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# BMJ Open

## Efficacy and Safety of Hyperbaric Oxygen Therapy for Fibromyalgia: A Systematic Review and Meta-analysis

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|-------------------------------|--|
| Journal:                      | <i>BMJ Open</i>  |
| Manuscript ID                 | bmjopen-2022-062322  |
| Article Type:                 | Original research  |
| Date Submitted by the Author: | 01-Mar-2022  |
| Complete List of Authors:     | Chen, Xinxin; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine<br>You, JiuHong; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine<br>Ma, Hui; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine<br>Zhou, Mei; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine<br>Huang, Cheng; Sichuan University, Department of Rehabilitation Medicine Center; Sichuan University |
| Keywords:                     | Rheumatology < INTERNAL MEDICINE, PAIN MANAGEMENT, Rehabilitation medicine < INTERNAL MEDICINE   |
|                               |  |

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# 1 Efficacy and Safety of Hyperbaric Oxygen Therapy for Fibromyalgia:

## 2 A Systematic Review and Meta-analysis

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## ABSTRACT

**Objective** Previous researches reported that hyperbaric oxygen therapy (HBOT) could improve symptoms and quality of life in patients with fibromyalgia (FM) and reduce their abnormal brain activities in pain-related areas. However, HBOT has not been regarded as standard therapy for FM. This study aims to qualify the safety and overall efficacy of HBOT for FM.

**Methods** A systematic review was conducted based on the recommendations provided in PRISMA Guidelines. PubMed, EMBASE, Cochrane Library, Web of Science, VIP (China Science and Technology Journal Database), CNKI (China National Knowledge Infrastructure), and WanFang database were searched to comprehensively collect clinical trials of HBOT for FM. The retrieval time is from September 9, 2021, until October 1, 2021. Two researchers independently screened literature, extracted data, and evaluated the quality of included studies according to inclusion and exclusion criteria, with disagreements resolved by a third researcher. A meta-analysis was performed by RevMan 5.4.1 software.

**Results** Four studies (three randomized controlled trials and one prospective clinical trial) with 161 patients were eventually included. Results of meta-analysis showed that HBOT alleviated pain [SMD=-1.68, 95%CI (-2.04, -1.31),  $P<0.001$ ] in patients with FM compared with control groups. Two studies were reporting adverse events which included mild barotrauma, new-onset myopia, increased pain/sensation, and headache. However, the predominant adverse event was mild barotrauma that resolved spontaneously and did not prevent patients from completing the treatment.

**Conclusions** HBOT showed a positive effect on pain alleviation in patients with FM. The reported side effects were self-limited, which showed the safety of HBOT. Due to the small samples of these included studies, it is necessary to carry out more high-quality and large-sample randomized controlled trials to further evaluate its efficacy.

**Key words** hyperbaric oxygen therapy, fibromyalgia, systematic review, meta-analysis

**Ethics approval statement** This study does not involve human participants. This study does not involve animal subjects. This is a systematic review and the PROSPERO trial registration number is CRD42021282920.

## INTRODUCTION

Fibromyalgia (FM) is an incurable common syndrome with unclear origin(1). It is characterized by chronic pain at multiple tender points lasting for more than 3 months and is usually accompanied by clinical manifestations such as fatigue, sleep disturbance, cognitive dysfunction, and depressive symptoms(2, 3). It is estimated that 2-8% of the population is affected by FM in the world(4). FM is more frequent in females, with a female-to-male ratio of 9:1(5).

The cause of FM syndrome is not fully understood yet, while the symptoms may be induced by infection, diabetes, rheumatic diseases, traumatic brain injury, or mental trauma(4, 6). Certain

67 studies have reported that some patients with FM had a history of childhood sexual abuse(7, 8).  
 68 Currently, treatment options mainly include pharmacological therapies, physical exercise,  
 69 meditative exercise therapy, and behavioral therapy(9-12). But these methods only temporarily  
 70 or moderately alleviate pain symptoms and often produce unbearable adverse effects which  
 71 interfere with the patients' quality of life and reduce their compliance(13). Therefore, it is  
 72 necessary to find a safer and more effective therapy.

73 Hyperbaric oxygen therapy (HBOT) is conducted by intermittently breathing 100% oxygen in  
 74 a pressure chamber above 1 atmospheric absolute pressure (ATA). HBOT can increase the partial  
 75 pressure of oxygen in alveoli, leading to a favorable increase of the dissolved oxygen in  
 76 plasma(14). The increase of pressure and oxygen causes more dissolved oxygen to be delivered  
 77 to the tissue through the blood which oxygenates the ischemic tissue(15). HBOT has shown  
 78 strong anti-inflammatory potential by reducing the activation of glial cells and inflammatory  
 79 mediators so that it could relieve pain under different chronic pain conditions (16). Anti-  
 80 inflammatory effects of HBOT also correct associated abnormal brain activities and alter  
 81 abnormal glial function which may benefit FM patients(17). The increase in oxygen concentration  
 82 caused by HBOT has been shown to improve the mitochondrial dysfunction of FM patients,  
 83 leading to changes in brain metabolism and glial function, and may reduce the abnormal brain  
 84 activities associated with FM(17).

85 To better understand the overall impact of HBOT on FM, we conducted a systematic review  
 86 and meta-analysis to quantify the safety and effectiveness of HBOT for FM.

87

## 88 METHODS

### 89 Search strategy

90 A literature search was conducted to identify all articles involving the use of hyperbaric  
 91 oxygen to treat FM. PubMed, EMBASE, Web of Science, Cochrane library, VIP (China Science and  
 92 Technology Journal Database), CNKI (China National Knowledge Infrastructure), and WanFang  
 93 database were searched from September 9, 2021, until October 1, 2021. The search included  
 94 MeSH and free text terms such as "hyperbaric oxygen therapy" "fibromyalgia" and synonyms.  
 95 There were no language or study design restrictions. Take PubMed as an example and its specific  
 96 retrieval strategy is shown in Table 1.

97 **Table 1. Search strategy in PubMed database.**

| Search items |                                    |
|--------------|------------------------------------|
| 1            | Hyperbaric oxygenation [MeSH]      |
| 2            | HBOT [Title/Abstract]              |
| 3            | Hyperbaric [Title/Abstract]        |
| 4            | 1 OR 2 OR 3                        |
| 5            | Fibromyalgia [MeSH]                |
| 6            | Fibromyalgia [All fields]          |
| 7            | "fibrositic nodule" [All fields]   |
| 8            | Fibrositis [All fields]            |
| 9            | "fibrositis syndrome" [All fields] |
| 10           | "myalgia, fibro" [All fields]      |
| 11           | 5 OR 6 OR 7 OR 8 OR 9 OR 10        |
| 12           | 4 AND 11                           |

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### **Inclusion and exclusion criteria**

We considered including all available information for systematic review due to the lack of data on this disease and the suspected lack of randomized controlled trials (RCTs). The criteria for inclusion were as follows: 1) study design: RCT, prospective clinical trial, cohort study or case-control study; 2) subjects: FM patients conform to the 2016 American college of rheumatology (ACR) diagnostic criteria(18) [i.e. they should meet the following criteria: generalized pain for at least 3 months and a widespread pain index (WPI)  $\geq 7$  and symptom severity scale (SSS)  $\geq 5$  or a WPI of 4–6 and a SSS score  $\geq 9$ ]. 3) the intervention: experimental group: HBOT + conventional treatment; control group: conventional treatment or blank control. Conventional treatment is any pharmacological or non-pharmacological therapy other than HBOT. All interventions except HBOT should be consistent between the two groups. The course of treatment and parameters are unlimited. 4) the outcome indicators: degree of improvement in fibromyalgia symptoms (pain, functional impairment, fatigue, depression, or quality of life).

### **Literature screening and data collection**

Two reviewers (JHY and HM) independently assessed the eligibility of each article. Duplicate articles were eliminated. Irrelevant articles were excluded by reading the title and abstract, and then the full text was read to further screen out articles that met the inclusion criteria. Articles without full text or data will only be excluded after three or more attempts to email the lead author and get no response. The decision to include each article was made independently according to the inclusion criteria, with disagreements resolved by a third reviewer (XXC). Reviewers followed PRISMA criteria for systematic evaluation.

A pre-designed form was used for information extraction. The content includes: the article basic information (author, year of publication, title); research types; patient demographics (age, gender); intervention and control measures (duration, frequency, sessions, follow-up); outcome indicators, the data of results and indicators which reflect research quality. Data collection was completed independently by two researchers (JHY and HM) and checked with each other. In case of disagreement, a third researcher (XXC) would assist to resolve the disagreement.

### **Risk of bias assessment**

Reviewers assessed the quality of the included articles using the Cochrane Collaboration checklists(19) for three RCTs and the ROBINS-I checklists(20) for a non-randomized trial. These checklists assess selection bias, implementation bias, measurement bias, follow-up bias, reporting bias, and other potential biases. In the Cochrane ROB tool, the risk of bias is classified as "low risk," "high risk," and "unclear". Review Manager version 5.4.1 was used to generate the risk of bias graph and summary of the three RCTs(21-23). On the ROBINS-I checklist, the risk score is classified as "low," "moderate," "severe," or "critical," or if there is insufficient information, as "NI" (no information). The quality of included studies was assessed independently by two reviewers (JHY and HM). Again, any controversy in the assessment is resolved through discussion with a third reviewer (XXC). A pre-designed form was used for information extraction. The content includes: the article basic information (author, year of publication, title); research types; patient demographics (age, gender); intervention and control measures (duration, frequency, sessions, follow-up); outcome indicators, the data of results and indicators which reflect research quality. Data collection was completed independently by two researchers (JHY and HM) and

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3 144 checked with each other. In case of disagreement, a third researcher (XXC) would assist to  
4 145 resolve the disagreement.  
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### 7 147 **Statistical analysis**

8 148 The RevMan 5.4.1 software provided by Cochrane Collaboration was used to conduct a  
9 149 meta-analysis of the primary outcome. Standardized mean difference (SMD) and its 95% CI were  
10 150 used as the analysis statistics. Firstly, the chi-square test is used to analyze whether there is  
11 151 statistical heterogeneity among the results of each study, and then  $I^2$  was used to quantitatively  
12 152 determine the size of the heterogeneity. If  $P \geq 0.1$ ,  $I^2 < 50\%$ , it means that the heterogeneity is not  
13 153 obvious and then use a fixed-effect model; if  $P < 0.1$ ,  $I^2 > 50\%$ , it indicates that the heterogeneity is  
14 154 obvious and then use a random effect model. If the heterogeneity is too obvious, the cause and  
15 155 source of heterogeneity would be further analyzed.  
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### 20 157 **Patient and public involvement**

21 158 Patients and public were not involved in this study.  
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## 24 160 **RESULTS**

25 161 A total of 82 eligible articles were obtained by literature search. After screening, four  
26 162 studies met the inclusion criteria(21-24). (Figure 1) These studies include three RCTs and one  
27 163 prospective clinical trial. A total of 161 patients were included in this review. And there were 81  
28 164 patients (50.3%) who received HBO therapy.  
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### 32 166 **Characteristics of included studies**

33 167 Table 2 shows an overview of the features of the included articles. HBOT protocols were  
34 168 mostly delivered at 100% oxygen at 2.0 atmospheres, 90 minutes per session, 5 days per week.  
35 169 Only two RCTs used the pressure 2.4 ATA and 1.45 ATA respectively(22, 23). The total number of  
36 170 sessions ranged from 15 to 60, of which, Yildiz(23) used 15 courses, Hadanny(21) used 60 courses,  
37 171 and the rest of the studies used 40 courses. The sample sizes of these studies were small, ranging  
38 172 from 30-50, with little difference. All the included studies did not mention a follow-up  
39 173 measurement. Four studies used pain-related scales as outcome indicators(21-24).  
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42 174

43 175 The included patients were mostly female, with a percentage of 90.7%. The patients  
44 176 included by Hadanny et al., Izquierdo et al., and Efrati et al. were all females(21, 22, 24). Hadanny  
45 177 et al. included women with a history of childhood sexual abuse (21). Hadanny et al. and Efrati et  
46 178 al. included patients with a duration of fibromyalgia of more than 2 years(21, 24).  
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55 184 **Table 2. Characteristics of included studies.**  
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| Author         | Year | Study design       | HBOT size | Control size | HBOT protocol        | Number of sessions | Follow-up | Outcome measures   |
|----------------|------|--------------------|-----------|--------------|----------------------|--------------------|-----------|--|
| Yildiz (23)    | 2004 | RCT                | 26        | 24           | 90mins,2.4ATA, 5d/w  | 15                 | Unclear   | Number of tender points, Pain threshold, VAS                             |
| Hadanny (21)   | 2018 | RCT                | 15        | 15           | 90mins,2ATA, 5d/w    | 60                 | Unclear   | WPI, FIQ, SF-36, BSI-18, Brain SPECT                                     |
| Izquierdo (22) | 2020 | RCT                | 17        | 16           | 90mins,1.45ATA, 5d/w | 40                 | None      | CR-10 Borg scale, VAS, Pain threshold                                    |
| Efrati (24)    | 2015 | Prospective trails | 24        | 24           | 90mins,2ATA, 5d/w    | 40                 | Unclear   | Number of tender points, Pain threshold, FIQ, SCL-90, SF-36, Brain SPECT |

VAS, Visual Analogue Scale; WPI, Widespread Pain Index; FIQ, Fibromyalgia Impact Questionnaire; SF-36, Quality of life-related questionnaires; BSI-18, The Brief Symptom Inventory—18; SCL-90, The Symptom Check List.

### 186 Quality assessment

187 Figure 2 shows the risk of bias summary of the three RCTs according to the Cochrane  
 188 checklists. Most risk biases were classified as “unclear”, which might have potential risk bias.  
 189 Table 3 shows the results of the ROBINS-I checklists for risk of bias of one non-randomized study  
 190 which showed a moderate overall risk of bias.

192 **Table 3. ROBINS-I checklists for risk of bias.**

|             | Confounding | Selection of patients | Classification of interventions | Deviation from intervention | Missing data | Measurement errors | Selective reporting | The overall risk of bias |
|-------------|-------------|-----------------------|---------------------------------|-----------------------------|--------------|--------------------|---------------------|--------------------------|
| Efrati (24) | Low         | Low                   | Low                             | Low                         | Moderate     | Low                | Moderate            | Moderate                 |

### 194 Outcome measures

195 The included studies used pain reduction as the primary outcome indicator. There were four  
 196 studies(21-24) reporting rating scales related to pain, as shown in Table 2. Some studies have  
 197 also reported functional impairment, fatigue, quality of life, anxiety, depression, brain SPECT and  
 198 adverse reactions. A meta-analysis was performed meaningfully for pain reduction.

### 200 Pain reduction

201 Four studies(21-24) reported pain reduction. Meta-analysis of a fixed-effect model showed  
 202 that the reduction of pain in the HBOT group was significantly higher than that in the control  
 203 group [SMD=-1.68, 95%CI (-2.04, -1.31),  $P<0.001$ ]. (Figure 3)

### 205 Other outcome indicators

206 Some studies have also reported outcomes of functional impairment, fatigue, quality of life,  
 207 depression, and brain SPECT. As the number of studies that could be combined is small or high  
 208 heterogeneity, meta-analysis was not performed for these outcome indicators. Hadanny(21) and  
 209 Efrati(24) reported HBOT could improve the functional impairment of FM patients. Izquierdo(22)  
 210 found that HBOT could reduce the fatigue of patients with FM. Hadanny(21) and Efrati(24) found  
 211 HBOT could improve the quality of life in FM patients. In terms of brain imaging, Hadanny(21)  
 212 found HBOT significantly improves brain function and brain microstructure in FM patients with

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2  
3 213 childhood sexual abuse. Efrati(24) showed that HBOT could rectify abnormal brain activities in  
4 214 pain-related areas and induce neuroplasticity in patients with FM.

5 215

### 6 216 **Adverse events**

7 217 There were two studies(21, 24) reporting the safety and side effects of HBOT for FM. The  
8 218 adverse events included mild barotrauma, new-onset myopia, increased pain/sensation, and  
9 219 headache. Efrati(24) reported that 5 patients withdrew from treatment because they didn't  
10 220 adapt to adverse reactions, and the incidence of adverse events in the rest of the patients was  
11 221 56.25%. Hadanny(21) reported the incidence of adverse events was 40%. However, the  
12 222 predominant adverse event was mild barotrauma that resolved spontaneously and did not  
13 223 prevent patients from completing the treatment regimen. Therefore, HBOT for FM could be  
14 224 considered safe.

15 225

### 16 226 **DISCUSSION**

17 227

18 228 FM is a central sensitivity disorder characterized by increased transmission and processing of  
19 229 pain within the central nervous system(25), which includes symptoms such as joint stiffness,  
20 230 generalized muscle pain at tender points, cognitive impairment, sleep disturbances, fatigue, and  
21 231 depressive symptoms(26, 27). Patients experience degenerative changes of muscle, abnormal  
22 232 oxygen pressure, and lower muscle blood flow due to hypoxia(28, 29). Local ischemia makes the  
23 233 mitochondria need to produce higher levels of free radicals to induce apoptosis, reduce ATP  
24 234 synthesis and increase lactate concentration in the muscle, thus ultimately leading to muscle  
25 235 weakness and pain(30, 31).

26 236 In 2021, Mascarenhas(32) published a systematic review and meta-analysis of therapies  
27 237 with reduced pain and improved quality of life in patients with FM. However, only two studies on  
28 238 HBOT for FM were included and there was no meta-analysis for them. And it suggested that  
29 239 HBOT for the management of FM was moderate evidence. Therefore, we included more studies  
30 240 to conduct a systematic review and meta-analysis for hyperbaric oxygen in the treatment of FM.  
31 241 It shows that HBOT significantly improves the diffuse pain in patients with FM. For the additional  
32 242 outcome indicators, we did a descriptive analysis. Although the incidence of adverse events  
33 243 reported in the included studies is close to 50%, most patients can relieve themselves and  
34 244 complete the treatment. Therefore, HBOT for FM could be considered safe.

35 245 Even with randomization and blinding in analysis, there was no blinding performed on the  
36 246 participants due to the inherent difficulty conducting sham control in HBOT trials. Most of the  
37 247 included studies used the same HBOT protocol which is 100% oxygen at 2.0 atmospheres, 90  
38 248 minutes per day, and repeated 5 times. Only Izquierdo(22) used 1.45 ATA to avoid the side  
39 249 effects of HBOT. The included patients were mostly female with a percentage of 90.7%, which  
40 250 might due to the high incidence in women. However, no studies conducted a follow-up for the  
41 251 effectiveness after HBOT intervention. Therefore, we remain skeptical about the long-term  
42 252 efficacy of HBOT for FM. Interestingly, Etorai(16) published a narrative review on the long-term  
43 253 treatment of FM with hyperbaric oxygen and aerobic exercise in 2016. The author reviewed that  
44 254 because of the lack of large-scale clinical trials and evidence about HBOT for FM (33), there is still  
45 255 controversy about the prospects for the application of HBOT for FM. Furthermore, whether  
46 256 HBOT should be used as adjuvant treatment or an independent primary treatment for FM is still

1  
2  
3 257 an unresolved problem(33).

4 258 There is growing evidence that HBOT is a non-invasive way to treat chronic pain diseases with  
5 259 long-lasting efficacy and minor adverse effects(13). In murine models of pain, HBOT has been  
6 260 shown to inhibit pain sensation which may be due to the NO-dependent release of opiate  
7 261 peptides and could be restrained by an antagonist, naltrexone(34, 35). This effect works in the  
8 262 central system but also involves HBO activating  $\mu$ - and K-opioid receptors in the spinal cord and  
9 263 releasing neuronal dynorphins(36). In murine models of arthritic, HBOT has also been shown to  
10 264 affect inflammatory pain through reducing mechanical hypersensitivity and inflammation(37).  
11 265 HBOT improves muscle oxygenation in FM which can reduce tissue lactate concentration and  
12 266 help maintain ATP levels, thus possibly preventing tissue damage in ischemic tissue(38). And it  
13 267 raises oxygen concentration in all tissues far above the physiological levels to cause hyperoxia,  
14 268 which breaks the hypoxic-pain cycle in patients with FM(38). In addition, the high excitability of  
15 269 pain processing pathways in the brain and low activity of pain inhibition pathways may cause  
16 270 excessive pain in FM(39). Studies have shown that patients with FM have higher activity in the  
17 271 somatosensory cortex and lower activity in the frontal, medial frontal, cingulate gyrus, and  
18 272 cerebellar cortex compared to healthy subjects(40). HBOT has been shown to increase  
19 273 neurotrophic and nitric oxide levels, reduce oxidative stress, promote cell metabolism by  
20 274 enhancing the mitochondrial function of neurons and glial cells, and may even promote the  
21 275 production of endogenous neural stem cells(41). The specific mechanism of HBOT on FM needs  
22 276 to be further investigated.

23 277 The main limitation of this systematic review is the small number of related studies which  
24 278 may lead to insufficient evidence. Also, it remains unresolved whether HBOT should be used as  
25 279 an adjunctive therapy or independent treatment because the control groups included in the  
26 280 studies were inconsistent. Therefore, it was unable to directly compare HBOT with conventional  
27 281 therapy.

28 282 For the future, it is suggested that high-quality and large-sample RCTs should be carried out  
29 283 to further evaluate the efficacy of HBOT. Furthermore, the efficacy of HBOT for FM should be  
30 284 compared or combined with conventional treatment. This will determine whether HBOT should  
31 285 be used as an independent or adjunctive treatment for FM.

32 286 In conclusion, the present study shows that HBOT has a significant effect on FM, especially  
33 287 on pain alleviation. In the future, high-quality and large-sample RCTs should be carried out, and  
34 288 the efficacy of HBOT for FM should be compared or combined with conventional treatment.

35 289  
36 290 **Author contributors:** Conceptualization: CH, XXC, JHY. Funding Acquisition: CH. Formal Analysis:  
37 291 XXC. Investigation: CH. Writing-Original Draft Preparation: XXC and JHY. Writing-Review &  
38 292 Editing: all the authors. All the authors fulfill the ICMJE criteria for authorship.

39 293  
40 294 **Funding statement:** Key research and development project of Sichuan Provincial Science and  
41 295 Technology Department (No. 2018SZ0082); 1·3·5 project for disciplines of excellence—Clinical  
42 296 Research Incubation Project, West China Hospital, Sichuan University (No. 2021HXFH063)

43 297  
44 298 **Disclaimer:** The authors declare no financial relationships with any organizations that might have  
45 299 an interest in the submitted work, no other relationships or activities that could appear to have  
46 300 influenced the submitted work.

301  
302 **Competing interests:** None declared.

303  
304 **Data sharing statement:** All data are available within the appendices.  
305

306  
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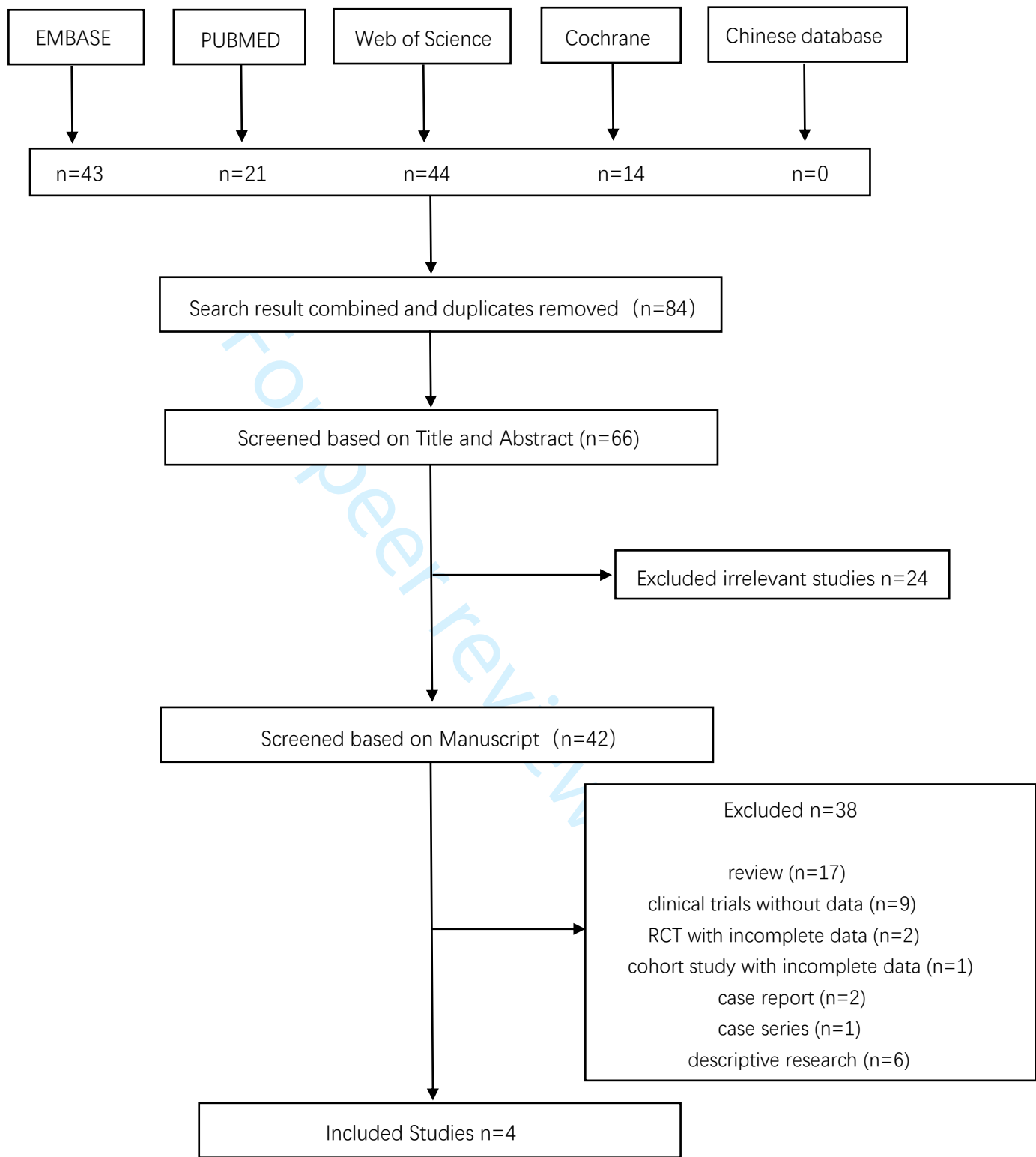
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32 411 **Figure 1. PRISMA flowchart.**  
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34 413 **Figure 2. Risk of bias for included studies across five domains.** The red circle indicates a high risk of  
35 414 bias within that domain for a given study, the yellow circles indicate an unclear risk of bias and the  
36 415 green circles indicate a low risk of bias.  
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38 417 **Figure 3. Forest plot of pain reduction.**  
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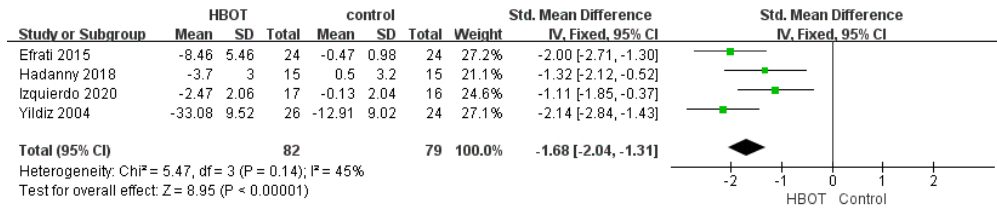
|                | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|----------------|---|---|---|---|--|--------------------------------------|------------|
| Hadanny 2018   | ?   | ?                                       | -   | +   | +  | +                                    | ?          |
| Izquierdo 2020 | +   | +                                       | ?   | +   | +  | +                                    | ?          |
| Yildiz 2004    | ?   | ?                                       | ?   | +   | +  | +                                    | ?          |

Figure 2. Risk of bias for included studies across five domains.

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Forest plot of pain reduction.

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# Reporting checklist for systematic review (with or without a meta-analysis).

Based on the PRISMA guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews

|              |   | Page   |
|--------------|---|--------|
|              | Reporting Item  | Number |
| <b>Title</b> |   |        |
| Title        | <a href="#">#1</a> Identify the report as a systematic review | 1      |

## Abstract

|    |                      |                    |  |   |
|----|----------------------|--------------------|--|---|
| 1  | Abstract             | <a href="#">#2</a> | Report an abstract addressing each item in the PRISMA          | 2 |
| 2  |                      |                    |  |   |
| 3  |                      |                    |  |   |
| 4  |                      |                    | 2020 for Abstracts checklist                                   |   |
| 5  |                      |                    |  |   |
| 6  | <b>Introduction</b>  |                    |  |   |
| 7  |                      |                    |  |   |
| 8  |                      |                    |  |   |
| 9  |                      |                    |  |   |
| 10 | Background/rationale | <a href="#">#3</a> | Describe the rationale for the review in the context of        | 2 |
| 11 |                      |                    |  |   |
| 12 |                      |                    | existing knowledge   |   |
| 13 |                      |                    |  |   |
| 14 |                      |                    |  |   |
| 15 | Objectives           | <a href="#">#4</a> | Provide an explicit statement of the objective(s) or           | 2 |
| 16 |                      |                    |  |   |
| 17 |                      |                    | question(s) the review addresses                               |   |
| 18 |                      |                    |  |   |
| 19 |                      |                    |  |   |
| 20 | <b>Methods</b>       |                    |  |   |
| 21 |                      |                    |  |   |
| 22 |                      |                    |  |   |
| 23 | Eligibility criteria | <a href="#">#5</a> | Specify the inclusion and exclusion criteria for the review    | 4 |
| 24 |                      |                    |  |   |
| 25 |                      |                    | and how studies were grouped for the syntheses                 |   |
| 26 |                      |                    |  |   |
| 27 |                      |                    |  |   |
| 28 |                      |                    |  |   |
| 29 | Information sources  | <a href="#">#6</a> | Specify all databases, registers, websites, organisations,     | 3 |
| 30 |                      |                    |  |   |
| 31 |                      |                    | reference lists, and other sources searched or consulted to    |   |
| 32 |                      |                    |  |   |
| 33 |                      |                    | identify studies. Specify the date when each source was        |   |
| 34 |                      |                    |  |   |
| 35 |                      |                    | last searched or consulted                                     |   |
| 36 |                      |                    |  |   |
| 37 |                      |                    |  |   |
| 38 |                      |                    |  |   |
| 39 | Search strategy      | <a href="#">#7</a> | Present the full search strategies for all databases,          | 3 |
| 40 |                      |                    |  |   |
| 41 |                      |                    | registers, and websites, including any filters and limits used |   |
| 42 |                      |                    |  |   |
| 43 |                      |                    |  |   |
| 44 | Selection process    | <a href="#">#8</a> | Specify the methods used to decide whether a study met         | 4 |
| 45 |                      |                    |  |   |
| 46 |                      |                    | the inclusion criteria of the review, including how many       |   |
| 47 |                      |                    |  |   |
| 48 |                      |                    | reviewers screened each record and each report retrieved,      |   |
| 49 |                      |                    |  |   |
| 50 |                      |                    | whether they worked independently, and, if applicable,         |   |
| 51 |                      |                    |  |   |
| 52 |                      |                    | details of automation tools used in the process                |   |
| 53 |                      |                    |  |   |
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| 56 | Data collection      | <a href="#">#9</a> | Specify the methods used to collect data from reports,         | 4 |
| 57 |                      |                    |  |   |
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| 1  | process            |                      | including how many reviewers collected data from each        |   |
| 2  |                    |                      | report, whether they worked independently, any processes     |   |
| 3  |                    |                      | for obtaining or confirming data from study investigators,   |   |
| 4  |                    |                      | and, if applicable, details of automation tools used in the  |   |
| 5  |                    |                      | process  |   |
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| 12 | Data items         | <a href="#">#10a</a> | List and define all outcomes for which data were sought.     | 4 |
| 13 |                    |                      | Specify whether all results that were compatible with each   |   |
| 14 |                    |                      | outcome domain in each study were sought (for example,       |   |
| 15 |                    |                      | for all measures, time points, analyses), and, if not, the   |   |
| 16 |                    |                      | methods used to decide which results to collect              |   |
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| 24 | Study risk of bias | <a href="#">#11</a>  | Specify the methods used to assess risk of bias in the       | 4 |
| 25 | assessment         |                      | included studies, including details of the tool(s) used, how |   |
| 26 |                    |                      | many reviewers assessed each study and whether they          |   |
| 27 |                    |                      | worked independently, and, if applicable, details of         |   |
| 28 |                    |                      | automation tools used in the process                         |   |
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| 37 | Effect measures    | <a href="#">#12</a>  | Specify for each outcome the effect measure(s) (such as      | 4 |
| 38 |                    |                      | risk ratio, mean difference) used in the synthesis or        |   |
| 39 |                    |                      | presentation of results                                      |   |
| 40 |                    |                      |  |   |
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| 44 | Synthesis methods  | <a href="#">#13a</a> | Describe the processes used to decide which studies were     | 5 |
| 45 |                    |                      | eligible for each synthesis (such as tabulating the study    |   |
| 46 |                    |                      | intervention characteristics and comparing against the       |   |
| 47 |                    |                      | planned groups for each synthesis (item #5))                 |   |
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| 54 | Synthesis methods  | <a href="#">#13b</a> | Describe any methods required to prepare the data for        | 5 |
| 55 |                    |                      | presentation or synthesis, such as handling of missing       |   |
| 56 |                    |                      |  |   |
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| 1  |                      | summary statistics or data conversions   |   |
| 2  |                      |  |   |
| 3  |                      |  |   |
| 4  | Synthesis methods    | <a href="#">#13c</a> Describe any methods used to tabulate or visually display | 5 |
| 5  |                      | results of individual studies and syntheses                                    |   |
| 6  |                      |  |   |
| 7  |                      |  |   |
| 8  |                      |  |   |
| 9  | Synthesis methods    | <a href="#">#13d</a> Describe any methods used to synthesise results and       | 5 |
| 10 |                      | provide a rationale for the choice(s). If meta-analysis was                    |   |
| 11 |                      | performed, describe the model(s), method(s) to identify the                    |   |
| 12 |                      | presence and extent of statistical heterogeneity, and                          |   |
| 13 |                      | software package(s) used   |   |
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| 21 | Synthesis methods    | <a href="#">#13e</a> Describe any methods used to explore possible causes of   | 5 |
| 22 |                      | heterogeneity among study results (such as subgroup                            |   |
| 23 |                      | analysis, meta-regression)   |   |
| 24 |                      |  |   |
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| 29 | Synthesis methods    | <a href="#">#13f</a> Describe any sensitivity analyses conducted to assess     | 5 |
| 30 |                      | robustness of the synthesised results  |   |
| 31 |                      |  |   |
| 32 |                      |  |   |
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| 34 | Reporting bias       | <a href="#">#14</a> Describe any methods used to assess risk of bias due to    | 5 |
| 35 | assessment           | missing results in a synthesis (arising from reporting                         |   |
| 36 |                      | biases)  |   |
| 37 |                      |  |   |
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| 42 | Certainty assessment | <a href="#">#15</a> Describe any methods used to assess certainty (or          | 4 |
| 43 |                      | confidence) in the body of evidence for an outcome                             |   |
| 44 |                      |  |   |
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| 47 | Data items           | <a href="#">#10b</a> List and define all other variables for which data were   | 4 |
| 48 |                      | sought (such as participant and intervention characteristics,                  |   |
| 49 |                      | funding sources). Describe any assumptions made about                          |   |
| 50 |                      | any missing or unclear information   |   |
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| 57 | <b>Results</b>       |  |   |
| 58 |                      |  |   |
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|----|-------------------------|----------------------|---|---|
| 1  | Study selection         | <a href="#">#16a</a> | Describe the results of the search and selection process,   | 6 |
| 2  |                         |                      | from the number of records identified in the search to the  |   |
| 3  |                         |                      | number of studies included in the review, ideally using a   |   |
| 4  |                         |                      | flow diagram ( <a href="http://www.prisma-statement.org/PRISMAStatement/FlowDiagram">http://www.prisma-</a> |   |
| 5  |                         |                      | statement.org/PRISMAStatement/FlowDiagram)  |   |
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| 12 |                         |                      |   |   |
| 13 | Study selection         | <a href="#">#16b</a> | Cite studies that might appear to meet the inclusion criteria,  | 6 |
| 14 |                         |                      | but which were excluded, and explain why they were  |   |
| 15 |                         |                      | excluded  |   |
| 16 |                         |                      |   |   |
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| 20 |                         |                      |   |   |
| 21 | Study characteristics   | <a href="#">#17</a>  | Cite each included study and present its characteristics  | 6 |
| 22 |                         |                      |   |   |
| 23 |                         |                      |   |   |
| 24 | Risk of bias in studies | <a href="#">#18</a>  | Present assessments of risk of bias for each included study   | 6 |
| 25 |                         |                      |   |   |
| 26 |                         |                      |   |   |
| 27 | Results of individual   | <a href="#">#19</a>  | For all outcomes, present for each study (a) summary  | 5 |
| 28 | studies                 |                      | statistics for each group (where appropriate) and (b) an  |   |
| 29 |                         |                      | effect estimate and its precision (such as  |   |
| 30 |                         |                      | confidence/credible interval), ideally using structured tables  |   |
| 31 |                         |                      | or plots  |   |
| 32 |                         |                      |   |   |
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| 38 |                         |                      |   |   |
| 39 | Results of syntheses    | <a href="#">#20a</a> | For each synthesis, briefly summarise the characteristics   | 6 |
| 40 |                         |                      | and risk of bias among contributing studies   |   |
| 41 |                         |                      |   |   |
| 42 |                         |                      |   |   |
| 43 |                         |                      |   |   |
| 44 |                         |                      |   |   |
| 45 | Results of syntheses    | <a href="#">#20b</a> | Present results of all statistical syntheses conducted. If  | 6 |
| 46 |                         |                      | meta-analysis was done, present for each the summary  |   |
| 47 |                         |                      | estimate and its precision (such as confidence/credible   |   |
| 48 |                         |                      | interval) and measures of statistical heterogeneity. If   |   |
| 49 |                         |                      | comparing groups, describe the direction of the effect  |   |
| 50 |                         |                      |   |   |
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| 57 | Results of syntheses    | <a href="#">#20c</a> | Present results of all investigations of possible causes of   | 6 |
| 58 |                         |                      |   |   |
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heterogeneity among study results

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| 2  |                          |                      |  |
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| 4  | Results of syntheses     | <a href="#">#20d</a> | Present results of all sensitivity analyses conducted to       |
| 5  |                          |                      |  |
| 6  |                          |                      | assess the robustness of the synthesised results               |
| 7  |                          |                      |  |
| 8  |                          |                      |  |
| 9  | Risk of reporting        | <a href="#">#21</a>  | Present assessments of risk of bias due to missing results     |
| 10 |                          |                      |  |
| 11 | biases in syntheses      |                      | (arising from reporting biases) for each synthesis assessed    |
| 12 |                          |                      |  |
| 13 |                          |                      |  |
| 14 | Certainty of evidence    | <a href="#">#22</a>  | Present assessments of certainty (or confidence) in the        |
| 15 |                          |                      |  |
| 16 |                          |                      | body of evidence for each outcome assessed                     |
| 17 |                          |                      |  |
| 18 |                          |                      |  |
| 19 | <b>Discussion</b>        |                      |  |
| 20 |                          |                      |  |
| 21 |                          |                      |  |
| 22 |                          |                      |  |
| 23 | Results in context       | <a href="#">#23a</a> | Provide a general interpretation of the results in the context |
| 24 |                          |                      |  |
| 25 |                          |                      | of other evidence  |
| 26 |                          |                      |  |
| 27 |                          |                      |  |
| 28 | Limitations of included  | <a href="#">#23b</a> | Discuss any limitations of the evidence included in the        |
| 29 | studies                  |                      | review   |
| 30 |                          |                      |  |
| 31 |                          |                      |  |
| 32 |                          |                      |  |
| 33 | Limitations of the       | <a href="#">#23c</a> | Discuss any limitations of the review processes used           |
| 34 |                          |                      |  |
| 35 | review methods           |                      |  |
| 36 |                          |                      |  |
| 37 |                          |                      |  |
| 38 |                          |                      |  |
| 39 | Implications             | <a href="#">#23d</a> | Discuss implications of the results for practice, policy, and  |
| 40 |                          |                      |  |
| 41 |                          |                      | future research  |
| 42 |                          |                      |  |
| 43 |                          |                      |  |
| 44 | <b>Other information</b> |                      |  |
| 45 |                          |                      |  |
| 46 |                          |                      |  |
| 47 | Registration and         | <a href="#">#24a</a> | Provide registration information for the review, including     |
| 48 |                          |                      |  |
| 49 | protocol                 |                      | register name and registration number, or state that the       |
| 50 |                          |                      |  |
| 51 |                          |                      | review was not registered                                      |
| 52 |                          |                      |  |
| 53 |                          |                      |  |
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| 55 | Registration and         | <a href="#">#24b</a> | Indicate where the review protocol can be accessed, or         |
| 56 |                          |                      |  |
| 57 | protocol                 |                      | state that a protocol was not prepared                         |
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| 1  | Registration and      | <a href="#">#24c</a> | Describe and explain any amendments to information         | 2 |
| 2  |                       |                      |  |   |
| 3  | protocol              |                      | provided at registration or in the protocol                |   |
| 4  |                       |                      |  |   |
| 5  |                       |                      |  |   |
| 6  | Support               | <a href="#">#25</a>  | Describe sources of financial or non-financial support for | 8 |
| 7  |                       |                      | the review, and the role of the funders or sponsors in the |   |
| 8  |                       |                      | review   |   |
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| 12 |                       |                      |  |   |
| 13 |                       |                      |  |   |
| 14 | Competing interests   | <a href="#">#26</a>  | Declare any competing interests of review authors          | 9 |
| 15 |                       |                      |  |   |
| 16 |                       |                      |  |   |
| 17 | Availability of data, | <a href="#">#27</a>  | Report which of the following are publicly available and   | 9 |
| 18 | code, and other       |                      | where they can be found: template data collection forms;   |   |
| 19 |                       |                      | data extracted from included studies; data used for all    |   |
| 20 | materials             |                      | analyses; analytic code; any other materials used in the   |   |
| 21 |                       |                      | review   |   |
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# BMJ Open

## Efficacy and Safety of Hyperbaric Oxygen Therapy for Fibromyalgia:A Systematic Review and Meta-analysis

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| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2022-062322.R1   |
| Article Type:                   | Original research  |
| Date Submitted by the Author:   | 17-Nov-2022  |
| Complete List of Authors:       | Chen, Xinxin; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine<br>You, Jiahong; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine<br>Ma, Hui; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine<br>Zhou, Mei; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine<br>Huang, Cheng; Sichuan University, Department of Rehabilitation Medicine Center; Sichuan University |
| <b>Primary Subject Heading</b>: | Rheumatology   |
| Secondary Subject Heading:      | Complementary medicine, Public health, Rehabilitation medicine   |
| Keywords:                       | Rheumatology < INTERNAL MEDICINE, PAIN MANAGEMENT, Rehabilitation medicine < INTERNAL MEDICINE   |
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1 **Efficacy and Safety of Hyperbaric Oxygen Therapy for Fibromyalgia:**  
2 **A Systematic Review and Meta-analysis**

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## ABSTRACT

**Objective** To investigate the efficacy and safety of hyperbaric oxygen therapy (HBOT) for fibromyalgia (FM).

**Design** A systematic review and meta-analysis.

**Data sources** PubMed, EMBASE, Cochrane Library, Web of Science, VIP (China Science and Technology Journal Database), CNKI (China National Knowledge Infrastructure), and WanFang database were searched from December 30, 2020, until October 22, 2022.

**Eligibility criteria** We included clinical trials (randomized controlled and nonrandomized controlled trials) of HBOT for FM.

**Data extraction and synthesis** Two researchers independently screened the literature, extracted data, and evaluated the quality of the included studies, with disagreements resolved by a third researcher. The Cochrane Collaboration checklists and the Methodological Index for Nonrandomized Studies were used to assess the risk of bias. Meta-analysis was performed by RevMan 5.4.1 software. Random effect models were used for meta-analysis.

**Results** Nine studies were included in this review, with a total of 288 patients. For pain assessment, we combined the results of the Visual Analogue Scale and Widespread Pain Index. The results showed that HBOT could relieve the pain of FM patients compared with the control intervention [SMD=-1.56, 95% CI (-2.18, -0.93),  $P<0.001$ ,  $I^2=51\%$ ]. Most included studies reported that HBOT ameliorated tender points, fatigue, multidimensional function, patient global, and sleep disturbance in FM. Adverse events occurred in 44 of 185 patients (23.8%). Twelve patients (6.5%) withdrew because of adverse reactions. No serious adverse events or complications were observed.

**Conclusions** HBOT might have a positive effect in improving pain, tender points, fatigue, multidimensional function, patient global, and sleep disturbance in FM, with reversible side effects. Low pressure (less than 2.0 ATA) may be beneficial to reduce adverse events in FM. Further studies should be carried out to evaluate the optimal protocol of HBOT in FM.

**PROSPERO registration number** CRD42021282920.

**Keywords** hyperbaric oxygen therapy, fibromyalgia, safety, efficacy, systematic review, meta-analysis.

### Strengths and limitations of this study

This is the first systematic review and meta-analysis to comprehensively identify clinical trials evaluating the efficacy and safety of hyperbaric oxygen therapy for fibromyalgia.

The GRADE system was used to assess the quality of evidence.

The small number of randomized controlled trials included in the studies may lead to an overall

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3 67 risk of bias or insufficient evidence.

4 68 We only retrieved data from Chinese and English databases, which may limit the data available or  
5 69 cause language bias.

6 70 The quality of the pooled effect was affected by the original trials.  
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## 10 72 **1. Introduction**

11 73 Fibromyalgia (FM) is an incurable common syndrome with unclear origin(1). It is  
12 74 characterized by chronic pain at multiple tender points lasting for more than 3 months and is  
13 75 usually accompanied by clinical manifestations such as fatigue, sleep disturbance, cognitive  
14 76 dysfunction, and depressive symptoms(2, 3). It is estimated that 2-8% of the population is affected  
15 77 by FM worldwide(4). FM is more frequent in females, with a female-to-male ratio of 9:1(5).

16 78 The cause of FM syndrome is not yet fully understood, while the symptoms may be induced  
17 79 by infection, diabetes, rheumatic diseases, traumatic brain injury, or mental trauma(4, 6). Certain  
18 80 studies have reported a history of childhood sexual abuse in some patients with FM(7, 8).  
19 81 Currently, treatment options mainly include pharmacological therapies, physical exercise,  
20 82 meditative exercise therapy, and behavioral therapy(9-12). However, these methods only  
21 83 temporarily or moderately alleviate pain symptoms and often produce unbearable adverse effects  
22 84 that interfere with the patient's quality of life and reduce their compliance(13). Therefore, there is  
23 85 a need for new and effective chronic pain treatments that can be tolerated by patients without  
24 86 significant adverse effects.

25 87 Accumulating evidence suggests that hyperbaric oxygen therapy (HBOT) is a noninvasive  
26 88 modality with lasting efficacy that can be used to treat FM(14-17). HBOT is conducted by  
27 89 intermittently breathing 100% oxygen in a pressure chamber above 1 atmospheric absolute  
28 90 pressure (ATA). HBOT can increase the partial pressure of oxygen in alveoli, leading to a  
29 91 favorable increase in dissolved oxygen in plasma(18). The increase in pressure and oxygen causes  
30 92 more dissolved oxygen to be delivered to the tissue through the blood, which oxygenates the  
31 93 ischemic tissue(19). HBOT has shown strong anti-inflammatory potential by reducing the  
32 94 activation of glial cells and inflammatory mediators so that it could relieve pain under different  
33 95 chronic pain conditions (14). The anti-inflammatory effects of HBOT also correct associated  
34 96 abnormal brain activities and alter abnormal glial function, which may benefit FM patients(20).  
35 97 The increase in oxygen concentration caused by HBOT has been shown to improve the  
36 98 mitochondrial dysfunction of FM patients, leading to changes in brain metabolism and glial  
37 99 function, and may reduce the abnormal brain activities associated with FM(20). Although some  
38 100 studies have reported a positive effect of HBOT on FM, HBOT has not been recommended by  
39 101 guidelines as a complementary treatment for FM due to a lack of sufficient evidence(21, 22).

40 102 Mascarenhas(23) proposed that HBOT for the management of FM was moderate evidence in  
41 103 a systematic review. However, only two studies on HBOT for FM were included, and there was no  
42 104 meta-analysis. In addition, only two outcome measures (pain and quality of life) were investigated.  
43 105 To better understand the overall efficacy and safety of HBOT for FM, we conducted a systematic  
44 106 review and meta-analysis with more studies to investigate HBOT in the treatment of the inner  
45 107 Core Outcome Set of FM symptoms (pain, tenderness, fatigue, multidimensional function, patient  
46 108 global, sleep disturbance)(24) and estimate its safety.  
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## 110 109 **2. Methods**

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3 111 This study was conducted following the Preferred Reporting Items for Systematic Reviews  
4 112 and Meta-Analyses (PRISMA) statement(25). The protocol for this study is available online  
5 113 (PROSPERO trial registration number: CRD42021282920).  
6 114

### 8 115 **2.1. Search strategy**

10 116 A literature search was conducted to identify all articles involving the use of hyperbaric  
11 117 oxygen to treat FM. The search strategy is shown in Supplementary appendix A. PubMed,  
12 118 EMBASE, Web of Science, Cochrane library, VIP (China Science and Technology Journal  
13 119 Database), CNKI (China National Knowledge Infrastructure), and WanFang database were  
14 120 searched from December 30, 2020, until October 22, 2022. The search included MeSH and free  
15 121 text terms such as “hyperbaric oxygen therapy”, “fibromyalgia” and synonyms.  
16 122

### 18 123 **2.2. Inclusion and exclusion criteria**

20 124 We considered including all available information for systematic review due to the lack of  
21 125 data on this disease and the suspected lack of randomized controlled trials (RCTs). The criteria for  
22 126 inclusion were as follows: 1) study design: RCTs and non-RCTs; 2) subjects: FM patients  
23 127 conformed to the 2016 American College of Rheumatology (ACR) diagnostic criteria(26) [i.e.  
24 128 they met the following criteria: generalized pain for at least 3 months and a widespread pain index  
25 129 (WPI)  $\geq 7$  and symptom severity scale (SSS)  $\geq 5$  or a WPI of 4–6 and a SSS score  $\geq 9$ ]; 3) the  
26 130 intervention: patients in the experimental group received HBOT as the intervention measure, and  
27 131 patients in the control group received conventional treatment or nothing. The conventional  
28 132 treatment was any pharmacological or nonpharmacological therapy other than HBOT. The course  
29 133 of treatment and parameters were unlimited. 4) outcome indicators: the inner Core Outcome Set of  
30 134 FM symptoms (pain, tenderness, fatigue, multidimensional function, patient global, sleep  
31 135 disturbance) and adverse events. The exclusion criteria were as follows: animal studies, reviews,  
32 136 duplicate publications, irrelevant studies, editorial materials, patients, case reports, or meeting  
33 137 abstracts.  
34 138

### 36 139 **2.3. Literature screening and data collection**

38 140 Two reviewers (JHY and HM) independently assessed the eligibility of each article.  
39 141 Duplicate articles were eliminated. Irrelevant articles were excluded by reading the title and  
40 142 abstract, and then the full text was read to further screen out articles that met the inclusion criteria.  
41 143 Articles without full text or data were excluded after three or more attempts to email the lead  
42 144 author and obtain no response. The decision to include each article was made independently  
43 145 according to the inclusion criteria, with disagreements resolved by a third reviewer (XXC).  
44 146 Reviewers followed PRISMA criteria for systematic evaluation.

46 147 A predesigned form was used for information extraction. The content included the article’s  
47 148 basic information (author, year of publication, title); research types; patient demographics (age,  
48 149 gender); intervention and control measures (duration, frequency, sessions, follow-up); outcome  
49 150 indicators; the data of results; and indicators that reflected research quality. Data collection was  
50 151 completed independently by two researchers (JHY and HM) and checked with each other. In case  
51 152 of disagreement, a third researcher (XXC) assisted in resolving the disagreement.  
52 153

### 54 154 **2.4. Types of outcome measures**

155 The inner Core Outcome Set of FM symptoms suggested by Mease et al.(24) can be  
156 quantitatively or qualitatively analysed. The primary outcome measure was pain, and the  
157 secondary outcome measures included tenderness, fatigue, multidimensional function, patient  
158 global, sleep disturbance, and adverse events.

#### 160 2.4.1. Pain and tenderness

161 Assessment methods included the Pain Visual Analogue Scale (VAS), number of tender  
162 points, pain threshold, and Widespread Pain Index (WPI).

#### 164 2.4.2. Multidimensional function

165 Assessment methods included the Fibromyalgia Impact Questionnaire (FIQ) and Quality of  
166 Life-related questionnaires (SF-36).

#### 168 2.4.3. Fatigue

169 Assessment methods of fatigue included the Fatigue Severity Scale (FSS), Functional  
170 Assessment of Chronic Illness Therapy Fatigue (FACIT fatigue) scale, Fatigue VAS, and CR-10  
171 Borg Scale.

#### 173 2.4.4. Patient global

174 The Patient Global Impression of Change (PGIC) was used to assess this outcome measure.

#### 176 2.4.5. Sleep disturbance

177 Assessment methods included the Jenkins Sleep Scale (JSS) and Pittsburgh Sleep Quality  
178 Index (PSQI).

#### 180 2.4.6. Adverse events

181 This indicator included adverse events (AEs), withdrawals due to AEs, and complications.

### 183 2.5. Risk of bias assessment

184 Reviewers assessed the quality of the included articles using the Cochrane Collaboration  
185 checklists(27) for three RCTs and the Methodological Index for Nonrandomized Studies  
186 (MINORS)(28) for six non-RCTs. The Cochrane checklists assessed selection bias,  
187 implementation bias, measurement bias, attrition bias, reporting bias, and other bias. In the  
188 Cochrane ROB tool, the risk of bias was classified as "low risk," "unclear," and "high risk".  
189 Review Manager version 5.4.1 was used to generate the risk of bias graph of the three RCTs. The  
190 MINORS checklists included twelve items (0-24 scores) for comparative studies and eight items  
191 (0-16 scores) for noncomparative studies. The score for each item was 0 (not reported), 1 (reported  
192 but inadequate), or 2 (reported and adequate). Comparative studies scoring > 19 or  
193 noncomparative studies scoring > 12 were considered high quality. The quality of the included  
194 studies was assessed independently by two reviewers (JHY and HM). Again, any controversy in  
195 the assessment was resolved through discussion with a third reviewer (XXC).

### 197 2.6. Statistical analysis

198 RevMan 5.4.1 software provided by the Cochrane Collaboration was used to conduct a meta-



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199 analysis. The standardized mean difference (SMD) and its 95% CI were used as the analysis  
200 statistics because different studies use different rating instruments to measure the same  
201 outcome(29). Forest plot tests were conducted, and meta-regression analysis was used to test  
202 heterogeneity. The chi-square test was used to analyse whether there was statistical heterogeneity  
203 among the results of each study. This study used the random effects model for meta-analysis  
204 because the random effects meta-analysis allowed for differences (treatment areas, concomitant  
205 treatments, and HBOT regimen) in treatment effects among different studies(30).

206

### 207 **2.7. Grade the quality of evidence**

208 The Grading of Recommendations Assessment, Development and Evaluation System  
209 (GRADE) system was used to grade the quality of the evidence(31). The risk of bias,  
210 inconsistency, indirectness, imprecision, and publication bias were assessed. The quality of  
211 evidence was rated 'high', 'moderate', 'low', or 'very low'.

212

### 213 **2.8. Patient and public involvement**

214 Patients and the public were not involved in this study.

215

## 216 **3. Results**

### 217 **3.1. Characteristics of the included studies**

218 A total of 69 eligible articles were obtained by a literature search. After screening, nine  
219 studies (three RCTs and six non-RCTs) met the inclusion criteria(32-40). The flow diagram is  
220 shown in Figure 1. A total of 288 patients were included in this study. Table 1 shows the  
221 characteristics of the included articles.

222



223 **Table 1. Characteristics of the included articles.**

| Author,<br>year           | Patients (N) |         | Intervention (HBOT)         |                     | Comparison              | Outcome<br>measures   | Adverse events and the number<br>of patients (N)  |              | Study<br>design |
|---------------------------|--------------|---------|-----------------------------|---------------------|-------------------------|---|---|--------------|-----------------|
|                           | Intervention | Control | protocol                    | sessions/<br>length |                         |   | Adverse events  | Patients (N) |                 |
| Yildiz<br>2004<br>(40)    | 26           | 24      | 90 mins,2.4ATA,<br>5d/w     | 15/<br>3 weeks      | 90 mins,1ATA,<br>5d/w   | Number of<br>tender points,<br>Pain threshold,<br>Pain VAS                              | -   | -            | RCT             |
| Hadanny<br>2018<br>(38)   | 15           | 15      | 90 mins,2ATA,<br>5d/w       | 60/<br>12 weeks     | Psychotherapy           | WPI, FIQ,<br>SF-36  | mild barotrauma<br>headache   | 12<br>1      | RCT             |
| Izquierdo<br>2020<br>(33) | 17           | 16      | 90<br>mins,1.45ATA,<br>5d/w | 40/<br>8 weeks      | Conventional<br>therapy | VAS,<br>Pain threshold,<br>CR-10 Borg<br>scale  | -   | -            | RCT             |
| Efrati<br>2015<br>(39)    | 27           | 26      | 90 mins,2ATA,<br>5d/w       | 40/<br>8 weeks      | No treatment            | Number of<br>tender points,<br>Pain threshold,<br>FIQ, SF-36                            | mild barotrauma<br>dizziness,<br>claustrophobia<br>and inability to<br>adjust<br>ear pressure by<br>“ear pumping” | 13<br>5      | NCT             |
| Guggino<br>2020<br>(34)   | 22           | 14      | 90 mins,2ATA,<br>5d/w       | 40/<br>8 weeks      | No treatment            | Number of<br>tender points,<br>Pain VAS,<br>Fatigue VAS,<br>WPI, FACIT<br>fatigue, PSQI | -   | -            | NCT             |
| Curtis<br>2021<br>(32)    | 9            | 8       | 90 mins,2ATA,<br>5d/w       | 40/<br>8 weeks      | Conventional<br>therapy | FIQR, FSS,<br>JSS,<br>PGIC, Fatigue<br>VAS  | mild middle-ear<br>barotrauma<br>new-onset<br>myopia  | 3<br>4       | NCT             |

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|------------------------|----|---|-------------------------|----------------|---|--|---|---------------------|-----|
| Casale<br>2019<br>(35) | 25 | - | 91 mins,2.4ATA          | 20/<br>4 weeks | - | Neuromuscular<br>efficiency              | side effects  | 2                   | NCT |
| Bosco<br>2019<br>(36)  | 12 | - | 90 mins,2ATA,<br>5d/w   | 20/<br>4 weeks | - | WPI                                      | -   | -                   | NCT |
| Atzeni<br>2019<br>(37) | 32 | - | 90 mins,2.5ATA,<br>3d/w | 20/<br>4 weeks | - | Pain VAS,<br>FACIT, PSQI,<br>FIQR, SF-36 | mild, reversible<br>middle ear<br>barotrauma<br>dizziness<br>claustrophobia | 2<br><br><br>1<br>1 | NCT |

224 Abbreviations: ATA, atmospheric absolute pressure; d/w, days/week; VAS, Visual Analogue Scale; WPI, Widespread Pain Index; FIQ, Fibromyalgia Impact  
 225 Questionnaire; SF-36, Quality of Life-related questionnaires; FACIT fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; PSQI, Pittsburgh  
 226 Sleep Quality Index; FIQR, Revised Fibromyalgia Impact Questionnaire; FSS, Fatigue Severity Scale; JSS, Jenkins Sleep Scale; PGIC, Patient Global Impression of  
 227 Change; RCT, randomized controlled trial; NCT, nonrandomized controlled trial.

### 229 3.2. Quality assessment

230 Figure 2 shows the risk of bias graph of the three RCTs according to the Cochrane ROB tool.  
231 Of the RCTs included, studies by Yildiz et al.(40) and Hadanny et al(38). had an unclear risk of  
232 selection bias because of the lack of specific randomization methods and no indication of  
233 allocation concealment. All RCTs were judged to have an unclear or high risk of performance bias  
234 because researchers did not adopt blinding. All RCTs were at low risk for detection bias and  
235 attrition bias. However, the risk of reporting bias and other bias in all RCTs were unclear, mainly  
236 due to the lack of follow-up. Table 2 shows the quality assessment of the six non-RCTs. The  
237 average MINORS scores for noncomparative and comparative studies were 9.7 and 19.7,  
238 respectively. Studies by Efrati et al.(39) and Curtis et al.(32) were considered high quality. In non-  
239 RCTs, lack of bias assessment, study size calculation, and follow-up were the most common  
240 reasons for low MINORS scores.

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**Table 2. Quality assessment of the included nonrandomized controlled trials using the Methodological Index for Nonrandomized Studies (MINORS).**

| Assessment  | Efrati 2015 | Guggino 2020 | Curtis 2021 | Casale 2019 | Bosco 2019 | Atzeni 2019 |
|---|-------------|--------------|-------------|-------------|------------|-------------|
| 1. A clearly stated aim                                 | 2           | 2            | 2           | 2           | 2          | 2           |
| 2. Inclusion of consecutive patients                    | 2           | 2            | 2           | 2           | 2          | 2           |
| 3. Prospective collection of data                       | 2           | 2            | 2           | 2           | 2          | 2           |
| 4. Endpoints appropriate to the aim of the study        | 2           | 2            | 2           | 2           | 2          | 2           |
| 5. Unbiased assessment of the study endpoint            | 2           | 0            | 1           | 1           | 0          | 0           |
| 6. Follow-up period appropriate to the aim of the study | 0           | 0            | 2           | 0           | 2          | 0           |
| 7. Loss to follow up less than 5%                       | 0           | 0            | 2           | 0           | 0          | 0           |
| 8. Prospective calculation of the study size            | 2           | 2            | 0           | 0           | 0          | 2           |
| 9. An adequate control group                            | 2           | 2            | 2           | -           | -          | -           |
| 10. Contemporary groups                                 | 2           | 2            | 2           | -           | -          | -           |
| 11. Baseline equivalence of groups                      | 2           | 2            | 2           | -           | -          | -           |
| 12. Adequate statistical analyses                       | 2           | 2            | 2           | -           | -          | -           |
| Total score   | 20          | 18           | 21          | 9           | 10         | 10          |

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### 276 3.3. Efficacy of HBOT

277 Because of the small number of studies, insufficient data that could be pooled, and  
278 heterogeneity among different study types, only pain relief from three RCTs was included in the  
279 meta-analysis, and the other outcome indicators were only analysed descriptively.  
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#### 281 3.3.1. Pain relief

282 Seven studies (three RCTs and four non-RCTs)(33, 34, 36-40) reported that HBOT alleviated  
283 the pain level of FM documented by the decrease in rating scales related to pain. We conducted a  
284 meta-analysis on pain relief of three RCTs(33, 38, 40). For pain assessment, we combined the  
285 results of VAS and WPI. Meta-analysis of a random effect model showed that the pain relief in the  
286 HBOT group was better than that in the control group [SMD=-1.56, 95% CI (-2.18, -0.93),  
287  $P<0.001$ ,  $I^2=51%$ ] (Figure 3).  
288

#### 289 3.3.2. Tenderness

290 Three studies(34, 39, 40) reported that HBOT reduced the number of tender points in FM.  
291 Jeschonneck et al.(41) found that vasoconstriction in patients with FM occurred in the skin above  
292 the tender point. This confirmed that FM syndrome was associated with local hypoxia of the skin  
293 covering the tender points. Lund et al.(42) proposed that in FM with primary aetiology, muscle  
294 oxygenation was abnormal or low, at least in the muscle trigger point region, as recorded by  
295 oxygen multipoint electrodes on the muscle surface. HBOT could break the vicious cycle of pain-  
296 hypoxia because it increased the pain threshold to reduce the number of tender points in patients  
297 with FM(40).  
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#### 299 3.3.3. Multidimensional function

300 Three studies(32, 38, 39) reported that HBOT improved FM-related functional impairment  
301 and overall symptoms, as documented by the decreased score of the FIQ or FIQ-R questionnaire.  
302 These studies may support the use of HBOT to reduce the effects of FM on global symptoms and  
303 functional activities. Studies by Hadanny et al.(38), Efrati et al.(39) and Atzeni et al.(37) reported  
304 the SF-36, which was used to assess the quality of life. All three studies showed that HBOT could  
305 effectively improve the quality of life of FM. In addition, Hadanny et al.(38) have shown that  
306 improvements in quality of life with FM were associated with improvements in brain performance  
307 parameters seen in brain function (SPECT) and structure (MRI-DTI) imaging. This may be  
308 because HBOT can improve brain function and microstructure by inducing neural plasticity in  
309 humans(43, 44).  
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#### 311 3.3.4. Fatigue

312 Three studies(33, 34, 37) showed that HBOT could reduce fatigue in FM patients, while  
313 Curtis et al.(32) reported that HBOT had no significant effect on fatigue in FM. Reports have  
314 shown that HBOT reduced fatigue in chronic fatigue syndrome(45), which was attributed to its  
315 ability to reduce reactive oxygen species and acid-lactic acid levels, as well as muscle fatigue after  
316 exercise(46). HBOT alleviated fatigue in FM patients, possibly because HBOT increased oxygen  
317 supply to the musculoskeletal system, thereby activating cellular activity and promoting the  
318 metabolism of fatigue-related substances(47). Clinical studies have shown that increased plasma  
319 proinflammatory cytokine levels trigger symptoms such as fatigue, fever, sleep, pain, and myalgia  
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in FM patients(48). HBOT can improve FM symptoms by reducing the upregulated proinflammatory cytokines in FM. Atzen et al.(37) proposed that the fatigue of FM was only improved after 20 treatments, indicating that the number of treatments would affect the efficacy of HBOT. In Curtis's study(32), the lack of an effect of HBOT on fatigue may be attributed to baseline differences in the small sample size. In addition, Casale et al.(35) found that HBO did not directly increase FM muscle strength or alter muscle fiber content to alleviate fatigue but increased the ability of the central motor command to generate the same effort with fewer recruited fibers.

### 3.3.5. Patient global

Only one study(32) reported PGIC, which assessed global response to treatment and has been associated with clinical symptoms in patients with FM. Curtis(32) reported that patients with FM had a different degree of symptom improvement after HBOT and at a three-month follow-up. After HBOT treatment, “almost the same” was the most common impression of global symptoms in FM patients (44.4%). However, at the three-month follow-up, “a great deal better” was the most common impression of global symptoms in FM patients (41.7%). This showed that HBOT may be effective for a long time.

### 3.3.6. Sleep disturbance

Three studies reported sleep quality. Guggino et al.(34) reported that HBOT did not improve the total sleep time of FM patients but improved their sleep quality. Curtis et al.(32) proposed that HBOT improved sustained sleep quality in FM at a three-month follow-up assessment. However, Atzeni et al.(37) indicated that HBOT did not significantly improve the sleep quality of FM. This inconsistency may be related to the different number of HBOT sessions, which needs further study.

## 3.4. Adverse events of HBOT

Five studies reported the side effects of HBOT for FM (as shown in Table 1). Adverse events occurred in 44 of 185 patients (23.8%). Twelve patients (6.5%) withdrew because they could not tolerate adverse reactions. Of these adverse events, there were 25 cases of mild barotrauma, five cases of mild middle-ear barotrauma, four cases of new-onset myopia, one case of headache, seven cases of dizziness, claustrophobia, inability to adjust ear pressure by “ear pumping”, and two cases of side effects (not clearly reported). The predominant adverse event was mild barotrauma that could be resolved spontaneously and did not prevent patients from completing the treatment regimen. No serious side effects, complications, or deaths were reported.

## 3.5. Grade analysis of the evidence

The quality of pain relief was “Moderate”. Although there was a serious risk of bias and inconsistency, there was no serious directness or imprecision. In addition, the outcome of pain relief has a larger effect. The GRADE evidence profile is shown in Table 3.

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**Table 3. GRADE evidence profile.**

| Outcome     | Certainty assessment |                      |                          |                      |                           | Effect            |                       |                                | Certainty        |
|-------------|----------------------|----------------------|--------------------------|----------------------|---------------------------|-------------------|-----------------------|--------------------------------|------------------|
|             | Ris of bias          | Inconsistency        | Directness               | Imprecision          | Others                    | Number of Studies | Number of Individuals | Rate (95%CI)                   |                  |
| Pain Relief | Serious <sup>a</sup> | Serious <sup>b</sup> | Not serious <sup>c</sup> | Serious <sup>d</sup> | Large effect <sup>e</sup> | three RCTs        | 113                   | SMD: -1.56<br>(-2.18 to -0.93) | ⊗⊗⊗○<br>Moderate |

Abbreviations: CI, confidence intervals; SMD, standardized mean difference.

Notes: <sup>a</sup> most of the included studies were assessed as some concerns/high-risk bias; <sup>b</sup>  $I^2 > 50\%$ ; <sup>c</sup> direct participants, intervention and outcomes; <sup>d</sup> total sample size > 100; <sup>e</sup> SMD > 0.8.

#### 4. Discussion

In this study, we focused on the efficacy of HBOT on inner core outcomes of FM. Pain relief was the primary outcome measure and could be meta-analysed (three RCTs). Tenderness, fatigue, multidimensional function, patient global, sleep disturbance, and adverse events were secondary outcome measures and were analysed descriptively because of the limited number of studies or limited available data that could be combined. After a systematic review, we found that HBOT could relieve the pain of FM patients compared with the control intervention [SMD=-1.56, 95% CI (-2.18, -0.93),  $P<0.001$ ,  $I^2=51\%$ ]. In addition, most of the included studies have shown that HBOT could significantly improve tender points, fatigue, quality of life, patient global, and sleep disturbance in patients with FM. However, Curtis et al.(32) found that HBOT had no positive effect on fatigue reduction of FM, and Atzeni et al.(37) indicated that HBOT did not significantly improve the quality of life of FM. This inconsistency might be due to baseline differences in small sample sizes or the insufficient number of HBOT sessions. Of the 185 patients with FM who received HBOT, 44 patients had adverse reactions during HBOT treatment (23.8%), and 12 patients withdrew (6.5%) because they could not tolerate the side effects. However, in one retrospective study of 1.5 million cases of treatment with HBOT, the adverse event rate was only 0.68%(49). We speculated that patients with FM might have a lower pain threshold and may be more sensitive to discomfort than patients with other diseases. Mild barotrauma was the most common complication of HBOT for FM. Patients may experience pressure, difficulty in ear balance, earache, and discomfort during compression(50). However, mild barotrauma can be resolved spontaneously and does not prevent patients from completing the treatment and can usually be prevented by appropriate screening(51). Oliaei et al.(52) found that most complications of HBOT occurred when the pressure applied exceeded 2.0 ATA. The articles included in this study mostly used hyperbaric oxygen chambers of 2 to 2.5 ATA for the treatment of FM, which may lead to side effects. A randomized controlled study(33) confirmed that low-pressure HBOT (1.45 ATA) was effective in the treatment of FM without adverse events. Therefore, a pressure lower than 2.0 ATA may be a good choice for patients with FM to avoid side effects and has good efficacy. Further studies are needed to explore the efficacy and safety of low-pressure HBOT for FM. In addition, contraindications for HBOT should be strictly screened before treatment, and the appropriate pressure and duration of treatment should be determined according to the patient's tolerance.

Patients with FM in the control group received conventional treatment or nothing in the included studies. Yildiz et al.(40), Efrati et al.(39) and Guggino et al.(34) did not give any treatment to the patients in the control group, while Hadanny et al.(38), Izquierdo et al.(33) and Curtis et al.(32) performed conventional treatment for the patients in the control group. The conventional treatment that FM received as usual included psychotherapy, medications, physical activity, nutrition therapy, massage, acupuncture, behavioral therapy, or cognitive therapy. Therefore, HBOT may be effective both as an adjunctive therapy and as an independent treatment. Most of the included studies used the same HBOT protocol, which was 100% oxygen at 2 to 2.5 ATA, 90 minutes per session, five days per week. Only a study by Izquierdo et al.(33) used 1.45 ATA to avoid the side effects of HBOT. The length of treatment in the included studies ranged from three to twelve weeks, of which the study by Yildiz et al.(40) lasted three weeks, the study by Hadanny et al.(38) lasted twelve weeks, three noncomparative studies(35-37) lasted four weeks, and the rest of the studies lasted eight weeks. A rodent study found that the anti-injury



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3 411 effects of HBOT were apparent immediately after treatment and lasted for up to five hours(19). In  
4 412 a rat neuropathic pain model, two weeks of HBOT resulted in a significant improvement in pain  
5 413 levels during and after treatment(53). Atzeni et al.(37) proposed that two to four weeks of HBOT  
6 414 treatment significantly improved pain and anxiety symptoms in FM, while fatigue only was  
7 415 improved after four weeks. In addition, sleep quality and depressive symptoms were not positively  
8 416 affected in FM after 4 weeks of HBOT. In this review, only Curtis et al.(32) mentioned a follow-  
9 417 up measurement (three months) and found that HBOT can continuously improve patient global,  
10 418 psychological symptoms, and sleep quality in FM. Another study(16) showed that HBOT for 10  
11 419 days had a rapid onset, dose dependent, and long-lasting analgesic effect in patients with  
12 420 idiopathic trigeminal neuralgia documented a reduction in the dosage of carbamazepine analgesics  
13 421 and lower pain VAS. Therefore, long-term treatment with HBOT may be beneficial to improve  
14 422 symptoms of FM or prolong efficacy. However, the prolonged treatment window of patients is  
15 423 likely to cause side effects. Studies have shown that human lenses exposed to 2.0-2.5 ATA and  
16 424 100% oxygen for 90 minutes once a day will lead to the development of myopia and cataracts  
17 425 after 150-850 courses of HBOT(54). However, when exposed to 2.5 ATA and 100% oxygen for  
18 426 90 minutes once a day for 48 courses, the above side effects rarely occur(55). It is challenging to  
19 427 establish the effect and optimal dose–response curves of HBOT in FM considering both safety and  
20 428 efficacy.

21 429 There is growing evidence that HBOT is a noninvasive way to treat chronic pain diseases with  
22 430 long-lasting efficacy and minor adverse effects(13). In murine models of pain, HBOT has been  
23 431 shown to inhibit pain sensation, which may be due to the NO-dependent release of opiate peptides  
24 432 and could be restrained by an antagonist, naltrexone(56, 57). This effect works in the central  
25 433 system but also involves HBO activating  $\mu$ - and K-opioid receptors in the spinal cord and  
26 434 releasing neuronal dynorphins(58). In murine models of arthritis, HBOT has also been shown to  
27 435 affect inflammatory pain by reducing mechanical hypersensitivity and inflammation(59). Patients  
28 436 with FM often experience degenerative changes in muscle, abnormal oxygen pressure, and lower  
29 437 muscle blood flow due to hypoxia(16, 60). Local ischemia makes the mitochondria need to  
30 438 produce higher levels of free radicals to induce apoptosis, reduce ATP synthesis and increase  
31 439 lactate concentration in the muscle, thus ultimately leading to muscle weakness and pain(61, 62).  
32 440 HBOT improves muscle oxygenation in FM, which can reduce the tissue lactate concentration and  
33 441 help maintain ATP levels, thus possibly preventing tissue damage in ischemic tissue(63). It raises  
34 442 the oxygen concentration in all tissues far above physiological levels to cause hyperoxia, which  
35 443 breaks the hypoxic-pain cycle in patients with FM(63). In addition, the high excitability of pain  
36 444 processing pathways in the brain and low activity of pain inhibition pathways may cause excessive  
37 445 pain in FM(64). Studies have shown that patients with FM have higher activity in the  
38 446 somatosensory cortex and lower activity in the frontal, medial frontal, cingulate gyrus, and  
39 447 cerebellar cortex than healthy subjects(65). HBOT has been shown to increase neurotrophic and  
40 448 nitric oxide levels, reduce oxidative stress, promote cell metabolism by enhancing the  
41 449 mitochondrial function of neurons and glial cells, and may even promote the production of  
42 450 endogenous neural stem cells(66). The specific mechanism of HBOT on FM needs to be further  
43 451 investigated.

44 452 The quality of evidence (pain relief of HBOT for FM) assessed using the GRADE system  
45 453 was moderate. There are inherently ethical and logistical difficulties in handling the sham-control  
46 454 in HBOT experiments. In two RCTs, the researchers did not use sham-control/placebo in the

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control group, which may lower the quality of the evidence. The heterogeneity of the outcome may be caused by the population and HBOT regimen. However, the larger effect (SMD > 0.8) may increase the quality of the evidence. Therefore, we have a moderate degree of confidence in our estimated effect. The true value may be close to the estimated value, but there is still a chance that they could be very different.

There are some limitations in the systematic review. The main limitation is that the small number of RCTs included may lead to an overall risk of bias or insufficient evidence. Second, HBOT protocols (the length of treatment and pressure parameters) have clinical heterogeneity, which may introduce bias to the results. Third, we only retrieved data from Chinese and English databases, which may limit the data availability or cause language bias. Finally, due to the small number of included studies and the heterogeneity, we did not conduct a subgroup analysis. Therefore, we cannot evaluate the efficacy of different HBOT regimens.

In conclusion, the present study shows that HBOT may have a good effect in improving pain, tender points, fatigue, multidimensional function, patient global, and sleep disturbance in FM, with reversible side effects. Low pressure (less than 2.0 ATA) may be beneficial to reduce adverse events in patients with FM. Further high-quality and large-sample RCTs should be carried out to further evaluate its efficacy and safety.

**Author contributors:** Conceptualization: CH, XXC, JHY. Funding Acquisition: CH. Formal Analysis: XXC. Investigation: CH. Writing-Original Draft Preparation: XXC, JHY, MZ, HM. Writing-Review & Editing: all the authors. All the authors fulfil the ICMJE criteria for authorship.

**Funding statement:** Key Research and Development Project of Sichuan Provincial Science and Technology Department (No. 2018SZ0082); 1·3·5 Project for Disciplines of excellence-Clinical Research Incubation Project, West China Hospital, Sichuan University (No. 2021HXFH063)

**Disclaimer:** The authors declare no financial relationships with any organizations that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval statement:** Not applicable.

**Competing interests:** None declared.

**Data sharing statement:** Data are available upon reasonable request.

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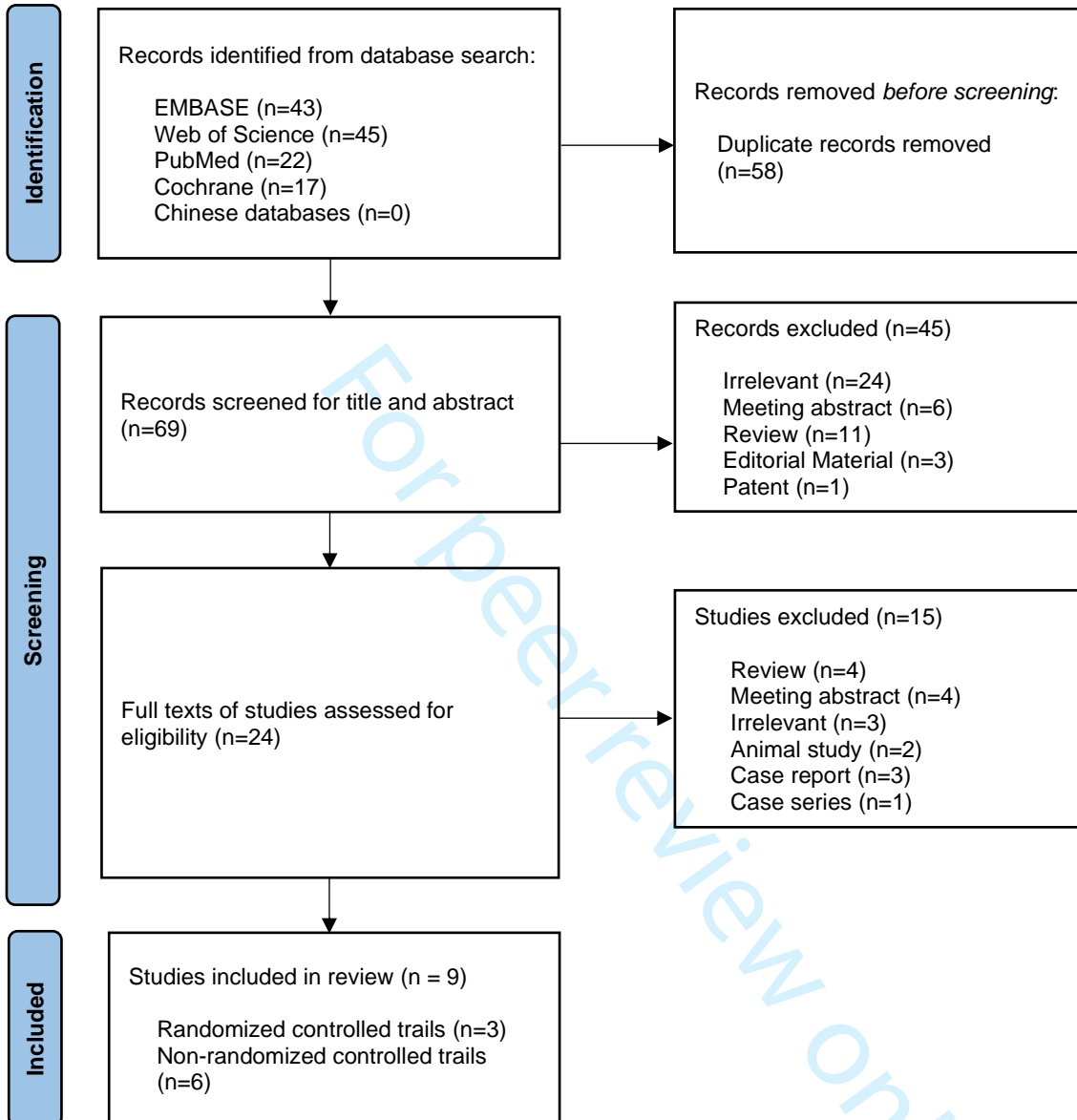
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665 **Figure 1. PRISMA flowchart.**

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667 **Figure 2. Risk of bias graph for the included randomized controlled trials across five domains.**

668 The red circle indicates a high risk of bias within that domain for a given study, the yellow circles  
669 indicate an unclear risk of bias, and the green circles indicate a low risk of bias.

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671 **Figure 3. Forest plot of pain relief.**

**Identification of studies via databases**



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|  | Yildiz 2004 | Izquierdo 2020 | Hadanny 2018 |   |
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|  | ?           | +              | ?            | Random sequence generation (selection bias)               |
|  | ?           | +              | ?            | Allocation concealment (selection bias)                   |
|  | ?           | ?              | -            | Blinding of participants and personnel (performance bias) |
|  | +           | +              | +            | Blinding of outcome assessment (detection bias)           |
|  | +           | +              | +            | Incomplete outcome data (attrition bias)                  |
|  | +           | +              | +            | Selective reporting (reporting bias)                      |
|  | ?           | ?              | ?            | Other bias  |

Risk of bias graph for the included randomized controlled trials across five domains. The red circle indicates a high risk of bias within that domain for a given study, the yellow circles indicate an unclear risk of bias, and the green circles indicate a low risk of bias.

288x211mm (38 x 38 DPI)



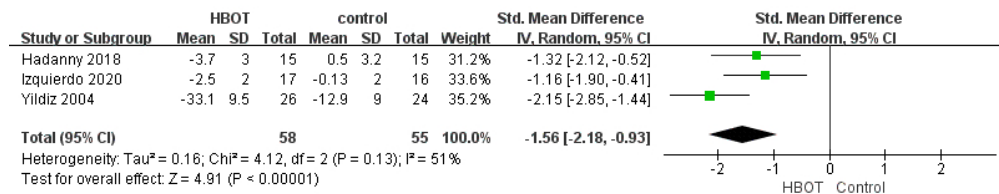


Figure 3. Forest plot of pain relief.

282x56mm (72 x 72 DPI)

## Pubmed

| Search | Query   | Results       | Time     |
|--------|---|---------------|----------|
| #7     | Search: ((hyperbaric oxygenation [MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract]))) AND ((fibromyalgia[MeSH Terms]) OR ("fibromyalgia" OR "fibrositic nodule" OR "fibrositic nodule" OR "fibrositis" OR "fibrositis syndrome" OR "myalgia, fibro")) | <u>22</u>     | 20:08:04 |
| #6     | Search: "fibromyalgia" OR "fibrositic nodule" OR "fibrositic nodule" OR "fibrositis" OR "fibrositis syndrome" OR "myalgia, fibro"   | <u>13,579</u> | 20:06:54 |
| #5     | Search: (hyperbaric oxygenation[MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract]))  | <u>18,499</u> | 20:04:55 |
| #4     | Search: fibromyalgia[MeSH Terms]  | <u>9,569</u>  | 20:04:01 |
| #3     | Search: (hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract])  | <u>15,251</u> | 20:02:45 |
| #2     | Search: hyperbaric oxygenation[MeSH Terms]  | <u>12,570</u> | 20:02:10 |

| Search | Actions | Details | Query  | Results       | Time     |
|--------|---------|---------|--|---------------|----------|
| #7     | ...     | >       | Search: ((((((fibromyalgia) OR (fibrositic nodule)) OR (fibrositic nodule) OR (fibrositis) OR (fibrositis syndrome)) OR (myalgia, fibro)) OR (fibromyalgia[MeSH Terms])) AND ((hyperbaric oxygenation[MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract])))) | <u>22</u>     | 20:08:04 |
| #6     | ...     | >       | Search: ((((((fibromyalgia) OR (fibrositic nodule)) OR (fibrositic nodule) OR (fibrositis) OR (fibrositis syndrome)) OR (myalgia, fibro))  | <u>13,579</u> | 20:06:54 |
| #5     | ...     | >       | Search: (hyperbaric oxygenation[MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract]))   | <u>18,499</u> | 20:04:55 |
| #4     | ...     | >       | Search: fibromyalgia[MeSH Terms]   | <u>9,569</u>  | 20:04:01 |
| #3     | ...     | >       | Search: (hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract])   | <u>15,251</u> | 20:02:45 |
| #2     | ...     | >       | Search: hyperbaric oxygenation[MeSH Terms]   | <u>12,570</u> | 20:02:10 |

## EMBASE

Database(s): Embase

Search Strategy:

#

Searches

Results

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'hyperbaric oxygen therapy'/exp

18807

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'high pressure oxygen':ab,ti OR 'high tension o2':ab,ti OR 'high tension oxygen':ab,ti OR

'hyperbaric medicine':ab,ti OR 'hyperbaric o2':ab,ti OR 'hyperbaric oxygen':ab,ti OR 'hyperbaric oxygenation':ab,ti OR 'hyperbaric oxygenisation':ab,ti OR 'hyperbaric oxygenization':ab,ti OR 'oxygen, hyperbaric':ab,ti OR 'hbot':ab,ti

13020

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1 OR 2

20223

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'fibromyalgia'/exp

21352

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'fibromyalgia':ab,ti OR 'fibrositic nodule':ab,ti OR 'fibrositis':ab,ti OR 'fibrositis syndrome':ab,ti OR 'myalgia, fibro':ab,ti

17507

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22891

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| <input type="checkbox"/> History | Save   Delete   Print view   Export   Email   | Combine > | using <input checked="" type="radio"/> And <input type="radio"/> Or | <input type="button" value="Collapse"/> |
|----------------------------------|---|-----------|---|---|
| <input type="checkbox"/> #7      | #3 AND #6   |           |   | 43                                      |
| <input type="checkbox"/> #6      | #4 OR #5  |           |   | 22,891                                  |
| <input type="checkbox"/> #5      | 'fibromyalgia':ab,ti OR 'fibrositic nodule':ab,ti OR 'fibrositis':ab,ti OR 'fibrositis syndrome':ab,ti OR 'myalgia, fibro':ab,ti  |           |   | 17,507                                  |
| <input type="checkbox"/> #4      | 'fibromyalgia'/exp  |           |   | 21,352                                  |
| <input type="checkbox"/> #3      | #1 OR #2  |           |   | 20,223                                  |
| <input type="checkbox"/> #2      | 'high pressure oxygen':ab,ti OR 'high tension o2':ab,ti OR 'high tension oxygen':ab,ti OR 'hyperbaric medicine':ab,ti OR 'hyperbaric o2':ab,ti OR 'hyperbaric oxygen':ab,ti OR 'hyperbaric oxygenation':ab,ti OR 'hyperbaric oxygenisation':ab,ti OR 'hyperbaric oxygenization':ab,ti OR 'oxygen, hyperbaric':ab,ti OR 'hbot':ab,ti |           |   | 13,020                                  |
| <input type="checkbox"/> #1      | 'hyperbaric oxygen therapy'/exp   |           |   | 18,807                                  |

**Web of Science (1900-present)**

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Topic=("fibromyalgia" OR "fibrositic nodule" OR "fibrositis" OR "fibrositis syndrome" OR "myalgia, fibro")

31305

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Topic=(Hyperbaric OR HBOT)

28136

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1 AND 2

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0/3 Combine Sets Export Clear History

|                          |   |  |        |                           |                |                |                |
|--------------------------|---|--|--------|---------------------------|----------------|----------------|----------------|
| <input type="checkbox"/> | 3 | #2 AND #1  | 45     | <span>Add to query</span> | <span>🔗</span> | <span>✎</span> | <span>🔔</span> |
| <input type="checkbox"/> | 2 | (TS=(Hyperbaric)) OR TS=(HBOT)   | 28,136 | <span>Add to query</span> | <span>🔗</span> | <span>✎</span> | <span>🔔</span> |
| <input type="checkbox"/> | 1 | (((TS=(fibromyalgia)) OR TS=(fibrositic nodule)) OR TS=(fibrositis)) OR TS=(fibrositis syndrome)) OR TS=(myalgia, fibro) | 31,305 | <span>Add to query</span> | <span>🔗</span> | <span>✎</span> | <span>🔔</span> |

## Cochrane

### ID Search Hits

#1 MeSH descriptor: [Hyperbaric Oxygenation] explode all trees 431

#2 hyperbaric or hbot:ti,ab,kw (Word variations have been searched) 3504

#3 MeSH descriptor: [Fibromyalgia] explode all trees 1598

#4 "fibromyalgia" OR "fibrositic nodule" OR "fibrositis" OR "fibrositis syndrome":ti,ab,kw 3469

#5 #1 OR #2 3504

#6 #3 OR #4 3469

#7 #5 AND #6 17

|     |   |        |             |
|-----|---|--------|-------------|
| #1  | MeSH descriptor: [Hyperbaric Oxygenation] explode all trees | MeSH   | 431         |
| #2  | (hyperbaric):ti,ab,kw                                       | S      | Limits 3501 |
| #3  | (hbot):ti,ab,kw   | S      | Limits 264  |
| #4  | #3 OR #2  | Limits | 3504        |
| #5  | MeSH descriptor: [Fibromyalgia] explode all trees           | MeSH   | 1598        |
| #6  | (fibromyalgia):ti,ab,kw                                     | S      | Limits 3427 |
| #7  | (fibrositic nodule):ti,ab,kw                                | S      | Limits 0    |
| #8  | (fibrositis):ti,ab,kw                                       | S      | Limits 63   |
| #9  | (fibrositis syndrome):ti,ab,kw                              | S      | Limits 10   |
| #10 | #1 OR #4  | Limits | 3504        |
| #11 | #6 OR #7 OR #8 OR #9  | Limits | 3469        |
| #12 | #5 OR #11   | Limits | 3469        |
| #13 | #10 AND #12   | Limits | 17          |

## CNKI (Chinese database)

(篇文摘=高压氧) AND (篇文摘=纤维肌痛)

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## VIP (Chinese database)

(题名或关键词=高压氧) AND (题名或关键词=纤维肌痛)

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## WANFANG (Chinese database)

题名或关键词: (高压氧 and 纤维肌痛)

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# PRISMA 2020 Checklist

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| Section and Topic             | Item # | Checklist item   | Location where item is reported |
|-------------------------------|--------|--|---------------------------------|
| <b>TITLE</b>                  |        |  | 1                               |
| Title                         | 1      | Identify the report as a systematic review.  |                                 |
| <b>ABSTRACT</b>               |        |  |                                 |
| Abstract                      | 2      | See the PRISMA 2020 for Abstracts checklist.   | 2                               |
| <b>INTRODUCTION</b>           |        |  |                                 |
| Rationale                     | 3      | Describe the rationale for the review in the context of existing knowledge.  | 2                               |
| Objectives                    | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses.   | 3                               |
| <b>METHODS</b>                |        |  |                                 |
| Eligibility criteria          | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.  | 4                               |
| Information sources           | 6      | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.  | 4                               |
| Search strategy               | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used.   | 4                               |
| Selection process             | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.                     | 4                               |
| Data collection process       | 9      | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 4                               |
| Data items                    | 10a    | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.                        | 4                               |
|                               | 10b    | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.   | 4                               |
| Study risk of bias assessment | 11     | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.                                    | 5                               |
| Effect measures               | 12     | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.  | 5                               |
| Synthesis methods             | 13a    | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).   | 4                               |
|                               | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.  | 6                               |
|                               | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses.   | 7                               |
|                               | 13d    | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.  | 6                               |
|                               | 13e    | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).   | 6                               |
|                               | 13f    | Describe any sensitivity analyses conducted to assess robustness of the synthesized results.   | 6                               |
| Reporting bias assessment     | 14     | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).  | 5                               |
| Certainty                     | 15     | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.  | 6                               |



## PRISMA 2020 Checklist

| Section and Topic                              | Item # | Checklist item   | Location where item is reported |
|--|--------|--|---------------------------------|
| assessment                                     |        |  |                                 |
| <b>RESULTS</b>                                 |        |  |                                 |
| Study selection                                | 16a    | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.   | 6-7                             |
|  | 16b    | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.  | 6                               |
| Study characteristics                          | 17     | Cite each included study and present its characteristics.  | 7                               |
| Risk of bias in studies                        | 18     | Present assessments of risk of bias for each included study.   | 8-9                             |
| Results of individual studies                  | 19     | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.   | 10-11                           |
| Results of syntheses                           | 20a    | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.   | 10-11                           |
|  | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 10-11                           |
|  | 20c    | Present results of all investigations of possible causes of heterogeneity among study results.   | 10-11                           |
|  | 20d    | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.   | 10-11                           |
| Reporting biases                               | 21     | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.  | 8-9                             |
| Certainty of evidence                          | 22     | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.  | 11-12                           |
| <b>DISCUSSION</b>                              |        |  |                                 |
| Discussion                                     | 23a    | Provide a general interpretation of the results in the context of other evidence.  | 13                              |
|  | 23b    | Discuss any limitations of the evidence included in the review.  | 15                              |
|  | 23c    | Discuss any limitations of the review processes used.  | 15                              |
|  | 23d    | Discuss implications of the results for practice, policy, and future research.   | 13-14                           |
| <b>OTHER INFORMATION</b>                       |        |  |                                 |
| Registration and protocol                      | 24a    | Provide registration information for the review, including register name and registration number, or state that the review was not registered.   | 4                               |
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|  | 24c    | Describe and explain any amendments to information provided at registration or in the protocol.  | 4                               |
| Support  | 25     | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.  | 15                              |
| Competing interests                            | 26     | Declare any competing interests of review authors.   | 15                              |
| Availability of data, code and other materials | 27     | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.   | 15                              |



## PRISMA 2020 Checklist

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10.1136/bmj.n71

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## Efficacy and Safety of Hyperbaric Oxygen Therapy for Fibromyalgia: A Systematic Review and Meta-analysis

|                                 |   |
|---------------------------------|---|
| Journal:                        | <i>BMJ Open</i>   |
| Manuscript ID                   | bmjopen-2022-062322.R2  |
| Article Type:                   | Original research   |
| Date Submitted by the Author:   | 19-Dec-2022   |
| Complete List of Authors:       | Chen, Xinxin; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine<br>You, JiuHong; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine<br>Ma, Hui; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine<br>Zhou, Mei; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine<br>Huang, Cheng; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, Key Laboratory of Rehabilitation Medicine in Sichuan Province, West China Hospital |
| <b>Primary Subject Heading</b>: | Rheumatology  |
| Secondary Subject Heading:      | Complementary medicine, Public health, Rehabilitation medicine  |
| Keywords:                       | Rheumatology < INTERNAL MEDICINE, PAIN MANAGEMENT, Rehabilitation medicine < INTERNAL MEDICINE  |
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# 1 **Efficacy and Safety of Hyperbaric Oxygen Therapy for Fibromyalgia:**

## 2 **A Systematic Review and Meta-analysis**

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## ABSTRACT

**Objective** To investigate the efficacy and safety of hyperbaric oxygen therapy (HBOT) for fibromyalgia (FM).

**Design** A systematic review and meta-analysis.

**Data sources** PubMed, EMBASE, Cochrane Library, Web of Science, VIP (China Science and Technology Journal Database), CNKI (China National Knowledge Infrastructure), and WanFang database were searched from December 30, 2020, until October 22, 2022.

**Eligibility criteria** We included clinical trials (randomized controlled and nonrandomized controlled trials) of HBOT for FM.

**Data extraction and synthesis** Two researchers independently screened the literature, extracted data, and evaluated the quality of the included studies, with disagreements resolved by a third researcher. The Cochrane Collaboration checklists and the Methodological Index for Nonrandomized Studies were used to assess the risk of bias. Meta-analysis was performed by RevMan 5.4.1 software. Random effect models were used for meta-analysis.

**Results** Nine studies were included in this review, with a total of 288 patients. For pain assessment, we combined the results of the Visual Analogue Scale and Widespread Pain Index. The results showed that HBOT could relieve the pain of FM patients compared with the control intervention [SMD=-1.56, 95% CI (-2.18, -0.93),  $P<0.001$ ,  $I^2=51\%$ ]. Most included studies reported that HBOT ameliorated tender points, fatigue, multidimensional function, patient global, and sleep disturbance in FM. Adverse events occurred in 44 of 185 patients (23.8%). Twelve patients (6.5%) withdrew because of adverse reactions. No serious adverse events or complications were observed.

**Conclusions** HBOT might have a positive effect in improving pain, tender points, fatigue, multidimensional function, patient global, and sleep disturbance in FM, with reversible side effects. Low pressure (less than 2.0 ATA) may be beneficial to reduce adverse events in FM. Further studies should be carried out to evaluate the optimal protocol of HBOT in FM.

**PROSPERO registration number** CRD42021282920.

**Keywords** hyperbaric oxygen therapy, fibromyalgia, safety, efficacy, systematic review, meta-analysis.

### Strengths and limitations of this study

- Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was used to assess the quality of evidence.
- Rigorous methodology was used in this study, including explicit eligibility criteria, extensive database search, study selection by two reviewers working independently, and risk of bias

67 assessment.

68 • Adverse events in hyperbaric oxygen therapy are negative outcomes that should be avoided, so it  
69 is important that we assess the risk of such effects to better understand the appropriate protocol  
70 regarding hyperbaric oxygen therapy.

71 • The small number of randomized controlled trials included in the studies may lead to an overall  
72 risk of bias or insufficient evidence.

## 74 1. Introduction

75 Fibromyalgia (FM) is an incurable common syndrome with unclear origin(1). It is  
76 characterized by chronic pain at multiple tender points lasting for more than three months and is  
77 usually accompanied by clinical manifestations such as fatigue, sleep disturbance, cognitive  
78 dysfunction, and depressive symptoms(2, 3). It is estimated that 2-8% of the population is affected  
79 by FM worldwide(4). FM is more frequent in females, with a female-to-male ratio of 9:1(5).

80 The cause of FM syndrome is not yet fully understood, while the symptoms may be induced  
81 by infection, diabetes, rheumatic diseases, traumatic brain injury, or mental trauma(4, 6). Certain  
82 studies have reported a history of childhood sexual abuse in some patients with FM(7, 8).  
83 Currently, treatment options mainly include pharmacological therapies, physical exercise,  
84 meditative exercise therapy, and behavioral therapy(9-12). However, these methods only  
85 temporarily or moderately alleviate pain symptoms and often produce unbearable adverse effects  
86 that interfere with the patient's quality of life and reduce their compliance(13). Therefore, there is  
87 a need for new and effective chronic pain treatments that can be tolerated by patients without  
88 significant adverse effects.

89 Accumulating evidence suggests that hyperbaric oxygen therapy (HBOT) is a noninvasive  
90 modality with lasting efficacy that can be used to treat FM(14-17). HBOT is conducted by  
91 intermittently breathing 100% oxygen in a pressure chamber above one atmospheric absolute  
92 pressure (ATA). HBOT can increase the partial pressure of oxygen in alveoli, leading to a  
93 favorable increase in dissolved oxygen in plasma(18). The increase in pressure and oxygen causes  
94 more dissolved oxygen to be delivered to the tissue through the blood, which oxygenates the  
95 ischemic tissue(19). HBOT has shown strong anti-inflammatory potential by reducing the  
96 activation of glial cells and inflammatory mediators so that it could relieve pain under different  
97 chronic pain conditions (14). The anti-inflammatory effects of HBOT also correct associated  
98 abnormal brain activities and alter abnormal glial function, which may benefit FM patients(20).  
99 The increase in oxygen concentration caused by HBOT has been shown to improve the  
100 mitochondrial dysfunction of FM patients, leading to changes in brain metabolism and glial  
101 function, and may reduce the abnormal brain activities associated with FM(20). Although some  
102 studies have reported a positive effect of HBOT on FM, HBOT has not been recommended by  
103 guidelines as a complementary treatment for FM due to the lack of sufficient evidence(21, 22).

104 Mascarenhas(23) proposed that HBOT for the management of FM was moderate evidence in  
105 a systematic review. However, only two studies on HBOT for FM were included, and there was no  
106 meta-analysis. In addition, only two outcome measures (pain and quality of life) were investigated.  
107 To better understand the overall efficacy and safety of HBOT for FM, we conducted a systematic  
108 review and meta-analysis with more studies to investigate HBOT in the treatment of the inner  
109 Core Outcome Set of FM symptoms (pain, tenderness, fatigue, multidimensional function, patient  
110 global, sleep disturbance)(24) and estimate its safety.

111

## 2. Methods

113 This study was conducted following the Preferred Reporting Items for Systematic Reviews  
114 and Meta-Analyses (PRISMA) statement(25). The protocol for this study is available online  
115 (PROSPERO trial registration number: CRD42021282920).

116

### 2.1. Search strategy

118 A literature search was conducted to identify all articles involving the use of hyperbaric  
119 oxygen to treat FM. The search strategy is shown in Supplementary appendix A. PubMed,  
120 EMBASE, Web of Science, Cochrane Library, VIP (China Science and Technology Journal  
121 Database), CNKI (China National Knowledge Infrastructure), and WanFang database were  
122 searched from December 30, 2020, until October 22, 2022. The search included MeSH and free  
123 text terms such as “hyperbaric oxygen therapy”, “fibromyalgia” and synonyms.

124

### 2.2. Inclusion and exclusion criteria

126 We considered including all available information for systematic review due to the lack of  
127 data on this disease and the suspected lack of randomized controlled trials (RCTs). The criteria for  
128 inclusion were as follows: 1) study design: RCTs and non-RCTs; 2) subjects: FM patients  
129 conformed to the 2016 American College of Rheumatology (ACR) diagnostic criteria(26) [i.e.  
130 They met the following criteria: generalized pain for at least three months and a widespread pain  
131 index (WPI)  $\geq 7$  and symptom severity scale (SSS)  $\geq 5$  or a WPI of 4–6 and a SSS score  $\geq 9$ ]; 3)  
132 the intervention: patients in the experimental group received HBOT as the intervention measure,  
133 and patients in the control group received conventional treatment or nothing. The conventional  
134 treatment was any pharmacological or nonpharmacological therapy other than HBOT. The course  
135 of treatment and parameters were unlimited. 4) outcome indicators: the inner Core Outcome Set of  
136 FM symptoms (pain, tenderness, fatigue, multidimensional function, patient global, sleep  
137 disturbance) and adverse events. The exclusion criteria were as follows: animal studies, reviews,  
138 duplicate publications, irrelevant studies, editorial materials, patients, case reports, or meeting  
139 abstracts.

140

### 2.3. Literature screening and data collection

142 Two reviewers (JHY and HM) independently assessed the eligibility of each article.  
143 Duplicate articles were eliminated. Irrelevant articles were excluded by reading the title and  
144 abstract, and then the full text was read to further screen out articles that met the inclusion criteria.  
145 Articles without full text or data were excluded after three or more attempts to email the lead  
146 author and obtain no response. The decision to include each article was made independently  
147 according to the inclusion criteria, with disagreements resolved by a third reviewer (XXC).  
148 Reviewers followed PRISMA criteria for systematic evaluation.

149

150 A predesigned form was used for information extraction. The content included the article’s  
151 basic information (author, year of publication, title); research types; patient demographics (age,  
152 gender); intervention and control measures (duration, frequency, sessions, follow-up); outcome  
153 indicators; the data of results; and indicators that reflected research quality. Data collection was  
154 completed independently by two researchers (JHY and HM) and checked with each other. In case  
of disagreement, a third researcher (XXC) assisted in resolving the disagreement.

155

## 156 **2.4. Types of outcome measures**

157 The inner Core Outcome Set of FM symptoms suggested by Mease et al.(24) can be  
158 quantitatively or qualitatively analysed. The primary outcome measure was pain, and the  
159 secondary outcome measures included tenderness, fatigue, multidimensional function, patient  
160 global, sleep disturbance, and adverse events.

161

### 162 2.4.1. Pain and tenderness

163 Assessment methods included the Pain Visual Analogue Scale (VAS), number of tender  
164 points, pain threshold, and Widespread Pain Index (WPI).

165

### 166 2.4.2. Multidimensional function

167 Assessment methods included the Fibromyalgia Impact Questionnaire (FIQ) and Quality of  
168 Life-related questionnaires (SF-36).

169

### 170 2.4.3. Fatigue

171 Assessment methods of fatigue included the Fatigue Severity Scale (FSS), Functional  
172 Assessment of Chronic Illness Therapy Fatigue (FACIT fatigue) scale, Fatigue VAS, and CR-10  
173 Borg Scale.

174

### 175 2.4.4. Patient global

176 The Patient Global Impression of Change (PGIC) was used to assess this outcome measure.

177

### 178 2.4.5. Sleep disturbance

179 Assessment methods included the Jenkins Sleep Scale (JSS) and Pittsburgh Sleep Quality  
180 Index (PSQI).

181

### 182 2.4.6. Adverse events

183 This indicator included adverse events (AEs), withdrawals due to AEs, and complications.

184

## 185 **2.5. Risk of bias assessment**

186 Reviewers assessed the quality of the included articles using the Cochrane Collaboration  
187 checklists(27) for three RCTs and the Methodological Index for Nonrandomized Studies  
188 (MINORS)(28) for six non-RCTs. The Cochrane checklists assessed selection bias,  
189 implementation bias, measurement bias, attrition bias, reporting bias, and other bias. In the  
190 Cochrane ROB tool, the risk of bias was classified as "low risk," "unclear," and "high risk".  
191 Review Manager version 5.4.1 was used to generate the risk of bias graph of the three RCTs. The  
192 MINORS checklists included twelve items (0-24 scores) for comparative studies and eight items  
193 (0-16 scores) for noncomparative studies. The score for each item was 0 (not reported), 1 (reported  
194 but inadequate), or 2 (reported and adequate). Comparative studies scoring > 19 or  
195 noncomparative studies scoring > 12 were considered high quality. The quality of the included  
196 studies was assessed independently by two reviewers (JHY and HM). Again, any controversy in  
197 the assessment was resolved through discussion with a third reviewer (XXC).

198

199

200

## 199 **2.6. Statistical analysis**

200 RevMan 5.4.1 software provided by the Cochrane Collaboration was used to conduct a meta-  
201 analysis. The standardized mean difference (SMD) and its 95% CI were used as the analysis  
202 statistics because different studies use different rating instruments to measure the same  
203 outcome(29). Forest plot tests were conducted, and meta-regression analysis was used to test  
204 heterogeneity. The chi-square test was used to analyse whether there was statistical heterogeneity  
205 among the results of each study. This study used the random effects model for meta-analysis  
206 because the random effects meta-analysis allowed for differences (treatment areas, concomitant  
207 treatments, and HBOT regimen) in treatment effects among different studies(30).

## 209 **2.7. Grade the quality of evidence**

210 Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was  
211 used to grade the quality of the evidence(31). The risk of bias, inconsistency, indirectness,  
212 imprecision, and publication bias were assessed. The quality of evidence was rated 'high',  
213 'moderate', 'low', or 'very low'.

## 215 **2.8. Patient and public involvement**

216 Patients and the public were not involved in this study.

## 218 **3. Results**

### 219 **3.1. Characteristics of the included studies**

220 A total of 69 eligible articles were obtained by a literature search. After screening, nine  
221 studies (three RCTs and six non-RCTs) met the inclusion criteria(32-40). The flow diagram is  
222 shown in Figure 1. A total of 288 patients were included in this study. Table 1 shows the  
223 characteristics of the included articles.

224



225 **Table 1. Characteristics of the included articles.**

| Author,<br>year           | Patients (N) |         | Intervention (HBOT)     |                     | Comparison              | Outcome<br>measures   | Adverse events and the number<br>of patients  |              | Study<br>design |
|---------------------------|--------------|---------|-------------------------|---------------------|-------------------------|---|---|--------------|-----------------|
|                           | Intervention | Control | protocol                | sessions/<br>length |                         |   | Adverse events  | Patients (N) |                 |
| Yildiz<br>2004<br>(40)    | 26           | 24      | 90 mins,2.4ATA,<br>5d/w | 15/<br>3 weeks      | 90 mins,1ATA,<br>5d/w   | Number of<br>tender points,<br>Pain threshold,<br>Pain VAS                              | -   | -            | RCT             |
| Hadanny<br>2018<br>(38)   | 15           | 15      | 90 mins,2ATA,<br>5d/w   | 60/<br>12 weeks     | Psychotherapy           | WPI, FIQ,<br>SF-36  | mild barotrauma<br>headache   | 12<br>1      | RCT             |
| Izquierdo<br>2020<br>(33) | 17           | 16      | 90mins,1.45ATA,<br>5d/w | 40/<br>8 weeks      | Conventional<br>therapy | VAS,<br>Pain threshold,<br>CR-10 Borg<br>scale  | -   | -            | RCT             |
| Efrati<br>2015<br>(39)    | 27           | 26      | 90 mins,2ATA,<br>5d/w   | 40/<br>8 weeks      | No treatment            | Number of<br>tender points,<br>Pain threshold,<br>FIQ, SF-36                            | mild barotrauma<br>dizziness,<br>claustrophobia<br>and inability to<br>adjust<br>ear pressure by<br>“ear pumping” | 13<br>5      | NCT             |
| Guggino<br>2020<br>(34)   | 22           | 14      | 90 mins,2ATA,<br>5d/w   | 40/<br>8 weeks      | No treatment            | Number of<br>tender points,<br>Pain VAS,<br>Fatigue VAS,<br>WPI, FACIT<br>fatigue, PSQI | -   | -            | NCT             |
| Curtis<br>2021<br>(32)    | 9            | 8       | 90 mins,2ATA,<br>5d/w   | 40/<br>8 weeks      | Conventional<br>therapy | FIQR, FSS,<br>JSS,<br>PGIC, Fatigue<br>VAS  | mild middle-ear<br>barotrauma<br>new-onset<br>myopia  | 3<br>4       | NCT             |



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| 4  |        |    |   |                 |                |   |  |                          |   |     |
| 5  | Casale | 25 | - | 91 mins,2.4ATA  | 20/<br>4 weeks | - | Neuromuscular<br>efficiency              | side effects             | 2 | NCT |
| 6  | 2019   |    |   |                 |                |   |  |                          |   |     |
| 7  | (35)   |    |   |                 |                |   |  |                          |   |     |
| 8  | Bosco  | 12 | - | 90 mins,2ATA,   | 20/<br>4 weeks | - | WPI                                      | -                        | - | NCT |
| 9  | 2019   |    |   | 5d/w            |                |   |  |                          |   |     |
| 10 | (36)   |    |   |                 |                |   |  |                          |   |     |
| 11 |        |    |   |                 |                |   |  | mild, reversible         |   |     |
| 12 | Atzeni | 32 | - | 90 mins,2.5ATA, | 20/<br>4 weeks | - | Pain VAS,<br>FACIT, PSQI,<br>FIQR, SF-36 | middle ear<br>barotrauma | 2 | NCT |
| 13 | 2019   |    |   | 3d/w            |                |   |  | dizziness                | 1 |     |
| 14 | (37)   |    |   |                 |                |   |  | claustrophobia           | 1 |     |
| 15 |        |    |   |                 |                |   |  |                          |   |     |

226 Abbreviations: ATA, atmospheric absolute pressure; d/w, days/week; VAS, Visual Analogue Scale; WPI, Widespread Pain Index; FIQ, Fibromyalgia Impact  
 227 Questionnaire; SF-36, Quality of Life-related questionnaires; FACIT fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; PSQI, Pittsburgh  
 228 Sleep Quality Index; FIQR, Revised Fibromyalgia Impact Questionnaire; FSS, Fatigue Severity Scale; JSS, Jenkins Sleep Scale; PGIC, Patient Global Impression of  
 229 Change; RCT, randomized controlled trial; NCT, nonrandomized controlled trial.

### 231 3.2. Quality assessment

232 Figure 2 shows the risk of bias graph of the three RCTs according to the Cochrane ROB tool.  
233 Of the RCTs included, studies by Yildiz et al.(40) and Hadanny et al(38). had an unclear risk of  
234 selection bias because of the lack of specific randomization methods and no indication of  
235 allocation concealment. All RCTs were judged to have an unclear or high risk of performance bias  
236 because researchers did not adopt blinding. All RCTs were at low risk for detection bias and  
237 attrition bias. However, the risk of reporting bias and other bias in all RCTs were unclear, mainly  
238 due to the lack of follow-up. Table 2 shows the quality assessment of the six non-RCTs. The  
239 average MINORS scores for noncomparative and comparative studies were 9.7 and 19.7,  
240 respectively. Studies by Efrati et al.(39) and Curtis et al.(32) were considered high quality. In non-  
241 RCTs, lack of bias assessment, study size calculation, and follow-up were the most common  
242 reasons for low MINORS scores.

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**Table 2. Quality assessment of the included nonrandomized controlled trials using the Methodological Index for Nonrandomized Studies (MINORS).**

| Assessment  | Efrati 2015 | Guggino 2020 | Curtis 2021 | Casale 2019 | Bosco 2019 | Atzeni 2019 |
|---|-------------|--------------|-------------|-------------|------------|-------------|
| 1. A clearly stated aim                                 | 2           | 2            | 2           | 2           | 2          | 2           |
| 2. Inclusion of consecutive patients                    | 2           | 2            | 2           | 2           | 2          | 2           |
| 3. Prospective collection of data                       | 2           | 2            | 2           | 2           | 2          | 2           |
| 4. Endpoints appropriate to the aim of the study        | 2           | 2            | 2           | 2           | 2          | 2           |
| 5. Unbiased assessment of the study endpoint            | 2           | 0            | 1           | 1           | 0          | 0           |
| 6. Follow-up period appropriate to the aim of the study | 0           | 0            | 2           | 0           | 2          | 0           |
| 7. Loss to follow up less than 5%                       | 0           | 0            | 2           | 0           | 0          | 0           |
| 8. Prospective calculation of the study size            | 2           | 2            | 0           | 0           | 0          | 2           |
| 9. An adequate control group                            | 2           | 2            | 2           | -           | -          | -           |
| 10. Contemporary groups                                 | 2           | 2            | 2           | -           | -          | -           |
| 11. Baseline equivalence of groups                      | 2           | 2            | 2           | -           | -          | -           |
| 12. Adequate statistical analyses                       | 2           | 2            | 2           | -           | -          | -           |
| Total score   | 20          | 18           | 21          | 9           | 10         | 10          |

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### 278 3.3. Efficacy of HBOT

279 Because of the small number of studies, insufficient data that could be pooled, and  
280 heterogeneity among different study types, only pain relief from three RCTs was included in the  
281 meta-analysis, and the other outcome indicators were only analysed descriptively.

#### 283 3.3.1. Pain relief

284 Seven studies (three RCTs and four non-RCTs)(33, 34, 36-40) reported that HBOT alleviated  
285 the pain level of FM, as documented by the decrease in rating scales related to pain. We conducted  
286 a meta-analysis on pain relief of three RCTs(33, 38, 40). For pain assessment, we combined the  
287 results of VAS and WPI. Meta-analysis of a random effect model showed that the pain relief in the  
288 HBOT group was better than that in the control group [SMD=-1.56, 95% CI (-2.18, -0.93),  
289  $P<0.001$ ,  $I^2=51%$ ] (Figure 3).

#### 291 3.3.2. Tenderness

292 Three studies(34, 39, 40) reported that HBOT reduced the number of tender points in FM.  
293 Jeschonneck et al.(41) found that vasoconstriction in patients with FM occurred in the skin above  
294 the tender point. This confirmed that FM syndrome was associated with local hypoxia of the skin  
295 covering the tender points. Lund et al.(42) proposed that in FM with primary aetiology, muscle  
296 oxygenation was abnormal or low, at least in the muscle trigger point region, as recorded by  
297 oxygen multipoint electrodes on the muscle surface. HBOT could break the vicious cycle of pain-  
298 hypoxia because it increased the pain threshold to reduce the number of tender points in patients  
299 with FM(40).

#### 301 3.3.3. Multidimensional function

302 Three studies(32, 38, 39) reported that HBOT improved FM-related functional impairment  
303 and overall symptoms, as documented by the decreased score of the FIQ or FIQ-R questionnaire.  
304 These studies may support the use of HBOT to reduce the effects of FM on global symptoms and  
305 functional activities. Studies by Hadanny et al.(38), Efrati et al.(39), and Atzeni et al.(37) reported  
306 the SF-36, which was used to assess quality of life. All three studies showed that HBOT could  
307 effectively improve the quality of life of FM. In addition, Hadanny et al.(38) have shown that  
308 improvements in quality of life with FM were associated with improvements in brain performance  
309 parameters seen in brain function (SPECT) and structure (MRI-DTI) imaging. This may be  
310 because HBOT can improve brain function and microstructure by inducing neural plasticity in  
311 humans(43, 44).

#### 313 3.3.4. Fatigue

314 Three studies(33, 34, 37) showed that HBOT could reduce fatigue in FM patients, while  
315 Curtis et al.(32) reported that HBOT had no significant effect on fatigue in FM. Studies have  
316 shown that HBOT reduced fatigue in chronic fatigue syndrome(45), which was attributed to its  
317 ability to reduce reactive oxygen species and acid-lactic acid levels, as well as muscle fatigue after  
318 exercise(46). HBOT alleviated fatigue in FM patients, possibly because HBOT increased oxygen  
319 supply to the musculoskeletal system, thereby activating cellular activity and promoting the  
320 metabolism of fatigue-related substances(47). Clinical studies have shown that increased plasma  
321 proinflammatory cytokine levels trigger symptoms such as fatigue, fever, sleep, pain, and myalgia

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3 322 in FM patients(48). HBOT can improve FM symptoms by reducing the upregulation of  
4 323 proinflammatory cytokines in FM. Atzen et al.(37) proposed that the fatigue of FM was only  
5 324 improved after 20 treatments, indicating that the number of treatments would affect the efficacy of  
6 325 HBOT. In Curtis's study(32), the lack of an effect of HBOT on fatigue may be attributed to  
7 326 baseline differences in the small sample size. In addition, Casale et al.(35) found that HBO did not  
8 327 directly increase FM muscle strength or alter muscle fiber content to alleviate fatigue but  
9 328 increased the ability of the central motor command to generate the same effort with fewer  
10 329 recruited fibers.  
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### 331 **3.3.5. Patient global**

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16 332 Only one study(32) reported PGIC, which assessed global response to treatment and has been  
17 333 associated with clinical symptoms in patients with FM. Curtis(32) reported that patients with FM  
18 334 had a different degree of symptom improvement after HBOT and at a three-month follow-up.  
19 335 After HBOT treatment, “almost the same” was the most common impression of global symptoms  
20 336 in FM patients (44.4%). However, at the three-month follow-up, “a great deal better” was the most  
21 337 common impression of global symptoms in FM patients (41.7%). This showed that HBOT may be  
22 338 effective for a long time.  
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### 340 **3.3.6. Sleep disturbance**

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27 341 Three studies reported sleep quality. Guggino et al.(34) reported that HBOT did not improve  
28 342 the total sleep time of FM patients but improved their sleep quality. Curtis et al.(32) proposed that  
29 343 HBOT improved sustained sleep quality in FM at a three-month follow-up assessment. However,  
30 344 Atzeni et al.(37) indicated that HBOT did not significantly improve the sleep quality of FM. This  
31 345 inconsistency may be related to the different number of HBOT sessions, which needs further study.  
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### 347 **3.4. Adverse events of HBOT**

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36 348 Five studies reported the side effects of HBOT for FM (as shown in Table 1). Adverse events  
37 349 occurred in 44 of 185 patients (23.8%). Twelve patients (6.5%) withdrew because they could not  
38 350 tolerate adverse reactions. Of these adverse events, there were 25 cases of mild barotrauma, five  
39 351 cases of mild middle-ear barotrauma, four cases of new-onset myopia, one case of headache,  
40 352 seven cases of dizziness, claustrophobia, inability to adjust ear pressure by “ear pumping”, and  
41 353 two cases of side effects (not clearly reported). The predominant adverse event was mild  
42 354 barotrauma that could be resolved spontaneously and did not prevent patients from completing the  
43 355 treatment regimen. No serious side effects, complications, or deaths were reported.  
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### 357 **3.5. Grade analysis of the evidence**

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48 358 The quality of pain relief was “Moderate”. Although there was a serious risk of bias and  
49 359 inconsistency, there was no serious directness or imprecision. In addition, the outcome of pain  
50 360 relief has a large effect. The GRADE evidence profile is shown in Table 3.  
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**Table 3. GRADE evidence profile.**

| Outcome     | Certainty assessment |                      |                          |                          |                           | Effect            |                       |                               | Certainty        |
|-------------|----------------------|----------------------|--------------------------|--------------------------|---------------------------|-------------------|-----------------------|-------------------------------|------------------|
|             | Ris of bias          | Inconsistency        | Directness               | Imprecision              | Others                    | Number of Studies | Number of Individuals | Rate (95%CI)                  |                  |
| Pain relief | Serious <sup>a</sup> | Serious <sup>b</sup> | Not serious <sup>c</sup> | Not Serious <sup>d</sup> | Large effect <sup>e</sup> | three RCTs        | 113                   | SMD: -1.56<br>(-2.18 to-0.93) | ⊗⊗⊗○<br>Moderate |

Abbreviations: CI, confidence intervals; SMD, standardized mean difference.

Notes: <sup>a</sup> most of the included studies were assessed as some concerns/high-risk bias; <sup>b</sup>  $I^2 > 50\%$ ; <sup>c</sup> direct participants, intervention, and outcomes; <sup>d</sup> total sample size > 100; <sup>e</sup> SMD > 0.8.

#### 4. Discussion

In this study, we focused on the efficacy of HBOT on the inner core outcomes of FM. Pain relief was the primary outcome measure and could be meta-analysed (three RCTs). Tenderness, fatigue, multidimensional function, patient global, sleep disturbance, and adverse events were secondary outcome measures and were analysed descriptively because of the limited number of studies or limited available data that could be combined. After a systematic review, we found that HBOT could relieve the pain of FM patients compared with the control intervention [SMD=-1.56, 95% CI (-2.18, -0.93),  $P<0.001$ ,  $I^2=51\%$ ]. In addition, most of the included studies have shown that HBOT could significantly improve tender points, fatigue, quality of life, patient global, and sleep disturbance in patients with FM. However, Curtis et al.(32) found that HBOT had no positive effect on fatigue reduction of FM, and Atzeni et al.(37) indicated that HBOT did not significantly improve the quality of life of FM. This inconsistency might be due to baseline differences in small sample sizes or the insufficient number of HBOT sessions. Of the 185 patients with FM who received HBOT, 44 patients had adverse reactions during HBOT treatment (23.8%), and 12 patients withdrew (6.5%) because they could not tolerate the side effects. However, in one retrospective study of 1.5 million cases of treatment with HBOT, the adverse event rate was only 0.68%(49). We speculated that patients with FM might have a lower pain threshold and may be more sensitive to discomfort than patients with other diseases. Mild barotrauma was the most common complication of HBOT for FM. Patients may experience pressure, difficulty in ear balance, earache, and discomfort during compression(50). However, mild barotrauma can be resolved spontaneously and does not prevent patients from completing the treatment and can usually be prevented by appropriate screening(51). Oliaei et al.(52) found that most complications of HBOT occurred when the pressure applied exceeded 2.0 ATA. The articles included in this study mostly used hyperbaric oxygen chambers of 2 to 2.5 ATA for the treatment of FM, which may lead to side effects. A randomized controlled study(33) confirmed that low-pressure HBOT (1.45 ATA) was effective in the treatment of FM without adverse events. Therefore, a pressure lower than 2.0 ATA may be a good choice for patients with FM to avoid side effects and has good efficacy. Further studies are needed to explore the efficacy and safety of low-pressure HBOT for FM. In addition, contraindications for HBOT should be strictly screened before treatment, and the appropriate pressure and duration of treatment should be determined according to the patient's tolerance.

Patients with FM in the control group received conventional treatment or nothing in the included studies. Yildiz et al.(40), Efrati et al.(39) and Guggino et al.(34) did not give any treatment to the patients in the control group, while Hadanny et al.(38), Izquierdo et al.(33) and Curtis et al.(32) performed conventional treatment for the patients in the control group. The conventional treatment that FM received as usual included psychotherapy, medications, physical activity, nutrition therapy, massage, acupuncture, behavioral therapy, or cognitive therapy. Therefore, HBOT may be effective both as an adjunctive therapy and as an independent treatment. Most of the included studies used the same HBOT protocol, which was 100% oxygen at 2 to 2.5 ATA, 90 minutes per session, five days per week. Only a study by Izquierdo et al.(33) used 1.45 ATA to avoid the side effects of HBOT. The length of treatment in the included studies ranged from three to twelve weeks, of which the study by Yildiz et al.(40) lasted three weeks, the study by Hadanny et al.(38) lasted twelve weeks, three noncomparative studies(35-37) lasted four weeks, and the rest of the studies lasted eight weeks. A rodent study found that the anti-injury effects of



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3 413 HBOT were apparent immediately after treatment and lasted for up to five hours(19). In a rat  
4 414 neuropathic pain model, two weeks of HBOT resulted in a significant improvement in pain levels  
5 415 during and after treatment(53). Atzeni et al.(37) proposed that two to four weeks of HBOT  
6 416 treatment significantly improved pain and anxiety symptoms in FM, while fatigue only improved  
7 417 after four weeks. In addition, sleep quality and depressive symptoms were not positively affected  
8 418 in FM after 4 weeks of HBOT. In this review, only Curtis et al.(32) mentioned a follow-up  
9 419 measurement (three months) and found that HBOT can continuously improve patient global,  
10 420 psychological symptoms, and sleep quality in FM. Another study(16) showed that HBOT for 10  
11 421 days had a rapid onset, dose dependent, and long-lasting analgesic effect in patients with  
12 422 idiopathic trigeminal neuralgia documented a reduction in the dosage of carbamazepine analgesics  
13 423 and lower pain VAS. Therefore, long-term treatment with HBOT may be beneficial to improve  
14 424 symptoms of FM or prolong efficacy. However, the prolonged treatment window of patients is  
15 425 likely to cause side effects. Studies have shown that human lenses exposed to 2.0-2.5 ATA and  
16 426 100% oxygen for 90 minutes once a day will lead to the development of myopia and cataracts  
17 427 after 150-850 courses of HBOT(54). However, when exposed to 2.5 ATA and 100% oxygen for  
18 428 90 minutes once a day for 48 courses, the above side effects rarely occur(55). It is challenging to  
19 429 establish the effect and optimal dose–response curves of HBOT in FM considering both safety and  
20 430 efficacy.

21 431 There is growing evidence that HBOT is a noninvasive way to treat chronic pain diseases with  
22 432 long-lasting efficacy and minor adverse effects(13). In murine models of pain, HBOT has been  
23 433 shown to inhibit pain sensation, which may be due to the NO-dependent release of opiate peptides  
24 434 and could be restrained by an antagonist, naltrexone(56, 57). This effect works in the central  
25 435 system but also involves HBO activating  $\mu$ - and K-opioid receptors in the spinal cord and  
26 436 releasing neuronal dynorphins(58). In murine models of arthritis, HBOT has also been shown to  
27 437 affect inflammatory pain by reducing mechanical hypersensitivity and inflammation(59). Patients  
28 438 with FM often experience degenerative changes in muscle, abnormal oxygen pressure, and lower  
29 439 muscle blood flow due to hypoxia(16, 60). Local ischemia causes mitochondria to produce higher  
30 440 levels of free radicals to induce apoptosis, reduce ATP synthesis and increase lactate concentration  
31 441 in the muscle, thus ultimately leading to muscle weakness and pain(61, 62). HBOT improves  
32 442 muscle oxygenation in FM, which can reduce the tissue lactate concentration and help maintain  
33 443 ATP levels, thus possibly preventing tissue damage in ischemic tissue(63). It raises the oxygen  
34 444 concentration in all tissues far above physiological levels to cause hyperoxia, which breaks the  
35 445 hypoxic-pain cycle in patients with FM(63). In addition, the high excitability of pain processing  
36 446 pathways in the brain and low activity of pain inhibition pathways may cause excessive pain in  
37 447 FM(64). Studies have shown that patients with FM have higher activity in the somatosensory  
38 448 cortex and lower activity in the frontal, medial frontal, cingulate gyrus, and cerebellar cortex than  
39 449 healthy subjects(65). HBOT has been shown to increase neurotrophic and nitric oxide levels,  
40 450 reduce oxidative stress, promote cell metabolism by enhancing the mitochondrial function of  
41 451 neurons and glial cells, and may even promote the production of endogenous neural stem cells(66).  
42 452 The specific mechanism of HBOT on FM needs to be further investigated.

43 453 The quality of evidence (pain relief of HBOT for FM) assessed using the GRADE system  
44 454 was moderate. There are inherently ethical and logistical difficulties in handling the sham control  
45 455 in HBOT experiments. In two RCTs, the researchers did not use sham control/placebo in the  
46 456 control group, which may lower the quality of the evidence. The heterogeneity of the outcome



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457 may be caused by the population and HBOT regimen. However, the large effect (SMD > 0.8) may  
458 increase the quality of the evidence. Therefore, we have a moderate degree of confidence in our  
459 estimated effect. The true value may be close to the estimated value, but there is still a chance that  
460 they could be very different.

461 There are some limitations in this systematic review. The main limitation is that the small  
462 number of RCTs included may lead to an overall risk of bias or insufficient evidence. Second,  
463 HBOT protocols (the length of treatment and pressure parameters) have clinical heterogeneity,  
464 which may introduce bias to the results. Third, we only retrieved data from Chinese and English  
465 databases, which may limit the data availability or cause language bias. Finally, due to the small  
466 number of included studies and heterogeneity, we did not conduct a subgroup analysis. Therefore,  
467 we cannot evaluate the efficacy of different HBOT regimens.

468 In conclusion, the present study shows that HBOT may have a good effect in improving pain,  
469 tender points, fatigue, multidimensional function, patient global, and sleep disturbance in FM,  
470 with reversible side effects. Low pressure (less than 2.0 ATA) may be beneficial to reduce adverse  
471 events in patients with FM. Further high-quality and large-sample RCTs should be carried out to  
472 further evaluate its efficacy and safety.

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474 **Author contributors:** Conceptualization: CH, XXC, JHY. Funding Acquisition: CH. Formal  
475 Analysis: XXC. Investigation: CH. Writing-Original Draft Preparation: XXC, JHY, MZ, HM.  
476 Writing-Review & Editing: all the authors. All the authors fulfil the ICMJE criteria for authorship.

477

478 **Funding statement:** Key Research and Development Project of Sichuan Provincial Science and  
479 Technology Department (No. 2018SZ0082); 1·3·5 Project for Disciplines of excellence-Clinical  
480 Research Incubation Project, West China Hospital, Sichuan University (No. 2021HXFH063)

481

482 **Disclaimer:** The authors declare no financial relationships with any organizations that might have  
483 an interest in the submitted work and no other relationships or activities that could appear to have  
484 influenced the submitted work.

485

486 **Ethical approval statement:** Not applicable.

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488 **Competing interests:** None declared.

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490 **Data sharing statement:** Data are available upon reasonable request.

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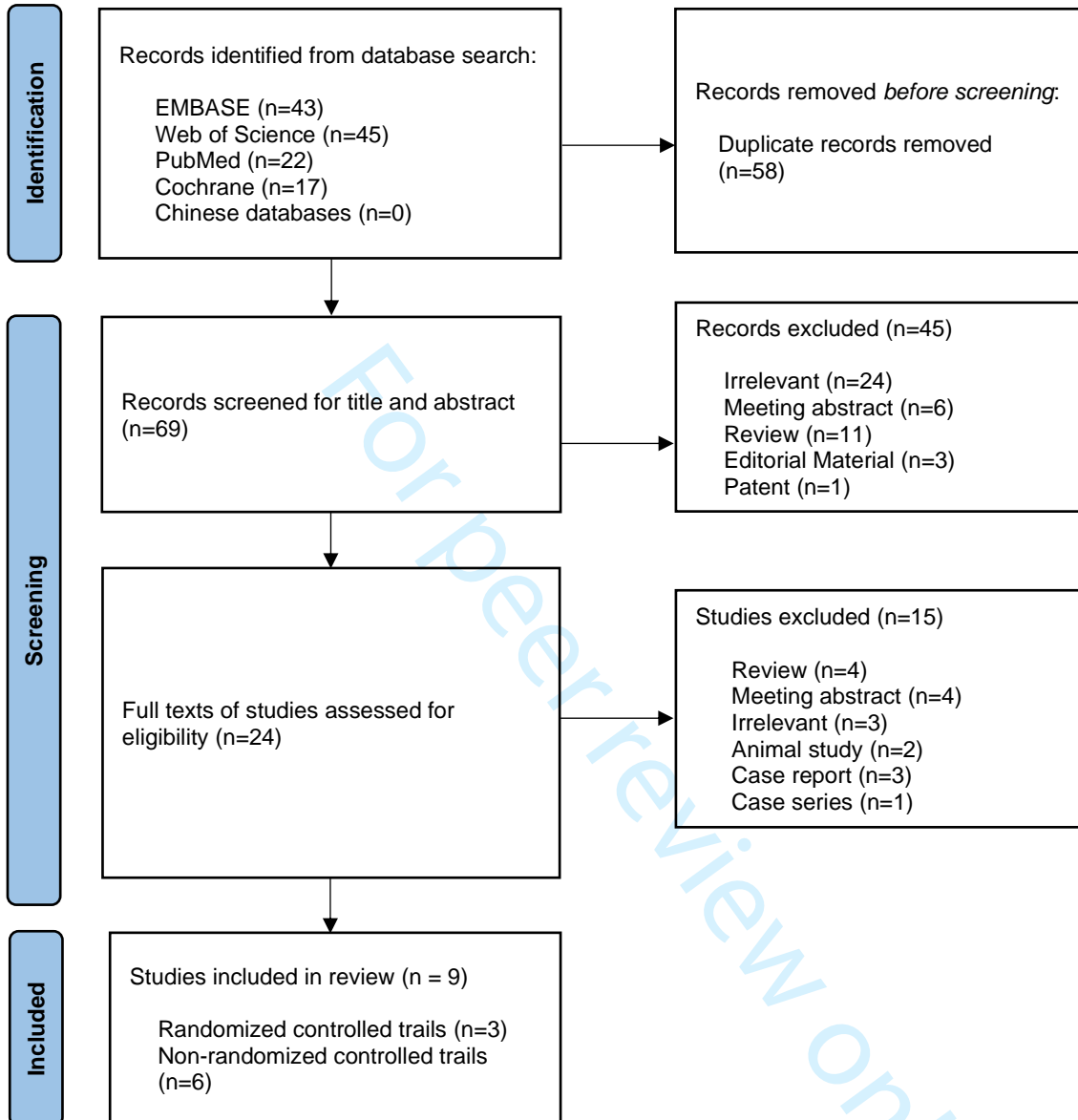
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46 666 **Figure 1. PRISMA flowchart.**

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48 668 **Figure 2. Risk of bias graph for the included randomized controlled trials across five domains.**  
49 669 The red circle indicates a high risk of bias within that domain for a given study, the yellow circles  
50 670 indicate an unclear risk of bias, and the green circles indicate a low risk of bias.

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54 672 **Figure 3. Forest plot of pain relief.**

**Identification of studies via databases**



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|  | Yildiz 2004 | Izquierdo 2020 | Hadanny 2018 |   |
|--|-------------|----------------|--------------|---|
|  | ?           | +              | ?            | Random sequence generation (selection bias)               |
|  | ?           | +              | ?            | Allocation concealment (selection bias)                   |
|  | ?           | ?              | -            | Blinding of participants and personnel (performance bias) |
|  | +           | +              | +            | Blinding of outcome assessment (detection bias)           |
|  | +           | +              | +            | Incomplete outcome data (attrition bias)                  |
|  | +           | +              | +            | Selective reporting (reporting bias)                      |
|  | ?           | ?              | ?            | Other bias  |

Risk of bias graph for the included randomized controlled trials across five domains. The red circle indicates a high risk of bias within that domain for a given study, the yellow circles indicate an unclear risk of bias, and the green circles indicate a low risk of bias.

288x211mm (38 x 38 DPI)



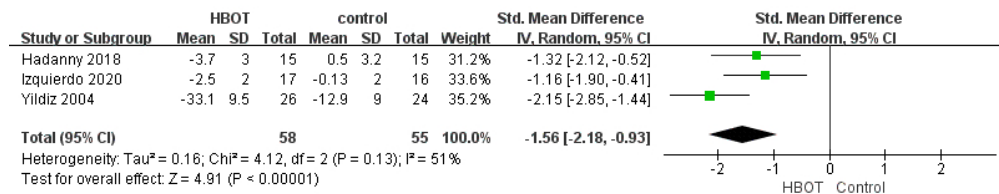


Figure 3. Forest plot of pain relief.

282x56mm (72 x 72 DPI)



## Pubmed

| Search | Query   | Results       | Time     |
|--------|---|---------------|----------|
| #7     | Search: ((hyperbaric oxygenation [MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract]))) AND ((fibromyalgia[MeSH Terms]) OR ("fibromyalgia" OR "fibrositic nodule" OR "fibrositic nodule" OR "fibrositis" OR "fibrositis syndrome" OR "myalgia, fibro")) | <u>22</u>     | 20:08:04 |
| #6     | Search: "fibromyalgia" OR "fibrositic nodule" OR "fibrositic nodule" OR "fibrositis" OR "fibrositis syndrome" OR "myalgia, fibro"   | <u>13,579</u> | 20:06:54 |
| #5     | Search: (hyperbaric oxygenation[MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract]))  | <u>18,499</u> | 20:04:55 |
| #4     | Search: fibromyalgia[MeSH Terms]  | <u>9,569</u>  | 20:04:01 |
| #3     | Search: (hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract])  | <u>15,251</u> | 20:02:45 |
| #2     | Search: hyperbaric oxygenation[MeSH Terms]  | <u>12,570</u> | 20:02:10 |

| Search | Actions | Details | Query  | Results       | Time     |
|--------|---------|---------|--|---------------|----------|
| #7     | ...     | >       | Search: ((((((fibromyalgia) OR (fibrositic nodule)) OR (fibrositic nodule) OR (fibrositis) OR (fibrositis syndrome)) OR (myalgia, fibro)) OR (fibromyalgia[MeSH Terms])) AND ((hyperbaric oxygenation[MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract])))) | <u>22</u>     | 20:08:04 |
| #6     | ...     | >       | Search: ((((((fibromyalgia) OR (fibrositic nodule)) OR (fibrositic nodule) OR (fibrositis) OR (fibrositis syndrome)) OR (myalgia, fibro))  | <u>13,579</u> | 20:06:54 |
| #5     | ...     | >       | Search: (hyperbaric oxygenation[MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract]))   | <u>18,499</u> | 20:04:55 |
| #4     | ...     | >       | Search: fibromyalgia[MeSH Terms]   | <u>9,569</u>  | 20:04:01 |
| #3     | ...     | >       | Search: (hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract])   | <u>15,251</u> | 20:02:45 |
| #2     | ...     | >       | Search: hyperbaric oxygenation[MeSH Terms]   | <u>12,570</u> | 20:02:10 |

## EMBASE

Database(s): Embase

Search Strategy:

#

Searches

Results

1

'hyperbaric oxygen therapy'/exp

18807

2

'high pressure oxygen':ab,ti OR 'high tension o2':ab,ti OR 'high tension oxygen':ab,ti OR

'hyperbaric medicine':ab,ti OR 'hyperbaric o2':ab,ti OR 'hyperbaric oxygen':ab,ti OR 'hyperbaric oxygenation':ab,ti OR 'hyperbaric oxygenisation':ab,ti OR 'hyperbaric oxygenization':ab,ti OR 'oxygen, hyperbaric':ab,ti OR 'hbot':ab,ti

13020

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1 OR 2

20223

4

'fibromyalgia'/exp

21352

5

'fibromyalgia':ab,ti OR 'fibrositic nodule':ab,ti OR 'fibrositis':ab,ti OR 'fibrositis syndrome':ab,ti OR 'myalgia, fibro':ab,ti

17507

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4 OR 5

22891

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3 AND 6

43

| <input type="checkbox"/> History | Save   Delete   Print view   Export   Email   | Combine > | using <input checked="" type="radio"/> And <input type="radio"/> Or | <input type="button" value="Collapse"/> |
|----------------------------------|---|-----------|---|---|
| <input type="checkbox"/> #7      | #3 AND #6   |           |   | 43                                      |
| <input type="checkbox"/> #6      | #4 OR #5  |           |   | 22,891                                  |
| <input type="checkbox"/> #5      | 'fibromyalgia':ab,ti OR 'fibrositic nodule':ab,ti OR 'fibrositis':ab,ti OR 'fibrositis syndrome':ab,ti OR 'myalgia, fibro':ab,ti  |           |   | 17,507                                  |
| <input type="checkbox"/> #4      | 'fibromyalgia'/exp  |           |   | 21,352                                  |
| <input type="checkbox"/> #3      | #1 OR #2  |           |   | 20,223                                  |
| <input type="checkbox"/> #2      | 'high pressure oxygen':ab,ti OR 'high tension o2':ab,ti OR 'high tension oxygen':ab,ti OR 'hyperbaric medicine':ab,ti OR 'hyperbaric o2':ab,ti OR 'hyperbaric oxygen':ab,ti OR 'hyperbaric oxygenation':ab,ti OR 'hyperbaric oxygenisation':ab,ti OR 'hyperbaric oxygenization':ab,ti OR 'oxygen, hyperbaric':ab,ti OR 'hbot':ab,ti |           |   | 13,020                                  |
| <input type="checkbox"/> #1      | 'hyperbaric oxygen therapy'/exp   |           |   | 18,807                                  |

**Web of Science (1900-present)**

1

Topic=("fibromyalgia" OR "fibrositic nodule" OR "fibrositis" OR "fibrositis syndrome" OR "myalgia, fibro")

31305

2

Topic=(Hyperbaric OR HBOT)

28136

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1 AND 2

45

0/3 Combine Sets Export Clear History

|                          |   |  |        |                           |                |                |                |
|--------------------------|---|--|--------|---------------------------|----------------|----------------|----------------|
| <input type="checkbox"/> | 3 | #2 AND #1  | 45     | <span>Add to query</span> | <span>🔗</span> | <span>✎</span> | <span>🔔</span> |
| <input type="checkbox"/> | 2 | (TS=(Hyperbaric)) OR TS=(HBOT)   | 28,136 | <span>Add to query</span> | <span>🔗</span> | <span>✎</span> | <span>🔔</span> |
| <input type="checkbox"/> | 1 | (((TS=(fibromyalgia)) OR TS=(fibrositic nodule)) OR TS=(fibrositis)) OR TS=(fibrositis syndrome)) OR TS=(myalgia, fibro) | 31,305 | <span>Add to query</span> | <span>🔗</span> | <span>✎</span> | <span>🔔</span> |

## Cochrane

### ID Search Hits

#1 MeSH descriptor: [Hyperbaric Oxygenation] explode all trees 431

#2 hyperbaric or hbot:ti,ab,kw (Word variations have been searched) 3504

#3 MeSH descriptor: [Fibromyalgia] explode all trees 1598

#4 "fibromyalgia" OR "fibrositic nodule" OR "fibrositis" OR "fibrositis syndrome":ti,ab,kw 3469

#5 #1 OR #2 3504

#6 #3 OR #4 3469

#7 #5 AND #6 17

|     |   |        |             |
|-----|---|--------|-------------|
| #1  | MeSH descriptor: [Hyperbaric Oxygenation] explode all trees | MeSH   | 431         |
| #2  | (hyperbaric):ti,ab,kw                                       | S      | Limits 3501 |
| #3  | (hbot):ti,ab,kw   | S      | Limits 264  |
| #4  | #3 OR #2  | Limits | 3504        |
| #5  | MeSH descriptor: [Fibromyalgia] explode all trees           | MeSH   | 1598        |
| #6  | (fibromyalgia):ti,ab,kw                                     | S      | Limits 3427 |
| #7  | (fibrositic nodule):ti,ab,kw                                | S      | Limits 0    |
| #8  | (fibrositis):ti,ab,kw                                       | S      | Limits 63   |
| #9  | (fibrositis syndrome):ti,ab,kw                              | S      | Limits 10   |
| #10 | #1 OR #4  | Limits | 3504        |
| #11 | #6 OR #7 OR #8 OR #9  | Limits | 3469        |
| #12 | #5 OR #11   | Limits | 3469        |
| #13 | #10 AND #12   | Limits | 17          |

## CNKI (Chinese database)

(篇文摘=高压氧) AND (篇文摘=纤维肌痛)

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## VIP (Chinese database)

(题名或关键词=高压氧) AND (题名或关键词=纤维肌痛)

0

## WANFANG (Chinese database)

题名或关键词: (高压氧 and 纤维肌痛)

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# PRISMA 2020 Checklist

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| Section and Topic             | Item # | Checklist item   | Location where item is reported |
|-------------------------------|--------|--|---------------------------------|
| <b>TITLE</b>                  |        |  | 1                               |
| Title                         | 1      | Identify the report as a systematic review.  |                                 |
| <b>ABSTRACT</b>               |        |  |                                 |
| Abstract                      | 2      | See the PRISMA 2020 for Abstracts checklist.   | 2                               |
| <b>INTRODUCTION</b>           |        |  |                                 |
| Rationale                     | 3      | Describe the rationale for the review in the context of existing knowledge.  | 2                               |
| Objectives                    | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses.   | 3                               |
| <b>METHODS</b>                |        |  |                                 |
| Eligibility criteria          | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.  | 4                               |
| Information sources           | 6      | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.  | 4                               |
| Search strategy               | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used.   | 4                               |
| Selection process             | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.                     | 4                               |
| Data collection process       | 9      | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 4                               |
| Data items                    | 10a    | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.                        | 4                               |
|                               | 10b    | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.   | 4                               |
| Study risk of bias assessment | 11     | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.                                    | 5                               |
| Effect measures               | 12     | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.  | 5                               |
| Synthesis methods             | 13a    | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).   | 4                               |
|                               | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.  | 6                               |
|                               | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses.   | 7                               |
|                               | 13d    | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.  | 6                               |
|                               | 13e    | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).   | 6                               |
|                               | 13f    | Describe any sensitivity analyses conducted to assess robustness of the synthesized results.   | 6                               |
| Reporting bias assessment     | 14     | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).  | 5                               |
| Certainty                     | 15     | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.  | 6                               |



## PRISMA 2020 Checklist

| Section and Topic                              | Item # | Checklist item   | Location where item is reported |
|--|--------|--|---------------------------------|
| assessment                                     |        |  |                                 |
| <b>RESULTS</b>                                 |        |  |                                 |
| Study selection                                | 16a    | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.   | 6-7                             |
|  | 16b    | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.  | 6                               |
| Study characteristics                          | 17     | Cite each included study and present its characteristics.  | 7                               |
| Risk of bias in studies                        | 18     | Present assessments of risk of bias for each included study.   | 8-9                             |
| Results of individual studies                  | 19     | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.   | 10-11                           |
| Results of syntheses                           | 20a    | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.   | 10-11                           |
|  | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 10-11                           |
|  | 20c    | Present results of all investigations of possible causes of heterogeneity among study results.   | 10-11                           |
|  | 20d    | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.   | 10-11                           |
| Reporting biases                               | 21     | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.  | 8-9                             |
| Certainty of evidence                          | 22     | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.  | 11-12                           |
| <b>DISCUSSION</b>                              |        |  |                                 |
| Discussion                                     | 23a    | Provide a general interpretation of the results in the context of other evidence.  | 13                              |
|  | 23b    | Discuss any limitations of the evidence included in the review.  | 15                              |
|  | 23c    | Discuss any limitations of the review processes used.  | 15                              |
|  | 23d    | Discuss implications of the results for practice, policy, and future research.   | 13-14                           |
| <b>OTHER INFORMATION</b>                       |        |  |                                 |
| Registration and protocol                      | 24a    | Provide registration information for the review, including register name and registration number, or state that the review was not registered.   | 4                               |
|  | 24b    | Indicate where the review protocol can be accessed, or state that a protocol was not prepared.   | 4                               |
|  | 24c    | Describe and explain any amendments to information provided at registration or in the protocol.  | 4                               |
| Support  | 25     | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.  | 15                              |
| Competing interests                            | 26     | Declare any competing interests of review authors.   | 15                              |
| Availability of data, code and other materials | 27     | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.   | 15                              |



## PRISMA 2020 Checklist

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10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

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