

Review Article

The effects of proprioceptive neuromuscular facilitation in treating chronic low back pain: A systematic review and meta-analysis

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Abstract.

BACKGROUND: Proprioceptive neuromuscular facilitation (PNF) has been widely used in the clinical treatment of chronic low back pain (LBP) in recent years. However, its role remains controversial and it is unclear whether PNF offers more advantages for patients with chronic LBP.

OBJECTIVE: The purpose of this systematic review is to evaluate the evidence on the effect of PNF on pain, waist function, pulmonary function and dynamic balance in patients with chronic LBP.

METHODS: Seven English and Chinese electronic databases were searched to identify articles published from 1970 to February 2020. Relevant randomized controlled trials (RCTs) were selected by two independent reviewers to investigate PNF in treatment of chronic LBP. Data extraction was performed by the same reviewers.

RESULTS: Twelve eligible trials involving 410 participants were included in this meta-analysis. Compared with the control group, the aggregated results suggested that PNF showed beneficial effects in relieving pain (SMD = -1.17 ; 95% CI: -1.50 to -0.84 ; $p < 0.00001$) and improving waist functional disability (MD = -1.63 ; 95% CI: -1.89 to -1.37 ; $p < 0.00001$). In addition, PNF was shown to have a significant effect on pulmonary function (MD = 0.65 ; 95% CI: 0.26 to 1.03 ; $p = 0.001$). However, the results of the study show that PNF could not significantly improve dynamic balance in patients with chronic LBP compared with the control group (MD = -0.04 ; 95% CI: -2.16 to 2.08 ; $p = 0.97$). A high risk of bias occurred in the areas of blinding (i.e., participants/personnel and outcome assessment).

CONCLUSIONS: PNF showed more beneficial effects in pain relief and waist function improvement in patients with chronic LBP in the short term (4 to 8 weeks of intervention) or at 12-week follow-up and also played a positive role in pulmonary function. However, no significant effect of PNF on dynamic balance was found compared with the control group. However, these results have certain limitations, and these conclusions were supported by low-quality data. Therefore, articles that are methodologically reasonable and more authoritative are required to verify the effects. In addition, articles with long-term follow-up and other outcomes are needed to confirm additional findings.

Keywords: Proprioceptive neuromuscular facilitation, pain, waist function, Oswestry Disability Index, chronic low back pain

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1. Introduction

Low back pain (LBP) is the most common musculoskeletal condition and constitutes a global public health problem. It is also one of the diseases that causes the most individual disability worldwide [1–3]. The painful areas of LBP are usually distributed below the costal margin and above the inferior gluteal folds and are often accompanied by clinical symptoms such as muscle tension, stiffness and even sciatica [4]. Back pain lasting longer than 12 weeks is defined as chronic LBP, which seriously affects people's work and life activities and reduces quality of life [5,6]. Recent research shows that the number of people with disabilities caused by chronic LBP has increased by 54% in the last 30 years [7,8]. Thus, LBP poses substantial challenges for the medical system, creates socioeconomic issues for working-age adults, and levies a severe medical burden on individuals and society [3,7,8]. According to statistics, the total cost of treatment for chronic LBP in the United States is estimated to exceed US \$100 billion per year [11,12].

Numerous factors have been proven as underlying causes of persistent LBP, including trunk proprioception dysfunction, back muscle weakness or delayed activation, lumbar joint imbalance and important defects in the neural control unit of spinal stabilization system [13–18]. Therefore, improving trunk proprioception function and back muscle strength were the focus of treatment [19]. In most clinical practice guidelines, physical therapy is a common treatment method for chronic LBP, including trunk muscle training, proprioceptive neuromuscular facilitation (PNF) and electromagnetic stimulation.

PNF is a multifaceted exercise therapy method based on the theory of human development and neurophysiology, and it has important physiological and health benefits in improving trunk proprioception, muscle strength, exercise control, balance and endurance [20–23]. Recently, PNF training has been widely used by physical therapists to treat patients with chronic LBP, and the mechanism elicits a neuromuscular response by stimulating proprioceptors to relieve the symptoms of low back pain [24–27,30–35]. Moreover, the proprioceptors of the joints and muscles in the lumbar region of patients with chronic LBP were stimulated by PNF training to improve sensorimotor regulation and balance performance [27]. PNF technology has multiple movement patterns. Studies have shown that PNF training promotes muscle performance of chronic LBP mainly through its movement patterns because its

movement patterns are basically consistent with topographic arrangement of muscles used in activities and sports [26,28]. Additionally, PNF training adopts diagonal and spiral directions, which are more effective than conventional single-direction exercise training in enhancing human performance and relieving clinical symptoms of chronic LBP [28].

Currently, no systematic review of PNF training for chronic LBP exists, although certain published articles have reported the positive effects of physical therapists using PNF training in chronic LBP. Therefore, it is highly meaningful to confirm whether PNF training produces more beneficial effects than general exercise or conventional therapy in chronic LBP according to evidence-based medical studies, which can offer reference suggestions for clinical treatment of chronic LBP. The purpose of this systematic review is to evaluate the effect of PNF on pain, waist function, pulmonary function and dynamic balance in patients with chronic LBP.

2. Methods

2.1. Search strategy

Randomized controlled trials (RCTs) were identified by electronically searching the following online databases up to February 2020: PubMed, Embase, Cochrane Library, Web of Science, EBSCO, China National Knowledge Infrastructure and WanFang Data.

Appendix 1 presents a detailed description of the complete electronic search strategy for PubMed. Generally, the medical subject headings (MeSH) were composed of the following: low back pain, proprioceptive neuromuscular facilitation and back pain. The keywords were randomized controlled trials (RCTs), single-blind method, double-blind method, random allocation, low back pain, back pain, low back ache, proprioceptive neuromuscular facilitation, PNF, and PNF stretching. Duplicate articles were removed if found in multiple database searches.

2.2. Inclusion criteria

1. Types of studies. Only RCT experiments were selected to examine the effects of PNF in treating chronic LBP. There were no language or publication date restrictions for this study.

2. Types of participants. The subjects in our selected article included participants (over 18 years old) who suffered from chronic LBP for longer than

Table 1
Characteristics of included studies

Author, year	Sample size Participant characteristic duration of complaint	Intervention	Exercise frequency and study duration	Outcomes	Follow-up (time)
Areedmwong 2019 (English)	44 subjects, mean age G1 = 38.20 ± 9.40 G2 = 39.57 ± 10.63 LBP duration (month): G1 = 8.20 ± 4.50; G2 = 9.20 ± 7.10	G1: PNF training G2: General trunk exercise	Three times per week for 4 weeks	NRS; RMDQ; CoP velocity; ellipse sway area	No
Kumar 2011 (English)	30 subjects, mean age G1 = 24.07 ± 2.17 G1 = 24.07 ± 2.17	G1: PNF training G2: Conventional treatment	Five times per week for 4 weeks	VAS; ODI; ROM Curl-up test; Sorensen test	No
Lee 2014 (English)	Complained of LBP for over 3 months 40 subjects, mean age G1 = 34.75 ± 0.85 G2 = 4.20 ± 0.69	G1: PNF training G2: Ball exercise	Four times per week for 6 weeks	VAS; EMG	No
Areedmwong 2017 (English)	LBP duration over 12 weeks 42 subjects, mean age G1 = 39.80 ± 5.47 G2 = 36.2 ± 9.9 LBP duration (month); G1 = 9.2 ± 6.2; G2 = 10.0 ± 7.2	G1: PNF training G2: LBP booklet	Five times per week for 4 weeks	NRS, RMDQ, HRQOL LES muscle activity Patient satisfaction	Yes, twelve weeks
Kim 2017 (English)	30 subjects, mean age G1 = 39.80 ± 5.47 G2 = 39.40 ± 5.69	G1: PNF-AMST program G2: Traditional physical therapy	Five times per week for 6 weeks	FEV ₁ (L); VAS, ODI	No
Areedmwong 2019 (English)	Complained of LBP for over 12 weeks 45 subjects, mean age G1 = 24.00 ± 8.47 G2 = 24.08 ± 1.00 G3 = 24.36 ± 9.97	G1: Therapeutic+PNF training G2: Therapeutic+core stabilization exercise G3: Therapeutic+trunk exercise	Four weeks of intervention	VAS; RMDQ, SEMG, Patient satisfaction	Yes, twelve weeks
Kofotolis 2006 (English)	LBP duration (month); G1 = 6.80 ± 3.97; G2 = 6.33 ± 3.28 G3 = 6.36 ± 2.36	G1: PNF-RST program G2: PNF-COI program G3: No intervention	Eight weeks of intervention	Borg Back Pain Intensity, ODI, ROM	No
Young 2015 (English)	86 subjects, mean age G1 = 40.6 ± 6.4 G2 = 41.8 ± 7.7 G3 = 40.6 ± 6.4	G1: PNF (PIP pattern) training G2: Swiss ball training	Three times per week for 6 weeks	Mean velocity in the X and Y directions FRT, TUG, VAS	No
Bong 2014 (Korean)	LBP duration for over 24 weeks 48 subjects, mean age (unclear) LBP duration for six month or longer 14 subjects, mean age G1 = 54.43 ± 2.23 G2 = 55.57 ± 2.07 LBP duration for over 12 weeks	G1: PNF abdominal training G2: Abdominal muscle exercise	Five times per week for 6 weeks	VAS; FEV ₁ (L), ODI	No

Table 1, continued

Author, year	Sample size Participant characteristic duration of complaint	Intervention	Exercise frequency and study duration	Outcomes	Follow-up (time)
Jeon 2017 (Korean)	20 subjects, mean age G1 = 59.50 ± 6.11 G2 = 59.90 ± 5.45 LBP duration for over 12 weeks	G1: PNF+core training G2: Conventional physiotherapy	Three times a week for 6 weeks	VAS; ODI	No
Kim 2017 (Korean)	30 subjects, mean age G1 = 47.00 ± 4.55 G2 = 47.60 ± 4.20 G3 = 47.10 ± 3.63 LBP duration for over 12 weeks	G1: PNF abdominal training G2: Abdominal strengthening training G3: Conventional physiotherapy	Three times per week for 6 weeks	VAS; BBS	No
Jeon 2013 (Korean)	34 subjects, mean age G1 = 60.06 ± 11.37 G2 = 57.00 ± 12.97 Chronic LBP duration time of over 12 weeks	G1: Integrated PNF on sprinter and skater patterns exercise G2: Swiss ball exercise	Three times per week for 6 weeks	X and Y speed, FRT, TUG	No

Abbreviations: LBP, low back pain; ODI, Oswestry Disability Index; MRDQ, Roland Morris Disability Questionnaire; VAS, Visual Analog Scale; NRS, Numerical Rating Scale; Borg, Borg Back Pain Intensity; BBS, Berg Balance Scale; FEV₁: forced expiratory volume at one second; FRT, functional reach test; TUG, timed up and go test.

12 weeks. The articles on chronic LBP caused by pathology or organic causes were excluded.

3. Types of interventions. Trials were divided into a PNF group and a control group. The control group only received one of the treatment methods of “general exercise, conventional physical therapy, electromagnetic therapy, electrotherapy, low back pain education” and the experimental group, received PNF training or treatment.

4. Types of outcome measures. The primary outcomes included pain intensity scores (VAS/Borg Back Pain Intensity Scale/NRS) and waist functional status (Oswestry Disability Index, ODI; Roland Morris Disability Questionnaire (RMDQ)). Secondary outcomes included other indices of forced expiratory volume at one second (FEV₁), functional reach test (FRT), and timed up and go test (TUG). In addition, any adverse events in the included studies were recorded.

2.3. Selection of studies

The relevant titles, abstracts and full reviews were screened by two reviewers (PG and FT) according to the included criteria. An article was deleted if it did not fulfill the inclusion criteria. If disagreement occurred between reviewers in reaching the final selection decisions, then it was necessary to consult the third reviewer (WL).

2.4. Data extraction

The relevant data from the eligible articles were extracted, such as author and year of publication, sample size, participant characteristics, duration of complaint, description of interventions between the experimental and control groups, outcomes, and follow-up status (Table 1).

2.5. Assessing the risk of bias

The risk of bias in all articles was evaluated using the Cochrane Collaboration recommendations [29]. The following information was assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other bias. The methodological quality of all articles was independently assessed by two reviewers (PG and YM). Any disagreements in the risk bias assessment were settled by consulting a third reviewer (WL).

2.6. Statistical analysis

Data analysis was conducted using Manager Software (RevMan5.3). The I² statistic and the Chi-squared test were used to examine the heterogeneity of the studies. If the heterogeneity test did not show statistical significance (I² < 50%; *P* > 0.1), a fixed-effect model was adopted. Otherwise, we used a random effects model. All variables of the included studies in this meta-analysis are continuous, and thus we adopted the mean difference (MD) or standard mean difference (SMD) and 95% confidence interval (CI) to analyze these studies. *P* < 0.05 indicated that the results were statistically significant.

3. Results

3.1. Search results

A total of 111 records were initially identified from PubMed, Embase, Cochrane Library, Web of Science, EBSCO, and China National Knowledge Infrastructure and WanFang Data (Fig. 1). A total of 21 duplicate articles identified in multiple database searches were removed, and 66 articles were retained according to their title and abstract. Furthermore, only 12 articles [25,26,30–39] fulfilled the inclusion criteria after these 54 potential articles were assessed in full texts. Table 1 shows the characteristics of each included study.

3.2. Risk of bias of included studies

According to the Cochrane Collaboration recommendations, eight studies described the process of random sequence generation [25,26,30,31,33–35,38], and the remaining trials only mentioned randomization without describing a specific method of random sequence generation [32,36,37,39]. Three articles described the allocation concealment method, but the allocation concealment of the other nine studies was not determined [25,26,30–32,36–39]. Seven articles were deemed at a high risk of bias in blinding of participants and personnel [26,30,35–39], and this issue was unclear in two articles [31,32]. Nine articles displayed a high risk of bias in blinding of outcome assessments [25,26,30–32,36–39]. Incomplete outcome data and selective reporting were at a low risk of bias in all articles. However, the possibility of other bias in each article was unclear [25,26,30–39]. Therefore, the evidence of this systematic review has a certain high risk of overall bias. The risk of bias assessment of all included studies is described in Figs 2 and 3.

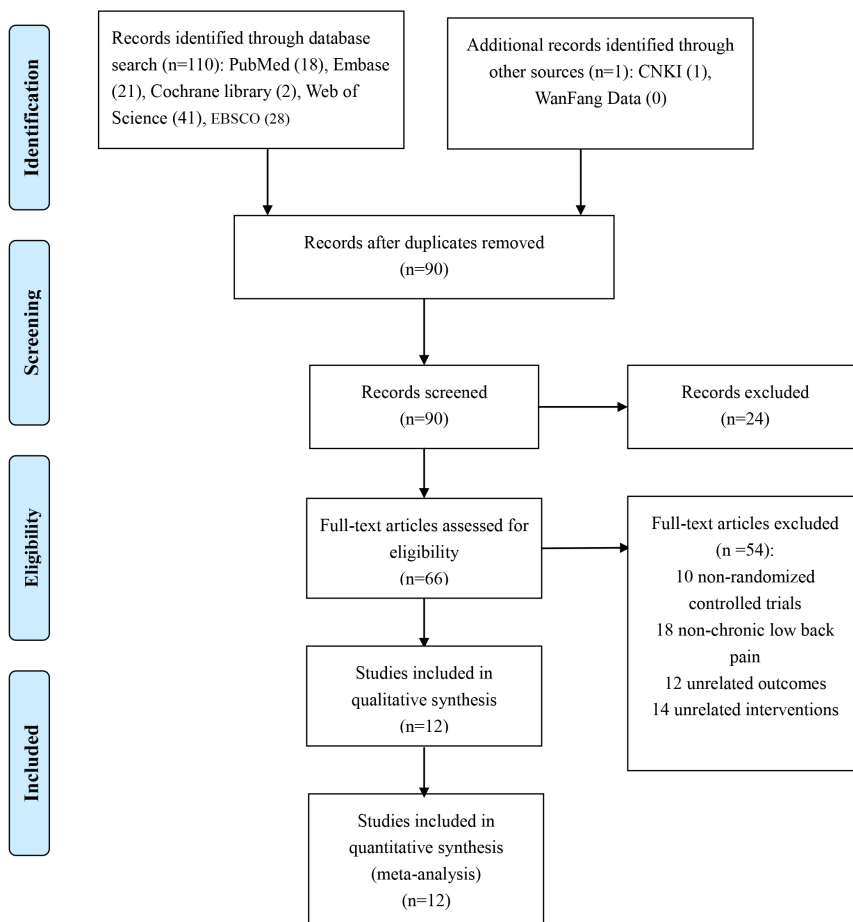


Fig. 1. Flowchart of the study selection procedure.

Author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Areudornwong P* 2019	+	+	+	+	+	+	?
Areudornwong P 2017	+	+	+	+	+	+	?
Areudornwong P 2019	+	+	+	+	+	+	?
Bong SY 2014	+	?	-	+	+	+	?
Jeon JK 2013	?	?	-	-	+	+	?
Jeon WM 2017	?	?	-	-	+	+	?
Kim BR 2017	+	?	?	-	+	+	?
Kim CH 2017	?	?	-	-	+	+	?
Kotobolis 2006	+	?	?	-	+	+	?
Kumar A 2011	?	?	?	-	+	+	?
Lee CW 2012	+	?	-	-	+	+	?
Young KJ 2015	+	?	-	-	+	+	?

Fig. 2. Risk of bias summary: Review authors' judgments of bias items for each included study.

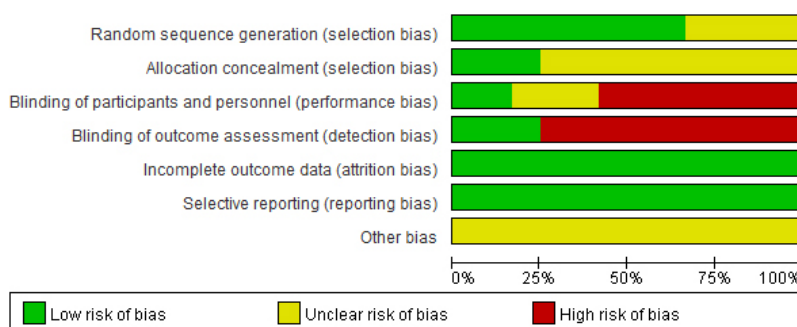


Fig. 3. Risk of bias graph: Reviewers' judgments of each bias item, presented as percentages.

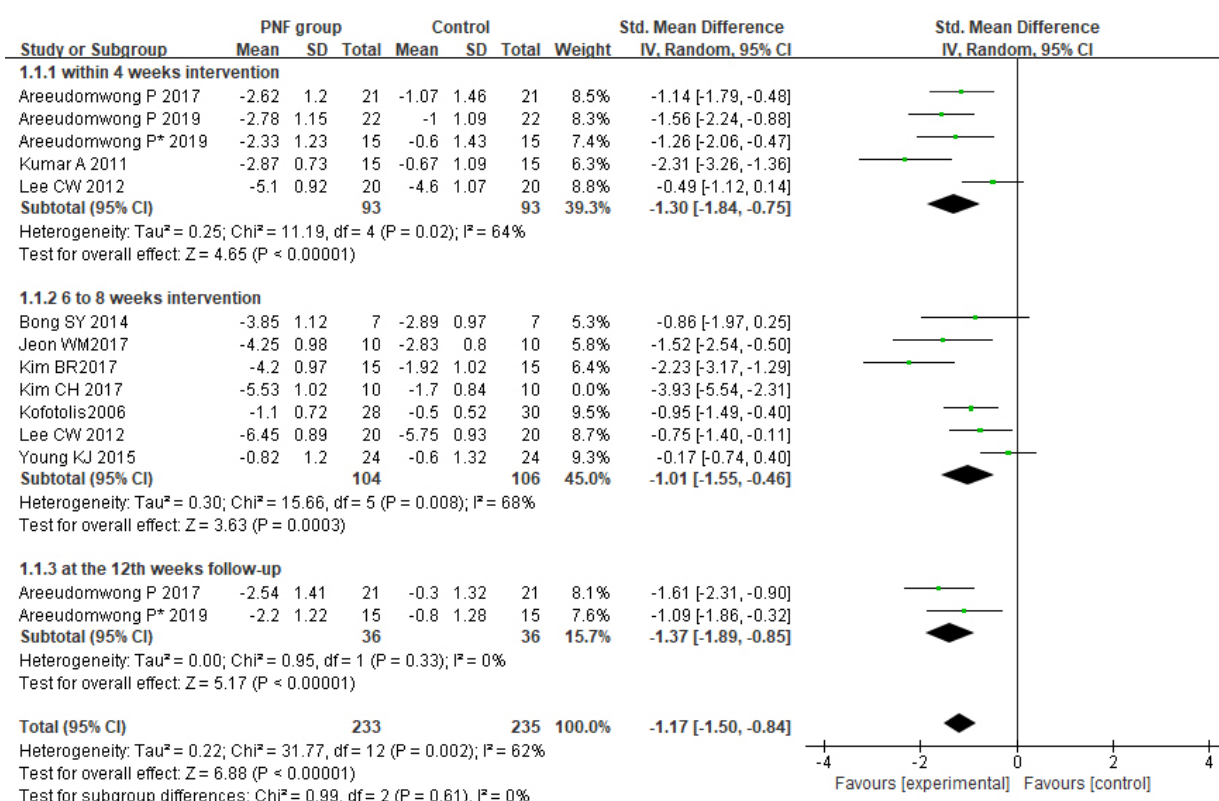


Fig. 4. Meta-analyses of the effect of PNF on pain intensity compared with the control group as conducted in different intervention duration and follow-up periods.

3.3. Effects of PNF on primary outcomes

The primary outcomes included pain intensity and waist functional status. First, a total of 11 articles used pain intensity as a low back pain evaluation index, including 8 articles using the visual analog scale (VAS), 2 articles using the numerical rating scale (NRS) and 1 article using the Borg Back Pain Intensity Scale. Overall, the results showed that compared with the control group, PNF significantly relieved pain (SMD = -1.17;

95% CI: -1.50 to -0.84; $p < 0.00001$) (Fig. 4). Patients in the PNF group had significantly better results in different research stages [(SMD = -1.30; 95% CI: -1.84 to -0.75; $p < 0.00001$, within 4 weeks intervention of the study), [(SMD = -1.01; 95% CI: -1.55 to -0.46; $p = 0.0003$, 6 to 8 weeks intervention of the study)], [(SMD = -1.37; 95% CI: -1.89 to -0.85; $p < 0.00001$, at the 12-week follow-up of the study)]. Second, 7 studies contained the waist functional status index. Of these, 4 articles used the ODI to record the

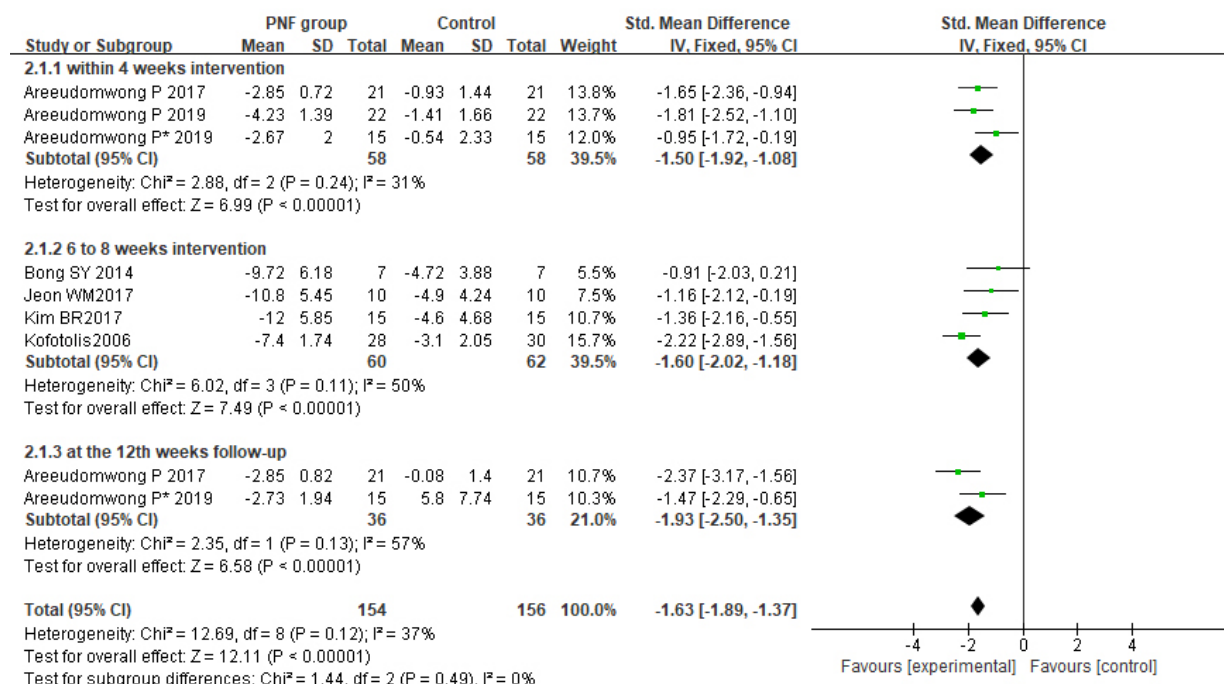


Fig. 5. Meta-analyses of the effect of PNF on functional disability compared with the control group as conducted in different intervention duration and follow-up periods.

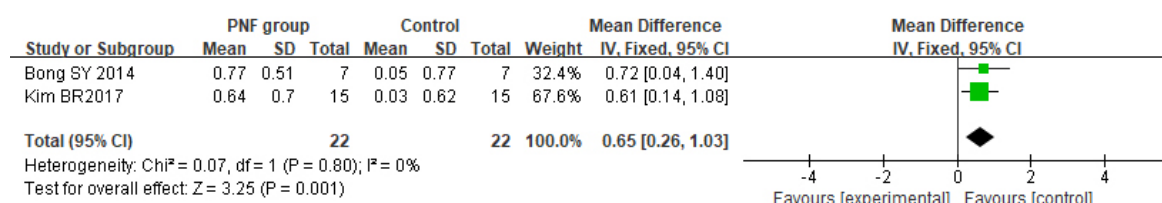


Fig. 6. Meta-analyses of the effect of PNF on pulmonary function.

waist functional status, and 3 articles used RMDQ for assessment of waist function. The results of the study show that overall, PNF could significantly improve the waist functional disability of patients compared with the control group (MD = -1.63; 95% CI: -1.89 to -1.37; $p < 0.00001$) (Fig. 5). The effect on improving functional disability was pronounced in each research period [(MD = -1.50; 95% CI: -1.92 to -1.08; $p < 0.00001$, within 4 weeks intervention of the study), (MD = -1.60; 95% CI: -2.02 to -1.18; $p < 0.00001$, 6 to 8 weeks intervention of the study), (MD = -1.93; 95% CI: -1.89 to -1.37; $p < 0.00001$, at the 12-week follow-up of the study)].

3.4. Effects of PNF on secondary outcomes

Two articles used pulmonary function and dynamic balance indicators. As displayed in Fig. 6, PNF was

shown to have a significant effect on pulmonary function (MD = 0.65; 95% CI: 0.26 to 1.03; $p = 0.001$), but the results of the study show that overall, PNF could not significantly improve the dynamic balance of patients with chronic LBP compared with the control group (MD = -0.04; 95% CI: -2.16 to 2.08; $p = 0.97$) (Fig. 7). Similarly, the meta-analysis found a negative effect of PNF on FRT and TUG compared with control group [(MD = 0.91; 95% CI: -2.32 to 4.15; $p = 0.58$, FRT), (MD = -1.65; 95% CI: -5.33 to 2.03; $P = 0.38$, TUG)].

3.5. Sensitivity analyses

High heterogeneity was found in the pain intensity index of 6 to 8 weeks intervention in forest plot (Fig. 4), and after sensitivity analysis, we found that the statistical heterogeneity of pain intensity was mainly caused

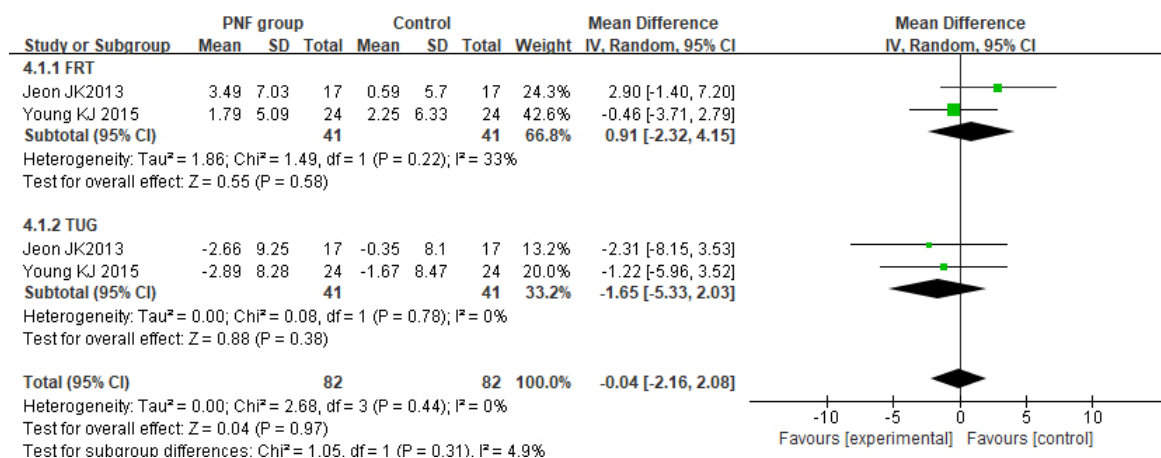


Fig. 7. Meta-analyses of the effect of PNF on dynamic balance. FRT (functional reach test); TUG: (timed up and go test).

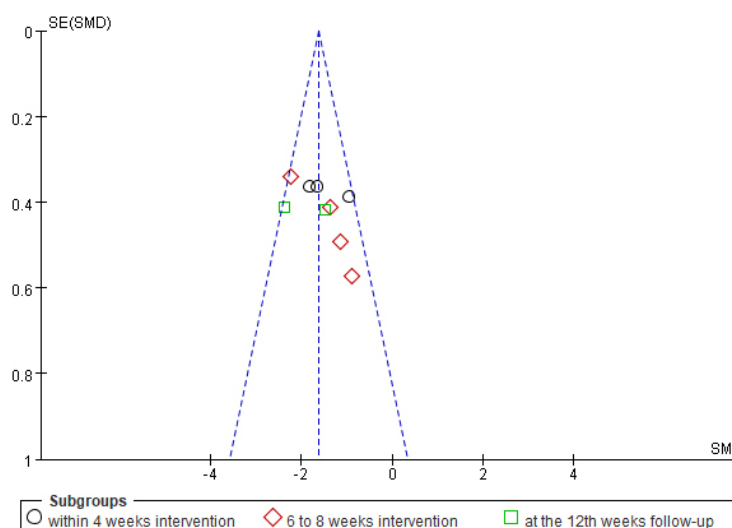


Fig. 8. Funnel plot for evaluating the publication bias of function disability.

by the trials of Kim [31], Kim [36], and Young [30], and we should thus pay additional attention to them in the analysis of the results.

3.6. Publication bias analysis

The publication bias of the 9 included studies in the meta-analysis (Fig. 4) was evaluated using the inverted funnel plots. The funnel plot (Fig. 8) was a bit symmetrical, suggesting that there was a certain publication bias.

4. Discussion

This study is conduct a systematic review and meta-

analysis of the pooled effects of PNF on chronic LBP. In this meta-analysis, we identified 12 RCTs involving 410 patients who explore the effects of PNF on chronic low back pain. The Cochrane Collaboration recommendations were used to evaluate the risk bias of each article. However, it is difficult to determine the other risks of bias in each article. No serious adverse events were found during PNF treatment in the eligible studies. In addition, we could not determine the safety of PNF training because the number of patients was too small.

Our research found that PNF is an effective therapy, and the results of this meta-analysis indicate that PNF intervention is superior to the control group for relieving pain and improving functional disability in short-term intervention within 4 weeks or 6 to 8 weeks, and

similar results were found at the 12-week follow-up. The results of this study are consistent with those of Paolucci et al. [40], suggesting that PNF is a beneficial nonpharmacological treatment for chronic LBP and has a unique effect on the treatment of pain and waist function in chronic LBP. In addition, the results of this meta-analysis showed that PNF can improve the pulmonary function of chronic LBP, but no significant effect of PNF on dynamic balance were observed in the results of the meta-analysis. PNF could improve waist function of chronic LBP patients mainly because it can improve the trunk muscle strength and coordination ability, so as to enhance the stability of the trunk. In the practice process, PNF not only improves the waist muscle strength, but also enhances the power of the abdominal muscle group at the same time, including the abdominis rectus and internal and external oblique muscle. Thus, PNF training indirectly improves lung function because the ability of abdominal breathing increased. Kim et al. [41] conducted PNF-AMST exercises on the waist and abdomen for 5 days in patients' caregivers with chronic LBP. They found that it significantly reduced VAS and improved FEV₁ for at least 5 days of intervention. Lee found that it improved FEV₁ by abdominal contractions training in 20 college women [42]. Bong et al. [38] added PNF training to the contraction of abdominal muscles on the basis of Lee's study, and FEV₁ was significantly improved. The above-mentioned studies prove that PNF can have a certain effect on the improvement of lung function in patients with low back pain. In this meta-analysis, only two articles reported the effect of PNF on lung function of patients with chronic LBP, and there is only one indicator of pulmonary function included in these two articles. Although positive results were obtained, the quality and methods of the articles had a high risk of bias, and the index of lung function is low and the number of included articles is insufficient. Therefore, evidence-based medicine is insufficient. Although certain articles reported the effect of PNF on the balance function of patients with low back pain, the measurement indicators differed. For example, Young et al. [30] used mean velocity in the X and Y directions to measure balance. CoP velocity and ellipse sway area were recorded to assess balance by Areeudomwong et al. [35]. Kim et al. [36] adopted the Berg Balance Scale, whereas other authors (Jeon [39] and Young et al. [30]) preferred to use FRT and TUG to record dynamic balance. The original literature included in this system is not scarce, however, the results of these documents lack a unified evaluation standard. Thus, more relevant articles are required for a systematic review to confirm these research results in the future.

It is worth noting that the eligible articles in this review only consider patients with chronic LBP (duration of pain > 12 weeks). In addition, selected differences appear in the duration of the PNF program, with interventions ranging from 3 to 8 weeks in length in this review. Therefore, we performed two subgroup analyses on the duration time of the intervention, and we found that a PNF intervention of 4 weeks or 6 to 8 weeks can improve the pain and waist function of patients with chronic LBP. Therefore, we determined that a dose of 4 to 8 weeks of intervention with PNF training played a positive therapeutic effect and that 6-week interventions were most common. This meta-analysis is considered more reliable based on this characteristic.

Previous studies have found that the activation and coordination of trunk muscles is impaired in patients with chronic LBP, which can further lead to excessive movement and lumbar spine instability, resulting in greater pain and dysfunction [43–45]. PNF emphasizes the overall movement of multiple joint proprioceptors and multiple trunk muscle groups rather than the movement of a single muscle, and thus PNF played a positive role in pain relief and waist functional improvement in chronic low back pain.

4.1. Limitations

This meta-analysis is not without limitations. First, the findings from the systematic reviews were based on relatively low-quality data, which have a potential high risk of bias, and the number of methodologically rigorous articles is still insufficient. Second, the sample size of the participants in this meta-analysis was too small to determine the effectiveness of PNF training for chronic LBP. The third limitation was the possibility of publishing bias, and we attempted to reduce this bias via a large number of database searches. However, we did not search for unpublished articles. Finally, this meta-analysis contains too few qualified articles for a secondary outcome index, and thus the secondary results of this meta-analysis require further demonstration.

4.2. Implications for practice

Previous research shows that the main roles of PNF technology include reducing pain and fatigue, enhancing muscle strength, increasing flexibility, improving coordination and control, improving stability and balance, and enhancing endurance in patients with chronic LBP [46–48]. Judging from the results of this systematic review, PNF could indeed improve the pain and

functional status of patients with chronic LBP, and thus it can be used in clinical treatment of chronic LBP. We determined that the dose of 4 to 8 weeks intervention of PNF training had a positive therapeutic effect. It still maintains a certain effect at the 12th week of follow-up after the treatment is over. However, the results of this systematic review show that the effects of PNF on dynamic balance were not ideal, and we lack sufficient eligible RCT trails to demonstrate the secondary outcome.

5. Conclusions

Compared with the control group, PNF showed more beneficial effects in relieving pain and improving the functional status of patients with chronic LBP in the short term of 4- to 8-week intervention and it remained a positive role at 12th-week follow-up. However, no significant effect of PNF on dynamic balance was found compared with the control group. However, these results have certain limitations. These conclusions were supported by low-quality data, and there was a certain publication bias, and thus articles that are methodologically rigorous and more authoritative are required to confirm the effects. In addition, articles with long-term follow-up and other outcomes are required to confirm more findings.

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Author contributions

The study was conceived by PG and FT. YM and PG primarily contributed to the collection of study information and data extraction. WG assisted in the search process for studies. All authors participated in drafting the manuscript, read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Conflict of interest

None of the authors have any competing interests to report.

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Systematic review registration

This study was registered at <https://www.crd.york.ac.uk/prospero/PROSPERO> under registration number CRD42020163955.

Supplementary data

The supplementary files are available to download from <http://dx.doi.org/10.3233/BMR-200306>.

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