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Review article

Is manual therapy of the diaphragm effective for people with obstructive lung diseases? A systematic review

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A B S T R A C T

Background: Diaphragm dysfunction is common among people with obstructive lung disease (OLD). The effectiveness of manual therapy (MT) techniques specifically targeting this region remains unclear. The scope of this systematic review is to investigate the effectiveness of MT on the zone of apposition (ZOA) of the diaphragm in lung function, diaphragm excursion (DE), chest expansion, exercise capacity (EC), maximal inspiratory pressure (PImax) and dyspnea in people suffering from OLD.
Methods: Key databases were systematically searched. Two independent reviewers screened the papers for inclusion. Methodological quality and the quality of evidence were assessed using the PEDro scale and the GRADE approach, respectively.
Results: Two studies were included. One showed that diaphragmatic stretching and the manual diaphragm release technique (MDRT) improved DE and CE (p<0.001, p<0.05, respectively). The other showed that MDRT improved DE and EC (p<0.05, p<0.05, respectively).
Conclusion: This systematic review provides preliminary evidence on the effectiveness of MT on the ZOA of the diaphragm in people with COPD. Further research is needed in order for definitive conclusions to be drawn.
Registration number in Prospero: CRD42022308595

1. Introduction

Obstructive lung disease (OLD) is the name for a category of lung conditions characterized by airway obstruction, such as asthma, bronchiectasis, bronchitis, and chronic obstructive pulmonary disease (COPD). Among these lung conditions, asthma and COPD are the most prevalent non-communicable diseases that have a significant negative impact on global health [1,2]. Asthma affects an estimated 1−18% of the population in various countries [3]. Between 1990 and 2015, the number of people suffering from asthma increased by 12.6% to 358.2 million worldwide [4]. Moreover, the World Health Organization estimates that COPD will be the third leading cause of death by 2030 [5].

On a pathophysiological basis, two of the main dysfunctions in people suffering from COPD are the abnormal mechanics of the thoracic cage and the respiratory muscles' poor length-tension relationship, which are a consequence of the disease's processes [6,7]. It is widely known that people suffering from COPD have a mechanical disadvantage to their diaphragm function [8,9]. Lung hyperinflation and air trapping, two prominent symptoms of COPD, impair the diaphragm's performance altering the mechanical connections between its numerous components [10].

The dysfunctional breathing in COPD is due to hyperinflation at exercise; while at rest, many COPD patients do not exhibit dysfunctional breathing. In contrast, some patients suffering from asthma can present hyperventilation syndrome, even at rest. Despite the difference in the pathomechanism responsible for these two lung conditions, the pulmonary hyperinflation and the hyperventilation syndrome that characterizes COPD and asthma, both cause similar pathological alterations that impair the diaphragm's capacity to raise and expand the lower ribcage [2,7,11]. However, for asthma patients, this is only true during acute exacerbations (i.e. in a stable state, asthma patients can still expand the lower rib cage). The ribcage's transverse diameter is increased due to the static hyperinflation in COPD during inspiration, which places the diaphragm in a disadvantageous position on the respiratory system's pressure-volume curve, reducing its capacity to generate force and increasing the work of breathing, (Fig. 1), [12,13].

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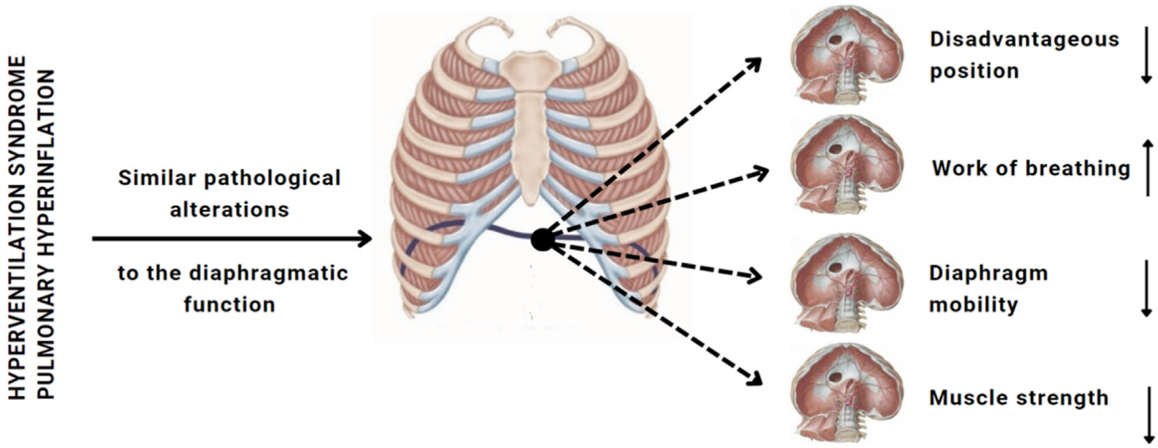

Fig. 1. The common diaphragm dysfunctions in COPD and asthma due to pulmonary hyperinflation and hyperventilation syndrome.

Therefore, the diaphragm muscle was the structure with the most interest in this investigation, not only due to the aforementioned factors but also because it is the primary muscle of respiration due to its anatomical characteristics and its contribution to minute ventilation (60−80%), [14,15]. The physiological diaphragmatic function acts as a protective mechanism against health issues linked to lymphatic flow, bad posture and musculoskeletal disorders in the neck and pelvis anatomical areas [14,16]. On the contrary, poor diaphragm function has been linked to respiratory symptoms such as fatigue, intolerance to exertion and shortness of breath [8].

From a rehabilitation standpoint, typical multidisciplinary approaches used in pulmonary rehabilitation programs (PRP) commonly focus on each patient's unique physical and social performance and autonomy [17]. These intervention programs frequently involve patient disease education, performance (endurance and strength training), behavioural and psychological therapies without any focus on chest wall mechanics [6,18]. Although the gold standard in PRP is exercise training, additional hands-on treatments can be performed to increase the efficacy of PRP [9]. For instance, manual therapy (MT) has also been suggested in PRP as a possible therapeutic technique for COPD individuals [19].

According to the literature, specific MT techniques could be beneficial for enhancing the mechanical respiratory pump's function [6]. MT techniques can directly improve the functioning of the surrounding tissues (e.g. increase joint motion and decrease muscle tone locally) and indirectly other functions (e.g. lung function, breathlessness, strength, and even physical performance) [6].

Although most RCTs have assessed the impact of MT on the rehabilitation of COPD patients, they do so by applying MT techniques to various structures of the thoracic cage [16]. This leads to the question of whether the patient ultimately benefited from a particular intervention or whether an alternative MT approach would have produced the same or better results. It is noteworthy that, up to this point, no study has comprehensively examined the impact of MT, in particular, on the zone of apposition (ZOA) of the diaphragm in adults suffering from COPD. This SR's structure was designed to look for indications that may reveal the necessity of the division of MT approaches applied on the chest wall by anatomical structures in people with OLD suffering from pathological adaptations of their chest wall or from respiratory symptoms.

Therefore, the purpose of this SR was to examine the effects of MT on the ZOA of the diaphragm on lung function, diaphragm excursion, chest expansion, exercise capacity, dyspnea, quality of life and maximal inspiratory pressure (PImax) in people suffering from OLD, either alone or as an adjustment to other standard treatments (exercise training).

2. Materials and methods

2.1. Protocol and registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were followed for the search strategy and reporting for this SR [20] (Table 1). The SR protocol has been made available in the Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42022308595).

2.2. Eligibility criteria

The PICOS framework (P: population, I: interventions, C: comparator/control, O: outcomes, and S: study design) was modified to reflect eligibility requirements (Table 2).

2.3. Information sources and search strategy

The lead author (DT) conducted a full search without time, place, or language restrictions in the following electronic databases from inception to February 2022: MEDLINE, EMBASE, CINAHL Plus, ZETOC, PubMed, Web of Science, PEDro, and MEDLINE. The PICOS framework (Table 2) was used to design the search strategy. Medical Subject Headings (MESH) were used when appropriate. An example of search strategy for the MEDLINE database can be found in Supplementary material 1.

2.4. Study selection

Both reviewers performed a pilot test before the investigation began on a small sample of articles to assess the screening forms' efficacy. The main author (DT) imported all the search outcomes into the Review Manager (RevMan Cochrane Collaboration's software) and identified and removed any duplicates. Both the two reviewers (DT, MA) screened the papers' titles and abstracts. Each reviewer's folder contained the final listings of the possibly eligible studies' abstracts and full texts (DT, MA). Screening the chosen papers against the inclusion/exclusion criteria was the first task for the independent reviewers (DT and MA) and it was conducted by each reviewer separately. The two reviewers (DT, MA) examined the titles and abstracts of all included articles. One folder was created for each reviewer (DT, MA) and contained the final listings of the possibly relevant research (abstracts and complete texts).

Table 1
PRISMA Checklist.

Section / topic	#	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2−3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Results			
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7−8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10−12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

2.5. Data collection process and data items

Two reviewers (DT and MA) separately extracted data using a personalized data extraction form comparing the effectiveness of (1) MT to no treatment, (2) MT to usual care (breathing retraining, inspiratory muscle training, exercise alone, stretching exercises, (3) MT to light manual interventions (e.g. gentle massage), or a combination of these interventions in people >18 years old, diagnosed with COPD (GOLD criteria) or with mild, moderate or severe asthma. Studies documenting any procedure of MT, including specific hands-on techniques, mobilization, massage, soft tissue therapy, manipulation, chiropractic, osteopathy, and passive movements (applied with hands-on pressure) to the diaphragm and generally in the region of interest (the zone of apposition), were included.

In this SR, MT approaches specifically on the ZOA of the diaphragm were the interventions of main interest. However, eligible therapies may be utilized with or without other interventions. If MT was not provided through direct hand contact, studies were excluded. Studies reporting therapeutic exercise, acupressure, spinal manipulative therapy, reflexology, and home-based self-treatment therapies performed by non-specialists were excluded. Outcome measures included: (1) spirometry, used to quantify the lung function, including FEV1, FVC, and FEV1/FVC, (2) ultrasonography, used to quantify diaphragm excursion (DE), [21,22], (3) chest expansion (CE) measured by inch tape [23], (4) exercise capacity (EC), (5) maximum inspiratory/expiratory pressures (MIP/MEP), [24,25], (6) the Medical Research Council (MRC) modified dyspnea scale [26].

Table 2
Eligibility criteria in accordance with PICOS framework.

Population
Inclusion criteria:
- Adults (≥18 years old)
- Mild, moderate, severe COPD **OR** mild, moderate, severe asthma

Exclusion criteria:
- Participants (<18 years old)
- Exacerbation of symptoms the last three months before participants enrolled on the program
- Thoracic scoliosis of more than 25° or a chest wall deformity
- Osteopathic or chiropractic treatment in the three months before.

Interventions
Studies reporting any type of manual therapy applied on the zone of apposition of the diaphragm such as:
- Specific hands-on techniques
- Mobilization
- Massage
- Soft tissue therapy
- Manipulation
- Chiropractic
- Osteopathy
- Passive movements

Comparator/Control
Eligible studies which compare:
MT to usual care (breathing retraining, inspiratory muscle training, exercise alone, stretching exercises)
MT to light manual interventions (e.g., gentle massage)
MT to a combination of these interventions

Outcomes of interest:
- Studies using spirometry to measure lung function
- Studies using ultrasonography to measure diaphragm mobility
- Studies using an inch tape or any other device (e.g. sensors) to measure chest expansion
- Inclusion of all types of dyspnea subjective measurement
- Inclusion of all types of functional subjective and objective assessment
- Exercise capacity

Study design
Eligibility criteria included:
- Randomized controlled trials **OR** randomized cross over trials

2.6. Quality assessment

Two reviewers (DT, MA) independently evaluated the methodology of thestudies included using the PEDro scale. The final studies were categorized into the following two groups: 5 = 'fair' and 9 −10 = 'excellent'. In order to avoid confusion, a third independent reviewer (MM) mediated the process of the quality assessment.

2.7. Summary measures and synthesis of results

The primary objective of this research was to combine studies for meta-analysis. However, this was not possible due to the small number of studies [9,19], and the included randomized cross-over trial study design. As a result, Table 3 summarizes the key features of the studies included.

2.8. Quality of evidence

The quality of the evidence was evaluated for each outcome domain using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method [26]. The overall classification of the evidence was "High," "Moderate," "Low," or "Very Low." Since only randomized trials were included, high-quality evidence was initially given to each outcome domain [27]. Then, five criteria were used to evaluate the quality of the evidence (limitations, inconsistency, indirectness, imprecision, and publication bias). Therefore, restrictions were classified as severe when information was gathered from poor methodological investigations.

SearchStrategy (MEDLINE)

1	musculoskeletal manipulations/
2	manipulation, chiropractic/
3	manipulation, osteopathic/
4	therapy, soft tissue/
5	muscle stretching exercises/
6	manual therapy.mp
7	manipulation.mp
8	mobilisation.mp
9	Manual therapy.mp
10	Trigger point.mp
11	Myofascial release.mp
12	Muscle stretching.mp
13	Diaphragm release technique.mp
14	(1-13) OR
15	Obstructive lung diseases/
16	bronchitis/
17	pulmonary disease, chronic obstructive/
18	asthma/
19	Obstructive pulmonary disease.mp
20	COPD.mp
21	Asthma.mp
22	Diaphragm.mp
23	(15-22) OR
24	**14 AND 23**
25	**/**: Map Term to Subject Heading
26	.mp : keyword

Fig. 2. MEDLINE search strategy.

3. Results

3.1. Flow of studies

A flowchart of the studies is presented in Fig. 3. From an initial search of databases, 2844 potential studies were identified, 1564 titles were screened, of which 1528 were excluded. Nineteen full-text studies were assessed for eligibility. Out of the remaining, seventeen were excluded as presented in Fig. 3. Two studies were included [9,19] in the SR because they met the inclusion criteria. The judgment of the third reviewer (MM) was deemed not necessary because of consensus between the two primary reviewers (DT-MA).

3.2. Characteristics of included studies

The two studies included made a similar hypothesis regarding MT's impact on the diaphragm. According to the GOLD criteria, the

Table 3
Characteristics of included studies.

	A. Nair et.al. (2018)	T. Rocha. et.al. (2015)
Age (years)	67 ± 8	71 ± 6
Design	RCT	Single centre RCT
Gender	Male: 12 Female: 8	Male: 14 Female: 5
Group: Control	Sham n = 10	Control group n = 9
Group: Intervention	DST+MDRT Groups crossed over	MDRT Sham
Number of treatments	1 Treatment WOP 3h	6 Sessions 2 Week period
Participants	Mild – Moderate COPD patients	COPD patients FEV1=<80% predicted
PEDro Score	5/11	9/10
OMT group	OMT n = 10	MDRT group n = 10
Outcome	DE, CE	DE, EC, MRP, ACWK

ACWK, Abdominal and Chest Wall kinematics; CE, Chest expansion; COPD, Chronic Obstructive Pulmonary Disease; DE, diaphragm excursion; DST, Diaphragmatic Stretching Technique; EC, exercise capacity; FEV1 forced expiratory volume in one second; FVC forced vital capacity; Sham, light touch with the same anatomical landmarks without exerting pressure or traction; MDRT, Manual Diaphragm Release Technique; MRP, Maximum Respiratory Pressures; OMT, Orthopaedic Manual Therapy; RCT, Randomized Controlled Trial; WOP, Wash-out period.

participants in both of the studies were outpatients with mild or moderate COPD [28].

3.3. Quality assessment of included studies

The quality of the studies methods varies widely, but overall evaluations were good to outstanding. For both studies included, each quality score is reported in Table 3.

3.4. Results of individual studies

The sample sizes of both studies were generally small, ranging between 19 participants [9], and 20 participants [19]. There were intervention regimens, ranging from 1 to 6 sessions lasting one day to two weeks. In the trial of Nair et al. (2019), theeffects of the DST and MDRT on DE following a single maneuver [19] were examined on patients from groups A and B who had crossed over to the other group. In contrast, the study of Rocha et al. (2015), [9] split the participants into two groups, an experimental and a control group. The patient's position and the therapist's use of hands-on approaches are described in detail in the studies [9,19] included. The following outcome domains were investigated in the included trials assessing the impact of MT techniques on the ZOA of the diaphragm: DM (in both of the studies) [9,19], and CE, MIP/MEP, SNIP, EC and OP (only in study, of Rocha et al. 2015). The results per outcome domain for each study are represented below. The findings are summarized in Tables 4 and 5.

3.4.1. Diaphragm mobility

DM following DST, on the right side, there was a difference of 0.29 ± 0.21 (p = 0.001) in the midclavicular line and 0.25 ± 0.20 (p = 0.003) in the midaxillary line. On the left side, there was a difference of 0.24 ± 0.24 (p = 0.004) in the midclavicular line and 0.35 ± 0.25 (p = 0.312) in the midaxillary line. In MDRT, on the right side, there was a difference of 0.24 ± 0.20 (p = 0.001) in the midclavicular line and 0.22 ± 0.20 (p = 0.001) in the midaxillary line. On the left side, there was a difference of 0.26 ± 0.28 (p = 0.002) in the midclavicular line and 0.29 ± 0.18 (p = 0.001) in the midaxillary [19].

The average acute effect during the first treatment session was a between-group difference of 2 mm in favor of the experimental technique, but this was not statistically significant (95% CI −2 to 6). The average acute effect during the sixth treatment session was larger,

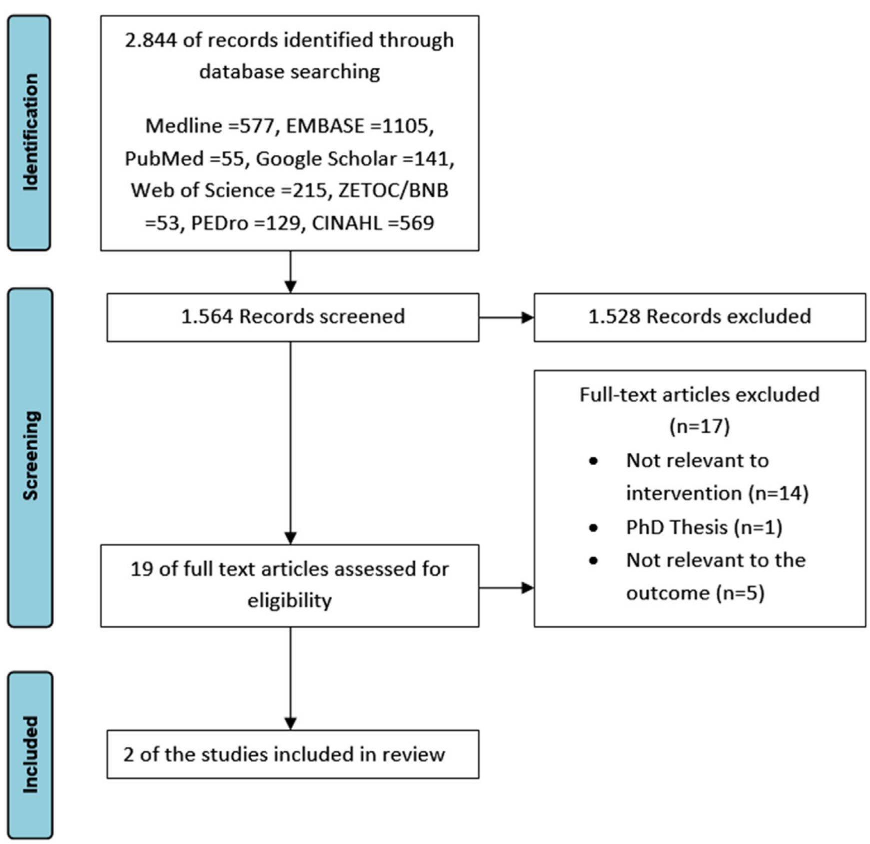

Fig. 3. Flowchart of the study selection.

Table 4
Findings of the included study Taciano Rocha. et.al. 2015.

Outcome	Groups								Difference between groups		
	Pre 1		Post 1		Pre 6		Post 6		Post 1 minus Pre 1	Post 6 minus Pre 6	Pre 6 minus Pre 1
	Exp *n* = 10	Con n = 9	Exp *n* = 10	Con n = 9	Exp *n* = 10	Con n = 9	Exp *n* = 10	Con n = 9	Exp minus Con	Exp minus Con	Exp Minus Con
DM	71	68	73	69	82	61	87	61	2	6	18
(ML, RH) (mm)	−16	−15	−17	−17	−11	−17	−10	−17	(−2 to 6)	(2 to 9)	(8 to 28)
MIP	64	64	67	59	64	61	69	61	8	4	4
(cm H2O)	−20	−11	−18	−19	−20	−14	−25	−14	(−1 to 17)	(0 to 9)	(−2 to 10)
MEP	98	99	101	89	104	105	105	102	13	6	−2
(cm H2O)	−30	−22	−27	−19	−30	−32	−32	−17	(1 to 24)	(1 to 12)	(−20 to 16)
SNIP	48	53	56	50	51	49	59	48	10	9	6
(cm H2O)	−12	−12	−8	−10	−12	−8	−13	−8	(5 to 16)	(4 to 14)	(−3 to 16)
OP	554	418	564	456	449	435	506	461	−28	31	−122
Vcw (ml)	−151	−69	−158	−101	−168	−126	−157	−124	(−99 to 54)	(−46 to 108)	(−263 to 19)
	144	102	143	107	102	112	134	113	−7	31	−52
Vrcp (ml)	−66	−41	−79	−42	−65	−42	−66	−52	(−40 to 27)	(6 to 56)	(−86 to -18)
	67	48	66	50	41	65	49	59	−3	15	−43
Vrca (ml)	−43	−18	−45	−14	−31	−20	−30	−22	(−21 to 16)	(2 to 27)	(−86 to -5)
	344	272	355	303	307	262	323	293	−21	−15	−27
Vap (ml)	−92	−102	−99	−138	−102	−129	−97	−140	(−85 to 40)	(−79 to 48)	(−131 to 77)

Con, Control group; DM, Diaphragm mobility; Exp, Experimental group; MEP, Maximal expiratory pressure; MIP, Maximal inspiratory pressure ML, midclavicular line; OP, Optoelectronic plethysmography; Pre 1, before first session; Post 1, after first session; Post 6, after sixth session; Pre 6, before sixth session; RH, Right Hemidiaphragm; SNIP, Sniff Nasal Inspiratory Pressure; Vab, volume abdomen, Vcw, total chest wall volume, Vrca, volume abdominal rib cage, Vrcp, volume pulmonary rib cage.

with a between-group difference of 6 mm, which was statistically significant (95% CI 2 to 9). When the cumulative effect of the treatments was estimated by the change from before the first session to before the sixth session, the between-group difference was 18 mm in favor of the experimental technique, which was also statistically significant (95% CI 8 to 28) [9].

3.4.2. *Chest expansion*

Concerning the CE, after the DST, there was a difference of 0.76 ± 0.71 (p = 0.001) at the level of 4th intercostal space and 0.62 ± 0.64 (p = 0.001) at the level of the xiphoid process. After MDRT, there was a difference of 0.82 ± 0.06 (p = 0.002) at the level of the 4th intercostal space and 0.72 ± 0.88 (p = 0.002) at the level of the xiphoid process. The difference in the post-intervention values at the level of the 4th intercostal space was found to be −0.11 ± 0.16, and at the level of the xiphoid process was found to be −0.09 ± 0.08 [19].

3.4.3. *Exercise capacity*

The experimental group showed a mean cumulative improvement on the 6-minute walk test of 15 m (SD 14) from before the first session to before the sixth session, whereas the control group deteriorated by a mean of 6 m (SD 6). This equated to a statistically significant between-group difference in change for the 6-minute walk distance in favor of the experimental group by 22 m (95% CI 11 to 32) [9].

3.4.4. *MIP/MEP*

The mean between-group difference in change in MIP favoured the experimental group when analysed as change during the first session, change during the sixth session, and cumulative change over the course of treatments. However, none of these changes were statistically significant. MEP and sniff nasal inspiratory pressure both showed significant acute benefits of the MDRT during the first and sixth treatments. Neither measure showed a significant benefit when the cumulative change was analysed [9].

3.4.5. *Optoelectronic plethysmography*

During the first treatment, the experimental group showed a significant benefit in vital capacity (mean between-group difference in change 295 ml, 95% CI 151 to 439) and similarly during the sixth

Table 5
Findings of the included study Aisharaya Nair et al.

		Diaphragm mobility		Chest Expansion	
DST		R.S. (cm)	L.S. (cm)		
	Midclavicular Line	Pre: 2.56 ± 0.56 Post: 2.86 ± 0.59 Difference: 0.29 ± 0.21 P: 0.001**	Pre: 2.57 ± 0.54 Post: 2.79 ± 0.52 Difference: 0.24 ± 0.24 P: 0.004**	**4th intercostal space (inches)**	Pre: 34.98 ± 2.95 Post: 35.69 ± 2.85 Difference: 0.76 ± 0.71 P: 0.001**
	Midaxillary Line	Pre: 2.74 ± 0.63 Post: 2.95 ± 0.70 Difference: 0.25 ± 0.20 P: 0.003**	Pre: 2.69 ± 0.63 Post: 2.85 ± 0.6 Difference: 0.35 ± 0.25 P: 0.312	**Xiphoid process (inches)**	Pre: 36.10 ± 3.22 Post: 36.73 ± 3.26 Difference: 0.62 ± 0.64 P: 0.001**
MDRT		R.S. (cm)	L.S. (cm)		
	Midclavicular Line	Pre: 2.56 ± 0.56 Post: 2.78 ± 0.52 Difference: 0.24 ± 0.20 P: 0.001**	Pre: 2.57 ± 0.54 Post: 2.84 ± 0.59 Difference: 0.26 ± 0.28 P: 0.002**	**4th intercostal space (inches)**	Pre: 34.98 ± 2.95 Post: 35.80 ± 3.01 Difference: 0.82 ± 0.06 P: 0.002**
	Midaxillary Line	Pre: 2.74 ± 0.63 Post: 2.98 ± 0.62 Difference: 0.22 ± 0.20 P: 0.001**	Pre: 2.69 ± 0.63 Post: 2.95 ± 0.55 Difference: 0.29 ± 0.18 P: 0.001**	**Xiphoid process (inches)**	Pre: 36.10 ± 3.22 Post: 36.82 ± 3.34 Difference: 0.72 ± 0.88 P: 0.002**

DST, Diaphragmatic Stretching Technique; MDRT, Manual Diaphragm Release Technique; R.S., Right Side; L.S., Left Side;.
** Highly significant; Pre, Before session; Post, after session.

Table 6
Quality assessment of evidence per outcome domain of included studies in people with obstructive lung diseases (GRADE).

Quality assessment per outcome domain-Randomized Control - Crossover trials						
N of patients (studies)	Factors					
	Limitations in study design	Inconsistency of results	Indirectness of evidence	Imprecision	Publication Bias	Overall
Outcome: Diaphragm mobility						
30 (2)	Not serious	Not Serious	Serious	Serious	Not Serious	⊕○○○ Very low
Outcome: Chest expansion						
20 (1)	Serious	Not Serious	Serious	Serious	Not Serious	⊕○○○ Very low
Outcome: Spirometry						
20 (1)	Serious	Not Serious	Serious	Serious	Not Serious	⊕○○○ Very low
Outcome:6MWT						
20 (1)	Serious	Not Serious	Serious	Serious	Not Serious	⊕○○○ Very low
Outcome: Optoelectronic plethysmography						
20 (1)	Serious	Not Serious	Serious	Serious	Not Serious	⊕○○○ Very low
Outcome: Maximal inspiratory pressure						
20 (1)	Serious	Not Serious	Serious	Serious	Not Serious	⊕○○○ Very low
Outcome: Maximal expiratory pressure						
20 (1)	Serious	Not Serious	Serious	Serious	Not Serious	⊕○○○ Very low
Outcome: Sniff nasal inspiratory pressure						
20 (1)	Serious	Not Serious	Serious	Serious	Not Serious	⊕○○○ Very low

GRADE, Grading of Recommendations, Assessment, Development and Evaluation guidelines.

treatment (249 ml, 95% CI 114 to 383).However, no significant cumulative benefit was observed. There were no noticeable between-group differences in Vcw or Vab when compartmental volumes were analyzed during the inspiratory capacity maneuver. Although Vrcp and Vrca both had an immediate benefit from the experimental intervention during the sixth session, when the cumulative effect was examined, they also showed deterioration as a result of the experimental intervention [9].

3.5. *Synthesis of results and additional analysis*

The results from several investigations were classified according to the outcome domains. According to GRADE, the quality of the evidence for each outcome domain was compiled and is shown in Table 6.

Regarding the meta-analysis, although the combination of the studies was not applicable, it was considered necessary to report the main findings of DM across the studies. The effectiveness of the MDRT was examined using ultrasonography in both of the studies included. In the study of Rocha et al. 2015, [9] the mobility of both hemidiaphragms was examined in two different anatomical areas (midclavicular and midaxillary lines). Nair et al. 2018 only studied the mobility of the right hemidiaphragm. The data from both studies (right hemidiaphragm from midclavicular line measurements) are reported in Table 7.

4. Discussion

4.1. *Summary of evidence*

This was the first SR investigating the effectiveness of MT on the ZOA of the diaphragm in people suffering from OLD. Previous published SRs have investigated the effectiveness of MT on general regions of the thorax and the cervical spine in people with COPD [29–31] concluding that the role of MT in people suffering from COPD is not sufficiently supported by the existing research. The included RCTs [9,19] applied MT techniques to the diaphragm as the primary intervention. In some of the final nineteen studies before the final selection process, the interventions included MT techniques on the diaphragm and other regions. (e.g. the cervical spine). Only the studies with MT techniques as the main intervention on the ZOA compared to other or between groups were included. We examined the DMRT and the DST, two RCTs assessing manual treatment approaches' efficacy. A total of 39 mild and moderate COPD patients with a mean age of (71) and (66.85 ± 8.37) years, respectively, were included. The analysis of the two included RCTs showed "fair" and "high" PEDro scale scores (Table 3). Interventions were feasible, and adverse events were not mentioned. The results of the studies revealed statistically significant differences immediately after the intervention of the DM, CE and 6MWT. The between-group difference in the 6MWT of Rocha et al. (2015) [9] study was 15 m (SD 14). More specifically, the experimental group could walk longer distances

Table 7
Mobility of the right hemi-diaphragm in both of the included studies before and after MDRT.

Study (Year)	Pre 1 Session ML, RH (mm)	Post 1 Session ML, RH (mm)	Post 6 Session ML, RH (mm)	Difference between Pre 1 Post 1 sessions (mm)	Difference between Pre 1 Post 6 sessions (mm)
Aishwarya Nair et.al. (2018)	25.6 ± 5.6	27.8 ± 5.2	–	2.4 ± 0.2	–
Taciano Rocha. et.al. (2015)	70.63 ±15.50	73.37 ± 29.31	86.82 ± 9.83	2.74 ± 13.81	16.63 ± 1.69

ML, Midclavicular line; RH, Right Hemidiaphragm.

during the 6MWT. According to a recent SR that summarized the available information on the MCID for the 6MWT performed by people with a pathology (e.g., people suffering from COPD), an improvement of 14−30.5 m on the 6MWT may be considered clinically important [52]. This improvement in 6MWD due to MT could be attributed to several factors. The experimental group that received the MT treatment showed a considerable improvement in 6MWD compared to the control group that received the sham technique. Thus improvements in 6MWD could possibly be attributed to the MTtechnique. According to a previous study by Zanotti et al. [38], a potential reduction in RV might contribute to improvements in 6MWD. Additionally, it is important to mention that DM is an important parameter that could reveal information about the mechanics of the respiratory system and functional ability in COPD patients. [39]. As previously shown, patients with reduced DM exhibit poorer 6MWD performance [40]. Since MT might have a positive effect on DM by increasing it, this could explain the improvement in 6MWD observed in the experimental group. On top of this, another possible mechanism that could explain the improvements in 6MWD is the positive association between dynamic lung hyperinflation and exercise capacity [41]. Thus, any intervention that could reduce lung hyperinflation can possibly improve EC [40]. Therefore, further research is needed to investigate the effects of MT in improving EC in people with COPD. Concerning the other outcomes, the only outcome shared in the studies included is the DE as measured by ultrasonography between outcome measures. Significant improvements in the DE are shown in both of the studies. This constitutes the first important finding of this research. Even though dyspnea (shortness of breath) is one of the main symptoms of people with OLD [42,43], it was not one of the parameters assessed by the two studies included. Therefore, it is appropriate to mention that dyspnea can have a negative impact on both the level of EC and quality of life (QoL). [44−47]. Previous studies have demonstrated that even only one MT session can have a positive effect on chest wall mechanics, dyspnea, and peripheral oxygen saturation (SpO2) in people with COPD [48,49]. Specifically, according to the study of Yelvar et al. (2016), [48] a single MT session of soft tissue and joint mobilization immediately improved dyspnea (Borg Scale 0−10, pre: 2.3 ± 0.8 vs 1.8 ± 0.5). The authors reported that the mechanism underlying this improvement could be the increase in the respiratory muscle length and thoracic cage flexibility induced by MT. As a result, the breathing effort and the development of dyspnea in people with COPD are reduced [50]. However, the results are not consistent. For example, according to the findings of another study [51], MT did not result in any immediate improvements in lung function, dyspnea, or exercise performance [51]. Therefore, it is crucial for further research to be conducted in order to have a clearer understanding of whether MT can decrease the levels of dyspnea in people suffering from COPD or not.

In the studies included, it seems that although diaphragm mobilization techniques benefit people suffering from COPD [30−33], adults with asthma have not been investigated. That is the subsequent important finding of the present study because it reveals the need for more research on people with asthma.

In this investigation, the attention was focused on the ZOA of the diaphragm on purpose. The protocolof the study is based on findings from earlier studies. As previously mentioned [34], the radius (r) of the curvature of the diaphragm is a crucial factor in its force production. La Place's law states that the relationship between transdiaphragmatic pressure (Pdi) and the tangential tension (Tdi) created by the diaphragm is (PdiTdi/r2). A more tightly and curled diaphragm produces a smaller r and more efficient translation of diaphragmatic tension (Tdi) to pressure difference (Pdi). The pathological changes of the diaphragm affect its curvature by increasing its radius (r) and reducing the ability of the diaphragm to raise and expand the lower rib cage in people suffering from OLD. A recent study [35] reported the results of a subsequent static MRI study by Gauthier et al. (1994). This study showed that lung inflation, the shortening of the diaphragm, and the broadening of the lower rib cage affect the ZOA's dimension [36].

Previous studies have examined how MT hampers the development of respiratory muscle exhaustion [37]. These studies have suggested that MT techniques lead to a reduction in the workload of the respiratory muscles. Specifically, this is thought to happen because the increased sensory afferent stimulus increases: (a) neuromotor response, (b) muscle tension and (c) thoracic mobility, improving muscle viscoelasticity and decreasing muscle stiffness [9,37]. Stretching the muscles may also activate the Golgi tendon organs, which have receptors in the muscle-tendon area and could lead to diaphragm muscle inhibition [19,33].

As mentioned before, the pathological changes of the diaphragm in people suffering from OLD are a common feature. For this reason, answering which anatomical areas and hands-on therapy techniques are the most effective for increasing the diaphragm's excursion in people suffering from OLD is crucial. The present study's primary purpose was to improve the current knowledge regarding the role of MT in the functioning of the diaphragm in people suffering from OLD and provide important insights for future research.

4.2. Strengths and limitations

The study's strengths include the in-depth analysis of how MT on the ZOA of the diaphragm can affect people suffering from OLD, which is essential in improving our understanding of the role of MT in PRP. Another notable feature is the study's high-strength/systematic methodology, which rates the overall strength of the evidence for each outcome domain using checklists and the GRADE system. Two reviewers conducted screening, quality assessment, and data extraction independently. The small number of included studies revealed to us one of the main strengths of this study because it provides insights for future research.

Finally, some important limitations need to be considered. The low-quality evidence and the lack of dyspnea assessment of the included studies, the differences in the study designs, and methodological differences (e.g., the frequency, the duration of treatments, the outcomes measures and the age of the participants) are the main weaknesses. Since only two studies were included in this systematic review, conducting a meta-analysis was not possible.

5. Conclusions

This systematic review demonstrates that there are indications to support that MT on the ZOA of the diaphragm can be effective in improving DE, CE and EC in people suffering from COPD. However, there is no evidence to support the use of MT on the diaphragm in treating people with asthma. Further experimental investigations are needed to estimate the effectiveness of MT in PR programs in people suffering from OLD and, most importantly, in people with asthma.

Authors' contributions

D.T., E.G. and G.G. conceived this review; searches, study selection, data extraction and data handling were conducted by D.T., M.A., M. M., and G.K. The manuscript was prepared by D.T., M.A., M.P., G.K. and E.G. All authors were involved in drafting and approving the final version.

Declaration of Competing Interest

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