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Joint Association of Moderate-to-vigorous Intensity Physical Activity and Sedentary Behavior With Incident Functional Limitation: Data From the Osteoarthritis Initiative

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ABSTRACT. ***Objective.*** To examine the joint association of moderate-to-vigorous intensity physical activity (MVPA) and sedentary behavior with the risk of developing functional limitation 4 years later in adults with knee osteoarthritis (OA).

Methods. Using 48-month (baseline) accelerometry data from the Osteoarthritis Initiative, we classified participants as Active-Low Sedentary (≥ 1 10-min bout/week of MVPA, lowest tertile for standardized sedentary time), Active-High Sedentary (≥ 1 10-min bout/week of MVPA, top 2 tertiles for standardized sedentary time), Inactive-Low Sedentary (zero 10-min bouts/week of MVPA, lowest tertile for standardized sedentary time), and Inactive-High Sedentary (zero 10-minute bouts/week of MVPA, top 2 tertiles for standardized sedentary time) groups. Functional limitation was defined as > 12 seconds for the 5-repetition sit-to-stand test (5XSST) and < 1.22 m/s gait speed during the 20-meter walk test. To investigate the association of exposure groups with risk of developing functional limitation 4 years later, we calculated adjusted risk ratios (aRR; adjusted for potential confounders).

Results. Of 1091 and 1133 participants without baseline functional limitation, based on the 5XSST and 20-meter walk test, respectively, 15% and 21% developed functional limitation 4 years later. The Inactive-Low Sedentary and Inactive-High Sedentary groups had increased risk of developing functional limitations compared to the Active-Low Sedentary and Active-High Sedentary groups. The Inactive-Low Sedentary group had 72% (aRR 1.72, 95% CI 1.00–2.94) and 52% (aRR 1.52, 95% CI 1.03–2.25) more risk of developing functional limitation based on the 5XSST and 20-meter walk test, respectively, compared to the Active-Low Sedentary group.

Conclusion. Regardless of sedentary category, being inactive (zero 10-min bouts/week in MVPA) may increase the risk of developing functional limitation in adults with knee OA.

Key Indexing Terms: functional limitation, moderate-to-vigorous intensity physical activity, osteoarthritis, physical activity, sedentary behavior

Over 14 million Americans have symptomatic knee osteoarthritis (OA),[1] which is a leading cause of functional limitation such as difficulty getting up from a chair or slow walking.[2,3,4,5,6] Regular participation in physical activity is recommended as a first-line treatment for adults with knee OA.[7,8,9] The intensity of physical activity is particularly relevant for knee OA.[10,11,12] Different intensities of physical activity include moderate-to-vigorous intensity physical activity (MVPA), defined as any activity with

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≥ 3 metabolic equivalents like brisk walking, and sedentary behavior, defined as any activity with ≤ 1.5 metabolic equivalents like sitting on a couch.[13] Both intensities have been linked to health outcomes. Replacing time in sedentary behavior with time in MVPA is important to reduce the risk of developing future functional limitation[11] and pain that interferes with work.[12] At the same time, prolonged time in sedentary behavior increases the risk of disability,[14] decline in physical function,[15] and lower quality of life[16] and physical functioning[17] in adults with knee OA.

At present, the joint association between MVPA and sedentary behavior with functional limitation is unclear. It is therefore important to determine this association because engaging in MVPA and spending prolonged time in sedentary behavior coexist throughout the day. For instance, adults may walk briskly for 10 minutes for exercise in the morning, and then spend the rest of the day sitting for work. We are particularly interested in functional limitation (i.e., the restriction in the performance of physical function, or difficulty in the execution of a task or action).[18] We focus on established categories that represent clinically meaningful restrictions in physical functioning or functional limitation in adults with knee OA.[19,20,21]

The purpose of this study was to investigate the joint association of MVPA and sedentary behavior with incident functional limitation over 4 years in adults with or at risk of knee OA. Additionally, we investigated the stability of this association among adults with radiographic and symptomatic knee OA given the presence of knee OA and/or symptoms that may affect daily walking[22] and physical function.[23] In this study, we used a similar approach employed by prior studies to examine the joint association of MVPA and sedentary behavior with health markers in population-based samples from the United States and England.[24,25] Specifically, in this study, a 4-level mutually exclusive exposure variable was created based on thresholds for time spent in sustained (bouted) MVPA to classify being inactive vs active in adults with arthritis[26,27,28] and a distribution-based approach for time spent in sedentary behavior to classify being more vs less sedentary. Based on the findings of prior studies by Loprinzi, *et al*,[24] and Bakrania, *et al*,[25], we hypothesized that regardless of time spent in sedentary behavior, adults with knee OA who are classified as being inactive will have a higher risk of functional limitation compared to those who are active. This investigation is important for assessing to what extent the different combinations of activity (i.e., MVPA and sedentary behavior) are associated with functional limitation in adults with knee OA.

METHODS

Study participants. We used publicly available deidentified data from the Osteoarthritis Initiative (OAI), a large prospective observational cohort study of 4796 adults with or at risk of knee OA. Participants with risk of knee OA were determined based on BMI (being at least overweight), knee pain, and prior knee injury or knee surgery. A detailed description of the study protocol can be found on the US National Institutes of Health website (https://nda.nih.gov/oai/). Participants were recruited from 4 clinical sites (Maryland, Pennsylvania, Rhode Island, and Ohio). Institutional review board approval was obtained from all OAI sites. Adults with rheumatoid or inflammatory arthritis, bilateral endstage disease defined as severe joint space narrowing or total knee replacements in both knees, and those who used ambulatory aids other than a cane at baseline were excluded from the OAI. For this study, we used data from 48-month and 96-month clinic visits. We considered the 48-month visit as our study baseline because it was the first visit at which device-assessed physical activity data were collected. We considered the 96-month visit as the 4-year follow-up. We excluded participants who did not have valid device-assessed physical activity data, and who had functional limitation at baseline. Supplementary Figures 1 and 2 (available from the authors on request) provide a summary of the number of participants at baseline and reasons for exclusion from our analytical sample.

Ethics. The OAI study had institutional review board (IRB) approval from each recruitment site and the OAI coordinating center (Memorial Hospital/Brown University, the Ohio State University, University of Maryland and Johns Hopkins University joint center, University of Pittsburgh, and University of California, San Francisco; approval #10-00532). All participants provided written informed consent before enrollment in the OAI study. In this study, since publicly available data were used to investigate the research question, IRB exemption was obtained from the site (University of Delaware) where the analysis was conducted (approval #1125357).

Study outcomes.

- *Incident functional limitation.* Our primary outcome was incident functional limitation at the 4-year follow-up. We defined incident functional limitation using 2 performance-based clinical tests as separate study outcomes since they represent difficulty in different activities (i.e., sit-to-stand vs walking over a short distance).

- *5-repetition sit-to-stand test.* Our first definition of functional limitation was taking > 12 seconds to complete the 5XSST, as this threshold is associated with increased risk for falls in older adults[29] and the inability to walk at least 6000 steps/day in adults with knee OA.[20] Each participant was instructed to fold their arms across their chest, stand from a chair, and return to sitting 5 times as quickly as possible. A digital stopwatch was used to measure total time in seconds needed to complete 1 trial of 5XSST. Time was recorded as the average of 2 trials. The 5XSST has a high test-retest reliability in older adults with symptomatic hip or knee OA.[30,31] Participants who were classified as having functional limitation at baseline were removed from the analytic sample. We defined participants as having the outcome if they developed functional limitation at the 4-year follow-up.

- *Gait speed*. Our second definition of functional limitation was gait speed < 1.22 m/s, as this threshold is the minimum gait speed needed to safely cross timed crosswalks in the community[32] and is associated with lower odds of walking at least 6000 steps/day[20] and increased mortality risk[21] in adults with knee OA. Each participant was instructed to walk at their usual speed over a marked, 20-meter course in an unobstructed and dedicated corridor. Gait speed was calculated by dividing the total distance, (i.e., 20 meters) by total time (seconds) needed to complete the test. Measuring gait speed using the 20-meter walk test has high test-retest reliability in adults with knee OA.[33] Participants who were classified as having functional limitation at baseline were removed from the analytic sample. We defined participants as having the outcome if they developed functional limitation at the 4-year follow-up.

Study exposures. Time spent in MVPA and sedentary behavior was collected at baseline using a uniaxial accelerometer (Actigraph GT1M; ActiGraph). The Actigraph GT1M is a valid device for measuring physical activity in free-living conditions.[34,35] Though uniaxial accelerometers cannot classify body positions, they provide valid time spent in overall sedentary behavior that is shown to be associated with health outcomes in population-based studies.[36,37] Subjects were fitted with the accelerometer above the right hip and were instructed to wear it during waking hours for 7 consecutive days. Previously published methods were used to determine valid physical activity data.[38] Briefly, we defined a valid wear day as days with > 10 hours of wear time and included participants with > 4 valid wear days, as this is the minimum time for a reliable estimate of physical activity behavior.[26] We

identified and eliminated nonwear time (i.e., time when the Actigraph was not worn) if the accelerometer had registered > 90 minutes of consecutive activity of < 100 counts/minute.[39] This nonwear criterion was applied in accordance with a previously published study validating such criteria for the Actigraph.[39]

Based on thresholds recommended by the National Cancer Institute, MVPA was defined as an intensity of ≥ 2020 activity counts/minute.[38] This threshold is intended to capture ambulatory activities that reach > 3 metabolic equivalents, including brisk walking. Based on national survey data from the US, adults with arthritis who did not engage in at least 10 continuous minutes of MVPA over a week were considered as being inactive.[28] Therefore, we classified adults who did not accumulate any 10-minute bouts/week in MVPA as being inactive and those with ≥ 1 bout/week in MVPA as being active. The bouts allowed for an interruption of 1 or 2 minutes. Accumulating zero 10-minute bouts/week in MVPA was previously used to define adults with knee OA who were inactive.[26]

Sedentary behavior was defined as < 100 activity counts/minute.[36] We standardized the time in sedentary behavior to a 16-hour wear day since minimal wear time for a valid day was 10 hours, yet the average wear time ranged from 10 hours to 19 hours. This standardization approach has been used by prior studies to account for typical waking periods during the day.[16,40,41] At present, there is no known threshold of time spent in sedentary behavior that is predictive of poor health outcomes. Therefore, a conservative distribution-based approach was used to classify adults who were more vs less sedentary. We classified adults as more sedentary if they resided in the top 2 tertiles of the standardized time spent in sedentary behavior. Adults were classified as less sedentary if they resided in the lowest tertile of the standardized time spent in sedentary behavior.

We formulated categories of activity by combining the MVPA and sedentary behavior classifications to create a 4-level mutually exclusive exposure variable. Active-Low Sedentary was defined as those who were active and less sedentary (≥ 1 10-minute bout/week of MVPA, lowest tertile for standardized sedentary time). Active-High Sedentary was defined as those who were active and more sedentary (≥ 1 10-minute bout/week of MVPA, top 2 tertiles for standardized sedentary time). This group had more time in sedentary behavior, but the similar time in bouted MVPA over a week as Active-Low Sedentary group. Inactive-Low Sedentary was defined as those who were inactive and less sedentary (zero 10-minute bouts/week of MVPA, lowest tertile for standardized sedentary time). This group had a similar time in sedentary behavior, but spent no time in bouted MVPA over a week compared to the Active-Low Sedentary group. Inactive-High Sedentary was defined as those who were inactive and more sedentary (zero 10-minute bouts/week of MVPA, top 2 tertiles for standardized sedentary time). This group had more time in sedentary behavior and spent no time in bouted MVPA over a week compared with Active-Low Sedentary group.

Potential confounders. We considered the following factors as potential confounders based on their known association with physical activity and physical function[23,42]: age, sex (female vs male), race (White vs non-White), education (< college graduate vs ≥ college graduate), BMI (kg/m^2) computed from weight and height assessment, comorbidity using the modified Charlson Comorbidity Index[43] (> 1 comorbidity vs no comorbidity), presence of knee pain, aching or stiffness on most days in past month during the previous year in either right or left knee (yes vs no), and presence of radiographic knee OA defined as Kellgren–Lawrence grade ≥ 2 on radiograph in 1 or both knees (yes vs no). All potential confounders were measured at the study enrollment or baseline (i.e., a 48-month visit by interview by questionnaire and/or direct measurement) as appropriate.

Statistical analysis. We described the study sample using means and SDs for continuous variables and percentages for categorical variables. To examine the joint association of MVPA and sedentary behavior with the risk of incident function limitation at 4-year follow-up, we calculated risk ratios (RRs) and 95% CIs using regression models with a log-link function and robust standard errors adjusted for potential confounders.[44] We repeated the analyses restricting our sample to adults with radiographic knee OA only and symptomatic knee OA only. Symptomatic knee OA was defined as the presence of radiographic knee OA and the presence of pain, aching, or stiffness on most days of a month during the previous year in either knee. The intent of these subgroup analyses was to investigate the generalizability of the study findings across adults with varying degrees of disease severity. All analyses were performed using SAS software, version 9.4 (SAS Institute).

RESULTS

Of 1927 participants with valid accelerometer data, 1091 and 1133 were without baseline functional limitation and completed the 4-year follow-up, defined by 5XSST and gait speed, respectively (Supplementary Figures 1 and 2, available from the authors on request).

Incident functional limitation as defined by 5XSST. Of the 1091 participants free of functional limitation based on 5XSST at baseline, 15% of the sample developed functional limitation at the 4-year follow-up (Table 1). The sample was (mean ± SD) 63.1 ± 8.4 years of age with BMI 28.0 ± 4.6 kg/m^2, and over half were women (51%). The majority were White (88%) and graduated from college (71%).

Of participants classified as Active-Low Sedentary, 10.6% developed functional limitation at the 4-year follow-up. Of participants classified as Inactive-Low Sedentary, 18.9% developed functional limitation at 4-year follow-up and had 72% greater risk (adjusted RR [aRR] 1.72, 95% CI 1.00–2.94) of developing the outcome compared to the Active-Low Sedentary group. Of participants classified as Inactive-High Sedentary, 22.1% developed functional limitation at 4-year follow-up and had a 50% greater risk (aRR 1.50, 95% CI 0.98–2.31) of incident functional limitation by the 4-year follow-up compared to Active-Low Sedentary group. The Active-High Sedentary group had a similar risk of incident functional limitation as the Active-Low Sedentary group (Table 2). We found similar trends in the incidence of the outcome when we restricted the sample to adults with radiographic knee OA only, as well as with symptomatic knee OA (Supplementary Table 1, available from the authors on request). However, the effect estimates did not reach statistical significance.

Incident functional limitation as defined by gait speed. Of the 1133 participants free of functional limitation based on gait speed at baseline, 21% of the sample developed the outcome at the 4-year follow-up (Table 3). The sample was (mean ± SD) 62.9 ± 8.4 years of age, with a BMI of 28.0 ± 4.5 kg/m^2, and over half were women (51%). The majority were White (89%) and had graduated from college (73%).

Of participants classified as Active-Low Sedentary, 14.5% developed functional limitation at the 4-year follow-up. Of participants classified as Inactive-Low Sedentary, 25.8% developed functional limitation at the 4-year follow-up and had a 52% greater risk (aRR 1.52, 95% CI 1.03–2.25) of incident functional limitation at the 4-year follow-up compared to those who were classified as Active-Low Sedentary (Table 2). Of participants classified as Inactive-High Sedentary, 31.7% developed functional limitation at the 4-year follow-up and had a 52% greater risk (aRR 1.52, 95% CI 1.09–2.14) of incident functional limitation by the 4-year follow-up compared

Table 1. Characteristics of study participants for the 5XSST analytic sample at baseline.

	All	Active-Low Sedentary[a]	Active-High Sedentary[b]	Inactive-Low Sedentary[c]	Inactive-High Sedentary[d]
Total sample	1091	293	412	106	280
Demographics					
Age, yrs, mean ± SD (n)	63.1 ± 8.4 (1091)	61.4 ± 7.2 (293)	62.3 ± 8.5 (412)	62.1 ± 8.3 (106)	66.4 ± 8.7 (280)
Women, % (n)	50.6 (552)	50.9 (149)	41.3 (170)	72.6 (77)	55.7 (156)
Race, White, % (n)	87.9 (947)	85.8 (248)	93.4 (383)	83.0 (88)	83.8 (228)
Education, at least college graduate, % (n)	71.1 (774)	74.0 (216)	74.0 (216)	79.8 (327)	53.8 (57)
BMI, kg/m^2, mean ± SD (n)	28.0 ± 4.6 (1091)	27.0 ± 4.2 (293)	27.9 ± 4.3 (412)	28.6 ± 5.4 (106)	29.0 ± 4.8 (280)
Presence of knee pain, aching or stiffness, > half the days/month, past 12 months, Y/N, % (n)					
Right	24.0 (261)	24.7 (72)	24.0 (99)	22.6 (24)	23.9 (66)
Left	23.6 (257)	26.3 (77)	21.8 (90)	19.8 (21)	24.8 (69)
Comorbidity	23.9 (259)	21.9 (64)	21.0 (86)	22.6 (24)	30.6 (85)
Time in bouted MVPA/day, min					
Mean ± SD (n)	10.8 ± 15.5 (1091)	19.2 ± 18.9 (293)	14.8 ± 14.3 (412)	0 ± 0 (106)	0 ± 0 (280)
Time in SED[e]/day, min					
Mean ± SD (n)	627.6 ± 79.4 (1091)	543.8 ± 49.8 (293)	667.8 ± 41.2 (412)	545.3 ± 58.3 (106)	687.1 ± 48.3 (280)
Baseline performance on 5XSST, sec					
Mean ± SD (n)	9.1 ± 1.7 (1091)	9.0 ± 1.7 (293)	9.0 ± 1.7 (412)	9.3 ± 1.6 (106)	9.4 ± 1.7 (280)
4-yr incident function limitation (outcome)					
5XSST > 12 sec, % (n)	14.9 (162)	10.6 (31)	11.9 (49)	18.9 (20)	22.1 (62)

[a] Active-Low Sedentary were people who had ≥ 1 bout of MVPA during the week and did not spend the majority of time in SED. [b] Active-High Sedentary were people who had at least 1 bout of MVPA during the week but spent the majority of time in SED. [c] Inactive-Low Sedentary were people who did not have any bouts of MVPA during the week but did not spend the majority of time in SED. [d] Inactive-High Sedentary were people who did not have any bouts of MVPA during the week and spent the majority of time in SED. [e] Time in SED was standardized to average wear time over 16 hours. 5XSST: 5-repetition sit-to-stand test; MVPA: moderate-to-vigorous intensity physical activity; SED: sedentary behavior.

Table 2. Joint association of MVPA and sedentary behavior with incident functional limitation at the 4-year follow-up as measured by the 5XSST and gait speed test among all the study participants.

	Baseline Mean ± SD	Incident Function Limitation/Total	%	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[a]
5XSST, > 12 sec, n = 1091					
Active-Low Sedentary[b]	9.0 ± 1.7	31/293	10.6	1.00 (Ref)	1.00 (Ref)
Active-High Sedentary[c]	9.0 ± 1.7	49/412	11.9	1.13 (0.74–1.72)	1.08 (0.70–1.67)
Inactive-Low Sedentary[d]	9.3 ± 1.6	20/106	18.9	**1.79 (1.07–2.99)**	**1.72 (1.00–2.94)**
Inactive-High Sedentary[e]	9.4 ± 1.7	62/280	22.1	**2.10 (1.41–3.12)**	1.50 (0.98–2.31)
Gait speed, < 1.22 m/sec, n = 1133					
Active-Low Sedentary[b]	1.46 ± 0.15	45/311	14.5	1.00 (Ref)	1.00 (Ref)
Active-High Sedentary[c]	1.46 ± 0.16	75/434	17.3	1.20 (0.86–1.68)	1.25 (0.88–1.77)
Inactive-Low Sedentary[d]	1.41 ± 0.14	31/120	25.8	**1.79 (1.19–2.68)**	**1.52 (1.03–2.25)**
Inactive-High Sedentary[e]	1.40 ± 0.14	85/268	31.7	**2.20 (1.59–3.03)**	**1.52 (1.09–2.14)**

Values in bold are statistically significant. [a] Adjusted for baseline age, education, race, sex, BMI, the presence of > 1 comorbidities on Charlson Comorbidity Index, radiographic knee osteoarthritis, and pain, aching, or stiffness on most days in a past month during the previous year in either right or left knee. [b] Active-Low Sedentary were people who had ≥ 1 bout of MVPA during the week and did not spend the majority of time in sedentary behavior. [c] Active-High Sedentary were people who had at least 1 bout of MVPA during the week but spent the majority of time in sedentary behavior. [d] Inactive-Low Sedentary were people who did not have any bouts of MVPA during the week but did not spend the majority of time in sedentary behavior. [e] Inactive-High Sedentary were people who did not have any bouts of MVPA during the week and spent the majority of time in sedentary behavior. 5XSST: 5-repetition sit-to-stand test; MVPA: moderate-to-vigorous intensity physical activity; RR: risk ratio.

to those were defined as Active-Low Sedentary (Table 2). The Active-High Sedentary group had a similar risk of incident functional limitation as the Active-Low Sedentary group. We found similar trends in the incidence of the outcome when we restricted the sample to adults with radiographic knee OA only, as well as with symptomatic knee OA (Supplementary Table 1, available from the authors on request). However, the effect estimates did not reach statistical significance.

DISCUSSION

We observed that adults with or at high risk of knee OA who were inactive had a greater risk of developing functional limitation

Table 3. Characteristics of study participants for the gait speed analytic sample at baseline.

	All	Active-Low Sedentary[a]	Active-High Sedentary[b]	Inactive-Low Sedentary[c]	Inactive-High Sedentary[d]
Total sample	1133	311	434	120	268
Demographics					
Age, yrs, mean ± SD (n)	62.9 ± 8.4 (1133)	61.5 ± 7.2 (311)	62.5 ± 8.6 (434)	61.8 ± 8.4 (120)	65.9 ± 8.8 (268)
Women, % (n)	50.9 (577)	53.1 (165)	40.6 (176)	73.3 (88)	55.2 (148)
Race, White, % (n)	88.8 (995)	87.9 (269)	92.8 (401)	81.7 (98)	86.6 (227)
Education, at least college graduate, % (n)	72.5 (819)	74.5 (231)	80.8 (349)	52.5 (63)	65.7 (176)
BMI, kg/m^2, mean ± SD (n)	28.0 ± 4.5 (1133)	27.1 ± 4.1 (311)	27.8 ± 4.2 (434)	28.8 ± 5.2 (120)	28.9 ± 4.9 (268)
Presence of knee pain, aching or stiffness, > half the days/month, past 12 months, Y/N, % (n)					
Right	26.9 (303)	24.6 (76)	27.0 (117)	30.0 (36)	27.9 (74)
Left	25.4 (287)	24.8 (77)	22.9 (99)	25.8 (31)	30.0 (80)
Comorbidity	23.4 (263)	21.0 (65)	20.0 (86)	22.7 (27)	32.1 (85)
Time in bouted MVPA/day, min					
Mean ± SD (n)	11.0 ± 15.7 (1133)	18.9 ± 18.8 (311)	15.2 ± 14.9 (434)	0 ± 0 (120)	0 ± 0 (268)
Time in SED[e]/day, min					
Mean ± SD (n)	624.5 ± 80.2 (1133)	543.2 ± 50.0 (311)	668.5 ± 41.7 (434)	541.7 ± 59.3 (120)	684.7 ± 49.4 (268)
Baseline gait speed, m/sec					
Mean ± SD (n)	1.44 ± 0.15 (1133)	1.46 ± 0.15 (311)	1.46 ± 0.16 (434)	1.41 ± 0.14 (120)	1.40 ± 0.14 (268)
4-yr incident function limitation (outcome)					
< 1.22 m/sec, % (n)	20.8 (236)	14.5 (45)	17.3 (75)	25.8 (31)	31.7 (85)

[a] Active-Low Sedentary were people who at least had 1 bout of MVPA during the week and did not spend the majority of time in SED. [b] Active-High Sedentary were people who had at least 1 bout of MVPA during the week but spent the majority of time in SED. [c] Inactive-Low Sedentary were people who did not have any bouts of MVPA during the week but did not spend the majority of time in SED. [d] Inactive-High Sedentary were people who did not have any bouts of MVPA during the week and spent the majority of time in SED. [e] Time in SED was standardized to average wear time over 16 hours. MVPA: moderate-to-vigorous intensity physical activity; SED: sedentary behavior.

compared to those who were minimally active, irrespective of their sedentary category. These findings were consistent for both definitions of incident functional limitation. We found similar effects after restricting the sample to adults with radiographic knee OA and symptomatic knee OA. Our findings suggest that healthcare professionals should encourage adults with knee OA to avoid inactivity in order to minimize the risk of incident functional limitation.

Our findings highlight the importance of MVPA for reducing risk of functional limitation, in terms of limited sit-to-stand ability or slower gait speed, and are consistent with previous literature.[10,11] Studies in the general population have shown that engaging in MVPA results in favorable health measures, such as lower BMI and waist circumference even in those adults who spend prolonged time in sedentary behavior.[24,25] Engaging in MVPA preserves or increases lower extremity muscle strength,[45] and reduces pain interference with work.[12] These benefits likely contribute to reducing the risk of functional limitation and disability.[46,47,48]

Based on this study, engaging in at least 10 minutes of sustained MVPA/exercise once a week may be a reasonable starting point for adults with knee OA who may spend the majority of their time in sedentary behavior. This finding aligns with guideline recommendations that "some activity is better than none" and with studies that found that adverse effects of sedentary behavior can be attenuated by engaging in MVPA.[49] In this study, we used device-assessed MVPA to accurately define inactivity,[26,27,28] which is a separate construct compared to time spent in sedentary behavior. Further, the goal of this study was not to investigate an optimal threshold or to investigate a dose-response relationship between activity and functional limitation. Rather, we were interested in investigating the effects of being inactive among participants with knee OA who were less sedentary as well as the effects of being active among those who were more sedentary.

We did not find our definition of low sedentary behavior to be related to functional limitation in this analysis. Previous studies have found a modest association of sedentary behavior with physical function. For example, more sedentary time was found to be associated with a decline in gait speed and longer time to complete 5 repeated chair stands, adjusting for MVPA using data from the OAI.[15] As well, spending more time in sedentary behavior was associated with lower quality adjusted life-years in adults from the OAI who spent > 11.6 hours/day being sedentary,although this association was not present in those who spent 10.7 hours/day to 11.6 hours/day being sedentary.[16] We find it important to note that these previous studies analytically employed a continuous definition of their study outcomes. This is in contrast to our study, where we were interested in categories that represent clinically meaningful restrictions (i.e., functional limitation). Thus, it is possible that sedentary time may have a relationship with physical function, albeit not as strong as MVPA.

This study has limitations. First, there is a potential for reverse causation between our exposure (MVPA and sedentary behavior) and outcome (functional limitation) given the

observational nature of the study. Further, functional limitation can fluctuate over time. Even though we have removed participants with functional limitation at baseline, we cannot ensure that our study outcome, incident functional limitation, was truly the first instance at the 4-year follow-up. Regardless, we have taken advantage of standardized follow-up timepoints from the OAI that allow for the systematic investigation of the relationship between MVPA and sedentary behavior with functional limitation. Second, the majority of our analytical sample were White and highly educated. Therefore, we caution generalizing the results of this study to more diverse knee OA population, in terms of race and education. Third, we used a single cutpoint to classify whether participants were inactive vs active and more vs less sedentary. Categorizing continuous variables may lead to loss of power and bias. However, we used this approach so we could create 4 meaningful and mutually exclusive groups to enhance clinical interpretation. Last, there is a potential for unmeasured confounding in our analyses because we were not able to account for an exhaustive list of potential confounders. For instance, there is a possibility that participation in MVPA and sedentary behavior may be influenced by psychosocial factors, such as fear of movement and catastrophizing. Future studies are needed to explore the role of psychosocial factors related to the association between different activities and functional limitation.

In conclusion, we found that adults with or at risk of knee OA who were inactive had a greater risk of developing functional limitation compared to those who were active, regardless of their sedentary category. When possible, healthcare professionals should recommend to adults with knee OA that they avoid inactivity by encouraging them to go for a 10-minute continuous brisk walk at least once a week. This recommendation may serve as starting point among adults with knee OA who are highly sedentary.

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