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Efficacy and Safety of the Pulsed Electromagnetic Field in Osteoarthritis: A Meta-analysis

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Manuscripts

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5 **1 Efficacy and Safety of the Pulsed Electromagnetic Field in Osteoarthritis: A Meta-analysis**

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23 **Abstract**

24 **Objective:** To investigate the efficacy and safety of the pulsed electromagnetic field (PEMF) therapy in
25 treating osteoarthritis (OA).

26 **Methods:** Relevant studies were identified by searching the database of PubMed, Embase, the
27 Cochrane Library and Web of Science. Randomized controlled trials (RCTs) comparing PEMF with
28 sham-control were included.

29 **Results:** Twelve trials (n=770) comparing PEMF with sham-control were included, among which ten
30 trials involved knee OA, two involved cervical OA and one involved hand OA. The PEMF group
31 showed more significant pain alleviation than the sham group in knee OA (SMD = -0.54, 95% CI:
32 -1.04, -0.04, $P = 0.03$) and hand OA (SMD = -2.85, 95% CI: -3.65, -2.04, $P < 0.00001$), but not in
33 cervical OA. Similarly, comparing with the sham-control treatment, significant function improvement
34 was observed in the PEMF group in both knee and hand OA patients (SMD = -0.34, 95%CI: -0.53,
35 -0.14, $P = 0.0006$, and SMD = -1.49, 95%CI: -2.12, -0.86, $P < 0.00001$, respectively), but not in
36 cervical OA patients. Sensitivity analyses suggested that the exposure duration ≤ 30 minutes per
37 session exhibited better effects compared with the exposure duration > 30 minutes per session. Three
38 trials reported adverse events, and the combined results showed that there was no significant difference
39 between PEMF and the sham group.

40 **Conclusions:** The present study revealed that PEMF could alleviate pain and improve physical
41 function for knee and hand OA patients, but not for cervical OA patients. Meanwhile, a short PEMF
42 treatment duration (within 30 minutes) may achieve more favorable efficacy.

43 **Level of Evidence:** Level I, meta-analysis

44 **Key words:** osteoarthritis, pulsed electromagnetic field, meta-analysis, randomized controlled trial

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5 **45 Strengths and limitations of this study**

6 46 1. This study provided a comprehensive assessment on the efficacy and safety of the pulsed
7
8 47 electromagnetic field (PEMF) therapy in patients with knee, hand and cervical osteoarthritis (OA).

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10 48 2. All included studies in this meta-analysis were randomised controlled trials.

11
12 49 3. There was a high level of heterogeneity among various studies, because different treatment protocols
13
14 50 of PEMF were used in the included studies.

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16 51 4. There were sparse eligible trials available for the efficacy analysis of hand OA and cervical OA, and
17
18 52 the reliability of the conclusions on these two joints were limited.

53 INTRODUCTION

54 Osteoarthritis (OA) is a widespread degenerative disease, which can lead to pain, physical dysfunction
55 and even disability. The joints most commonly affected by OA include knees, hips, hands, neck, and
56 feet.^{1 2} A variety of medications and physical therapies have been used in the treatment of OA.
57 However, some widely-applied drugs (e.g., chondroitin, glucosamine, intraarticular hyaluronic acid,
58 etc.) or physical treatments (e.g., transcutaneous electrical nerve stimulation, and ultrasound) are
59 actually not advocated by the recent Osteoarthritis Research Society International (OARSI) guidelines.³
60 To date, few effective treatments for knee OA are available.

61 Since the early 1980s, researchers have found that pulsed electromagnetic field (PEMF) therapy
62 could be applied to accelerate wound healing, repair fracture, reduce hematoma, and treat soft tissue
63 injury and inflammation.⁴ In addition, some studies have demonstrated that PEMF could activate the
64 signal transduction pathway⁵⁻⁷ and induce the human articular chondrocyte proliferation.⁸ Being a
65 simple, noninvasive and safe physical therapy, PEMF was considered to be an alternative treatment
66 regimen for OA. During the past two decades, more than ten randomized controlled trials (RCTs) were
67 conducted to explore the efficacy of PEMF in the treatment of OA, but no consensus was reached
68 yet.⁹⁻²² Several previous meta-analyses have evaluated the combined effects of PEMF and pulsed
69 electrical stimulation on OA.^{23 24} However, the mechanisms of PEMF and pulsed electrical stimulation
70 are totally different. For example, PES is delivered through capacitive coupling using transcutaneous
71 electrodes and coupling agents²⁵ relying on the direct application of an electrical field; whereas PEMF
72 creates induced current through magnetic impulse.²⁴ To the best of our knowledge, few meta-analyses
73 have evaluated the efficacy and safety of single PEMF for OA.

74 To fill in this knowledge gap, the purpose of the present study was to provide a comprehensive
75 assessment on the efficacy and safety of single PEMF in patients with OA at different joints. It was
76 hypothesized that PEMF could relieve pain and improve the physical function of OA patients without
77 producing side effects.

79 METHODS

80 Search strategies and studies selection

81 The study records were identified in four electronic databases of PubMed, Embase, the Cochrane

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5 82 Library and Web of Science through using the combination of a series of keywords and text terms
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7 83 describing OA and PEMF (Appendix 1). The latest literature search was conducted at October 13, 2017.
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9 84 Studies were included if: (1) subjects with symptomatic or radiographic OA, (2) the intervention
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11 85 containing PEMF versus sham-control, (3) the study was designed as a RCT, (4) the primary outcome
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13 86 including pain and/or function. Studies were excluded if: (1) in vitro or animal or cadaveric studies, (2)
14
15 87 PEMF therapy used for post-operation rehabilitation, (3) other non-medicine therapy (e.g., short wave
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17 88 or PES), (4) cannot get full-text, (5) no data available, (6) unbalanced additional non-pharmacological
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19 89 treatments (e.g., exercise or hot-pack) between groups.
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21 **Quality assessment**

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23 92 The methodological quality of each included trial was evaluated by two independent authors based on
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25 93 the Cochrane handbook,^{26 27} which consists of seven domains: generation of randomization sequences,
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27 94 allocation concealment, blinding of participants and implementers, blinding of outcome assessment,
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29 95 incomplete outcome data, selective reporting and other potential bias. Furthermore, any of divergence
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31 96 was to be discussed and a third consultant was needed if necessary.^{28 29} Trials involving three or more
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33 97 high risks of bias were considered as poor methodological quality.³⁰
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35 36 **Data extraction and outcome measure**

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38 100 All the data extracted by two independent authors. The extracted information included the
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40 101 characteristics of participants (age, gender, body mass index, and duration of OA), balance intervention
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42 102 between groups, number of participants about each trial, treatment protocol of PEMF, and the type of
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44 103 outcome measures, baseline data, post-treatment data and change means, and standard deviations (SD)
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46 104 or the information from which SD could be derived, such as standard error (SE) or confidence interval
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48 105 (CI). The primary goal of this study was to assess the efficacy of pain alleviation and function
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50 106 improvement by applying the PEMF therapy for OA patients. Adverse events were considered as the
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52 107 secondary outcome. The efficacy of pain alleviation was measured by change of pain intensity from
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54 108 baseline.³¹ Data from the last follow-up time point after treatment was extracted to calculate the change
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56 109 degree. According to Jüni *et al.*,^{32 33} the higher score one on hierarchy of continuous pain-related
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58 110 outcomes was used if multiple pain scale measured in one study. The number of participants reported

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5 111 adverse events were also extracted in order to evaluate the safety of interventions.

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9 113 **Statistical analysis**

10 114 The Review Manager Version 5.2 was used to perform all the statistical analyses. For the reason that
11 115 outcome of pain and function reported by continuous data and various scales were used for outcome
12 116 assessment, the standardized mean differences (SMDs) were calculated to compare the effect of pain
13 117 alleviation and function improvement between different intervention groups. For the safety outcome,
14 118 the relative risk (RR) was calculated to compare the safety between two groups. Trials reported zero
15 119 adverse event in both the PEMF and the sham groups were not included in the adverse events
16 120 analysis.²⁶ 95% CI was calculated for pooled estimates for each outcome. Statistical significance was
17 121 considered at $P < 0.05$. A random model was applied to pool the data. Q and I^2 statistics were
18 122 calculated to assess the heterogeneity among the included studies, with a p value > 0.05 of the Q
19 123 statistics and I^2 value $< 50\%$ indicating statistical homogeneity. Different exposure duration of PEMF,
20 124 disease location was hypothesized to influence treatment effect. Therefore, subgroup analyses were
21 125 performed according to the exposure duration of PEMF therapy (no more than 30 minutes per session
22 126 or more than 30 minutes per session)⁵⁻⁷ and location of OA. Funnel plots were inspected to assess
23 127 publication bias.

24 128

25 129 **Patient and public involvement**

26 130 No patients or members of public were involved in the present study. No patients were asked to advise
27 131 on interpretation or writing up of results. The results of present research will be communicated to the
28 132 relevant patient community.

29 133

30 134 **RESULTS**

31 135 **Study screening and characteristics of included studies**

32 136 Figure 1 showed the flow diagram for studies screening. 192 records were identified initially and
33 137 twelve studies⁹⁻²⁰ met the eligibility criteria and were included in this meta-analysis. The characteristics
34 138 of included studies were summarized in Table 1. The risk of bias assessment (Figure 2) showed that
35 139 one study⁹ was regarded as low quality.

140

141 Pain relief

142 Twelve RCTs were included for meta-analysis of pain management.⁹⁻²⁰ As shown in Figure 3, PEMF
143 group achieved a significant difference in pain improvement compared with sham group (SMD = -0.94,
144 95% CI: -1.49, -0.39, $P = 0.0008$), while significant heterogeneity was observed ($I^2 = 92%$; $P <$
145 0.00001). Subgroup analysis showed that significant differences were observed between the PEMF and
146 sham group on pain improvement in knee OA (SMD = -0.54, 95% CI: -1.04, -0.04, $P = 0.03$) and hand
147 OA patients (SMD = -2.85, 95% CI: -3.65, -2.04, $P < 0.00001$), whereas no significant difference was
148 achieved between groups in cervical OA patients (SMD = -2.33, 95% CI: -6.26, 1.61, $P = 0.25$). As for
149 subgroup analysis of different exposure duration, significant difference was observed when exposure
150 duration within 30 minutes (SMD = -1.01, 95%CI: -1.64, -0.39, $P = 0.001$), and no significant
151 difference was achieved between intervention groups when exposure duration more than 30 minutes
152 (SMD = -0.61, 95%CI: -2.25, 1.02, $P = 0.46$) (see Table 2). Besides, substantial asymmetry was not
153 identified in the funnel plot.

154

155 Function improvement

156 Eight RCTs were included for meta-analysis of physical function improvement.^{9 10 12 13 15 16 19 20} Figure 4
157 illustrated the beneficial effect of PEMF on physical function improvement (SMD = -0.45, 95% CI:
158 -0.71, -0.19, $P = 0.0005$), and substantial heterogeneity was observed ($I^2 = 54%$; $P = 0.03$). However,
159 the subgroup analysis of different OA locations suggested significant differences both in knee OA and
160 hand OA (SMD = -0.34, 95%CI: -0.53, -0.14, $P = 0.0006$, and SMD = -1.49, 95%CI: -2.12, -0.86, $P <$
161 0.00001 , respectively, see in Table 2), whereas there was no significant difference between groups in
162 cervical OA patients (SMD = -0.27, 95% CI: -0.71, 0.16, $P = 0.22$). In addition, there was a significant
163 difference on effect of function improvement when exposure duration within 30 minutes (SMD = -0.50,
164 95%CI: -0.81, -0.18, $P = 0.002$), and no significant difference was observed in more than 30 minutes
165 group (SMD = -0.33, 95%CI: -0.82, 0.17, $P = 0.20$). Funnel plot also did not identify substantial
166 asymmetry.

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168 Adverse events

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5 169 There were ten RCTs that reported adverse events.^{9-11 13 14 16-20} Seven of them claimed that no adverse
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7 170 events were observed both in PEMF and sham group.^{9 10 13 14 17 18 20} Three trials reported the adverse
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9 171 events of each treatment group, such as hip pain, spine pain, increased knee pain, vomiting, warming
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11 172 sensation, increased blood pressure, numbness of feet, paraesthesia of foot and et al, and there was no
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13 173 AE related drop outs in each trial.^{11 16 19} There was no significant difference between the PEMF and the
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15 174 sham group regarding adverse events (RR = 0.83, 95%CI: 0.26, 2.64, $P = 0.75$) (Figure 5). Substantial
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17 175 asymmetry was not identified in the funnel plot.
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177 **DISCUSSION**

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21 178 This study provided a comprehensive assessment on the efficacy and safety of the PEMF therapy in
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23 179 patients with knee, hand and cervical OA. The results showed that, in comparison with the
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25 180 sham-control group, PEMF was more effective in both pain relief and function improvement for
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27 181 patients with knee OA and hand OA, but not for patients with cervical OA. In addition, PEMF did not
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29 182 lead to specific adverse events compared with the sham control group. Interestingly, a short duration of
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31 183 PEMF treatment for ≤ 30 minutes per session seems to achieve more favorable results. This finding
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33 184 may have significant implications for the clinical application of PEMF in the OA field.

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35 185 Some previous systematic reviews have combined PEMF and other physical therapies together to
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37 186 examine their efficacy in OA patients, which might bias the results. McCarthy *et al.*³⁴ demonstrated that
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39 187 PEMF and short-wave together had limited effect in treating knee OA. In contrast, We *et al.*³⁵ reported
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41 188 different results. Based on the follow-up data extracted from different time points for subgroup analysis,
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43 189 they concluded that the combination of PEMF and short-wave was more effective in functional
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45 190 improvement, but not in pain relief, at 8 weeks after the first treatment.³⁵ It should be noted that³⁶
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47 191 short-wave therapy was considered to be another type of physical therapy which was different from
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49 192 PEMF.³⁶ Similarly, another study conducted by Li *et al.*²⁴ reported that PEMF and PES might provide
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51 193 moderate benefit for OA sufferers in terms of pain relief. However, considering that PES relies on the
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53 194 direct application of an electrical field and PEMF creates induced current through magnetic impulse,
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55 195 the combined analysis of these two physical therapies may also bias the results.

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57 196 The results of the present study showed that PEMF had significant effects in pain alleviation and
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59 197 function improvement comparing with the sham-control group in knee and hand OA patients, but not in

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4 198 cervical OA patients. The poor efficacy of the treatment for cervical OA may due to the anatomical
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6 199 factors of cervical spine. The neurovascular structures contained in the cervical spinal canal may be
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8 200 compressed due to cervical OA, which will then induce a series of symptoms, such as the upper limb
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10 201 nerve root pain induced by nerve root compression; the chronic vertebral and basilar arterial
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12 202 insufficiency due to compression of vertebral arteries; the numbness of limbs and easiness to falling
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14 203 caused by spinal cord compression.^{37 38} Although some studies showed that PEMF could enhance
15
16 204 articular cartilage regeneration,^{39 40} no evidence yet demonstrated that PEMF can reduce osteophytes
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18 205 formation, which may induce nerve root compression then lead to deterioration of pain and function.

19 206 The present study further examined the association between the exposure duration of PEMF and
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21 207 efficacy for patients with OA. The results suggested that the exposure duration ≤ 30 minutes per
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23 208 session could achieved better efficacy both in pain relief and function improvement. The reason could
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25 209 be explained by several previous laboratory studies. A recent study exploring the effects of different
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27 210 PEMF treatment durations (ranged from 5 to 60 minutes) over the mesenchymal stem cells (MSC)
28
29 211 chondrogenic differentiation reported that the expression of MSC chondrogenic markers showed the
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31 212 greatest increase in response to 5-20 minutes PEMF treatment.⁴¹ Similarly, another two studies which
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33 213 have shown that PEMF could activate cellular signaling transduction rapidly within 5-10 minutes,
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35 214 whereas the signaling might be largely benumbed after 30 minutes.⁵⁻⁷

36 215 Nevertheless, limitations of the present study should be acknowledged. Firstly, since different
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38 216 treatment protocols of PEMF were used in the included studies, there was a high level of heterogeneity
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40 217 among various studies. Secondly, there were sparse eligible trials available for the efficacy analysis of
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42 218 hand OA and cervical OA, and the reliability of the conclusions on these two joints were limited.
43
44 219 Finally, morphological change is a meaningful outcome for exploring the treatment efficacy of PEMF
45
46 220 further;¹⁹ however, the morphological changes were not reported in the present study due to the lack of
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48 221 relevant data. More trials are needed to evaluate the morphological changes after PEMF therapy.

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50 223 **CONCLUSION**

51 224 The present study revealed that PEMF could alleviate pain and improve physical function for knee and
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53 225 hand OA patients, but not for cervical OA. Meanwhile, a short PEMF treatment duration (within 30
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55 226 minutes) may achieve more favorable efficacy.

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227 **Author contributions**

228 ZYW, DXX, XD and YLW were responsible for conception and design of the study. ZYW, XD, DXX,
229 and YLW contributed to study retrieval. YC and YLX contributed to quality assessment. HL, TY and
230 JTL contributed to data collection. JW and CZ contributed to statistical analysis. ZYW, XD, DXX and
231 YLW drafted the manuscript. CZ and GHJ contributed to revision of the manuscript. All authors read
232 and approved the final manuscript.

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244 **Declaration of financial/other relationships**

245 None of the authors has any financial and personal relationships with other people or organizations that
246 could potentially and inappropriately influence this work and its conclusions.

247 **Competing Interests statement:** All authors declare that they have no conflict of interest.

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Table 1. Characteristics of included studies

Studies	Balance	N	Location of OA	Age, years (mean ± SD)	Female %	Mean BMI, kg/m ² (mean ± SD)	Duration of OA, years (mean ± SD)	Exposure of intervention		Time point for outcome measure	
								Daily time	Exposure duration		
Ay 2009	PEMF	Hot pack, TENS	55	Knee	58.9 ± 8.8	70.0	NA	3.6 ± 4.6	30 minutes	3 weeks (15 sessions)	After treatment
	Placebo				57.7 ± 6.5	76.0	NA	3.5 ± 4.1			
Bagnato 2016	PEMF	None	60	Knee	67.7 ± 10.9	70.0	27.4 ± 4.3	12.1 ± 8.2	A minimum of 12 hours	1 month (30 sessions)	1 month
	Placebo				68.6 ± 11.9	73.3	27.7 ± 4.6	12.4 ± 9.1			
Fischer 2006	PEMF	None	71	Knee	52.1 ± 1.9	71.4	29.2 ± 1.0	6.8 ± 0.7	16 minutes	6 weeks (42 sessions)	Therapy-End, 4weeks after therapy-End
	Placebo				62.1 ± 1.5	72.2	29.4 ± 0.7	6.2 ± 0.6			
Lee 2004	PEMF	None	51	Knee	63.5 ± 8.9	8.0	26.1 ± 3.1	12.7 ± 7.5	30 minutes	6weeks (18 sessions)	3, 6 weeks during treatment, 4 weeks after finishing
	Placebo				66.2 ± 8.8	11.5	27.1 ± 3.7	12.8 ± 7.6			
Nelson 2013	PEMF	Current standard of care	34	Knee	55.5 ± 2.5	73.7	33.5 ± 1.9	NA	15 minutes	6 weeks (84 sessions)	14, 29, 42 days
	Placebo				58.4 ± 2.5	66.7	34.7 ± 1.7	NA			
Nicolakis 2002	PEMF	None	36	Knee	69.0 ± 5.0	73.3	NA	NA	30 minutes	6 weeks (84 sessions)	After treatment
	Placebo				67.0 ± 7.0	47.1	NA	NA			
Pipitone (2001)	PEMF	None	75	Knee	62.0 (40–84) *	35.3	NA	4.0 (1.0–18.0) *	10 minutes and 3 times a day	6 weeks	2, 4, 6 weeks after study entry
	Placebo				64.0 (48–84) *	20.0	NA	8.0 (0.5–31.0) *			

Tejero Sánchez 2003	PEMF Placebo	None	83	Knee	67.4 ± 8.7 68.0 ± 8.3	87.9 88.2	NA NA	NA NA	30 minutes	20 sessions	The end of therapy, one month after therapy
Thamsborg 2005	PEMF Placebo	None	83	Knee	60.4 ± 8.7 59.6 ± 8.6	46.5 61.0	27.0 ± 4.0 27.5 ± 5.7	7.5 ± 5.2 7.9 ± 7.7	2 hours	6 weeks (30 sessions)	2 weeks, end of treatment, 6 weeks after end of treatment
Trock 1994 §	PEMF Placebo	Do not change basic therapeutic	86	Knee	69.2 ± 11.5 65.8 ± 11.7	69.0 70.5	NA NA	9.1 ± 8.9 7.4 ± 7.2	30 minutes	4-5 weeks (18 sessions)	Midway of therapy, the last treatment, and one month later
Sutbeyaz 2006	PEMF Placebo	None	34	Cervical	43.2 ± 10.3 42.1 ± 10.1	64.7 66.7	NA NA	NA NA	30 minutes	3 weeks (42 sessions)	After treatment
Trock 1994 §	PEMF Placebo	Do not change basic therapeutic	81	Cervical	61.2 ± 13.4 67.4 ± 8.0	28.6 30.8	NA NA	7.4 ± 6.7 8.1 ± 8.0	30 minutes	4-5 weeks (18 sessions)	Midway of therapy, the last treatment, and one month later
Kanat 2013	PEMF Placebo	Active range of motion and resistive	50	Hand	64.0 ± 2.60 62.0 ± 2.40	NA NA	NA NA	5.01 ± 2.3 4.31 ± 4.7	20 minutes	10 days	After treatment

N, number of participates; BMI, body mass index; OA, osteoarthritis; PEMF, pulsed electromagnetic field; NA, not available; TENS, transcutaneous electrical nerve stimulation.

* Age and duration of OA in this trial were expressed by median (range).

§ This trial provided data of knee OA and cervical OA patients respectively.

Table 2. Results of subgroup analyses.

Reason for subgroup analyses	Pooled Results of Subgroups		Heterogeneity of Subgroups		
	SMD/RR	95% CI	I ² (%)	p Value	
Pain					
Location	Knee OA	-0.54	[-1.04, 0.04]	88	0.03
	Cervical OA	-2.33	[-6.26, 1.61]	97	0.25
	Hand OA	-2.85	[-3.65, -2.04]	NA	< 0.00001
Exposure duration	No more than 0.5hr/session	-1.01	[-1.64, -0.39]	91	0.001
	More than 0.5hr/session	-0.61	[-2.25, 1.02]	95	0.46
Function					
Location	Knee OA	-0.34	[-0.53, -0.14]	0	0.0006
	Cervical OA	-0.27	[-0.71, 0.16]	NA	0.22
	Hand OA	-1.49	[-2.12, -0.86]	NA	< 0.00001
Exposure duration	No more than 0.5hr/session	-0.50	[-0.81, -0.18]	59	0.002
	More than 0.5hr/session	-0.33	[-0.82, 0.17]	54	0.20
Adverse event					
Exposure duration	No more than 0.5hr/session	0.42	[0.14, 1.29]	0	0.13
	More than 0.5hr/session	1.95	[0.81, 4.71]	NA	0.14

OA, osteoarthritis; SMD, standard mean difference; RR, relative risk; CI, confidence interval; NA, not available.

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Figure 1. Flowchart of studies screening process based on the PRISMA guideline.

OA: osteoarthritis, PEMF: pulsed electromagnetic field

Figure 2. Risk of bias summary of twelve included studies.

Figure 3. Forest plot of PEMF compared to sham-control on pain.

PEMF: pulsed electromagnetic field

Figure 4. Forest plot of PEMF compared to sham-control on function.

PEMF: pulsed electromagnetic field

Figure 5. Forest plot of PEMF compared to sham-control on adverse events.

PEMF: pulsed electromagnetic field

For peer review only

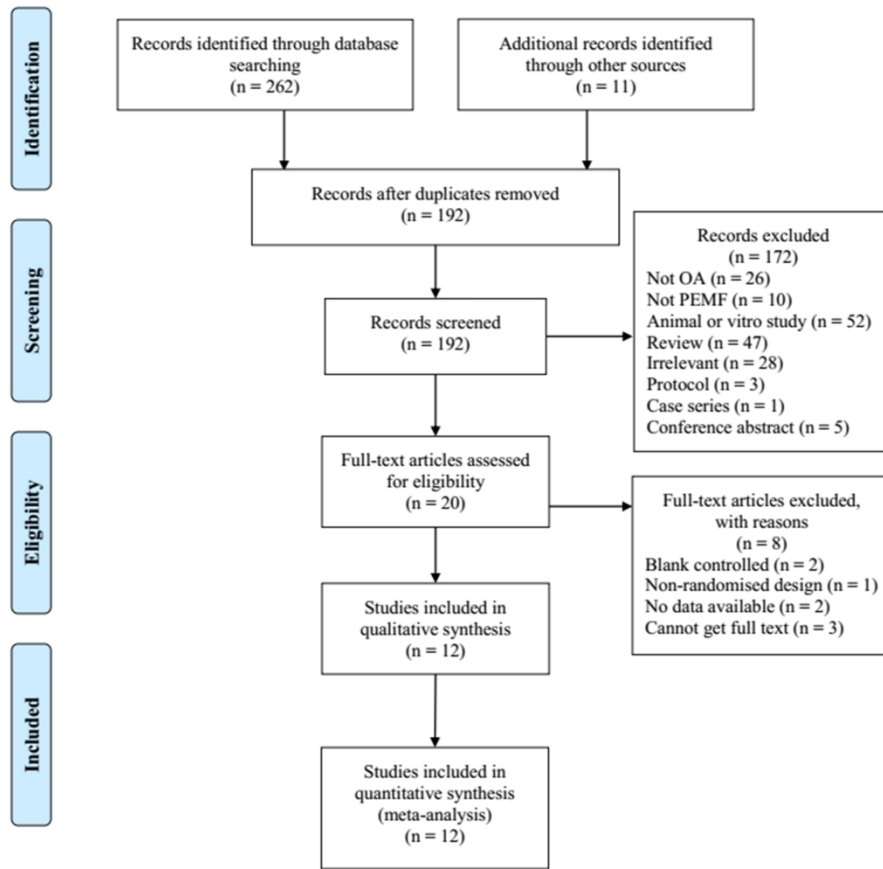


Figure 1. Flowchart of studies screening process based on the PRISMA guideline.
OA: osteoarthritis; PEMF: pulsed electromagnetic field

173x155mm (300 x 300 DPI)

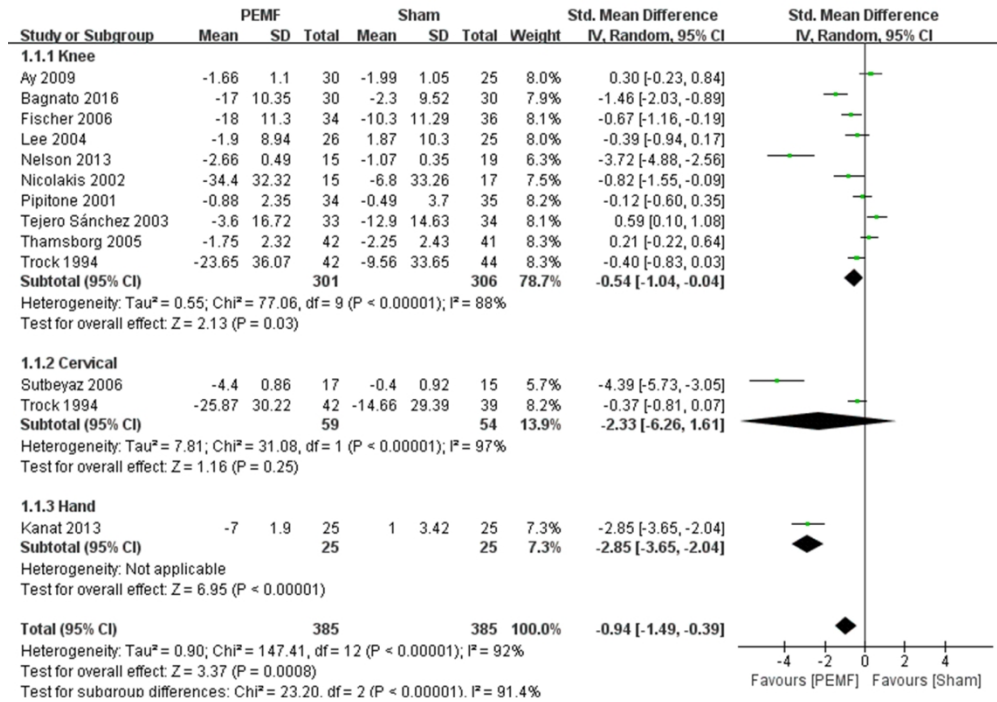


Figure 3. Forest plot of PEMF compared to sham-control on pain.
PEMF: pulsed electromagnetic field

173x123mm (300 x 300 DPI)

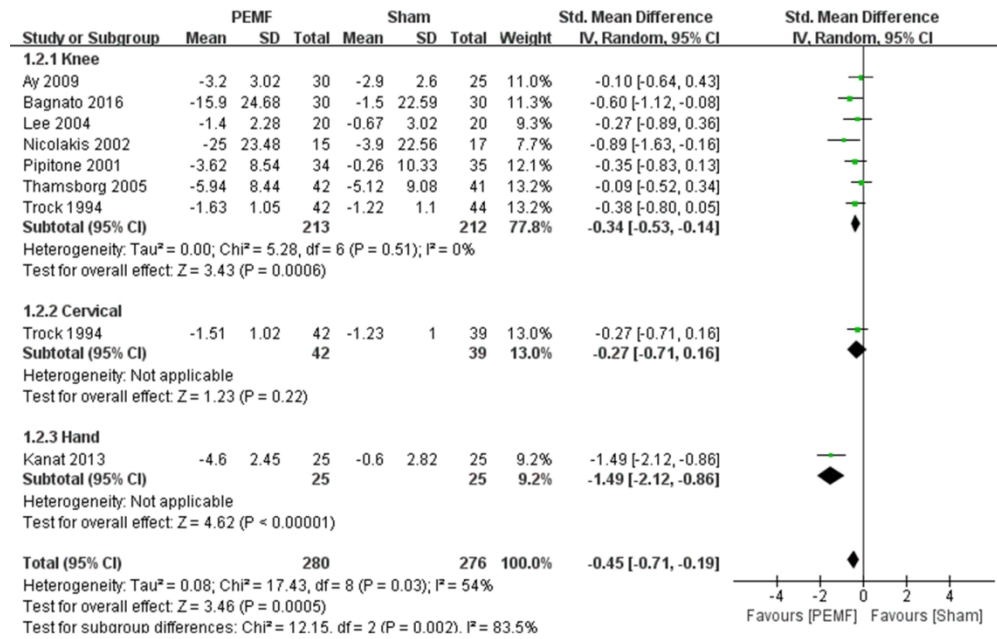


Figure 4. Forest plot of PEMF compared to sham-control on function.
PEMF: pulsed electromagnetic field

173x109mm (300 x 300 DPI)

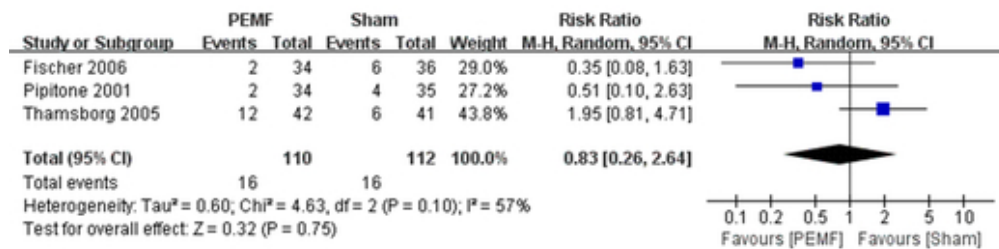


Figure 5. Forest plot of PEMF compared to sham-control on adverse events.
 PEMF: pulsed electromagnetic field

43x11mm (300 x 300 DPI)

Search Strategies

PubMed search strategy

#1 Pulsed electromagnetic field[Title/Abstract]

#2 Pulsed electromagnetic fields[Title/Abstract]

#3 Pulsed electromagnetic field[mesh]

#4 #1 or #2 or #3

#5 Osteoarthritis[Mesh]

#6 (osteoarthro*[tiab] or gonarthriti*[tiab] or gonarthro*[tiab] or coxarthriti*[tiab] or coxarthro*[tiab] or osteo?arthritis[tiab])

#7 #5 or #6

#8 randomized[tiab]

#9 placebo[tiab]

#10 controlled[tiab]

#11 random*[tiab]

#12 trial*[tiab]

#13 groups[tiab]

#14 ((singl*[tiab] or doubl*[tiab] or tripl*[tiab]) and (mask*[tiab] or blind*[tiab]))

#15 #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 #4 and #7 and #15

Embase search strategy

#1 'Pulsed electromagnetic field'/exp

#2 Pulsed electromagnetic fields:ti,ab

#3 Pulsed electromagnetic field: ti,ab

#4 #1 or #2 or #3

#5 osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or osteoarthritis:ti,ab

#6 'Osteoarthritis'/exp

#7 #5 or #6

#8 random* or control* or trial* or placebo:ti,ab

#9 groups:ti,ab

#10 (singl* or doubl* or tripl*) and (mask* or blind*):ti,ab

#11 #8 or #9 or #10

#12 #4 and #7 and #11

Cochrane Library search strategy

#1 MeSH descriptor Pulsed electromagnetic field explode all trees

#2 Pulsed electromagnetic field:ti,ab,kw

#3 #1 or #2

#4 MeSH descriptor osteoarthritis explode all trees

#5 osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or osteo?arthritis:ti,ab,kw

#6 #4 or #5

#7 random* or control* or trial* or placebo:ti,ab,kw

#8 Groups:ti,ab,kw

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3 #9 (singl* or doubl* or tripl*) and (mask* or blind*):ti,ab,kw

4 #10 #7 or #8 or #9

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6 #11 #3 and #6 and #10

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8 **Web of Science search strategy**

9 #1 Topic:(Pulsed electromagnetic field)

10 #2 Topic:(Pulsed electromagnetic fields)

11 #3 #1 or #2

12 #4 Topic:(Osteoarthritis)

13 #5 Topic:(osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or osteo?arthritis)

14 #6 #4 or #5

15 #7 Topic:(randomized or placebo or controlled or random* or trial* or groups)

16 #8 Topic:((singl* or doubl* or tripl*) and (mask* or blind*))

17 #9 #7 or #8

18 #10 #3 and #6 and #9



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4, 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Details in Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, details in figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6, details in table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6, details in figure 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

BMJ Open

Efficacy and Safety of the Pulsed Electromagnetic Field in Osteoarthritis: A Meta-analysis

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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	osteoarthritis, pulsed electromagnetic field, meta-analysis, randomized controlled trial

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Manuscripts

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5 **1 Efficacy and Safety of the Pulsed Electromagnetic Field in Osteoarthritis: A Meta-analysis**

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57 ² Dongxing Xie and Yilun Wang contributed equally to this article.

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18 **Abstract**

19 **Objective** To investigate the efficacy and safety of the pulsed electromagnetic field (PEMF) therapy in
20 treating osteoarthritis (OA).

21 **Design** meta-analysis.

22 **Data sources** PubMed, Embase, the Cochrane Library and Web of Science were searched through
23 October 13, 2017.

24 **Eligibility criteria for selecting studies** Randomized controlled trials compared the efficacy of PEMF
25 therapy with sham control in OA patients.

26 **Data extraction and synthesis** Pain, function, adverse effects and characteristics of participants were
27 extracted. RevMan 5.2 was used to perform statistical analyses.

28 **Results** Twelve trials were included, among which ten trials involved knee OA, two involved cervical
29 OA and one involved hand OA. The PEMF group showed more significant pain alleviation than the
30 sham group in knee OA (SMD = -0.54, 95% CI: -1.04, -0.04, $P = 0.03$) and hand OA (SMD = -2.85,
31 95% CI: -3.65, -2.04, $P < 0.00001$), but not in cervical OA. Similarly, comparing with the sham-control
32 treatment, significant function improvement was observed in the PEMF group in both knee and hand
33 OA patients (SMD = -0.34, 95%CI: -0.53, -0.14, $P = 0.0006$, and SMD = -1.49, 95%CI: -2.12, -0.86, P
34 < 0.00001 , respectively), but not in cervical OA patients. Sensitivity analyses suggested that the
35 exposure duration ≤ 30 minutes per session exhibited better effects compared with the exposure
36 duration > 30 minutes per session. Three trials reported adverse events, and the combined results
37 showed that there was no significant difference between PEMF and the sham group.

38 **Conclusions** PEMF could alleviate pain and improve physical function for knee and hand OA patients,
39 but not for cervical OA patients. Meanwhile, a short PEMF treatment duration (within 30 minutes) may
40 achieve more favorable efficacy. However, given the limited number of study available in hand and
41 cervical OA, the implication of this conclusion should be cautious for hand and cervical OA.

42 **Key words:** osteoarthritis, pulsed electromagnetic field, meta-analysis, randomized controlled trial

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5 **43 Strengths and limitations of this study**

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7 **44** 1. This study provided a comprehensive assessment on the efficacy and safety of the pulsed
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9 **45** electromagnetic field (PEMF) therapy in patients with knee, hand and cervical osteoarthritis (OA).

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11 **46** 2. All included studies in this meta-analysis were randomized controlled trials.

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13 **47** 3. There was a high level of heterogeneity among various studies, because different treatment protocols
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15 **48** of PEMF were used in the included studies.

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17 **49** 4. There were sparse eligible trials available for the efficacy analysis of hand OA and cervical OA, and
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19 **50** the reliability of the conclusions on these two joints were limited.

51 INTRODUCTION

52 Osteoarthritis (OA) is a widespread degenerative disease, which can lead to pain, physical dysfunction
53 and even disability. The joints most commonly affected by OA include knees, hips, hands, neck, and
54 feet.^{1 2} A variety of medications and physical therapies have been used in the treatment of OA.
55 However, some widely-applied drugs (e.g., chondroitin, glucosamine, intraarticular hyaluronic acid,
56 etc.) or physical treatments (e.g., transcutaneous electrical nerve stimulation, and ultrasound) are
57 actually not advocated by the recent Osteoarthritis Research Society International (OARSI) guidelines.³
58 To date, few effective treatments for knee OA are available.

59 Since the early 1980s, researchers have found that pulsed electromagnetic field (PEMF) therapy
60 could be applied to accelerate wound healing, repair fracture, reduce hematoma, and treat soft tissue
61 injury and inflammation.⁴ In addition, some studies have demonstrated that PEMF could activate the
62 signal transduction pathway⁵⁻⁷ and induce the human articular chondrocyte proliferation.⁸ Being a
63 simple, noninvasive and safe physical therapy, PEMF was considered to be an alternative treatment
64 regimen for OA. During the past two decades, more than ten randomized controlled trials (RCTs) were
65 conducted to explore the efficacy of PEMF in the treatment of OA, but no consensus was reached
66 yet.⁹⁻²² Several previous meta-analyses have evaluated the combined effects of PEMF and pulsed
67 electrical stimulation on OA.^{23 24} However, the mechanisms of PEMF and pulsed electrical stimulation
68 (PES) was totally different. For example, PES is delivered through capacitive coupling using
69 transcutaneous electrodes and coupling agents²⁵ relying on the direct application of an electrical field;
70 whereas PEMF creates induced current through magnetic impulse.²⁴ To the best of our knowledge, few
71 meta-analyses have evaluated the efficacy and safety of single PEMF for OA.

72 To fill in this knowledge gap, the purpose of the present study was to provide a comprehensive
73 assessment on the efficacy and safety of single PEMF in patients with OA at different joints. It was
74 hypothesized that PEMF could relieve pain and improve the physical function of OA patients without
75 producing side effects.

77 METHODS

78 Search strategies and studies selection

79 The study records were identified in four electronic databases of PubMed, Embase, the Cochrane

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5 80 Library and Web of Science through using the combination of a series of keywords and text terms
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7 81 describing OA and PEMF (Appendix 1). The latest literature search was conducted at October 13, 2017.
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9 82 Studies were included if: (1) subjects with symptomatic or radiographic OA, (2) the intervention
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11 83 containing PEMF versus sham-control, (3) the study designed as a RCT, (4) the primary outcome
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13 84 including pain and/or function. Studies were excluded if: (1) in vitro or animal or cadaveric studies, (2)
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15 85 PEMF therapy used for post-operation rehabilitation, (3) other non-medicine therapy (e.g., short wave
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17 86 or PES), (4) cannot get full-text, (5) no data available, (6) unbalanced additional non-pharmacological
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19 87 treatments (e.g., exercise or hot-pack) between groups.
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21 89 **Quality assessment**

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23 90 The methodological quality of each included trial was evaluated by two independent authors based on
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25 91 the Cochrane handbook,^{26 27} which consists of seven domains: generation of randomization sequences,
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27 92 allocation concealment, blinding of participants and implementers, blinding of outcome assessment,
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29 93 incomplete outcome data, selective reporting and other potential bias. Furthermore, any of divergence
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31 94 was to be discussed and a third consultant was needed if necessary.^{28 29} Trials involving three or more
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33 95 high risks of bias were considered as poor methodological quality.³⁰
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36 97 **Data extraction and outcome measure**

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38 98 All the data extracted by two independent authors. The extracted information included the
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40 99 characteristics of participants (age, gender, body mass index, and duration of OA), balance intervention
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42 100 between groups, number of participants about each trial, treatment protocol of PEMF, and the type of
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44 101 outcome measures, baseline data, post-treatment data and change means, and standard deviations (SD)
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46 102 or the information from which SD could be derived, such as standard error (SE) or confidence interval
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48 103 (CI). The primary goal of this study was to assess the efficacy of pain alleviation and function
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50 104 improvement by applying the PEMF therapy for OA patients. Adverse events were considered as the
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52 105 safety outcome. The efficacy of pain alleviation was measured by change of pain intensity from
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54 106 baseline.³¹ Data at the last follow-up time point after treatment was extracted to calculate the change
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56 107 degree from baseline to the last follow-up. According to the recommended hierarchy of continuous
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58 108 pain-related outcomes used in the meta-analyses,^{32 33} the outcome data that expressed in higher ranking

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5 109 scale was extracted if multiple pain scale measured simultaneously. WOMAC function was preferred
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7 110 measure for function outcome. If a study did not measure or report the WOMAC function, WOMAC
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9 111 total, SF-36 social function score or total score and physician global assessment scores were used in the
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11 112 analysis instead.³⁴ The number of participants reported adverse events were also extracted in order to
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13 113 evaluate the safety of interventions.

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15 115 **Statistical analysis**

16
17 116 The Review Manager Version 5.2 was used to perform all the statistical analyses. For the reason that
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19 117 outcome of pain and function reported by continuous data and various scales were used for outcome
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21 118 assessment, the standardized mean differences (SMDs) were calculated to compare the effect of pain
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23 119 alleviation and function improvement between different intervention groups. For the safety outcome,
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25 120 the relative risk (RR) was calculated to compare the safety between two groups. Trials reported zero
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27 121 adverse event in both the PEMF and the sham groups were not included in the adverse events
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29 122 analysis.²⁶ 95% CI was calculated for pooled estimates for each outcome. Statistical significance was
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31 123 considered at $P < 0.05$. A random model was applied to pool the data. Q and I^2 statistics were
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33 124 calculated to assess the heterogeneity among the included studies, with a p value > 0.05 of the Q
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35 125 statistics and I^2 value $< 50\%$ indicating statistical homogeneity. Different exposure duration of PEMF,
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37 126 disease location was hypothesized to influence treatment effect. Therefore, subgroup analyses were
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39 127 performed according to the exposure duration of PEMF therapy (no more than 30 minutes per session
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41 128 or more than 30 minutes per session)⁵⁻⁷ and location of OA. Funnel plots were inspected to assess
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43 129 publication bias.

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45 131 **Patient and public involvement**

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47 132 No patients or members of public were involved in the present study. No patients were asked to advise
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49 133 on interpretation or writing up of results. The results of present research will be communicated to the
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51 134 relevant patient community.

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53 136 **RESULTS**

54 137 **Study screening and characteristics of included studies**

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5 138 Figure 1 showed the flow diagram for studies screening. 192 records were identified initially and
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7 139 twelve studies⁹⁻²⁰ met the eligibility criteria and were included in this meta-analysis. The characteristics
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9 140 of included studies were summarized in Table 1. The risk of bias assessment (Figure 2) showed that
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11 141 one study⁹ was regarded as low quality.

12 142

13 143 **Pain relief**

14 144 Twelve RCTs were included for meta-analysis of pain management.⁹⁻²⁰ As shown in Figure 3, PEMF
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16 145 group achieved a significant difference in pain improvement compared with sham group (SMD = -0.94,
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18 146 95% CI: -1.49, -0.39, $P = 0.0008$), while significant heterogeneity was observed ($I^2 = 92%$; $P <$
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20 147 0.00001). Subgroup analysis showed that significant differences were observed between the PEMF and
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22 148 sham group on pain improvement in knee OA (SMD = -0.54, 95% CI: -1.04, -0.04, $P = 0.03$) and hand
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24 149 OA patients (SMD = -2.85, 95% CI: -3.65, -2.04, $P < 0.00001$), whereas no significant difference was
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26 150 achieved between groups in cervical OA patients (SMD = -2.33, 95% CI: -6.26, 1.61, $P = 0.25$). As for
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28 151 subgroup analysis of different exposure duration, significant difference was observed with exposure
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30 152 duration within 30 minutes (SMD = -1.01, 95%CI: -1.64, -0.39, $P = 0.001$), and no significant
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32 153 difference was achieved between intervention groups with exposure duration more than 30 minutes
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34 154 (SMD = -0.61, 95%CI: -2.25, 1.02, $P = 0.46$) (see Table 2). Besides, substantial asymmetry was not
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36 155 identified in the funnel plot.

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38 157 **Function improvement**

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40 158 Eight RCTs were included for meta-analysis of physical function improvement.^{9 10 12 13 15 16 19 20} Figure 4
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42 159 illustrated the beneficial effect of PEMF on physical function improvement (SMD = -0.45, 95% CI:
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44 160 -0.71, -0.19, $P = 0.0005$), and substantial heterogeneity was observed ($I^2 = 54%$; $P = 0.03$). However,
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46 161 the subgroup analysis of different OA locations suggested significant differences both in knee OA and
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48 162 hand OA (SMD = -0.34, 95%CI: -0.53, -0.14, $P = 0.0006$, and SMD = -1.49, 95%CI: -2.12, -0.86, $P <$
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50 163 0.00001 , respectively, see in Table 2), whereas there was no significant difference between groups in
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52 164 cervical OA patients (SMD = -0.27, 95% CI: -0.71, 0.16, $P = 0.22$). In addition, there was a significant
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54 165 difference on effect of function improvement with exposure duration within 30 minutes (SMD = -0.50,
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56 166 95%CI: -0.81, -0.18, $P = 0.002$), and no significant difference was observed in more than 30 minutes

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5 167 group (SMD = -0.33, 95%CI: -0.82, 0.17, $P = 0.20$). Funnel plot also did not identify substantial
6 168 asymmetry.

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9 10 170 **Adverse events**

11 171 There were ten RCTs that reported adverse events.^{9-11 13 14 16-20} Seven of them claimed that no adverse
12 172 events were observed both in PEMF and sham group.^{9 10 13 14 17 18 20} Three trials reported the adverse
13 173 events of each treatment group, which mainly included increased knee pain, hip pain, spine pain,
14 174 vomiting, warming sensation, increased blood pressure, numbness of feet, paraesthesia of foot and
15 175 cardiomyopathy, and there were no AE related drop outs in each trial.^{11 16 19} There was no significant
16 176 difference between the PEMF and the sham group regarding adverse events (RR = 0.83, 95%CI: 0.26,
17 177 2.64, $P = 0.75$) (Figure 5). Substantial asymmetry was not identified in the funnel plot.

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24 25 26 179 **DISCUSSION**

27 180 This study provided a comprehensive assessment of the scientific literature on the efficacy and safety
28 181 of the PEMF therapy in patients with knee, hand and cervical OA. The results showed that, in
29 182 comparison with the sham-control group, PEMF was more effective in both pain relief and function
30 183 improvement for patients with knee OA and hand OA, but not for patients with cervical OA. In
31 184 addition, PEMF did not lead to specific adverse events compared with the sham control group.
32 185 Interestingly, a short duration of PEMF treatment for ≤ 30 minutes per session seems to achieve more
33 186 favorable results. This finding may have significant implications for the clinical application of PEMF
34 187 in the OA field.

35 188 As a noninvasive, safe and simple therapy, the PEMF therapy is widely used to treat soft injury
36 189 and bone fracture, relieve pain and inflammation, as well as many other types of diseases and
37 190 pathologies.³⁵ In the past two decades, researchers have turned their attention to the efficacy of treating
38 191 OA. Some previous systematic reviews have combined PEMF and other physical therapies together to
39 192 examine their efficacy in OA patients, which might bias the results. McCarthy *et al.*³⁶ demonstrated that
40 193 PEMF and short-wave together had limited effect in treating knee OA. In contrast, We *et al.*³⁷ reported
41 194 different results. Based on the follow-up data extracted from different time points for subgroup analysis,
42 195 they concluded that the combination of PEMF and short-wave was more effective in functional

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5 196 improvement, but not in pain relief, at 8 weeks after the first treatment.³⁷ It should be noted that
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7 197 short-wave therapy was considered to be another type of physical therapy which was different from
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9 198 PEMF.³⁸ Similarly, another study conducted by Li *et al.*²⁴ reported that PEMF and PES might provide
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11 199 moderate benefit for OA sufferers in terms of pain relief. However, considering that PES relies on the
12
13 200 direct application of an electrical field and PEMF creates induced current through magnetic impulse,
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15 201 the combined analysis of these two physical therapies may also bias the results.

16 202 The results of the present study showed that PEMF had significant effects in pain alleviation and
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18 203 function improvement comparing with the sham-control group in knee and hand OA patients, but not in
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20 204 cervical OA patients. The poor efficacy of the treatment for cervical OA may be due to the anatomical
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22 205 factors of cervical spine. The neurovascular structures contained in the cervical spinal canal may be
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24 206 compressed due to cervical OA, which will then induce a series of symptoms, such as the upper limb
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26 207 nerve root pain induced by nerve root compression; the chronic vertebral and basilar arterial
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28 208 insufficiency due to compression of vertebral arteries; the numbness of limbs and easiness to falling
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30 209 caused by spinal cord compression.^{39 40} Although some studies showed that PEMF could enhance
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32 210 articular cartilage regeneration,^{41 42} no evidence yet demonstrated that PEMF can reduce osteophytes
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34 211 formation, which may induce nerve root compression that can lead to deterioration of pain and function.
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36 212 In addition, the limited number of studies available is another reason should not be ignored.

37 213 The present study further examined the association between the exposure duration of PEMF and
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39 214 efficacy for patients with OA. The results suggested that the exposure duration ≤ 30 minutes per
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41 215 session could achieved better efficacy both in pain relief and function improvement. The reason could
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43 216 be explained by several previous laboratory studies. A recent study exploring the effects of different
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45 217 PEMF treatment durations (ranged from 5 to 60 minutes) over the mesenchymal stem cells (MSC)
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47 218 chondrogenic differentiation reported that the expression of MSC chondrogenic markers showed the
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49 219 greatest increase in response to 5-20 minutes PEMF treatment.⁴³ Similarly, another two studies which
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51 220 have shown that PEMF could activate cellular signaling transduction rapidly within 5-10 minutes,
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53 221 whereas the signaling might be largely benumbed after 30 minutes.⁵⁻⁷

54 222 Nevertheless, limitations of the present study should be acknowledged. Firstly, since different
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56 223 treatment protocols of PEMF were used in the included studies, there was a high level of heterogeneity
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58 224 among various studies. Secondly, there were sparse eligible trials available for the efficacy analysis of

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5 225 hand OA and cervical OA, and the accuracy of the conclusions on these two joints were limited. In
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7 226 addition, because the number of studies reporting the pulse frequency of application, pulse intensity,
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9 227 pulsed rate and other parameters of PEMF was very limited, subgroup analyses were restricted
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11 228 according to these parameters of PEMF. Finally, morphological change is a meaningful outcome for
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13 229 exploring the treatment efficacy of PEMF further;¹⁹ however, the morphological changes were not
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15 230 reported in the present study due to the lack of relevant data. More trials are needed to evaluate the
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17 231 morphological changes after PEMF therapy.
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19 233 **CONCLUSION**

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21 234 The present study revealed that PEMF could alleviate pain and improve physical function for knee and
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23 235 hand OA patients, but not for cervical OA. Meanwhile, a short PEMF treatment duration (within 30
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25 236 minutes) may achieve more favorable efficacy. However, given the limited number of study available
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27 237 in hand and cervical OA, the implication of this conclusion should be cautious for hand and cervical
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29 238 OA.
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239 **Author contributions**

240 ZYW, DXX, XD and YLW were responsible for conception and design of the study. ZYW, XD, DXX,
241 and YLW contributed to study retrieval. YC and YLX contributed to quality assessment. HL, TY and
242 JTL contributed to data collection. JW and CZ contributed to statistical analysis. ZYW, XD, DXX and
243 YLW drafted the manuscript. CZ and GHJ contributed to revision of the manuscript. All authors read
244 and approved the final manuscript.

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258 **Declaration of financial/other relationships**

259 None of the authors has any financial and personal relationships with other people or organizations that
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261 **Competing Interests statement:** All authors declare that they have no conflict of interest.

262 **Data sharing statement:** No additional data available.

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25 368

Table 1. Characteristics of included studies

Studies	Balance	N	Location of OA	Age, years (mean ± SD)	Female %	Mean BMI, kg/m ² (mean ± SD)	Duration of OA, years (mean ± SD)	Exposure of intervention		Time point for outcome measure
								Daily time	Exposure duration	
Ay 2009	PEMF	55	Knee	58.9 ± 8.8	70.0	NA	3.6 ± 4.6	30 minutes	3 weeks (15 sessions)	After treatment
	Placebo			57.7 ± 6.5	76.0	NA	3.5 ± 4.1			
Bagnato 2016	PEMF	60	Knee	67.7 ± 10.9	70.0	27.4 ± 4.3	12.1 ± 8.2	A minimum of 12 hours	1 month (30 sessions)	1 month
	Placebo			68.6 ± 11.9	73.3	27.7 ± 4.6	12.4 ± 9.1			
Fischer 2006	PEMF	71	Knee	52.1 ± 1.9	71.4	29.2 ± 1.0	6.8 ± 0.7	16 minutes	6 weeks (42 sessions)	Therapy-End, 4weeks after therapy-End
	Placebo			62.1 ± 1.5	72.2	29.4 ± 0.7	6.2 ± 0.6			
Lee 2004	PEMF	51	Knee	63.5 ± 8.9	8.0	26.1 ± 3.1	12.7 ± 7.5	30 minutes	6weeks (18 sessions)	3, 6 weeks during treatment, 4 weeks after finishing
	Placebo			66.2 ± 8.8	11.5	27.1 ± 3.7	12.8 ± 7.6			
Nelson 2013	PEMF	34	Knee	55.5 ± 2.5	73.7	33.5 ± 1.9	NA	15 minutes	6 weeks (84 sessions)	14, 29, 42 days
	Placebo			58.4 ± 2.5	66.7	34.7 ± 1.7	NA			
Nicolakis 2002	PEMF	36	Knee	69.0 ± 5.0	73.3	NA	NA	30 minutes	6 weeks (84 sessions)	After treatment
	Placebo			67.0 ± 7.0	47.1	NA	NA			
Pipitone 2001	PEMF	75	Knee	62.0 (40–84) *	35.3	NA	4.0 (1.0–18.0) *	10 minutes and 3 times a day	6 weeks	2, 4, 6 weeks after study entry
	Placebo			64.0 (48–84) *	20.0	NA	8.0 (0.5–31.0) *			

Tejero Sánchez 2003	PEMF Placebo	None	83	Knee	67.4 ± 8.7 68.0 ± 8.3	87.9 88.2	NA NA	NA NA	30 minutes	20 sessions	The end of therapy, one month after therapy
Thamsborg 2005	PEMF Placebo	None	83	Knee	60.4 ± 8.7 59.6 ± 8.6	46.5 61.0	27.0 ± 4.0 27.5 ± 5.7	7.5 ± 5.2 7.9 ± 7.7	2 hours	6 weeks (30 sessions)	2 weeks, end of treatment, 6 weeks after end of treatment
Trock 1994 §	PEMF Placebo	Do not change basic therapeutic	86	Knee	69.2 ± 11.5 65.8 ± 11.7	69.0 70.5	NA NA	9.1 ± 8.9 7.4 ± 7.2	30 minutes	4-5 weeks (18 sessions)	Midway of therapy, the last treatment, and one month later
Sutbeyaz 2006	PEMF Placebo	None	34	Cervical	43.2 ± 10.3 42.1 ± 10.1	64.7 66.7	NA NA	NA NA	30 minutes	3 weeks (42 sessions)	After treatment
Trock 1994 §	PEMF Placebo	Do not change basic therapeutic	81	Cervical	61.2 ± 13.4 67.4 ± 8.0	28.6 30.8	NA NA	7.4 ± 6.7 8.1 ± 8.0	30 minutes	4-5 weeks (18 sessions)	Midway of therapy, the last treatment, and one month later
Kanat 2013	PEMF Placebo	Active range of motion and resistive	50	Hand	64.0 ± 2.60 62.0 ± 2.40	NA NA	NA NA	5.01 ± 2.3 4.31 ± 4.7	20 minutes	10 days	After treatment

N, number of participates; BMI, body mass index; OA, osteoarthritis; PEMF, pulsed electromagnetic field; NA, not available; TENS, transcutaneous electrical nerve stimulation.

* Age and duration of OA in this trial were expressed by median (range).

§ This trial provided data of knee OA and cervical OA patients respectively.

Table 2. Results of subgroup analyses.

Reason for subgroup analyses	Pooled Results of Subgroups		Heterogeneity of Subgroups		
	SMD/RR	95% CI	I ² (%)	p Value	
Pain					
Location	Knee OA	-0.54	[-1.04, 0.04]	88	0.03
	Cervical OA	-2.33	[-6.26, 1.61]	97	0.25
	Hand OA	-2.85	[-3.65, -2.04]	NA	< 0.00001
Exposure duration	No more than 0.5hr/session	-1.01	[-1.64, -0.39]	91	0.001
	More than 0.5hr/session	-0.61	[-2.25, 1.02]	95	0.46
Function					
Location	Knee OA	-0.34	[-0.53, -0.14]	0	0.0006
	Cervical OA	-0.27	[-0.71, 0.16]	NA	0.22
	Hand OA	-1.49	[-2.12, -0.86]	NA	< 0.00001
Exposure duration	No more than 0.5hr/session	-0.50	[-0.81, -0.18]	59	0.002
	More than 0.5hr/session	-0.33	[-0.82, 0.17]	54	0.20
Adverse event					
Exposure duration	No more than 0.5hr/session	0.42	[0.14, 1.29]	0	0.13
	More than 0.5hr/session	1.95	[0.81, 4.71]	NA	0.14

OA, osteoarthritis; SMD, standard mean difference; RR, relative risk; CI, confidence interval; NA, not available.

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2
3 Figure 1. Flowchart of studies screening process based on the PRISMA guideline.

4 OA: osteoarthritis, PEMF: pulsed electromagnetic field
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6
7 Figure 2. Risk of bias summary of twelve included studies.

8 The green background with “+” means low risk of bias; the red background with “-” means high risk of
9 bias; the yellow background with “?” means unknown risk of bias. Trials involving three or more high
10 risks of bias were considered as poor methodological quality.
11

12
13 Figure 3. Forest plot of PEMF compared to sham-control on pain.

14 PEMF: pulsed electromagnetic field

15 Significant differences were observed between the PEMF and sham group on pain improvement in
16 knee OA ($P = 0.03$) and hand OA patients ($P < 0.00001$), whereas no significant difference was
17 achieved between groups in cervical OA patients ($P = 0.25$).
18

19
20 Figure 4. Forest plot of PEMF compared to sham-control on function.

21 PEMF: pulsed electromagnetic field

22 Significant differences both in knee OA ($P = 0.0006$) and hand OA ($P < 0.00001$), whereas there was
23 no significant difference between groups in cervical OA patients ($P = 0.22$).
24

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26 Figure 5. Forest plot of PEMF compared to sham-control on adverse events.

27 PEMF: pulsed electromagnetic field

28 There was no significant difference between the PEMF and the sham group regarding adverse events (P
29 $= 0.75$).
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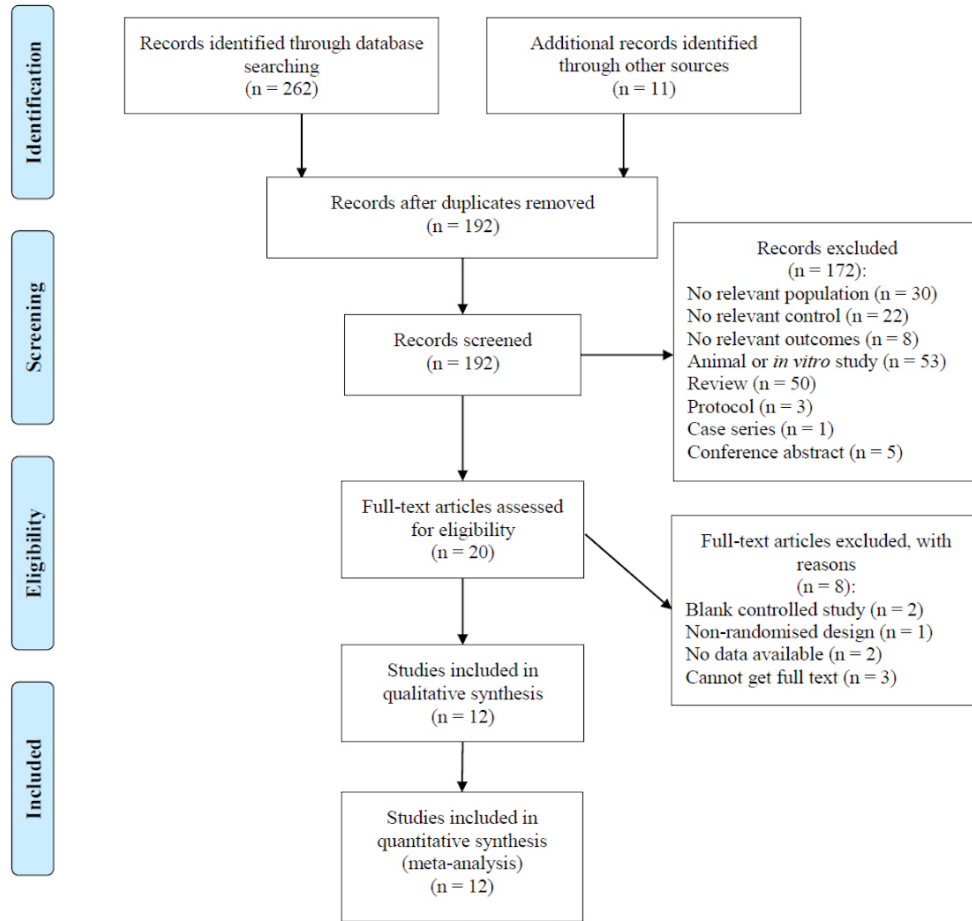


Figure 1. Flowchart of studies screening process based on the PRISMA guideline.
 OA: osteoarthritis, PEMF: pulsed electromagnetic field

95x90mm (300 x 300 DPI)

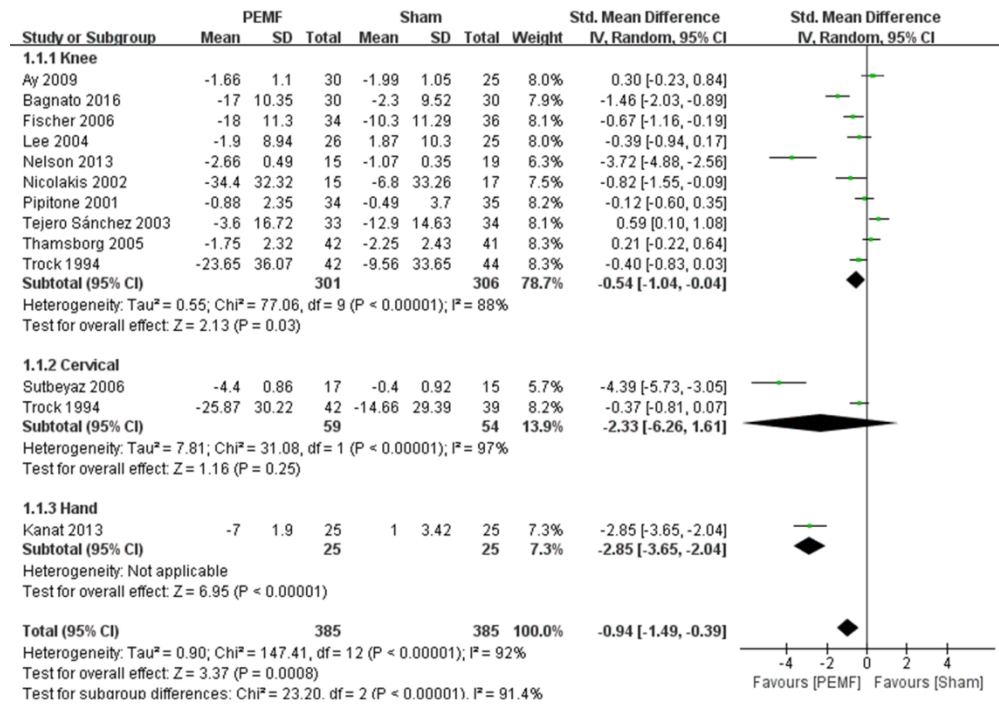


Figure 3. Forest plot of PEMF compared to sham-control on pain.
PEMF: pulsed electromagnetic field

173x123mm (300 x 300 DPI)

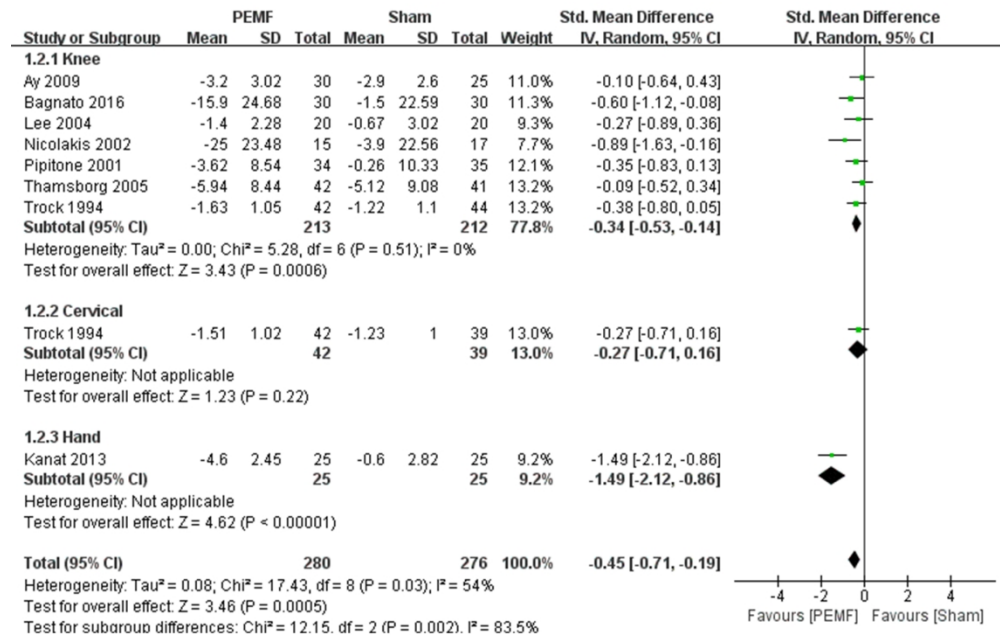


Figure 4. Forest plot of PEMF compared to sham-control on function.
PEMF: pulsed electromagnetic field

173x109mm (300 x 300 DPI)

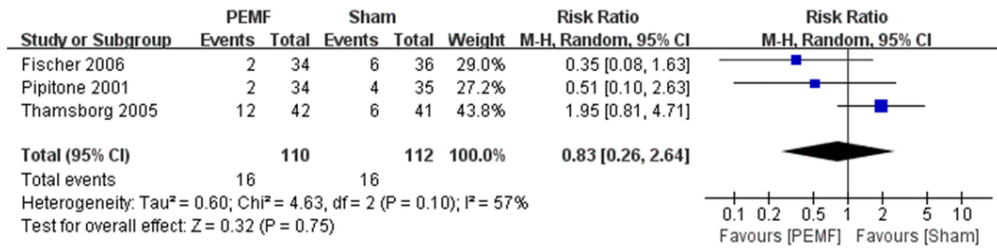


Figure 5. Forest plot of PEMF compared to sham-control on adverse events.
 PEMF: pulsed electromagnetic field

89x22mm (300 x 300 DPI)

Search Strategies

PubMed search strategy

#1 Pulsed electromagnetic field[Title/Abstract]

#2 Pulsed electromagnetic fields[Title/Abstract]

#3 Pulsed electromagnetic field[mesh]

#4 #1 or #2 or #3

#5 Osteoarthritis[Mesh]

#6 (osteoarthro*[tiab] or gonarthriti*[tiab] or gonarthro*[tiab] or coxarthriti*[tiab] or coxarthro*[tiab] or osteo?arthritis[tiab])

#7 #5 or #6

#8 randomized[tiab]

#9 placebo[tiab]

#10 controlled[tiab]

#11 random*[tiab]

#12 trial*[tiab]

#13 groups[tiab]

#14 ((singl*[tiab] or doubl*[tiab] or tripl*[tiab]) and (mask*[tiab] or blind*[tiab]))

#15 #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 #4 and #7 and #15

Embase search strategy

#1 'Pulsed electromagnetic field'/exp

#2 Pulsed electromagnetic fields:ti,ab

#3 Pulsed electromagnetic field: ti,ab

#4 #1 or #2 or #3

#5 osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or osteoarthritis:ti,ab

#6 'Osteoarthritis'/exp

#7 #5 or #6

#8 random* or control* or trial* or placebo:ti,ab

#9 groups:ti,ab

#10 (singl* or doubl* or tripl*) and (mask* or blind*):ti,ab

#11 #8 or #9 or #10

#12 #4 and #7 and #11

Cochrane Library search strategy

#1 MeSH descriptor Pulsed electromagnetic field explode all trees

#2 Pulsed electromagnetic field:ti,ab,kw

#3 #1 or #2

#4 MeSH descriptor osteoarthritis explode all trees

#5 osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or osteo?arthritis:ti,ab,kw

#6 #4 or #5

#7 random* or control* or trial* or placebo:ti,ab,kw

#8 Groups:ti,ab,kw

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2
3 #9 (singl* or doubl* or tripl*) and (mask* or blind*):ti,ab,kw

4 #10 #7 or #8 or #9

5 #11 #3 and #6 and #10

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7
8 **Web of Science search strategy**

9 #1 Topic:(Pulsed electromagnetic field)

10 #2 Topic:(Pulsed electromagnetic fields)

11 #3 #1 or #2

12 #4 Topic:(Osteoarthritis)

13 #5 Topic:(osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or osteo?arthritis)

14 #6 #4 or #5

15 #7 Topic:(randomized or placebo or controlled or random* or trial* or groups)

16 #8 Topic:((singl* or doubl* or tripl*) and (mask* or blind*))

17 #9 #7 or #8

18 #10 #3 and #6 and #9



PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Appendix 2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Details in Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, details in figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, details in table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7, details in figure 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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