TKR) from baseline to two years follow-up [n=39].

Note: Physical function was measured as gait speed while depressive symptoms were measured with centre for epidemiologic studies depression scale (CES-D).

Table 2: Mediation analyses through physical function or depressive symptoms on the association between physical activity and fatigue

Exposure	Total association between physical activity and fatigue (path c)	Mediator variables	Direct association between physical activity and fatigue adjusted for mediators (path c')	Association between physical activity and potential mediators (path a)	Association between potential mediators and fatigue (path b)	Mediation effect (ab)
	B (95% CI), β		B (95% CI), β	B (95% CI), β	B (95% CI), β	β B (95% CI), β
<i>Whole sample [n=484]</i>						
Physical function						
Physical activity	-0.037(-0.094, 0.019), [-0.054]; $p=0.197$	Follow-up physical function	-0.032(-0.088, 0.025), [-0.052]; $p=0.274$	0.004(-0.000, 0.008), [0.058]; $p=0.067$	-1.447(-2.650, -0.245), [-0.143]; $p=0.018^{\#}$	-0.006(-0.018, 0.001), [-0.008]
Depressive symptoms						
Physical activity	-0.046(-0.101, 0.009), [-0.067]; $p=0.102$	Follow-up depressive symptoms	-0.054(-0.107, -0.002), [-0.080]; $p=0.041^{\#}$	0.081(-0.074, 0.236), [0.037]; $p=0.306$	0.108(0.078, 0.138), [0.346]; $p<0.001^{\#}$	0.009(-0.009, 0.028), [0.013]
<i>High baseline fatigue group (4) [n=207]</i>						
Physical function						
Physical activity	-0.110(-0.215, -0.005), [-0.166]; $p=0.041^{\#}$	Follow-up physical function	-0.107(-0.212, -0.002), [-0.162]; $p=0.046^{\#}$	0.002(-0.005, 0.009), [0.029]; $p=0.603$	-1.538(-3.613, 0.537), [-0.149]; $p=0.145$	-0.003(-0.025, 0.011), [-0.004]
Depressive symptoms						
Physical activity	-0.080(-0.175, 0.016), [-0.121]; $p=0.101$	Follow-up depressive symptoms	-0.110(-0.120, -0.020), [-0.167]; $p=0.017^{\#}$	0.247(-0.038, 0.533), [0.095]; $p=0.089$	0.121(0.078, 0.165), [0.480]; $p<0.001^{\#}$	0.030(-0.007, 0.073), [0.046]
<i>No/low baseline fatigue group (<4) [n=277]</i>						
Physical function						
Physical activity	-0.035(-0.109, 0.040), [-0.064]; $p=0.358$	Follow-up physical function	-0.022(-0.097, 0.053), [-0.040]; $p=0.565$	0.007(0.001, 0.012), [0.102]; $p=0.013^{\#}$	-1.962(-3.660, -0.264), [0.234]; $p=0.024^{\#}$	-0.013(-0.033, -0.000), [-0.024]^{\#}
Depressive symptoms						
Physical activity	-0.048(-0.120, 0.024), [-0.089]; $p=0.187$	Follow-up depressive symptoms	-0.038(-0.107, 0.031), [-0.070]; $p=0.277$	-0.079(-0.248, 0.090), [-0.056]; $p=0.357$	0.129(0.080, 0.178), [0.338]; $p<0.001^{\#}$	-0.010(-0.031, 0.010), [-0.019]

Abbreviations: B, unstandardized coefficient; 95% CI, 95% confidence interval; β , standardised coefficient

* Adjusted for age, sex, study sites, BMI, baseline fatigue and physical function; † Adjusted for age, sex, study sites, BMI, baseline fatigue and depressive symptoms; ‡95% bootstrap confidence interval for the mediation effect

** Adjusted for age, sex, study sites, BMI and baseline physical function; †† Adjusted for age, sex, study sites, BMI and baseline depressive symptoms; ‡‡95% bootstrap confidence interval for the mediation effect

*** Adjusted for age, sex, study sites, BMI and baseline physical function; ††† Adjusted for age, sex, study sites, BMI and baseline depressive symptoms; ‡‡‡95% bootstrap confidence interval for the mediation effect

Note: Physical function was measured as gait speed while depressive symptoms were measured with centre for epidemiologic studies depression scale (CES-D).

[#]Indicates p value < 0.05

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