The Long-Term Benefit of Exercise With and Without Manual Therapy for Mild Chronic Obstructive Pulmonary Disease

A RANDOMIZED CONTROLLED TRIAL

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Purpose: Chronic obstructive pulmonary disease (COPD) is characterized by decreasing exercise capacity and deteriorating quality of life (QoL). Recent evidence indicates that combining exercise with manual therapy (MT) delivers greater improvements in exercise capacity than exercise alone in moderate COPD. The aim of this study was to investigate whether this combination delivers similar results in mild COPD.

Methods: A total of 71 participants aged 50-65 yr with mild COPD were randomly allocated to two groups: exercise only (Ex) or MT plus exercise (MT + Ex). Both groups received 16 wk of exercise with the MT + Ex group also receiving 8 MT sessions. Lung function (forced vital capacity [FVC] and forced expiratory volume in the 1st sec [FEV_1]), exercise capacity (6-min walk test [6MWT]), and QoL (St George's Respiratory Questionnaire [SGRQ] and Hospital Anxiety and Depression Scale [HADS]) were measured at baseline, 4, 8, 16, 24, 32, and 48 wk.

Results: Although there was no difference in the mean effect over time between groups for lung function (FEV_1, P = .97; FVC, P = .98), exercise capacity (6MWT, P = .98), and QoL (SGRQ, P = .41; HADS anxiety, P = .52; and HADS depression, P = .06), there were clinically meaningful improvements at 48 wk for 6MWT (30 m; 95% CI, 10-51 m; P < .001), SGRQ (6.3 units; 95% CI, 2.5-10.0; P < .001), and HADS anxiety (1.5 units; 95% CI, 0.3-2.8 units; P = .006) across the entire cohort.

Conclusions: While adding MT to Ex did not produce any additional benefits, exercise alone did deliver sustained modest improvements in exercise capacity and QoL in mild COPD.

Key Words: chronic obstructive pulmonary disease • COPD • exercise • manual therapy • quality of life

KEY PERSPECTIVES

What is novel?

- Chronic obstructive pulmonary disease (COPD) is characterized by decreasing thoracic compliance and declining exercise capacity. Administering a combination of manual therapy and exercise delivers greater improvements in exercise capacity compared to exercise alone in people with moderate COPD. These improvements are thought to be the result of a synergistic effect between interventions that lead to sustained increases in thoracic compliance.
- The results from this study on people with mild COPD showed that the same combination of interventions did not deliver additional improvements in exercise capacity.

What are the clinical and research implications?

- The study findings support the use of exercise for people with mild COPD.
- The findings also show that administering MT to the muscles and joints of the chest wall is only effective in more advanced stages of COPD where there is an assumption that there is a moderate degree of alteration in thoracic compliance.

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Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation, decreasing exercise capacity, and deteriorating quality of life (QoL).[1-3] Guidelines for the management of COPD recommend pulmonary rehabilitation (PR) for all stages of the disease.[1,2] Despite the benefits, PR is universally underutilized with referral, uptake, and completion rates alarmingly low.[4-6] As a result, there is a substantial unmet demand for services.[7]

Spirometry is the primary method used to diagnose COPD. The threshold for diagnosis is a ratio of <0.7 for

forced expiratory volume in the 1st sec (FEV_1) divided by forced vital capacity (FVC; FEV_1/FVC). There is, however, some controversy surrounding the optimal cutoff for defining airflow limitation, with evidence showing that the fixed ratio can lead to overdiagnosis of COPD in older populations, underdiagnosis in younger people, and sex imbalances as women tend to have higher FEV_1/FVC ratios than men.[2,8-11]

The goals of treatment differ for the different stages of COPD. In moderate to very severe COPD, prevention of respiratory complications such as exacerbations and respiratory mortality are the primary goals of treatment, whereas for mild COPD, there is a greater focus on symptom relief, slowing disease progression, and mitigating the risk of comorbidities.[12] As patients with mild COPD already experience a level of dyspnea that restricts their daily activities, exercise programs designed to reduce dyspnea levels have the potential to provide improvements in QoL.[13] However, these benefits have only been reported for the short term, with medium- to long-term benefits still unclear.[14]

One of the contributors to the onset of exertional dyspnea is chest tightness.[15-17] Chest tightness is a product of lung hyperinflation that results from air being trapped in the lungs. It alters the thixotropic characteristics of the chest wall muscles, causing an increase in the effort required to breathe.[18] This increase leads to muscle fatigue and the early onset of dyspnea. Delaying the onset allows for more exercise to be performed. If repeated over time, this approach has the potential to increase exercise capacity.

Manual therapy (MT) increases muscle length and joint mobility.[19,20] If applied to the thoracic spine and ribs, MT has the capability of increasing flexibility within the chest wall (thoracic compliance) and, with it, the potential to reduce the symptom of chest tightness, at least over the short term.[21] A number of studies have reported the benefits of administering MT to people with moderate to severe COPD.[22-29] What these studies suggest is the potential of MT to improve thoracic compliance by addressing chest tightness and its effect on dyspnea.

The aim of this trial was to evaluate the medium- to long-term effect of exercise, with and without MT, on lung function, exercise capacity, and QoL in people with mild COPD.

METHODS

The design of this randomized controlled trial has been reported previously.[30] Participants were randomly allocated to two groups: exercise only (Ex) and MT plus Ex (MT + Ex). MT included spinal manipulation (SM) and soft tissue therapy to the thoracic spine and ribs. Participants were recruited through self-referral in response to a public lung function screening program conducted at a local sports center, public hospital foyer, community library, local council chambers, and council works depot. The screening program included adults 50-65 yr of age and involved the completion of a short respiratory history questionnaire and non-challenged spirometry. Those with an FEV_1/FVC ratio of <0.7 and an FEV_1% predicted of 60-80% were offered a more comprehensive respiratory assessment and the opportunity to enroll in the trial. Volunteers who were eligible following the screening program but were currently smoking (within the past 6 mo) were excluded. This decision was based on literature suggesting individuals with COPD who do and do not smoke may represent two different clinical entities.[31] Volunteers were also excluded if they stated that they could not walk continuously on a flat surface for 6 min unassisted by a walking aid or supplemental oxygen, had a diagnosis of osteoporosis (T score < –2.5 and Z score < –1),[27,28] or had a contraindication to MT as assessed by a review of their medical history and a physical assessment conducted by the Chief Investigator (R.M.E.). Inclusion and exclusion criteria are described in Table 1. Volunteers who met the inclusion criteria were asked to provide written consent to participate in the trial. A volunteer was then enrolled in the trial, given a trial-specific ID number, and randomly allocated to one of the two groups using a computer-generated random sequence list drawn up prior to the start of the trial by a person not otherwise involved in the trial. The trial was conducted in the PR facility at Sutherland Hospital (Southcare) in Sydney, Australia.

Standard procedure for PR at Sutherland Hospital includes spirometry (FEV_1 and FVC), functional exercise capacity (6-min walk test [6MWT] distance), and QoL (St George's Respiratory Questionnaire [SGRQ], Hospital Anxiety and Depression Scale [HADS] anxiety, and HADS depression). Measurements were taken at baseline, 4, 8, 16,

Table 1

Inclusion and Exclusion Criteria for This Randomized Clinical Trial of Exercise With and Without MT for Mild Chronic Obstructive Pulmonary Disease

Inclusion	Exclusion
• Male or Female • 50-65 yr • Mild COPD (60% ≤ FEV_1% < 80%: COPDX) • Stable COPD (no exacerbations in preceding 6 mo) • Nonsmoking (for preceding 6 mo) • Willingness to provide written consent • Willingness to participate in and comply with the study requirements	• Inability to complete 6-min walking test unassisted • Contraindication to thoracic SM as assessed by a review of medical history and physical screening o Bone density (DEXA) scores below minimum levels (T score < –2.5 and/or Z score < –1) o Thoracic joint instability o Acute pain on thoracic joint range of motion testing o Advanced chest wall muscle wasting o High level of anxiety related to receiving thoracic spinal manipulation • Inability to understand English • Inability to provide informed consent, e.g., people with a cognitive impairment, an intellectual disability, or a mental illness • Completed a PR program in the previous 12 mo

Abbreviations: COPD, chronic obstructive pulmonary disease; COPDX, the COPD-X Plan (Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease)[2]; DEXA, dual-energy X-ray absorptiometry; FEV_1%, forced expiratory volume in the 1st second percent predicted (age-matched); MT, manual therapy; PR, pulmonary rehabilitation; SM, spinal manipulation.

24, 32, and 48 wk. The follow-up data points were chosen so that change from baseline could be assessed mid- and post-intervention, as well as in the medium and long term. The minimum clinically important difference (MCID) is 100 mL for FEV_1,[32,33] 200 mL for FVC,[34] 25 m for 6MWT distance,[35] 4 units for SGRQ,[36] and 15 units for HADS anxiety and depression.[37]

All outcome measures were taken by hospital staff blinded to participant group allocation. Apart from during the screening process, all lung function measurements in the trial were collected according to the guidelines set down by the Australian and New Zealand Thoracic Society,[38] and all 6MWT were conducted according to the American Thoracic Society guidelines.[39] The respective time points for enrollment, interventions, and assessments are reported according to the Standard Protocol Items: Recommendations for Interventional Trials guidelines (Supplemental Digital Content 1, available at: http://links.lww.com/JCRP/A525).

The exercise component of the trial was modeled on the standard exercise program for patients enrolled in the Sutherland Hospital PR program and consisted of 32 exercise sessions over a 16-wk period at a rate of 2 sessions/wk. Each session lasted for 45 min and included graded aerobic and resistance exercise training ranging in intensity from 60-80% of the maximum workload. The MT protocol used in this trial has been described previously[30] and was the same as the one used in two previous trials on patients with COPD.[27,28] It consisted of soft tissue therapy and thoracic SM administered 2 times/wk over a 4-wk period. The frequency and duration were based on results from two studies on patients with moderate to severe COPD.[27,28] The ST component involved gentle effleurage and cross-fiber friction therapy applied to the muscles of the posterior chest wall. The SM intervention consisted of two manipulations (Grade V mobilizations),[40] each involving the application of a high-velocity, low-amplitude posterior to anterior force with a superior component directed at the intervertebral, costovertebral, and costotransverse joints (Supplemental Digital Content 2, available at: http://links.lww.com/JCRP/A526). The first SM was administered to the upper/middle thoracic spine and the second to the middle/lower thoracic spine. All SM were nonspecific, multi-joint (group) manipulations. Administering SM in this way reduced the total number of manipulations in a single session as each manipulation had the potential to affect several thoracic vertebrae and ribs simultaneously. Each MT session lasted approximately 20 min and was administered just prior to exercise intervention in the MT + Ex group.

Exercise was administered during weeks 1 to 16, whereas MT was administered during weeks 4 to 8. The reason for positioning the MT intervention in this manner in the MT + Ex group was to allow participants time to acclimatize to the exercise regime before the introduction of MT intervention. All MTs were administered by chiropractors or osteopaths with >15 yr of clinical experience.

The trial was approved by the South Eastern Sydney Local Health District—Human Research Ethics Committee (approval number 13/004) and registered with the Australian New Zealand Clinical Trials Registry (ANZCTRN: 12614000766617). The trial was conducted from October 2014 to May 2019.

STATISTICAL ANALYSES

The sample size was calculated based on a change in FVC of 200 mL (MCID) at 48 wk with an SD of 480 mL obtained from previous studies.[27,28] Using 80% power and a significance level of .05, the minimum sample size per group was 92. With 2 equal groups and an estimated drop-out rate of 10%, the planned total cohort size was 204.

Baseline variables were summarized using mean and SD for numeric variables and count with percentages for categorical variables. The Ex and MT + Ex groups were compared at baseline using 2-sample *t* tests or chi-squared tests as appropriate. Linear mixed-effects models were used to determine change over time between groups with a random intercept used to control for repeated measurements on individuals. An interaction between time and treatment was used to determine if there was a difference between treatment groups over time. Missing data were accounted for by using an intention-to-treat analysis.

Where no significant interaction occurred, the interaction effect was removed from the model, and the main effects of treatment group and time were examined. Tukey pairwise tests were used to compare the mean outcomes between time points of interest. Negative estimates indicate a decrease over time, and positive estimates indicate an increase from baseline. The results are reported as estimated mean ± SD or 95% CI.

A Bonferroni-type correction was made to give a significance level of $\alpha = .008$ (=.05/6). The significance of main effects and interactions was determined using this significance level. Baseline comparisons used a 5% significance level.

DATA MONITORING

A Data Safety Monitoring Board oversaw the study. The primary responsibilities of a data safety monitoring board are to review and evaluate the accumulated study data and to make recommendations concerning the continuation, modification, or termination of a trial.[41] An interim data analysis at 30% enrollment was included in the study design to assist the data safety monitoring board in fulfilling these responsibilities.

RESULTS

An interim data analysis was conducted in November 2018. At that time, 440 volunteers had been assessed for eligibility through the screening program with 369 excluded. A total of 71 participants were enrolled in the trial (Figure 1) and randomly allocated to one of the two groups with 35 participants in the Ex group and 36 participants in the MT + Ex group. Baseline characteristics for each group are shown in Table 2. At baseline, the MT + Ex group had a higher proportion of males, walked further, had lower anxiety and depression scores, and had better lung function than the Ex group, suggesting the possibility of imbalance. All participants had an FEV_1/FVC ratio of <0.7 at enrollment and were categorized as having mild COPD according to the COPD-X guidelines.[2] The average age across the cohort was 59 ± 3.9 yr.

A total of 11 participants dropped out of the trial (7 from the Ex group; 4 from the MT + Ex group). The 4 that dropped out of the MT + Ex group did so before they received any MT intervention. Reasons given for dropping out included insufficient time, unexpected family duties, and a lack of transport.

The main finding of the interim analysis was that there was no difference in mean effect over time between groups for any outcome measure (Figure 2). This suggests that MT did not produce any additional benefits in lung function (FEV_1, $P = .97$; FVC, $P = .98$), exercise capacity (6MWT, $P = .98$), or QoL (SGRQ total, $P = .41$; HADS anxiety, $P = .52$; HADS

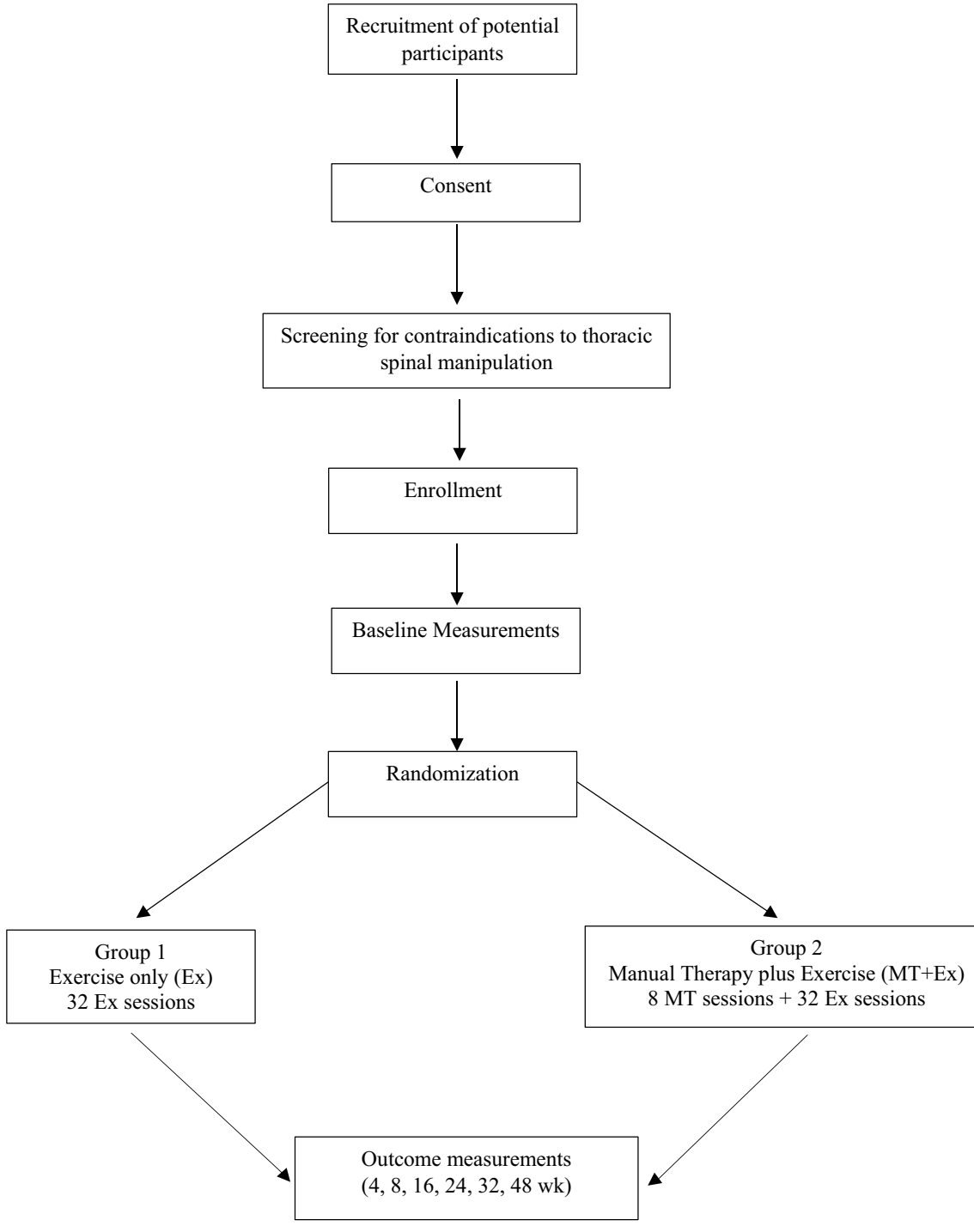

Figure 1. Flow chart of participants randomized to exercise with and without MT for mild COPD. Abbreviations: COPD, chronic obstructive pulmonary disease; MT, manual therapy.

depression, $P = .06$) over the long term (48 wk). After reviewing the results from this analysis, a decision was made to terminate the trial as additional data were unlikely to change the main finding regarding the effect of MT with exercise.

Despite the absence of a significant interaction between groups, several outcome measures had significant changes over time for the entire cohort ($P < .001$). These included FEV_1 at 32 and 48 wk, FVC at 48 wk, 6MWT at 8, 16, 24,

Table 2

Baseline Characteristics of Participants Randomized to Exercise With and Without MT for Mild COPD[a]

Characteristic	All Participants n = 71	Exercise n = 35	MT Plus Exercise n = 36	*P* Value[b]
Age, yr	58.6 ± 3.8	58.5 ± 4.0	58.7 ± 3.7	.869
Sex, Female:Male	53:18	29:6	24:12	<.001
FEV_1, L	2.51 ± 0.56	2.37 ± 0.41	2.64 ± 0.65	.041
FVC, L	3.52 ± 0.85	3.26 ± 0.59	3.77 ± 0.98	.009
SGRQ total	21.9 ± 15.4	26.1 ± 15.9	18.4 ± 14.2	.049
HADS anxiety	5.8 ± 3.7	7.0 ± 4.4	4.5 ± 2.4	.006
HADS depression	3.5 ± 3.3	4.5 ± 3.9	2.7 ± 2.3	.023
6MWT, m	595 ± 63	574 ± 65	614 ± 56	.006

Abbreviations: 6MWT, 6-min walk test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the 1st second; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; MT, manual therapy; SGRQ, St George's Respiratory Questionnaire.

[a]Data are presented as mean ± SD or n.

[b]Two-sample *t* tests were used to compare participants in the exercise and the MT + Ex groups except for sex where a chi-squared test was used.

32, and 48 wk, SGRQ at 8, 16, 24, 32, and 48 wk, and HADS anxiety at 24, 32, and 48 wk. All changes represented improvements that met or exceeded the MCID for the respective measure (Table 3).

There were no severe or moderate adverse events reported during the trial following exercise or MT intervention. There were 21 mild adverse events reported by 14 of the 36 (39%) participants in the MT + Ex group representing an incident rate of 4.1% (21 out of 512 SM). All mild adverse events were self-limiting, did not require further medical attention, and resolved within 48 hr. They included muscle soreness in the back, ribs, and/or neck regions.

DISCUSSION

The main finding in this study was that the combination of MT and Ex did not produce any additional benefits in lung function, exercise capacity, or QoL compared to exercise alone. One of the reasons to expect to see a difference in the MT + Ex group was the results from previous studies showing improvements in lung function and exercise capacity following the combination of MT and exercise in people with moderate to severe COPD.[26-28] In those trials, the thixotropic properties of the chest wall muscles in participants with more advanced stages of COPD would have contributed to an increase in exercise-limiting dyspnea. In mild COPD, the potential for MT to affect chest tightness and, therefore, the onset of dyspnea may be reduced as the extent of chest tightness is markedly less. This view is supported in the literature.[42]

As there was no evidence of a difference between groups and both received the same exercise program, change over time after adjusting for group was estimated. Analysis showed improvements in lung function (FEV_1 and FVC), exercise capacity (6MWT), and QoL (SGRQ and HADS anxiety) that were at or above the MCID. These increases are in line with the results from previous studies on people with mild COPD for exercise capacity and QoL.[13,43-45] However, those studies looked primarily at the short-term effects of PR with only one study[45] assessing the longer-term benefits, but only in terms of emergency department visits and hospitalization days at 1 yr. While the improvements in FEV_1 and FVC did meet the threshold for statistical significance, they should not be considered clinically meaningful as they were only in the order of 5-6%. Notwithstanding, this is the first study to report statistically significant improvements in lung function (both FEV_1 and FVC) following exercise in people with mild COPD. This finding is at odds with previous studies that showed no change or a decrease in static lung function over time following exercise.[7,46-48] It is possible that our finding may have been the result of a more extensive exercise program (16 wk) compared to the more common program length of 8-12 wk,[7,47] although a physiological basis to explain these changes has not been identified. Nevertheless, our findings support the recommendation that all patients with mild COPD be encouraged to exercise regularly, as regular physical activity independent of other factors is associated with a slower progression of the disease.[7,12,49]

We reported clinically meaningful increases in exercise capacity and QoL (SGRQ) after only 8 wk of exercise. While these results are in line with findings from other studies that reported improvements in exercise capacity following either a 6- or 8-wk PR program,[43,45] we are the first to report these improvements still present at 48 wk. The majority of people who are referred to and undertake PR in Australia have moderate to severe COPD.[6] This situation is perpetuated by guidelines that recommend PR for patients with a high symptom burden and risk of exacerbations[1] or who are limited by shortness of breath on exertion.[2] As many people with mild COPD are asymptomatic,[13] measuring the effect of exercise in this group has been difficult to determine.

There is evidence that COPD is not well recognized or optimally managed in its early stages and that effective treatment strategies designed to improve symptoms and delay progression are underutilized.[50] Our trial is larger than previous studies in the field that had 31,[45] 37,[43] and 26[13] participants and rates higher in quality as an RCT with a more extensive (16-wk) intervention period. Of the three previous studies, one was a retrospective study that measured the effect of a 6- to 8-wk standard exercise program,[45] while the other two measured the effect of a 6- or 12-wk exercise program without the inclusion of a comparator (control) group.[13,43] The results from these three studies cannot therefore be directly compared to the results from our study.

SAFETY AND ADVERSE EVENTS

The majority of adverse events associated with MT are mild, self-limiting, require no further medical attention,

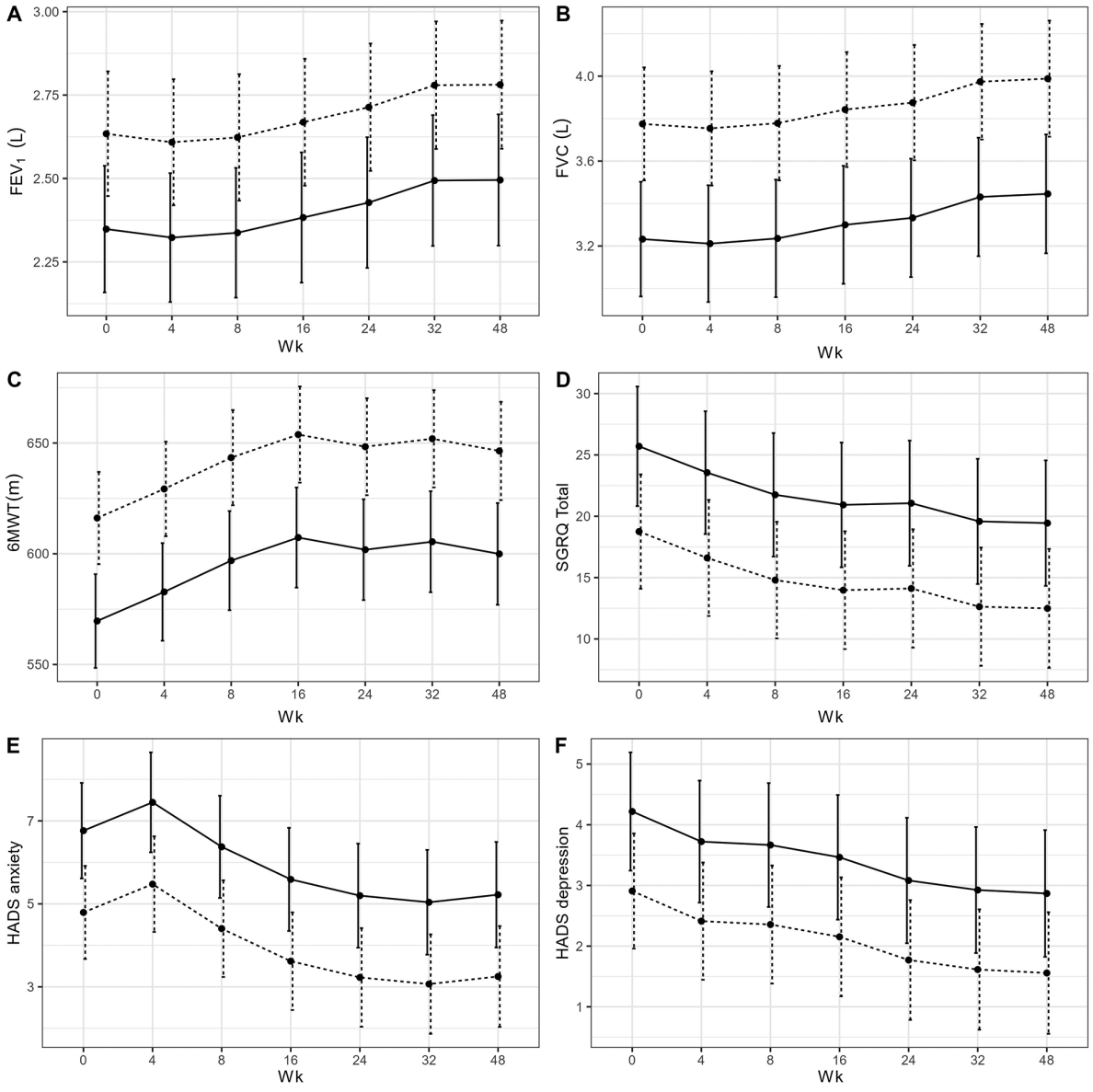

Figure 2. Mean and 95% CI for outcomes over time in participants randomized to exercise with and without MT for mild COPD, chronic obstructive pulmonary disease. The solid line denotes the exercise group, and the dotted line denotes the MT + Ex group. Abbreviations: 6MWT, 6-min walk test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the 1st sec; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; MT, manual therapy; SGRQ, St George's Respiratory Questionnaire.

and resolve within 48 hr.[51] Moderate adverse events have also been reported following SM,[52] while major or catastrophic adverse events are nearly all associated with neck (cervical) manipulation.[53] A recent systematic review and meta-analysis of the risk of adverse events associated with exercise in both healthy and non-healthy participants reported no increase in the risk of serious adverse events but an increase in the risk of nonserious adverse events from participating in exercise.[54]

This trial involved MT that included thoracic SM. In trials on people with moderate to severe COPD, there were no major or moderate adverse events reported, with mild adverse events reported following 18 out of 112 manipulations (15%) in moderate COPD (average age 56.1 yr)[27] and 2 out of 403 (< 1%) in moderate to severe COPD (average age 65.5 yr).[28] The rate of adverse events reported in the current study was 4.1%, which is comparable to those in the two previous trials with the nature of the adverse events also similar. With appropriate screening, MT that includes thoracic SM should be considered at the lower end of the spectrum of risk for 50- to 65-yr-old people with mild COPD.

LIMITATIONS

There were several limitations associated with this study. First, the results being reported here are from a trial that was discontinued following an interim analysis that

Table 3

Estimated Mean Change from Baseline, 95% CI, and *P* Value by Outcome Over Time After Adjusting for Treatment Group

Outcome Measure	Week					
	4	8	16	24	32	48
FEV_1,[a] mL	−26 −128 to 77	−11 −117 to 95	35 −74 to 144	80 −32 to 191	146[b] 33-258	147[b] 32-262
P value	.990	.999	.965	.346	.003	.004
FVC,[a] mL	−21 −168 to 125	3 −148 to 155	68 −88 to 223	100 −59 to 259	199 38-359	213[b] 49-378
P value	1.000	1.000	.857	.502	.005	.003
6MWT,[a] m	13 -5 to 31	27[b] 9-46	38[b] 18-57	32[b] 13-52	36[b] 16-56	30[b] 10-51
P value	.323	<.001	<.001	<.001	<.001	<.001
SGRQ total[a]	−2.1 −5.5 to 1.2	−4.0[b] −7.4 to −0.5	−4.8[b] −8.4 to −1.2	−4.6[b] −8.3 to −1.0	−6.1[b] −9.8 to −2.5	−6.3[b] −10.0 to −2.5
P value	.491	.014	.002	.004	<.001	<.001
HADS anxiety[a]	.7 −0.4 to 1.8	−.4 −1.5 to 0.8	−1.2 −2.4 to 0.0	−1.6[b] −2.8 to −0.4	−1.7[b] −3.0 to −0.5	−1.5[b] −2.8 to −0.3
P value	.524	.952	.051	.003	.001	.006
HADS depression[a]	−0.5 −1.3 to 0.3	−0.6 −1.3 to 0.2	−0.8 −1.6 to 0.1	−1.1 −2.0 to −0.3	−1.3 −2.1 to −0.5	−1.4 −2.2 to −0.5
P value	.447	.366	.083	.001	<.001	<.001

Abbreviations: 6MWT, 6-min walk test; FEV_1, forced expiratory volume in the 1st second; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; MCID, minimum clinically important difference; SGRQ, St George's Respiratory Questionnaire.

Tukey pairwise test results in bold are significant ($P < .05$).

[a]Main effect for time indicated significant differences between at least 1 pair of time points, $P < .001$.

[b]Mean effect met or exceeded the MCID for the outcome measure.

showed additional data were unlikely to change the main finding regarding the effect of MT and exercise compared to exercise alone for people with mild COPD. While there was no additional benefit from MT intervention, the estimated change was considered worth reporting given the limited number and small sample sizes of previous studies in the field. Second, the accepted values of the MCID for FEV_1, FVC, 6MWT, and HADS were determined on people with moderate to severe COPD and may not be directly applicable to people with mild COPD. In the absence of specific values for mild COPD, it was considered acceptable to use the values developed for moderate to severe COPD. Third, to avoid the group imbalances at baseline reported in this study, future studies could modify randomization to stratify by baseline 6MWT performance. Fourth, it is possible that medication-associated reversibility may have had an impact on the results. Future studies should include data on medication use during the intervention and measurement stages. Finally, as we did not collect data on the level of physical activity at baseline, it is possible that the reported improvements in exercise capacity (6MWT) may be the result of normal improvement following exercise in certain types of patients with COPD, such as those with a mainly sedentary lifestyle. We recommend that future studies include data on levels of physical activity at baseline.

CONCLUSIONS

While the combination of MT and exercise did not provide any additional benefit in mild COPD, exercise was associated with modest sustainable improvements in exercise capacity and QoL. Given its potential to delay disease progression and improve prognosis, our results support the recommendation that exercise be recommended for people with mild COPD.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2023 report) 2023. https://goldcopd.org/2023-gold-report-2/. Accessed November 29, 2023.
2. Lung Foundation Australia. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2023. Version 2.71, July 2023. https://copdx.org.au/. Accessed November 22, 2023.
3. World Health Organization. Chronic obstructive pulmonary disease (COPD) 2023. www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd). Accessed November 29, 2023.
4. Lahham A, Holland AE. The need for expanding pulmonary rehabilitation services. *Life*. 2021;11(11):1236.
5. Stone PW, Hickman K, Steiner MC, Roberts CM, Quint JK, Singh SJ. Predictors of referral to pulmonary rehabilitation from UK primary care. *Int J Chron Obstruct Pulmon Dis*. 2020;15:2941-2952.
6. Australian Institute of Health and Welfare. Monitoring pulmonary rehabilitation and long-term oxygen therapy for people with chronic obstructive pulmonary disease (COPD). https://www.aihw.gov.au/reports/chronic-respiratory-conditions/monitoring-pulmonary-rehabilitation-and-long-term/summary. Accessed November 22, 2023.
7. Alison JA, McKeough ZJ, Johnston K, et al. Australian and New Zealand Pulmonary Rehabilitation Guidelines. *Respirology*. 2017;22(4):800-819.
8. Cerveri I, Corsico AG, Accordini S, et al. Underestimation of airflow obstruction among young adults using FEV_1/FVC <70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. *Thorax*. 2008;63(12):1040-1045.

9. Vollmer WM, Gíslason T, Burney P, et al. Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study. *Eur Respir J*. 2009;34(3):588-597.
10. Swanney MP, Ruppel G, Enright PL, et al. Using the lower limit of normal for the FEV_1/FVC ratio reduces the misclassification of airway obstruction. *Thorax*. 2008;63(12):1046-1051.
11. Guerra S. Asthma and chronic obstructive pulmonary disease. *Curr Opin Allergy Clin Immunol*. 2009;9(5):409-416.
12. Chee A, Sin DD. Treatment of mild chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2008;3(4):563-573.
13. Jácome C, Marques A. Impact of pulmonary rehabilitation in subjects with mild COPD. *Respir Care*. 2014;59(10):1577-1582.
14. Jácome C, Marques A. Pulmonary rehabilitation for mild COPD: a systematic review. *Respir Care*. 2014;59(4):588-594.
15. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;171(9):972-977.
16. Theander K, Jakobsson P, Jorgensen N, Unosson M. Effects of pulmonary rehabilitation on fatigue, functional status and health perceptions in patients with chronic obstructive pulmonary disease: a randomized controlled trial. *Clin Rehabil*. 2009;23(2):125-136.
17. O'Donnell DE, Ora J, Webb KA, Laveneziana P, Jensen D. Mechanisms of activity-related dyspnea in pulmonary diseases. *Respir Physiol Neurobiol*. 2009;167(1):116-132.
18. Izumizaki M, Iwase M, Ohshima Y, Homma I. Acute effects of thixotropy conditioning of inspiratory muscles on end-expiratory chest wall and lung volumes in normal humans. *J App Physiol*. 2006;101(1):298-306.
19. Bogduk N, Mercer S. Selection and application of treatment. In: Refshauge K and Gass K, eds. *Musculoskeletal Physiotherapy: Clinical Science and Evidence-based Practice*. 2nd ed. Oxford, UK: Butterworth-Hinemann; 2004:245-257.
20. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Man Ther*. 2009;14(5):531-538.
21. Lange U, Sperling M, Richter K, Dischereit G, Muller-Ladner U, Tarner IH. The effects of manual mobilization on the mobility of the thoracic spine in patients with ankylosing spondylitis. *J Musc Dis Treat*. 2016;2:011.
22. Howell RK, Allen TW, Kappler RE. The influence of osteopathic manipulative therapy in the management of patients with chronic obstructive lung disease. *J Am Osteopath Assoc*. 1975;74(8):757-760.
23. Noll DR, Degenhardt BF, Johnson JC, Burt SA. Immediate effects of osteopathic manipulative treatment in elderly patients with chronic obstructive pulmonary disease. *J Am Osteopath Assoc*. 2008;108(5):251-259.
24. Noll DR, Johnson JC, Baer RW, Snider EJ. The immediate effect of individual manipulation techniques on pulmonary function measures in persons with chronic obstructive pulmonary disease. *Osteopath Med Prim Care*. 2009;3:9.
25. Dougherty P, Engel R, Vemulpad S, Burke J. The use of spinal manipulative therapy for elderly patients with chronic obstructive pulmonary disease: a case series. *J Manip Physiol Ther*. 2011;34(6):413-417.
26. Zanotti E, Berardinelli P, Bizzarri C, et al. Osteopathic manipulative treatment effectiveness in severe chronic obstructive pulmonary disease: a pilot study. *Compl Ther Med*. 2012;20(1-2):16-22.
27. Engel RM, Vemulpad S, Beath K. Short term effects of combining manual therapy and exercise in people with moderate chronic obstructive pulmonary disease (COPD): a preliminary clinical trial. *J Manip Physiol Ther*. 2013;36(8):490-496.
28. Engel RM, Gonski P, Beath K, Vemulpad S. Medium term effects of including manual therapy in a pulmonary rehabilitation program for chronic obstructive pulmonary disease (COPD): a randomized controlled pilot trial. *J Man Manip Ther*. 2016;24(2):80-89.
29. Wearing J, Beaumont S, Forbes D, Brown B, Engel R. The use of spinal manipulative therapy in the management of chronic obstructive pulmonary disease: a systematic review. *J Altern Complement Med*. 2016;22(2):108-114.
30. Engel RM, Wearing J, Gonski P, Vemulpad S. The effect of combining manual therapy with exercise for mild chronic obstructive pulmonary disease: study protocol for a randomised controlled trial. *Trials*. 2017;18(1):282.
31. Lopez CC, Macario CC, Marrero FL, et al. Differences in COPD: smokers versus non smokers. *Eur Resp J*. 2015;46(suppl 59):PA4077.
32. Donohue JF. Minimal clinically important differences in COPD lung function. *COPD*. 2005;2(1):111-124.
33. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. *Am J Respir Crit Care Med*. 2014;189(3):250-255.
34. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Resp J*. 2005;26(5):948-968.
35. Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil*. 2010;91(2):221-225.
36. Jones PWS. St. George's respiratory questionnaire: MCID. *COPD*. 2005;2(1):75-79.
37. Puhan MA, Frey M, Buchi S, Schunemann HJ. The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. *Health Qual Life Outcomes*. 2008;6(1):46.
38. Thoracic Society of Australia and New Zealand. Standards for the delivery of spirometry. 2022. www.thoracic.org.au/respiratorylaboratoryaccreditation/spirometry-standards. Accessed November 29, 2023.
39. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Resp J*. 2014;44(6):1428-1446.
40. Maitland GD. *Maitland's Vertebral Manipulation*. 8th ed. Hengeveld E and Banks K, eds. Edinburgh, UK: Elsevier; 2014.
41. National Health and Medical Research Council. Data Safety Monitoring Moards (DSMBs); 2018. https://www.nhmrc.gov.au/sites/default/files/documents/reports/data-safety-monitoring-boards.pdf Accessed November 22, 2023.
42. Aliverti A. Chest wall mechanics in COPD. *Current Respir Med Rev*. 2008;4(4):240-249.
43. Riario-Sforza GG, Incorvaia C, Paterniti F, et al. Effects of pulmonary rehabilitation on exercise capacity in patients with COPD: a number needed to treat study. *Int J Chron Obstruct Pulmon Dis*. 2009;4:315-319.
44. Tong H, Liu Y, Zhu Y, Zhang B, Hu J. The therapeutic effects of qigong in patients with chronic obstructive pulmonary disease in the stable stage: a meta-analysis. *BMC Complement Altern Med*. 2019;19(1):239.
45. Golmohammadi K, Jacobs P, Sin DD. Economic evaluation of a community-based pulmonary rehabilitation program for chronic obstructive pulmonary disease. *Lung*. 2004;182(3):187-196.
46. Foglio K, Bianchi L, Bruletti G, et al. Seven-year time course of lung function, symptoms, health-related quality of life, and exercise tolerance in COPD patients undergoing pulmonary rehabilitation programs. *Resp Med*. 2007;101(9):1961-1970.
47. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2015;2015(2):CD003793.
48. Jácome C, Marques A. Short- and long-term effects of pulmonary rehabilitation in patients with mild COPD. *J Cardiopulm Rehabil Prev*. 2016;36(6):445-453.
49. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Antó JM. Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study. *Am J Respir Crit Care Med*. 2007;175(5):458-463.
50. Johnston CL, Maxwell LJ, Alison JA. Establishing and delivering pulmonary rehabilitation in rural and remote settings: the opinions, attitudes and concerns of health care professionals. *Aust J Rural Health*. 2016;24(2):106-114.
51. Carnes D, Mars TS, Mullinger B, Froud R, Underwood M. Adverse events and manual therapy: a systematic review. *Man Ther*. 2010;15(4):355-363.

52. Ernst E. Adverse effects of spinal manipulation: a systematic review. *J Royal Soc Med*. 2007;100(7):330-338.
53. Swait G, Finch R. What are the risks of manual treatment of the spine? A scoping review for clinicians. *Chiropr Man Therap*. 2017;25:37.
54. Niemeijer A, Lund H, Stafne SN, et al. Adverse events of exercise therapy in randomised controlled trials: a systematic review and meta-analysis. *Br J Sports Med*. 2020;54(18):1073-1080.