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Mediating role of effusion-synovitis in knee pain worsening following quadriceps weakness: data from the osteoarthritis initiative

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Abstract

Objective The cause of increased knee pain related to quadriceps weakness in knee osteoarthritis remains unclear. This study aimed to assess the impact of alterations in the effusion-synovitis, a special kind of nociceptive structure, on changes in knee pain associated with quadriceps weakness.

Methods Based on the osteoarthritis initiative cohort, knees with comprehensive records of quadriceps strength, effusion-synovitis, and knee pain assessments at baseline, 12-month and 24-month intervals were included. Quadriceps strength was measured isometrically at baseline, while effusion-synovitis and knee pain were assessed at baseline, 12-month, and 24-month follow-ups. Effusion-synovitis was assessed using the Magnetic Resonance Imaging Osteoarthritis Knee Score while knee pain was evaluated with the Western Ontario and McMaster Universities Osteoarthritis Index. Mediation-effect models were utilized to quantify the extent to which changes in effusion-synovitis, induced by quadriceps weakness, could mediate the impact on the knee pain scale.

Results The analysis involved 1377 knees of 1235 participants with both baseline and 12-month follow-up data (61.1% females, mean age of 61.7 years). Baseline quadriceps strength was significantly associated with knee pain changes over 12 and 24 months, while changes in effusion-synovitis were also directly associated with worsening knee pain at 12- and 24-month follow-ups. More importantly, effusion-synovitis changes mediated the association between baseline quadriceps strength and knee pain worsening over 12 and 24 months, with the mediating proportion of 17.72% and 10.31%, respectively. Additionally, this mediation association remained significant in the population with radiographic osteoarthritis during 12-month follow-up.

Conclusion Effusion-synovitis mediates approximately one-fifth of the association between baseline quadriceps strength and knee pain changes, suggesting that interventions targeting effusion-synovitis could facilitate the treatment of knee pain, especially caused by quadriceps weakness.

Keywords Osteoarthritis, Quadriceps strength, Effusion-synovitis, Knee pain

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Innovation

- This study provides the first evidence elucidating the mediating effect of effusion-synovitis on the relationship between quadriceps weakness and worsening knee pain.
- The mediating effect of effusion-synovitis was observed solely within the population of individuals diagnosed with radiographic osteoarthritis.

Significance

- Interventions aimed at addressing effusion-synovitis can potentially be beneficial in treating knee pain associated with the quadriceps muscles.

Introduction

Knee osteoarthritis (KOA), characterized by knee pain, is a major cause of disability among the elderly, affecting over 240 million adults worldwide [1, 2]. Quadriceps weakness is widely acknowledged as a significant risk factor for knee pain [3–7] and international guidelines recommend strength training as part of the first line of treatment for KOA [8–11]. However, specific pathways and mechanisms by which quadriceps weakness contributes to knee pain pathogenesis remain undefined, although there have been several studies attributing the knee pain to the abnormal biomechanical environment caused by quadriceps weakness [3, 5].As reported, low-grade chronic inflammation within arthritic joints has been suggested to play a critical role in the pain generation and pain perception [12, 13]. When the inflammation was appeared in knee structures with rich innervation, like the synovial membrane or subchondral bone, it would lead to the inflammation-related knee pain [14, 15]. A recent systematic review found a positive association between local signs of inflammation in effusion/synovitis and neuropathic-like pain as well as signs of pain sensitivity [16]. In our previous study, we discovered a significant correlation between the baseline quadriceps strength and the progression of effusion-synovitis over a period of 1 to 2 years [17]. This finding suggests that quadriceps weakness could be a significant predictor for the progression of effusion-synovitis. Effusion-synovitis is typically assessed in the suprapatellar bursa, situated between the quadriceps tendon, patella, and femur [18]. Due to this anatomical proximity, it maintains a close biomechanical relationship with the patellofemoral joint and the quadriceps muscle. The quadriceps serves as a critical dynamic stabilizer of the knee joint. Weakness in this muscle group can disrupt normal patellofemoral tracking, leading to aberrant friction and stress within the joint [19, 20]. Such mechanical dysfunction may contribute to the progression of effusive synovitis. Furthermore, emerging research highlights the role of skeletal muscle-derived myokines (e.g., irisin, TNF, and IL-6) in modulating inflammatory responses [21–24]. The quadriceps, as an important skeletal muscle around the suprapatellar synovium, may have different myokine secretion levels depending on its functional state (particularly muscle strength), which could potentially influence the progression of synovitis to some extent. Given the strong association between effusion-synovitis and knee pain, is there a potential pathway, mediated by effusion-synovitis, that contributes to the exacerbation of knee pain in relation to quadriceps weakness?

It is hypothesized that quadriceps weakness has the potential to contribute to the development of effusion-synovitis, which consequently induces knee pain. In other words, the impact of quadriceps weakness on effusion-synovitis may partly mediate the association between quadriceps weakness and the progression of knee pain. To test this hypothesis, this study applied mediation effect models, which decompose the total effect into direct (non-mediated) and indirect (mediated) effects, to determine the presence and extent of the mediated relationship. The total effect of quadriceps weakness on knee pain can be decomposed into the direct effect of quadriceps weakness on knee pain and the indirect effect mediated by effusion-synovitis. When both the indirect effect and the direct effect exist and are in the same direction, effusion-synovitis is likely to partially mediate (enhance) the effect of quadriceps weakness on knee pain.

Furthermore, considering the co-occurrence of quadriceps weakness and effusion-synovitis, the latter may confound the relationship between quadriceps weakness and knee pain in cross-sectional studies. Therefore, we investigated the mediating effect of effusion-synovitis in the osteoarthritis initiative (OAI) longitudinal cohort. More specifically, we aimed to quantify the degree to which changes in effusion-synovitis following baseline quadriceps weakness could mediate the impact of baseline quadriceps weakness on the progression of knee pain over follow-ups. This indirect pathway, mediated by effusion-synovitis, has the potential to offer valuable insights into the underlying mechanisms of knee pain and propose innovative strategies for pain management.

Materials and methods

Study population

We performed analyses using publicly available data from the OAI, a multicenter prospective cohort of KOA registered under ClinicalTrials.gov with the identifier NCT00080171. The OAI recruited a total of 4796 participants from four distinct centers: University of Pittsburgh, University of California, University of Maryland and Johns Hopkins University Joint Center, the Ohio State University, and Memorial Hospital/Brown University, all

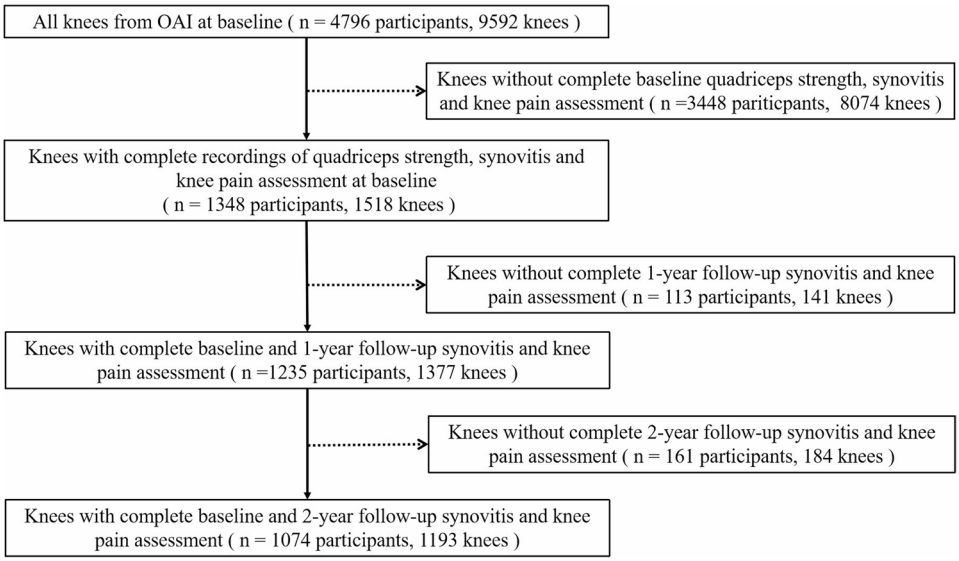

Fig. 1 Flow chart of knee selection from the Osteoarthritis Initiative (OAI). The synovitis was evaluated according to the Magnetic Resonance Imaging Osteoarthritis Knee Score (MOAKS). The knee pain was assessed according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Table 1 Baseline characteristics of included participants at 12-month follow-up

	Mean (SD)
Age (years)	61.7 (8.8)
Female (%)	61.1
BMI (kg/m^2)	29.4 (4.7)
Caucasian (%)	84.0
KLG (%)	17.1/30.2/23.6/22.9/8.1
Alignment (°)	−0.4 (3.8)
Physical activity (PASE)	167.7 (83.4)
Depressive symptom (CESD)	6.3 (6.8)
Quadriceps strength (Nm/kg)	1.3 (0.5)
Effusion-synovitis (MOAKS)	44.1/37.6/13.9/4.4
Knee pain (WOMAC)	2.6 (3.2)

Note: Our analyses included 1235 participants with a total of 1377 knees at 12-month follow-up. The above results are based on knee-level statistical descriptions

Values are mean (SD) unless otherwise specified

BMI body mass index, *KLG* Kellgren-Lawrence grading, grade as 0/1/2/3/4 Alignment, degrees (valgus, negative), *PASE* Physical Activity Scale for the Elderly, *CESD* Center for Epidemiologic Studies Depression Scale, effusion-synovitis, graded as 0/1/2/3 according to MOAKS system, *MOAKS* magnetic resonance imaging Osteoarthritis Knee Score, *WOMAC*, Western Ontario and McMaster Universities Osteoarthritis Index

of whom were diagnosed with KOA or exhibited high-risk KOA features. The specific details of this cohort's protocol have been previously well-documented [25].

In this study, we used the knee as the primary unit of analysis and included knees that had a complete assessment of quadriceps strength, effusion-synovitis, and knee pain at baseline, as well as at 1- or 2-year follow-ups from the OAI. It is possible that two included knees may originate from the same participant. The specific selection flowchart is presented in Fig. 1.

The characteristics of the study population were assessed across various dimensions, including age, sex, race, body mass index (BMI), radiographic osteoarthritis (ROA), knee alignment, physical activity, depressive symptoms, quadriceps strength, effusion-synovitis assessments, and knee pain at baseline. Upon enrollment, age, sex, race, and BMI were recorded. ROA was evaluated using the Kellgren-Lawrence grading (KLG) system, which is based on X-ray radiographs. To account for the potential influence of knee alignment on quadriceps strength within the knee joint, the degree of alignment for each knee was measured using the femorotibial angle (FTA) [26, 27]. Physical activity and depressive symptoms were assessed using the Physical Activity Scale for the Elderly (PASE) and the Center for Epidemiologic Studies Depression Scale (CESD), respectively. Isometric quadriceps strength was measured at baseline, while effusion-synovitis and knee pain were evaluated at baseline, 1-year, and 2-year follow-ups. The Magnetic Resonance Imaging Osteoarthritis Knee Score (MOAKS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were employed to quantify the levels of effusion-synovitis and knee pain, respectively. All of these baseline characteristics of included participants were considered as covariates in our analyses to account for their potential influence on final results.

Quadriceps strength

The measurement of quadriceps strength was collected at baseline. According to the protocol established by the OAI, the isometric measurement of quadriceps strength for each knee was conducted using the Good Strength Chair (Metitur Oy, Jyvaskyla, Finland) [28]. Prior to the

testing, all research technicians underwent training followed a standardized protocol, and the test-retest reliability yielded range of 0.88 to 0.92 [29]. Participants were seated in the Good Strength Chair, with the tested knee fixated at a 60° angle. Straps were used to secure the pelvis and thigh, stabilizing the participants' trunk and lower limb. A load cell, situated on a lever arm, was attached approximately 2 cm proximal to the calcaneus [30]. Before the formal test, participants completed two warm-up trials at 50% of their maximum effort. During the test, three repetitions were performed with the participant's maximum effort, and the peak force (measured in Newtons) was recorded as the maximum quadriceps strength. To account for variations in participant weight and height, the maximum quadriceps strength was normalized using body mass and leg length, resulting in units of Nm/kg.

Effusion-synovitis

The assessment of effusion-synovitis was collected at baseline, 12-month and 24-month follow-ups, utilizing magnetic resonance imaging (MRI). The structure of each knee was evaluated using identical 3.0 Tesla Trio MRI systems (Siemens) at each OAI clinical center. The specific MRI pulse sequence parameters outlined in the OAI protocol were previously published elsewhere [31].

Two fellowship-trained musculoskeletal radiologists, A.G. and F.W.R., who had over 10 years of experience in evaluating knee structure, performed the reading of the MRIs using the MOAKS [18]. They were blinded to the participants' clinical information. For this study, our primary focus was on the changes in effusion-synovitis within the initial two-year period. Therefore, semi-quantitative assessments were conducted at baseline, 12-month, and 24-month follow-ups. In accordance with the MOAKS system, the distention of the synovial cavity within the intercondylar region, referred to as effusion-synovitis, was categorized into four levels: level 0 (none, representing a physiological amount), level 1 (small, less than 33% maximum distention), level 2 (medium, between 33% and 66% maximum distention), and level 3 (large, more than 66% maximum distention). The effusion-synovitis assessment demonstrated a high level of inter-rater reliability (0.95, 95% CI 0.61-1.00). Changes in effusion-synovitis were defined as the difference between the follow-up score and the baseline score.

Knee pain

The severity of knee pain at each visit (baseline, 12- and 24-month follow-ups) was evaluated using the WOMAC pain subscale. This subscale assesses knee pain during five daily activities over a past seven-day period, including lying, sitting, standing, stair climbing, and walking on a flat surface. The cumulative score of each activity is then combined to derive the total points of the WOMAC scale, which spans from 0 to 20 [32]. Higher scores indicate more severe pain. The WOMAC pain scale has been rigorously validated for its reliability and validity [33]. Changes in knee pain were determined by subtracting the WOMAC pain score at baseline from the WOMAC pain score at follow-ups.

Statistical analysis

The baseline characteristics of the study population were summarized using mean ± SD or percentages. Linear regression models were employed to analyze the association between quadriceps strength or effusion-synovitis with WOMAC pain. Adjustments were made in the models for sex, age, BMI, race, KLG, alignment, PASE score, CESD score, and WOMAC pain at baseline. Longitudinal regression analyses were conducted using generalized estimating equations (GEE) to account for within-individual correlations between the two knees. The results were reported as unstandardized beta coefficients along with their respective 95% confidence intervals (95% CIs).

In this study, baseline quadriceps strength was treated as the independent variable (X), the change in effusion-synovitis over 12 or 24 months as the mediator (M), and the corresponding change in pain scores as the dependent variable (Y). The effect of X on M was denoted as path (a), the effect of M on Y as path (b), and the direct effect of X on Y as path (c). The mediated effect was defined as a×b, while the total effect (c') was defined as the sum of the direct effect (c) and the mediated effect (a×b). The proportion of mediation was calculated as the ratio of the mediated effect (a×b) to the total effect (c'), with its absolute value representing the strength of mediation. To assess the significance of mediation effects, we applied bootstrap testing with 2,000 iterations at a 95% confidence level. A mediation effect was considered statistically significant if its 95% confidence interval did not include zero. Following the mediation classification criteria proposed by Zhao et al. [34], we categorized the results into five scenarios (three mediation and two non-mediation cases): Complementary mediation: Occurs when both the mediated effect (a×b) and direct effect (c) exist and point in the same direction, indicating that the mediator enhances the effect of X on Y (mediation effect 95% CI lower bound > 0); Competitive mediation: Occurs when the mediated effect (a×b) and direct effect (c) exist but point in opposite directions, indicating that the mediator suppresses the effect of X on Y (mediation effect 95% CI upper bound < 0); Indirect-only mediation: Occurs when a significant mediated effect (a×b) exists but no direct effect (c) is observed, suggesting that X affects Y entirely through M; Direct-only nonmediation: Occurs when a direct effect (c) exists but no significant mediated effect (a×b) is detected; No-effect nonmediation: Occurs

when neither a direct effect (c) nor a mediated effect (a×b) is present.

A mediation analysis was conducted using the Mediation Package (version 4.5.0) in R (version 4.2.2) to examine the mediating role of effusion-synovitis in the relationship between quadriceps weakness and worsening knee pain. Notably, the mediator in this study—the change in effusion-synovitis scores between time points—and the outcome variable—the change in knee pain scores between time points—are both multi-level ordinal variables (each with more than five levels) with a reasonable distribution of participants across levels. Therefore, we treated these variables as approximately continuous. In R, we first fitted linear regression models for (1) the association between baseline quadriceps strength and changes in knee pain, and (2) the association between baseline quadriceps strength and changes in effusion-synovitis, followed by mediation analysis using the Mediation Package (version 4.5.0). The mediation model was adjusted for sex, age, race, BMI, KLG, alignment, CESD score, PASE score, and WOMAC knee pain at baseline. Furthermore, a sensitivity analysis was conducted to account for potential confounding factors, specifically the diagnosis of radiographic osteoarthritis at baseline. In the sensitivity analysis, knees were categorized as with ROA (KLG ≥ 2) or without ROA at baseline, considering the potential influence of ROA on changes in knee pain.

Regression analyses were performed using IBM SPSS (version 27.0), and mediation analyses were conducted using R software (version 4.2.2). A statistical significance level of $P < 0.05$ was used.

Table 2 Association of quadriceps strength and effusion-synovitis with change in WOMAC knee pain over 12 or 24 months

	Outcome over 12 months		**Outcome over 24 months**	
	Change in WOMAC knee pain over 12 months *		**Change in WOMAC knee pain over 24 months** *	
	β (95% CI)	***P***	**β (95% CI)**	***P***
Baseline				
Baseline quadriceps strength	−0.39 (−0.76 to −0.02) **	0.037	−0.74 (−1.18 to −0.31) **	< 0.001
Baseline effusion-synovitis	0.06 (−0.14 to 0.26)	0.571	0.11 (−0.11 to 0.33)	0.318
12- month follow-up				
Change in effusion-synovitis	0.62 (0.37 to 0.88) **	< 0.001	- #	- #
24- month follow-up				
Change in effusion-synovitis	- #	- #	0.77 (0.53 to 1.01) **	< 0.001

Generalized estimating equation models were applied. The association between 24-month quadriceps strength loss and 12-month change in WOMAC pain was not considered in this study. The association between 24-month effusion-synovitis worsening and 12-month change in WOMAC pain was not considered in this study. Aforementioned associations were not considered in this study due to their limited clinical significance

BMI body mass index, *KLG* Kellgren-Lawrence grading, Alignment, degrees (valgus, negative), *PASE* Physical Activity Scale for the Elderly, *CESD* Center for Epidemiologic Studies Depression Scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

Positive (+) beta coefficient indicates an increase in WOMAC pain

** Significant

The association between 12-month effusion-synovitis worsening and 24-month change in WOMAC pain was not considered in this study

Results

Characteristics of study participants

Among the 4796 participants in the OAI cohort, 3448 were excluded from this study due to missing baseline assessments of quadriceps strength, effusion-synovitis, and knee pain. Of the remaining participants ($n = 1348$), 113 were excluded at the 12-month follow-up and 161 were excluded at the 24-month follow-up due to incomplete assessments of effusion-synovitis and knee pain. At the 12-month and 24-month follow-ups, there were 1235 and 1074 participants (1377 and 1193 knees) remaining, respectively.

The baseline characteristics of the included participants at 12-month follow-up are displayed in Table 1. Our analyses consisted of 1235 participants with a total of 1377 knees at 12-month follow-up. The participants had an average age of 61.7 ± 8.8 years and a BMI of 29.4 ± 4.7 kg/m^2. The sample demographics indicated that 84.0% of participants were of white race and 61.1% identified as female. Over half of participants (54.6%) experienced ROA (KL ≥ 2), and a significant majority (55.9%) had effusion-synovitis (MOAKS ≥ 1) at baseline. At baseline, the average quadriceps strength was 1.3 ± 0.5 N m/kg, and the mean WOMAC knee pain score was 2.6 ± 3.2. Moreover, the data from 1193 knees of 1074 participants were left at 24-month follow-up. The baseline characteristics of the population remain consistent from 12 months to 24-month follow-up. The baseline characteristics of included participants at 24-month follow-up are shown in Supplemental Table 1.

Association of quadriceps strength and effusion-synovitis with changes in WOMAC knee pain over 12 or 24 months

Table 2 presents the significant association between baseline quadriceps strength and the changes in WOMAC knee pain over 12 and 24 months (12 months: adjusted β = −0.39, 95% CI −0.76 - −0.02, $P = 0.037$; 24 months: adjusted β = −0.74, 95% CI −1.18 - −0.31, $P < 0.001$). In contrast to quadriceps strength, the baseline assessment of effusion-synovitis did not display a statistically significant association with the changes in knee pain during any follow-up period. However, a significant relationship was observed between the changes in effusion-synovitis and

knee pain over 12 and 24 months (12 months: adjusted $\beta = 0.62$, 95% CI 0.37–0.88, $P < 0.001$; 24 months: adjusted $\beta = 0.77$, 95% CI 0.53–1.01, $P < 0.001$).

Association of quadriceps strength with changes in effusion-synovitis over 12 or 24 months

The relationship between baseline quadriceps strength and the changes in effusion-synovitis at the 12-month follow-up is presented in Supplemental Table 2, indicating a significant association (12 months: adjusted β = −0.49, 95% CI −0.81 - −0.17, $P = 0.003$). Although there was no significant association between baseline quadriceps strength and the changes in effusion-synovitis over 24 months, an underlying tendency was observed (24 months: adjusted β = −0.27, 95% CI −0.61–0.08, $P = 0.126$).

Mediation effects of effusion-synovitis for outcome WOMAC knee pain over 12 and 24 months: association of quadriceps strength with WOMAC knee pain

Based on the results presented in Table 3., there was a significant mediation effect of the alterations in the effusion-synovitis score on the association between the baseline quadriceps strength and increased WOMAC pain at the 12-month follow-up (mediation proportion: 17.72%, 95% CI 9.58% – 28.35%, $P = 0.012$). Similar findings were observed for the relationship between baseline quadriceps strength and knee pain from baseline to 24 months, with a mediation proportion of 10.31% (95% CI 3.17% – 19.21%, $P = 0.036$) for the changes in effusion-synovitis (Fig. 2).

Table 3 Mediation effects for outcome WOMAC knee pain over 12 and 24 months in the whole population: association of quadriceps strength with WOMAC knee pain

	Outcome: Change in WOMAC knee pain Mediator: Change in effusion-synovitis			
	12-month follow-up * N = 1377 knees		**24-month follow-up * N = 1193 knees**	
Exposure: Baseline quadriceps strength	**β (95% CI)**	***P***	**β (95% CI)**	***P***
Direct effect	−0.33 (−0.70 to −0.03) **	0.032	−0.67 (−1.16 to −0.24) **	< 0.001
Indirect effect	−0.07 (−0.12 to −0.02) **	< 0.001	−0.08 (−0.15 to −0.01) **	0.036
Total effect	−0.40 (−0.77 to −0.07) **	0.012	−0.74 (−1.23 to −0.31) **	< 0.001
Proportion mediated †	17.72% (9.58% to 28.35%) **	0.012	10.31% (3.17% to 19.21%) **	0.036

BMI body mass index, *KLG* Kellgren-Lawrence grading; Alignment, degrees (valgus, negative), *PASE* Physical Activity Scale for the Elderly, *CESD* Center for Epidemiologic Studies Depression Scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

Positive (+) beta coefficient indicates an increase in WOMAC pain

* Models for mediation by change in effusion-synovitis score adjusted for sex, age, race, BMI, KLG, alignment, CESD score, PASE score and WOMAC knee pain at baseline

** Significant

† The mediation percentage = β of indirect effect/β of total effect

Sensitivity analysis

In the sensitivity analysis, similar findings were observed when examining the population with ROA. The association between baseline quadriceps strength and changes in WOMAC knee pain over 12 and 24 months was found to be statistically significant (see Supplemental Table 3.). Furthermore, changes in effusion-synovitis were found to correspond with changes in knee pain at the same follow-up intervals (see Supplemental Table 3.). This relationship between baseline quadriceps strength and effusion-synovitis changes remained consistent in the population with ROA (see Supplemental Table 4). When focusing on the knees with ROA, the association between baseline quadriceps strength and changes in WOMAC knee pain was partly influenced (mediation proportion: 9.66%, 95% CI 2.32% – 17.61%, $P = 0.008$) by the changes in effusion-synovitis score at the 12-month follow-up, although this mediation was not observed at the 24-month follow-up (see Supplemental Table 5). In contrast, in the group without ROA, no significant association was found between baseline quadriceps strength and changes in WOMAC knee pain or effusion-synovitis during any follow-up periods (see Supplemental Tables 3. and 4). Additionally, no mediating effect of changes in effusion-synovitis on the relationship between baseline quadriceps strength and changes in WOMAC knee pain was observed at the 12-month or 24-month follow-up in this non-ROA group (see Supplemental Table 5).

Discussion

In the present study, our findings revealed a significant effect of baseline quadriceps strength on WOMAC knee pain over a two-year period in the individuals studied, where this could be partially explained by the changes in effusion-synovitis. A mediation model was employed to investigate and elucidate the underlying mechanism, indicating that quadriceps strength can influence effusion-synovitis, which in turn impacts changes in knee pain. Stratification of the subjects based on the presence of ROA at baseline showed that these associations were stronger in individuals with ROA compared to those without ROA.

The relationship between baseline quadriceps strength and changes in knee pain

Quadriceps weakness has been widely recognized as a potential risk factor for knee pain, as supported by numerous studies [30, 35–37]. Our findings regarding the relationship between baseline quadriceps strength and changes in knee pain agree with previous reports [35, 36]. Importantly, the significant associations between

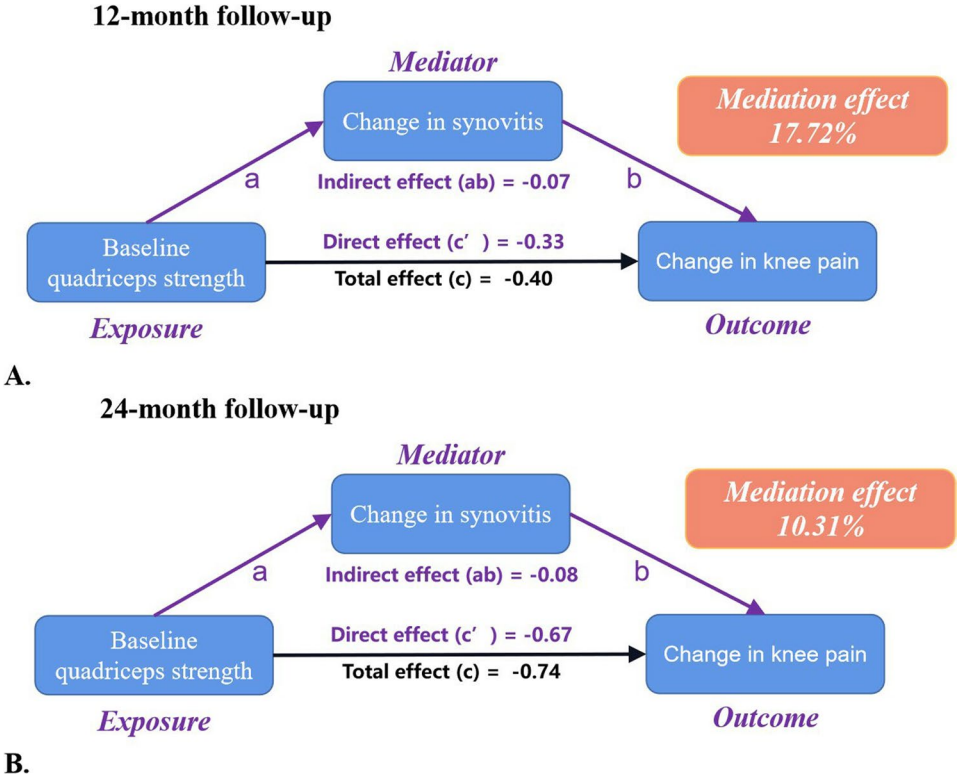

Fig. 2 Schematic diagram of the mediating effect of effusion synovitis changes on quadriceps strength and WOMAC pain. **a**: effect of independent variable on intermediary variable; **b**: effect of mediating variable on dependent variable; **ab**: mediating effect; **c**: total effect of independent variable on dependent variable; **c**′: direct effect of independent variable on dependent variable, that is, effect value after controlling intermediary variable

baseline quadriceps strength and changes in knee pain exclusively in subjects with ROA were observed, but not in those without ROA at baseline. This finding may be attributed to the disparity in baseline quadriceps strength levels between the two groups, with ROA knees exhibiting significantly lower strength compared to their normal counterparts. It implies that quadriceps strength below the threshold required to protect the knee joint offers limited protection to the knee and renders it more susceptible to other sources of pain. Therefore, the presence of ROA might have influenced the association between quadriceps strength and knee pain to some extent. Quadriceps strength training could potentially contribute to alleviating or preventing the worsening of knee pain in individuals with ROA.

The relationship between changes in effusion synovitis and knee pain

Previous reports have suggested that synovitis plays a crucial role in the development of knee pain [38]. Additionally, significant relationships were found between changes in effusion-synovitis and WOMAC knee pain, offering additional evidence for the involvement of synovitis in the development of knee pain. The assessment of effusion-synovitis was conducted on synovium tissue, which is rich in nociceptors. Inflammation in this tissue has potential to lower the threshold of nociception [39, 40]. This mechanism could provide an explanation for the observations. Furthermore, the relationships remained independent of other stratification factors (i.e., ROA), further indicating that effusion-synovitis is directly associated with knee pain.

The relationship between baseline quadriceps strength and changes in effusion-synovitis

The primary analysis revealed a significant relationship between baseline quadriceps strength and changes in effusion-synovitis [17]. In a cross-sectional study of 105 patients with KOA, Knoop et al. [41] discovered a similar relationship. In this study, effusion-synovitis was assessed in the suprapatellar bursa, which is surrounded by the quadriceps tendon, patella, and femur [18]. Weakness in the quadriceps during walking or other lower limb activities can lead to an abnormal local mechanical environment (friction and stress) in the patellofemoral joint, given the direct association between the patella trajectory and quadriceps strength [19]. From a biomechanical standpoint, insufficient quadriceps strength fails to effectively protect the synovium in the knee. Recent advances in skeletal muscle research have highlighted the inflammatory regulatory roles of various myokines (e.g., irisin, TNF-α, and IL-6) secreted by muscle tissue [21–24].

Wang et al. [23] demonstrated that irisin exhibits chondroprotective effects through suppression of pro-inflammatory pathways. Similarly, Rainbow et al. [42] elucidated the genetic mechanisms by which skeletal muscle modulates cartilage homeostasis via inflammatory regulation. The quadriceps, as a crucial skeletal muscle, may show differences in myokine secretion depending on its muscle strength levels. These differential secretory patterns could potentially influence adjacent articular structures, particularly the suprapatellar synovium, thereby modulating the progression of effusive synovitis through local paracrine effects.

The mediating effect of effusion-synovitis

In our mediating analyses, the associations between baseline quadriceps strength and changes in WOMAC knee pain at 12- and 24-month follow-ups was partly mediated by changes in effusion-synovitis, accounting for 17.72% and 10.31% of their association effect, respectively. The mediating effect of effusion-synovitis weakened as the duration of follow-up increased. Interestingly, the associations between baseline quadriceps strength and changes in effusion-synovitis were attenuated over a longer follow-up period. This suggests that the mediating effect of effusion-synovitis appears to be heavily influenced by the correlation between quadriceps strength and effusion-synovitis. In addition, effusion-synovitis was shown to be more sensitive to quadriceps weakness compared to knee pain. This raises the possibility that the changes in effusion-synovitis resulting from quadriceps weakness may precede the onset of knee pain.

Furthermore, our analysis was stratified based on the presence of ROA at baseline, and the significant mediating effect of effusion-synovitis was only observed during the 12-month follow-up in the population with baseline ROA. In other words, effusion-synovitis may play a crucial role in the relationship between quadriceps strength and knee pain in short terms for patients with ROA. However, when the follow-up period was extended to 24 months, the relationship could be more susceptible to influence from additional confounding factors, such as fluctuations in quadriceps strength. Additionally, these confounding factors also influenced the magnitude of the mediating effect of effusion-synovitis. Interestingly, we discovered that effusion-synovitis mediated nearly 10% of the effect of quadriceps strength on knee pain, which was significantly lower than the mediation effect observed in the whole population (accounting for 17.72% of the total effect). This may be related to the complex knee conditions in ROA patients. Compared with healthy individuals, ROA patients' knees typically exhibit more complicated biomechanical and inflammatory issues. When multiple mediating factors coexist, the proportion mediated by effusion-synovitis may be quite limited.

This study observed that the mediation effect of effusion-synovitis changes and the direct effect of quadriceps strength on knee pain were in the same direction, indicating that effusion-synovitis changes represent a complementary mediator that enhances the impact of quadriceps strength on knee pain. This finding may provide new insights for clinical prevention and treatment of knee pain. Based on quadriceps strengthening exercises, adjuvant therapies targeting knee effusion-synovitis (e.g., infrared, ultrasound, or shockwave therapy) might yield better outcomes. This hypothesis urgently requires verification through interventional studies. Notably, the mediation effect size did not exceed 20%, suggesting that while effusion-synovitis is likely a mediator in the relationship between quadriceps strength and knee pain, it is clearly not the only one. This may be related to the assessment location of effusion-synovitis [18]. According to the MOAKS scoring system, clinicians perform semi-quantitative assessments of effusion-synovitis in the suprapatellar pouch based on MRI data. Isolated evaluation of inflammation in the suprapatellar pouch may not fully reflect the overall inflammatory status of the knee joint. Additionally, knee pain has diverse etiologies [43], and not all reported pain in our study participants may necessarily be inflammatory in nature, which could contribute to the relatively low mediation proportion observed.

To the best of our knowledge, this study is the first to investigate into the mediating role of effusion-synovitis in the causal pathway connecting quadriceps strength and knee pain over a longitudinal period. Despite conducting our analyses in accordance with the AGReMA guidelines to ensure comprehensive and accurate results, some limitations of this study should also be noted. Firstly, our analyses only included subject knees with complete clinical data, potentially introducing selection bias and limiting the generalizability of our findings. Secondly, our study utilized isometric quadriceps strength as the measurement of exposure, which may only partially reflect the state of the quadriceps. While this measure is commonly used in clinical settings due to accessibility, it does not replicate daily activities like walking, running, and squatting. Consequently, future studies should aim to assess the actual state of quadriceps strength by considering daily activities to better understand the association between the quadriceps and knee structures or symptoms. Thirdly, quantitative measurements of effusion-synovitis were not obtained in our study, which may influence the sensitivity of measurement in effusion-synovitis changes. In the present study, we adopted a well-recognized semiquantitative assessment, MOAKS system, to estimate the effusion-synovitis changes and benefit the promotion of our results. Fourth, in our mediation analysis, since the R Mediation Package does not support ordinal categorical data, we approximated the

change in effusion-synovitis (mediator) and the change in knee pain (outcome)—both multi-level ordinal variables (with more than five levels and adequate sample distribution)—as continuous variables. While this approach is reasonable given the distribution of the data, we acknowledge that it may introduce some bias. Future studies could employ more rigorous methods, such as structural equation modeling, to better handle ordinal variables. Finally, our investigation focused solely on examining the mediating effect of effusion-synovitis in the association between quadriceps weakness and WOMAC pain over a span of 24 months. Subsequent studies should consider extending the duration of follow-up to gain further insights into the relationship among these variables.

Conclusions

To summarize, the present study found that the association between quadriceps strength and knee pain is partially mediated by effusion-synovitis, suggesting that interventions specifically targeting effusion-synovitis may provide benefits in alleviating knee pain related to quadriceps strength. Additional interventional studies are required to establish the efficacy of targeted effusion treatment in alleviating knee pain associated with quadriceps strength.

Abbreviations

KOA	Knee osteoarthritis
OAI	Osteoarthritis Initiative
GEE	Generalized estimating equation
BMI	Body mass index
ROA	Radiographic osteoarthritis
KLG	Kellgren-Lawrence grading
FTA	Femorotibial angle
PASE	Physical Activity Scale for the Elderly
CESD	Center for Epidemiologic Studies Depression Scale
MOAKS	Magnetic Resonance Imaging Osteoarthritis Knee Score
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Authors' contributions

All authors participated in the drafting and critical revision of the article for important intellectual content, and they all provided their approval for the final version submitted for publication. LL had complete access to all study data and is accountable for data integrity and accuracy of the analysis. The study was conceived and designed by ZG and LL. ZG was responsible for data acquisition. Data analysis and interpretation were carried out by ZG, LL, and TL. Manuscript preparation was done by ZG, DA and TL. ZG and TL performed the statistical analysis.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study received approval from the medical ethical committee, and participants gave written informed consent. ClinicalTrials.gov registration no.: NCT00080171. The first registration Date is March 24, 2004. Specifically, this study is derived from OAI cohort. The OAI study was approved by institutional review boards at each OAI clinical site and the coordinating center: Memorial Hospital of Rhode Island Institutional Review Board, The Ohio State University's Biomedical Sciences Institutional Review Board, University of Pittsburgh Institutional Review Board, University of Maryland Baltimore – Institutional Review Board, and Committee on Human Research at University of California, San Francisco. All participants provided written informed consent. The Tufts Medical Center Institutional Review Board deemed that the work done at our institution was not human research because we analyzed publicly available data. This study has met all criteria for ethical standards regarding human studies as described in the 1964 Declaration of Helsinki and all amendments.

Competing interests

The authors declare no competing interests.

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