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ORIGINAL ARTICLE

Effects of interaction between varus thrust and ambulatory physical activity on knee pain in individuals with knee osteoarthritis: an exploratory study with 12-month follow-up

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Abstract

Introduction This study aimed to examine the interaction effect between ambulatory physical activity (PA) and varus thrust on knee pain in individuals with knee osteoarthritis (OA).

Method Subjects ($n = 207$; mean age: 73.1 years, 71.5% women) in orthopedic clinics with diagnosed knee OA (Kellgren/Lawrence grade ≥ 1) were enrolled in this 12-month observational cohort study. Participants underwent gait observation for varus thrust assessment and pedometer-based ambulatory PA measurements at baseline and 12-month follow-up. Knee pain intensity was assessed using the Japanese Knee Osteoarthritis Measure pain subscale as a primary outcome measure. Multiple linear regression analyses were performed to evaluate ambulatory PA–thrust interaction on knee pain intensity.

Results Ninety-two subjects (mean age, 73.4 years; 68.5% women) completed the 12-month follow-up assessment. Baseline ambulatory PA–thrust interaction was significant ($P = 0.017$) in the cross-sectional analysis, adjusting for covariates, which yielded $R^2 = 0.310$. Subgroup analysis showed that varus thrust was significantly associated with worse knee pain in subjects walking ≥ 5000 steps/day adjusting for covariates (beta: 7.94; 95% CI: 3.82, 12.1; $P < 0.001$) with a higher predictive ability ($R^2 = 0.664$). In contrast, ambulatory PA–thrust interaction in the longitudinal analysis showed no significant association with knee pain changes.

Conclusions Ambulatory PA interacted with varus thrust in the association with knee pain, as coexisting high ambulatory PA and varus thrust had the strongest association with higher knee pain. Maximal pain relief effects might be achieved when both ambulatory PA and varus thrust are treated simultaneously, rather than treating each separately.

Keywords Interaction · Knee pain · Physical activity · Varus thrust

Introduction

Knee pain, attributed to knee osteoarthritis (OA), is a common disabling problem [1]. Since most subjects with knee OA are not physically active [2, 3], increasing ambulatory physical activity (PA) has been consistently recommended, and its effectiveness for pain reduction has been reported in systematic reviews [4]. However, both physical therapists and older

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adults with knee pain have concerns regarding the safety of long-term ambulatory PA [5–7]. Quicke et al. recently conducted an extensive literature review evaluating PA safety and found that increased knee pain after PA intervention was reported in 0–22% of cases [8]. Although they concluded that long-term PA is safe without any severe adverse events [8], exacerbation of knee pain should be minimized, given that these may cause PA avoidance and subsequent functional decline, owing to fear of worsening knee pain [9].

Excessive and repetitive abnormal loading may be critical factors in the development of knee pain [10, 11] with an interaction of psychosocial factors [12]; yet, the underlying mechanisms are unclear. Varus thrust during gait is an easily assessed measure of frontal plane dynamic knee motion that is defined as the dynamic worsening or abrupt onset of varus motion during weight acceptance [13, 14]. The varus thrust is associated with higher knee pain [15], worsening knee pain within 24 months [16], and higher odds of structural progression of knee OA within 18 to 24 months [17, 18]. It is plausible that assessing knee loading frequency (i.e., ambulatory PA) in conjunction with varus thrust, a surrogate of excessive loading, may be a better indicator of worsened knee pain in subjects with knee OA [11]. Specifically, varus thrust may modify the relationship between ambulatory PA and knee pain, or vice versa. If a significant interaction relationship exists, one might expect subjects with varus thrust with high ambulatory PA to have the greatest knee pain. However, no research has directly tested the interaction between ambulatory PA and varus thrust on knee pain.

This exploratory 12-month cohort study aimed to examine the interaction effects between varus thrust and concurrent and/or change in ambulatory PA on concurrent and/or change in knee pain in individuals with knee OA. A plausible hypothesis was that (1) varus thrust and ambulatory PA produce interaction effects on concurrent knee pain, and coexisting high ambulatory PA and observed varus thrust have the strongest association with higher knee pain; (2) varus thrust and change in ambulatory PA produce interaction effects on change in knee pain, and coexisting varus thrust and increased ambulatory PA during a 12-month follow-up period aggravate knee pain at the 12-month follow-up.

Materials and methods

Participants

A 12-month cohort study, subjects described in the previous study, investigated the relationship between ambulatory PA, knee pain, and physical function (mean age: 73.1 years, BMI: 24.2, 71.5% women) [2]. The required sample size in the previous observational study was calculated based on the pilot data from a community orthopedic clinic (20 subjects) to detect the statistically significant difference in gait velocity between four ambulatory PA-based groups. Details for sample size calculation are provided in the original study [2]. In total, 207 patients with knee OA were recruited from the community orthopedic clinic. An advertisement requesting patients who were visiting clinics for conservative OA knee treatment was distributed; thus, all recruited patients had a history of pain in one or both knees. Inclusion criteria were (i) age ≥ 50 years; (ii) knees with a Kellgren/Lawrence [K/L] grade [19] ≥ 1 in one or both knees, evaluated using anteroposterior weight-bearing radiographs of the tibiofemoral (TF) joint; and (iii) ability to walk independently on a flat surface, without walking aids. The exclusion criteria were (i) history of knee surgery, (ii) rheumatoid arthritis, (iii) periarticular fracture, or (iv) presence of neurological diseases. Written informed consent was obtained from all participants before enrollment. This study was approved by the ethical committee of our institution (approval number: E1923). We included patients with K&L grade ≥ 1 because pre-radiographically defined knee OA, particularly K&L grade 1, predicts radiographic OA progression to at least grade 2 within 3–5 years [20, 21].

Measurements

For all patients, the following measurements were evaluated at both the baseline and the 12-month follow-up: (i) ambulatory PA, (ii) varus thrust during gait, and (iii) OA-related knee pain intensity [22]. Demographic characteristics (i.e., age, sex, weight, and height) and radiographic OA severity were also assessed as covariates.

Ambulatory PA

Free-living step counts (steps/day) were evaluated using a pedometer (Yamax Power Walker EX-300; Yamasa Tokei Keiki Co., Ltd., Tokyo, Japan) that provided mean step counts within 3% of the actual step counts [23] and were validated in free-living conditions [24]. A pedometer is a simple tool to objectively quantify ambulatory PA and is used clinically to motivate sedentary individuals with musculoskeletal disease [25]. We distributed the pedometer and an activity calendar to the participants for recording step counts at the time of each measurement. Patients were instructed to wear the pedometer in the pocket of their dominant leg for 14 consecutive days and to remove it when bathing, sleeping, or performing water-based activities. The patients were also asked to write down the number of steps at the end of each day. The pedometers and activity calendars were sent to our laboratory by mail after 14 days and the average number of steps was calculated. The sample was restricted to patients who wore the pedometer for at least 10 days, which was more than enough to reliably estimate PA (i.e., 3 days) [26].

Varus thrust

Gait was recorded while the patients were walking 10 m away from and toward a 60 fps stationary camera (HDR-CX550V; Sony Corp, Sony Marketing Inc., Tokyo, Japan) at a self-selected speed, with their pants rolled up to expose the knees. Footwear influences balance performance [27, 28] and walking speed [28]; thus, to prevent potential bias from their own footwear, all participants walked under barefoot. During recording, camera location and height of the stationary camera were consistent for all subjects. The height of the camera was set for the sacrum to lower lumbar levels that correspond to the center of mass, although there was inter-individual variability of patients' height. Two experienced physical therapists (HI and NF) who had > 6 years of clinical experience in the orthopedic field classified varus thrust in patients' knees as being definitely present, possibly present, or definitely absent using recorded movies [15]. These patients were categorized into two groups: "with definite varus thrust" (including patients with only varus thrust being definitely present) and "without definite varus thrust" (including those with varus thrust being possibly present and those with varus thrust being definitely absent) [15]. The examiners evaluated both knees in each patient using the recorded movies without knowledge of each patient's clinical status. Previously reported intra-rater reliability was excellent ($\kappa = 0.92$ [NF] and 0.81 [HI]) and inter-rater reliability between the examiners was good ($\kappa = 0.73$) [29].

JKOM pain and stiffness

The Japanese Knee Osteoarthritis Measure (JKOM) is a patient-based, self-answered evaluation scoring system that assesses "pain and stiffness" (8 questions, 0–32 points), "activities of daily living" (10 questions, 0–40 points), "participation in social activities" (5 questions, 0–20 points), and "general health conditions" (2 questions, 0–8 points), with a maximum score of 100 points in a person-specific assessment [22]. Severity of self-reported knee pain was evaluated using the JKOM subcategory "pain and stiffness" that focuses on knee pain during daily activities, such as using the stairs, knee bending, standing up, and walking (higher score represents extreme pain). The JKOM is a patient-based self-answered evaluation score that includes pain-related items reflecting the Japanese cultural lifestyle [22]; thus, JKOM pain and stiffness score was included as primary outcome in this study. The concurrent and construct validities of the JKOM were established by comparing the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the Medical Outcomes Study 36-item Short-Form Health Survey [22].

Covariates

Data on age, sex, and height were self-reported by patients. Body mass was measured on a scale, with participants wearing their clothes without shoes. Radiographic OA severity at baseline was assessed in the anteroposterior short view in the weight-bearing position using the K/L grading system by trained examiners (TA) [19].

Statistical analyses

Since this was an exploratory study, rather than a hypothesis testing study, the sample size was not estimated before conducting the study. The number of eligible patients attending the clinics during the study period was determined as the sample size. To minimize any bias produced by similarities between the right and left knees of the same patients, only the index knee was evaluated which was defined as the more painful knee in the baseline or past. If patients felt that their knees were equally painful, the index knee was selected randomly.

To test the hypotheses that statistical interaction exists between (i) baseline ambulatory PA and varus thrust on the knee pain intensity and (ii) change in ambulatory PA and varus thrust on the change in knee pain intensity, multiple linear regression analyses were performed based on the following two scenarios: (i) cross-sectional: baseline JKOM pain and stiffness as a dependent variable and baseline ambulatory PA, varus thrust, and their interaction as an independent variable; (ii) longitudinal: change in JKOM pain and stiffness as dependent variable and change in ambulatory PA, varus thrust, and their interaction as an independent variable. We checked the regression model features by comparing the residuals vs. fitted values (i.e., the residuals had to be normally distributed around 0) and independence between observations. In these analyses, age, sex, body mass index (BMI), and index knee TF joint K/L grade were included as covariates. These covariates were chosen a priori based on clinical judgment, as they might be associated with ambulatory PA, varus thrust, and OA clinical symptoms. Mixed linear regression was not performed in this study due to the concern that we were underpowered to assess three-way interactions (i.e., time, ambulatory PA, and varus thrust). Results were presented as beta with a 95% confidence interval (CI) per 1000 steps since it is more reasonable and interpretable than a single step.

Post hoc subgroup analyses were performed. To test the interaction when the effect modifier was varus thrust, separate multiple regression analyses were performed, with varus thrust included as an independent variable at each ambulatory PA level. In this analysis, ambulatory PA was categorized into step-based PA groups based on previously suggested cut-off points by Tudor-Locke et al. [30] (1: < 2500 steps/day, 2: 2500–4999 steps/day, and 3: ≥ 5000 steps/day). These cut-

off values corresponded to the tertile of participants in this study. Furthermore, to test the interaction when the effect modifier was ambulatory PA, multiple regression analysis was performed with ambulatory PA (continuous) as an independent variable in patients with and without varus thrust. In these analyses, covariates were included as mentioned above. Each model in these subgroup analysis had two steps. In step 1, covariates were included. In step 2, varus thrust or ambulatory PA was further included. Since this was an exploratory study, the type I error rate was not adjusted for multiple comparisons. Data analyses were performed using JMP Pro 13.0 (SAS Institute, 100 SAS Campus Drive Cary, NC, USA). $P < 0.05$ was considered to be statistically significant.

Results

In total, 207 patients were initially enrolled at the baseline; however, 115 patients were lost to follow-up; the final sample included 92 patients/knees. Patients who failed to complete the follow-up study were unable to be contacted or declined to be followed up for non-specific reasons. No patients' characteristics at baseline statistically differed between completers and non-completers (Table 1). Changes in clinical symptoms, disability, and ambulatory PA during the 12-month follow-up had a large variability among patients; the mean changes in the JKOM score were − 0.12 ± 4.56 points in pain and stiffness, 0.74 ± 5.00 points in activities of daily living, and 0.76 ± 11.8 points in the total score. The mean change in the ambulatory PA was 441 ± 1143 steps/day.

Interaction relationship between varus thrust and ambulatory PA

In the cross-sectional analysis, varus thrust and baseline ambulatory PA × varus thrust were significantly associated with baseline JKOM pain and stiffness after adjustment of covariates (Table 2). The adjusted model in the cross-sectional

Table 1 Comparison of baseline characteristics between completers ($n = 92$) and non-completers ($n = 115$)*

Variable	Completer ($n = 92$)	Non-completer ($n = 115$)	P value**
Age, years	73.4 ± 7.91	72.9 ± 7.48	0.759
Female, no. (%)	63 (68.5)	85 (73.9)	0.390
Height, meters	1.56 ± 0.08	1.55 ± 0.07	0.715
Body mass, kg	58.8 ± 10.4	58.6 ± 10.4	0.779
BMI, kg/m^2	24.1 ± 3.58	24.3 ± 4.08	0.850
Tibiofemoral joint K/L grade, no. (%)			0.600
Grade 1	32 (34.8)	35 (30.4)	
Grade 2	36 (39.1)	40 (34.8)	
Grade 3	16 (17.4)	25 (21.7)	
Grade 4	8 (8.7)	15 (13.0)	
JKOM			
Pain and stiffness (0–32 points)	7.97 ± 5.85; 7 [3, 12]†	8.80 ± 5.95; 8 [4, 12]†	0.298
Activities of daily living (0–40 points)	6.95 ± 6.95; 5 [1, 11]†	7.49 ± 6.35; 6 [2, 12]†	0.280
Participation in social activities (0–20 points)	3.43 ± 3.82; 2 [1, 5]†	3.56 ± 3.46; 3 [1, 5]†	0.567
General health conditions (0–8 points)	2.83 ± 1.60; 3 [2, 4]†	3.09 ± 1.58; 3 [2, 4]†	0.324
Total score (0–100 points)	21.2 ± 15.3; 17 [10, 29]†	22.9 ± 14.9; 19 [12, 33]†	0.320
Presence of varus thrust, no. (%)	19 (20.7)	27 (23.5)	0.627
Ambulatory PA, steps/day	4113 ± 2424	4542 ± 2872	0.481
PA category, no. (%)			0.543
< 2500 steps/day	29 (31.5)	29 (25.2)	
2500–4999 steps/day	32 (34.8)	47 (40.9)	
≥ 5000 steps/day	31 (33.7)	39 (33.9)	

BMI body mass index, *K/L grade* Kellgren/Lawrence grade, *JKOM* Japanese Knee Osteoarthritis Measure, *PA* physical activity

*Except where otherwise indicated, values are mean ± SD

**P values are calculated using Mann-Whitney U test (age, height, body mass, BMI, JKOM score, and ambulatory PA), Chi-square test (female, tibiofemoral joint K/L grade, presence of varus thrust, and PA category)

†Median [lower interquartile range, upper interquartile range] of the JKOM scores is also provided

Table 2 Results of multiple regression analyses illustrating the association between ambulatory PA and the JKOM pain and stiffness score in cross-sectional and longitudinal studies ($n = 92$)

Independent variable	Dependent variable	Beta (95% CI)	Standard beta	R^2	P value
Cross-sectional				0.370	
Baseline ambulatory PA, per 1000 steps/day	Baseline JKOM pain and stiffness	− 0.324 (− 0.797, 0.149)	− 0.133		0.177
Varus thrust (0: absence, 1: presence)		*3.231 (0.485, 5.977)*	*0.222*		*0.022*
Baseline ambulatory PA × varus thrust		*1.173 (0.248, 2.098)*	*0.228*		*0.014*
Longitudinal				0.048	
Ambulatory PA change, per 1000 steps/day	JKOM pain and stiffness change	− 0.294 (− 1.188, 0.600)	− 0.074		0.515
Varus thrust (0: absence, 1: presence)		− 0.118 (− 2.884, 2.649)	− 0.011		0.933
Ambulatory PA change × varus thrust		0.880 (− 1.567, 3.328)	0.084		0.477

JKOM Japanese Knee Osteoarthritis Measure, *PA* physical activity, *95% CI* 95% confidence interval

Beta (95% CI) and standard beta were calculated to indicate predictive ability of ambulatory PA, varus thrust, and ambulatory PA × varus thrust, while simultaneously including (one-step model) age (continuous), female sex, BMI (continuous), and K/L grade (continuous) in the multiple regression model

Italics represent a statistically significant result

analysis yielded $R^2 = 0.370$. In contrast, longitudinal analysis showed no significant association of any independent variables with JKOM pain and stiffness changes.

Post hoc subgroup analysis

Patients' characteristics stratified by PA category are provided in Supplementary Table 1. Varus thrust was significantly associated with worsened knee pain in subjects walking ≥ 5000 steps/day ($R^2 = 0.664$), however not in those walking < 2500 steps/day ($R^2 = 0.514$) and 2500–4999 steps/day ($R^2 = 0.270$) after adjustment of covariates (Table 3). Among subjects walking ≥ 5000 steps/day, the additive effects of varus thrust explained an additional 21.1% of variance (i.e., ΔR^2) above that of covariates which was much higher than in subjects walking < 2500 steps/day ($\Delta R^2 = 1.8\%$) and 2500–4999 steps/day ($\Delta R^2 = 0.2\%$).

When ambulatory PA was included as a predictor (Table 4), increased ambulatory PA was significantly associated with decreased knee pain in subjects without varus thrust ($R^2 = 0.265$), however not in those with varus thrust, after adjustment of covariates ($R^2 = 0.336$). The additive effects of ambulatory PA above that of covariates were comparable between subjects with ($\Delta R^2 = 8.0\%$) and without ($\Delta R^2 = 5.8\%$) varus thrust.

A graphic illustration of the cross-sectional ambulatory PA–varus thrust interaction is provided in Fig. 1a. Ambulatory PA was significantly associated with JKOM pain and stiffness only in knees without varus thrust. The relationship in knees with varus thrust did not show significance; however, a positive association was shown. Figure 1b shows the comparison of JKOM pain and stiffness between subjects with and without varus thrust in each ambulatory PA category, which clearly shows that

Table 3 Subgroup analysis of the relationship between varus thrust and the JKOM pain and stiffness score in cross-sectional study in each standardized PA category ($n = 92$)

Independent variable	Step	< 2500 steps/day $n = 29$			2500–4999 steps/day $n = 32$			≥ 5000 steps/day $n = 31$		
		With thrust $n = 8$			*With* thrust $n = 5$			*With* thrust $n = 6$		
		Without thrust $n = 21$			*Without* thrust $n = 27$			*Without* thrust $n = 25$		
		Beta (95% CI)	R^2	ΔR^2	Beta (95% CI)	R^2	ΔR^2	Beta (95% CI)	R^2	ΔR^2
Covariate	1	¬	0.252	0.252	¬	0.512	0.512	¬	0.453	0.453
Varus thrust	2	2.316 (− 4.203, 8.834)	0.270	0.018	0.715 (− 3.891, 5.321)	0.514	0.002	*7.942 (3.820, 12.06)*	*0.664*	*0.211*

95% CI 95% confidence interval

Beta (95% CI) was calculated with the presence of varus thrust to indicate their predictive ability while simultaneously including (one-step model) age (continuous), female sex, BMI (continuous), and K/L grade (continuous) in the multiple regression model

Italics represent a statistically significant result

Table 4 Subgroup analysis of the relationship between ambulatory PA and the JKOM pain and stiffness score in cross-sectional study in knee *with* and *without* varus thrust ($n = 92$)

Independent variable	Step	*With* varus thrust $n = 19$			*Without* varus thrust $n = 73$		
		Beta(95% CI)	R^2	ΔR^2	Beta(95% CI)	R^2	ΔR^2
Covariate	1	¬	0.256	0.256	¬	0.207	0.207
Ambulatory PA (per 1000 steps/day)	2	0.604 (− 0.434, 1.641)	0.336	0.080	*− 0.643 (− 1.202, − 0.085)*	*0.265*	*0.058*

PA physical activity, *95% CI* 95% confidence interval

Beta (95% CI) was calculated with the increase in ambulatory PA per 1000 steps/day to indicate their predictive ability while simultaneously including (one-step model) age (continuous), female sex, BMI (continuous), and K/L grade (continuous) in the multiple regression model

Italics represent a statistically significant result

the difference in mean of JKOM pain and stiffness increases as PA shifts to the more active group.

Discussion

This study found that varus thrust and ambulatory PA produced interaction effects on knee pain (Fig. 2a), and the impact of varus thrust on increased knee pain was the strongest in individuals walking ≥ 5000 steps/day (Fig. 2b). These results support our hypothesis. Although results of a longitudinal study did not support the interaction relationship and our hypothesis, this study enlightened the novel cross-sectional relationship between PA and knee pain or varus thrust and knee pain. These preliminary findings warrant validation in future studies with larger sample sizes.

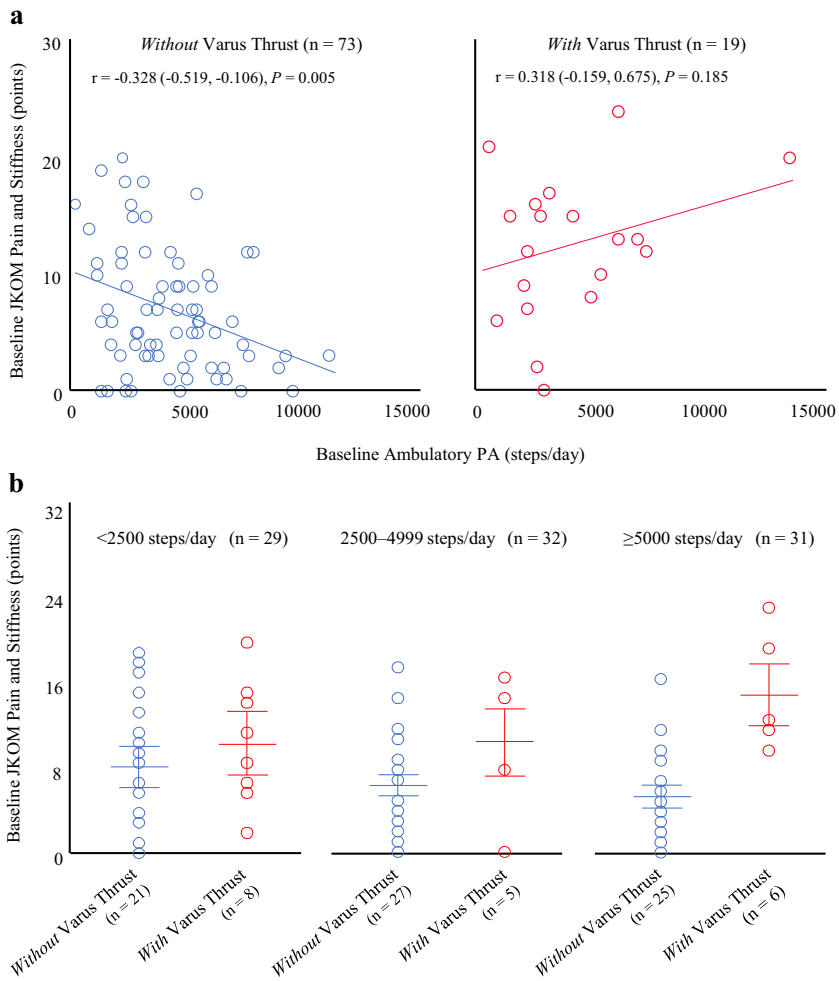

Fig. 1 Illustration of the interaction relationship of the ambulatory PA with varus thrust. **a** Relationship of baseline ambulatory PA and JKOM pain and stiffness score in subjects with and without varus thrust. Spearman correlation coefficients (95% CI) are provided in the figure. Linear regression lines are also provided. Note that individuals with varus thrust had a high variability in ambulatory PA. **b** Relationship of the varus thrust and JKOM pain and stiffness in subjects walking < 2500 steps/day, 2500–4999 steps/day, and ≥ 5000 steps/day. Values are the means ± 95% CI of the independent experiment

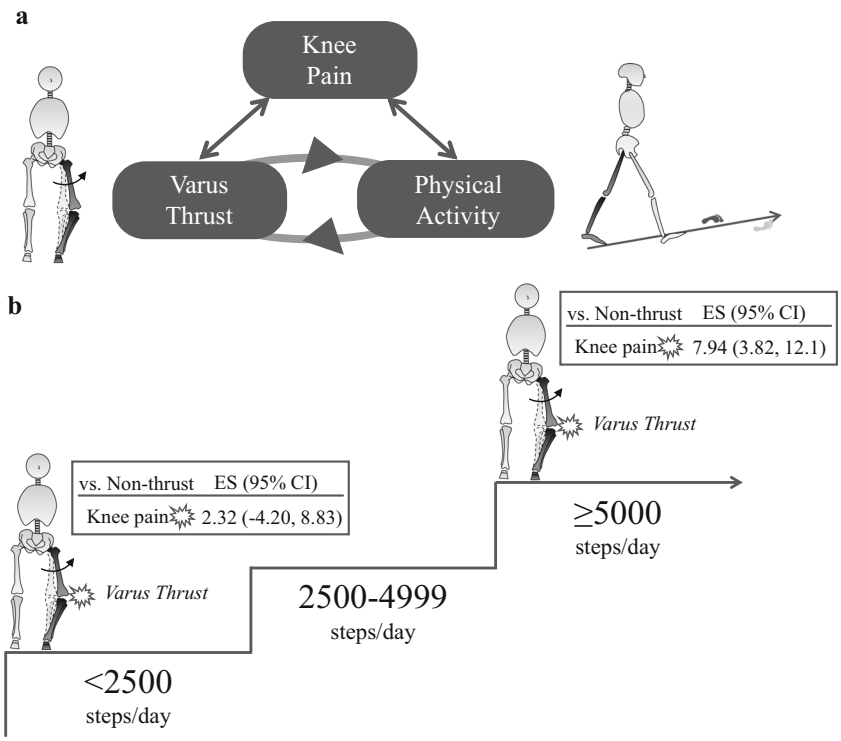

Fig. 2 Graphic abstract. **a** Varus thrust during gait interacts with ambulatory PA in the association with knee pain. **b** Influence of varus thrust on higher knee pain was the strongest in individuals walking ≥ 5000 steps/day. Effect sizes (ESs) with their 95% confidence intervals (CIs) of thrust presence (vs. non-thrust) on knee pain in individuals walking < 2500 and ≥ 5000 steps/day are provided

Key findings and potential mechanism of the interaction between varus thrust and ambulatory PA

The observed significant interaction relationship between ambulatory PA and varus thrust on knee pain intensity has not been previously reported. Results of subgroup analysis stratified by ambulatory PA demonstrated that the variance on increased knee pain explained by varus thrust in individuals walking ≥ 5000 steps/day was much higher than those in individuals walking < 2500 steps/day and 2500–4999 steps/day. This data indicate an improved explanatory power of varus thrust on knee pain intensity by stratifying ambulatory PA. Moreover, results of subgroup analysis stratified by varus thrust demonstrated that subjects with coexisting higher ambulatory PA and varus thrust showed significantly higher knee pain, while those with higher ambulatory PA without varus thrust showed non-significant lower knee pain. These data indicate the importance of assessing ambulatory PA in the relationship between varus thrust and knee pain or assessing varus thrust in the relationship between ambulatory PA and knee pain.

Longitudinal data did not clearly support these relationships with a low predictive ability of the included model, indicating an existence of other factors associated with change in knee pain intensity. A previous systematic review suggested that bilateral knee symptoms and depressive symptoms are strong prognostic factors of knee pain deterioration [31]. Biomechanical alterations during long-distance walking might be a potential confounder, since some older adults change their walking strategy for long-term walking [32]. These potential confounders should be considered in future studies. Furthermore, the follow-up period in the present study was 12 months, which might be too short to show knee pain exacerbation. Wink et al. revealed in a large cohort study that people with varus thrust worsened WOMAC knee pain within 24 months [16]. Bastick et al. identified patients who had different pain trajectories over 5-year follow-up; however, the mean change in knee pain intensity was small at 1-year follow-up, even in those showing progressive exacerbation of knee pain at the 5-year follow-up [33], which supports this interpretation.

Potential mechanisms underlying the significant interaction between ambulatory PA and varus thrust observed in the cross-sectional data are unclear. Previous work showed that individuals with varus thrust have larger knee adduction moment during gait [13] and higher odds of worsening medial cartilage loss and bone marrow lesions [18], thought to be related to bone trauma. Knees with varus thrust may undergo an abnormal loading that may exceed the articular tissue capacity through repetitive daily walking, which might cause development or enlargement of the bone marrow lesions. Observed interaction relationship between ambulatory PA and varus thrust might be due in part to the abnormal and cumulative joint loading, which should be verified in the future studies.

Practical relevance and future direction

Varus thrust during gait and ambulatory PA are mechanical factors that can be managed non-surgically. Varus thrust is treatable using bracing, neuromuscular training, and gait retraining [34]. Ambulatory PA can be controlled by using a pedometer [25]. The practical relevance of the interaction between two modifiable factors was a function of treatment objectives. When treating the varus thrust to reduce knee pain, evaluating the ambulatory PA would be important since the relationship of varus thrust with knee pain may be moderated by PA level. Treating varus thrust may be less effective in improving knee pain in sedentary patients. Conversely, when controlling ambulatory PA, evaluating the presence of varus thrust during gait is important. The relationship between ambulatory PA and knee pain becoming significant when subjects were restricted to those without varus thrust should be noted, which build upon an evidence from previous studies that increased ambulatory PA is effective to reduce knee pain in older adults [4, 35].

Varus thrust has been shown to be associated with worsened knee pain in patients with knee OA [15, 29, 36]. However, difference in knee pain between knees with and without varus thrust would not reach a minimal clinically significant difference (MCID) [37], which was similar in this study. In contrast, subgroup analysis stratified by ambulatory PA showed that the difference in the mean JKOM was increased in those walking ≥ 5000 steps/day that would reach the MCID level, highlighting the clinically important role of stratification by ambulatory PA in treating varus thrust. These preliminary findings suggest that further research evaluating the clinical impact of varus thrust in this specific subgroup is required.

No clear dose-response relationship was observed between steps/day and knee pain intensity in individuals with varus thrust, although increased PA was possibly associated with severe knee pain. A small sample size of those with varus thrust with a large variability in ambulatory PA would make 95% CI wide, thereby produced non-significant results. Given that some cases had increased knee pain after PA intervention including exercise [5–7], further studies with larger sample sizes should be conducted to identify particular subgroups that negatively respond to PA intervention.

Limitations

First, missing data during the 12-month follow-up may affect preliminary findings in this study. Some patients were unable to be contacted without any specific reason; thus, mechanism of missing data was unclear. Minimized follow-up losses are needed to illustrate exact interaction relationships. However, no significant differences were found in baseline characteristics between completers and non-completers, which might indicate that data are missing at random. Second, this study does not evaluate PA intensity, frequency, or duration. Since prevalence of varus thrust would be increased with a faster walking speed, walking intensity may be a critical parameter in the interaction between varus thrust and ambulatory PA on knee pain. Third, lack of patient information regarding pain medication, history of injury and knee pain, disease duration, use of assistive device, and psychosocial factors restricted our analysis. Fourth, varus thrust is a subjective measure determined by gait observation by trained physical therapists. A quantitative evaluation of varus thrust may result in different findings, although this simple clinical assessment had high reliability [13, 15, 29].

Conclusions

Ambulatory PA interacts with varus thrust during gait in the association with knee pain, as coexisting high ambulatory PA and varus thrust had the strongest association with severe knee pain. If our findings are replicated in a larger trial, the results may be a first step in justifying the therapeutic strategy that targets both ambulatory PA and varus thrust simultaneously, rather than either ambulatory PA or varus thrust separately.

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