Title

Longitudinal Relationship Between Physical Activity and Joint Space Narrowing: Forty-Eight—Month Follow-Up Data From the Osteoarthritis Initiative

Journal
Arthritis Care & Research, 74(7)

ISSN
2151-464X

Authors
Hu, Bo
Han, DongBai
Nevitt, Michael C
et al.

Publication Date
2022-07-01

DOI
10.1002/acr.24554

Peer reviewed

Arthritis Care & Research
Vol. 0, No. 0, Month 2022, pp 1–9
DOI 10.1002/acr.24554

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Longitudinal Relationship Between Physical Activity and Joint Space Narrowing: Forty-Eight-Month Follow-Up Data From the Osteoarthritis Initiative

Bo Hu,[1] DongBai Han,[2] Michael C. Nevitt,[3] Barton L. Wise,[4] and Neil A. Segal[5]

Objective. To determine whether the amount of physical activity (PA) is a determinant of joint space narrowing (JSN) worsening over 48 months in participants with knee osteoarthritis.

Methods. Data were obtained from the Osteoarthritis Initiative. PA, measured using the Physical Activity Scale for the Elderly (PASE), was defined as the mean value of the annual measurements conducted prior to development of worsening JSN. Worsening JSN was defined as at least a partial grade increase in the Osteoarthritis Research Society International JSN score over 48 months, in comparison with baseline. Restricted cubic spline function was used to group participants based on the linear association between PA and JSN worsening. A pooled logistic regression model was used to evaluate the association between PA and JSN worsening adjusted for confounders.

Results. A total of 2,167 participants were included. In total, 625 participants (28.8%) had JSN worsening over 48 months. Compared with a PASE score of 141–180, PASE scores of 101–140 and >220 were associated with an increased risk of JSN worsening in men, with odds ratios (ORs) of 1.73 (95% confidence interval [95% CI] 1.07–2.81) and 1.83 (95% CI 1.14–2.93), respectively. Similarly, in participants with Kellgren/Lawrence (K/L) grade 2, compared with a PASE score of 141–180, PASE scores of ≤100 and >220 were associated with increased risks of JSN worsening, with an OR of 1.69 (95% CI 1.13–2.54) and 1.64 (95% CI 1.05–2.56), respectively.

Conclusion. Compared to moderate PA, higher or lower amounts of PA are associated with an elevated risk for JSN worsening in men and in participants with K/L grade 2 knees.

INTRODUCTION

The prevalence of knee osteoarthritis (OA) and knee replacements is increasing each year (1). Approximately 40 million Americans are living with OA, and the number will increase by 50% over the next decade (2). Knee OA is a primary cause of disability among the elderly (3). Disability due to OA is associated with an extremely high economic burden and elevated risks of hospitalization, institutionalization, and mortality (4,5).

Physical activity (PA) is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" and is a broad classification of movement that encompasses sport and exercise in addition to other activities (6). The broad components of PA are occupational, transportation-related, domestic, and leisure time (which consists of exercise and recreational or competitive sport). Evidence supports the idea that PA is a modifiable factor with beneficial effects on overall health (6), although either too little or too much PA could negatively influence joint health (7,8).

ClinicalTrials.gov identifier: NCT00080171.

This article does not necessarily reflect the opinions or views of the OAI investigators, the NIH, or the private funding partners.

This article was prepared using an Osteoarthritis Initiative (OAI) public-use data set, and its contents do not necessarily reflect the opinions or views of the OAI Study Investigators, the NIH, or the private funding partners of the OAI. The OAI is a public–private partnership between the NIH (contracts N01-AR-2-2258, N01-AR-2-2259, N01-AR-2-2260, N01-AR-2-2261, and N01-AR-2-2262) and private funding partners (Merck Research Laboratories, Novartis Pharmaceuticals, GlaxoSmithKline, and Pfizer, Inc.) and is conducted by the OAI Study Investigators. Private sector funding for the OAI is managed by the Foundation for the NIH. Dr. Nevitt was a part of the OAI investigative team.

[1]Bo Hu, PhD: Fuwai Hospital, Peking Union Medical College, and Chinese Academy of Medical Sciences, Beijing, China; [2]DongBai Han, MS: Yantai Center for Disease Control and Prevention, Yantai, Shandong Province, China; [3]Michael C. Nevitt, PhD, MPH: University of California, San Francisco; [4]Barton L. Wise, MD, MSc, FACP: University of California, Davis School of Medicine, Sacramento; [5]Neil A. Segal, MD, MS: University of Kansas, Kansas City.

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

Address correspondence to Neil A. Segal, MD, MS, Department of Rehabilitation Medicine, University of Kansas Medical Center, 3901 Rainbow Boulevard–MS 1046, Kansas City, KS 66160. Email: segal-research@kumc.edu.

Submitted for publication June 17, 2020; accepted in revised form January 5, 2021.

SIGNIFICANCE & INNOVATIONS

- Evidence of an association between physical activity amount and the risk for worsening of knee joint space narrowing could guide recommendations for the amount of physical activity that can optimize positive health outcomes.
- The finding that men with the highest or lower amounts of physical activity had a greater risk for worsening of joint space narrowing over 48 months follow-up suggests a need to moderate physical activity in men at elevated risk for knee osteoarthritis worsening.
- The finding that participants with Kellgren/Lawrence grade 2 knees with the highest and lowest amounts of physical activity had elevated risk for worsening of joint space narrowing over 48 months suggests a need to moderate physical activity in these participants at elevated risk for knee osteoarthritis worsening.

Several studies have explored the association of PA and progression of knee OA. However, whether PA may be harmful or protective on progression of knee OA remains unclear, possibly due to the populations and methods used in prior studies. Cooper et al (9) found that leisure activities such as sports, walking, cycling, gardening, and dancing were not associated with progression of knee OA. The negative result may have been related to a smaller number of subjects in whom progression was detected or by the limited definition of assessed PA. In a study of middle-aged men and women, leisure time PA, assessed by a questionnaire adapted from the Minnesota Leisure Time Physical Activity Questionnaire (10), showed no consistent overall relationship with incidence of severe knee OA over 11 years, defined as joint replacement due to OA (11). Therefore, there is uncertainty regarding whether PA is associated with OA structural progression.

Structural progression of knee OA can be defined by quantitative radiographic joint space narrowing (JSN) (12) or by semiquantitative measurement (13). Semiquantitative assessment has been used extensively in epidemiologic studies and has been the primary measure of structural progression accepted by regulatory agencies for clinical trials (14).

In this study, we tested the hypothesis that higher amounts of PA are longitudinally associated with an increased risk for worsening of JSN over 48 months of follow-up. Considering that there are different determinants of risk for knee OA progression in women and men (15–17), we tested this hypothesis separately in men and women.

PATIENTS AND METHODS

Subjects. Data were obtained from the Osteoarthritis Initiative (OAI) database, which is available for public access at https://oai.epi-ucsf.org/datarelease/. The OAI offers high-quality longitudinal data with detailed information on 4,796 participants with, or at elevated risk of developing, symptomatic knee OA (e.g., daily knee symptoms, overweight, history of knee injury/surgery, family history of knee replacement, or repetitive knee flexion [https://oai.epi-ucsf.org/datarelease/docs/StudyDesignProtocol.pdf]). This study of progression of knee OA structural worsening included participants with both preradiographic (Kellgren/Lawrence [K/L] grade 1 [18]) and radiographic knee OA (K/L grade ≥2), who did not have end-stage JSN (<3) at baseline. We excluded healthy reference subjects without knee OA or risk factors for knee OA (n = 122), participants who had knee replacements at baseline (n = 64), participants who had rheumatoid arthritis or some other type of inflammatory arthritis at baseline or follow-up (n = 408), participants with missing main information (n = 546), and participants with K/L grade of 0 at baseline (n = 1,489).

Assessment of PA. General PA was assessed using the Physical Activity Scale for the Elderly (PASE), an instrument that quantifies multiple domains of activity in older adults that has been validated for use in persons with knee OA (19). Questions included on the PASE were designed to evaluate both occupational and nonoccupational walking, recreational activities, exercise, housework, yard work, and caring for others in the past 7 days, adapted from a widely used instrument that has shown associations of these activities with knee OA in multiple studies (19,20). The PASE score correlated with performance on the 6-minute walk test, the isokinetic thigh strength test, and the perceived difficulty with physical functioning test, which supports both convergent and construct validity (19).

Image acquisition and assessment of JSN. Bilateral posteroanterior fixed-flexed knee radiographs were acquired using a SynaFlexer frame to position participants' feet reproducibly (21). In the OAI data sets, a key measure of structural worsening of knee OA is Osteoarthritis Research Society International (OARSI) JSN (13). This individual grading scale uses an atlas to compare radiographs to representative images and assign a grade for the severity of JSN from 0 to 3 in the medial or lateral tibiofemoral compartments (13). Radiographs were centrally read for this measurement as part of the OAI (22).

Version 8 of the OAI data release provided summary radiograph outcome variables for the first visit at which JSN had progressed compared to baseline. These radiographic measurements of JSN worsening were assessed at 12, 24, 36, and 48 months. Worsening was defined by at a least partial grade increase in OARSI JSN score between baseline and follow-up. Bilateral knee radiographs were acquired on each OAI participant at each time point and used for assessing JSN. JSN was treated as a person-based outcome. Participants were defined as demonstrating progression if at least 1 knee demonstrated JSN worsening.

Follow-up assessments. The OAI protocol included measurements of PA, JSN, and other covariates, including knee pain and knee injury every 12 months. The time point at which worsening occurred was defined as the follow-up visit at which JSN worsening was detected. The earlier follow-up time point was selected if both of a participant's knees demonstrated worsening. Participants who had undergone knee replacement by follow-up were included in the definition of JSN worsening.

Assessment of potential confounders. Age, sex (23), race (24), and body mass index (BMI) (25) have been found to be related to knee OA and were therefore entered as potential confounders in multivariable analyses for exploring the relationship between PA and JSN worsening. BMI was defined as body mass divided by the square of height (kg/m^2). Race was collapsed into 2 categories, White and non-White. K/L grades were scored by 2 radiograph readers (26). Knee pain is an important risk factor for knee OA. The pain subscale (range 0–20) of The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used, as described in the statistical methods below, to characterize participants' knee pain. The WOMAC, a survey based on self-report, is the most extensively validated instrument used to assess change in persons with OA and is both recommended for and widely used in studies of participants with OA. The WOMAC pain score was used as a potential confounder in multivariate analyses. In our study, K/L grade and WOMAC pain scores were collected separately for each knee within participants. Thus, K/L grade and pain scores were included for the knee in which JSN worsening occurred. K/L grade and WOMAC pain score of the knee with earlier worsening was selected if both of a participant's knees met the definition for worsening. When there was no difference in the time to either worsening or lack of worsening of a participant's knees, the K/L grade and pain score were selected for the leg with which the participant preferred to kick a ball.

Because of the likelihood that previously injured knees would be at high risk of OA (27), knee injury was also included in analyses as a potential confounder. Knee injury was defined as a knee having been injured badly enough to limit a participant's ability to walk for at least 2 days since their last annual visit for OAI. Similar to knee pain, knee injury was also included for the knee in which JSN progressed.

Statistical analysis. Baseline differences in characteristics between different PASE scores were compared using a chi-square test and analysis of variance. Exact time for JSN worsening could not be identified definitively because JSN was measured and recorded annually as interval censored data in data sets. Since PASE scores and all confounders were measured annually in the OAI, a pooled logistic regression model, validated by the Framingham Heart Study (28), was selected to estimate the risk for knee JSN worsening associated with the PASE score. Every follow-up interval was treated as a mini–follow-up study, and risk factors at the interval start to predict relative events in the same interval (e.g., for the 12–24-month interval, values of confounders collected at 12-month follow-up were used in the logistic model, for the 24–36-month interval, values of confounders collected by 24-month follow-up were used in the logistic model, etc.). In our study, confounders (age, sex, race, BMI, knee pain, and history of knee injury) at relevant time intervals were adjusted in pooled logistic regression models. In addition to sex-stratified analyses, a subgroup analysis was conducted by K/L grade. The strength and direction of the associations were assessed with odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs). Sensitivity analyses were conducted to assess the impact of including versus excluding 24 knees that, at baseline, had a JSN score of 2 and also were graded K/L 4.

Based on an unclear association between the PASE score and JSN worsening, we initially analyzed the PASE score as a continuous variable, fitting a restricted cubic spline (RCS) function (29) with 4 knots (located at the 5th, 35th, 65th, and 95th percentiles) using pooled data sets, to make a proper grouping by finding the participants with the lowest risk for JSN worsening. The median of the PASE score was chosen to be the reference value for all spline plots. The RCS function was used to estimate and list all hazard ratios for JSN worsening for each PASE score by comparing it with the median of the PASE score. Age, sex, race, BMI, knee injury, and WOMAC pain score over the observation period were included as adjustment variables in logistic regression models. An SAS macro (29) was used to build the RCS function. A *P* value of 0.05 or less was considered to indicate statistical significance. All statistical analyses were performed using SAS software, version 9.4.

RESULTS

Of the 4,796 participants, the following were ineligible for inclusion: healthy reference participants (n = 122), participants who had knee replacement at baseline (n = 64), participants who had inflammatory arthritis at baseline (n = 408), participants with missing main information at baseline (n = 546), and participants with K/L grade score of 0 at baseline (n = 1,489). Thus, 2,167 participants were included in statistical analyses. The mean ± SD age was 62.2 ± 9.0 years, 38.4% of participants were male, and 79.0% were White (Table 1). After pooling 4 time intervals (baseline–12-month follow-up, 12–24-month follow-up, 24–36-month follow-up, and 36–48-month follow-up), a total of 7,407 data items were included in the analytic data set (Figure 1). Chronologically at the 4 respective time points, there were 287 cases of JSN worsening in 2,167 participants, 145 cases of JSN worsening in 1,880, 110 cases of JSN worsening in 1,735 participants, and 83 cases of JSN worsening in 1,625 participants (Table 2), providing a total of 625 participants with JSN worsening, 235 men and 390 women. Over 48 months, in participants with baseline K/L grades 1, 2, 3, and 4, respectively,

Table 1. Baseline characteristics of participants*

Characteristic	Overall (n = 2,167)	Men (n = 834)	Women (n = 1,333)
Age, mean ± SD years	62.2 ± 9.0	62.3 ± 9.3	62.2 ± 8.9
White	1,712 (79.0)	711 (85.3)	1,001 (75.1)
BMI, mean ± SD kg/m^2	29.4 ± 4.8	29.2 ± 4.1	29.5 ± 5.2
Knee pain, median (IQR)†	1.0 (0.0–4.0)	1.0 (0.0–4.0)	2.0 (0.0–5.0)
Knee injury	659 (30.4)	309 (37.1)	350 (26.3)
K/L grade			
1	689 (31.8)	267 (32.0)	422 (31.7)
2	965 (44.5)	336 (40.3)	629 (47.2)
3	489 (22.6)	219 (26.3)	270 (20.3)
4	24 (1.1)	12 (1.4)	12 (0.9)

* Values are the number (%) unless indicated otherwise. BMI = body mass index; IQR = interquartile range; K/L = Kellgren/Lawrence grading scale.
† Measured with the Western Ontario and McMaster Universities Osteoarthritis Index scale.

4.7%, 7.9%, 14.0%, and 46.8% demonstrated worsening JSN (Table 3).

In both men and women, no linear (*P* values for linear trend in Table 2) or nonlinear (Figure 2) associations were found between the PASE score and JSN worsening. Based on the results of RCS analyses, the risk for JSN worsening plateaus when PASE scores are between 100 and 200 in the total cohort (test for overall association $P = 0.4721$; test for nonlinear association $P = 0.6813$ with the median PASE reference value of 143), as well as in men (Figure 2A) and in women (Figure 2B). We selected the range of PASE score of 141–180 as the reference category because this was the range associated with the lowest risk (OR range from 1.00 to 1.00) for JSN worsening. The OR ranges in men and women corresponding to PASE score of 141–180 are 1.01–1.01 and 0.96–1.00, respectively. Given the number of participants with PASE scores between 141–180 and the plateaus of the distribution for the risk of JSN worsening on RCS curves, participants were divided into 5 groups by PASE score: ≤100, 101–140, 141–180, 181–220, and >220.

In men, after adjusting for potential confounders, compared with a PASE score of 141–180, a PASE score of >220 was associated with an increased risk of JSN worsening, with an OR of 1.83 (95% CI 1.14–2.93), and a PASE score of 101–140 was associated with an increased risk of JSN worsening, with an OR of 1.73 (95% CI 1.07–2.81). However, in women, compared with a PASE score of 141–180, PASE scores >220 were not associated with an increased risk (OR 0.99 [95% CI 0.68–1.45]) of JSN worsening. Compared with PASE scores of 141–180, we found no association between PASE score groups other than those

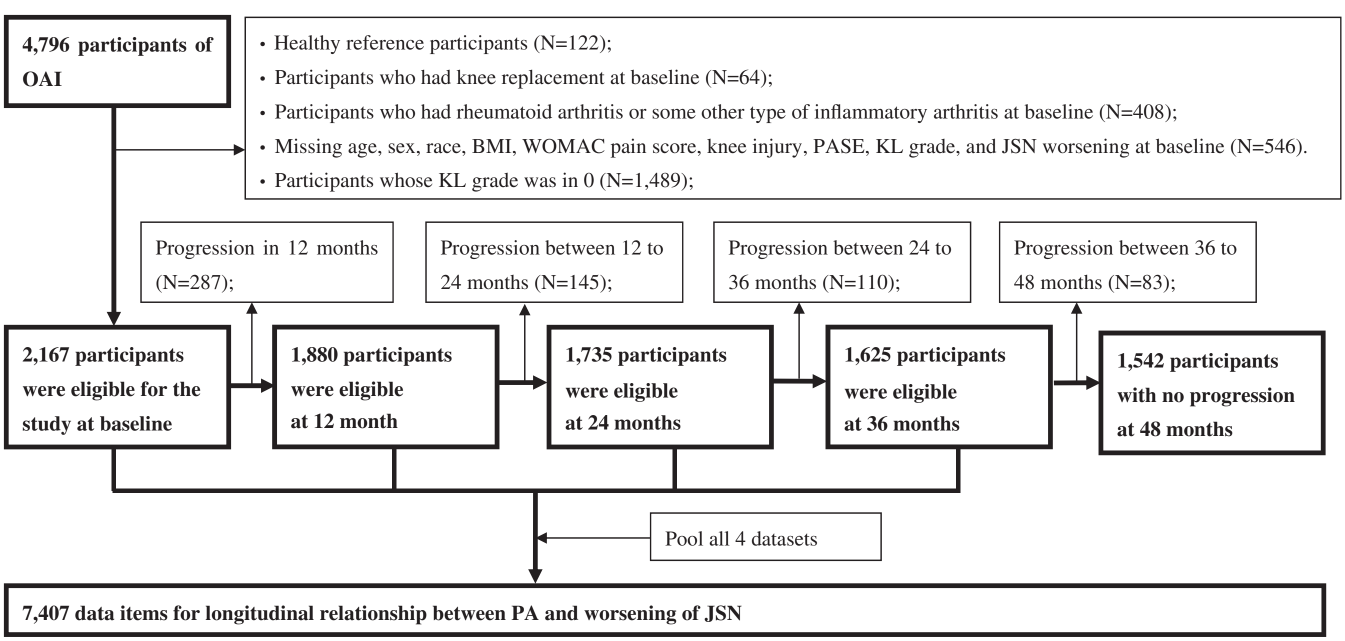

Figure 1. Flow chart of the identification of participants for study inclusion. Missing main information included age, sex, race, body mass index, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), knee injury, Physical Activity Scale for the Elderly (PASE) score, Kellgren/Lawrence (KL) grading scale, or joint space narrowing (JSN) worsening. BMI = body mass index; OAI = Osteoarthritis Initiative.

Table 2. Participants with joint space narrowing progression by annual PASE score*

Time, months	Overall	≤100	101–140	141–180	181–220	>220	*P* for trend
Total							
Baseline–12 (n = 2,167)	287	87 (14.8)	54 (13.2)	52 (12.9)	29 (10.4)	65 (13.4)	0.3143
12–24 (n = 1,880)	145	2 (18.2)	76 (8.5)	14 (4.2)	21 (7.8)	32 (8.5)	0.8146
24–36 (n = 1,735)	110	39 (7.6)	24 (6.5)	20 (6.3)	12 (5.6)	15 (4.7)	0.0830
36–48 (n = 1,625)	83	29 (5.9)	14 (4.1)	11 (3.7)	12 (6.0)	17 (5.8)	0.8693
Men							
Baseline–12 (n = 834)	101	20 (10.8)	18 (12.9)	16 (11.0)	11 (9.7)	36 (14.3)	0.3979
12–24 (n = 733)	55	2 (33.3)	29 (9.5)	0 (0.0)	7 (6.5)	17 (8.7)	0.5368
24–36 (n = 678)	43	14 (8.2)	10 (7.5)	8 (5.8)	4 (5.3)	7 (4.4)	0.1140
36–48 (n = 635)	36	8 (5.1)	5 (4.0)	5 (4.4)	7 (9.0)	11 (6.8)	0.2524
Women							
Baseline–12 (n = 1,333)	186	67 (16.5)	36 (13.3)	36 (14.0)	18 (10.9)	29 (12.3)	0.0844
12–24 (n = 1,147)	90	0 (0.0)	47 (8.0)	14 (6.5)	14 (8.6)	15 (8.3)	0.7864
24–36 (n = 1,057)	67	25 (7.4)	14 (5.9)	12 (6.6)	8 (5.7)	8 (5.1)	0.3421
36–48 (n = 990)	47	21 (6.2)	9 (4.1)	6 (3.4)	5 (4.1)	6 (4.6)	0.3042

* Values are the number (%) unless indicated otherwise. PASE = Physical Activity Scale for the Elderly.

reported above and JSN worsening in either men or women (Table 4). In participants with K/L grade 2, compared with a PASE score of 141–180, PASE scores ≤100 and >220 were associated with increased risks of JSN worsening after adjusting for potential confounders; ORs were 1.69 (95% CI 1.13–2.54) and 1.64 (95% CI 1.05–2.56), respectively. However, no associations were found in participants with K/L grade 1 and 3 (Table 4).

There were 24 knees that were graded K/L 4 but had a JSN score of 2 at baseline and therefore had the potential to demonstrate JSN worsening. Of these, 4 knees worsened in the 0–12-month, 10 knees worsened in 12–24-month, and 10 knees worsened in 24–36-month assessment periods. Sensitivity analyses revealed that ORs were unchanged based on inclusion or exclusion of these knees. An RCS plot for these knees is presented in the supplementary materials (see Supplementary Figures 1–5, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24554).

DISCUSSION

Our results revealed that, in men, both higher amounts of PA (PASE score >220) and lower amounts of PA (PASE scores 101–

Table 3. Participants with joint space narrowing progression by annual PASE score*

Time (months), K/L grade	Overall	≤100	101–140	141–180	181–220	>220
Pooled time points						
1 (n = 2,383)	113 (4.7)	30 (4.6)	24 (5.0)	21 (4.7)	11 (3.8)	27 (5.4)
2 (n = 3,466)	274 (7.9)	96 (9.5)	53 (7.8)	35 (5.6)	30 (6.5)	60 (8.7)
3 (n = 1,496)	209 (14.0)	64 (14.3)	41 (13.0)	37 (14.1)	30 (14.6)	37 (13.9)
4 (n = 62)	29 (46.8)	8 (42.1)	9 (64.3)	4 (28.6)	3 (75.0)	5 (45.5)
Baseline–12 (n = 2,167)						
1 (n = 689)	45 (6.5)	13 (7.6)	8 (5.8)	9 (6.7)	5 (5.8)	10 (6.3)
2 (n = 965)	132 (13.7)	36 (13.7)	30 (16.3)	22 (12.9)	13 (10.3)	31 (13.9)
3 (n = 489)	106 (21.7)	36 (24.7)	16 (18.6)	21 (22.8)	9 (14.1)	24 (23.8)
4 (n = 24)	4 (16.7)	2 (20.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)
12–24 (n = 1,880)						
1 (n = 601)	27 (4.5)	0 (0.0)	16 (5.8)	4 (3.9)	2 (2.3)	5 (2.8)
2 (n = 873)	53 (6.1)	1 (25.0)	29 (7.1)	4 (2.4)	5 (4.2)	14 (8.0)
3 (n = 382)	54 (14.1)	1 (20.0)	23 (12.1)	6 (9.8)	13 (20.6)	11 (17.5)
4 (n = 24)	11 (45.8)	0 (0.0)	8 (57.1)	0 (0.0)	1 (50.0)	2 (40.0)
24–36 (n = 1,721)						
1 (n = 564)	20 (3.5)	3 (1.8)	6 (5.0)	5 (4.4)	1 (1.8)	5 (4.6)
2 (n = 829)	44 (5.3)	22 (8.9)	5 (3.0)	4 (2.9)	7 (6.0)	6 (3.8)
3 (n = 328)	32 (9.8)	11 (11.7)	9 (11.3)	7 (11.1)	4 (9.8)	1 (2.0)
4 (n = 14)	14 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	0 (0.0)	3 (100.0)
36–48 (n = 1,625)						
1 (n = 529)	21 (2.6)	5 (3.2)	3 (2.8)	3 (3.1)	3 (4.8)	7 (6.8)
2 (n = 799)	45 (5.6)	16 (6.6)	10 (5.8)	5 (3.3)	5 (5.1)	9 (6.6)
3 (n = 297)	17 (5.7)	8 (8.4)	1 (1.5)	3 (6.5)	4 (10.8)	1 (1.9)
4 (n = 0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

* Values are the number (%). K/L = Kellgren/Lawrence grading scale; PASE = Physical Activity Scale for the Elderly.

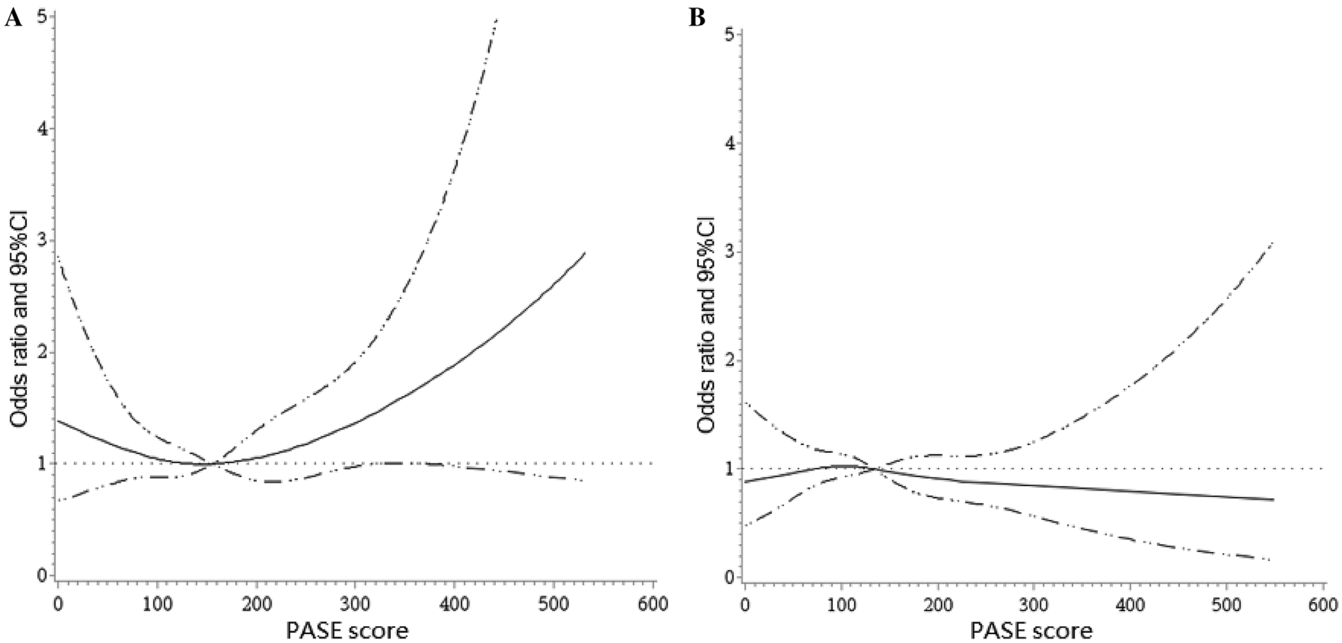

Figure 2. Association between Physical Activity Scale for the Elderly (PASE) score and joint space narrowing progression over 48 months using the restricted cubic spline method (4 nodes), spline plot for adjusted logistic models, adjusted for age, sex, race, body mass index, knee pain, and knee injury. **A**, Men (test for overall association *P* = 0.1103; test for nonlinear association *P* = 0.1507, with median PASE score reference value of 155.5); **B**, Women (test for overall association *P* = 0.4339; test for nonlinear association *P* = 0.4869, with median PASE score reference value of 134). 95% CI = 95% confidence interval. Solid gray line shows adjusted odds ratios of joint space narrowing progression. Broken dash/dot line shows 95% confidence interval. Broken dotted line corresponds to 1.

140) were associated with an increased risk of JSN worsening compared with a PASE score of 141–180 over a 48-month follow-up. In addition, in participants with baseline K/L grade 2, both higher and lower amounts of PA were associated with an elevated risk for JSN worsening (PASE scores ≤100 or >220 compared to 141–180).

While the current study focused on worsening of radiographic JSN in knees with preexisting radiographic OA, these

Table 4. Association between PASE score and JSN worsening over 48 months by sex and K/L grade*

	≤100	101–140	141–180	181–220	>220
JSN total (pooled no. = 7,407)					
Worsening, pooled no. (%)	198 (9.3)	127 (8.5)	97 (7.2)	74 (7.7)	129 (8.8)
Pooled logistic regression†	1.23 (0.95–1.59)	1.20 (0.91–1.59)	1 (Ref.)	1.08 (0.78–1.49)	1.27 (0.95–1.69)
JSN men (pooled no. = 2,880)					
Worsening, pooled no. (%)	57 (8.3)	49 (9.2)	29 (5.6)	29 (7.8)	71 (9.2)
Pooled logistic regression‡	1.40 (0.87–2.25)	1.73 (1.07–2.81)	1 (Ref.)	1.34 (0.77–2.32)	1.83 (1.14–2.93)
JSN women (pooled no. = 4,527)					
Worsening, pooled no. (%)	141 (9.8)	78 (8.2)	68 (8.2)	45 (7.7)	58 (8.2)
Pooled logistic regression‡	1.12 (0.82–1.53)	0.98 (0.70–1.39)	1 (Ref.)	0.95 (0.64–1.42)	0.99 (0.68–1.45)
K/L 1 (pooled no. = 2,383)					
JSN worsening, pooled no. (%)	30 (4.6)	24 (5.0)	21 (4.7)	11 (3.8)	27 (5.4)
Pooled logistic regression†	0.88 (0.49–1.57)	1.03 (0.56–1.88)	1 (Ref.)	0.73 (0.34–1.55)	1.20 (0.65–2.21)
K/L 2 (pooled no. = 3,466)					
JSN worsening, pooled no. (%)	96 (9.5)	53 (7.8)	35 (5.6)	30 (6.5)	60 (8.7)
Pooled logistic regression†	1.69 (1.13–2.54)	1.43 (0.91–2.23)	1 (Ref.)	1.20 (0.72–1.99)	1.64 (1.05–2.56)
K/L 3 (pooled no. = 1,496)					
JSN worsening, pooled no. (%)	64 (14.3)	41 (13.0)	37 (14.1)	30 (14.6)	37 (13.9)
Pooled logistic regression†	1.00 (0.63–1.57)	0.98 (0.60–1.61)	1 (Ref.)	1.06 (0.62–1.80)	0.85 (0.51–1.43)
K/L 4 (pooled no. = 62)					
JSN worsening, pooled no. (%)	8 (42.1)	9 (64.3)	4 (28.6)	3 (75.0)	5 (45.5)
Pooled logistic regression†	1.93 (0.41–9.03)	3.25 (0.62–16.98)	1 (Ref.)	11.13 (0.60–204.92)	0.92 (0.07–12.67)

* Values are the odds ratio (95% confidence interval) unless indicated otherwise. JSN = joint space narrowing; K/L = Kellgren/Lawrence grading scale; PASE = Physical Activity Scale for the Elderly; Ref. = reference.
† Adjusted for age, sex, race, body mass index (BMI), knee pain, and knee injury.
‡ Adjusted for age, race, BMI, knee pain, and knee injury.

findings are consistent with those of a study of knees without symptomatic or radiographic OA (WOMAC pain of 0 and K/L grade <2) (8). In that study of T2 relaxation time worsening in OAI participants without pain or knee OA, PASE scores in the highest 33% and lowest 15% were associated with T2 progression, indicative of more rapid cartilage damage in comparison with those in the middle tertile of PASE scores (8).

Overall, studies of the association between PA and worsening of radiographic OA, defined by JSN, have had inconsistent results. Felson et al (26) combined data from the Multicenter Osteoarthritis Study and OAI and determined the effect of PA on knee OA development in 3,542 knees without radiographic knee OA at baseline. In that incidence study, JSN occurred in 3.41% of knees in the active group (highest quartile of PASE score) versus 4.04% in the other groups (OR 0.9 [95% CI 0.5–1.5]). Øiestad et al (30) investigated the association between objectively measured daily walking and knee structural change, defined either as radiographic worsening or as cartilage loss by magnetic resonance imaging, in 1,179 participants age ≥60 years in the Multicenter Osteoarthritis Study. They found no significant associations between daily walking and radiographic worsening or cartilage loss after adjusting for confounders. More recently, Qin et al investigated the association between moderate-to-vigorous PA detected by uniaxial accelerometry and development of incident knee OA in OAI participants without knee OA at baseline (31). No association was detected between PA and risk for developing incident knee OA or JSN over 48 months of follow-up. With regard to cartilage morphology, Racunica et al (32) reported that vigorous PA appeared to have a beneficial effect on knee articular cartilage in 297 healthy, community-based adults with no history of knee injury or disease.

In contrast, consistent with the results of our current study in knees with preexisting pathology, some studies have found associations between higher amounts of PA and JSN worsening. Doré et al (33) reported that walking ≥10,000 steps/day was associated with a greater risk of an increasing cartilage defect score in those with prevalent bone marrow lesions at baseline (risk ratio 1.36 [95% CI 1.03–1.69]) in 405 community-dwelling adults ages 51–81 years. Doré et al suggested that individuals with knee abnormalities should avoid walking ≥10,000 steps/day.

One explanation for conflicting results in these studies may be thresholds for the association between PA and JSN worsening. We found a plateau section in the RCS curves for the associations of PA and JSN worsening. This finding would suggest that a significantly increased risk for JSN worsening may be found in participants with the higher or lower PA amounts. Thus, the seemingly disparate results may be due to different classification methods for PA used in these studies. In prior studies, PA was classified as the lowest versus highest quartile (26), as <5,859 steps/day and >7,846 steps/day versus 5,859–7,846 steps/day (30), as vigorous PA versus less vigorous PA (32), as sedentary activity and moderate-to-vigorous versus light PA (34), or as <10,000 steps/day versus >10,000 steps/day (33). Stratifying into fewer groups (2–3 in these prior studies) may have reduced the ability to detect differences between groups by pooling heterogeneity within the broader categories, thereby potentially failing to detect associations between PA and radiographic worsening or cartilage loss in those studies. Additionally, the studies of incident JSN in people without radiographic OA seem to have different outcomes than the current study of progression of JSN in people with radiographic OA.

Other reasons for differences in findings could include the use of different measures of PA. Jayabalan et al reported on a substudy of OAI that collected accelerometry data at the 48-month visit, finding that worsening of K/L grade between 48 and 96 months was not associated with either light or moderate-to-vigorous PA (34). The participants in that study differed from our current study of worsening OA severity in that 57% of the knees included in the accelerometry study had K/L grade 0 at baseline. In addition, the number of minutes classified as moderate-to-vigorous PA in that study sample was very low (~2.2% of all PA minutes) (34). The focus on mixed incidence and progression of knee OA, as well as the relative lack of higher-level PA in that study, may contribute to divergent findings with our study.

Accelerometers may reflect PA differently or may reflect different types of PA than self-report and also may reflect the fact that survey instruments may suffer from recall bias. The PASE instrument has been validated for adults age ≥55 years (35) over a range of age and health status as well as for older adults with knee pain (19). On a similar instrument (e.g., IPAQ), unlike accelerometers, respondents tended to underestimate sedentary time and overestimate higher intensities of PA, a bias that was most pronounced in men (36). In our study, assessing the magnitude of recall bias on measured PASE scores is difficult. However, based on the RCS results, recall bias seems unlikely to result in 2 opposite trends on the association between PA and JSN worsening, given that both lower reported PA and higher reported PA were associated with a greater risk for worsening JSN in men.

Through subgroup analyses, we found that the associations between PA and JSN worsening were observed in men, but not in women. Very few published studies have explored sex differences when assessing associations between PA and worsening of knee OA. Doré et al (33) did not find any sex differences when examining PA and tibial bone area change. However, Wise et al found that at every level of functional limitation, the risk ratio for total knee arthroplasty was higher for men than women (37). Reasons for sex differences are complex and multifactorial. Bone and muscle strength, alignment, ligamentous laxity, pregnancy history, and neuromuscular activation could contribute to the sex differences (38). Srikanth et al (16) found that women tended to have more severe knee OA, particularly in those age >55 years (after menopause). The age range of 45–79 for participants in our study is in the perimenopausal period. However, we did not find any clear association between PA and JSN worsening in women.

Finding that higher PA was associated with an increased risk of JSN worsening in men, we feel a possible explanation for this result may be a lower amount of PA among women in the study sample.

We found a PASE score >220 was associated with an increased risk of JSN worsening compared with a PASE score of 141–180, after adjusting for other known risk factors for knee OA progression. The 2018 Physical Activity Guidelines for Americans from the Department of Health and Human Services (DHHS) recommend that all adults accumulate at least 150–300 minutes/week of moderate intensity PA in at least 10-minute bouts (39). Furthermore, similar guidelines were issued by other organizations (39–41). In addition, some researchers have reported that 10,000 steps/day was more effective in increasing the PA amount than the DHHS recommendation in low-active overweight and obese populations (42,43). As the PASE score cannot be directly translated into PA level (low, moderate, and high) or steps/day, we cannot directly compare our findings with these recommendations. However, these recommendations focused on the health risks of low PA, specifically to improve cardiorespiratory and muscular fitness, and to reduce the risk of chronic diseases, depression, and cognitive decline. The results of our study suggest that ~15% of the OAI cohort, who have knee OA, may increase the risk for worsening of JSN over 4 years by following recommendations at the upper range of PA. This finding suggests that there may be a need to examine PA recommendations for people with knee OA.

One limitation of our study was the inclusion of OAI participants with radiographic evidence of knee OA at baseline, so the findings are generalizable to similar people, rather than generalizable to the overall population. Another potential limitation was the investigation method of PA in our study. The PASE score is a comprehensive scoring method involving leisure, household, and occupational PA but does not distinguish between the weight-bearing and nonweight-bearing impact of PA. Most likely, only weight-bearing PA aggravates symptoms such as pain and inflammation (44,45). Thus, evaluating the effects for different types of PA on JSN is difficult in our study. This study included knees with radiographic knee OA (K/L grade ≥1) and potential for JSN to worsen (JSN <3) at baseline. Due to different radiographic reading methods, in the OAI data set, 24 knees that were scored K/L grade 4 at baseline were not rated as JSN score of 3 at baseline. While this study excluded JSN grade 3 knees at baseline due to inability for JSN to worsen, it did not exclude these 24 knees that had the potential to demonstrate worsening (4 knees worsened in the 0–12-month, 10 knees worsened in the 12–24-month, and 10 knees worsened in the 24–36-month assessment periods). Sensitivity analyses were completed to determine the effect of including versus excluding these knees, and ORs were unchanged.

Strengths of this study include the large number of participants and outcomes, and the availability of detailed covariates to adjust for a broad range of potential confounders. In summary, compared to moderate PA, higher and lower PA appears to increase the risk for JSN worsening over a 48-month follow-up period in men and in people with a baseline K/L grade of 2.

AUTHOR CONTRIBUTIONS

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

Study conception and design. Hu, Nevitt, Segal.

Acquisition of data. Nevitt.

Analysis and interpretation of data. Hu, Han, Nevitt, Wise, Segal.

REFERENCES

1. Yu D, Jordan KP, Bedson J, Englund M, Blyth F, Turkiewicz A, et al. Population trends in the incidence and initial management of osteoarthritis: age-period-cohort analysis of the Clinical Practice Research Datalink, 1992-2013. Rheumatology (Oxford) 2017;56:1902–17.
2. Garstang SV, Stitik TP. Osteoarthritis: epidemiology, risk factors, and pathophysiology. Am J Phys Med Rehabil 2006;85 Suppl:S2–11.
3. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2163–96.
4. Cutler DM. Disability and the future of Medicare. N Engl J Med 2003; 349:1084–5.
5. Lubitz J, Cai L, Kramarow E, Lentzner H. Health, life expectancy, and health care spending among the elderly. N Engl J Med 2003;349:1048–55.
6. Khan KM, Thompson AM, Blair SN, Sallis JF, Powell KE, Bull FC, et al. Sport and exercise as contributors to the health of nations. Lancet 2012;380:59–64.
7. Eckstein F, Hudelmaier M, Putz R. The effects of exercise on human articular cartilage. J Anat 2006;208:491–512.
8. Lin W, Alizai H, Joseph GB, Srikhum W, Nevitt MC, Lynch JA, et al. Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2013;21:1558–66.
9. Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000;43:995–1000.
10. Calling S, Hedblad B, Engstrom G, Berglund G, Janzon L. Effects of body fatness and physical activity on cardiovascular risk: risk prediction using the bioelectrical impedance method. Scand J Public Health 2006;34:568–75.
11. Ageberg E, Engstrom G, Gerhardsson de Verdier M, Rollof J, Roos EM, Lohmander LS. Effect of leisure time physical activity on severe knee or hip osteoarthritis leading to total joint replacement: a population-based prospective cohort study. BMC Musculoskelet Disord 2012;13:73.
12. Ornetti P, Brandt K, Hellio-Le Graverand MP, Hochberg M, Hunter DJ, Kloppenburg M, et al. OARSI-OMERACT definition of relevant radiological progression in hip/knee osteoarthritis. Osteoarthritis Cartilage 2009;17:856–63.
13. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15 Suppl A:A1–56.
14. Laslett LL, Pelletier JP, Cicuttini FM, Jones G, Martel-Pelletier J. Measuring disease progression in osteoarthritis. Curr Treatm Opt Rheumatol 2016;2:97–110.

15. Glass N, Segal NA, Sluka KA, Torner JC, Nevitt MC, Felson DT, et al. Examining sex differences in knee pain: the multicenter osteoarthritis study. Osteoarthritis Cartilage 2014;22:1100–6.
16. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis Cartilage 2005;13:769–81.
17. Segal NA, Glass NA, Torner J, Yang M, Felson DT, Sharma L, et al. Quadriceps weakness predicts risk for knee joint space narrowing in women in the MOST cohort. Osteoarthritis Cartilage 2010;18:769–75.
18. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
19. Martin KA, Rejeski WJ, Miller ME, James MK, Ettinger WH Jr, Messier SP. Validation of the PASE in older adults with knee pain and physical disability. Med Sci Sports Exerc 1999;31:627–33.
20. Coggon D, Croft P, Kellingray S, Barrett D, McLaren M, Cooper C. Occupational physical activities and osteoarthritis of the knee. Arthritis Rheum 2000;43:1443–9.
21. Kothari M, Guermazi A, von Ingersleben G, Miaux Y, Sieffert M, Block JE, et al. Fixed-flexion radiography of the knee provides reproducible joint space width measurements in osteoarthritis. Eur Radiol 2004;14:1568–73.
22. The Osteoarthritis Initiative. URL: https://nda.nih.gov/oai/.
23. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. Arthritis Rheum 1997;40:728–33.
24. Allen KD. Racial and ethnic disparities in osteoarthritis phenotypes. Curr Opin Rheumatol 2010;22:528–32.
25. Zheng H, Chen C. Body mass index and risk of knee osteoarthritis: systematic review and meta-analysis of prospective studies. BMJ Open 2015;5:e007568.
26. Felson DT, Niu J, Yang T, Torner J, Lewis CE, Aliabadi P, et al. Physical activity, alignment and knee osteoarthritis: data from MOST and the OAI. Osteoarthritis Cartilage 2013;21:789–95.
27. Wilder FV, Hall BJ, Barrett JP Jr, Lemrow NB. History of acute knee injury and osteoarthritis of the knee: a prospective epidemiological assessment: the Clearwater Osteoarthritis Study. Osteoarthritis Cartilage 2002;10:611–6.
28. D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. Stat Med 1990;9:1501–15.
29. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med 2010;29: 1037–57.
30. Øiestad BE, Quinn E, White D, Roemer F, Guermazi A, Nevitt M, et al. No association between daily walking and knee structural changes in people at risk of or with mild knee osteoarthritis: prospective data from the Multicenter Osteoarthritis Study. J Rheumatol 2015;42:1685–93.
31. Qin J, Barbour KE, Nevitt MC, Helmick CG, Hootman JM, Murphy LB, et al. Objectively measured physical activity and risk of knee osteoarthritis. Med Sci Sports Exerc 2018;50:277–83.
32. Racunica TL, Teichtahl AJ, Wang Y, Wluka AE, English DR, Giles GG, et al. Effect of physical activity on articular knee joint structures in community-based adults. Arthritis Rheum 2007;57:1261–8.
33. Doré DA, Winzenberg TM, Ding C, Otahal P, Pelletier JP, Martel-Pelletier J, et al. The association between objectively measured physical activity and knee structural change using MRI. Ann Rheum Dis 2013;72:1170–5.
34. Jayabalan P, Kocherginsky M, Chang AH, Rouleau GW, Koloms KL, Lee J, et al. Physical activity and worsening of radiographic findings in persons with or at higher risk of knee osteoarthritis. Arthritis Care Res (Hoboken) 2019;71:198–206.
35. Washburn RA, McAuley E, Katula J, Mihalko SL, Boileau RA. The physical activity scale for the elderly (PASE): evidence for validity. J Clin Epidemiol 1999;52:643–51.
36. Dyrstad SM, Hansen BH, Holme IM, Anderssen SA. Comparison of self-reported versus accelerometer-measured physical activity. Med Sci Sports Exerc 2014;46:99–106.
37. Wise BL, Niu J, Felson DT, Hietpas J, Sadosky A, Torner J, et al. Functional impairment is a risk factor for knee replacement in the Multicenter Osteoarthritis Study. Clin Orthop Relat Res 2015;473: 2505–13.
38. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. Best Pract Res Clin Rheumatol 2014;28:5–15.
39. Physical activity guidelines for Americans. 2nd edition. Washington (DC): US Department of Health and Human Services; 2018.
40. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43:1334–59.
41. World Health Organization. Global recommendations on physical activity for health. Geneva: World Health Organization; 2010. URL: https://www.ncbi.nlm.nih.gov/books/NBK305057/.
42. Pal S, Cheng C, Ho S. The effect of two different health messages on physical activity levels and health in sedentary overweight, middle-aged women. BMC Public Health 2011;11:204.
43. Jones DB, Richeson NE, Croteau KA, Farmer BC. Focus groups to explore the perceptions of older adults on a pedometer-based intervention. Res Q Exerc Sport 2009;80:710–7.
44. Baliunas AJ, Hurwitz DE, Ryals AB, Karrar A, Case JP, Block JA, et al. Increased knee joint loads during walking are present in subjects with knee osteoarthritis. Osteoarthritis Cartilage 2002;10:573–9.
45. Lephart SM, Pincivero DM, Rozzi SL. Proprioception of the ankle and knee. Sports Med 1998;25:149–55.