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RESEARCH

Which matters more for preventing knee replacements: reducing overactivity or combating inactivity?

Masashi Kanai[1,2] · Upul Cooray[3,4] · Takahiro Miki[1,5] · Yuta Hagiwara[1] · Masayasu Murakami[6] · Ken Osaka[7] · Takaaki Ikeda[1,6,7]

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Abstract

Background Daily physical activity (PA) has been gaining attention for the management and prevention of knee osteoarthritis (OA).

Aims This study aimed to compare the effects of various hypothetical daily PA regimens on the incidence of knee replacement (KR) surgery using a targeted learning approach.

Methods We analyzed data from the Osteoarthritis Initiative on adults in the US with symptomatic knee OA or at risk. Daily PA was measured by the Physical Activity Scale for the Elderly (PASE) score. Seven hypothetical daily PA treatment regimens were developed based on the baseline PASE scores. The outcome was the incidence of KR surgery over a 96-month follow-up period. The effects of the PA interventions were estimated using a doubly robust targeted minimum loss–based estimator.

Results Maintaining the baseline PASE score resulted in a KR surgery incidence ratio of 4.71% (95% CI: 4.37% to 5.05%). Reducing the PASE scores to 200 only for those with scores > 242 decreased the incidence ratio to 2.98% (95% CI: 2.39% to 3.57%). Increasing the PASE scores by 10% and 20% among those with low baseline scores further reduced the risk of KR surgery, whereas increasing them by 30%–50% diminished the additional benefit.

Discussion Optimizing daily PA levels, particularly by reducing excessive PA to optimal levels, was beneficial for reducing the risk of KR surgery in older adults with or at risk for knee OA.

Conclusion Our results suggest that tailoring daily PA to an optimal level is most beneficial.

Significance and Innovations

- Increasing physical activity by 10% in those who were inactive further reduced the risk.
- Reducing physical activity to optimal levels reduced the risk of knee replacement.
- Optimizing physical activity is beneficial for preventing knee replacement.

Keywords Knee osteoarthritis · machine learning · modified treatment policy · Physical Activity Scale for the Elderly · total knee arthroplasty

✉ Takaaki Ikeda
tikeda@med.id.yamagata-u.ac.jp

1 Insight Lab, PREVENT Inc., Nagoya, Aichi, Japan

2 Institute of Transdisciplinary Sciences for Innovation, Kanazawa University, Ishikawa, Kanazawa, Japan

3 University of Sydney School of Dentistry, Sydney, Australia

4 Charles Perkins Centre, Faculty of Medicine and Health, University of Sydney, Sydney, Australia

5 Graduate School of Rehabilitation Science, Saitama Prefectural University, Koshigaya, Japan

6 Department of Health Policy Science, Graduate School of Medical Science, Yamagata University, 2-2-2 Iidanishi, Yamagata 990-9585, Japan

7 Department of International and Community Oral Health, Tohoku University Graduate School of Dentistry, Sendai, Japan

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Introduction

Osteoarthritis (OA), which primarily affects the knee and hip joints, has been a major cause of pain and disability worldwide [1]. In fact, a study examining the global health burden of knee OA estimated that around 654.1 million individuals (40 years and older) suffered from knee OA in 2020 worldwide [2]. The prevalence of knee OA has increased in recent years [3], corresponding with a rise in the number of patients undergoing total knee arthroplasty (TKA) [4]. Some contributing factors include the aging population and increase in obesity rates [4, 5]. Consequently, the US Evidence-Based Clinical Practice Guideline recommends sustained weight loss to decrease pain and improve function among overweight and obese individuals with knee OA [6]. Simultaneously, the guideline recommends engaging in exercise, a subset of physical activity (PA), to reduce pain and improve physical functioning among patients with OA [6]. Recently, daily PA has been gaining attention for the management and potential prevention of OA [7]. For example, the recently updated The European Alliance of Associations for Rheumatology recommendations for OA management emphasized the importance of incorporating exercise programs into individual PA plans while considering pain and other symptoms, even among patients with advanced knee OA [8].

Several studies have suggested that daily PA is beneficial in preventing and treating knee OA, reducing pain, and improving function [9, 10]. However, whether greater daily PA lowers the risk of knee replacement (KR) surgery has been investigated, with mixed findings. According to the Singapore Chinese Health Study, prolonged daily PA was associated with an elevated risk of undergoing knee replacement [11]. In contrast, Master et al., in the US Osteoarthritis Initiative (OAI) cohort, found that greater daily walking volume and intensity did not increase 5-year KR risk and may be protective [12]. The inconsistency between studies might stem from differences in the duration of the follow-up period or the characteristics of the participants (general older population vs. individuals with knee OA). Furthermore, previous studies measured daily PA only at baseline, omitting the time-varying nature of PA. Generally, omitting time-varying exposure is reported to lead to an underestimation of its effect on the outcome [13]. In fact, PA levels generally decrease with the progression of symptoms, such as pain [14, 15]. Using baseline values as exposure in observational studies is also problematic for estimating causal effects, as measurements from the baseline survey are commonly used to assess eligibility for hypothetical trials [16].

The main purpose of this study was to explore strategies that optimize daily PA tailored to the characteristics of participants with knee OA. Specifically, this study aimed to examine whether increasing daily PA among those who were physically inactive, and reducing daily PA among those who were excessively active, could prevent KR surgery in participants at risk for knee OA and those with knee OA without severe pain symptoms.

Materials and methods

Study design

Data for this study were derived from the OAI, a National Institutes of Health–sponsored multicenter longitudinal cohort study [17]. The OAI enrolled community-dwelling adults in the US aged 45–79 years who are at high-risk for knee OA or are currently suffering from symptomatic knee OA. Baseline measurements were obtained from September 2008 to December 2010, and follow-up data were obtained from surveys conducted 12, 24, and 96 months after the baseline.

Participants

Participants were selected from the publicly accessible OAI database. Among the 4,796 men and women the OAI cohort who were eligible to participate in this study, those with a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score ≥ 5 points ($n = 1{,}497$) and without WOMAC pain scores ($n = 2$) were excluded. The cut-off value was determined based on previous studies that defined none-to-mild pain as a WOMAC pain score ≤ 4 [18, 19]. Consequently, our primary analysis included 4,858 knees from 2,729 participants (Fig. 1). Participants who were lost to follow-up (e.g., died) were not excluded but were treated as censoring events in the analysis.

Exposure and treatment regimens

The exposure of this study was the Physical Activity Scale for the Elderly (PASE) score assessed at 12 and 24 months from the baseline. The PASE is a validated self-reported daily PA measurement comprising occupational, household, and leisure activities during a 1-week period, with higher scores indicating greater PA levels [20]. In this study, we conceptualized as daily PA is a compound treatment consisting of leisure activity, household activity, and work-related activity domains of the PASE [21]. The hypothetical treatment strategy involved participants receiving an individualized PA education program based on their baseline PA levels.

To ensure internal validity, we referred to a previous study using the same OAI data that evaluated knee cartilage

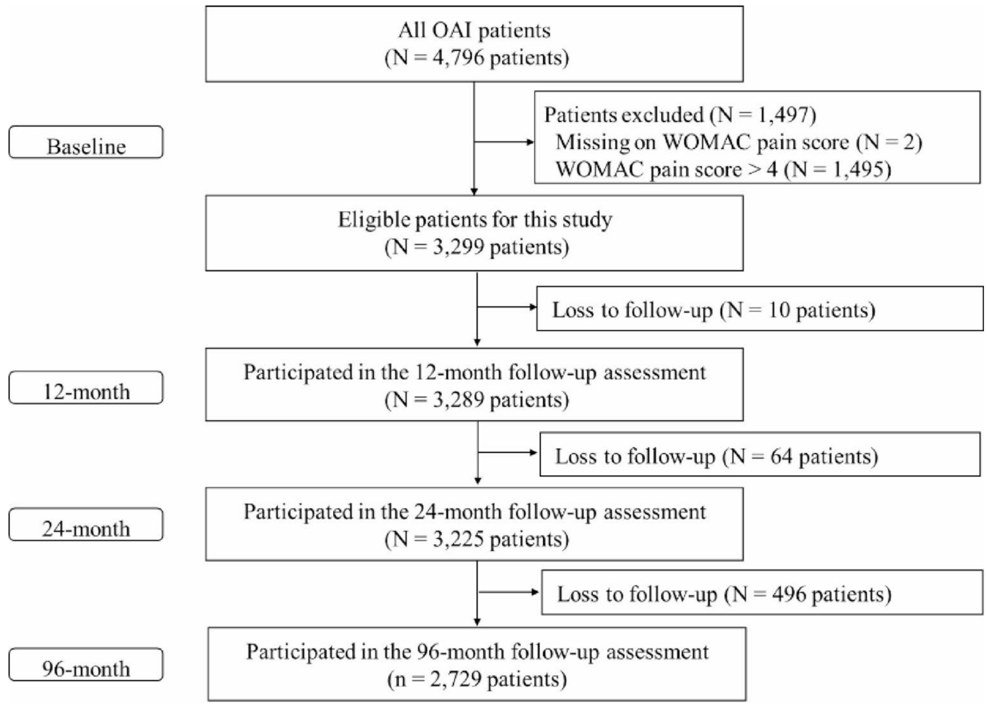

Fig. 1 Flow chart diagram for the study participants

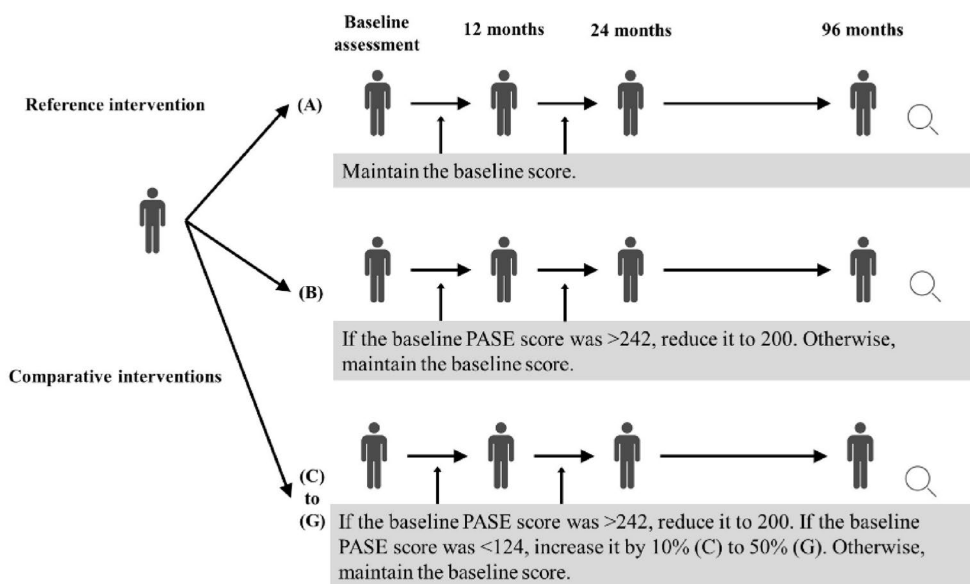

Fig. 2 Hypothetical physical activity intervention strategies

T2 progression over a 4-year period based on the PA levels measured using the PASE score [22]. In the previous study, a U-shaped relationship was observed between PASE score and knee OA progression, with both higher (PASE > 242) and lower PASE scores (PASE < 120) having been associated with an increased risk of knee OA progression compared to middle scores. Additionally, the previous study reported that a PASE score of 200 points was associated with the lowest OA progression [22]. Based on the findings, we defined the following seven treatment regimens (see Fig. 2):

(A) Maintain the baseline PASE score (for the reference scenario);
(B) If the baseline PASE score was >242, reduce it to 200. Otherwise, maintain the baseline;
(C) If the baseline PASE score was >242, reduce it to 200. If the baseline PASE score was <124, increase it by 10%. Otherwise, maintain the baseline;
(D) If the baseline PASE score was >242, reduce it to 200. If the baseline PASE score was <124, increase it by 20%. Otherwise, maintain the baseline;

(E) If the baseline PASE score was > 242, reduce it to 200. If the baseline PASE score was < 124, increase it by 30%. Otherwise, maintain the baseline;
(F) If the baseline PASE score was > 242, reduce it to 200. If the baseline PASE score was < 124, increase it by 40%. Otherwise, maintain the baseline;
(G) If the baseline PASE score was > 242, reduce it to 200. If the baseline PASE score was < 124, increase it by 50%. Otherwise, maintain the baseline.

Covariates

We considered both time-invariant and time-varying variables as covariates. Time-invariant covariates included age (continuous), sex (men or women), race (white, African American, Asian, or others), education level (less than high school graduate, high school graduate, some college, college graduate, some graduate school, or graduate degree), income level (<\$10,000 \$10,000–<\$25,000, \$25,000–<\$50,000, \$50,000–<\$100,000, or ≥\$100,000), marital status (married, widowed, divorced, separated, or never married), alignment (neither, varus, or valgus), Charlson Comorbidity Index (continuous), 400-m walk time (continuous), total distance in 400-m walk test (continuous), and family history of knee/hip replacement (no or yes).

Time-variant covariates included Kellgren/Lawrence (K/L) grade (0–4), the WOMAC pain/stiffness/disability scores (continuous), chair stand time (continuous), 20-m walk test (continuous), Center for Epidemiologic Studies Depression score (continuous), body mass index (BMI; continuous), history of a knee injury with walking difficulty for ≥2 days (no or yes), hip pain, aching, or stiffness in the past 12 months (no or yes), regular user of NSAIDs or COX-2 inhibitor prescription in the past 12 months (no or yes), and regular use of prescription opioids in the past 12 months (no or yes).

Outcome

The primary outcome was the occurrence of KR (either total or partial) as documented in the OAI via medical reports or radiographic adjudication, with the follow-up period extending until 96 months from the baseline assessment.

Statistical analysis

After descriptive analyses, the targeted minimum loss-based estimator, one of the targeted learning approaches, along with a longitudinal modified treatment policy was used to investigate the per-protocol effect of the PA regimens [23]. In this approach, both the outcome model (G-computation model) and exposure model (inverse probability weighting model) are applied to obtain unbiased results. This is because robust estimation of either model provides a consistent estimate of the treatment effect [24]. Furthermore, this methodology addresses time-varying confounding and selection bias arising from loss to follow-up [25]. To enhance the robustness of our exposure and outcome models against potential model misspecification, we used the SuperLearner algorithm [26]. Generalized linear models, multivariate adaptive regression splines [27], random forests [28], and extreme gradient-boosted trees [29] were used as candidate algorithms for the SuperLearner. To reduce overfitting and obtain asymptotically valid estimates, we applied cross-fitting with 5 folds. To handle missing values, we implemented multiple imputations using the chained equations approach with a random forest algorithm [30].

For our analysis, we initially estimated the outcomes for each hypothetical PASE score scenario outlined previously. These regimens were implemented analytically using the observed data to estimate counterfactual outcomes under each intervention strategy. Subsequently, we compared the computed outcomes for each exposure scenario against the reference exposure scenario to derive the risk and incidence ratios, accompanied by their respective 95% CIs. Standard errors were clustered at the participant level. For comparison, we conducted additional analyses in which we modified the treatment regimen for participants with a baseline PASE score > 242. In the main analysis, we set the PASE score for those with scores > 242 to 200. However, given that individuals with knee OA are generally less active than the PA levels recommended by the US guidelines [31], we redefined the regimen for this subgroup by maintaining their original baseline PASE score. We also conducted two types of sensitivity analyses. First, we calculated the E-value to assess the potential impact of unmeasured confounding [32]. Second, we re-estimated the models after excluding variables that could plausibly act as mediators, given that the exposure (daily PA) might influence them within the same survey wave (e.g., higher daily PA could lead to greater pain intensity). Specifically, we excluded the following variables: time-invariant covariates (400-m walk time and total distance in the 400-m walk test) and time-variant covariates (K/L grade, WOMAC pain score, chair stand time, and 20-m walk test). All statistical analyses were performed using R software (version 4.2.2).

Results

Table 1 presents the baseline characteristics of the participants categorized according to KR status. The number and percentage of missing values in our study are presented in Supplementary Table (1) The distributions of PASE scores

Table 1 Baseline characteristics of the study participant according to the knee surgery status during the follow-up period

Baseline characteristics	All	Did not undergo knee surgery	Underwent knee surgery
	$n=6,598$	$n=6,471$	$n=127$
Age, years	61.3 (9.2)	61.3 (9.2)	64.8 (9.0)
Sex, no. (%)			
Men	2874 (43.6%)	2,822 (43.6%)	52 (40.9%)
Women	3724 (56.4%)	3,649 (56.4%)	75 (59.1%)
Race, no. (%)			
Other	94 (1.4%)	91 (1.4%)	3 (2.4%)
White	5,670 (86.0%)	5,555 (85.9%)	115 (90.6%)
African American	762 (11.6%)	753 (11.6%)	9 (7.1%)
Asia	68 (1.0%)	68 (1.1%)	0 (0.0%)
Education level, no (%)			
Less than high school graduate	132 (2.0%)	131 (2.0%)	1 (0.8%)
High school graduate	656 (10.0%)	636 (9.9%)	20 (15.9%)
Some college	1,350 (20.6%)	1,326 (20.6%)	24 (19.0%)
College graduate	1,526 (23.3%)	1,503 (23.4%)	23 (18.3%)
Some graduate school	560 (8.5%)	548 (8.5%)	12 (9.5%)
Graduate degree	2,328 (35.5%)	2,282 (35.5%)	46 (36.5%)
Income level, no. (%)			
<$10K	102 (1.7%)	99 (1.6%)	3 (2.6%)
$10K to <$25K	500 (8.1%)	497 (8.2%)	3 (2.6%)
$25K to <$50K	1,452 (23.6%)	1,420 (23.5%)	32 (27.4%)
$50K to <$100K	2,424 (39.4%)	2,380 (39.4%)	44 (37.6%)
≥$100K	1,676 (27.2%)	1,641 (27.2%)	35 (29.9%)
Marital status, no. (%)			
Married	4,560 (69.6%)	4,466 (69.5%)	94 (74.6%)
Widowed	490 (7.5%)	480 (7.5%)	10 (7.9%)
Divorced	856 (13.1%)	842 (13.1%)	14 (11.1%)
Separated	90 (1.4%)	89 (1.4%)	1 (0.8%)
Never married	556 (8.5%)	549 (8.5%)	7 (5.6%)
Body mass index, kg/m^2	27.9 (4.6)	27.9 (4.6)	29.2 (4.1)
Kellgren/Lawrence scale, no. (%)			
0	2,724 (43.5%)	2,718 (44.3%)	6 (4.8%)
1	1,173 (18.8%)	1,165 (19.0%)	8 (6.4%)
2	1,528 (24.4%)	1,498 (24.4%)	30 (24.0%)
3	705 (11.3%)	660 (10.8%)	45 (36.0%)
4	126 (2.0%)	90 (1.5%)	36 (28.8%)
Alignment, no. (%)			
Neither	1,864 (29.3%)	1,839 (29.5%)	25 (19.7%)
Varus	1,731 (27.2%)	1,688 (27.0%)	43 (33.9%)
Valgus	2,773 (43.5%)	2,714 (43.5%)	59 (46.5%)
Charlson comorbidity index	0.3 (0.8)	0.3 (0.8)	0.3 (0.7)
WOMAC Pain Score	0.9 (1.2)	0.9 (1.2)	2.0 (1.6)
WOMAC Stiffness Score	0.9 (1.2)	0.9 (1.2)	1.6 (1.6)
WOMAC Disability Score	3.6 (5.3)	3.5 (5.2)	8.2 (7.5)
Chair stand time, seconds	10.8 (3.0)	10.7 (3.0)	11.9 (2.9)
20-meter walk test, meter/second	1.4 (0.2)	1.4 (0.2)	1.3 (0.2)
400-meter walk time, seconds	298.8 (48.4)	298.5 (48.3)	313.6 (50.5)
Total walked distance in 400-meter walk test, meters	399.3 (12.3)	399.3 (12.2)	398.4 (17.9)
Center for Epidemiologic Studies Depression Scale score	5.6 (6.0)	5.6 (6.0)	4.5 (3.9)
Physical Activity Scale for the Elderly score	163.7 (81.4)	163.7 (81.2)	161.3 (91.6)
<124	2,260 (34.4%)	2,213 (34.4%)	47 (37.0%)
124–242	3,148 (48.0%)	3,087 (48.0%)	61 (48.0%)
>242	1,154 (17.6%)	1,135 (17.6%)	19 (15.0%)

Table 1 (continued)

Baseline characteristics	All	Did not undergo knee surgery	Underwent knee surgery
	n = 6,598	n = 6,471	n = 127
History of a knee injury with walking difficulty for ≥2 days, no. (%)			
No	4,910 (75.2%)	4,831 (75.5%)	79 (62.2%)
Yes	1,615 (24.8%)	1,567 (24.5%)	48 (37.8%)
Hip pain, aching, or stiffness in past 12 months, no. (%)			
No	4,125 (62.7%)	4,050 (62.8%)	75 (59.1%)
Yes	2,456 (37.3%)	2,404 (37.2%)	52 (40.9%)
Family history of knee replacement, no. (%)			
No	5,590 (85.9%)	5,486 (86.0%)	104 (83.2%)
Yes	916 (14.1%)	895 (14.0%)	21 (16.8%)
Family history of hip replacement, no. (%)			
No	5,886 (90.4%)	5,774 (90.4%)	112 (88.9%)
Yes	628 (9.6%)	614 (9.6%)	14 (11.1%)
Regular user of prescription NSAIDs or COX-2 inhibitors in past 12 months, no. (%)			
No	6,392 (96.9%)	6,275 (97.0%)	117 (92.1%)
Yes	206 (3.1%)	196 (3.0%)	10 (7.9%)
Regular prescription opioids use in past 12 months, no. (%)			
No	6,594 (99.9%)	6,468 (100.0%)	126 (99.2%)
Yes	4 (0.1%)	3 (<1%)	1 (0.8%)

WOMAC, The Western Ontario and McMaster Universities Arthritis Index. Several values may not sum to 100% due to rounding

Table 2 Estimated knee-level risk of knee replacement under various hypothetical daily physical activity intervention strategies

Maintain the baseline PASE score	Risk ratio	95% confidence intervals		Incidence ratio	95% confidence intervals	
	Reference			4.71	4.37	5.05
If the baseline PASE score was > 242, reduce it to 200. Otherwise, maintain the baseline score.	**0.66**	**0.42**	**0.89**	2.98	2.39	3.57
If the baseline PASE score was > 242, reduce it to 200. If the baseline PASE score was < 124, increase it by 10%. Otherwise, maintain the baseline score.	**0.60**	**0.37**	**0.84**	2.71	2.11	3.30
If the baseline PASE score was > 242, reduce it to 200. If the baseline PASE score was < 124, increase it by 20%. Otherwise, maintain the baseline score.	**0.58**	**0.37**	**0.80**	2.71	2.17	3.24
If the baseline PASE score was > 242, reduce it to 200. If the baseline PASE score was < 124, increase it by 30%. Otherwise, maintain the baseline score.	**0.74**	**0.49**	**0.998**	3.37	2.57	4.17
If the baseline PASE score was > 242, reduce it to 200. If the baseline PASE score was < 124, increase it by 40%. Otherwise, maintain the baseline score.	**0.79**	**0.63**	**0.94**	3.51	3.00	4.03
If the baseline PASE score was > 242, reduce it to 200. If the baseline PASE score was < 124, increase it by 50%. Otherwise, maintain the baseline score.	**0.77**	**0.63**	**0.91**	3.54	3.10	3.98

Abbreviations: PASE, Physical Activity Scale for the Elderly

The model was adjusted for the following time-invariant covariates: Age, sex, race, education level, income level, marital status, alignment, Charlson Comorbidity Index, 400-m walk time, total distance in 400-m walk test, and family history of knee/hip replacement. The model was also adjusted for the following time-variant covariates: Kellgren/Lawrence (K/L) grade, the Abbreviations: WOMAC, The Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain/stiffness/disability scores, chair stand time, 20-m walk test, Center for Epidemiologic Studies Depression score, body mass index, history of a knee injury with walking difficulty for ≥2 days, hip pain, aching, or stiffness in the past 12 months, regular user of NSAIDs or COX-2 inhibitor prescription in the past 12 months, and regular use of prescription opioids in the past 12 months

across questionnaire items and subdomains are shown in Supplementary Table (2) Overall, participants with higher PASE scores exhibited relatively higher values across all PASE domains. In particular, participants with PASE scores > 242 demonstrated markedly higher scores in the work-related activity domain.

Table 2 presents our key findings. In the reference scenario (Scenario A), the incidence ratio of KR surgery was 4.71% (95% CI: 4.37% to 5.05%). Scenario B, where only participants with PASE scores > 242 had their scores reduced to 200, whereas others had their baseline scores maintained, showed a lower incidence ratio of 2.98% (95% CI: 2.39%

to 3.57%) compared with that of Scenario A. Although incidence rates in Scenarios C and D (Scenario B plus interventions to increase PASE scores to 10% and 20%) decreased to 2.71%, such rates increased in Scenarios E through G (Scenario E: 3.37%, Scenario F: 3.51%, Scenario G: 3.54%).

Regarding the risk ratios in relation to the reference group (Scenario A), Scenario B showed a risk ratio of 0.66 (95% CI: 0.42 to 0.89), indicating significantly reduced the risk of KT surgery. Scenario D reported the lowest risk ratio among all scenarios, with a risk ratio of 0.58 (95% CI: 0.37 to 0.80). In Scenarios E to G, the risk ratios ranged from 0.74 to 0.79 [Scenario E: 0.74 (95% CI: 0.49 to 0.998), Scenario F: 0.79 (95% CI: 0.63 to 0.94), Scenario G: 0.77 (95% CI: 0.63 to 0.91)].

The results of our additional analysis are shown in Supplementary Table 3. Overall, the analyses in which we modified the treatment regimen by maintaining the original baseline PASE score for participants with a score > 242 showed a higher incidence ratio compared to our main regimen, in which PASE scores > 242 were reduced to 200. The calculated E-values are presented in Supplementary Table 4. The E-values from our main analysis indicate modest robustness to unmeasured confounding. We also showed another type of sensitivity analysis in which we excluded possible mediators (Supplementary Table 5). The results of this analysis were more likely to be toward the null compared with our main analysis.

Discussion

Through a multisite longitudinal cohort of community-dwelling older participants with knee OA or at risk of OA without severe pain, the current study examined whether increasing daily PA for those who were physically inactive and decreasing daily PA for those who were excessively active would prevent KR surgery. We found that reducing the PASE score to optimal levels over 2 years in participants who were excessively active at baseline reduced the risk of KR surgery. Additionally, increasing PASE scores by 10% and 20% over 2 years in participants who were inactive at baseline further reduced the risk of KR surgery compared to maintaining their PASE scores. However, this additional effect diminished when the PASE scores were increased by 30% to 50%.

The current study found that interventions capable of reducing PASE scores among participants with excessive active at baseline to optimal values (i.e., 200 points) were beneficial in reducing the risk of KR replacement. This result was consistent with that presented in a previous study that used subjectively measured daily PA (PASE, same as our study) [11, 22] but was inconsistent with a previous study that used objectively measured daily steps as their daily PA measurement [33]. This discrepancy could be attributed to the differences in the measurement of daily PA used among the studies. In particular, one study found that the correlation between the PASE score and daily steps was modest [34]. Therefore, future studies are warranted to investigate the effectiveness of optimizing daily steps in preventing KR surgery.

The possible mechanism by which reducing (optimizing) the daily PA in participants who were excessively active prevents KR surgery was as follows. Reducing and optimizing daily PA levels, particularly activities that involve repetitive or high-impact movements, could potentially decrease the mechanical load on the knee joint [35, 36]. This reduction in stress may be expected to slow the progression of joint degeneration and alleviate pain symptoms [37], potentially delaying the need for KR surgery. Furthermore, incorporating home-based exercise, such as low-impact exercises, strength training, and flexibility exercises, into a patient's routine could possibly improve joint stability, muscle strength, and range of motion [37, 38]. This can help support the knee joint, reduce the risk of injury, and enhance overall joint function, thereby reducing the likelihood of requiring KR surgery in excessively active participants. Notably, participants with PASE scores > 242 had markedly higher scores in the work-related activity domain (Supplementary Table 2). Thus, interventions focusing on optimizing work-related PAs may be particularly effective in reducing excessive mechanical stress on the knee joint among highly active individuals.

Compared to the effects of the intervention that optimized daily PA among those who were excessively active at baseline, the effects of the intervention that increase daily PA among those who were inactive at baseline was modest, despite the significant difference in the proportion of inactive (34.4%) and excessively active (17.6%) participants. Furthermore, the effect was diminished in the intervention scenario wherein the baseline PASE score was increased by 30% to 50%. In addition, our supplementary analysis, in which the original baseline PASE score was maintained for participants who were excessively active, showed a higher incidence ratio compared to our main regimen, in which their PASE scores were optimized to an adequate level. These findings suggest that participants who were excessively active are the primary target for interventions aimed at preventing KR surgery through the optimization of daily PA levels. In particular, for individuals at high risk for knee OA or those with knee OA who experience little pain, rather than promoting the daily PA levels recommended by current guidelines [39–41], it may be more appropriate to focus on correcting excessive daily PA.

The current study has several limitations worth noting. First, the generalizability of our findings to other cohorts may be limited, as we assumed treatment-variation irrelevance across all versions of the intervention. The overall effect was estimated while keeping the original distribution of activity domains (leisure, household, and work-related) among those exposed to the daily PA program. Therefore, our findings mainly apply to populations with similar characteristics and domain compositions in hypothetical PA interventions (Supplementary Table 2). Second, we did not use pathological information (e.g., K/L grade) for the inclusion criteria but instead used symptomatic information (i.e., WOMAC pain score). This approach was based on the clinical recommendation that engaging in PA is important even for participants with advanced knee OA [8], reflecting real-world clinical settings. Third, we did not use objectively measured daily PA level but instead relied on self-reported PASE scores to determine daily PA levels. Therefore, future studies will need to use objectively measured PA in relation to KR surgery. Fourth, our results might still have been affected by unmeasured confounders despite vigorous adjustment. For example, a previous study revealed that relationships with health professionals are key factors in the decision to undergo KR surgery [42]. However, the calculated E-values from our main analysis indicate moderate robustness to unmeasured confounding. Fifth, although the time-variant variables were considered in our statistical model, we did not account for correlations between variables at the same time point. In other words, we possibly underestimating the effect of daily PA on the KR surgery owing to the adjustment of possible mediators at the same time point. To address this potential bias, we conducted a sensitivity analysis excluding variables that might act as mediators. The estimates tended to move toward the null compared with the main analysis, suggesting that these variables likely functioned as confounders rather than mediators. Sixth, we did not consider the PA score after the 2-year intervention given that we assessed the effects of 2-year PA program on KR surgery. RCTs are generally 1–2 years in duration, which can be considered short in terms of assessing KR as an outcome [43–45].

In conclusion, our findings showed that optimizing daily PA is beneficial for preventing KR surgery among older participants at risk for or already suffering from knee OA without severe pain symptoms. Rather than simply reducing daily PA, our results suggest that tailoring daily PA to an optimal level—by moderately reducing activity among excessively active individuals and appropriately increasing it among inactive individuals—is most beneficial.

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Author contributions Access to data and responsibility for data integrity: Drs. Kanai and Ikeda had full access to all study data. Dr. Ikeda takes responsibility for the integrity of the data and the accuracy of the data analysis.Concept and design: All authors.Acquisition, analysis, or interpretation of data: All authors.Drafting of the manuscript: Drs. Kanai and Ikeda. Critical revision of the manuscript for important intellectual content: All authors.Statistical analysis: Dr. Ikeda.Supervision: Drs. Murakami and Osaka.

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Data availability The data are available upon request from the OAI (https://dataarchive.nimh.nih.gov/oai/).

Declarations

Competing interests The authors declare no competing interests.

Ethics approval The institutional review boards at all OAI clinical sites and the OAI coordinating center (University of California, San Francisco) approved the OAI study (10–00532). All participants signed the written informed consent form.

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