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Efficacy and Safety of Hyperbaric Oxygen Therapy for Fibromyalgia: 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

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

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

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

METHODS

Search strategy

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

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

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) ⩾7 and symptom severity scale (SSS) ⩾ 5 or a WPI of 4–6 and a SSS score ⩾ 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

checked with each other. In case of disagreement, a third researcher (XXC) would assist to resolve the disagreement.

Statistical analysis

The RevMan 5.4.1 software provided by Cochrane Collaboration was used to conduct a meta-analysis of the primary outcome. Standardized mean difference (SMD) and its 95% CI were used as the analysis statistics. Firstly, the chi-square test is used to analyze whether there is statistical heterogeneity among the results of each study, and then I^2 was used to quantitatively determine the size of the heterogeneity. If $P \geq 0.1$, $I^2 < 50\%$, it means that the heterogeneity is not obvious and then use a fixed-effect model; if $P < 0.1$, $I^2 > 50\%$, it indicates that the heterogeneity is obvious and then use a random effect model. If the heterogeneity is too obvious, the cause and source of heterogeneity would be further analyzed.

Patient and public involvement

Patients and public were not involved in this study.

RESULTS

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

Characteristics of included studies

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

The included patients were mostly female, with a percentage of 90.7%. The patients included by Hadanny et al., Izquierdo et al., and Efrati et al. were all females(21, 22, 24). Hadanny et al. included women with a history of childhood sexual abuse (21). Hadanny et al. and Efrati et al. included patients with a duration of fibromyalgia of more than 2 years(21, 24).

Table 2. Characteristics of included studies.

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.

Quality assessment

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

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

Outcome measures

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

Pain reduction

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

Other outcome indicators

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

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

Adverse events

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

DISCUSSION

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

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

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

an unresolved problem(33).

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

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

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

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

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References

1. Sueiro Blanco F, Estévez Schwarz I, Ayán C, Cancela J, Martín V. Potential benefits of non-pharmacological therapies in fibromyalgia. The open rheumatology journal. 2008;2:1-6.
2. Thomas EN, Blotman F. Aerobic exercise in fibromyalgia: a practical review. Rheumatology international. 2010;30(9):1143-50.
3. Alciati A, Nucera V, Masala IF, Giallanza M, La Corte L, Giorgi V, et al. One year in review 2021: fibromyalgia. Clinical and experimental rheumatology. 2021;39 Suppl 130(3):3-12.
4. Siracusa R, Paola RD, Cuzzocrea S, Impellizzeri D. Fibromyalgia: Pathogenesis, Mechanisms, Diagnosis and Treatment Options Update. International journal of molecular sciences. 2021;22(8).
5. Schmidt-Wilcke T, Clauw DJ. Fibromyalgia: from pathophysiology to therapy. Nature reviews Rheumatology. 2011;7(9):518-27.
6. Sarzi-Puttini P, Atzeni F, Mease PJ. Chronic widespread pain: from peripheral to central evolution. Best practice & research Clinical rheumatology. 2011;25(2):133-9.
7. Häuser W, Galek A, Erbslöh-Möller B, Köllner V, Kühn-Becker H, Langhorst J, et al. Posttraumatic stress disorder in fibromyalgia syndrome: prevalence, temporal relationship between posttraumatic stress and fibromyalgia symptoms, and impact on clinical outcome. Pain. 2013;154(8):1216-23.
8. Imbierowicz K, Egle UT. Childhood adversities in patients with fibromyalgia and somatoform pain disorder. European journal of pain (London, England). 2003;7(2):113-9.
9. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. Lancet (London, England). 1999;354(9186):1248-52.
10. Gouvinhas C, Veiga D, Mendonça L, Sampaio R, Azevedo LF, Castro-Lopes JM. Interventional Pain Management in Multidisciplinary Chronic Pain Clinics: A Prospective Multicenter Cohort Study with One-Year Follow-Up. Pain research and treatment. 2017;2017:8402413.
11. Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. The Journal of rheumatology Supplement. 2005;75:6-21.
12. Smith BH, Elliott AM, Chambers WA, Smith WC, Hannaford PC, Penny K. The impact of chronic pain in the community. Family practice. 2001;18(3):292-9.
13. Sutherland AM, Clarke HA, Katz J, Katznelson R. Hyperbaric Oxygen Therapy: A New Treatment for Chronic Pain? Pain practice : the official journal of World Institute of Pain. 2016;16(5):620-8.
14. KK J. Textbook of Hyperbaric Medicine, 3rd ed.. Seattle, WA: Hogrefe and Huber Publishers. 1999.
15. Wilson HD, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment decreases inflammation and mechanical hypersensitivity in an animal model of inflammatory pain. Brain Res. 2006;1098(1):126-8.
16. El-Shewy KM, Kunbaz A, Gad MM, Al-Husseini MJ, Saad AM, Sammour YM, et al. Hyperbaric oxygen and aerobic exercise in the long-term treatment of fibromyalgia: A narrative review. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2019;109:629-38.
17. Efrati S, Golan H, Bechor Y, Faran Y, Daphna-Tekoah S, Sekler G, et al. Hyperbaric oxygen therapy can diminish fibromyalgia syndrome--prospective clinical trial. PloS one. 2015;10(5):e0127012.

18. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Seminars in arthritis and rheumatism. 2016;46(3):319-29.
19. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2011;343:d5928.
20. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ (Clinical research ed). 2016;355:i4919.
21. Hadanny A, Bechor Y, Catalogna M, Daphna-Tekoah S, Sigal T, Cohenpour M, et al. Hyperbaric Oxygen Therapy Can Induce Neuroplasticity and Significant Clinical Improvement in Patients Suffering From Fibromyalgia With a History of Childhood Sexual Abuse-Randomized Controlled Trial. Front Psychol. 2018;9:2495.
22. Izquierdo-Alventosa R, Inglés M, Cortés-Amador S, Gimeno-Mallench L, Sempere-Rubio N, Chirivella J, et al. Comparative study of the effectiveness of a low-pressure hyperbaric oxygen treatment and physical exercise in women with fibromyalgia: randomized clinical trial. Therapeutic Advances in Musculoskeletal Disease. 2020;12.
23. Yildiz Ş, Kiralp MZ, Akin A, Keskin I, Ay H, Dursun H, et al. A new treatment modality for fibromyalgia syndrome: Hyperbaric oxygen therapy. Journal of International Medical Research. 2004;32(3):263-7.
24. Efrati S, Golan H, Bechor Y, Faran Y, Daphna-Tekoah S, Sekler G, et al. Hyperbaric oxygen therapy can diminish fibromyalgia syndrome--prospective clinical trial. PloS one. 2015;10(5):e0127012.
25. Ablin JN, Efrati S, Buskila D. Building up the pressure on chronic pain. Clinical and experimental rheumatology. 2016;34(2 Suppl 96):S3-5.
26. Wang SM, Han C, Lee SJ, Patkar AA, Masand PS, Pae CU. Fibromyalgia diagnosis: a review of the past, present and future. Expert review of neurotherapeutics. 2015;15(6):667-79.
27. Chinn S, Caldwell W, Gritsenko K. Fibromyalgia Pathogenesis and Treatment Options Update. Current pain and headache reports. 2016;20(4):25.
28. Park JH, Phothimat P, Oates CT, Hernanz-Schulman M, Olsen NJ. Use of P-31 magnetic resonance spectroscopy to detect metabolic abnormalities in muscles of patients with fibromyalgia. Arthritis and rheumatism. 1998;41(3):406-13.
29. Gu N, Niu JY, Liu WT, Sun YY, Liu S, Lv Y, et al. Hyperbaric oxygen therapy attenuates neuropathic hyperalgesia in rats and idiopathic trigeminal neuralgia in patients. European journal of pain (London, England). 2012;16(8):1094-105.
30. Behan WM, More IA, Behan PO. Mitochondrial abnormalities in the postviral fatigue syndrome. Acta neuropathologica. 1991;83(1):61-5.
31. Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. International journal of clinical and experimental medicine. 2009;2(1):1-16.
32. Mascarenhas RO, Souza MB, Oliveira MX, Lacerda AC, Mendonça VA, Henschke N, et al. Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia: A Systematic Review and Meta-analysis. JAMA internal medicine. 2021;181(1):104-12.
33. D.J. Clauw, L.M. Arnold, McCarberg BH. The science of fibromyalgia. Mayo Clin Proc 2011;86 (9):907–11.
34. Chung E, Zelinski LM, Ohgami Y, Shirachi DY, Quock RM. Hyperbaric oxygen treatment induces a

2-phase antinociceptive response of unusually long duration in mice. The journal of pain. 2010;11(9):847-53.

35. Gibbons CR, Liu S, Zhang Y, Sayre CL, Levitch BR, Moehlmann SB, et al. Involvement of brain opioid receptors in the anti-allodynic effect of hyperbaric oxygen in rats with sciatic nerve crush-induced neuropathic pain. Brain research. 2013;1537:111-6.

36. Heeman JH, Zhang Y, Shirachi DY, Quock RM. Involvement of spinal cord opioid mechanisms in the acute antinociceptive effect of hyperbaric oxygen in mice. Brain research. 2013;1540:42-7.

37. Wilson HD, Toepfer VE, Senapati AK, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment is comparable to acetylsalicylic acid treatment in an animal model of arthritis. The journal of pain. 2007;8(12):924-30.

38. Yildiz S, Uzun G, Kiralp MZ. Hyperbaric oxygen therapy in chronic pain management. Current pain and headache reports. 2006;10(2):95-100.

39. Barilaro G, Francesco Masala I, Parracchini R, Iesu C, Caddia G, Sarzi-Puttini P, et al. The Role of Hyperbaric Oxygen Therapy in Orthopedics and Rheumatological Diseases. The Israel Medical Association journal : IMAJ. 2017;19(7):429-34.

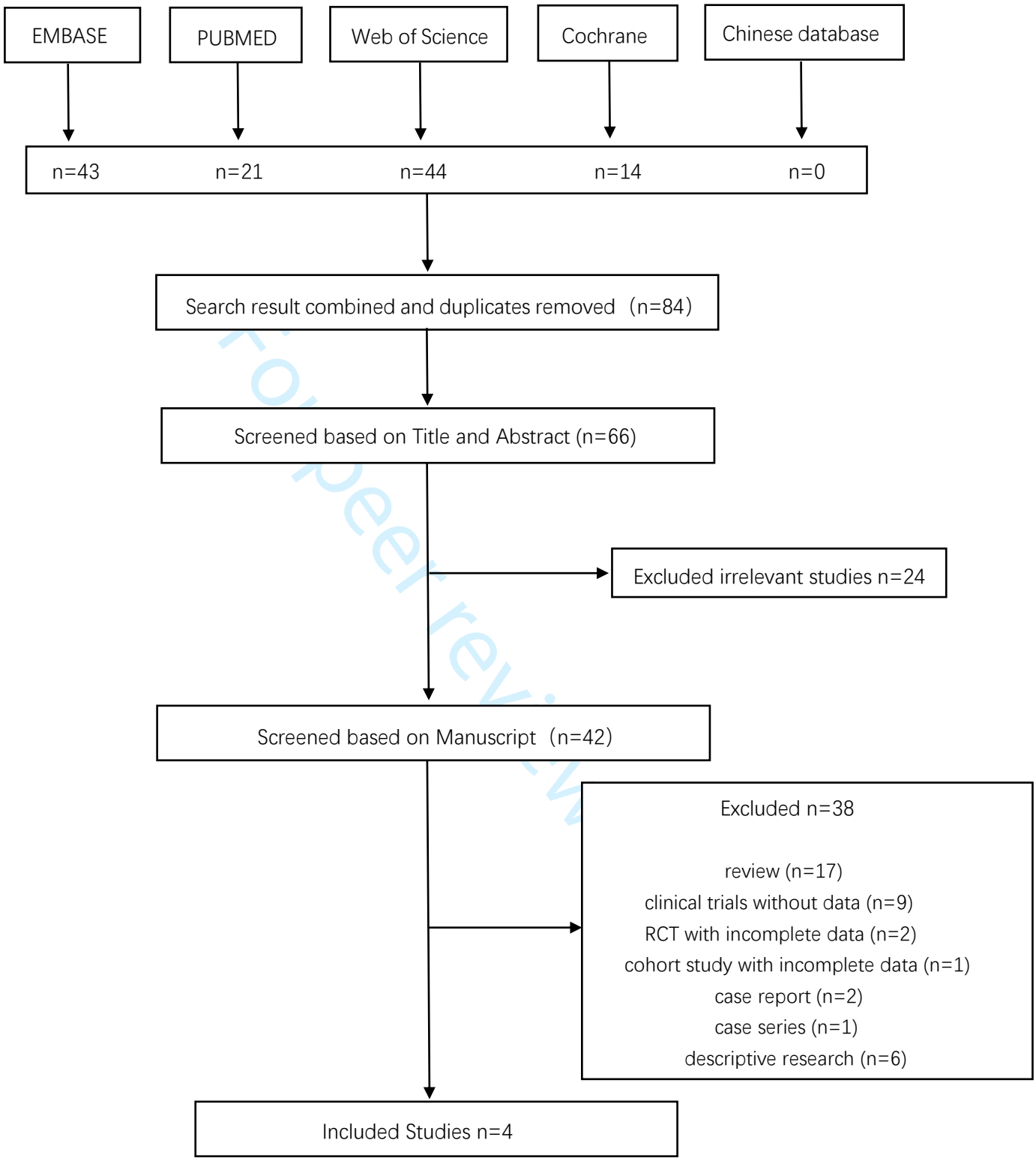
40. Guedj E, Cammilleri S, Niboyet J, Dupont P, Vidal E, Dropinski JP, et al. Clinical correlate of brain SPECT perfusion abnormalities in fibromyalgia. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2008;49(11):1798-803.

41. Lin KC, Niu KC, Tsai KJ, Kuo JR, Wang LC, Chio CC, et al. Attenuating inflammation but stimulating both angiogenesis and neurogenesis using hyperbaric oxygen in rats with traumatic brain injury. The journal of trauma and acute care surgery. 2012;72(3):650-9.

Figure 1. PRISMA flowchart.

Figure 2. Risk of bias for included studies 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.

Figure 3. Forest plot of pain reduction.



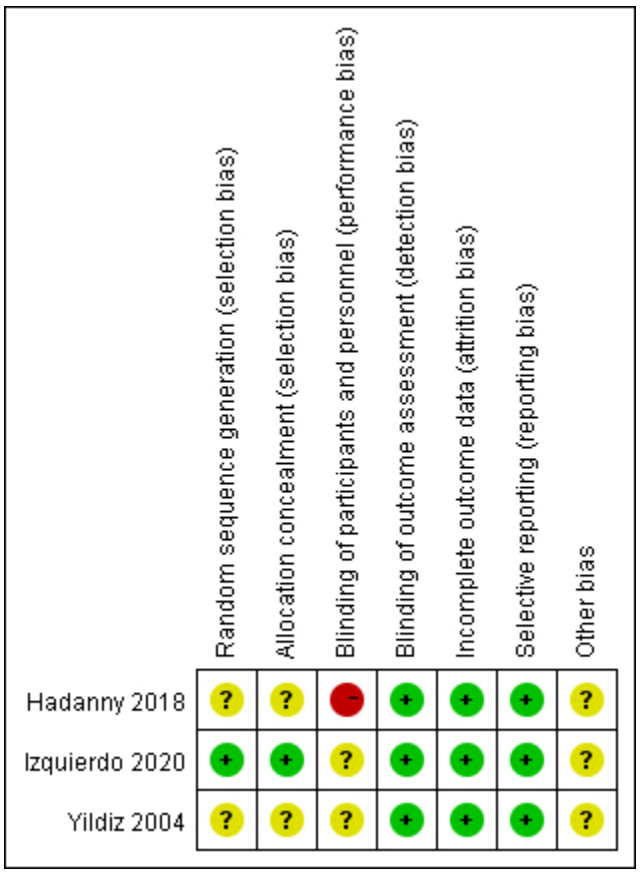
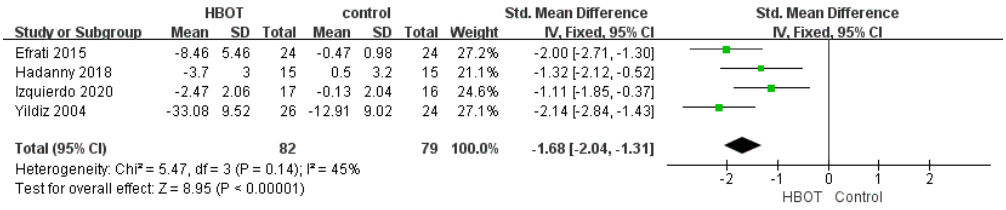


Figure 2. Risk of bias for included studies across five domains.

111x152mm (72 x 72 DPI)



Forest plot of pain reduction.

290x62mm (72 x 72 DPI)

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.

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		Reporting Item	Page Number
Title			
Title	#1	Identify the report as a systematic review	1
Abstract			

Abstract	#2	Report an abstract addressing each item in the PRISMA 2020 for Abstracts checklist	2
Introduction			
Background/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	2
Methods			
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	3
Search strategy	#7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used	3
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	#9	Specify the methods used to collect data from reports,	4

process		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	
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 (for example, for all measures, time points, analyses), and, if not, the methods used to decide which results to collect	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	4
Effect measures	#12	Specify for each outcome the effect measure(s) (such as risk ratio, mean difference) used in the synthesis or presentation of results	4
Synthesis methods	#13a	Describe the processes used to decide which studies were eligible for each synthesis (such as tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5))	5
Synthesis methods	#13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing	5

		summary statistics or data conversions	
Synthesis methods	#13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	5
Synthesis methods	#13d	Describe any methods used to synthesise 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	5
Synthesis methods	#13e	Describe any methods used to explore possible causes of heterogeneity among study results (such as subgroup analysis, meta-regression)	5
Synthesis methods	#13f	Describe any sensitivity analyses conducted to assess robustness of the synthesised results	5
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 assessment	#15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	4
Data items	#10b	List and define all other variables for which data were sought (such as participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	4

Results

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 (http://www.prisma-statement.org/PRISMAStatement/FlowDiagram)	6
Study selection	#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	6
Risk of bias in studies	#18	Present assessments of risk of bias for each included study	6
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 (such as confidence/credible interval), ideally using structured tables or plots	5
Results of syntheses	#20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	6
Results of syntheses	#20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (such as confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	6
Results of syntheses	#20c	Present results of all investigations of possible causes of	6

		heterogeneity among study results	
Results of syntheses	#20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results	6
Risk of reporting biases in syntheses	#21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	6
Certainty of evidence	#22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	6
Discussion			
Results in context	#23a	Provide a general interpretation of the results in the context of other evidence	7
Limitations of included studies	#23b	Discuss any limitations of the evidence included in the review	8
Limitations of the review methods	#23c	Discuss any limitations of the review processes used	8
Implications	#23d	Discuss implications of the results for practice, policy, and future research	7
Other information			
Registration and protocol	#24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	2
Registration and protocol	#24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	2

Registration and protocol	#24c	Describe and explain any amendments to information provided at registration or in the protocol	2
Support	#25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	8
Competing interests	#26	Declare any competing interests of review authors	9
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	9

BMJ Open

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

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Efficacy and Safety of Hyperbaric Oxygen Therapy for Fibromyalgia: 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

risk of bias or insufficient evidence.
We only retrieved data from Chinese and English databases, which may limit the data available or cause language bias.
The quality of the pooled effect was affected by the original trials.

1. 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 worldwide(4). FM is more frequent in females, with a female-to-male ratio of 9:1(5).

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

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

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

2. Methods

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

2.1. Search strategy

A literature search was conducted to identify all articles involving the use of hyperbaric oxygen to treat FM. The search strategy is shown in Supplementary appendix A. PubMed, EMBASE, Web of Science, Cochrane library, 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. The search included MeSH and free text terms such as “hyperbaric oxygen therapy”, “fibromyalgia” and synonyms.

2.2. 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: RCTs and non-RCTs; 2) subjects: FM patients conformed to the 2016 American College of Rheumatology (ACR) diagnostic criteria(26) [i.e. they met the following criteria: generalized pain for at least 3 months and a widespread pain index (WPI) $\geqslant$7 and symptom severity scale (SSS) $\geqslant$ 5 or a WPI of 4–6 and a SSS score $\geqslant$ 9]; 3) the intervention: patients in the experimental group received HBOT as the intervention measure, and patients in the control group received conventional treatment or nothing. The conventional treatment was any pharmacological or nonpharmacological therapy other than HBOT. The course of treatment and parameters were unlimited. 4) outcome indicators: the inner Core Outcome Set of FM symptoms (pain, tenderness, fatigue, multidimensional function, patient global, sleep disturbance) and adverse events. The exclusion criteria were as follows: animal studies, reviews, duplicate publications, irrelevant studies, editorial materials, patients, case reports, or meeting abstracts.

2.3. 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 were excluded after three or more attempts to email the lead author and obtain 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 predesigned form was used for information extraction. The content included the article’s 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 that reflected 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) assisted in resolving the disagreement.

2.4. Types of outcome measures

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

2.4.1. Pain and tenderness

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

2.4.2. Multidimensional function

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

2.4.3. Fatigue

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

2.4.4. Patient global

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

2.4.5. Sleep disturbance

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

2.4.6. Adverse events

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

2.5. Risk of bias assessment

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

2.6. Statistical analysis

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

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

2.7. Grade the quality of evidence

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

2.8. Patient and public involvement

Patients and the public were not involved in this study.

3. Results

3.1. Characteristics of the included studies

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

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

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

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

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

3.2. Quality assessment

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

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

3.3. Efficacy of HBOT

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

3.3.1. Pain relief

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

3.3.2. Tenderness

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

3.3.3. Multidimensional function

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

3.3.4. Fatigue

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

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.

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[a]	Serious[b]	Not serious[c]	Serious[d]	Large effect[e]	three RCTs	113	SMD: -1.56 (-2.18 to-0.93)	⊗⊗⊗○ Moderate

Abbreviations: CI, confidence intervals; SMD, standardized mean difference.
Notes: [a] most of the included studies were assessed as some concerns/high-risk bias; [b] I^2>50%; [c] direct participants, intervention and outcomes; [d] total sample size > 100; [e] 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

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

There is growing evidence that HBOT is a noninvasive way to treat chronic pain diseases with long-lasting efficacy and minor adverse effects(13). In murine models of pain, HBOT has been shown to inhibit pain sensation, which may be due to the NO-dependent release of opiate peptides and could be restrained by an antagonist, naltrexone(56, 57). This effect works in the central system but also involves HBO activating μ- and K-opioid receptors in the spinal cord and releasing neuronal dynorphins(58). In murine models of arthritis, HBOT has also been shown to affect inflammatory pain by reducing mechanical hypersensitivity and inflammation(59). Patients with FM often experience degenerative changes in muscle, abnormal oxygen pressure, and lower muscle blood flow due to hypoxia(16, 60). Local ischemia makes the mitochondria need to produce higher levels of free radicals to induce apoptosis, reduce ATP synthesis and increase lactate concentration in the muscle, thus ultimately leading to muscle weakness and pain(61, 62). HBOT improves muscle oxygenation in FM, which can reduce the tissue lactate concentration and help maintain ATP levels, thus possibly preventing tissue damage in ischemic tissue(63). It raises the oxygen concentration in all tissues far above physiological levels to cause hyperoxia, which breaks the hypoxic-pain cycle in patients with FM(63). In addition, the high excitability of pain processing pathways in the brain and low activity of pain inhibition pathways may cause excessive pain in FM(64). Studies have shown that patients with FM have higher activity in the somatosensory cortex and lower activity in the frontal, medial frontal, cingulate gyrus, and cerebellar cortex than healthy subjects(65). HBOT has been shown to increase neurotrophic and nitric oxide levels, reduce oxidative stress, promote cell metabolism by enhancing the mitochondrial function of neurons and glial cells, and may even promote the production of endogenous neural stem cells(66). The specific mechanism of HBOT on FM needs to be further investigated.

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

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.

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References

1. Sueiro Blanco F, Estévez Schwarz I, Ayán C, Cancela J, Martín V. Potential benefits of non-pharmacological therapies in fibromyalgia. The open rheumatology journal. 2008;2:1-6.
2. Thomas EN, Blotman F. Aerobic exercise in fibromyalgia: a practical review. Rheumatology international. 2010;30(9):1143-50.
3. Alciati A, Nucera V, Masala IF, Giallanza M, La Corte L, Giorgi V, et al. One year in review 2021: fibromyalgia. Clinical and experimental rheumatology. 2021;39 Suppl 130(3):3-12.
4. Siracusa R, Paola RD, Cuzzocrea S, Impellizzeri D. Fibromyalgia: Pathogenesis, Mechanisms,

Diagnosis and Treatment Options Update. International journal of molecular sciences. 2021;22(8).

5. Schmidt-Wilcke T, Clauw DJ. Fibromyalgia: from pathophysiology to therapy. Nature reviews Rheumatology. 2011;7(9):518-27.

6. Sarzi-Puttini P, Atzeni F, Mease PJ. Chronic widespread pain: from peripheral to central evolution. Best practice & research Clinical rheumatology. 2011;25(2):133-9.

7. Häuser W, Galek A, Erbslöh-Möller B, Köllner V, Kühn-Becker H, Langhorst J, et al. Posttraumatic stress disorder in fibromyalgia syndrome: prevalence, temporal relationship between posttraumatic stress and fibromyalgia symptoms, and impact on clinical outcome. Pain. 2013;154(8):1216-23.

8. Imbierowicz K, Egle UT. Childhood adversities in patients with fibromyalgia and somatoform pain disorder. European journal of pain (London, England). 2003;7(2):113-9.

9. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. Lancet (London, England). 1999;354(9186):1248-52.

10. Gouvinhas C, Veiga D, Mendonça L, Sampaio R, Azevedo LF, Castro-Lopes JM. Interventional Pain Management in Multidisciplinary Chronic Pain Clinics: A Prospective Multicenter Cohort Study with One-Year Follow-Up. Pain research and treatment. 2017;2017:8402413.

11. Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. The Journal of rheumatology Supplement. 2005;75:6-21.

12. Smith BH, Elliott AM, Chambers WA, Smith WC, Hannaford PC, Penny K. The impact of chronic pain in the community. Family practice. 2001;18(3):292-9.

13. Sutherland AM, Clarke HA, Katz J, Katznelson R. Hyperbaric Oxygen Therapy: A New Treatment for Chronic Pain? Pain practice : the official journal of World Institute of Pain. 2016;16(5):620-8.

14. El-Shewy KM, Kunbaz A, Gad MM, Al-Husseini MJ, Saad AM, Sammour YM, et al. Hyperbaric oxygen and aerobic exercise in the long-term treatment of fibromyalgia: A narrative review. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2019;109:629-38.

15. Efrati S, Hadanny A, Daphna-Tekoah S, Bechor Y, Tiberg K, Pik N, et al. Recovery of Repressed Memories in Fibromyalgia Patients Treated With Hyperbaric Oxygen - Case Series Presentation and Suggested Bio-Psycho-Social Mechanism. Frontiers in psychology. 2018;9:848.

16. Gu N, Niu JY, Liu WT, Sun YY, Liu S, Lv Y, et al. Hyperbaric oxygen therapy attenuates neuropathic hyperalgesia in rats and idiopathic trigeminal neuralgia in patients. European journal of pain (London, England). 2012;16(8):1094-105.

17. Yildiz S, Kiralp MZ, Akin A, Keskin I, Ay H, Dursun H, et al. Hyperbaric oxygen therapy reduces muscle tenderness and raises pain threshold in patients suffering from fibromyalgia. Diving and Hyperbaric Medicine. 2007;37(4):225-.

18. KK J. Textbook of Hyperbaric Medicine, 3rd ed.. Seattle, WA: Hogrefe and Huber Publishers. 1999.

19. Wilson HD, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment decreases inflammation and mechanical hypersensitivity in an animal model of inflammatory pain. Brain research. 2006;1098(1):126-8.

20. Efrati S, Golan H, Bechor Y, Faran Y, Daphna-Tekoah S, Sekler G, et al. Hyperbaric oxygen therapy can diminish fibromyalgia syndrome--prospective clinical trial. PloS one. 2015;10(5):e0127012.

21. Evcik D, Ketenci A, Sindel D. The Turkish Society of Physical Medicine and Rehabilitation (TSPMR) guideline recommendations for the management of fibromyalgia syndrome. Turkish journal of physical medicine and rehabilitation. 2019;65(2):111-23.

22. Hawk C, Whalen W, Farabaugh RJ, Daniels CJ, Minkalis AL, Taylor DN, et al. Best Practices for

Chiropractic Management of Patients with Chronic Musculoskeletal Pain: A Clinical Practice Guideline. Journal of alternative and complementary medicine (New York, NY). 2020;26(10):884-901.
23. Mascarenhas RO, Souza MB, Oliveira MX, Lacerda AC, Mendonça VA, Henschke N, et al. Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia: A Systematic Review and Meta-analysis. JAMA internal medicine. 2021;181(1):104-12.
24. Mease P, Arnold LM, Choy EH, Clauw DJ, Crofford LJ, Glass JM, et al. Fibromyalgia syndrome module at OMERACT 9: domain construct. The Journal of rheumatology. 2009;36(10):2318-29.
25. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed). 2021;372:n71.
26. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Seminars in arthritis and rheumatism. 2016;46(3):319-29.
27. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2011;343:d5928.
28. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ journal of surgery. 2003;73(9):712-6.
29. Andrade C. Mean Difference, Standardized Mean Difference (SMD), and Their Use in Meta-Analysis: As Simple as It Gets. The Journal of clinical psychiatry. 2020;81(5).
30. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ (Clinical research ed). 2011;342:d549.
31. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. Journal of clinical epidemiology. 2011;64(4):380-2.
32. Curtis K, Katz J, Djaiani C, O'Leary G, Uehling J, Carroll J, et al. Evaluation of a Hyperbaric Oxygen Therapy Intervention in Individuals with Fibromyalgia. Pain Medicine. 2021;22(6):1324-32.
33. Izquierdo-Alventosa R, Inglés M, Cortés-Amador S, Gimeno-Mallench L, Sempere-Rubio N, Chirivella J, et al. Comparative study of the effectiveness of a low-pressure hyperbaric oxygen treatment and physical exercise in women with fibromyalgia: randomized clinical trial. Therapeutic Advances in Musculoskeletal Disease. 2020;12.
34. Guggino G, Schinocca C, Lo Pizzo M, Di Liberto D, Garbo D, Raimondo S, et al. Erratum: T helper 1 response is correlated with widespread pain, fatigue, sleeping disorders and the quality of life in patients with fibromyalgia and is modulated by hyperbaric oxygen therapy (Clinical and experimental rheumatology). Clinical and experimental rheumatology. 2020;38(6):1275.
35. Casale R, Boccia G, Symeonidou Z, Atzeni F, Batticciotto A, Salaffi F, et al. Neuromuscular efficiency in fibromyalgia is improved by hyperbaric oxygen therapy: looking inside muscles by means of surface electromyography. Clinical and experimental rheumatology. 2019;37(1):75-80.
36. Bosco G, Ostardo E, Rizzato A, Garetto G, Paganini M, Melloni G, et al. Clinical and morphological effects of hyperbaric oxygen therapy in patients with interstitial cystitis associated with fibromyalgia. BMC Urology. 2019;19(1).
37. Atzeni F, Casale R, Alciati A, Masala IF, Batticciotto A, Talotta R, et al. Hyperbaric oxygen treatment of fibromyalgia: a prospective observational clinical study. Clinical and experimental rheumatology. 2019;37(1):63-9.

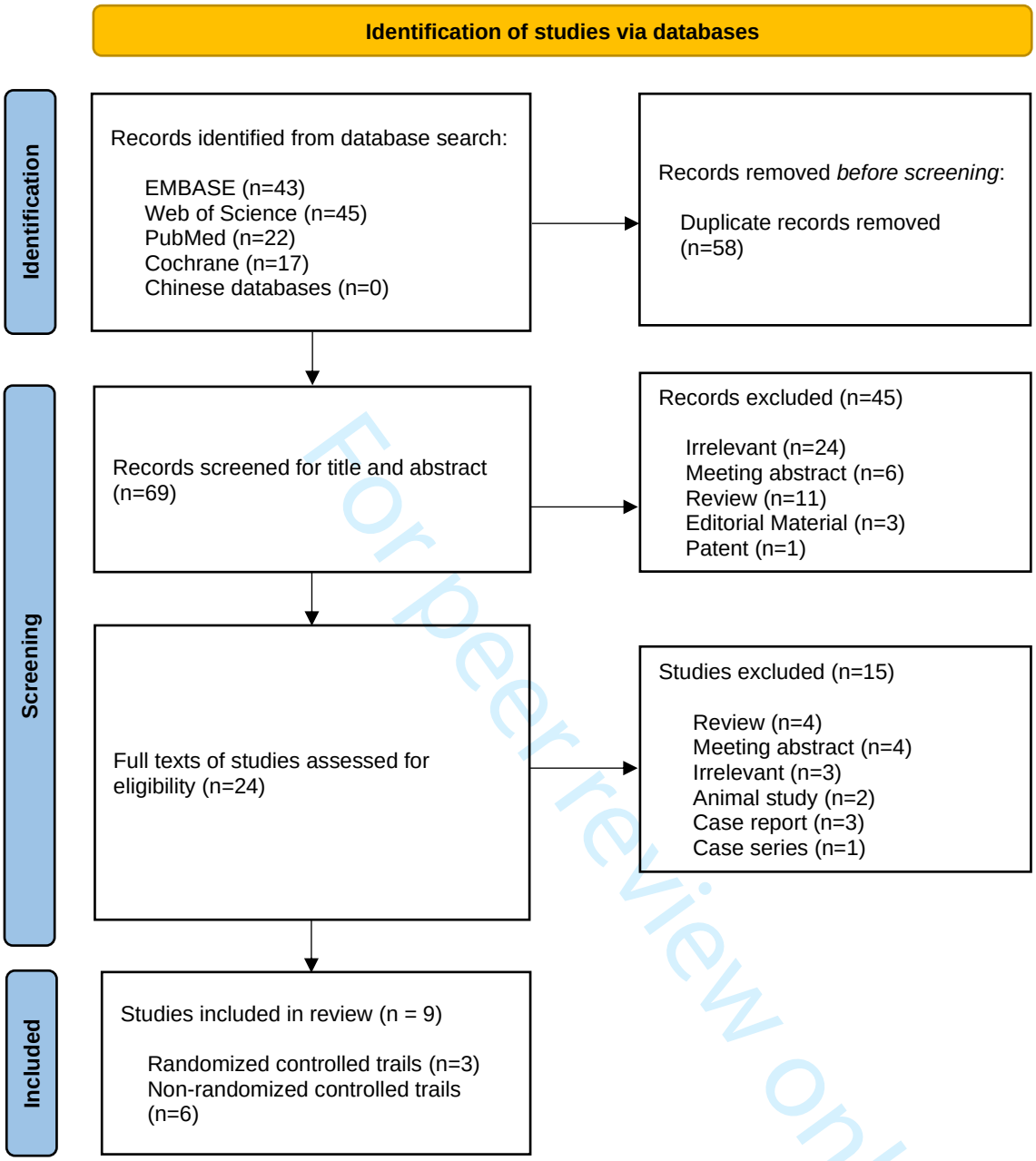
38. Hadanny A, Bechor Y, Catalogna M, Daphna-Tekoah S, Sigal T, Cohenpour M, et al. Hyperbaric Oxygen Therapy Can Induce Neuroplasticity and Significant Clinical Improvement in Patients Suffering From Fibromyalgia With a History of Childhood Sexual Abuse-Randomized Controlled Trial. Frontiers in psychology. 2018;9:2495.
39. Efrati S, Golan H, Bechor Y, Faran Y, Daphna-Tekoah S, Sekler G, et al. Hyperbaric oxygen therapy can diminish fibromyalgia syndrome--prospective clinical trial. PloS one. 2015;10(5):e0127012.
40. Yildiz Ş, Kiralp MZ, Akin A, Keskin I, Ay H, Dursun H, et al. A new treatment modality for fibromyalgia syndrome: Hyperbaric oxygen therapy. Journal of International Medical Research. 2004;32(3):263-7.
41. Jeschonneck M, Grohmann G, Hein G, Sprott H. Abnormal microcirculation and temperature in skin above tender points in patients with fibromyalgia. Rheumatology (Oxford, England). 2000;39(8):917-21.
42. Lund N, Bengtsson A, Thorborg P. Muscle tissue oxygen pressure in primary fibromyalgia. Scandinavian journal of rheumatology. 1986;15(2):165-73.
43. Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, et al. Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury - randomized prospective trial. PloS one. 2013;8(11):e79995.
44. Efrati S, Fishlev G, Bechor Y, Volkov O, Bergan J, Kliakhandler K, et al. Hyperbaric oxygen induces late neuroplasticity in post stroke patients--randomized, prospective trial. PloS one. 2013;8(1):e53716.
45. Akarsu S, Tekin L, Ay H, Carli AB, Tok F, Simşek K, et al. The efficacy of hyperbaric oxygen therapy in the management of chronic fatigue syndrome. Undersea & hyperbaric medicine : journal of the Undersea and Hyperbaric Medical Society, Inc. 2013;40(2):197-200.
46. Shimoda M, Enomoto M, Horie M, Miyakawa S, Yagishita K. Effects of hyperbaric oxygen on muscle fatigue after maximal intermittent plantar flexion exercise. Journal of strength and conditioning research. 2015;29(6):1648-56.
47. Ishii Y, Deie M, Adachi N, Yasunaga Y, Sharman P, Miyanaga Y, et al. Hyperbaric oxygen as an adjuvant for athletes. Sports medicine (Auckland, NZ). 2005;35(9):739-46.
48. Kaufmann I, Eisner C, Richter P, Huge V, Beyer A, Chouker A, et al. Lymphocyte subsets and the role of TH1/TH2 balance in stressed chronic pain patients. Neuroimmunomodulation. 2007;14(5):272-80.
49. Jokinen-Gordon H, Barry RC, Watson B, Covington DS. A Retrospective Analysis of Adverse Events in Hyperbaric Oxygen Therapy (2012-2015): Lessons Learned From 1.5 Million Treatments. Advances in skin & wound care. 2017;30(3):125-9.
50. Jain KK. Springer International Publishing; 2017. Textbook of Hyperbaric Medicine.
51. Hoggan BL, Cameron AL. Systematic review of hyperbaric oxygen therapy for the treatment of non-neurological soft tissue radiation-related injuries. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2014;22(6):1715-26.
52. Oliaei S, SeyedAlinaghi S, Mehrtak M, Karimi A, Noori T, Mirzapour P, et al. The effects of hyperbaric oxygen therapy (HBOT) on coronavirus disease-2019 (COVID-19): a systematic review. European journal of medical research. 2021;26(1):96.
53. Thompson CD, Uhelski ML, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment decreases pain in two nerve injury models. Neuroscience research. 2010;66(3):279-83.
54. Palmquist BM, Philipson B, Barr PO. Nuclear cataract and myopia during hyperbaric oxygen

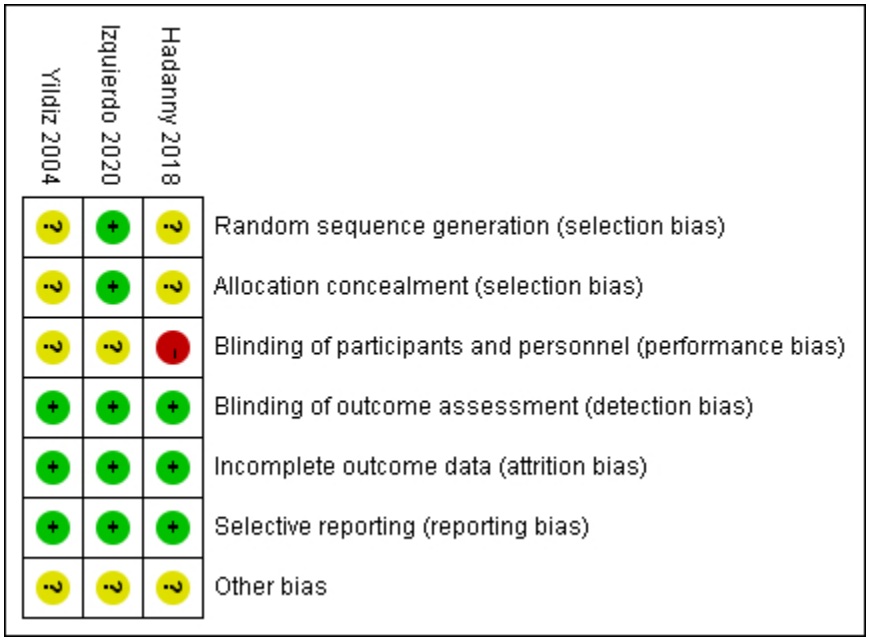
therapy. The British journal of ophthalmology. 1984;68(2):113-7.
55. Gesell LB, Trott A. De novo cataract development following a standard course of hyperbaric oxygen therapy. Undersea & hyperbaric medicine : journal of the Undersea and Hyperbaric Medical Society, Inc. 2007;34(6):389-92.
56. Chung E, Zelinski LM, Ohgami Y, Shirachi DY, Quock RM. Hyperbaric oxygen treatment induces a 2-phase antinociceptive response of unusually long duration in mice. The journal of pain. 2010;11(9):847-53.
57. Gibbons CR, Liu S, Zhang Y, Sayre CL, Levitch BR, Moehlmann SB, et al. Involvement of brain opioid receptors in the anti-allodynic effect of hyperbaric oxygen in rats with sciatic nerve crush-induced neuropathic pain. Brain research. 2013;1537:111-6.
58. Heeman JH, Zhang Y, Shirachi DY, Quock RM. Involvement of spinal cord opioid mechanisms in the acute antinociceptive effect of hyperbaric oxygen in mice. Brain research. 2013;1540:42-7.
59. Wilson HD, Toepfer VE, Senapati AK, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment is comparable to acetylsalicylic acid treatment in an animal model of arthritis. The journal of pain. 2007;8(12):924-30.
60. Park JH, Phothimat P, Oates CT, Hernanz-Schulman M, Olsen NJ. Use of P-31 magnetic resonance spectroscopy to detect metabolic abnormalities in muscles of patients with fibromyalgia. Arthritis and rheumatism. 1998;41(3):406-13.
61. Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. International journal of clinical and experimental medicine. 2009;2(1):1-16.
62. Behan WM, More IA, Behan PO. Mitochondrial abnormalities in the postviral fatigue syndrome. Acta neuropathologica. 1991;83(1):61-5.
63. Yildiz S, Uzun G, Kiralp Z. Hyperbaric oxygen therapy in chronic pain management. Current pain and headache reports. 2006;10(2):95-100.
64. Barilaro G, Francesco Masala I, Parracchini R, Iesu C, Caddia G, Sarzi-Puttini P, et al. The Role of Hyperbaric Oxygen Therapy in Orthopedics and Rheumatological Diseases. The Israel Medical Association journal : IMAJ. 2017;19(7):429-34.
65. Guedj E, Cammilleri S, Niboyet J, Dupont P, Vidal E, Dropinski JP, et al. Clinical correlate of brain SPECT perfusion abnormalities in fibromyalgia. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2008;49(11):1798-803.
66. Lin KC, Niu KC, Tsai KJ, Kuo JR, Wang LC, Chio CC, et al. Attenuating inflammation but stimulating both angiogenesis and neurogenesis using hyperbaric oxygen in rats with traumatic brain injury. The journal of trauma and acute care surgery. 2012;72(3):650-9.

Figure 1. PRISMA flowchart.

Figure 2. 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.

Figure 3. Forest plot of pain relief.





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)

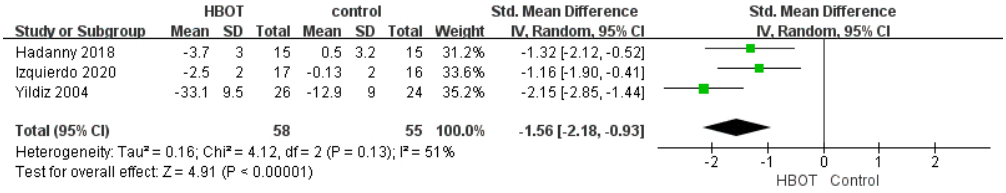


Figure 3. Forest plot of pain relief.

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"))**	22	20:08:04
#6	Search: **"fibromyalgia" OR "fibrositic nodule" OR "fibrositic nodule" OR "fibrositis" OR "fibrositis syndrome" OR "myalgia, fibro"**	13,579	20:06:54
#5	Search: **(hyperbaric oxygenation[MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract]))**	18,499	20:04:55
#4	Search: **fibromyalgia[MeSH Terms]**	9,569	20:04:01
#3	Search: **(hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract])**	15,251	20:02:45
#2	Search: **hyperbaric oxygenation[MeSH Terms]**	12,570	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])))**	22	20:08:04
#6	•••	›	Search: **(((((fibromyalgia) OR (fibrositic nodule)) OR (fibrositic nodule)) OR (fibrositis)) OR (fibrositis syndrome)) OR (myalgia, fibro)**	13,579	20:06:54
#5	•••	›	Search: **(hyperbaric oxygenation[MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract]))**	18,499	20:04:55
#4	•••	›	Search: **fibromyalgia[MeSH Terms]**	9,569	20:04:01
#3	•••	›	Search: **(hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract])**	15,251	20:02:45
#2	•••	›	Search: **hyperbaric oxygenation[MeSH Terms]**	12,570	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
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4
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21352
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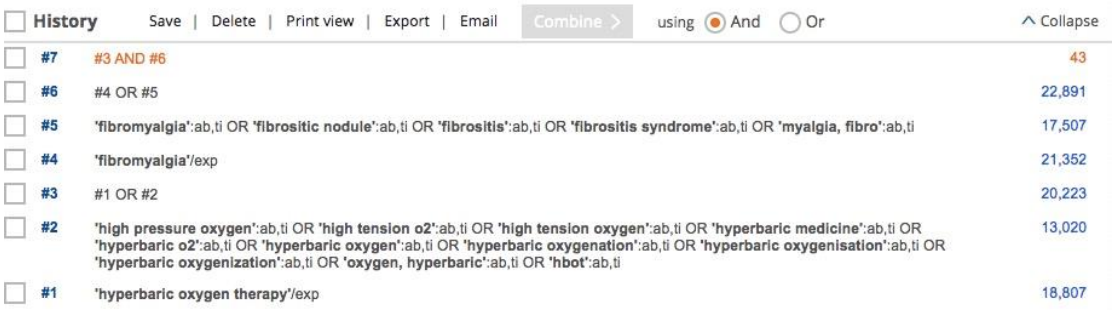
17507
6
4 OR 5
22891
7
3 AND 6
43



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
3
1 AND 2
45

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

CNKI (Chinese database)
(篇关摘=高压氧) AND (篇关摘=纤维肌痛)
0

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）
0

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			1
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
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
METHODS			
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			
RESULTS			
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
DISCUSSION			
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
OTHER INFORMATION			
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

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:

PRISMA 2020 Checklist

10.1136/bmj.n71

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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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Manuscript ID	bmjopen-2022-062322.R2
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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 You, Jiuhong; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine Ma, Hui; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine Zhou, Mei; Sichuan University, Department of Rehabilitation Medicine Center, West China Hospital; Sichuan University, School of Rehabilitation Sciences, West China School of Medicine 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
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Complementary medicine, Public health, Rehabilitation medicine
Keywords:	Rheumatology < INTERNAL MEDICINE, PAIN MANAGEMENT, Rehabilitation medicine < INTERNAL MEDICINE

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

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¶These authors contributed equally to this work.

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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

assessment.

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

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

1. 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 three 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 worldwide(4). FM is more frequent in females, with a female-to-male ratio of 9:1(5).

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

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

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

2. Methods

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

2.1. Search strategy

A literature search was conducted to identify all articles involving the use of hyperbaric oxygen to treat FM. The search strategy is shown in Supplementary appendix A. PubMed, EMBASE, Web of Science, Cochrane Library, 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. The search included MeSH and free text terms such as “hyperbaric oxygen therapy”, “fibromyalgia” and synonyms.

2.2. 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: RCTs and non-RCTs; 2) subjects: FM patients conformed to the 2016 American College of Rheumatology (ACR) diagnostic criteria(26) [i.e. They met the following criteria: generalized pain for at least three months and a widespread pain index (WPI) ⩾7 and symptom severity scale (SSS) ⩾ 5 or a WPI of 4–6 and a SSS score ⩾ 9]; 3) the intervention: patients in the experimental group received HBOT as the intervention measure, and patients in the control group received conventional treatment or nothing. The conventional treatment was any pharmacological or nonpharmacological therapy other than HBOT. The course of treatment and parameters were unlimited. 4) outcome indicators: the inner Core Outcome Set of FM symptoms (pain, tenderness, fatigue, multidimensional function, patient global, sleep disturbance) and adverse events. The exclusion criteria were as follows: animal studies, reviews, duplicate publications, irrelevant studies, editorial materials, patients, case reports, or meeting abstracts.

2.3. 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 were excluded after three or more attempts to email the lead author and obtain 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 predesigned form was used for information extraction. The content included the article’s 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 that reflected 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) assisted in resolving the disagreement.

2.4. Types of outcome measures

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

2.4.1. Pain and tenderness

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

2.4.2. Multidimensional function

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

2.4.3. Fatigue

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

2.4.4. Patient global

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

2.4.5. Sleep disturbance

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

2.4.6. Adverse events

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

2.5. Risk of bias assessment

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

2.6. Statistical analysis

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

2.7. Grade the quality of evidence

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

2.8. Patient and public involvement

Patients and the public were not involved in this study.

3. Results

3.1. Characteristics of the included studies

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

Table 1. Characteristics of the included articles.

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

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

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

3.2. Quality assessment

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

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

3.3. Efficacy of HBOT

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

3.3.1. Pain relief

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

3.3.2. Tenderness

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

3.3.3. Multidimensional function

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

3.3.4. Fatigue

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

in FM patients(48). HBOT can improve FM symptoms by reducing the upregulation of 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 large effect. The GRADE evidence profile is shown in Table 3.

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[a]	Serious[b]	Not serious[c]	Not Serious[d]	Large effect [e]	three RCTs	113	SMD: -1.56 (-2.18 to-0.93)	⊗⊗⊗○ Moderate

Abbreviations: CI, confidence intervals; SMD, standardized mean difference.
Notes: [a] most of the included studies were assessed as some concerns/high-risk bias; [b] I^2>50%; [c] direct participants, intervention, and outcomes; [d] total sample size > 100; [e] 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

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

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

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

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References

1. Sueiro Blanco F, Estévez Schwarz I, Ayán C, Cancela J, Martín V. Potential benefits of non-pharmacological therapies in fibromyalgia. The open rheumatology journal. 2008;2:1-6.
2. Thomas EN, Blotman F. Aerobic exercise in fibromyalgia: a practical review. Rheumatology international. 2010;30(9):1143-50.
3. Alciati A, Nucera V, Masala IF, Giallanza M, La Corte L, Giorgi V, et al. One year in review 2021: fibromyalgia. Clinical and experimental rheumatology. 2021;39 Suppl 130(3):3-12.
4. Siracusa R, Paola RD, Cuzzocrea S, Impellizzeri D. Fibromyalgia: Pathogenesis, Mechanisms, Diagnosis and Treatment Options Update. International journal of molecular sciences. 2021;22(8).

5. Schmidt-Wilcke T, Clauw DJ. Fibromyalgia: from pathophysiology to therapy. Nature reviews Rheumatology. 2011;7(9):518-27.
6. Sarzi-Puttini P, Atzeni F, Mease PJ. Chronic widespread pain: from peripheral to central evolution. Best practice & research Clinical rheumatology. 2011;25(2):133-9.
7. Häuser W, Galek A, Erbslöh-Möller B, Köllner V, Kühn-Becker H, Langhorst J, et al. Posttraumatic stress disorder in fibromyalgia syndrome: prevalence, temporal relationship between posttraumatic stress and fibromyalgia symptoms, and impact on clinical outcome. Pain. 2013;154(8):1216-23.
8. Imbierowicz K, Egle UT. Childhood adversities in patients with fibromyalgia and somatoform pain disorder. European journal of pain (London, England). 2003;7(2):113-9.
9. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. Lancet (London, England). 1999;354(9186):1248-52.
10. Gouvinhas C, Veiga D, Mendonça L, Sampaio R, Azevedo LF, Castro-Lopes JM. Interventional Pain Management in Multidisciplinary Chronic Pain Clinics: A Prospective Multicenter Cohort Study with One-Year Follow-Up. Pain research and treatment. 2017;2017:8402413.
11. Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. The Journal of rheumatology Supplement. 2005;75:6-21.
12. Smith BH, Elliott AM, Chambers WA, Smith WC, Hannaford PC, Penny K. The impact of chronic pain in the community. Family practice. 2001;18(3):292-9.
13. Sutherland AM, Clarke HA, Katz J, Katznelson R. Hyperbaric Oxygen Therapy: A New Treatment for Chronic Pain? Pain practice : the official journal of World Institute of Pain. 2016;16(5):620-8.
14. El-Shewy KM, Kunbaz A, Gad MM, Al-Husseini MJ, Saad AM, Sammour YM, et al. Hyperbaric oxygen and aerobic exercise in the long-term treatment of fibromyalgia: A narrative review. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2019;109:629-38.
15. Efrati S, Hadanny A, Daphna-Tekoah S, Bechor Y, Tiberg K, Pik N, et al. Recovery of Repressed Memories in Fibromyalgia Patients Treated With Hyperbaric Oxygen - Case Series Presentation and Suggested Bio-Psycho-Social Mechanism. Frontiers in psychology. 2018;9:848.
16. Gu N, Niu JY, Liu WT, Sun YY, Liu S, Lv Y, et al. Hyperbaric oxygen therapy attenuates neuropathic hyperalgesia in rats and idiopathic trigeminal neuralgia in patients. European journal of pain (London, England). 2012;16(8):1094-105.
17. Yildiz S, Kiralp MZ, Akin A, Keskin I, Ay H, Dursun H, et al. Hyperbaric oxygen therapy reduces muscle tenderness and raises pain threshold in patients suffering from fibromyalgia. Diving and Hyperbaric Medicine. 2007;37(4):225-.
18. KK J. Textbook of Hyperbaric Medicine, 3rd ed.. Seattle, WA: Hogrefe and Huber Publishers. 1999.
19. Wilson HD, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment decreases inflammation and mechanical hypersensitivity in an animal model of inflammatory pain. Brain research. 2006;1098(1):126-8.
20. Efrati S, Golan H, Bechor Y, Faran Y, Daphna-Tekoah S, Sekler G, et al. Hyperbaric oxygen therapy can diminish fibromyalgia syndrome--prospective clinical trial. PloS one. 2015;10(5):e0127012.
21. Evcik D, Ketenci A, Sindel D. The Turkish Society of Physical Medicine and Rehabilitation (TSPMR) guideline recommendations for the management of fibromyalgia syndrome. Turkish journal of physical medicine and rehabilitation. 2019;65(2):111-23.
22. Hawk C, Whalen W, Farabaugh RJ, Daniels CJ, Minkalis AL, Taylor DN, et al. Best Practices for Chiropractic Management of Patients with Chronic Musculoskeletal Pain: A Clinical Practice Guideline.

Journal of alternative and complementary medicine (New York, NY). 2020;26(10):884-901.
23. Mascarenhas RO, Souza MB, Oliveira MX, Lacerda AC, Mendonça VA, Henschke N, et al. Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia: A Systematic Review and Meta-analysis. JAMA internal medicine. 2021;181(1):104-12.
24. Mease P, Arnold LM, Choy EH, Clauw DJ, Crofford LJ, Glass JM, et al. Fibromyalgia syndrome module at OMERACT 9: domain construct. The Journal of rheumatology. 2009;36(10):2318-29.
25. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed). 2021;372:n71.
26. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Seminars in arthritis and rheumatism. 2016;46(3):319-29.
27. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2011;343:d5928.
28. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ journal of surgery. 2003;73(9):712-6.
29. Andrade C. Mean Difference, Standardized Mean Difference (SMD), and Their Use in Meta-Analysis: As Simple as It Gets. The Journal of clinical psychiatry. 2020;81(5).
30. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ (Clinical research ed). 2011;342:d549.
31. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. Journal of clinical epidemiology. 2011;64(4):380-2.
32. Curtis K, Katz J, Djaiani C, O'Leary G, Uehling J, Carroll J, et al. Evaluation of a Hyperbaric Oxygen Therapy Intervention in Individuals with Fibromyalgia. Pain Medicine. 2021;22(6):1324-32.
33. Izquierdo-Alventosa R, Inglés M, Cortés-Amador S, Gimeno-Mallench L, Sempere-Rubio N, Chirivella J, et al. Comparative study of the effectiveness of a low-pressure hyperbaric oxygen treatment and physical exercise in women with fibromyalgia: randomized clinical trial. Therapeutic Advances in Musculoskeletal Disease. 2020;12.
34. Guggino G, Schinocca C, Lo Pizzo M, Di Liberto D, Garbo D, Raimondo S, et al. Erratum: T helper 1 response is correlated with widespread pain, fatigue, sleeping disorders and the quality of life in patients with fibromyalgia and is modulated by hyperbaric oxygen therapy (Clinical and experimental rheumatology). Clinical and experimental rheumatology. 2020;38(6):1275.
35. Casale R, Boccia G, Symeonidou Z, Atzeni F, Batticciotto A, Salaffi F, et al. Neuromuscular efficiency in fibromyalgia is improved by hyperbaric oxygen therapy: looking inside muscles by means of surface electromyography. Clinical and experimental rheumatology. 2019;37(1):75-80.
36. Bosco G, Ostardo E, Rizzato A, Garetto G, Paganini M, Melloni G, et al. Clinical and morphological effects of hyperbaric oxygen therapy in patients with interstitial cystitis associated with fibromyalgia. BMC Urology. 2019;19(1).
37. Atzeni F, Casale R, Alciati A, Masala IF, Batticciotto A, Talotta R, et al. Hyperbaric oxygen treatment of fibromyalgia: a prospective observational clinical study. Clinical and experimental rheumatology. 2019;37(1):63-9.
38. Hadanny A, Bechor Y, Catalogna M, Daphna-Tekoah S, Sigal T, Cohenpour M, et al. Hyperbaric

Oxygen Therapy Can Induce Neuroplasticity and Significant Clinical Improvement in Patients Suffering From Fibromyalgia With a History of Childhood Sexual Abuse-Randomized Controlled Trial. Frontiers in psychology. 2018;9:2495.

39. Efrati S, Golan H, Bechor Y, Faran Y, Daphna-Tekoah S, Sekler G, et al. Hyperbaric oxygen therapy can diminish fibromyalgia syndrome--prospective clinical trial. PloS one. 2015;10(5):e0127012.

40. Yildiz Ş, Kiralp MZ, Akin A, Keskin I, Ay H, Dursun H, et al. A new treatment modality for fibromyalgia syndrome: Hyperbaric oxygen therapy. Journal of International Medical Research. 2004;32(3):263-7.

41. Jeschonneck M, Grohmann G, Hein G, Sprott H. Abnormal microcirculation and temperature in skin above tender points in patients with fibromyalgia. Rheumatology (Oxford, England). 2000;39(8):917-21.

42. Lund N, Bengtsson A, Thorborg P. Muscle tissue oxygen pressure in primary fibromyalgia. Scandinavian journal of rheumatology. 1986;15(2):165-73.

43. Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, et al. Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury - randomized prospective trial. PloS one. 2013;8(11):e79995.

44. Efrati S, Fishlev G, Bechor Y, Volkov O, Bergan J, Kliakhandler K, et al. Hyperbaric oxygen induces late neuroplasticity in post stroke patients--randomized, prospective trial. PloS one. 2013;8(1):e53716.

45. Akarsu S, Tekin L, Ay H, Carli AB, Tok F, Simşek K, et al. The efficacy of hyperbaric oxygen therapy in the management of chronic fatigue syndrome. Undersea & hyperbaric medicine : journal of the Undersea and Hyperbaric Medical Society, Inc. 2013;40(2):197-200.

46. Shimoda M, Enomoto M, Horie M, Miyakawa S, Yagishita K. Effects of hyperbaric oxygen on muscle fatigue after maximal intermittent plantar flexion exercise. Journal of strength and conditioning research. 2015;29(6):1648-56.

47. Ishii Y, Deie M, Adachi N, Yasunaga Y, Sharman P, Miyanaga Y, et al. Hyperbaric oxygen as an adjuvant for athletes. Sports medicine (Auckland, NZ). 2005;35(9):739-46.

48. Kaufmann I, Eisner C, Richter P, Huge V, Beyer A, Chouker A, et al. Lymphocyte subsets and the role of TH1/TH2 balance in stressed chronic pain patients. Neuroimmunomodulation. 2007;14(5):272-80.

49. Jokinen-Gordon H, Barry RC, Watson B, Covington DS. A Retrospective Analysis of Adverse Events in Hyperbaric Oxygen Therapy (2012-2015): Lessons Learned From 1.5 Million Treatments. Advances in skin & wound care. 2017;30(3):125-9.

50. Jain KK. Springer International Publishing; 2017. Textbook of Hyperbaric Medicine.

51. Hoggan BL, Cameron AL. Systematic review of hyperbaric oxygen therapy for the treatment of non-neurological soft tissue radiation-related injuries. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2014;22(6):1715-26.

52. Oliaei S, SeyedAlinaghi S, Mehrtak M, Karimi A, Noori T, Mirzapour P, et al. The effects of hyperbaric oxygen therapy (HBOT) on coronavirus disease-2019 (COVID-19): a systematic review. European journal of medical research. 2021;26(1):96.

53. Thompson CD, Uhelski ML, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment decreases pain in two nerve injury models. Neuroscience research. 2010;66(3):279-83.

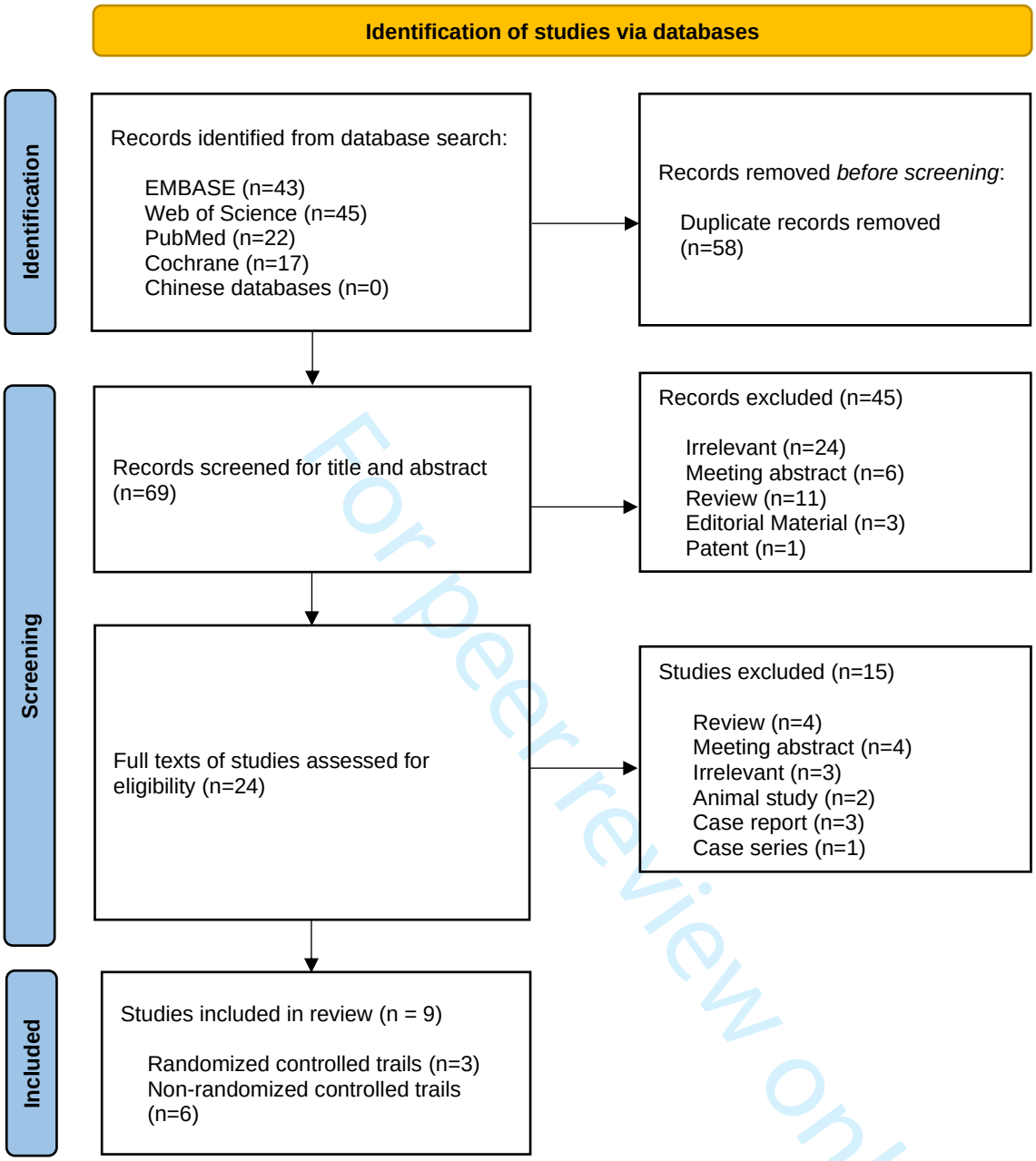
54. Palmquist BM, Philipson B, Barr PO. Nuclear cataract and myopia during hyperbaric oxygen therapy. The British journal of ophthalmology. 1984;68(2):113-7.

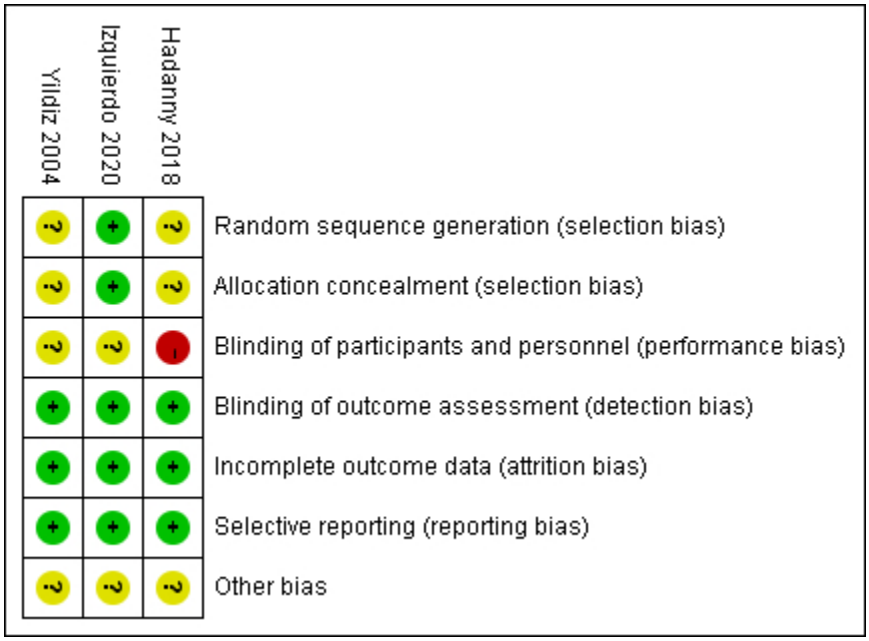
55. Gesell LB, Trott A. De novo cataract development following a standard course of hyperbaric oxygen therapy. Undersea & hyperbaric medicine : journal of the Undersea and Hyperbaric Medical Society, Inc. 2007;34(6):389-92.
56. Chung E, Zelinski LM, Ohgami Y, Shirachi DY, Quock RM. Hyperbaric oxygen treatment induces a 2-phase antinociceptive response of unusually long duration in mice. The journal of pain. 2010;11(9):847-53.
57. Gibbons CR, Liu S, Zhang Y, Sayre CL, Levitch BR, Moehlmann SB, et al. Involvement of brain opioid receptors in the anti-allodynic effect of hyperbaric oxygen in rats with sciatic nerve crush-induced neuropathic pain. Brain research. 2013;1537:111-6.
58. Heeman JH, Zhang Y, Shirachi DY, Quock RM. Involvement of spinal cord opioid mechanisms in the acute antinociceptive effect of hyperbaric oxygen in mice. Brain research. 2013;1540:42-7.
59. Wilson HD, Toepfer VE, Senapati AK, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment is comparable to acetylsalicylic acid treatment in an animal model of arthritis. The journal of pain. 2007;8(12):924-30.
60. Park JH, Phothimat P, Oates CT, Hernanz-Schulman M, Olsen NJ. Use of P-31 magnetic resonance spectroscopy to detect metabolic abnormalities in muscles of patients with fibromyalgia. Arthritis and rheumatism. 1998;41(3):406-13.
61. Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. International journal of clinical and experimental medicine. 2009;2(1):1-16.
62. Behan WM, More IA, Behan PO. Mitochondrial abnormalities in the postviral fatigue syndrome. Acta neuropathologica. 1991;83(1):61-5.
63. Yildiz S, Uzun G, Kiralp Z. Hyperbaric oxygen therapy in chronic pain management. Current pain and headache reports. 2006;10(2):95-100.
64. Barilaro G, Francesco Masala I, Parracchini R, Iesu C, Caddia G, Sarzi-Puttini P, et al. The Role of Hyperbaric Oxygen Therapy in Orthopedics and Rheumatological Diseases. The Israel Medical Association journal : IMAJ. 2017;19(7):429-34.
65. Guedj E, Cammilleri S, Niboyet J, Dupont P, Vidal E, Dropinski JP, et al. Clinical correlate of brain SPECT perfusion abnormalities in fibromyalgia. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2008;49(11):1798-803.
66. Lin KC, Niu KC, Tsai KJ, Kuo JR, Wang LC, Chio CC, et al. Attenuating inflammation but stimulating both angiogenesis and neurogenesis using hyperbaric oxygen in rats with traumatic brain injury. The journal of trauma and acute care surgery. 2012;72(3):650-9.

Figure 1. PRISMA flowchart.

Figure 2. 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.

Figure 3. Forest plot of pain relief.





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)

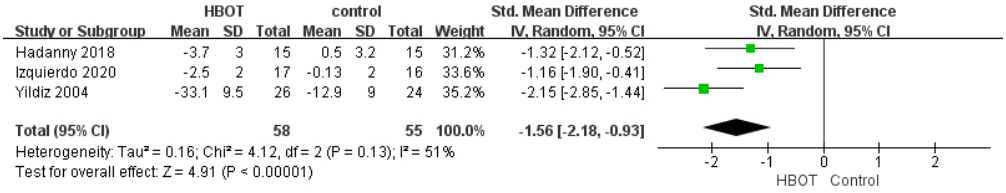


Figure 3. Forest plot of pain relief.

282x56mm (72 x 72 DPI)

Pubmed

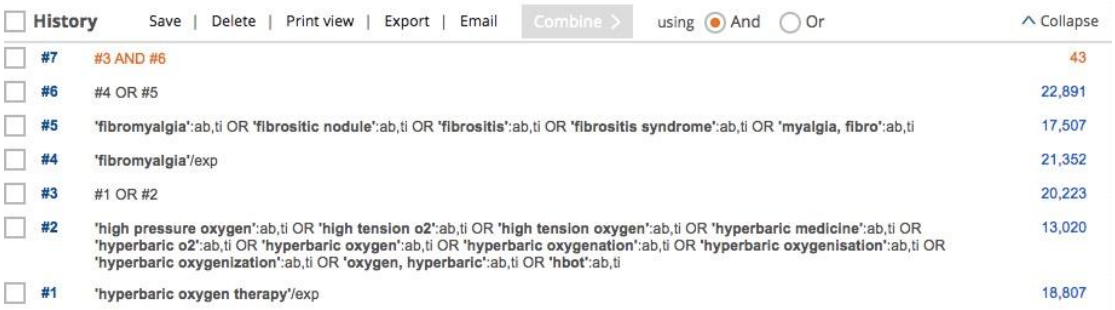
Search	Query	Results	Time
#7	Search: **((hyperbaric oxygenation [MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract]))) AND ((fibromyalgia[MeSH Terms]) OR ("fibromyalgia" OR "fibrositic nodule" OR "fibrositic nodule" OR "fibrositis" OR "fibrositis syndrome" OR "myalgia, fibro"))**	22	20:08:04
#6	Search: **"fibromyalgia" OR "fibrositic nodule" OR "fibrositic nodule" OR "fibrositis" OR "fibrositis syndrome" OR "myalgia, fibro"**	13,579	20:06:54
#5	Search: **(hyperbaric oxygenation[MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract]))**	18,499	20:04:55
#4	Search: **fibromyalgia[MeSH Terms]**	9,569	20:04:01
#3	Search: **(hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract])**	15,251	20:02:45
#2	Search: **hyperbaric oxygenation[MeSH Terms]**	12,570	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])))**	22	20:08:04
#6	•••	›	Search: **(((((fibromyalgia) OR (fibrositic nodule)) OR (fibrositic nodule)) OR (fibrositis)) OR (fibrositis syndrome)) OR (myalgia, fibro)**	13,579	20:06:54
#5	•••	›	Search: **(hyperbaric oxygenation[MeSH Terms]) OR ((hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract]))**	18,499	20:04:55
#4	•••	›	Search: **fibromyalgia[MeSH Terms]**	9,569	20:04:01
#3	•••	›	Search: **(hyperbaric[Title/Abstract]) OR (HBOT[Title/Abstract])**	15,251	20:02:45
#2	•••	›	Search: **hyperbaric oxygenation[MeSH Terms]**	12,570	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
3
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
6
4 OR 5
22891
7
3 AND 6
43



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
3
1 AND 2
45

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

CNKI (Chinese database)
(篇关摘=高压氧) AND (篇关摘=纤维肌痛)
0

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）
0

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			1
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
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
METHODS			
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			
RESULTS			
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
DISCUSSION			
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
OTHER INFORMATION			
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

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:

PRISMA 2020 Checklist

10.1136/bmj.n71

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