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근골격계 질환의 수기요법에 관한 경제성 평가: 체계적 문헌 고찰 및 근거 합성 연구

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Economic evaluation of manual therapy for musculoskeletal diseases: a systematic review and narrative synthesis of evidence

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연구 목적 : 본 연구는 근골격계 질환에 대한 수기치료가 갖는 경제적 효과를 체계적으로 평가해 보기 위해 시행되었다.

연구 방법 : 2017년 2월 2일까지 국내외 관련 문헌을 체계적으로 검색 하였으며, 연관된 체계적 고찰 논문의 참고문헌을 조사하였다. 두 명의 연구자가 독립적으로 문헌을 선택하고, 비뚤림 위험 평가 및 경제성 평가 질 평가, 자료 추출을 시행하였다.

연구 결과 : 총 3,327개의 논문을 검토하여 최종적으로 18개의 무작위 대조 연구가 포함되었다. 경제성 평가는 수기요법과 다른 치료방법간의 유효성 비교를 통해 시행되었다. 요부 통증, 견관절 통증 및 외측 상과염 치료에 있어 침치료, 견인치료, 주사치료, 일반의 치료, 척추 안정화 기법 및 통증관리 치료보다 비용 효과적인 것으로 나타났다. 또한 또한, 수기치료는 경항통, 흉통, 고관절염 혹은 슬관절염, 경추신경병증 및 수부손상 치료에 있어 일반적 치료, 물리치료, 자가 치료 프로그램, 견인 치료에 비하여 효과적인 치료인 것으로 확인되었다.

결론 : 18개의 논문 중 10개의 논문에서 근골격계 질환 치료에 있어 수기치료가 경제적으로 효과가 있는 것으로 나타났다. 이러한 결과는 다른 치료방법에 비해 수기요법이 근골격계 질환에 있어서 경제적 가치가 있음을 시사하는 내용이다. 하지만, 근골격계 질환 수기치료의 경제성 평가에 대한 선행 연구는 전반적으로 부족한 실정으로, 보다 정확한 결과를 제시하고 정책결정을 위한 효과적인 제안을 위해서는 체계적인 추가 연구가 필요하다 사료되는 바이다.

주제어 : 경제성 평가, 수기요법, 근골격계 질환, 체계적 문헌고찰

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Ⅰ. INTRODUCTION

Manual therapy(MT) is a conservative treatment that is defined as the delivery of manually applied forces using hands on the body for treating, diagnosing, and assessing diseases[1,2]. This technique is usually applied on soft tissues and joints, can be used separately or in combination with other treatments[3]. The use of MT for musculoskeletal diseases has been recommended worldwide by clinical practice guidelines[4-6]. Musculoskeletal diseases are a health problem affecting almost a quarter of the world's population[7,8].

Previous studies have provided sufficient evidence on effectiveness and safety of MT, but insufficient evidence on cost-effectiveness[9-25]. Economic evaluations investigate the value for money of interventions. For patients, policy makers, and health care providers this information is important to determine whether or not to provide, or obtain a specific intervention[26].

Therefore, a comprehensive review to evaluate trial-based economic evidence for MT is necessary. Although the subject has been reviewed by Tsertsvadze (2014), this study extended the review by including new studies. Furthermore, we added information from Korean and Chinese databases, since Chuna MT (Korean) and Tuina(Chinese) are widely used in the treatment of musculo-skeletal diseases in Korea and China[27,28].

The purpose of this study was to conduct a systematic review and narrative synthesis of the evidence in randomized controlled trial(RCT)-based economic evaluations of MT.

Ⅱ. METHODS

A. Search strategy

The protocol of this review was previously published in the BMJ Open Journal[29]. It has been updated to include studies published up to 2 February 2017 using following databases: Medline, Embase, the Cochrane Central Register of Controlled Trials, CINAHL, Econlit, Mantis, Index to Chiropractic Literature, Science Citation Index, Social Science Citation Index, AMED, NHS DARE, NHS HTA, NHS EED, and CENTRAL; Korean medical databases, including OASIS, RISS, DBPIA, KTKP, and KoreaMed; and Chinese databases, including CNKI, VIP, and Wanfang. In addition, we have investigated grey literature including the sites of the following organization: CIHI, CIHR, NICE, CADTH, Tufts Medical Center Cost-effectiveness Analysis Registry, Agency for Healthcare Research and Quality and National Institute for Health Research Health Technology Assessment program.

The full search strategy for Medline is shown in Table Ⅰ. Search terms were limited to title and free-text terms. We did not include broader terms "physiotherapy". Because early tests suggested that the amount of the literature using such an extensive search strategy would be unmanageable. No publication year and language restriction was applied.

Table Ⅰ. Search Strategy for Medline via Pubmed

1	"Musculoskeletal Manipulations"[Mesh] or "Chiropractic"[Mesh] or "Osteopathic Medicine"[Mesh]
2	(orthopaedic[TIAB] or orthopedic[TIAB] or chiropract*[TIAB] or chirother*[TIAB] or osteopath*[TIAB] or spine[TIAB] or spinal[TIAB] or vertebra*[TIAB] or craniocervical[TIAB] or craniosacral[TIAB] or "cranio sacral"[TIAB] or cervical[TIAB] or lumbar[TIAB] or occiput[TIAB] or invertebral[TIAB] or thoracic[TIAB] or sacral[TIAB] or sacroilial[TIAB] or joint*[TIAB]) AND (manipulat*[TIAB] or adjustment*[TIAB] or mobilis*[TIAB] or mobiliz*[TIAB] or traction*[TIAB])
3	(manual[TIAB] or manipulat*[TIAB] or mobilis*[TIAB] or mobiliz*[TIAB]) AND (therap*[TIAB] or intervention*[TIAB] or treat*[TIAB] or rehab*[TIAB])
4	osteopath*[TIAB] or chiropractic*[TIAB] or chirother*[TIAB] or "friction massage*"[TIAB] or naprapath*[TIAB] or Rolfing[TIAB] or "myofascial release"[TIAB] or "Bowen technique"[TIAB] or "apophyseal glide*"[TIAB] or "bone setting"[TIAB] or bonesetting[TIAB] or "body work*"[TIAB] or "high-velocity low-amplitude"[TIAB] or HVLA[TIAB] or Maitland[TIAB] or Kaltenborn[TIAB] or Evejenth[TIAB] or Evjenth[TIAB] or Mulligan[TIAB] or McKenzie[TIAB] or Cyriax[TIAB] or Mills[TIAB] or Mennell[TIAB] or Stoddard[TIAB]
5	1 OR 2 OR 3 OR 4
6	economics[Mesh:NoExp] or "costs and cost analysis"[Mesh] or "economics, dental"[Mesh] or "economics, hospital"[Mesh] or "economics, medical"[Mesh] or "economics, nursing"[Mesh] or "economics, pharmaceutical"[Mesh] or economic*[TIAB] or cost[TIAB] or costs[TIAB] or costly[TIAB] or costing[TIAB] or price[TIAB] or prices[TIAB] or pricing[TIAB] or pharmacoeconomic*[TIAB] or (expenditure*[TIAB]) NOT energy[TIAB] or value for money[TIAB] or budget*[TIAB]
7	"Randomized Controlled Trial"[PT] OR trial*[TI] OR groups[TIAB] OR placebo*[TIAB] OR random*[TIAB]
8	#5 AND #6 AND #7

B. Study selection

Two independent reviewers(CGK and KNK) screened titles and abstracts of all studies and selected studies through a full text review by eligibility criteria. Any disagreements between the two reviewers were resolved by discussion. Another reviewer(JHL) was consulted if necessary[30].

We included English and Chinese-language full economic evaluation studies(cost-effectiveness, and cost-utility analysis) based on RCTs. Studies describing the use of any MT were included. No limitations regarding the duration of the treatment and comparison of two or more different interventions were imposed. The control group included placebo, waiting list, no treatment, or usual general practitioner(GP) care. Patients with musculoskeletal diseases, such as muscles, ligaments, tendons, intervertebral discs and cartilage were included.

We excluded studies in which MT was used to treat acute injuries such as fractures and dislocations, except for rehabilitation. Studies reporting only costs and other types of economic analysis(cost-consequence analysis) were also excluded, since they presented an array of different outcomes and cost measures. Studies that were not economic evaluations did not involve relevant

interventions, were non-RCTs, and that had insufficient information to calculate the incremental cost-effectiveness ratios(ICERs) for cost-effectiveness analysis(CEA) or cost-utility analysis(CUA) were excluded. Lastly, abstracts, commentaries, letters, protocol studies, and reviews were excluded.

C. Data extraction

Data was independently extracted by two independent reviewers(CGK and KNK). Publications about included studies are listed in Table Ⅱ and were used to support these analyses. The results were organized by the condition and the type of MT. A data extraction sheet was used to collect information (publication year, name of author, country, sample size, and follow-up duration), types of participants (condition, age, sex, and criteria), perspective type, cost methods, discounting, pain and disability scores, quality of life(QOL) measures, quality adjusted life-years (QALYs), costs, ICERs, types of interventions and comparisons, type of economic analysis, and currency which was the primary outcome.

In studies where one treatment was associated with cost reduction and found to produce greater effects, the treatment is said to be dominant and the description of an ICER is not needed[31].

Table Ⅱ. Publications Relevant to the Included Studies

Included studies	Related publications
Williams et el[46]	Williams et al[47]
Yu et al[48]	None
Bosmans et al[49]	Pool et al[50,51]
Korthals-de Bos et al[52]	Hoving et al[53]
Lewis et al[54]	Dziedzic et al[55]
Van Dongen et al[56]	Groeneweg et al[57]
Stochkendahl et al[58]	Stochkendahl et al[59,60]
Critchley et al[61]	None
Neimisto et al[62]	Niemisto et al[63]
Rivero-Arias et al[64]	Frost et al[65]
UK BEAM trial team[66]	Brealey et al[67], UK BEAM* Trial Team[68]
Whitehurst et el[69]	Hay et al[70]
Bergman et al[71]	Berman et al[72-74]
Coombes et al[75]	Coombes et al[76]
Zhang et al[77]	None
Lin et al[78]	Lin et al[79]
Pinto et al[80]	Abbott et al[40,81], Pinto et al[82]
Hu et al[83]	None

*BEAM = back pain exercise and manipulation

D. Quality assessment

Two independent reviewers(CGK and KNK) assessed the risk of bias of the included studies according to an assessment tool using 12 criteria. The quality of each trial in the risk of bias was rated as low, high risk, or unclear. Studies that met at least 6 of the 12 criteria were considered low risk, while those that met 5 or fewer criteria were rated high risk[32]. In support of this system, the previous studies have indicated that studies with higher risk of bias tend to overestimate the treatment effects[33,34].

Studies were evaluated using a recommended tool with the Drummond checklist(10 items) for the critical appraisal of the economic evaluation[35]. The response options for each item are yes, no, not clear or not appropriate. This enabled the investigators to develop a qualitative assessment of the complete study.

E. Data analysis

To make comparisons across countries and years, we converted the costs to the USD 2015. An international exchange rate based on purchasing power parities(PPP) was used to convert cost estimates to the USD, and country-specific gross domestic product (GDP) deflators were used to convert cost estimates to 2015 equivalents. GDP and PPP data were taken from the World Economic

Table Ⅲ. Exchange Rate of Original Currency and 2015 United States Dollar

	Original Currency	Exchange Rate
Williams et al[46]	£1999-2000	2.12
Yu et al[48]	元2005	0.24
Bosmans et al[49]	€2004	2.15
Korthals-de Bos et al[52]	€2000	2.16
Lewis et al[54]	£2003	2.39
van Dongen et al[56]	€2010	1.37
Stochkendahl et al[58]	€2014	1.33
Critchley et al[61]	£2003-2004	1.94
Niemisto et al[62]	$2002	1.24
Rivero-Arias et al[64]	£2004	1.94
UK BEAM* trial team[66]	£2010	2.13
Whitehurst et al[69]	£2001-2002	2.02
Bergman et al[71]	€2000	1.98
Coombes et al[75]	AU$†2013	1.40
Zhang et al[77]	元2006	0.22
Lin et al[78]	AU$2005	4.37
Pinto et al[80]	NZ$†2009	1.23
Hu et al[83]	元2009	0.19

*BEAM = back pain exercise and manipulation; †AU$ = Australian dollar; †NZ$ = New Zealand dollar

Outlook Database and PPP Database(Table Ⅲ). The threshold for the national health policy of the Republic of Korea has not been formally announced; however, based on the contents of the Asian collaboration on cost-effectiveness in health care decision making(2012) announced by the National Evidence-based healthcare Collaborating Agency(www.neca.re.kr) and preceding articles, we used a single willingness to pay(WTP) threshold of $26,963/QALY as an indicator of cost-effectiveness. That is, if a treatment resulted in an ICER that was lower than the threshold when compared to an alternative, the treatment was considered relatively cost-effective.

Ⅲ. RESULTS

A total of 3,327 references were screened, of which 142 passed at the title and abstract level and were considered for full-text review, and 124 studies were excluded at the

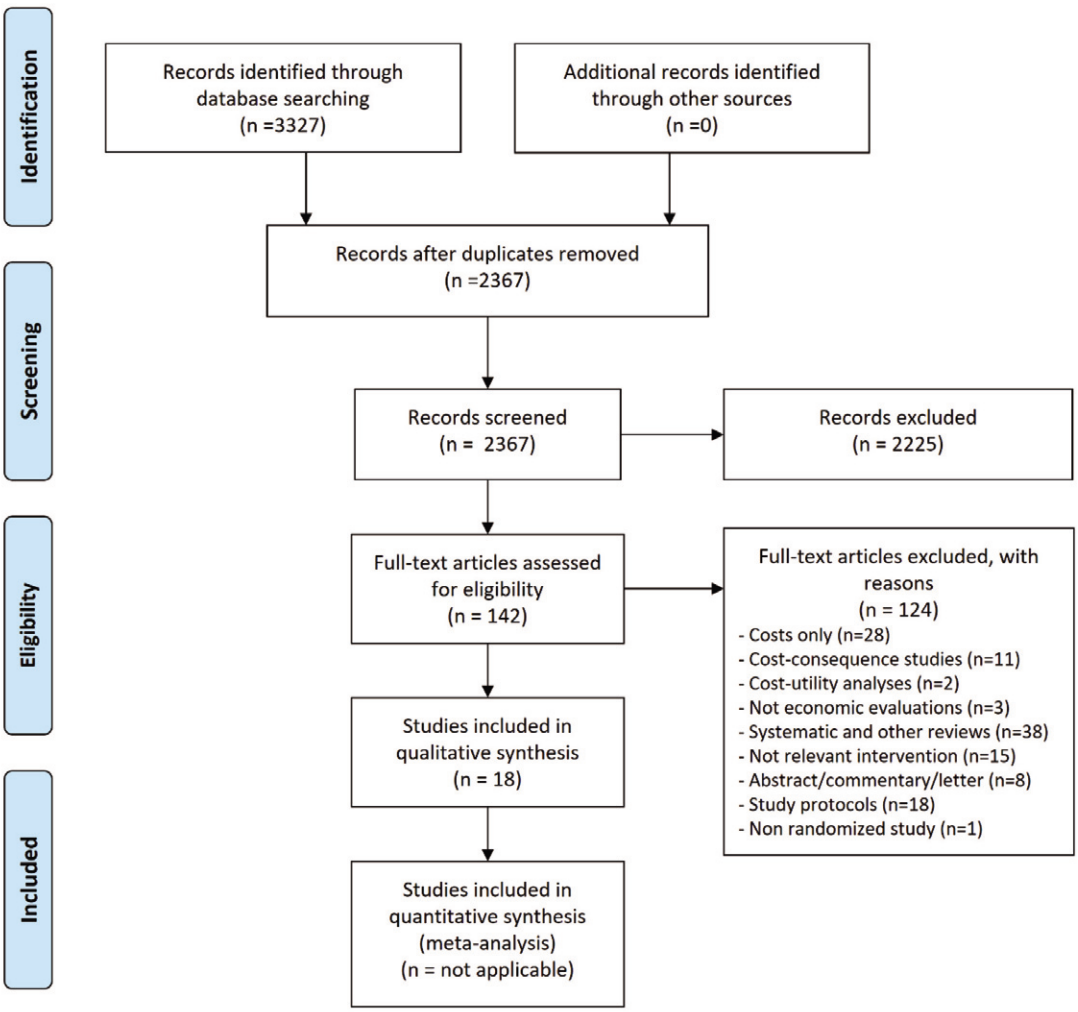

Fig. 1. Flow chart of the study selection progress.

full-text level. The remaining 18 RCTs included in the systematic review(Fig. 1).

Table Ⅳ reports the basic study, participant and perspective type of methods, intervention, outcome characteristics, and analysis. The included studies were conducted in China[38,67,74], Denmark[48], New Zealand[70], the United Kingdom[36,44,51,54,56,59], the Netherlands[39,42,46,61], Finland[52], and Australia[65,68]. 15 studies were published in English; 3 studies were published in Chinese. The publication year ranged from 2003 to 2016. The size of sample ranged from 50 to 1334 participants. The follow-up duration across reports ranged from 1 to 24 months. The participants mean age ranged from 29.35[67] to

Table Ⅳ. Characteristics of Included Randomized Controlled Trials

Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up
Spinal pain (low back, upper back, and/or neck)				
Williams[46] 2004 UK National Health Service	Size: 201 (randomized), 136(analyzed) Age (mean): NR* Male (%): NR	Direct medical costs: GP† and outpatient consultations, hospital stay, investigations, prescribing Direct non-medical costs: NA† Indirect costs: NA Discounting: None	Intervention 1: OSM§ + Usual GP care [3-4 sessions] Intervention 2: Usual GP care [3-4 sessions] Duration: 2 months	Mean QALY‖ (based on quality of life score EQ-5D¶) ICER#, Last follow-up: 6 months
Cervical spondylotic radiculopathy				
Yu[48] 2008 China Societal	Size: 69 (randomized and analyzed) Age (mean): 54.44 Male (%): 26.08	Direct medical costs: treatment and registration fees Direct non-medical costs: transportation costs Indirect costs: loss of working time Discounting: None	Intervention 1: Tuina manipulative therapy group [1time/2days] Intervention 2: Traction therapy group [1time/1day] Duration: 2 weeks	ICER (based on perceived recovery), Last follow-up: 4 weeks
Neck pain				
Bosmans[49] 2011 The Netherlands Societal	Size: 146 (randomized and analyzed) Age (mean): 45 Male (%): 40	Direct medical costs: primary care (GP, SMT**, BGA††, massage, homeopathy, outpatient visit, x-ray, tomography, MRI†‡), supportive care Direct non-medical costs: Informal care, paid home help Indirect costs: absenteeism from paid/unpaid work Discounting: None	Intervention 1: SMT(manipulation using passive movement of a joint beyond its active and passive limit of motion with a localized thrust of small amplitude to regain motion) [6 sessions] Intervention 2: BGA (gradually increasing exercise program) [18 sessions] Duration: 6 weeks	Mean QALY ICER (based on QALY, pain; perceived recovery; NDI§§), Last follow-up: 12 months

Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up
Korthals-de Bos[52] 2003 The Netherlands Societal	Size: 183 (randomized), 178 (analyzed) Age (mean): 45 Male (%): 40	Direct medical costs: GP, PT‖, SMT, outpatient appointments, hospitalization, exercise, home care Direct non-medical costs: alternative therapy, home care, friend's or partner's help, travel Indirect costs: Absenteeism from paid/unpaid work Discounting: None	Intervention 1: SMT (combination of techniques described by Cyriax, Kaltenborn, Maitland, and Mennel using hands-on muscular and articular mobilization techniques, coordination or stabilization techniques, and joint mobilization) [6 sessions] Intervention 2: PT (active, postural, or relaxation exercises, stretching, massage, manual traction) [12 sessions] Intervention 3: GP care (standard care, advice on self-care, education, ergonomic issues, paracetamol or NSAIDs¶¶, if necessary) [1 session and optional biweekly follow-up visits] Duration: 6 weeks	Mean QALY ICER (based on EQ-5D, pain; NDI), Last follow-up: 12 months
Lewis[54] 2007 UK National Health Service and Societal	Size: 350 (randomized), 346 (analyzed) Age (mean): 51 Male (%): 37	Direct medical costs: GP consultations, study intervention sessions, outpatient attendance Direct non-medical costs: patient expenses Indirect costs: absenteeism from paid work Discounting: None	Intervention 1: A & E## [8 sessions] Intervention 2: A & E + SMT (passive/active assisted hands-on movements, joint and soft tissue mobilization or manipulations graded as appropriate to the patient's signs and symptoms) [8 sessions] Intervention 3: A & E + PSWD*** [8 sessions] Duration: 6 weeks	Mean QALY ICER (based on EQ-5D; NPQ†††) Last follow-up: 6 months

Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up
van Dongen[56] 2016 The Netherlands, Societal	Size: 181 (randomized and analyzed) Age (mean): 48.9 Male (%): 38.1	Direct medical costs: intervention costs of MTU†††† or PT costs, healthcare utilization included care by a healthcare provider Direct non-medical costs: prescribed and over-the-counter medication. healthcare utilization informal care Indirect costs: absenteeism, unpaid productivity losses Discounting: None	Intervention 1: MTU group (combination of rolling and sliding, or rocking and gliding, in the joints of the spine and extremities) [≤6 sessions, 1time/1-2weeks] Intervention 2: PT group (active exercises, muscle stretching, manual traction, and massage) [≤9 sessions, 1-2times/1week] Duration: 6 weeks	Mean QALY ICER (based on mean QALY, recovery, NDI-DV§§§) Last follow-up: 12 months
Musculoskeletal chest pain				
Stochkendahl[58] 2015 Denmark Societal	Size: 115 (randomized and analyzed) Age (mean): 51.1 Male (%): 58.3	Direct medical costs: intervention costs, additional visits to mainstream healthcare and complementary and alternative medicine providers and hospital contacts Direct non-medical costs: prescriptive and non-prescriptive drugs Indirect costs: NR Discounting: None	Intervention 1: Chiropractic treatment (high-velocity, low-amplitude manipulation directed toward the thoracic and/ or cervical spine, joint mobilization, soft tissue techniques) [≤10 sessions] Intervention 2: Self-management (consultation consisting of reassurance, advice and individual instructions regarding posture and 2 to 3 home exercises) [1 sessions] Duration: 4 weeks	Mean QALY (based on quality of life score EQ-5D, SF-36‖‖‖) ICER, Last follow-up : 12 months
Low Back pain				
Critchley[61] 2007 UK National Health Service	Size: 212 (randomized), 148 (analyzed) Age (mean): 44 Male (%): 35.8	Direct medical costs: healthcare visits, hospital stays, staff time, inpatient procedures, investigations, medication Direct non-medical costs: NA Indirect costs: NA Discounting: 3.50%	Intervention 1: Individual PT (joint manipulation, mobilization, massage, back care advice, individual exercises including trunk muscle retraining) [12 sessions] Intervention 2: Spinal stabilization PT (transverses abdominis and lumbar multifidus muscle training, exercise for spinal stability) [8 sessions] Intervention 3: Pain management [8 sessions] Duration: NR	Mean QALY (based on quality of life score EQ-5D) ICER, Last follow-up: 18 months

Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up
Neimisto[62] 2005 Finland Societal	Size: 204 (randomized), 138 (analyzed) Age (mean): 37 Male (%): 46	Direct medical costs: visits to physician, PT visits, outpatient clinics, hospital stays, x-rays Direct non-medical costs: drug and travel costs Indirect costs: productivity loss costs Discounting: None	Intervention 1: Manipulative combination treatment (manipulation with muscle energy technique to correct any biomechanical dysfunction in the lumbar or pelvic segments) [4 sessions] Intervention 2: GP advice (booklet, advice on exercise, muscle stretch) [1 session] Duration: 4 weeks	ICER (based on pain and ODI¶¶¶ scores), Last follow-up: 24 months
Rivero-Arias[64] 2006 UK National Health Service and Societal	Size: 286 (randomized and analyzed) Age (mean): 41 Male (%): 47.5	Direct medical costs: NHS### costs (intervention, GP visits, hospitalizations, prescribed items) Direct non-medical costs: health care purchased by patient (private consultations with osteopaths, chiropractors, over the counter drugs) Indirect costs: employment costs (number of days off work) Discounting: None	Intervention 1: PT (joint manipulation, mobilization, massage, stretching, spinal mobility and strengthening exercise, heat/cold therapy) + advice to remain active [5 sessions] Intervention 2: Advice to remain active (back book) [1 session] Duration: NR	Mean QALY (based on quality of life score EQ-5D) ICER, Last follow-up: 12 months
UK BEAM[66] 2004 UK National Health Service	Size: 1334 (randomized), 1287 (analyzed) Age (mean): 43.1 Male (%): 44	Direct medical costs: GP care/ consultations, visits, outpatient attendance, hospital stay, programmes of exercise, manipulation Direct non-medical costs: NA Indirect costs: NA Discounting: None	Intervention 1: GP care Intervention 2: Exercise + GP care [9 sessions] Intervention 3: Manipulation (a multidisciplinary group developed a package of techniques representative of those used by the UK chiropractic, osteopathic) + GP care [9 sessions] Intervention 4: Manipulation + exercise + GP care [9 sessions] Duration: 12 weeks	Mean QALY ICER (based on EQ-5D, RMDQ**** score), Last follow-up: 12 months

Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up
Whitehurst[69] 2007 UK National Health Service	Size: 402 (randomized and analyzed) Age (mean): 41 Male (%): 47	Direct medical costs: treatment sessions (PT and brief pain management), outpatient attendance, inpatient attendance, primary care contacts, other health professionals Direct non-medical costs: NA Indirect costs: NA Discounting: None	Intervention 1: Manual PT (articulatory mobilization, manipulation, or soft tissue techniques, spinal stabilization, back exercise, ergonomic advice, back education) [7 sessions] Intervention 2: Brief pain management (general fitness, exercise for spinal mobility, explanation about pain mechanisms, distress, coping strategies) [2 days course plus clinical tutoring] Duration: NR	Mean QALY ICER (based on EQ-5D, RMDQ score), Last follow-up: 12 months
Shoulder pain				
Bergman[71] 2010 The Netherlands Societal	Size: 150 (randomized), 140 (analyzed, excluding 2) Age (mean): 48 Male (%): 49	Direct medical costs: treatment by GP, physiotherapist, manual, occupational, exercise or complementary health therapists, visits to consultant in orthopedic surgery, acupunc turist, neurology, rheumatology, rehabilitation medicine, and hospitalization Direct non-medical costs: out-of-pocket expenses, costs for paid/unpaid help Indirect costs: loss of production due to sick leave from paid/ unpaid work Discounting: None	Intervention 1: SMT (high velocity low amplitude manipulation and passive low velocity mobilization with in the range of joint motion) [6 sessions] + Usual GP care (advice on daily living, if needed analgesics, NSAIDs, corticosteroid injections, or PT including massage and exercise) Intervention 2: Usual GP care [number sessions: NR] Duration: 12 weeks	ICER (based on perceived recovery, shoulder pain, shoulder disability, general health), Last follow-up: 6 months
Lateral epicondylalgia				
Coobmes[75] 2015 Australia Societal	Size: 165 (randomized), 154 (analyzed) Age (mean): 49.7 Male (%): 62	Direct medical costs: intervention costs of medical injection, PT, other Direct non-medical costs: over the counter medication, assistive devices, paid or unpaid labor, transportation	Intervention 1: Saline injection (0.5mL of 0.9% isotonic saline) + GP care (advice to avoid activities for 2 weeks, after 2 weeks) [1 session] Intervention 2: Saline injection + PT (MT†††, concentric and eccentric wrist extension exercises, motor control retraining	Mean QALY (based on quality of life score EQ-5D) ICER, Last follow-up: 12 months

Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up
		Indirect costs: work absence, leisure time loss Discounting: None	and global upper body strengthening, a daily home exercise program) + GP care [1 session of injection, 8 sessions of PT] Intervention 3: Corticosteroid injection (10mg/mL of triamcinolone acetonide + 1 mL of 1% lignocaine) + GP care [1 session] Intervention 4: Corticosteroid injection + PT + GP care [1 session of injection, 8 sessions of PT] Duration: 10 weeks	
Hand injury				
Zhang[77] 2009 China Societal	Size: 50 (randomized and analyzed) Age (mean): 29.36 Male (%): 90	Direct medical costs: rehabilitation costs, hospital-related costs, diagnostic costs of complications Direct non-medical costs: non-hospitalized treatment and medication costs Indirect costs: NR Discounting: None	Intervention 1: Rehabilitation group (routine hand surgery + individual rehabilitation education, rehabilitation treatment program, PT, occupational therapy, stress treatment, psychological treatment) [after surgery 2 times/day] Intervention 2: Control group (routine hand surgery + guidance function training) [NR] Duration: 12 weeks	ICER (based on Tendon total active motion, Minnesota manual dexterity, Purdue pegboard assessment systems), Last follow-up: 3 months
Ankle pain				
Lin[78] 2008 Australia Health care system and patient	Size: 94 (randomized), 92 (analyzed) Age (mean): 41.5 Male (%): 54	Direct medical costs: outpatient PT, GP, medical specialists, emergency department, hospitalization, medication, investigations, private health providers Direct non-medical costs: public transport, private vehicle Indirect costs: None Discounting: None	Intervention 1: MT (large amplitude oscillatory anterior -posterior glides of the talus) + PT (exercise, gait retraining, walking aids, advice, ice, elevation, progression if required) [8 sessions] Intervention 2: PT (exercise, gait retraining, walking aids, advice, ice, elevation, progression if required) [5 sessions] Duration: 4 weeks	ICER (based on quality of life AQol†††: QALY), Last follow-up: 6 months

Study ID, Perspective	Participants	Costs Methods	Interventions	Outcome, Follow-up
Osteoarthritis of the hip or knee				
Pinto[80)] 2013 New Zealand New Zealand health system and Societal	Size: 206 (randomized and analyzed) Age (mean): 66.6 Male (%): 44.7	Direct medical costs: health professionals, public and private hospital use, medications, aids and adaptations, and community service Direct non-medical costs: out-of-pocket costs, transportation costs and informal care Indirect costs: lost earnings, productivity loss Discounting: None	Intervention 1: Usual care (routine care offered by their (routine care offered by their own GP and other healthcare providers) [9 sessions] Intervention 2: MT + usual care (application of therapist-applied manual forces in procedures intended to modify the quality and range of motion of the target joint and soft tissue structures) [9 sessions] Intervention 3: Exercise therapy + usual care (multi-modal, supervised programme of warm-up/aerobic, muscle strengthening, muscle stretching, and neuromuscular control exercises) [9 sessions] Intervention 4: Combined therapy + usual care (MT + exercise therapy) [9 sessions] Duration: 9 weeks	Mean QALY ICER (based on mean QALY, Western Ontario and McMaster University osteoarthritis index, Outcomes Measures in Rheumatology Clinical Trials - Osteoarthritis Research Society International), Last follow-up: 12 months
Osteoarthritis of the knee				
Hu[84)] 2012 China NR	Size: 60 (randomized and analyzed) Age (mean): 63.55 Male (%): 16.7	Direct medical costs: intervention costs of Tuina manipulative therapy, acupuncture Direct non-medical costs: None Indirect costs: NA Discounting: None	Intervention 1: Acupuncture group (acupuncture + electroacupuncture) [12 sessions] Intervention 2: Tuina manipulative therapy group (Tuina manipulative therapy like revolving method + knee flexion and extension of passive movement and active exercise) [12 sessions] Duration: 4 weeks	ICER (based on Western Ontario and McMaster University osteoarthritis index), Last follow-up: 4 weeks

*NR = not reported; †GP = general practitioner; ‡NA = not applicable; §OSM = osteopathic manual therapy; ‖QALY = quality-adjusted life year; ¶EQ-5D = European Quality of Life-5 Dimensions; #ICER = incremental cost-effectiveness ratio; **SMT = spinal manual therapy; ††BGA = behavioral graded activity; ‡‡MRI = magnetic resonance imaging; §§NDI = Neck Disability Index; ‖‖PT = physiotherapy; ¶¶NSAIDs = nonsteroidal anti-inflammatory drugs; ##A&E = advice and exercise; ***PSWD = pulsed shortwave diathermy; †††NPQ = Northwick Park Neck Pain Questionnaire; ‡‡‡MTU = manual therapy according to the Utrecht School; §§§DV = Dutch Version; ‖‖‖SF-36 = Short Form 36-item Health Survey; ¶¶¶ODI = Oswestry Disability Index; ###NHS = National Health Service; ****RMDQ = Roland-Morris Disability Questionnaire; ††††MT = manual therapy; ‡‡‡‡AQoL = assessment of quality of life

66.6[70] years. Most interventions lasted from 6 to 12 weeks (Table Ⅳ).

Most economical analyses of cost-effectiveness were based on pain intensity (visual analogue scale; VAS), functional disability, and recovery measures. Utilities were measured using European QOL-5 Dimensions (EQ-5D), the six-dimensional health status short form (SF-6D), or the Assessment of QOL, and then transformed into QALYs. The perspective of the reports was either societal[38,39,42,44,46,48,52,54,61,65,67,70] or from the health care system[36,44,51,54,56,59,68]. Most societal perspective studies included direct medical, direct nonmedical and indirect costs with the exception of one report[67]. In most studies, discounting was not considered in the context of a short follow-up of 12 months.

A. Quality of economic evaluations (Table Ⅴ)

Most studies reported all important costs

Table Ⅴ. The Drummond Checklist for Critical Appraisal of Economical Evaluation

Item number	1	2	3	4	5	6	7	8	9	10	%of yes
Bergman et al[71]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	Yes	Yes	90
Bosmans et al[49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Coombes et al[75]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	Yes	Yes	90
Critchley et al[61]	Yes	Yes	Yes	Can't tell (costs)	Can't tell (costs)	Yes	Yes	Yes	Yes	Yes	80
Hu et al[84]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	No	No	70
Korthals-de Bos et al[52]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	Yes	No	80
Lewis et al[54]	Yes	Yes	Yes	No (costs)	Can't tell (costs)	Yes	Yes	Yes	Yes	Yes	80
Lin et al[78]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	No	No	Yes	70
Niemisto et al[62]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	Yes	Yes	90
Pinto et al[80]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Rivero-Arias et al[64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Stochkendahl et al[58]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	No	Yes	80
UK BEAM trial team[66]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
van Dongen et al[56]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	Yes	Yes	90
Whitehurst et al[69]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Williams et al[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100
Yu et al[48]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	Yes	No	80
Zhang et al[77]	Yes	Yes	Yes	Yes	Can't tell (costs)	Yes	Yes	Yes	No	No	90

1 = Was a well-defined question posed in answerable form?; 2 = Was a comprehensive description of the competing alternatives given?; 3 = Was the effectiveness of the programmes or services established?; 4 = Were all the important and relevant costs and consequences for each alternative identified?; 5 = Were costs and consequences measured accurately in appropriate physical units?; 6 = Were costs and consequences valued credibly?; 7 = Were costs and consequences adjusted for differential timing?; 8 = Was an incremental analysis of costs and consequences of alternatives performed?; 9 = Was allowance made for uncertainty in the estimates of costs and consequences?; 10 = Did the presentation and discussion of study results include all issues of concern to users?

and consequences. The ICERs and/or incremental cost-utility ratios (ICURs) were reported in all studies; except for 1 study where details were provided in order calculate this ratio[68]. 4 studies did not consider the uncertainty of the cost-effectiveness ratio estimation[48,67,68,74]. 14 studies provided detailed discussion sections by emphasizing the most important issues.

B. Risk of bias assessments

Risk of bias assessments are presented in Fig. 2. Sixteen studies were evaluated as having a low risk of bias[38,39,42,44,46,48,51,52,54,56,59,61,65,68,70,74], whereas 2 studies were found to have a high risk[36,67] as patients and care providers were not blinded to the intervention type. Thirteen trials reported adequate methods of randomization and

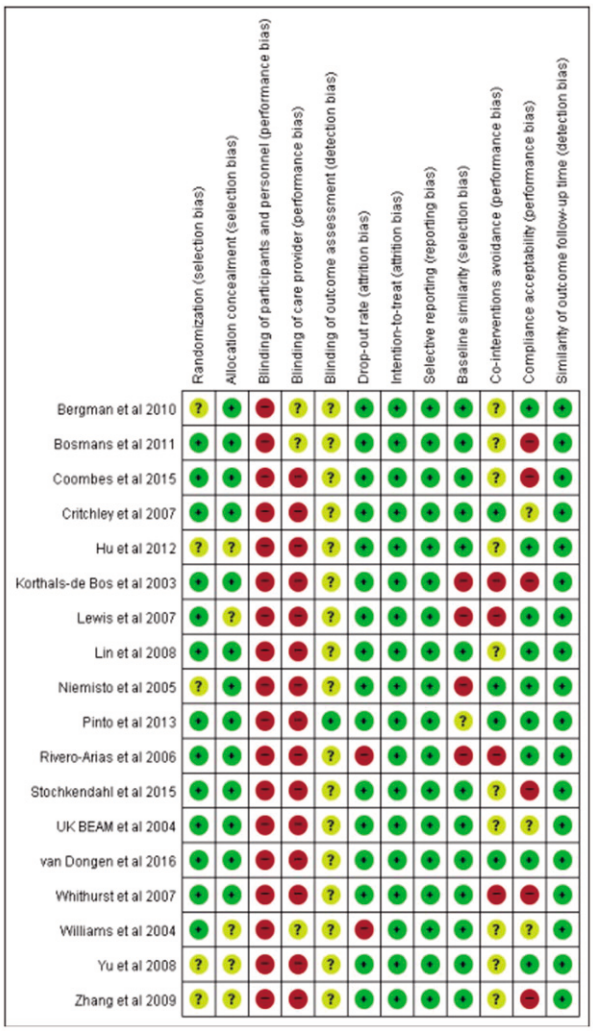

Fig. 2. Summary assessments of risk of bias.
Green circle = low risk; red circle = high risk; yellow circle: unclear.

treatment allocation concealment. Since the outcomes were self-reported, blinding of assessors was considered not applicable; only except one study referred to outcome assessor blinding. Results of all studies were based on intention-to-treat analyses.

C. Cost-effectiveness and/or cost-utility of MT (Table Ⅵ)

1) Spinal pain

The trial by Williams et al[36,37], the combination of osteopathic manipulation and usual GP care was more effective in the incremental QALYs gain(0.025) and also more expensive compared with GP care alone. The combination group was relevant to an ICER estimate of $7,471 per QALYs gained. Because this estimate is lower than the threshold of £30,000($63,600) (suggested by the NICE), this intervention may be regarded as a cost-effective selection.

2) Cervical spondylotic radiculopathy

The trial by Yu et al[38] assessed the cost-effectiveness of Tuina MT(rotation technique) and traction therapy. The Tuina MT was dominant compared with traction therapy.

3) Neck pain

The trial by Bosmans et al[39-41] assessed the cost-utility and cost-effectiveness of spinal MT(SMT) compared with behavioral graded activity(BGA). BGA was more effective in pain intensity and disability compared with SMT. BGA was costlier compared with SMT. BGA was possibly more cost-effective than SMT. However, SMT was not more cost-effective compared with BGA for perceived recovery.

The trial by Korthals-de Bos et al[42,43] assessed the cost-effectiveness and cost-utility of SMT, PT, and GP care. SMT was significantly less expensive compared with PT and GP care. Moreover, SMT was more effective than PT in improving pain intensity significantly, but not disability. Furthermore, SMT was more effective in reducing pain compared with both PT and GP care. SMT was more effective in pain intensity and disability compared with GP care. Moreover, SMT was most effective in QALYs gain compared with PT or GP care. SMT was dominant over PT for pain intensity, perceived recovery, and QALYs. It was also dominant over GP care for perceived recovery and QALYs.

The trial by Lewis et al[44,45] assessed the cost-utility and cost-effectiveness of advice and exercise(A&E) plus SMT, pulsed shortwave diathermy(PSWD) plus A&E, and A&E only. Compared with SMT and PSWD, A&E alone care was more expensive, and more effective numerically in disability and QALYs. According to acceptability curve WTP values, A&E had a higher probability of being cost-effective(up to 60%) than SMT and PSWD at all of the WTP thresholds over $97. At WTP thresholds below $97, SMT had a higher probability of being cost-effective (up to 55%) than A&E and PSWD in QALYs. At

the WTP threshold of £30,000 ($71,700) per QALYs gained, the probabilities for SMT, A&E, and PSWD were 44%, 30%, and 26%.

The trial by van Dongen et al[46,47] assessed the cost-utility and cost-effectiveness of MT by analyzing an Utrecht school group and a PT group. Compared with PT, the MT group was less costly, more effective in terms of perceived recovery, but, less effective in terms of functional status and QALYs. MT group was not found to be cost-effective compared with PT.

4) Musculoskeletal chest pain

The trial by Stochkendahl et al[48-50] assessed the cost-utility of a chiropractic treatment and a self-management. The chiropractic treatment was more effective in QALYs based on the EQ-5D, Short Form 36-item Health Survey(SF-36), EQ-5D, and SF-36 and less expensive compared with the self-management. The chiropractic treatment was dominant over the self-management in QALYs, EQ-5D, and the SF-36.

5) Low back pain

The trial by Critchley et al[51] assessed the cost-effectiveness of individual PT, spinal stabilization PT, and pain management. The pain management was dominant compared with individual PT and spinal stabilization PT. Individual PT was more expensive and statistically significantly more effective compared with spinal stabilization PT with a mean ICER estimate of $2,043 per QALYs gained.

The trial by Niemisto et al[52,53] assessed the cost-effectiveness of manipulative combination treatment and GP advice. This study demonstrated reduced pain intensity for the combination treatment compared to the GP advice. According to the acceptability curve using the VAS, the ICER of the combination treatment versus GP advice was acceptable 75%. According to the acceptability curve using the ODI, the ICER for the combination treatment versus GP advice was acceptable only 65% of the time in terms of disability.

The trial by Rivero-Arias et al[54,55] assessed the cost-utility of the combination of PT and advice to remain active compared with advice to remain active alone in patients. The combination group was more effective and also more expensive compared with advice alone. The combination group was relevant to an ICER estimate of $23,807 per QALYs gained. Despite the fact that this estimation fell within the acceptability threshold of WTP ($9,677 per QALY gained), the probability that combination group was a more cost-effective intervention than advice alone was calculated at only 60%.

The trial by the UK Back Pain Exercise and Manipulation(BEAM)[56-58] assessed the cost-utility of GP care, exercise plus GP care, manipulation plus GP care, and manipulation plus exercise and GP care from 14 general practices. The exercise therapy($1,009), manipulation therapy($1,151), and combination therapy($978) groups incurred higher mean total costs compared with the GP care group($718). The mean number of

Table Ⅵ. Results of Cost-effectiveness and Cost-utility Analyses

Study ID	Analysis	Outcomes	Mean Costs	Mean Effects (SD)	Costs Difference	ICER*
Spinal pain (low back, upper back, and/or neck)						
Williams[46] 2004 UK	CUA †	EuroQoL EQ-5D ‡	OSM§ + usual GP‖ care costs: $643	EQ-5D: 0.717 (0.248) QALY: 0.056 (0.101)	$186	Cost per QALY¶ gained: $7,471
			Usual GP care costs: $457	EQ-5D: 0.656 (0.289) QALY: 0.031 (0.105)		
Cervical spondylotic radiculopathy						
Yu[48] 2008 China	CEA#	perceived recovery	Tuina manipulative therapy group: $168	Recovery: 12.17 Recovery (%): 58.94	-$89	Dominance of Tuina manipulative therapy over traction therapy in terms of perceived recovery
			Traction therapy group: $257	Recovery: 8.45 Recovery (%): 43.40		
Neck pain						
Bosmans[49] 2011 The Netherlands	CEA, CUA	VAS**, NDI††, perceived recovery, quality of life	SMT‡‡ costs: $1,316	VAS: 3.5 (SE 0.31) NDI: 8.3 (SE 0.77) Recovery: 0.76 (SE 0.05) QALY: 0.770 (SE 0.01)	-$561	Cost per unit of outcome improved in: BGA versus SMT Recovery: $27,884 Pain: $623 NDI: $243 Cost per QALY gained: -$27,884
			BGA§§ costs: $1,877	VAS: 4.4 (SE 0.31) NDI: 10.6 (SE 0.79) Recovery: 0.78 (SE 0.05) QALY: 0.750 (SE 0.01)		
Korthals-de Bos[52] 2003 The Netherlands	CEA, CUA	VAS, NDI, perceived recovery, EQ-5D	1. SMT costs: $965	VAS: 4.2 (2.4) NDI: 7.2 (7.5) Recovery: 71.7 (43) EQ-5D: 0.820 (0.13)	1-3: -$2,015	Dominance of SMT over GP care and PT in terms of recovery, pain and QALYs
			2. PT‖‖ costs: $2,802	VAS: 3.1 (2.9) NDI: 6.3 (8.0) Recovery: 62.7 (37) EQ-5D: 0.790 (0.14)	2-3: -$178	GP over PT care Pain: $178 NDI: $80 Dominance of PT over GP care in terms of QALYs
			3. GP care costs: $2,980	VAS: 4.1 (2.9) NDI: 8.5 (7.4) Recovery: 56.3 (36) EQ-5D: 0.770 (0.16)		
Lewis[54] 2007 UK	CEA, CUA	Disability (NPQ¶¶), EQ-5D	1. A&E## costs: $723	NPQ: 11.5 (15.7) QALY: 0.362 (0.114)	2-1: -$136	Cost per NPQ gained: A&E over SMT $104
			2. SMT + A&E costs: $587	NPQ: 10.2 (14.1) QALY: 0.342 (0.114)	3-1: -$68	Cost per QALY gained: A&E over SMT $7,468
			3. PSWD*** + A&E costs: $655	NPQ: 10.3 (15.0) QALY: 0.360 (0.094)		

Study ID	Analysis	Outcomes	Mean Costs	Mean Effects (SD)	Costs Difference	ICER*
van Dongen[56] 2016 The Netherlands	CEA, CUA	perceived recovery, disability (NDI-DV†††), SF-6D†††	MTU§§§ group : $3,351	NR	-$131 Incremental effects: Recovery: 0.09 NDI-DV (conti-nuous): -1.03 (dicho-tomous): -0.01 QALY: -0.01	Cost per recovery gained: -$1,413 NDI-DV (continuous): $126 (dichotomous): $10,038 Cost per QALY gained $19,984
			PT group : $3,482	NR		
Musculoskeletal chest pain						
Stochkendahl[58] 2015 Denmark	CUA	EQ-5D, SF-36‖‖‖	Chiropractic treatment: $4,039	EQ-5D: 0.826 SF-36: 0.788 QALY(EQ-5D): 0.811 QALY(SF-36): 0.765	-$2,994	Dominance of Chiropractic treatment over self-management program in terms of QALYs
			Self-management program: $7,033	EQ-5D: 0.823 SF-36: 0.774 QALY(EQ-5D): 0.802 QALY(SF-36): 0.756		
Low Back pain						
Critchley[61] 2007 UK	CUA	EQ-5D	1. Individual PT costs: $918	EQ-5D: 0.67 QALY: 0.990	1-2: $184	Cost per QALY gained: $2,043
			2. Spinal stabilization PT costs: $734	EQ-5D: 0.63 QALY: 0.900		Pain management dominant over both treatments
			3. Pain management costs: $320	EQ-5D: 0.68 QALY: 1.000		
Neimisto[62] 2005 Finland	CEA	VAS, ODI, HRQoL¶¶¶ (15D)	NR	NR	$2,060 Incremental effects: VAS: 4.97 (4.83-5.12) ODI: 1.24 (1.18-1.30)	Cost per VAS gained: $635 Cost per ODI gained: -$97
			NR	NR		

Study ID	Analysis	Outcomes	Mean Costs	Mean Effects (SD)	Costs Difference	ICER*
Rivero-Arias[64] 2006 UK	CUA	EQ-5D	PT costs: $512	EQ-5D: 0.73 (0.25) QALY: 0.740 (0.18)	$117	Cost per QALY gained: $2,324
			Physiotherapist advice cost: $395	EQ-5D: 0.72 (0.26) QALY: 0.690 (0.23)		
UK BEAM[66] 2004	CUA	EQ-5D	1. GP care Costs: $718	QALY: 0.618	2-1: $291	Cost per QALY gained: $17,091
UK			2. GP care + exercise Costs: $1,009	QALY: 0.635	3-1: $433	$9,871
			3. GP care + manipulation Costs: $1,151	QALY: 0.659	4-1: $260	$7,861
			4. GP care + manipulation +exercise Costs: $978	QALY: 0.651		
Whitehurst[69] 2007 UK	CUA, CEA	Disability (RMDQ### score), EQ-5D	Manual PT Costs: $393	disability(RMDQ): 8.887 QALY: 0.777	$105	Cost per RMDQ gained: $316
			BPM**** Costs: $288	disability(RMDQ): 8.553 QALY: 0.755		Cost per QALY gained: $4,805
Shoulder pain						
Bergman[71] 2010 The Netherlands	CEA	Perceived recovery, shoulder pain and disability, general health	SMT + GP care costs: $2,305	Recovery: 41% Pain: 5.9 (5.4) Disability: 33.0 (34.6) General health: 0.11 (0.19)	$1,208	Cost per recovery gained: $241 Cost per pain gained: $1,728
			GP care costs: $1,097	Recovery: 35% Pain: 5.2 (5.5) Disability: 20.3 (35.9) General health: 0.08 (0.21)		Cost per disability gained: $96 Cost per general health gained: $40,316
Lateral epicondylalgia						
Coobmes[75] 2015 Australia	CUA	EQ-5D	1. Saline injection: $124	EQ-5D: 0.737 (0.122) QALY: 0.880 (0.092)	2-1: $720	Cost per QALY gained $21,046
			2. Saline injection + PT: $844	EQ-5D: 0.744 (0.125) QALY: 0.920 (0.075)	3-1 : $88	-$22,772
			3. Corticosteroid injection: $212	EQ-5D: 0.692 (0.175) QALY: 0.873 (0.075)	4-1: $643	$163,532
			4. Corticosteroid injection + PT: $767	EQ-5D: 0.755 (0.036) QALY: 0.891 (0.084)		

Study ID	Analysis	Outcomes	Mean Costs	Mean Effects (SD)	Costs Difference	ICER*
Hand injury						
Zhang[77] 2009 China	CEA	TAM††††, MMDT‡‡‡‡, PPT§§§§	Rehabilitation group : $1,972 Control group: $2,103	TAM: 67.8 MMDT: 77 PPT: 42.5 TAM: 29.3 MMDT: 55 PPT: 31.2	-$131	Dominance of rehabilitation group treatment over control group treatment in terms of TAM, MMDT, PPT
Ankle pain						
Lin[78] 2008 Australia	CUA	Quality of life (AQoL‖‖‖‖), activity limitation (LEFS¶¶¶¶)	MT + PT costs: $3,624 PT costs: $2,804	NR NR	$820 Incremental effects: AQoL: 1.3 QALY: -0.09 LEFS: -1.0	Cost per QALY gained: -$9,111
Osteoarthritis of the hip or knee						
Pinto[80] 2013 New Zealand	CEA, CUA	SF-12v2, WOMAC ####, OMERACT-OARSI *****	1. Usual care $7,756 2. Manual therapy + usual care: $7,565 3. Exercise therapy + usual care: $8,437 4. Combined therapy + usual care: $9,335	QALYs: 0.647 (0.067) WOMAC: 80.90 (57.70) OMERACT-OARSI: 37% QALYs: 0.656 (0.062) WOMAC: 73.33 (54.93) OMERACT-OARSI: 59% QALYs: 0.687 (0.064) WOMAC: 66.25 (54.57) OMERACT-OARSI: 47% QALYs: 0.663 (0.062) WOMAC: 71.74 (50.01) OMERACT-OARSI: 52%	2-1: -$191 3-1: $681 4-1: $1,579	Dominance of 2 over 1 in terms of QALYs, WOMAC, OMERACT-OARSI Cost per QALY gained 3 versus 1: $28,830 4 versus 1: $65,664 WOMAC gained 3 versus 1: $89 4 versus 1: $159 OMERACT-OARSI gained 3 versus 1: $9,710 4 versus 1: $18,275
Osteoarthritis of the knee						
Hu[84] 2012 China	CEA	WOMAC	1. Acupunture group: $69 2. Tuina manipulative therapy group: $60	WOMAC: 47.66(8.73) WOMAC: 45.83(7.65)	2-1: -$9	Cost per WOMAC gained acupuncture versus Tuina manipulative therapy: $5

*ICER = incremental cost-effectiveness ratio; †CUA = cost-utility analysis; ‡EQ-5D = European Quality of Life-5 Dimensions; §OSM = osteopathic manual therapy; ‖GP = general practitioner; ¶QALY = quality-adjusted life year; #CEA = cost-effectiveness analysis; **VAS = visual analogue scale; ††NDI = Neck Disability Index; ‡‡SMT = spinal manual therapy; §§BGA = behavioral graded activity; ‖‖PT = physiotherapy; ¶¶NPQ = Northwick Park Neck Pain Questionnaire; ##A&E = advice and exercise; ***PSWD = pulsed shortwave diathermy; †††DV = Dutch Version; ‡‡‡SF-6D = Short Form 6-Dimensions; §§§MTU = manual therapy according to the Utrecht School; ¶¶¶SF-36 = Short Form 36-item Health Survey; ‖‖‖HRQoL = health-related quality of life; ###RMDQ = Roland-Morris Disability Questionnaire; ****BPM = brief pain management; ††††TAM = total active motion; ‡‡‡‡MMDT = Minnesota manual dexterity; §§§§PPT: Purdue pegboard assessment systems; ‖‖‖‖AQoL = assessment of quality of life; ¶¶¶¶LEFS = lower extremity functional scale; ####WOMAC = Western Ontario and McMaster University osteoarthritis index; *****OMERACT-OARSI = Outcomes Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International

QALYs gained was also enhanced in the 3 groups compared with the GP care group (0.618). Compared with GP care, the combination therapy was associated with a greater mean incremental number of QALYs gained than either the exercise therapy or the manipulation therapy. Compared with GP care, the ICURs for the manipulation therapy, exercise therapy, or combination therapy were $9,871, $17,091, and $7,861. The combination therapy was possibly a dominant intervention compared with exercise therapy. If the WTP was at least $20,743 per QALYs gained, according to the report conclusions, the combination therapy was the most cost-effective treatment.

The trial by the Whitehurst et al[59,60] assessed the cost-effectiveness and cost-utility of manual PT with brief pain management(BPM). Manual PT was more effective in disability and utility and was also more expensive compared with BPM. Manual PT(versus BPM) was relevant to an ICER ratio estimate of $4,805 per QALYs gained. According to the cost-utility plane and acceptability curve, the ICER for manual PT versus BPM was acceptable 83% of the time given the threshold of $20,343 per QALYs gained conservatively. According to the study results, manual PT was more cost-effective than BPM.

6) Shoulder pain

The trial by the Bergman et al[61-64] assessed the cost-effectiveness of the combination of SMT plus usual GP care compared with usual GP care alone. The combination care was more expensive and also more effective in perceived recovery, shoulder pain, and general health compared with usual GP care. The combination care was relevant to an ICERs estimate of $241(perceived recovery), $1,728(shoulder pain), $96(shoulder disability), and $40,316(general health). At WTP threshold of $15,794 per 1-point perceived recovery improvement, the probability that combination care was cost-effective was 65%.

7) Lateral epicondylalgia

The trial by the Coombes et al[65,66] assessed the cost-utility of saline injection plus GP care (A), saline injection plus PT and GP care (B), corticosteroid injection plus GP care (C), and corticosteroid injection plus PT and GP care (D), B, C, D were more expensive compared with A, B was statistically significantly more effective in terms of QALYs when compared with A, but not when compared with for C and D. According to entire range of the acceptability curve WTP threshold $35,862 values the probability of being more cost effective than A, was 81% for B, 53% for C and 24% for D. There is a possibility that PT was more cost effective than the alternatives.

8) Hand injury

The trial by the Zhang et al[67] assessed the cost-effectiveness of the rehabilitation treatment and control treatment with digital

flexor tendons injury. The rehabilitation treatment was numerically less expensive and more effective over control treatment for functional disability. The rehabilitation treatment was dominant compared with control group.

9) Ankle pain

The trial by the Lin et al[68,69] assessed the cost-utility of combination of MT and PT compared with PT only with ankle fractures. The combination group was more expensive compared with PT alone. Since there were no significant differences between two groups in the primary outcome measures, a CEA was not managed. The authors concluded that the combination treatment was not a cost-effective selection compared with PT alone.

10) Osteoarthritis of the hip or knee

The trial by the Pinto et al[30,70-72] assessed the cost-utility and the cost-effectiveness of usual care, MT plus usual care, exercise therapy plus usual care, combined therapy plus usual care. From the societal perspective, the MT plus usual care was statistically less expensive compared with usual care. The MT plus usual care, exercise therapy plus usual care and combined therapy plus usual care were more effective compared with usual care in QALYs. The MT plus usual care was dominant over usual care for QALYs, Western Ontario and McMaster University osteoarthritis index(WOMAC), Outcomes Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International(OMERACT-OARSI).

The trial by the Hu et al[73] assessed the cost-effectiveness of the Tuina MT group (revolving method plus knee flexion and extension of passive movement and active exercise) and the acupuncture group. The acupuncture group was more effective in terms of WOMAC ($p<0.01$), more expensive compared with the Tuina MT group. ICER was estimated $5 per unit of outcome improved in the acupuncture versus the Tuina MT.

Ⅳ. DISCUSSION

The strengths of the current research include the reviewer's use of comprehensive and systematic strategies to minimize the risk of bias in searching, selecting, extracting, and evaluating the initial studies. The search strategy was applied to multiple databases including China and Korea and others. All of the included studies were RCT-based economic evaluations, and this review provided a high level of evidence in judging clinical research. This study extends the review by including new studies published since the search endpoint of Tsertsvadze's report[3] as well as studies from Asian databases. Among Asian databases, Korean and Chinese database searches were conducted, but a Japanese database search was not conducted. Compared with the previous study, this research has reviewed 10 musculoskeletal diseases by adding 7 RCTs.

In addition, 16 of the 18 included trials were evaluated as having a low risk of bias. Although it was concluded that only 8 of the 16 studies with low risk of bias were cost-effective, there is a difference in the number of patients per studies, and attention should be paid to interpreting the results.

Through this process, we found limited evidences suggesting that manual therapy techniques(osteopathic spinal manipulation, PT consisting of manipulation and mobilization techniques, and chiropractic manipulation), in combination with other treatments or alone, are more cost-effective than usual GP care(alone or with exercise), spinal stabilization, GP advice, advice to remain active, and brief pain management for musculoskeletal diseases.

However, it is difficult to suggest conclusions about the comparative cost-effectiveness of manual therapy treatments in patients with musculoskeletal diseases, because there were several limitations. First, it is due to the limitations of the RCTs included in this study; the paucity, clinical heterogeneity, and study-related shortcomings(short follow-up, small sample, high uncertainty in the estimates of incremental cost-effectiveness ratios).

Second, the results of this review are not comparable with other systematic reviews[3,17-22,75-85]. The findings of these reviews were not conclusive because of the deficiency and heterogeneity of the evidence for MT[18-23], showed some extent of the cost-effectiveness of MT over other treatments[3,75,79,80,82,83,84].

Third, the applicability of the findings of the included studies may be limited to only countries with similar health care systems. In the 10 studies that MT was cost-effective in the treatment of musculoskeletal diseases, when the ICERs about QALYs were converted into USD, they did not exceed the threshold of $26,963. However, there are difficulties in comparisons due to differences in costs and health care system between countries. The applicability may also be limited by the differences in the MT interventions and short follow-ups periods of the studies.

Fourth, since none of the studies used a sham and a control arm, it is difficult to ascertain out the specific effects of treatment[74]. In addition, due to the characteristics of MT, blinding of patients and care providers could not be performed.

Lastly, among the studies that meet the inclusion criteria of this paper, there were 2 studies for which only the abstracts were available. We sent an email to the authors, but were unable to get a reply. We found that the ICER calculated using the cost and effect data in 2 studies did not match the ICER data presented in those studies[60,62]. We sent an email to the authors about this problem, but were unable to get a reply.

This study provides a platform for further research into the cost-effectiveness of MT for the treatment of musculoskeletal diseases. The findings emphasize the lack of good-quality published evidence. The insufficient evidence on cost-effectiveness may be attributed to difficulties in getting cost data, lack of expertise in economic outcomes, and/or the perceived societal

inconvenience of assigning monetary units to human health[21]. When the studies do not use QALYs as an outcome measure, it is difficult for decision makers to compare value for money across musculoskeletal diseases with other diseases.

We recommend that future studies present unit cost calculations with costs disassembled by each service in order to enable the judgment as to whether all relevant costs for a given perspective were considered and how the total costs were calculated. If ethically valid, future trials need to include sham or no treatment arms in order to permit the evaluation and detachment of nonspecific effects from treatment effects. Worldwide further studies including Asian countries such as China, Japan, and Korea are needed to evaluate the economic comparisons of Chuna and MT for nonspecific musculo-skeletal diseases.

Ⅴ. CONCLUSIONS

In ten out of 18 studies MT was cost-effective in the treatment of musculoskeletal diseases. The benefits and detriments of the MT interventions found in many of the reported disease treatments cannot be reliably concluded because of the lack of methodological quality and clinical variety of the included studies.

This study provides a basis for further research into the cost-effectiveness of MT in the treatment of a variety of musculoskeletal diseases. To expand the evidence base and address the complexity of this important discipline in health care, further well-organized research including Asian databases should be considered. .

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