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How Do Nonsurgical Interventions Improve Pain and Physical Function in People With Osteoarthritis? A Scoping Review of Mediation Analysis Studies

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Objective. Nonsurgical interventions are recommended for osteoarthritis (OA). However, how interventions change pain and physical function is unclear. Therefore, the objectives of this scoping review were to 1) identify what potential mediators of nonsurgical interventions on pain and physical function have been evaluated and 2) summarize the findings according to intervention, joint, and outcome.

Methods. We searched Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials, and Scopus databases. Studies were included if they conducted a mediation analysis on a randomized controlled trial evaluating a nonsurgical intervention on OA of any joint. Outcomes were pain and physical function.

Results. Nine knee OA studies, evaluating diet plus exercise, exercise, unloading shoes, high-expectation communication during acupuncture, and telephone-based weight loss plus exercise were identified. Except for weight loss and self-efficacy, putative mediators (knee muscle perfusion/extensor strength/adduction moment, systemic inflammatory biomarkers, physical activity, dietary intake, and pain beliefs) were evaluated by single studies. Ten mediators partially mediated intervention (diet plus exercise, exercise, high-expectation communication) effects on pain and physical function. Eight mediators were common to pain and function (reduced weight, increased knee extensor strength, and increased self-efficacy). Constant knee flexor muscle perfusion partially mediated exercise effects on pain, and knee pain relief partially mediated exercise effects on function.

Conclusion. In knee OA, some evidence suggests that the benefits of 1) diet and exercise are mediated through changes in body weight, systemic inflammation, and self-efficacy; 2) exercise is mediated through changes in knee muscle strength and self-efficacy; and 3) high-expectation communication style is mediated through changes in self-efficacy.

INTRODUCTION

Osteoarthritis (OA) is a major cause of pain and disability (1), typically affecting the knees, hips, hands, and feet (2). Clinical guidelines recommend nonpharmacologic and pharmacologic approaches prior to surgical intervention (3–5). However, the mechanism(s) by which many nonsurgical interventions improve pain and physical function remains unclear. With this limited understanding, it is perhaps unsurprising that nonsurgical interventions have, at best, modest clinical benefits and that increasing volumes of patients opt to undergo joint arthroplasty (6). Understanding the mechanisms that mediate intervention effects can result in more targeted delivery and implementation, in addition to providing the impetus for new treatments or treatment combinations.

One method for understanding how interventions influence outcomes is mediation analysis of a randomized controlled trial (RCT). Mediation analyses can estimate the effect of an intervention on an outcome through an intermediate variable (mediator) by partitioning the total effect into indirect and direct effects (7)

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SIGNIFICANCE & INNOVATIONS

- Identifying mediators of nonsurgical interventions for osteoarthritis (OA) will help guide their optimization and the development of new interventions.
- No studies have evaluated putative mediators of nonsurgical interventions on pain or physical function for osteoarthritic joints, other than the knee.
- Reduced inflammation, reduced body weight, increased knee extensor muscle strength, and increased self-efficacy may mediate beneficial effects of nonsurgical interventions on knee OA pain and/or physical dysfunction.

(Figure 1). Indirect effects work through mediators, whereas direct effects work through other mechanisms (7). Indirect effects can provide valuable insights into the relationship between the intervention and the mediator (i.e., path a) and between the mediator and the outcome (i.e., path b). For example, if a mediator is found to affect the outcome (i.e., path b), but the intervention does not affect the mediator (i.e., path a), it may be possible to refine or innovate interventions to better target the mediators. The identification and estimation of the mediators provide an indication of causal links between the intervention and outcomes (8). Mediation analyses of clinical trials are recommended by the US National Institutes of Health and UK Medical Research Council to understand how interventions work (9,10). The evaluation of mediators of nonsurgical interventions is an emerging topic, and an overview of the literature using a scoping review approach is required to inform the potential future synthesis of mediators (11). The objectives of this scoping review were to (1) identify what potential mediators of nonsurgical interventions on pain and physical function in people living with OA have been evaluated and (2) summarize the findings according to intervention, OA joint, and outcome.

MATERIALS AND METHODS

This scoping review was conducted in accordance with an established framework (12). It is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (13).

Data sources and search. An electronic search was performed in the following databases: Medline (Ovid), Embase (Ovid), CINAHL (EBSCO), Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus (Elsevier) from inception to January 24, 2022. The search strategy was composed of keywords and terms related to "OA" and "mediation analysis" used in previous reviews (14,15). The systematic search was conducted by a single author (YLL) (Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24983).

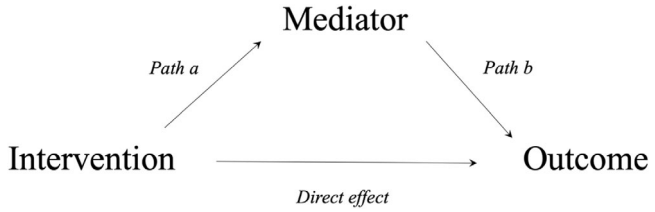


Figure 1. Simple mediator model showing the indirect effect is the product of paths a (effect from intervention to mediator) and b (effect from mediator to outcome). The total effect is the sum of direct and indirect effects.

Study selection. Following a search of the databases, duplicates were removed, and 2 authors (YLL and MH) independently screened titles and abstracts for inclusion. During screening of titles and abstracts, reviewers included any RCT conducted on humans for full-text review to account for the possibility that potentially eligible studies did not include the term "mediation analysis" or related terms. Full texts of potentially eligible articles were obtained and independently screened by 2 authors (YLL and MH) for eligibility. Disagreements were resolved through discussion and by a third author (HL) as necessary. Studies were included if they met the following criteria: 1) RCT evaluating nonsurgical interventions in people with OA of any joint (as defined by the original study authors or chronic joint pain [>3 months] consistent with OA in middle-aged adults or older [≥45 years of age]) (16–18); and (2) conducted a mediation analysis to test or estimate indirect effects of any nonsurgical intervention on self-reported pain and/or self-reported or performance-based physical function. Studies published in a language other than English, reviews, editorials, dissertations, and abstracts were not included. The Covidence software (Veritas Health Information) was used to screen and manage references.

Data charting. The following data were independently extracted by 2 authors (YLL and MH): participant characteristics (age, sex, main inclusion criteria), sample size, site of OA (e.g., knee, hip, hand), interventions, mediators and outcomes (construct, measurement tools, and follow-up times), method of mediation analysis, confounding control, point estimates, and CIs (path a, path b, total effects, direct effect and indirect effects, proportion mediated; Figure 1). If required information was not reported in the article, a maximum of 3 emails were sent to the authors of the included study to request data. Data were considered irretrievable if no response from the authors was received. When considered irretrievable, point estimates for the variables (total effects, indirect effects, direct effects, path a or path b) were calculated from the reported data using the following equations:

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Indirect effects =
path a × path b

Total effects =
direct effects + indirect effects

Proportion mediated =
(indirect effects/total effects) × 100

The proportion mediated represents the percentage of the total effect that is accounted for by the identified mediators. However, in accordance with recommendations (19), the proportion mediated was only estimated for studies in which the direct and indirect effects were in the same direction. Briefly, the proportion mediated is of questionable meaning (larger than 100%) when the indirect and direct effects operate in different directions. Hence, although the proportion mediation is a useful summary measure, it is only applicable when the direct and indirect effects are in the same direction (19).

Data synthesis. Estimates of direct, indirect and total effects, paths "a" and "b," and proportion mediated were extracted to narratively synthesize the evidence by site of OA, intervention, mediator, and outcome (pain or physical function).

Quality of the studies. The assessment of methodologic quality was conducted using the tool proposed by Vo et al (20). Two reviewers (YLL and MH) independently applied the criteria and scored (yes) or (no) for each item. Items deemed not applicable to a specific study were scored as (not applicable). Any disagreements were discussed by the authors (YLL and MH) and by a third author (HL) as necessary.

RESULTS

The search strategy identified 22,402 studies, of which 164 full texts were screened to determine eligibility (Figure 2). Nine

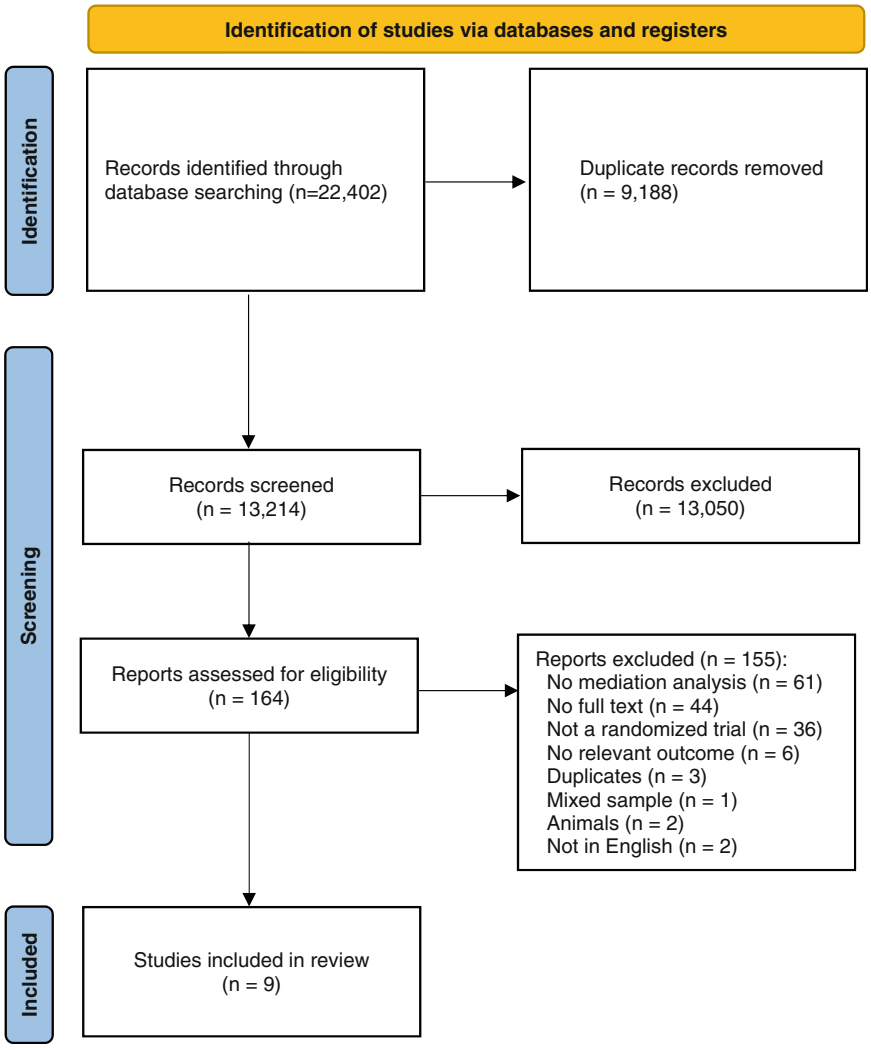


Figure 2. Flow chart of results for each stage of the search strategies.

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Table 1. Summary of eligible studies*

Author, year	Participant characteristics	Inclusion criteria	Site of osteoarthritis	Intervention	Comparison(s)	Mediator(s)	Outcome(s) (measure)/ time points	Analysis method/ significance test; confounding control; single or multiple mediator model
Bandak et al, 2019 (25)	N = 33; age, mean ± SD years = 64 ± 8; BMI = 28.4 ± 3.7 kg/m^2; 79% female	Age ≥40 years; clinical and radiographic knee OA; BMI between 20 and 35kg/m^2	Knee	Exercise	No intervention	Knee extensors and flexors muscle perfusion (voxel)	Pain (KOOS)/ 12 weeks	Model-based approach/ nonparametric bootstrapping for variance estimation; controlled; single
Foy et al, 2011 (21)	N = 1,759; age, mean ± SD years = 59 ± 7; BMI = 37.1 ± 6.2 kg/m^2; 65% female	Age 45–74 years; type 2 diabetes mellitus; BMI ≥25 or ≥27 kg/m^2 if taking insulin; knee pain	Knee	Diet and exercise	Diabetes mellitus support and education	Weight (kg)	Pain, physical function (WOMAC) / 1 year	Modified Baron and Kenny/ Sobel test; controlled; single
Hall et al, 2018 (26)	N = 97; age, mean ± SD years = 65 ± 9; BMI = 28.9 ± 4.8 kg/m^2; 50% female	Medial knee pain; medial radiographic knee OA	Knee	Exercise	No intervention	Isometric knee extensor muscle strength (Nm/kg)	Pain, physical function / 12 weeks	Wearden and Emsley/ bootstrapped; controlled; single
Hsiao-Wei Lo et al, 2016 (29)	N = 485; age, mean ± SD years = 65 ± 9; BMI 32.2 ± 7.5 kg/m^2; 63% female	Age ≥50 years; clinical and radiographic knee OA; pain in the knee in the past 2 weeks ≥3 of 10 on VAS	Knee	High-expectation communication style during acupuncture sessions	Neutral-expectation communication style during acupuncture sessions	Self-efficacy (modified Arthritis Self-Efficacy Questionnaire)	Pain (WOMAC)/ 3 months	Baron and Kenny; controlled; single
Mihalko et al, 2019 (22)	N = 454; age, mean ± SD years = 66 ± 6; BMI = 33.6 ± 3.7 kg/m^2; 72% female	Age ≥55 years; radiographic OA; knee pain most days of the week; BMI = ≥27 to ≤41 kg/m^2; sedentary lifestyle	Knee	Diet and exercise	1) Exercise 2) Diet	Self-efficacy for walking duration (Walking Efficacy Scale) and balance (Activities-specific balance confidence scale)	Pain (WOMAC), physical function (WOMAC; 6-minute walking test, gait speed)/ 18 months	Baron and Kenny/Sobel test; controlled; single
Paterson et al, 2018 (28)	N = 164; age, mean ± SD years = 64 ± 7; BMI = 29.7 ± 3.6 kg/m^2; 51% female	Age ≥50 years; knee pain most days of past month; average pain on walking ≥4 of 11 over past week; K/L grade 2; radiographic medial knee OA	Knee	Unloading shoes	Conventional shoes	Peak knee adduction moment (Nm/BW × Ht %); knee adduction moment impulse (Nm/BW × Ht %)	Pain during walking (NRS)/ 6 months	Causal mediation analysis/ bootstrapped standard errors; controlled; single

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Table 1. (*Cont'd*)

Author, year	Participant characteristics	Inclusion criteria	Site of osteoarthritis	Intervention	Comparison(s)	Mediator(s)	Outcome(s) (measure)/ time points	Analysis method/ significance test; confounding control; single or multiple mediator model
Rejeski et al, 1998 (27)	N = 157; age, mean ± SD years = 69 ± 6; BMI >30 kg/m^2 in 48%; 72% female	Age ≥60 years; pain on most days of the month in 1 or both knees; radiographic OA	Knee	Exercise	Education about OA	Pain (Knee pain scale), self-efficacy (stair-climbing self-efficacy)	Physical function (Timed-stair climb) / 18 months	Baron and Kenny; controlled; multiple
Runhaar et al, 2019 (23)	N = 99; age, mean ± SD years = 69 ± 6; BMI = 33.5 ± 4.7 kg/m^2; 71% female	Age ≥60 years; BMI ≥28kg/m^2; knee pain on most days of the month; sedentary lifestyle; radiographic OA	Knee	Diet and exercise	Education about OA and healthy living	Inflammatory biomarkers (IL-6, TNF, soluble IL-6 receptor, soluble IL-1 receptor, CRP), and BMI	Pain and physical function (WOMAC) / 18 months	Causal mediation analysis/ controlled; single and multiple
Williams et al, 2019 (24)	N = 119; age, mean ± SD years = 62 ± 13; BMI = 32.7 ± 3.3 kg/m^2; 62% female	OA pain >3 months; ≥18 years old; BMI = between ≥27 and <40kg/m^2; average pain of ≥3 of 10 in the NRS over the past week or moderate level of interference in activities of daily living	Knee	Diet and physical activity support	Usual care	Weight (kg), physical activity (Active Australia Survey), dietary intake (Food frequency questionnaire), pain beliefs (Survey of Pain Attitudes One-item Questionnaire)	Pain (NRS)/6 months	Causal mediation analysis/ bootstrap simulation; controlled; single

* BMI = body mass index; BW = body weight; CRP = C-reactive protein; DSE = diabetes mellitus support and education; Ht = height; IL = interleukin; K/L = Kellgren/Lawrence; KOOS = Knee and Osteoarthritis Outcome Score; NRS = Numerical Rating Scale; OA = osteoarthritis; TNF = tumor necrosis factor; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

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Table 2. Summary of mediator models*

Author, year	Intervention and control	Path a	Mediator	Path b	Outcome	Total effect (point estimate [95% CI])	Direct effect (point estimate [95% CI])	Indirect effect (point estimate [95% CI])	Proportion mediated, % (95% CI)
Bandak et al, 2019 (25)	Exercise vs. no intervention	✓	Total muscle – Proportion of highly perfused voxels (%)	–	Pain‡	10.70 (3.30, 18.10)	8.57 (−3.03, 15.58)	2.10 (−0.10, 9.60)	20 (−2, 123)
		✓	Total muscle – Initial rate of enhancement	–			8.40 (0.17, 15.38)	2.30 (−0.40, 6.30)	21 (−6, 81)
		✓	Total muscle – Initial rate of enhancement index (%)	—			8.79 (0.88, 15.78)	1.90 (−1.20, 6.00)	18 (−15, 88)
		NS	Total muscle – Maximal enhancement composite score	—			8.64 (−0.01, 15.66)	2.10 (−0.10, 7.00)	19 (−2, 88)
		✓	Total muscle – Maximal enhancement index (%)	—			8.58 (−1.70, 15.14)	2.10 (−0.10, 9.50)	20 (−1, 103)
		NS	Knee extensors – Proportion of highly perfused voxels (%)	—			7.95 (−2.79, 15.21)	0.60 (−0.70, 4.30)	5 (−7, 54)
		✓	Knee extensors – Initial rate of enhancement	—			7.91 (−0.05, 15.16)	0.90 (−1.80, 3.10)	9 (−26, 35)
		✓	Knee extensors – Initial rate of enhancement index (%)	—			8.86 (0.88, 15.98)	1.30 (−3.60, 5.10)	12 (−43, 53)
		NS	Knee extensors – Maximal enhancement composite score	—			7.68 (−3.24, 14.64)	0.20 (−0.60, 2.30)	2 (−7, 30)
		NS	Knee extensors – Maximal enhancement index (%)	—			7.73 (−3.12, 14.73)	0.50 (−0.70, 3.90)	5 (−9, 44)
		✓	Knee flexors – Proportion of highly perfused voxels (%)	—			10.15 (1.54, 17.31)	2.80 (0.00, 10.80)	26 (0, 138)
		✓	Knee flexors – Initial rate of enhancement	—			9.77 (2.46, 16.84)	2.80 (0.00, 7.70)†	26 (0, 124)†
		✓	Knee flexors – Initial rate of enhancement index (%)	—			9.38 (2.02, 17.49)	1.80 (−0.70, 5.50)	17 (−8, 82)
		✓	Knee flexors – Maximal enhancement composite score	—			10.50 (2.20, 26.93)	3.00 (0.10, 12.30)†	28 (1, 171)†
		✓	Knee flexors – Maximal enhancement index (%)	—			10.21 (2.93, 17.47)	3.00 (0.10, 11.50)†	28 (1, 146)†
Foy et al, 2011 (21)	Diet and exercise vs. diabetes mellitus support and education	✓	Weight	✓	Pain‡	−0.27	0.04 (0.18)§	−0.31 (0.15)¶	n/a
			Weight	✓	Physical function‡	−1.52	−0.07 (0.53)§	−1.45 (0.45)¶	95†

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Table 2. (*Cont'd*)

Author, year	Intervention and control	Path a	Mediator	Path b	Outcome	Total effect (point estimate [95% CI])	Direct effect (point estimate [95% CI])	Indirect effect (point estimate [95% CI])	Proportion mediated, % (95% CI)
Hall et al, 2018 (26)	Exercise vs. no intervention	✓	Knee extensor strength	✓	Pain‡	1.8 (0.8, 2.8)	1.1 (0.0, 2.2)	0.7 (0.1, 1.3)†	38 (24, 98)†
			Knee extensor strength	✓	Physical function‡	2.9 (−0.2, 5.8)	1.0 (−2.3, 4.3)	1.9 (0.1, 3.6)†	60 (−192, 356)†
Hsiao-Wei Lo et al, 2016 (29)	High-expectation vs. neutral-expectation communication during acupuncture	✓	Self-efficacy related to symptoms	✓	Pain‡	−2.01	−0.65 (−3.35, 2.05)	−1.36 (−2.80, −0.15)†	68†
Mihalko et al, 2019 (22)	Diet and exercise vs. exercise only	✓	Self-efficacy for walking duration	—	6-minute walk test‡	0.17	0.10	0.07†	41†
				—	Gait speed‡	0.17	0.08	0.09†	53†
				—	Physical function‡	−0.25	−0.14	−0.11†	44†
				—	Pain‡	−0.21	−0.13	−0.08†	38†
		✓	Balance efficacy	—	6-minute walk test‡	0.14	0.13	0.01	7
				—	Gait speed‡	0.14	0.10	0.04	29
				—	Physical function‡	−0.25	−0.18	−0.07†	28†
				—	Pain‡	−0.21	−0.17	−0.04	19
	Diet and exercise vs. diet only	✓	Self-efficacy for walking duration	—	6-minute walk test‡	0.33	0.24	0.09†	27†
				—	Gait speed‡	0.12	0.05	0.07†	58†
				—	Physical function‡	0.23	−0.05	−0.18†	−78†
				—	Pain‡	−0.25	−0.10	−0.15†	60†
		✓	Balance efficacy	—	6-minute walk test‡	0.30	0.27	0.03	10
				—	Gait speed‡	0.10	0.09	0.00	4
				—	Physical function‡	-0.19	−0.09	−0.10†	53†
				—	Pain‡	−0.22	−0.15	−0.07†	32†
Paterson et al, 2018 (28)	Unloading shoes vs. conventional shoes	✓	Peak knee adduction moment	✓	Walking knee pain‡	0.04 (−0.79, 0.86)	−0.20 (−1.06, 0.66)	0.23 (−0.03, 0.50)	n/a
		✓	Knee adduction moment impulse	NS	Walking knee pain‡	−0.02 (−0.84, 0.80)	−0.10 (−1.00, 0.79)	0.09 (−0.23, 0.40)	n/a
	Unloading shoes vs. conventional shoes (mild radiographic OA)		Peak knee adduction moment		Walking knee pain‡	−1.38 (−2.81, 0.06)	−1.26 (−2.71, 0.20)	−0.12 (−0.44, 0.20)	9
			Knee adduction moment impulse		Walking knee pain‡	−1.40 (−2.74, 0.06)	−1.32 (−2.70, 0.07)	−0.09 (−0.41, 0.24)	6
	Unloading shoes vs. conventional shoes (moderate and severe radiographic OA)		Peak knee adduction moment		Walking knee pain‡	0.70 (−0.31, 1.70)	1.01 (−0.01, 2.01)	−0.31 (−0.65, 0.03)	n/a
			Knee adduction moment impulse		Walking knee pain‡	0.63 (−0.40, 1.66)	0.74 (−0.36, 1.85)	−0.11 (−0.46, 0.24)	n/a

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Table 2. (*Cont'd*)

Author, year	Intervention and control	Path a	Mediator	Path b	Outcome	Total effect (point estimate [95% CI])	Direct effect (point estimate [95% CI])	Indirect effect (point estimate [95% CI])	Proportion mediated, % (95% CI)
Rejeski et al, 1998 (27)	Exercise vs. education control		Knee pain	NS	Physical function	—	—	—	—
		NS	Self-efficacy for climbing stairs	NS		—	—	—	—
Runhaar et al, 2019 (23)	Diet and exercise vs. education control	NS	IL-6	NS	Pain‡	−0.75	−0.71 (−1.18, −0.23)	−0.04†	5†
				NS	Physical function‡	−1.64	−1.50 (−3.00, −0.00)	−0.14†	8†
				NS	Pain#		−0.63 (−1.12, −0.15)		
				NS	Physical function#		−1.24 (−2.74, 0.27)		
		NS	TNF	NS	Pain‡	−0.74	−0.74 (−1.21, 0.27)	0.00†	0†
				NS	Physical function‡	−1.63	−1.62 (−3.11, −0.13)	−0.01†	1†
				NS	Pain#		−0.63 (−1.12, −0.15)		
				NS	Physical function#		−1.24 (−2.74, 0.27)		
		NS	IL-1R	NS	Pain‡	−0.74	−0.72 (−1.20, −0.24)	−0.02†	2†
				NS	Physical function‡	−1.63	−1.53 (−3.05, 0.02)	−0.10†	6†
				NS	Pain#		−0.63 (−1.12, −0.15)		
				NS	Physical function#		−1.24 (−2.74, 0.27)		
		NS	IL-6R	NS	Pain‡	−0.75	−0.75 (−1.20, −0.28)	0.00	n/a
				NS	Physical function‡	−1.64	−1.65 (−3.15, −0.15)	0.01	n/a
		NS	CRP	NS	Pain‡	−0.74	−0.68 (−1.16, −0.20)	−0.06†	8†
				NS	Physical function‡	−1.63	−1.47 (−3.00, 0.06)	−0.16†	10†
				NS	Pain#		−0.63 (−1.12, −0.15)		
				NS	Physical function#		−1.24 (−2.74, 0.27)		
Williams et al, 2019 (24)	Diet physical activity support vs. usual care	NS	Weight	NS	Pain‡	0.45 (−0.49, 1.34)	0.43 (−0.52, 1.29)	0.02 (−0.14, 0.20)	5
		NS	Physical activity	NS		0.39 (−0.50, 1.33)	0.47 (−0.43, 1.48)	−0.08 (−0.34, 0.08)	n/a
		NS	Dietary intake	NS		0.48 (−0.44, 1.41)	0.49 (−0.42, 1.40)	−0.01 (−0.17, 0.13)	n/a
		NS	Pain beliefs	NS		0.48 (−0.44, 1.35)	0.53 (−0.42, 1.43)	−0.04 (−0.23, 0.09)	n/a

* Check marks indicate that the study provided the values for the path and it was significant. CRP = C-reactive protein; IL-1R = soluble interleukin-1 receptor; n/a = not applicable to estimate, as direct and indirect effects are in opposite directions; NS = not significant; TNF = tumor necrosis factor.
† Significant (as indicated with the absence of zero in 95% confidence intervals).
‡ Single mediator model.
§ Values represent standard error as 95% CI.
¶ Significant; value represents standard error as 95% CI.
# Multiple mediator model.

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studies including 3,367 participants with knee OA were eligible. OA studies examining OA in other joints were not found. The mean age of the participants ranged from 59 to 69 years, 65% were female, and their average body mass index (BMI) ranged from 28.4 to 37.1 kg/m^2. Most studies (78% [n = 7]) included participants with radiographic knee OA. Three studies assessed diet and exercise (21–23), 1 study assessed telephone-based weight loss plus physical activity support (24), 3 studies assessed exercise (25–27), 1 study assessed unloading shoes (28), and 1 study assessed high-expectation communication during acupuncture sessions (29). Eight studies investigated putative mediators of intervention effects on pain, and 5 studies assessed putative mediators of physical function. For pain outcomes, 5 studies (21–23,26,29) used the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (30) pain subscale, 2 studies (24,28) used the numerical rating scale (31), and 1 study (25) used the Knee Injury and Osteoarthritis Outcome Score (32). For physical function, 4 studies (21–23,26) used the WOMAC physical function subscale, 1 study (22) used the 6-minute walking test and gait speed, and 1 study (27) used a stair-climb test (27). A summary of each study is provided in Table 1, with point estimates of pathway a and pathway b where available presented in Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24983).

Three studies assessed the mediational role of self-efficacy (22,27,29), 2 studies assessed the mediational role of body weight (21, 24), and single studies assessed the mediational role of knee muscle perfusion (25), knee extensor strength (26), the external knee adduction moment (28), inflammatory biomarkers (23), knee pain (27), physical activity (27), dietary intake (27) and pain beliefs (24). One study reported on the mediational effect of cardiovascular fitness on WOMAC summary score (21); however data specific to pain and physical function were not retrievable. Details of the results are provided in Table 2, with an overview of findings in Figure 3.

Thirty putative mediators were investigated for pain, of which 10 partially mediated the intervention effects on pain. Eleven putative mediators were investigated for physical function, of which 10 partially mediated the intervention effects on physical function. The following 8 mediators partially mediated both pain and physical function: reduced weight, increased knee extensor strength, increased self-efficacy with respect to ability to walk at increasing distances at moderately fast pace without stopping (22,33), increased confidence in performing common daily tasks that require balance and stability (34), and reductions in interleukin-6 (IL-6), tumor necrosis factor (TNF), soluble IL-1 receptor (IL-1R), and C-reactive protein (CRP) levels.

Increased self-efficacy described as confidence in capacity to function despite symptoms of OA (35) and constant knee flexor muscle perfusion were also found to partially mediate intervention effects on pain. Increased self-efficacy with respect to confidence in stair climbing and knee pain relief also partially mediated intervention effect on physical function (27). Eighteen of the investigated putative mediators did not mediate intervention effects on pain and/or physical function including changes in knee adduction moment (peak and impulse), soluble IL-6R, muscle perfusion (total muscle and knee extensor muscle perfusion variables, flexor

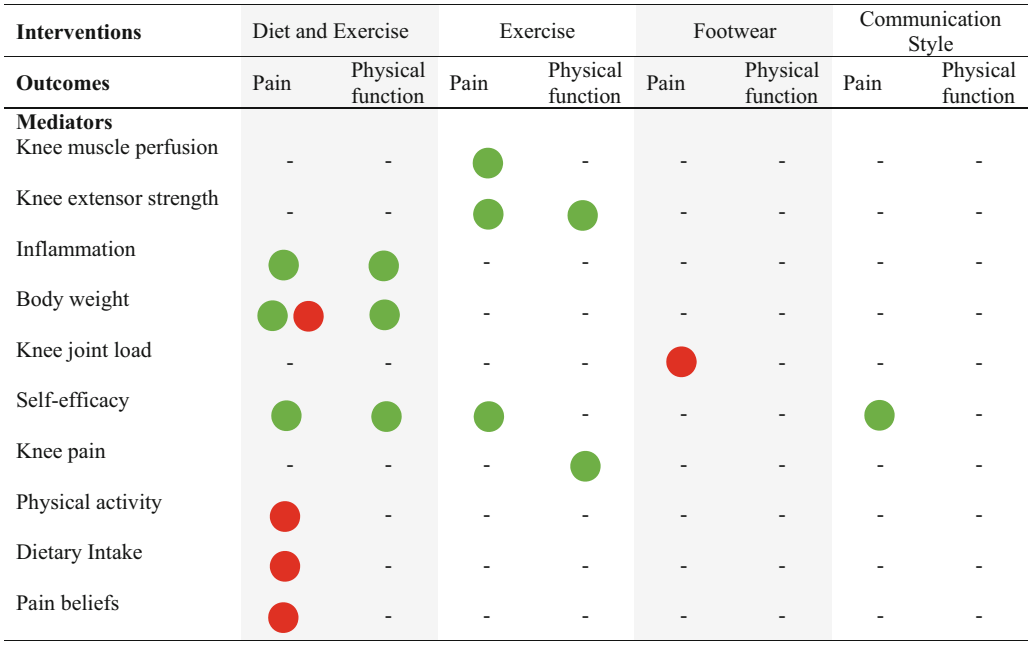


Figure 3. Overall summary of evidence in knee osteoarthritis populations. Green circles indicate evidence from a single study as a partial mediator. Red circle indicates no evidence from a single study as a partial mediator. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24983/abstract.

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proportion of highly perfused voxels, and flexor initial rate of enhancement index), physical activity, dietary intake, and pain beliefs.

Mediators of pain. *Diet and exercise combined interventions.* Four studies (4 RCTs) assessed diet and exercise interventions (21–24). One study showed that weight loss partially mediated the effects of diet and exercise compared to diabetes mellitus support and education on pain relief at 1 year (21). However, in another study the effects of a diet intervention combined with physical activity support on pain were not mediated by changes in weight, physical activity, dietary intake, or pain beliefs at 6 months compared to usual care (24). Changes in some inflammatory biomarkers (IL-6, TNF, soluble IL-1R, and CRP) partially mediated the effect of diet and exercise compared to an education control group on pain relief at 18 months, but changes in soluble IL-6R did not (23). Using the inflammatory biomarkers that significantly mediated effects in the single mediator models, changes in these biomarkers mediated 15% of pain relief at 18 months in a multimediator model. An increase in self-efficacy relating to tasks that require balance and stability partially mediated the effects of diet and exercise compared to diet only on pain relief at 18 months but not compared to exercise only (22). Increased self-efficacy for walking duration also partially mediated effects of diet and exercise on pain relief at 18-months compared to diet only and exercise only (22). The effects of weight loss plus physical activity support compared to usual care on pain at 6 months were not mediated by changes in weight, physical activity, dietary intake, or pain beliefs (24).

Exercise only. Three studies (3 RCTs) assessed the effects of exercise (25–27). Increases in knee extensor strength partially mediated the effects of a strengthening exercise program compared to no exercise on pain relief at 12 weeks (26). A constant level of knee flexor muscle perfusion partially mediated the effects of supervised facility-based functional and individualized exercise compared to no intervention control group on pain relief at 12 weeks (25). Several other changes in measures of knee extensor and total muscle perfusion did not mediate effects of the intervention (Table 2). In a multimediator model, reduced knee pain and increased self-efficacy to climb stairs partially mediated the effects between a combined aerobic and resistance exercise program and education on stair climb time (27).

Footwear. One study (28) assessed whether the effects of unloading shoes compared to conventional shoes on walking pain at 6 months were mediated by changes in the knee adduction moment (peak and impulse). These measures did not significantly mediate the effects of the unloading shoes on pain in the overall sample. Results of separate mediation analyses conducted by radiographic disease severity (Kellgren Lawrence grade 2 and grade 3 together with grade 4) also did not reach statistical significance.

Communication style. One study (29) assessed whether the effects of a "high expectation" versus a "neutral" communication style during acupuncture sessions on 3-month pain levels were mediated by changes in self-efficacy with respect to confidence in capacity to function despite symptoms of OA. Increased self-efficacy partially mediated the effects of high-expectation communication on pain at 3 months.

Mediators of physical function. *Diet and exercise combined interventions.* Three studies (3 RCTs) assessed the effects of diet and exercise combined interventions (21–23). Weight loss mediated the effect of diet and exercise compared to diabetes mellitus support and education on self-reported physical function improvement at 1 year (21). Increased self-efficacy for walking duration partially mediated the effects of a diet and exercise intervention on self-reported and objective physical function measures at 18 months compared to exercise only and diet only (22). The same study showed that increased self-efficacy (for tasks requiring balance/stability) partially mediated the effects of diet and exercise on self-reported physical function improvement at 18 months but did not mediate change in the 6-minute walk test or gait speed. Changes in inflammatory biomarkers partially mediated the effects of a diet and exercise intervention compared to education control on improved self-reported physical function at 18 months, but changes in soluble IL-1R did not (23). The inclusion of all significant inflammatory biomarkers (from the single mediating models) into a multimediating model mediated 29% of the improvement in self-reported physical function at 18 months.

Exercise only. One study (26) showed that increases in knee extensor strength mediated the effects of a strengthening exercise program compared to no intervention on self-reported physical function at 12 weeks.

Quality assessment. A detailed assessment of each study is presented in Table 3. All included studies reported an appropriate framework for the analysis, the approaches used for mediation analysis, and the clinical rationale for selecting the mediators. Most studies adjusted for, and reported, the mediator-–outcome confounders and reported the sample size of the mediation analysis, but not the sample size calculation of the mediation analysis. No study measured the mediators at a time point prior to outcomes, reported the goodness-of-fit of the models, or reported potential interactions between the intervention and confounding factors, intervention and mediator, and mediator and mediator in the mediator and outcomes models.

DISCUSSION

Only studies in knee OA were identified, with mediators of interventions including exercise with and without dietary intervention, footwear, and communication style evaluated. Putative mediators of changes in pain were evaluated more extensively

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Table 3. Summary of study quality*

	Bandak et al, 2019 (25)	Foy et al, 2011 (21)	Hall et al, 2018 (26)	Hsiao-Wei Lo et al, 2016 (29)	Mihalko et al, 2019 (22)	Paterson et al, 2018 (28)	Rejeski et al, 1998 (27)	Runhaar et al, 2019 (23)	Williams et al, 2019 (24)
Planning									
Was the mediation analysis planned a priori in the trial protocol?	✓	×	×	×	×	✓	×	×	✓
Were the mediators chosen based on the clinical rationale underlying mechanisms which the treatment affects the outcome?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the choice of mediators based on independent data?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was there a plan to collect pre- and post-randomization confounders of the exposure–mediator relationship?	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Was there a plan to collect pre- and post-randomization confounders of the mediator–mediator relationship?	×	n/a	n/a	n/a	n/a	n/a	×	×	×
Was there a plan to collect pre- and post-randomization confounders of the mediator–outcome relationship?	×	×	×	×	×	×	×	×	✓
Were the mediators measured prior to the outcome to assure the causal interpretation of the findings?	×	×	×	×	×	×	×	×	×
Was the mediator(s) measured repeatedly?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was a causal diagram reported, underlying the causal relationship of the treatment, mediator(s) and outcome?	×	×	×	×	×	×	×	×	✓
Was the sample size for the mediation analysis estimated?	×	×	×	×	×	×	×	×	✓
Was the conduct of a mediation analysis dependent on whether a statistically significant intention-to-treat treatment effect was found?	×	×	×	×	×	✓	×	×	✓
Conduct									
Was multiple imputation (or other valid approaches) used to handle missing data?	n/a	n/a	n/a	n/a	×	n/a	n/a	n/a	n/a
If a complete-case analysis was used, did they adjust for baseline covariates that were differentially distributed between responders and non-responders?	×	×	×	×	n/a	×	×	×	×
Was a sensitivity analysis conducted to assess the impact of different approaches on the findings?	×	×	×	×	×	×	×	×	✓
Does the study report separate analyses for separate mediators?	✓	✓	n/a	n/a	✓	✓	×	✓	✓
Does the study use an appropriate framework for analysis?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Does the study evaluate the goodness-of-fit of each model?	×	×	×	×	×	×	×	×	×
Does the study assess potential interaction(s) between treatment and confounding factors, treatment and mediator, mediator and mediator in the mediator and outcome models?	×	×	×	×	×	×	×	×	×
Does the study adjust for exposure-mediator and confounders?	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Does the study adjust for mediator-mediator confounders?	n/a	n/a	n/a	n/a	n/a	n/a	×	×	n/a
Does the study adjust for mediator-outcome confounders?	✓	✓	✓	✓	×	✓	✓	✓	✓
Does the study perform sensitivity analysis to assess sensitivity of the results to the assumption of no measured mediator-mediator or mediator-outcome confounder?	×	×	×	×	×	×	×	×	✓
Does the study perform sensitivity analysis to assess sensitivity of the results to potential measurement errors of the mediators?	×	×	×	×	×	×	×	×	×

(Continued)

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Table 3. (*Cont'd*)

	Bandak et al, 2019 (25)	Foy et al, 2011 (21)	Hall et al, 2018 (26)	Hsiao-Wei Lo et al, 2016 (29)	Mihalko et al, 2019 (22)	Paterson et al, 2018 (28)	Rejeski et al, 1998 (27)	Runhaar et al, 2019 (23)	Williams et al, 2019 (24)
Does the study use apt strategies when some of the mediator-mediator or mediator–outcome confounders are potentially affected by the treatment (e.g., by considering confounders as mediators themselves)?	×	×	×	×	×	×	×	×	×
Reporting									
Does the study report the approaches used for mediation analysis?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Does the study provide a causal diagram that underlies the analysis?	×	✓	✓	✓	×	✓	✓	✓	✓
Does the study report the sample size calculation?	×	×	×	×	×	×	×	×	✓
Does the study report the actual sample size of the mediation analysis?	✓	×	✓	✓	✓	✓	✓	✓	✓
Does the study report how missing data is handled?	n/a	n/a	n/a	n/a	×	n/a	n/a	n/a	n/a
Does the study report all confounders considered and adjusted for in the analysis?	✓	✓	✓	✓	×	✓	✓	✓	✓
Does the study report the model building procedure and the final form of all models used in the analysis?	×	×	✓	✓	×	✓	×	✓	✓
Does the study report the goodness-of-fit of the models?	×	×	×	×	×	×	×	×	×
Does the study report the point estimates and the confidence intervals of the different direct, indirect and total treatment effects?	×	×	✓	×	×	✓	×	×	✓
Does the study report the methods and results of all sensitivity and other additional analyses (in the main paper or appendices)?	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	✓
Does the study discuss the validity of all causal assumptions underlying the analysis (in the main paper or appendices)?	×	×	✓	✓	×	×	×	✓	✓

* N/a = not applicable to score yes (✓) or no (×).

than physical function. Weight loss and constructs related to self-efficacy were the only mediators investigated in more than 1 study, with all other putative mediators investigated by single studies only. Some evidence suggests that the benefits of 1) diet and exercise are mediated through body weight, systemic inflammation, and self-efficacy; 2) exercise is mediated through knee muscle strength and self-efficacy; and 3) high-expectation communication style is mediated through self-efficacy.

Regarding diet and exercise interventions, weight loss was found to mediate improved self-reported physical function (21) and pain relief (21), albeit inconsistently for pain relief (24). Weight did not significantly decrease (i.e., path a) in 1 study (24), which potentially hinders body weight as a mediator in this study. One study (23) showed that diet and exercise driven variations in systemic inflammation partially accounted for improvements in pain relief and physical function, independent of changes in BMI. Reductions in IL-6, TNF, soluble IL-1R, and CRP levels were associated with improved pain and physical function. These findings highlight the possibility that various other key proinflammatory and/or antiinflammatory mediators not evaluated here may influence OA symptoms and/or recovery. Examples include IL-8, TNF receptors (TNFR) (i.e., TNFR type 1 [TNFR1] and TNFR2), and monocyte chemoattractant protein 1, which have been linked with pain (36) and physical function (37). Inflammation is a highly complex, interactive response involving numerous cells and a balance of proinflammatory (e.g., TNF), antiinflammatory (e.g., IL-1R antagonist), and pleiotropic (e.g., IL-6) molecules. Consideration of these biomarkers, how they change in response to an intervention, and how they interrelate is needed to better understand their capacity to mediate health interventions, such as diet and exercise (23).

There was no evidence to suggest that changes in dietary intake, pain belief, or physical activity mediated pain relief with diet and physical activity support (24). Although changes in physical activity may not be sufficient to improve cardiovascular fitness, there is some evidence (21) to suggest that targeting cardiovascular fitness may improve OA outcomes. Specifically, improved cardiovascular fitness mediated improvement in the WOMAC summary score in individuals with knee pain and diabetes mellitus

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undergoing dietary and exercise intervention (21). However, as the overall WOMAC summary score accounts pain, physical function, and stiffness (30), it is unclear whether improved cardiovascular fitness mediates pain, physical function, or stiffness, or indeed all 3 constructs. Cardiovascular fitness as a mediator of symptoms warrants further attention.

Despite a plethora of possible mechanisms explaining the beneficial effects of exercise for knee OA symptoms (38,39), few have been evaluated as mediators. Measures of knee flexor muscle perfusion (25) were found to partially mediate pain relief through exercise. Although increased muscle perfusion has been associated with less pain (40), the effects of exercise were mediated by a constant rather than increased level of muscle perfusion in the knee flexors. Gains in knee extensor strength were found to partially mediate pain relief and improved physical function through strengthening exercise (26). The dose–response relationship between gains in muscle strength and OA symptom improvement is an area of interest. A clinical trial in knee OA comparing high-intensity training to low-intensity training found no difference in knee muscle strength gains or knee pain relief, but observed greater improvement in physical function with low-intensity training (41). These observations highlight the potential role of exercise intensity when considering mechanisms of symptom relief. Inflammatory processes likely underlie many of the muscular adaptations in response to exercise. For example, various inflammatory cytokines are reduced systemically (42,43) and at the local tissue (e.g., muscle, synovial fluid) level with aerobic exercise regimes (44), and these changes can be accompanied with less pain (45). Notably, physical inactivity leads to weight gain and visceral adipose accumulation, which is a potent source of inflammatory factors (46,47). A reduction in adipose tissue and, consequently, adiposity-related inflammation is another likely avenue via which exercise mediates improved symptoms. Finally, reduced knee pain and increased self-efficacy (stair climb) was shown to mediate stair climbing performance (i.e., improved time to climb a set of stairs) in a multimediator model that compared groups receiving aerobic and resistance exercise to controls (27). Taken together, the mechanisms explaining the effects of exercise and prescription (intensity, type, frequency) on knee OA symptoms remain unclear.

Self-efficacy is a particularly interesting potential mediator of symptom improvement, given it can manifest in several constructs (e.g., symptoms, balance, walking, stair climb), and its applicability to many lifestyle and self-management interventions. Self-efficacy for walking duration mediated the effect of diet and exercise on pain relief and improved physical function, assessed both as self-reported and through performance-based measures. However, the same study (22) found inconsistent observations for balance self-efficacy, with only evidence for improved self-reported physical function with diet and improved self-reported pain and function with exercise. Further work showed that increased self-efficacy to control OA symptoms mediated the effects of high-expectation but not neutral-expectation communication on pain at 3 months during acupuncture sessions (29). Together, these findings emphasize the potential benefits of enhancing self-efficacy to improve pain and physical function, which can be targeted through various strategies such as motivational interviewing (48).

Knee joint loading is widely targeted in biomechanical interventions for knee OA through various strategies. However, the only study to evaluate a biomechanical intervention determined that the effect of unloading footwear on knee pain was not mediated through a reduction in knee joint loading (28). Interestingly, there was some evidence to speculate that reduced knee joint loading potentially mediated a proportion of pain relief in persons with moderate-to-severe radiographic OA (28). However, a contrary clinical trial demonstrated that reducing knee loads walking with flat flexible footwear in those with moderate or severe radiographic OA did not reduce knee pain during walking compared to stable supportive shoes (49). This trial highlights the challenge of identifying mediators of biomechanical interventions.

Our review had strengths and weaknesses. A methodologic strength of the studies in our review was that all studies reported the appropriate framework for the analysis, and the approaches used in the mediation analysis and the choice of mediators were based on clinical rationale. However, critical methodological limitations were found. In particular, all of the included studies measured mediators and outcome at the same follow-up time points. Therefore, the causal interpretation (i.e., direction of effect) of the findings cannot be conclusively determined. In addition, the lack of reporting of goodness-of-fit of the models limits the understanding of how well the models fit the set of observations. The lack of assessment/reporting of potential interactions in the models hinders the understanding of interaction across interventions, mediators, outcomes, and confounders, as the incorrect assumption of these interactions may result in invalid inferences. The included studies were heterogeneous in terms of interventions, mediators, outcomes, and follow-up assessment time points, thus findings remain somewhat uncertain. Limiting our focus to mediation analysis to understand how interventions improve OA neglects a more granular understanding of the beneficial effects of interventions that can be gleaned from basic science studies. For example, basic science studies targeting therapeutic options for OA pain have explored new pathogenic pathways that encompasses molecular, omics, and preclinical levels, with studies investigating nerve growth factor and Wnt inhibitors showing promising results (50). However, results from basic science studies and how they align with trials are beyond the scope of this review.

The findings of this review are potentially relevant for knee OA management. The significant mediating effects of changes in body weight, systemic inflammation, knee extensor strength, and self-efficacy suggest these effects may be important targets

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for certain interventions. Regular monitoring of relevant mediators during treatment and targeting the intervention to improve these mediators may lead to improved symptoms. However, there is an important consideration. We caution extrapolating data pertaining to mediators beyond the specific interventions studied. Interventions are likely to improve symptoms through more than 1 mediator, as illustrated by individual studies evaluating mechanisms underpinning the benefits of exercise (26,27). Hence, it is questionable whether changes in a single mediator account for clinically meaningful change in OA symptoms with nonsurgical interventions.

In summary, we identified 9 studies assessing mediators of the effects of nonsurgical interventions for pain and physical function in people with knee OA. Some evidence suggests that the benefits of diet and exercise are mediated through changes in body weight, systemic inflammation and self-efficacy; exercise is mediated through changes in knee muscle strength and self-efficacy; and high-expectation communication style is mediated through changes in self-efficacy.

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AUTHOR CONTRIBUTIONS

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

Study conception and design. Lima, Lee, Klyne, Dobson, Hinman, Bennell, Hall.

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Analysis and interpretation of data. Lima, Lee, Klyne, Dobson, Hinman, Bennell, Hall.

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