# Network Meta-Analysis of Various Nonpharmacological Interventions on Pain Relief in Older Adults With Osteoarthritis

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**Abstract:** To compare the effectiveness of different nonpharmacological interventions on pain relief in older adults with osteoarthritis, literature databases, bibliographies, and other relevant sources were searched. No language limitations were applied. Thirty-two trials published from 1997 to 2017 were included in the systematic review and network meta-analyses. We included only randomized controlled trials and studies that evaluated the effects of nonpharmacological interventions on alleviating pain in elderly adults (age ≥60 yrs or mean age > 65 yrs) who experience osteoarthritis, irrespective of sex. In the network meta-analysis, resistance training was ranked as the most effective among all nonpharmacological interventions (surface under the cumulative ranking = 82.9%, standardized mean difference = 1.96, confidence interval = −1.39 to 5.31). In subgroup analyses, resistance training still ranked the most effective pain reduction intervention, followed by strengthening exercise and yoga. Among female subjects with intervention adherence rate more than 90%, the most effective intervention was yoga. Strengthening exercise was superior to all other forms of interventions when comparing long-term effect of selected interventions. Among older adults with osteoarthritis, resistance training can be considered a treatment option for pain relief. Yoga is an effective intervention strategy for female elderly, and strengthening exercise has a better long-term beneficial effect.

**Key Words:** Osteoarthritis, Physiotherapy, Physical Activity, Network Meta-Analysis

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Osteoarthritis (OA) is a chronic degenerative musculoskeletal condition, which is especially prevalent in older adults.[1] More than 10% of the population 65 yrs and older present with OA symptoms and more than half of the population have subclinical radiographic OA.[2] Osteoarthritis is the primary reason for disability in the aging population.[3] Due to pain, stiffness, and limited range of motion, adults with OA can lose functional independence and experience significant limitation in normal daily activities.[4] The annual average direct medical spending attributable to OA in the United States is estimated to be as high as US $21,335.[5] The rapid increase in life expectancy globally means that OA is becoming a major public health issue worldwide.

Managing the pain that is associated with OA is critical for patients, and many efforts have been made to find cost-effective treatments for this degenerative condition.[6] There is unanimous agreement that nonpharmacological treatment is the preferred option in the management of OA. However, the following key questions remain unanswered in selecting nonpharmacological treatments for this population. First, what types of nonpharmacological intervention are most effective in reducing pain in the older population with OA? Second, do sex differences between patients affect therapeutic results and intervention selection? Third, is there intervention effect variation by treatment adherence? Last, which intervention has greater long-term effects?

To address the existing gaps in knowledge, we conducted a systematic review, pairwise meta-analysis, and network analysis to compare the effects of different nonpharmacological interventions on pain relief in old adults with OA.

## METHODS

### Trial Registration

This review was registered on the PROSPERO database (Registration Number: CRD42016045283).

### Search Strategy and Study Selection

We searched the following databases from their inception to August 2018, with no language restrictions, to gather relevant randomized controlled trials (RCTs): PubMed, EMBASE, Ovid Medline, Web of Science, PsycINFO, Physiotherapy Evidence Database, Cochrane Library, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure. The search consisted of a combination of free-text words and MeSH terms using Boolean operators. The search strategies for each database are presented in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/PHM/A727). This study conforms to all PRISMA guidelines and reports the required information accordingly (see Supplemental

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QZ as the first author of the article have contributed the essential part of this manuscript. LY and FL assisted literature review, data management and analysis, interpretation, and multiple revisions of the draft critically. All co-authors gave the final approval of the version being submitted. We are accountable for the accuracy and integrity of all aspects of the article.

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Checklist, Supplemental Digital Content 2, http://links.lww.com/PHM/A728).

The databases were searched for relevant systematic reviews and meta-analyses. Titles, abstracts, key words, and reference lists were scanned to refine the search terms. If the abstracts met the inclusion criteria, the full-text article was accessed. In addition, the reference lists of all included studies were screened to identify potentially eligible studies ("snowball search"). Grey literature was not searched. Experts in this field were contacted to ensure that all relevant additional items were considered.

## Eligibility Criteria

We included only RCTs and studies that evaluated the effects of nonpharmacological interventions on alleviating pain in elderly adults who experience OA, irrespective of sex and joint location. Patients were 60 yrs or older (or mean age > 65 yrs). To obtain as much information as possible regarding the effectiveness of the eligible interventions, no studies were excluded based on outcomes. Pain intensity was the primary outcome consideration for this analysis.

## Data Extraction

Two independent reviewers screened all literature search results to identify qualified studies. The full-text articles were assessed by the two authors for inclusion and any uncertainties or discrepancies were resolved by discussion and careful reexaminations of the full text. A third reviewer resolved any discrepancies if consensus was not reached between the two reviewers in their assessments of the studies. The following information was collected: first author's name, year of publication, country of origin, study type, sample size (intervention and control groups), characteristics of participants, sex, age, type of intervention, exercise time, length of intervention, and reported outcomes. Data on effect size that could not be obtained directly were reanalyzed when possible. Authors of the studies were contacted when relevant data were missing. The risk of bias was assessed using procedures and criteria based on the Cochrane Collaboration Risk of Bias Assessment Tool for selection, attrition, performance, reporting, and detection biases.[7]

## Data Analysis

Because continuous data were from different scales, we calculated effect sizes by using the standardized mean difference (SMD) based on sample size with 95% confidence interval (CI) for each study.[8] A two-sided $P < 0.05$ was considered statistically significant. The studies assessed pain intensity at various follow-up times, and outcomes were split into two time periods: short-term (1 wk–6 mos) and long-term (>6 mos). If the pain scores were assessed at multiple time points, only data from baseline and last assessment were used. For the expected heterogeneity, all meta-analyses were performed using a more conservative random-effects model and subgroup analyses were conducted according to different control interventions.[9] For any study, if the standard deviation (SD) of the outcome was not reported, it would be estimated according to the 95% CI or on the basis of its figures.

First, heterogeneity was assessed from statistical, methodological, and clinical perspectives using the RevMan v5.1 software. Statistical heterogeneity was assessed both graphically and statistically. Funnel plots were generated when there were 10 or more trials and symmetry was assessed visually.[10] We quantified statistical heterogeneity by using the $\chi^2$ test and the $I^2$ statistic (interpreted as follows: 0%–40%: insignificant; 30%–60%: moderate; 50%–90%: substantial; 75%–100%: high).[11] Sensitivity analyses were done to investigate whether the risk of bias had an influence on effect estimates.

Second, we used STATA v14.0 to perform network meta-analysis, both direct and indirect estimates. It provides a simultaneous comparison of multiple treatments, even if a head-to-head comparison between the two treatment arms was unavailable. Ranking probabilities of competing interventions were made for each intervention arm. The value of surface under the cumulative ranking (SUCRA) ranged from 1 (most effective intervention) to 0 (least effective intervention).[12] In addition, network plots were used to provide a visual representation with the thickness of edges weighted by the proportional number of studies for each comparison, and nodes weighted by the proportional number of participants.

# RESULTS

## Search Results

There were 2507 records, with 63 additional records identified through relevant bibliographies found through the initial literature search (Fig. 1). After removing 1262 duplicates, 1308 of the records identified in the database search remained, and we found three additional RCTs from the reference list, making a total of 1311 studies for consideration. A further 1126 articles were excluded after screening and assessment of the titles and abstracts. Finally, the full text of 182 potentially relevant records was investigated. Of these 182 studies, 56 were excluded because they were not RCTs, and 33 did not meet the participant inclusion criteria. Only one of the authors responded to our e-mail request for additional information. The details of other reasons for excluding studies are outlined in Supplemental Table 2 (Supplemental Digital Content 3, http://links.lww.com/PHM/A729). In the end, 32 articles in 3228 patients were included in the meta-analyses.[13–44]

## Main Features of Included RCTs

Thirty-one of the included studies were published in English, only in Chinese[41] between 1997 and March 2017. Sample sizes ranged from 21 to 454 patients. Eleven came from the United States, six from China, and three were conducted in Denmark. The remaining studies originated in Brazil, Israel, Japan, New Zealand, Norway, Italy, France, the Netherlands, and Canada. Seven were multiarm trial designs and the rest were two-arm parallel group trial designs. The average ages of the participants in the different studies ranged between 65 and 83 yrs. In addition to Western Ontario McMaster Osteoarthritis Index, other instruments were used to measure pain outcomes. The studies included different types of exercise interventions, such as walking, strengthening exercise, Yoga, aquatic exercise, healing touch, Tai Chi, etc (Tables 1, 2).

## Risk of Bias

Regarding the methodological quality of the 32 included studies, all of the studies used randomization to assign study

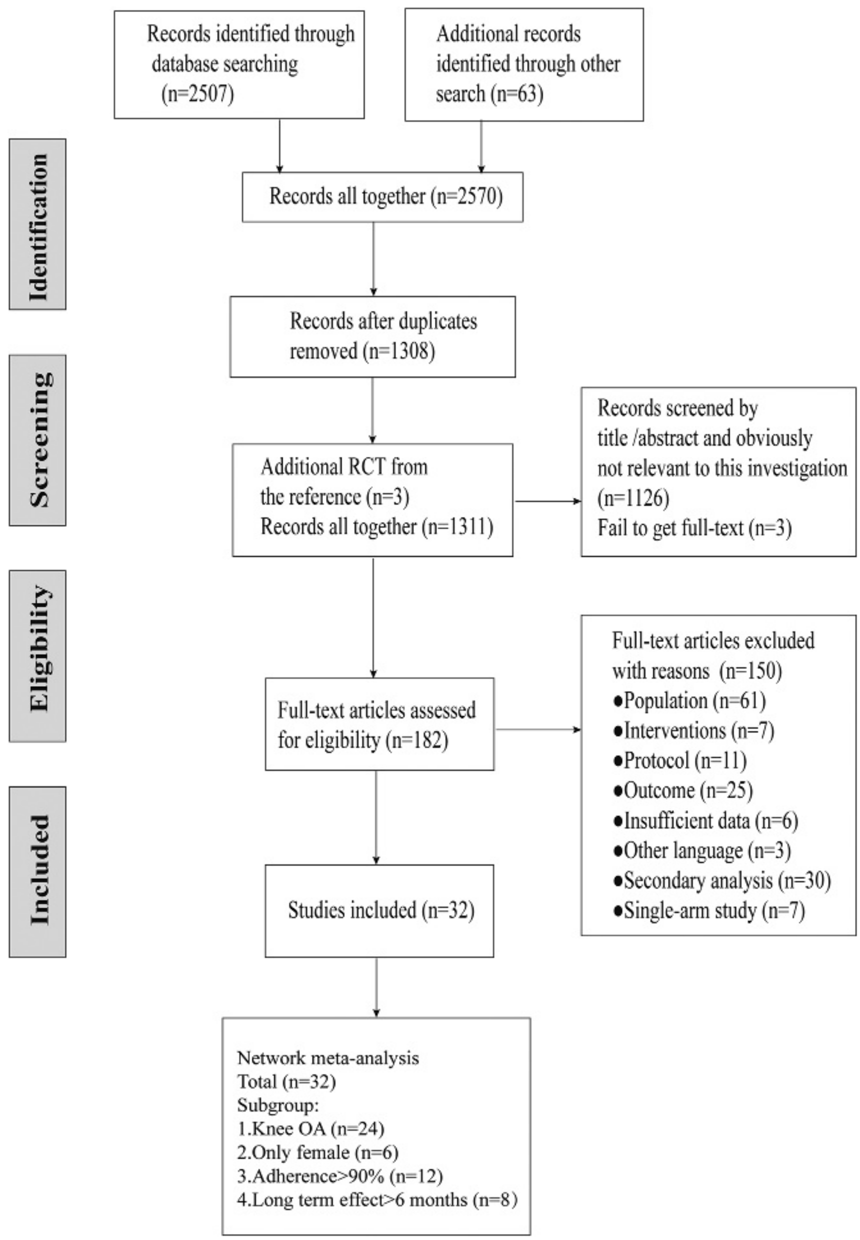


**FIGURE 1.** Flowchart identification, selection, and the inclusion of the studies.

populations to study arms, and the risk of bias was based on the Cochrane Systematic Reviews of Interventions (Fig. S1, Supplemental Digital Content 4, http://links.lww.com/PHM/A730). Most of the random sequence generation was by computer-generated random software and used serially numbered opaque envelopes for allocation concealment. Nevertheless, blinding was not clearly reported in all of the studies. The reasons for participant withdrawals and dropouts were also given in all these trials. The shape of the funnel plot was inspected and found to be roughly symmetrical (Fig. S2, Supplemental Digital Content 5, http://links.lww.com/PHM/A731).

## Network Meta-Analysis

All identified RCTs were included to compare the effectiveness between various nonpharmacological interventions, even when direct intervention comparisons were insufficient or unavailable (Fig. S3A, Supplemental Digital Content 6, http://links.lww.com/PHM/A732). Then, subgroup analyses were performed to identify potential moderators of the intervention effects, including location of OA (knee *vs.* hip) (Fig. S3B, Supplemental Digital Content 6, http://links.lww.com/PHM/A732), sex (Fig. S3C, Supplemental Digital Content 6, http://links.lww.com/PHM/A732), subjects' adherence with intervention (>90%) (Fig. S3D, Supplemental Digital Content 6, http://links.lww.com/PHM/A732), and timing effect of the intervention (short-term *vs.* long-term) (Fig. S3E, Supplemental Digital Content 6, http://links.lww.com/PHM/A732).

The closed loop was assessed and showed no evidence of inconsistency between direct and indirect evidence in the network. The results of the network meta-analysis were presented as

**TABLE 1.** Main characteristics of all eligible studies

| Study Authors (Year) | Country | Joint | Sample Size (*n*) Total Patients (N) Intervention (I) Control (C) | Completion *n*/*N* | Reported Inclusion/ Exclusion Criteria | Groups | Home-Based | Instructor |
|---|---|---|---|---|---|---|---|---|
| Aoki et al. (2009)[13] | Japan | Knee OA | N = 36 I = 17 C = 19 | 36/36 | No/no | G1: ST, G2: UC | Yes | |
| Avelar et al. (2011)[14] | Brazil | Knee OA, least 1 knee | N = 21 I = 11 C = 10 | 21/23 | Yes/yes | G1: WBV, G2: ST | No | |
| Baker et al. (2001)[15] | United States | Knee OA | N = 46 I = 23 C = 23 | 38/46 | Yes/yes | G1: STR, G2: HE | Yes | |
| Bezalel et al. (2010)[16] | Israel | Knee OA | N = 50 I = 25 C = 25 | 38/50 | Yes/yes | G1: STR, G2: HEA | Yes | PT |
| Bieler et al. (2017)[17] | Denmark | Hip OA | N = 152 I = 50 C1 = 50 C2 = 52 | 126/152 | Yes/no | G1: supervised STR, G2: WK, G3: unsupervised STR | Yes | PT |
| Brismee et al. (2007)[18] | United States | Knee OA | N = 41 I = 22 C = 19 | 31/41 | No/yes | G1: TAI, G2: HE | Yes | |
| Chang et al. (2012)[19] | Taiwan (China) | Knee OA | N = 45 I = 25 C = 20 | 41/45 | No/no | G1: RT, G2: UC | No | |
| Cheung et al. (2014)[21] | United States | Knee OA | N = 36 I = 18 C = 18 | 34/36 | Yes/yes | G1: YG, G2: UC | Yes | |
| Cheung et al. (2017)[20] | United States | Knee OA | N = 83 I = 32 C1 = 28 C2 = 23 | 73/83 | Yes/yes | G1: YG, G2: STR, G3: HE | No | |
| Dias et al. (2017)[22] | Brazil | Knee OA | N = 73 I = 37 C = 36 | 65/73 | Yes/no | G1: HEA, G2: HE | Yes | |
| Ettinge et al. (1997)[23] | United States | Knee OA | N = 439 I = 144 C1 = 146 C2 = 149 | 365/439 | Yes/yes | G1: WK, G2: RT, G3: HE | Yes | Physicians |
| Hale et al. (2012)[24] | New Zealand | Lower-extremity OA | N = 39 I = 23 C = 16 | 35/39 | Yes/yes | G1: AQ EX, G2: HE | No | Trained water exercise instructor |
| Hammer et al. (2016)[25] | Denmark | Hip OA | N = 40 I = 31 C = 9 | 40/52 | Yes/no | G1: STR, G2: WK | No | |
| Hermann et al. (2016)[26] | Denmark | Hip OA | N = 80 I = 40 C = 40 | 77/80 | No/yes | G1: RT, G2: UC | No | |
| Kao et al. (2012)[27] | Taiwan (China) | Knee OA | N = 259 I = 134 C = 125 | 205/259 | Yes/yes | G1: ST + HE, G2: UC | No | Nurse educators and nutritionists |
| Laufer et al. (2014)[28] | Israel | Knee OA | N = 50 I = 25 C = 25 | 44/50 | Yes/yes | G1: STR + NSTIM, G2: STR | No | |
| Lu et al. (2013)[29] | United States | Knee OA | N = 19 I = 12 C = 7 | 7/19 | Yes/yes | G1: HT, G2: HE | No | Nurses |
| Mangione et al. (1999)[30] | United States | Knee OA | N = 39 I = 19 C = 20 | 31/39 | Yes/yes | G1: high-intensity CE, G2: low-intensity CE | No | |
| Messier et al. (2013)[31] | United States | Knee OA | N = 454 I = 152 C1 = 152 C2 = 150 | 399/454 | No/no | G1: WEI + CO EX, G2: WEI, G3: CO EX | Yes | Physician |
| Østerås et al. (2014)[32] | Norway | Hand OA | N = 130 I = 65 C = 65 | 119/130 | Yes/yes | G1: STR, G2: UC | Yes | Occupational therapist |

| Intervention Duration | Pain Outcome Measures | Sex (Women/Men) | Age of Intervention and Control, Mean ± SD, yr | BMI of Intervention, and Control, $kg/m^2$ | Time Points Assessed | Adverse Effects Reported |
|---|---|---|---|---|---|---|
| Once a day for 80 d | Pain (VAS) | 36, 0 | 72.3 ± 5.2, 74.4 ± 6.4 | 26.6 ± 3.5, 25.8 ± 2.4 | B and posttreatment | NR |
| 12 wks, 3 times/wk | WOMAC | 20, 3 | 75 ± 5, 71 ± 4 | Not specified | 3 wks before the training, immediately before, and the end of the training | NR |
| 2 sets of 12 repetitions, 3 times/wk | WOMAC | 36, 10 | 69 ± 6, 68 ± 6 | 31 ± 4, 32 ± 5 | B and 4 mos | NR |
| Once a wk for 1 mo, each session lasted 45 mins | WOMAC | 37, 13 | 73.8 ± 4.7, 73.7 ± 5.5 | Not specified | B, 4 and 8 wks | NR |
| 1 hr three times weekly, 4 mos (2–3 times weekly) | WOMAC, SF-36 | 103, 49 | 69.6 ± 5.4, 70.0 ± 6.3, 69.3 ± 6.4 | 26.9 ± 4.8, 27.6 ± 5.1, 27.4 ± 4.7 | B and at 2, 4, and 12 mos | NR |
| 40 mins/session, 3 times/wk, followed by another 6 wks | WOMAC, VAS | 34, 7 | 70.89 ± 9.8, 68.89 ± 8.9 | 28 ± 5.92, 27.8 ± 6.57 | B, 3, 6, 9, and 12 wks | Minor pain mainly during the first few days |
| 16 sessions, 2–3 times/wk for 8 wks | WOMAC | 41, 0 | 65.0 ± 8.4, 70.8 ± 8.4 | 24.9 ± 3.3, 25.7 ± 3.6 | B, after the 8 wks intervention | NR |
| 60-min class/wk for 8 wks, 30-min yoga 4 times/wk | WOMAC | 36, 0 | 71.9 ± 2.7, 71.9 ± 3.1 | 29.1 ± 2.6, 28.8 ± 2.8 | B, 4, 8, and 20 wks | No adverse events |
| 8 weekly 45-min group classes with 2–4 d/wk home practice sessions | WOMAC | 83, 0 | 68.9 ± 7.7, 74.4 ± 7.5, 71.8 ± 8.0 | 29.8 ± 6.3, 29.2 ± 7.1, 27.8 ± 7.9 | B, 4 and 8 wks | 3 exercise-related injuries |
| Twice/wk for 6 wks | WOMAC | 73, 0 | 70.8 ± 5.00, 71.0 ± 5.20 | 30.5 ± 4.30, 30.0 ± 5.20 | B and posttreatment | NR |
| 3 times/wk, every 3 wks during months 6 through 9 and then monthly during month 10 through 18 | Scale developed specifically for patients with knee osteoarthritis | 308, 131 | 69 ± 6, 68 ± 6, 69 ± 6 | Not specified | B, 3, 9, and 18 mos | NR |
| 12 wks, twice weekly | WOMAC | 29, 10 | 73.6 ± 1.5, 75.7 ± 1.1 | Not specified | B and 12 wks | NR |
| 3 times weekly | ASES | 36, 16 | Not specified | Not specified | B and 12 mos | NR |
| Twice a week for 10 wks | VAS, WOMAC | 52, 28 | 70.0 ± 7.7, 70.8 ± 7.5 | 28.2 ± 5.3, 27.4 ± 3.8 | B and after intervention | No adverse events |
| Four 80 mins once a wk, 4 wks | SF-36 | 157, 48 | 67.3 ± 10.1, 68.2 ± 11.2 | Not specified | B, 4 and 8 wks | NR |
| 12 biweekly | VAS, WOMAC | 42, 8 | 68.3 ± 7.7, 69.4 ± 7.7 | 31.4 ± 6.7, 30.5 ± 5.3 | B, immediately posttreatment and 12 wks | NR |
| 3 times/wk for 6 wks | WOMAC, IPT, BPI [SF] | 16, 3 | 75.7 ± 9.2, 82.4 ± 13.5 | Not specified | B, 6 and 9 wks | NR |
| 25 mins, 3 times/wk for 10 wks | VAS, WOMAC | 26, 13 | 71.1 ± 7.7, 71.0 ± 6.2 | 29.6 ± 5.18, 29.1 ± 5.07 | B and 10 wks | No adverse events |
| Weekly menu plan, biweekly group sessions and an individual session every 2 mos | WOMAC, SF-36 | 325, 129 | 65 ± 6, 66 ± 6, 66 ± 6 | 33.6 ± 3.7, 33.7 ± 3.8, 33.5 ± 3.7 | B, 6 and 18 mos | 3 nonserious adverse events |
| 3 times weekly. 3 mos | NRS | 117, 13 | 67 ± 8, 65 ± 9 | 28 ± 5, 27 ± 4 | B, 3 and 6 mos | 3 adverse events |

*(Continued on next page)*

**TABLE 1** *(Continued)*

| Study Authors (Year) | Country | Joint | Sample Size (*n*) Total Patients (N) Intervention (I) Control (C) | Completion *n*/*N* | Reported Inclusion/ Exclusion Criteria | Groups | Home-Based | Instructor |
|---|---|---|---|---|---|---|---|---|
| Pascarelli et al. (2016)[33] | Italy | Knee OA | N = 103 I = 50 C = 53 | Not specified | Yes/yes | G1: BAL, G2: UC | No | |
| Peloquin et al. (1999)[34] | France | Knee OA | N = 137 I = 69 C = 68 | 124/137 | Yes/no | G1: CO EX, G2: HE | No | |
| Segal et al. (2016)[35] | United States | Knee OA | N = 58 I = 36 C = 22 | 56/58 | Yes/yes | G1: WK, G2: UC | No | PT |
| Suomi and Collier (2003)[36] | United States | Not specified | N = 32 I = 11 C1 = 11 C2 = 10 | 30/32 | Yes/yes | G1: AQ EX, G2: CO EX, G3: UC | No | |
| Tak et al. (2005)[37] | Netherlands | Hip OA | N = 109 I = 55 C = 54 | 94/109 | Yes/yes | G1: STR, G2: UC | No | |
| Takacs et al. (2017)[38] | Canada | Knee OA | N = 40 I = 20 C = 20 | 36/40 | No/yes | G1: TDBT, G2: UC | Yes | |
| van Baar et al. (2001)[39] | Netherlands | Hip and/or knee OA | N = 201 I = 99 C = 102 | 183/201 | Yes/yes | G1: STR + HE, G2: HE | Yes | PT |
| Wortley et al. (2013)[40] | United States | Knee OA | N = 31 I = 12 C1 = 13 C2 = 6 | 31/39 | Yes/yes | G1: TAI, G2: RT, G3: UC | No | Tai Ji master |
| Yip et al. (2007)[42] | China | Knee OA | N = 182 I = 88 C = 94 | 120/182 | Yes/yes | G1: CO EX, G2: UC | No | |
| Zeng et al. (2015)[43] | China | Hip OA | N = 97 I = 48 C = 49 | 59/97 | Yes/yes | G1: CO EX, G2: UC | Yes | PT |
| Xiaoju and Xiaojie (2015)[41] | China | Knee OA | N = 60 I = 20 C1 = 20 C2 = 20 | 60/60 | Yes/no | G1: ACU, G2: CO EX, G3: HE | No | |
| Zhu et al. (2016)[44] | China | Knee OA | N = 46 I = 23 C = 23 | 40/46 | Yes/yes | G1: TAI, G2: HE | No | Specialist in Tai Ji Quan |

ADL, activities of daily living; ACU, acupuncture; AIMS2, arthritis impact measurement scales 2; ASES, arthritis self-efficacy scale; AQ EX, aquatic exercise; BAL, balneotherapy; CE, cycle ergometry; CO EX, combined exercise; G1, group 1; G2, group 2; G3, group 3; HE, health education; HEA, heat treatment; HEP, home exercise program; HHS, Harris H; HT, healing touch; IPT, Iowa pain thermometer; KOOS, knee injury and osteoarthritis outcome score; NRS, numerical rating scale; NSTIM, neuromuscular electrical stimulation; OA, osteoarthritis; PT, physiotherapist; RT, resistance training; SF-36, Short-Form 36; ST, stretching exercise; STR, strengthening exercise; TAI, Tai Chi; TC, tai chi; TDBT, targeted dynamic balance training; UC, usual care; VAS, visual analog scale; WBV, whole-body vibration; WEI, weight loss; WK, walking; WOMAC, western Ontario mcMaster osteoarthritis index; YG, yoga.

five league tables (Fig. S4A–E, Supplemental Digital Content 7, http://links.lww.com/PHM/A733). In comparison with the control group, resistance training intervention was ranked as the most effective among all nonpharmacological interventions (SUCRA = 82.9%, SMD = 1.96, 95% CI = −1.39 to 5.31), followed by strengthening exercise (SUCRA = 74.1%, SMD = 1.21, 95% CI = −0.62 to 3.05), and aquatic exercise (SUCRA = 65.3%, SMD = 0.75, 95% CI = −2.18 to 3.67) (Fig. 2A). Weight loss exercise ranked as the least effective intervention (SUCRA = 17.8%, SMD = 3.77, 95% CI = −0.23 to 7.76), followed by healing touch (SUCRA = 35.1%, SMD = −0.63, 95% CI = −2.93 to 1.68), and acupuncture (SUCRA = 37.8%, SMD = −0.43, 95% CI = −2.08 to 1.22).

Figure 2 summarizes the results of subgroup network meta-analysis. Given that most of the RCTs included in our studies focused on knee OA adults, we first examined the moderating effect of location of OA on intervention effectiveness. The findings revealed that location of OA did not affect the intervention effects,[14–16,18–24,27–31,33–35,38,40–42,44] the cumulative rankings were unaffected (Fig. 2B). On the other hand, compared with male patients, the network meta-analysis showed that Yoga was the most effective intervention to reduce OA pain among female adults, followed by strengthening exercise, Tai chi and heat treatment[13,19–22,44] (Fig. 2C). Furthermore, we examined how subjects' adherence rate affected intervention effect (Fig. 2D). The included studies reported more than 90% adherence rate in intervention groups.[13,14,19,21,26,32,34–36,38,39,41] The findings showed that Yoga was the most effective intervention when more than 90% adherence rate was reached by subjects assigned to the intervention group. Acupuncture is

 

| Intervention Duration | Pain Outcome Measures | Sex (Women/Men) | Age of Intervention and Control, Mean ± SD, yr | BMI of Intervention, and Control, kg/m$^2$ | Time Points Assessed | Adverse Effects Reported |
|---|---|---|---|---|---|---|
| For a period of 2 wks | VAS, WOMAC | 74, 29 | 68.5 ± 9.01, 69.7 ± 11.1 | Not specified | 7 d before enrolment, B and after 2 wks | NR |
| Three 1-hr sessions/wk for 3 mos | AIMS2 | 87, 37 | 65.6 ± 7.4, 66.4 ± 8.3 | 29.8 ± 4.5, 29.7 ± 4.8 | B, 3 mos | NR |
| Biweekly for 3 mos | KOOS | 38, 18 | 69.7 ± 8.2, 68.9 ± 6.5 | Not specified | B, 3, 6, and 12 mos | No adverse events |
| 1 class/wk for the 8 wks | ADL | 24, 6 | 68.0 ± 6.8, 64.2 ± 3.3, 68.3 ± 6.2 | Not specified | 1-d pretest and posttest session, before and after an 8-wk exercise program | NR |
| 8, 1-hr weekly | VAS, HHS | 64, 30 | 67.4 ± 7.6, 68.9 | 26.4 ± 3.0, 26.6 ± 4.3 | B, posttest, and follow-up (3 mos) | NR |
| 4 times/wk, 10 wks | WOMAC, NRS | 32, 8 | 66.1 ± 8.7, 67.1 ± 5.4 | 28.5 ± 5.4, 28.9 ± 4.5 | B and 1 wk after treatment | 9 adverse events |
| 12 wks, with an ensuing 24-wk follow-up | VAS | 157, 200 | 68.3 ± 8.4, 67.7 ± 9.2 | Not specified | B, 12, 24, and 36 wks | 1 adverse exercise event |
| 1-hr group training session 2/wk, 10 wks | WOMAC | 22, 9 | 68.1 ± 5.3, 69.5 ± 6.7, 70.5 ± 5.0 | 35.1 ± 5.9, 30.5 ± 6.0, 30.0 ± 6.2 | Before and after the 10 wks intervention | NR |
| Six 2-hr classes held once a wk | VAS | 136, 46 | 65 yrs | Not specified | B, at 1 wk postintervention and again at 16 wks postintervention | NR |
| 45- to 60-min TC training, 20- to 30-min hip muscle strengthen training | WOMAC | 28, 31 | 65.2 ± 2.6, 64.8 ± 2.5 | 27.0 ± 2.23, 26.7 ± 2.16 | B and posttreatment | No serious adverse events occurred |
| 5 times/wk, 10 times as 1 course | VAS | 29, 31 | 66.7 ± 3.6, 71.2 ± 4.7, 68.5 ± 3.2 | Not specified | B and posttreatment | NR |
| 60-min session 3 times weekly, 24 wks | WOMAC | 46, 0 | 64.6 ± 3.4, 64.5 ± 3.4 | 25.2 ± 3.4, 25.1 ± 3.4 | B and 24 wks | No adverse events |

**TABLE 2.** Abbreviations of interventions arm

| | |
|---|---|
| RT | Resistance training |
| NSTIM | Neuromuscular electrical stimulation |
| WK | Walking, gait training; Nordic walking; targeted dynamic balance training; cycle ergometry; whole-body vibration |
| STR | Strengthening exercise |
| UC | Usual care; activities of daily living; health education |
| YG | Yoga; stretching exercise |
| ACU | Acupuncture |
| AQ EX | Aquatic exercise |
| HT | Healing touch |
| HEA | Heat treatment; intervention in a heated pool; short-wave diathermy therapy; balneotherapy; mud-bath therapy |
| TAI | Tai Chi |
| WEI | Weight loss |

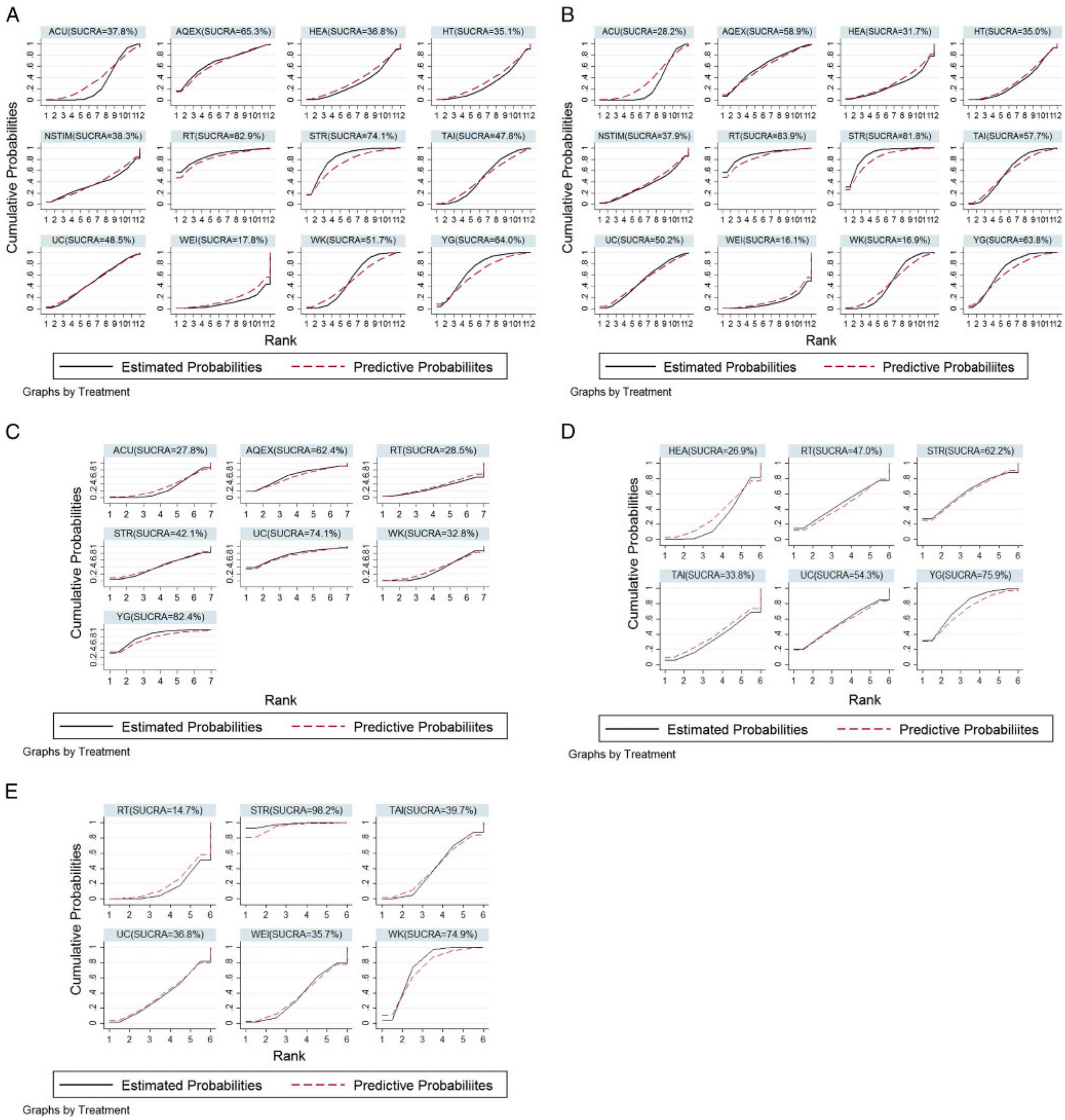


**FIGURE 2.** Cumulative ranking probability plot for the assessment of pain relief in older adults with OA (A: total, B: knee OA, C: only female, D: adherence >90%, E: long-term effect).

the least effective intervention (Fig. 2D). Compared with other types of nonpharmacological interventions, strengthening exercise was found to have greatest long-term effect on pain reduction followed by walking and Tai chi[17,23,25,31,32,35,39,44] (Fig. 2E).

There was no publication bias in the comparison-adjusted funnel plot. Finally, we assessed the potential adverse events attributed by nonpharmacology interventions. Of the 33 included studies, only 12 evaluated the occurrence of adverse events. Six of these studies reported no adverse events occurred.[21,26,30,35,43,44] Another six studies reported minor adverse events,[18,20,31,32,38,39] but none of the serious events were related to the treatment intervention.

## DISCUSSION

The current study is the first analysis to provide comparable estimates of different forms of nonpharmacological treatments for the older adult population with OA, which is essential for decision makers to adopt an effective intervention for alleviating pain. To complement the weakness of pairwise meta-analysis, network meta-analysis allows all relevant physical interventions to be compared with each other simultaneously.

Based on the cumulative ranking, resistance training is the most effective treatment regimen (ranking 81%) for pain relief in the older adult population with OA in general or at knee joint. This is inconsistent with previous findings from the study by Corbett et al,[45] who reported acupuncture was one of the more effective treatments for pain relief in adults with knee OA. One of the explanations could be the age differences between patients in the two studies. In our studies, we only included older patients, and a recent study indicates that exercise adherence is negatively associated with age.[46] Thus, the older patients could have lower adherence rate, which impacts the intervention effects. These findings should be considered in the application of these interventions to these patients.

As women age, they have a higher prevalence and severity symptoms of OA compared with men. It should be noted that when sex and adherence of participants were taken into account, Yoga becomes the most effective interventions for female patients or patients with high adherence rate. Considering the high prevalence of nonadherence to physical activity guidelines among the older population, Yoga could be a feasible and effective intervention to help pain relief in older adults with OA. However, the long-term impact of Yoga on pain relief was not examined in the study because of inadequate reporting and availability of the studies. As for chronic pain, more attention should be focused on the long-term effects of the interventions. On the other hand, our results show that strengthening exercise has an acceptable long-term effect on pain relief, which is congruent with another network analysis done by Uthman et al.[47] Their study showed that strengthening exercises were effective in the management of lower limb OA.

The results of this analysis need to be interpreted with caution for several limitations. First, there is significant heterogeneity in terms of the severity and duration of OA, as well as the methods, frequency, and duration of intervention sessions across studies. Second, conclusions based on this analysis were limited by the considerable variation among tools/instruments used for measuring study outcomes. Third, the pain outcome was measured using subjective self-report, introducing risk of bias. Fourth, the follow-up data collections in the included studies were carried out over a wide range of time intervals, ranging from 3 wks to 18 mos. The long-term impact of the nonpharmacological interventions has not been adequately reported and could be the focus of future research. Although our meta-analysis focuses on the older adult population, further evidence of the cost-effectiveness of these OA treatments in different ages is needed. In addition, studies targeting population with specific stages of OA should be conducted in the future to enhance more comprehensive understanding of the disease progression in relation to treatment interventions.

## CONCLUSIONS

The present analysis suggests that resistance training is a more effective treatment intervention in comparison with no treatment and other active treatments for pain relief in older adults with OA. Yoga is more effective for female patients and strengthening exercises have a better long-term beneficial effect.

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