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Pelvic floor muscle training in multiple sclerosis patients with lower urinary tract dysfunction: A systematic review and meta-analysis

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Abstract

Background: Pelvic floor muscle training (PFMT) is a conservative treatment programme for the management of lower urinary tract dysfunction (LUTD). This systematic review aimed to investigate the overall effectiveness of PFMT on LUTD in people with multiple sclerosis (MS).

Methods: Seven databases (PubMed/Medline, Scopus, PEDro, WOS, CINAHL, Cochrane, and Embase) were searched between 1990 and July 2019. We investigated urine leakage as our primary outcome. The secondary outcomes were neurogenic bladder symptoms measured by the overactive bladder questionnaire (OAB-V8 questionnaire) and the power/endurance of pelvic floor muscles.

Results: Fifteen studies were identified as eligible. Both urine leakage (standardised mean difference (SMD) = 0.50, 95% CI [-0.78, -0.23], and neurogenic bladder symptoms, SMD = -2.24, 95% CI [-4.44, -0.03] significantly decreased by PFMT in people with MS. PFMT increased the overall endurance and power of pelvic floor muscles moderately and significantly, SMD = 1.25, 95% CI [0.69, 1.81], and SMD = 0.64, 95% CI [0.24, 1.05], respectively.

Conclusions: Moderate to high-quality studies showed the overall efficacy of PFMT in decreasing urine leakage and neurogenic bladder symptoms and increasing endurance and power of pelvic floor muscles. MS patients with lower urinary tract symptoms could benefit from PFMT in the short term.

Key Words: multiple sclerosis, lower urinary tract dysfunction, pelvic floor muscle training, systematic review, meta-analysis

Introduction

Multiple Sclerosis (MS) is a chronic autoimmune demyelinating disease affecting the central nervous system. The most common form of MS generally presents as relapsing-remitting, which is characterised by episodes of neurological dysfunction followed by remission, or in the less common form, primarily progressive, presented by a continuous decline in neurological function, that in a short time, can cause multiple physical and cognitive disabilities [1-7]

The incidence and prevalence of MS have been globally increased since 1965. MS is about two to three times more common in women between 20 and 40 years of age [8]. Several common findings such as fatigue, muscle spasticity, cognitive disorders, depression, lower urinary tract dysfunction (LUTD), sexual dysfunction, and pain have been reported in people with MS, which could negatively impact their quality of life [9-13].

The LUTD is highly prevalent in people with MS, affecting up to 84% of patients [2, 12, 14-16]. Symptoms could differ based on the lesion's site, extent, and progress [16]. Unlike people with non-neurological problems (e.g., post-partum urinary incontinence), incontinence in people with MS (the population under investigation in this study) may result from detrusor or sphincter dysfunction or a combination of them. Therefore, they mainly report bladder symptoms such as storage, voiding or a combination of both with a higher prevalence of mixed symptoms [17-20]. Storage and voiding symptoms include urgency, stress urinary incontinence, frequency, nocturia, hesitation, slow urine stream, difficulty urinating and urinary retention [18-20].

Pelvic floor muscle training (PFMT) is recommended as the first-line conservative treatment of LUTD in people with MS [21-23]. The improvement rate has been reported between 56 and 70% [22, 23]. Some case-control studies reported PFM (Pelvic floor muscle) function, strength, and structural support significantly differ between the continent and incontinent people. Continent subjects have better muscle function and greater muscle thickness than LUTS [24-27]. Literature shows that both women and men with neurological disorders benefit from the effects of PFMT on LUTD [28]. However, the symptoms in males and females are moderately different, as males nearly have less leakage but more voiding dysfunction [29].

Several studies reported the efficacy of using PFMT to treat LUTD in people with MS. A systematic review by Cetinel et al. [30] reported the effectiveness of different treatments of LUTD in people with MS. They reported advantages from pelvic floor rehabilitation, together with neuromuscular electrical stimulation as a short-term treatment. Another systematic review by Tubaro et al. [31] found no consensus on managing LUTD in people with MS. Ferreira and Santos [32] and Luginbuehl et al. [33], in two systematic review studies, on the effectiveness of PFMT on LUTD in people with MS, could not conclude which PFMT programme is more effective as a consequence of different protocols and outcomes.

No review or meta-analysis has yet investigated the advantages and efficacy of PFMT in LUTD people with MS. To better understand the applicability and effectiveness of PFMT in these patients, we aimed to systematically review the literature to determine the overall effect of PFMT on LUTD in people with MS.

Material and Methods

Identifying and selecting studies

Eligibility criteria

The current systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Liberati 2009) [34]. The protocol was submitted to and published on PROSPERO (ref: CRD42020156797). This review includes randomised clinical trials (RCT) on people with MS who suffered from LUTD and underwent the PFMT treatment programme, published between 1990 and 2019. The present study received ethical approval from the Iran University of Medical Sciences (IR.IUMS.REC.1399.140).

Search strategy

Electronic databases PubMed/Medline (NLM), Scopus, Physiotherapy Evidence Database (PEDro), Web of Science (WOS), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane, and Embase were searched from July 1990 to July 2019. Other databases, including ProQuest, Google Scholar, and World Wide Science, were searched for grey literature. Furthermore, the included studies' reference list has been checked for other relevant studies. The combination of the following keywords "multiple sclerosis", "lower urinary tract dysfunction", "lower urinary tract symptoms", "overactive urinary bladder", "neurogenic bladder", "pelvic floor muscle training", and "pelvic floor exercises" were used. **Table 1** lists the complete search strategy in PubMed. No language restriction was applied. The database search was updated on 14 November 2020, and no new study was found as eligible for this review.

<<< Table 1 about here >>>

Study selection and data extraction

In the first stage, three reviewers (MKV, ZA, and FF) independently screened the title and abstracts of all retrieved studies and ruled out unrelated publications. In case of any disagreement based on title or abstracts, the article's full text was checked. In the second stage, the full texts of the selected articles were assessed by the same reviewers independently to select studies based on eligibility criteria. Data extraction was performed independently by the same reviewers according to the review's objectives and Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) criteria using a standardised data extraction form. A consensus meeting was held to resolve the existing disagreements among the reviewers.

Risk of bias assessment

The methodological quality of included studies was assessed by three reviewers (MKV, ZA, and FF) independently, based on PEDro scale items [35]. In the PEDro scale items, 2-9 demonstrate the internal validity of the article, and items 10 and 11 provide quality of statistical information. Item 1 shows the trial's external validity and is not included in the total score calculation. For each item, the answer must be either yes or no.

Intervention

PFMT is a technique employed by repetitive selective voluntary contraction and relaxation of specific muscles, improving pelvic floor muscle function via enhancing force generation, correction of timing and coordination of PFMs [36, 37]. During the bladder filling phase, PFM helps maintain continence by gradually increasing its tone. This increase of tone in PFM also occurs when abdominal pressure increases [36, 38]. It is postulated that the PFM contraction inhibits detrusor contraction, increases outlet pressure, reduces bladder pressure, and finally reduces the sensation of urgency [28].

Outcome measures

The primary and secondary outcomes in this review were selected based on the common use in the included studies and most relevant to assessing LUTD in people with MS. The urine leakage was considered as a primary outcome for evaluation. Urine leakage is measured via a three-day bladder diary [12, 39, 40]. As secondary outcomes, neurogenic bladder symptoms and pelvic floor muscle function were investigated in this review. The Overactive Bladder Questionnaire (OAB-V8) is a self-reported questionnaire to evaluate neurologic bladder symptoms. The questionnaire was designed to rate four OAB symptoms in patients concerned: urinary frequency, urgency, nocturia, and urge incontinence. OAB contains a 6-point Likert scale ranging from 0 (not at all) to 5 (a very great deal). LUTD is diagnosed if the subject's total score is more than eight. The questionnaire has been adapted for people with MS [9, 41-44]. Pelvic floor muscle function is assessed according to the PERFECT scheme, the assessment tool which evaluates power (P), endurance (E), number of repetitions (R), and number of fast contractions (F). Only power and endurance subscales were evaluated in this study as they were used commonly among included studies but not the other subscales. The instrument has been used in people with MS [41, 45-49].

Meta-analysis methods

Assessment of Heterogeneity

Chi^2 and I^2 were utilised to assess statistical heterogeneity. The I^2 is indicative of the amount of variability caused by heterogeneity between studies as opposed to chance. A low *p-value* of Chi^2 suggests heterogeneity of the effect. Values

above 25 and 50% indicate moderate and high heterogeneity, respectively. Values over 75% are highly heterogeneous[50].

Assessment of Publication Bias

Funnel plots were used to assess publication bias visually. Funnel plots present the effect sizes plotted against standard errors. When the publication bias presents, the funnel plot is expected to be skewed [51, 52]. Furthermore, Egger's weighted regression test was used to quantify the publication bias. Egger's test is a linear regression of the intervention effect estimates on standard errors weighted by inverse variance. The *p*-value of Egger's regression test was reported with a null hypothesis represented as no publication bias [53].

Meta-analysis

The package "meta" version 4.15-1 by Guido Schwarzer for R Statistics software version 4.0.2 was used to perform the meta-analysis. Studies were excluded if not reported required data for meta-analysis. When the outcomes were illustrated as figures or plots, WebPlotDigitizer (http://apps.automeris.io/wpd/) was used for digitising the figures for extracting data. In studies with multi-stage treatment follow-ups, the last follow-up data were used for the meta-analysis. The standardised mean differences (SMD) were calculated (Hedges g) and confidence interval of 95% (CI 95%) for the post-intervention difference between treatment and control groups. We used the random effect model and weighted means to measure the overall effect size. A CI 95% and $p < 0.05$ were considered to be significant. In the presence of heterogeneity, sensitivity analysis, by removing each study from the meta-analysis one by one, was carried out to determine each study's effect on the overall effect size.

Meta-analysis was conducted on urine leakage as a primary outcome and neurogenic bladder symptoms, pelvic floor muscle function and overactive bladder questionnaire as secondary outcomes.

Results

The PRISMA flow chart (**Figure 1**) presents the study selection process. A total of 1245 studies were retrieved from different databases. After screening the titles and abstracts, duplicated and not relevant articles (n = 1026) were excluded. Twenty-one full-text articles were assessed for eligibility. As a result, 15 articles were selected as eligible for review. The characteristics of included studies are summarised in **Table 2**.

<<<< Table 2 about here >>>>

Quality assessment

The quality assessment according to the PEDro scale is presented in **Table 3**. The level of inter-rater reliability for the assessment of quality was investigated by Cohen's Kappa [54] (K = 0.75±0.19). Of 15 trials, eight had high-quality (53%). Four studies were rated as fair quality (26%), and three studies were graded as low quality (20%). The risk of bias for the included studies is shown in **Figure 2**.

<<<< Table 3 about here >>>>

<<<< Figure 2 about here >>>>

Meta-analysis

Sufficient data were present in only nine studies, therefore, eligible for meta-analysis.

Primary outcome

Urine leakage

Five RCTs out of nine [12, 38, 55, 56], using urinary leakage as the primary outcome, were included in the meta-analysis. The leakage episode significantly decreased in the treatment groups post-intervention, SMD = -0.50, 95% CI [-0.78, -0.23]. The statistical heterogeneity tests (I^2 = 0.06) showed low heterogeneity among the studies (**Figure 3**).

<<<< Figure 3 about here >>>>

Vahtera et al. [55] showed that urine leakage was significantly decreased after six months in the treatment group compared to the control group, SMD = -0.86, 95% CI [-1.32, -0.40]. In a randomised control trial conducted by McClurg et al. (2006) [12], at week 24, the treatment groups demonstrated a statistically significant reduction in urine leakage compared to the control group (the group that only received PFMT). SMD = -0.55, 95% CI [-1.47, 0.37] and SMD = -0.51, 95% CI [-1.43, 0.41]. The study by McClurg et al. (2008) [56] showed that at week 24, the urine leakage of the treatment group was improved; however, it was not significant, SMD = -0.18, 95% CI [-0.64, 0.27]. Perez et al. [38] also showed that leakage was reduced in both treatment groups after 12 weeks, SMD = -0.42, 95% CI [-1.05, 0.20].

Secondary outcomes

Neurogenic bladder symptoms

Only three studies out of nine included [9, 38, 41] measured neurogenic bladder symptoms using OAB-V8. They compared results at baseline and the end of the PFMT. Overall effect showed marginally significant differences between

treatment and control on post-treatment mean scores for bladder storage symptoms, SMD = -2.24, 95% CI [-4.44, -0.03]. Statistical testing for heterogeneity showed considerable heterogeneity in the three studies (I^2 = 93%). (**Figure 4**).

<<<< Figure 4 about here >>>>

Lucio et al. (2011) [9] found a significant difference in the OAB-V8 questionnaire between the treatment and control group, SMD = -3.13, 95% CI [-4.31, -1.95]. Ferreira et al. (2016) [41] showed great potential of the therapeutic effect on the treatment group SMD = -3.40, 95% CI [-4.72, -2.08]. Perez et al. showed no significant improvement in the treatment group's storage symptoms compared with the control group, SMD = -0.34, 95% CI [-0.97, 0.28].

Pelvic floor muscle function

Seven studies [12, 41, 45, 57, 58] out of nine assessed pelvic floor muscle function using the PERFECT scheme. We found large significant differences between groups on post-treatment mean scores for the endurance, SMD = 1.25, 95% CI [0.69, 1.81] and the power, SMD = 0.64, 95% CI [0.24, 1.05] (**Figures 5**). The statistical heterogeneity tests showed moderate heterogeneity, I^2 (endurance) = 0.59 and I^2 (power) = 0.34. We found large significant differences between groups on post-treatment mean scores for the endurance, SMD = 1.25, 95% CI [0.69, 1.81] and the power, SMD = 0.64, 95% CI [0.24, 1.05] (**Figures 5**). The statistical heterogeneity tests showed moderate heterogeneity, I^2 (endurance) = 0.59 and I^2 (power) = 0.34.

Lucio et al. (2010) [45] reported significant improvement of the treatment group regarding power (p = 0.002) and endurance (p < 0.00). McClurg et al. (2006) [12] showed that PFMT in combination with electromyography biofeedback (EMG biofeedback) and neuromuscular electrical stimulation (NMES) could reduce urinary symptoms by increasing pelvic floor muscle function, more than PFMT alone. In two studies, Ferreira et al. [57] reported improvement in patient's pelvic floor muscle function (PERFECT scheme) in the treatment group.

<<<< Figure 5 about here >>>>

Subgroup analysis based on the duration of treatment

Subgroup analysis compared seven RCTs that used the PERFECT scheme based on the duration of treatment (three versus six months treatment subgroups). Three trials [45, 58] were included in the three-month treatment subgroup and four trials in 6-month treatment [12, 41, 57]. For three-month treatment, the overall effect indicated a low and insignificant between-group difference for the endurance, SMD = 0.81, 95% CI [-0.23, 1.84]. High heterogeneity was illustrated (I^2 = 0.75) (**Figure 5**). The overall effect of power was moderate and significant for three-month treatment, SMD = 0.97, 95% CI [0.46, 1.49]. The results showed no observed heterogeneity (**Figure 6**).

For 6-month treatment, the overall effect showed a significantly higher score in the treatment group versus control for the endurance, SMD = 1.55, 95% CI [1.06, 2.03]. No heterogeneity was shown (**Figure 5**). The overall difference was

low and insignificant for the power outcome, SMD = 0.42, 95% CI [-0.14, 0.98]. There was moderate heterogeneity between the studies in this subgroup (I^2 = 0.43). (**Figure 6**).

<<<< Figure 6 about here>>>>

Assessment of Publication Bias

Funnel plots did not show publication bias in the meta-analysis for primary and secondary outcomes (**Figures 7**). Eggers' test did not indicate funnel plot asymmetry for urine leakage p = 0.99, PERFECT endurance, p = 0.2, and PERFECT power, p = 0.3. The neurogenic bladder measure was not checked for publication bias as the number of publications was limited to three.

<<<< Figure 7 about here>>>>

Discussion

The present study systematically reviewed and performed a meta-analysis regarding the PFMT in MS patients with LUTD. The pooled effect sizes showed that PFMT, either used alone or in combination with electromyography biofeedback associated with electrostimulation, can successfully decrease urine leakage and neurogenic bladder symptoms and improve pelvic floor muscle function in MS patients with LUTD. In addition, there was significant heterogeneity among the included studies for one of the secondary outcomes.

The mechanism of action of PFMT in alleviating symptoms of LUTD (overactive bladder) is unclear. PFM contraction employs the pelvic floor levator ani and the puborectalis muscles. The levator ani is the evacuating muscle, and the puborectalis muscle is used during continence. During puborectalis contractions, the external sphincter muscles of the anus and urethra contract synchronously. The PFM contraction likely involves the puborectalis sphincter and urethra contraction, resulting in inhibition of contraction of the detrusor (rectum or bladder). The micturition reflex activates with vesical filling to the point of urging. Utilising PFM contractions, the voluntary urinary inhibition reflex could mediate an inhibition of the micturition reflex by puborectalis and external urethral sphincter contractions. Some studies support the treatment of the overactive bladder using PFM exercises [59].

Studies have used diverse assessment methods to verify the influence of PFMT on the treatment of LUTS in people with MS, including; assessment of urine leakage, neurogenic bladder symptoms, perineal contraction, pelvic floor muscle function (PERFECT scheme), uroflowmetry, level of anxiety and depression, treatment adherence, urinary incontinence severity and the measurement of its impact on participants' quality of life applied before and after the PFMT alone or with other conservative treatments [9, 12, 28, 38, 41, 45, 55-58, 60-64]. Among them, urine leakage, neurogenic bladder symptoms, and functionality of PFM (power, endurance) were considered as primary and secondary outcomes for the present systematic review [9, 12, 28, 38, 41, 45, 55-57]

The evidence from high and moderate-quality studies suggested that PFMT could improve leakage in people with MS. The results showed a good overall effect size favouring PFMT to diminish leakage episodes in people with MS. Regarding the present study's findings, the calculated effect size for each study confirmed the positive effects of PFMT. The effectiveness of PFMT has not been clearly stated, although improvements probably occurred because PFMT helps to postpone voiding, manage urinary latency and aid bladder emptying by relaxation of muscles. In addition, the results reinforced the benefit of using PFMT together with other conservative interventions (e.g., electrical stimulation, EMG biofeedback) [12, 38, 55, 56]. Pelvic floor muscles are predominantly made up of slow fibres, which are more resistant to fatigue. Ferreira et al. (2016) showed that fast and slow contractions of perineal muscle fibres were stimulated both in the group that undertook an exercise in isolation and in the group that undertook exercise associated with electrostimulation.

There is moderate evidence among high and moderate-quality studies that PFMT improves neurogenic bladder symptoms in people with MS in short-term duration. The overall effect size was large, favouring the use of PFMT to decrease neurogenic bladder symptoms in people with MS. Three included trials indicated a statistically significant reduction in neurogenic bladder symptoms in the treatment group compared with the control group [9, 38, 41].

Our findings in decreasing urinary symptoms are in accordance with those of Cetinel et al. and Gaspard et al. [65]. In a systematic review conducted by Cetinel et al., lower urinary tract dysfunction in people with MS was assessed. The results showed that pelvic floor rehabilitation combined with NMES was recommended to increase treatment success. In a systematic review, Gaspard et al. evaluated different treatment approaches to manage LUTD in people with MS. They reported a significant reduction in leakage episodes from 86% to 64% by the end of the treatment. Tubaro et al. assessed different treatments of LUTS in people with MS. The present review overview studies investigated the effect of using PFMT alone or in combination with electrical stimulation or EMG biofeedback to decrease urinary symptoms. They concluded that cohort studies with a large population are required to assess the effectiveness of different treatments.

PFMT could treat urinary symptoms by building up the structural support of the pelvic floor by closuring the levator hiatus and increasing in maximum urethral closure pressure to prevent leakage during the increase in intra-abdominal pressure. Additionally, strength training of the PFM could develop permanent morphological changes in the pelvic floor, stabilising neurogenic activity and ureteral pressure. Also, regarding the results of the review study by Oliveira M. et al., increasing the strength of PFM in a short time may not be related to a significant reduction in the amount of urine loss. This suggests that the increase in PFM strength and urethral resistance does not seem to guarantee the mechanism of urinary continence. According to some authors, coordination between early contraction of PFM and increased intra-abdominal pressure may be the most relevant factor in reducing urine leakage compared to the strength gain of PFM, which may justify the positive results of short training programmes.

PFM contractions could treat neurogenic bladder symptoms by decreasing detrusor pressure, increasing ureteral pressure suppression of the micturition reflex. Although, the rationale behind the use of PFMT to treat symptoms of neurogenic bladder is based on early observations of PFM voluntary contractions during the urodynamic assessment. In addition, the theoretical basis of how PFMT may work in the treatment of neurogenic bladder remains unclear.

Most of the studies showed a good overall effect size for pelvic floor muscle function (power, endurance), confirming the positive effect of PFMT on increasing power and endurance in people with MS. Subgroup analysis revealed a larger overall effect size for the power outcome within a 3-month treatment group. In the 6-month treatment group, a larger overall effect was for the endurance outcome [12, 41, 45, 57, 58].

Ferreira et al. suggested that PFMT could affect perineal muscles by improving their strength which could be considered a positive mechanism in the more remarkable improvement of the PERFECT scheme. According to Ferreira and Santos, the increase in strength during the first 6 to 8 weeks of treatment with PFMT could be predominantly neural. PFM are skeletal muscles and, therefore, the recommendations of strength training are not different from other skeletal muscles. In the first 8 weeks of training, the changes are essentially neural (increased number and frequency of motor unit activation), followed by muscle hypertrophy due to increased volume and number of myofibrils, essential for morphological or structural adaptations. The mean of the power outcome in this group was high.

The 6-month treatment, which resulted in a larger overall effect for the endurance outcome, could result from muscle hypertrophy. According to Ferreira and Santos, hypertrophy is a slower process, beginning at 6 to 8 weeks and possibly lasting for years. McClurg et al. suggested that 15 to 20 weeks of muscle training is necessary to produce hypertrophy, which leads to an increase in endurance and power. Although, a decrease in power in the 6-month treatment may be due to the progressive nature of MS.

The treatment protocols applied to the studies included in this systematic review consisted of voluntary contraction of pelvic floor muscle to improve muscle strength, resistance to fatigue and coordination of muscles. PFMT is also used unguided or guided, with EMG biofeedback and NMES. Period of intervention protocols among the selected studies varied from 12 weeks to 6 months with a weekly frequency of 2 times a week. According to the ICS recommendation, the initial treatment should last for 8 to 12 weeks before re-assessment. The PFMT protocols applied to the included studies varied regarding maintaining contraction time, the number of repetitions and series, the rest between contractions and/or series and the exercise progression.

The other main finding is considerable heterogeneity across the studies included for the secondary outcome (neurogenic bladder symptoms). A possible explanation for this considerable heterogeneity might be the lower number of studies in this section. Therefore, the results should be interpreted cautiously. Additionally, it might be due to differences in the studies regarding control intervention, number of cases and controls, and treatment protocols (duration, dosage and kind of treatment).

Limitation

The present study has some limitations. First, the studies included in this review were only designed to record the short-term treatment effect. Therefore, concluding the effect stability over a medium or long-term of using PFMT is not possible. Second, a limited number of studies existed in each outcome for meta-analysis, which might limit the conclusions of the effectiveness of PFMT on lower urinary tract dysfunction in people with MS. The heterogeneity statistic I^2 can be biased in meta-analyses with small numbers of studies [66]. As the number of studies, especially in regard to the outcome OAB, is only limited to three studies, the results must be interpreted with caution. According to the Handbook of Cochrane Collaboration, funnel plot asymmetry should be used when at least 10 studies and fewer studies may increase the risk of chance rather than real asymmetry. In this study, the Funnel plots were only presented for the Leakage (5 studies) and PERFECT (7 studies) and not OAB (3 studies) outcomes. These plots are only illustrated for exploration, and bias cannot be excluded completely. Finally, the validity of the findings is limited because included studies did not report power and sample size calculations.

Conclusions

In conclusion, moderate and high-quality studies confirmed the positive effect of PFMT in the treatment of urine leakage, neurogenic symptoms, and the PERFECT scheme. The meta-analysis showed a significant effect of PFMT on urine leakage and neurogenic symptoms decrement, with good overall effect sizes. Besides, the findings showed a significant effect of PFMT on increasing power and endurance with good overall effect sizes.

Statistical heterogeneity analysis included studies for the primary outcome, urine leakage, with very low heterogeneity. There was considerable heterogeneity for Neurogenic bladder symptoms and moderate heterogeneity for the power and endurance as secondary outcomes. Further high-quality studies to assess the long-term effect of PFMT on lower urinary tract dysfunction are recommended.

Most of the included studies (nine out of 15) assessed both genders with a wide age range in their studies. The EDSS score was lower than eight, and the MS duration since diagnosis covered a wide range. With reference to the variation in the baseline characteristics in the selected studies, the overall findings of the current systematic review, irrespective of gender and disease duration, could be more appropriately generalised to the MS patients with EDSS scores lower than eight.

Conflict of interest:

No conflict of interest

Author contribution:

MK: conceptualisation, data curation, supervision, validation, visualisation, methodology, project administration, writing original draft. ZA: data curation, interpretation of the results and drafting the article. AL: Review & editing. FF: conceptualisation, data curation, investigation, resources. RS: conceptualisation; supervision; interpretation of the results and drafting the article. FP: data curation, resources, software. MD: interpretation of the results and drafting the article. HJ: conceptualisation, investigation, methodology, project administration, formal analysis, interpretation of the results and drafting the article.

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Table 1. PubMed search strategy

Search number	Query	Results
1	((((Neurogenic bladder [Text Word]) OR Overactive urinary bladder [[Text Word]) OR Lower urinary tract symptoms [Text Word]) OR LUTS [Text Word]) OR Lower urinary tract dysfunction [Text Word]	15,041
2	("Multiple Sclerosis" [Mesh]) OR (("Multiple Sclerosis" [Title]) OR "Multiple Sclerosis" [Title/Abstract])	84,934
3	(((((((("Lower Urinary Tract Symptoms" [Mesh]) OR "Urinary Bladder, Overactive" [Mesh]) OR "Urinary Bladder, Neurogenic" [Mesh]) OR "Urinary Incontinence" [Mesh]) OR ((Lower urinary tract dysfunction [Title]) OR Lower urinary tract dysfunction [Title/Abstract])) OR ((((Lower urinary tract symptoms [Title]) OR Lower urinary tract symptoms [Title/Abstract]) OR LUTS [Title]) OR LUTS [Title/Abstract])) OR ((Overactive urinary bladder [Title]) OR Overactive urinary bladder [Title/Abstract])) OR ((Neurogenic bladder [Title]) OR Neurogenic bladder [Title/Abstract])	54,230
4	#1 AND #2	803
5	(((((Pelvic floor training [Title]) OR Pelvic floor training [Title/Abstract])) OR ((Pelvic floor exercise [Title]) OR Pelvic floor exercise[Title/Abstract])) OR ((((Pelvic floor muscle* training [Title]) OR Pelvic floor muscle* training [Title/Abstract]) OR Pelvic floor muscle* exercise [Title]) OR Pelvic floor muscle* exercise [Title/Abstract])) OR ((((PFMT [Title]) OR PFMT [Title/Abstract]) OR PFME [Title]) OR PFME[Title/Abstract])	1,682
6	#5 AND #4	14

Table 2. Characteristics of the included studies.

Outcome	Intervention	EDSS score (Mean(SD))	MS duration (years) (Mean(SD))	Patients, N, Age (Mean (SD)) /Gender(n)	Study design	Country	Study
quality-of-life, Hospital Anxiety and Depression questionnaire, [e] OAB-V8, and PERFECT scheme	TG[b]= [c]PFMT (three sets of 10 repetitions of Kegel exercises per day)+ Electrotherapy (Electrostimulation with two electrodes positioned on the S4 dermatome-perineum region) (frequency of 2 Hz, positive pulse duration of 1 msec, and tolerable intensity) CG[d]= PFMT (sets of home activities)	Between 3 to 5	NR	24, 43.25 (10.68)/ Only females	[a] RCT	Brazil	Ferreira et al. (2016)
Qualiveen questionnaire, OAB-V8, PERFECT scheme	TG= PFMT+ Electrotherapy(intravaginal electro stimulation, Frequency of 2 Hz, positive pulse duration of 1 msec, intensity tolerable, 30 minutes) CG= PFMT(sets of home activities)	TG: 3.5(1) CG: 3.5(0.5)	NR	30, TG :38.6(13.5) CG :49.8(16.5) Only females	RCT	Brazil	Ferreira et al. (2019)
The SF-Qualiveen questionnaire, USP questionnaire, 3-day bladder diary	TG1 = PFMT (by using biofeedback) TG2 = [f]TTNS	Median:3 for both groups	TG: 10 (10.3) CG: 8.6 (8.3)	31, TG1 = 43.5 (14) TG2 = 40.5 (9.5) 15 females, 16 males	RCT	Belgium	Gaspard et al. (2014)
[g]UDI6, [h]NDS , [i]AUA, [j]IIQ7	TG = Bladder Rehabilitation (bladder re-education, behavior management, pelvic floor exercises, strategies for timed and double voiding, intermittent catheterization techniques, use of prophylactic medication CG = Usual Care (regular reviews by general practitioners and neurologists)	Between 2 to 8	TG: 11.7 (6.2) CG: 11.0(9.3)	58, TG: 49.7 (9.1) CG:51.9 (9.2) 44 females, 14 males	RCT	Australia	Khan et al. (2010)
Pad weighting test Flowmetry Ultrasonography Water cystometry Surface EMG	TG1 = PFMT, TG2= biofeedback	Between 2.5 to 8	NR	22, Median age: 44 15 females, 5 males	RCT	Denmark	Klarskov et al. (1994)
OAB-V8, PERFECT scheme, 3-day bladder diary, and 24-hr Pad testing	TG = PFMT (intervention consisted of PFMT with the assistance of a vaginal perineometer CG = received a sham treatment consisting of the introduction of a perineometer inside the vagina with no contraction required. No orientations about exercises at home were given.	TG: 3.4 (1.5) CG: 3.3 (1.5)	TG: 9.1 (5.8) CG: 6.8 (3.5)	27, TG :36 (7.2) CG :34.7(8.8) Only females	RCT	Brazil	Lucio et al. (2010)
[l]ICIQ-SF, Study Short Form 36 (SF-36) questionnaire, Qualiveen questionnaire andOAB-V8	TG = PFMT (the treatment group underwent pelvic floor muscle training with assistance from a vaginal perineometer and instructions to practice daily exercises at home. CG = The sham group received a treatment consisting of introducing a perineometer inside the vagina with no exercises required	TG: 3.4 (1.5) CG: 3.3 (1.5)	TG: 9.1 (5.8) CG: 6.8 (3.5)	27, TG:36(7.2) CG:34.7 (8.8) Only females	RCT	Brazil	Lucio et al. (2011)
24-hour pad test, 3-day bladder diary, assessment of PFM function (strength and muscle tone), urodynamic studies, and validated questionnaires, including OAB-V8, ICIQ-SF, and Qualiveen instrument	TG1 = = PFMT+ (EMG) Biofeedback + sham NMES TG2 = PFMT+ (EMG) Biofeedback+ Intravaginal NMES TG3= PFMT+ (EMG) Biofeedback + TTNS	Lower than 6.5	TG1 = Median (range) 15(5-19) TG2 = Median 13.5(3-20) TG3 = Median 11(5-20)	30, TG1 : Median (range) 43.5 (25-51) TG2 : Median (range) 42 (27-54) TG3: Median (range) 45(22-52), Only females	RCT	Brazil	Lucio et al. (2016)
3-day Voiding Diary; 24 h Pad-Test; Uroflowmetry; Pelvic Floor Muscle Assessment; [m]IIQ; [n]UDI; [o]KHQ, and [p]MSQoL-54	TG1 = PFMT TG2 = PFMT + (EMG) Biofeedback TG3 = PFMT + (EMG) Biofeedback + NMES	TG1: 5.4 (1.3) TG2: 5.9 (1.3) TG3: 5.7 (1.0)	TG1: 6.0 (0.1) TG2: 10.2 (1.0) TG3: 11.3 (1.5)	30, TG1 = 49.5 (8.7) TG2 = 52.1 (11.5) TG3 = 49.9 (11.6) Only females	RCT	Northern Ireland, UK	McClurg et al. (2006)
Bladder diary, 24-hr pad test, Portable uroflowmetry, Portable bladder scanner, Pelvic floor muscle assessment Digital assessment, EMG biofeedback, incontinences Impact Questionnaire, Urinary distress inventory, The International Prostate Symptom Score, Visual Analogue Scale, Multiple Sclerosis Impact Scale 29, The Barthel index	TG1 = PFMT+ (EMG) Biofeedback+ placebo NMES TG2 = = PFMT+ (EMG) Biofeedback+ NMES	TG1: 4.9 (1.4) TG2: 4.7 (1.5)	TG1: 11.0 (7.6) TG2: 10.2 (8.6)	74, TG1 = 52 (8.8) TG2 = 48.3 (11.5) 57 Females, 17 males	RCT	Northern Ireland, UK	McClurg et al. (2008)
Digital and EMG biofeedback assessment of the PFMs; the number of leakage episodes (bladder diary); the amount of leakage (pad test); uroflowmetry; the International Prostate Symptom Score; and a Visual Analogue Scale.	PFMT + EMG Biofeedback	4.9 (1.4)	11.0 (7.6)	37, 52(8.8) 26 females, 11 males	RCT	Northern Ireland, UK	McClurg et al. (2008)
3-Day Bladder Diary, Quality of Life, UI Severity, LUTS, and treatment adherence	TG1 = Unguided PFMT TG2 = Guided PFMT	TG1: 4.83 (1.23) TG2: 4.82 (0.88)	NR	40, TG1 = 47.8 (7.24) TG2 = 45.8 (10.5) 22 Females, 18 males	RCT	Spain	Pérez et al. (2019)
[q]ICIQ-UI SF, DASS-21	TG = PFMT	Lower than 7	MS duration (range): 1-20	45, Age range :18-50 Both females and males	Quasi-Experimental Clinical Trial	Iran	Rafii et al. (2017)
ICIQ-UI SF, Qualiveen-30	TG = PFMT	Lower than 7	9.06± 5.1	45, 36.33(9.4) Both females and males	Quasi-Experimental Clinical Trial	Iran	Rafii et al. (2018)
Surface EMG, Biofeedback, questionnaire	TG = Electrical stimulation + Pelvic floor muscle exercises CG = No treatment	Lower than 6.5	TG (range): 1-30 TG (range): 1-41	80, TG Age range: 25-57 CG = Age range: 26-68 50 females,30 males	RCT	Finland	Vahtera et al. (1997)

[a] Randomized Clinical Trial; [b] Treatment group; [c] Pelvic floor muscle training; [d] Control group; [e] Overactive Bladder Questionnaire; [f] transcutaneous posterior tibial nerve stimulation; [u]rogenital Distress Inventory6; [h] Neurological Disability Scale; [i] American Urological Association Symptom Index; [j] Incontinence Impact Questionnaire 7; [l] International Consultation on Incontinence Questionnaire Short Form; [m] Incontinence Impact Questionnaire; [n] Urogenital Distress Inventory; [o] King's Health Questionnaire ; [p] Multiple Sclerosis Quality of Life-54 Instrument; [q] Incontinence Questionnaire-Urinary Incontinence Short Form; NR; Not Reported

Table 3. The PEDro scores for all included studies

Author	Year	Total PEDro Score	1	2	3	4	5	6	7	8	9	10	11
Ferreira	2016	8	Y	Y	Y	Y	N	Y	N	Y	N	Y	Y
Lucio	2010	7	Y	Y	N	Y	Y	N	Y	Y	N	Y	N
Lucio	2016	8	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N
Lucio	2011	7	Y	Y	Y	Y	Y	N	Y	N	N	Y	N
McClurg	2008	9	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N
McClurg	2008	4	Y	N	N	N	N	N	Y	Y	Y	N	N
McClurg	2006	8	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N
Vahtera	1997	6	Y	Y	N	Y	N	N	N	Y	Y	Y	N
Rafii	2018	3	Y	N	N	N	N	N	N	Y	N	N	Y
Rafii	2017	2	Y	N	N	N	N	N	N	Y	N	N	N
Perez	2019	6	Y	Y	Y	Y	N	N	N	N	N	Y	Y
Khan	2010	8	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y
Ferreira	2019	6	Y	Y	Y	Y	N	N	N	Y	N	Y	N
Klarskov	1994	5	Y	Y	Y	N	N	N	N	Y	N	Y	N
Gaspard	2014	7	Y	Y	N	Y	N	N	Y	Y	Y	Y	N

Items: 1. Eligibility criteria were specified, 2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received), 3. Allocation was concealed, 4. The groups were similar at baseline regarding the most important prognostic indicators, 5. There was blinding of all subjects, 6. There was blinding of all therapists who administered the therapy, 7. There was blinding of all assessors who measured at least one key outcome, 8. Measures of at least one key outcome were obtained from >85% of the subjects initially allocated to groups, 9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analyzed by intention to treat, 10. The results of between-group statistical comparisons are reported for at least one key outcome, 11. The study provides both point measures and measures of variability for at least one key outcome.

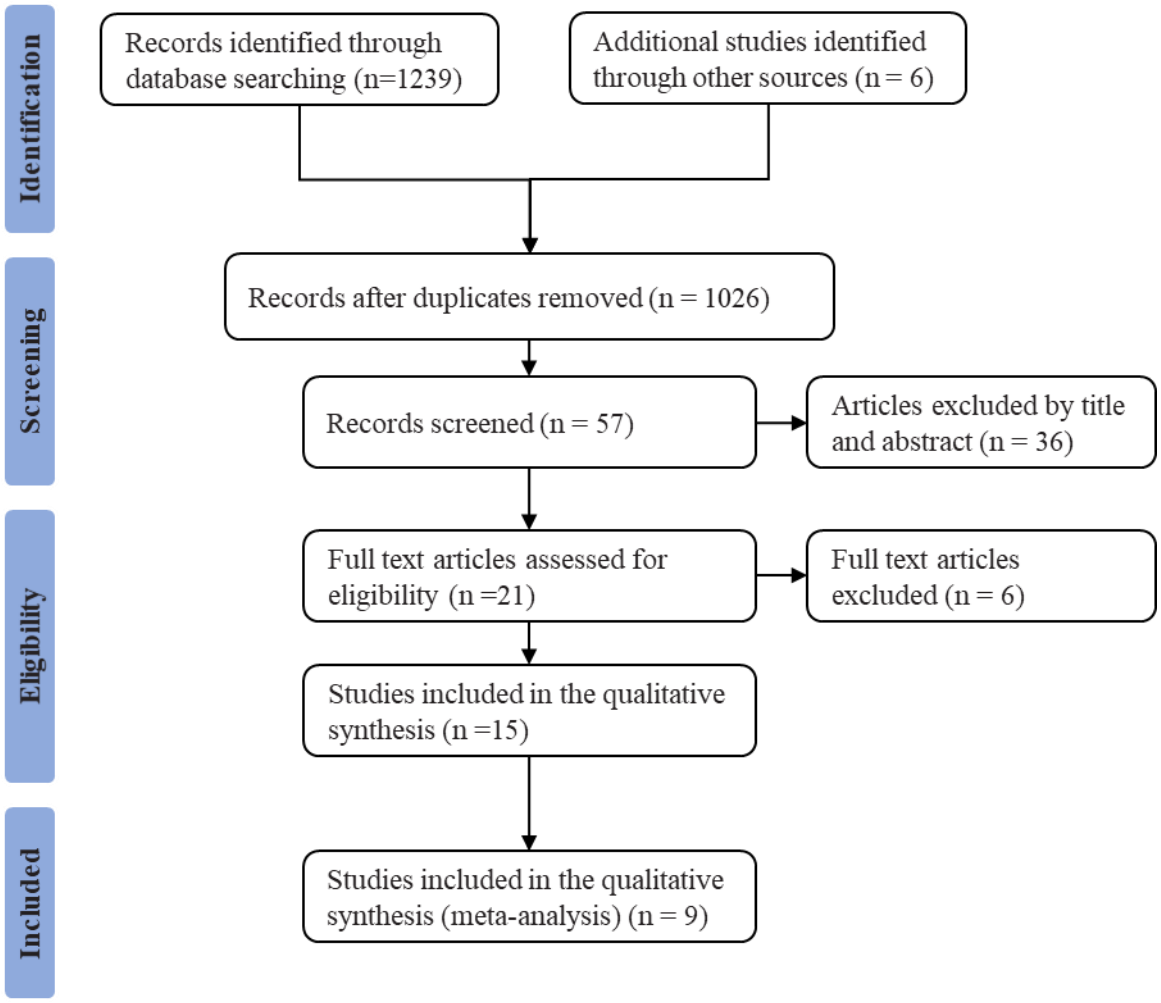

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram.

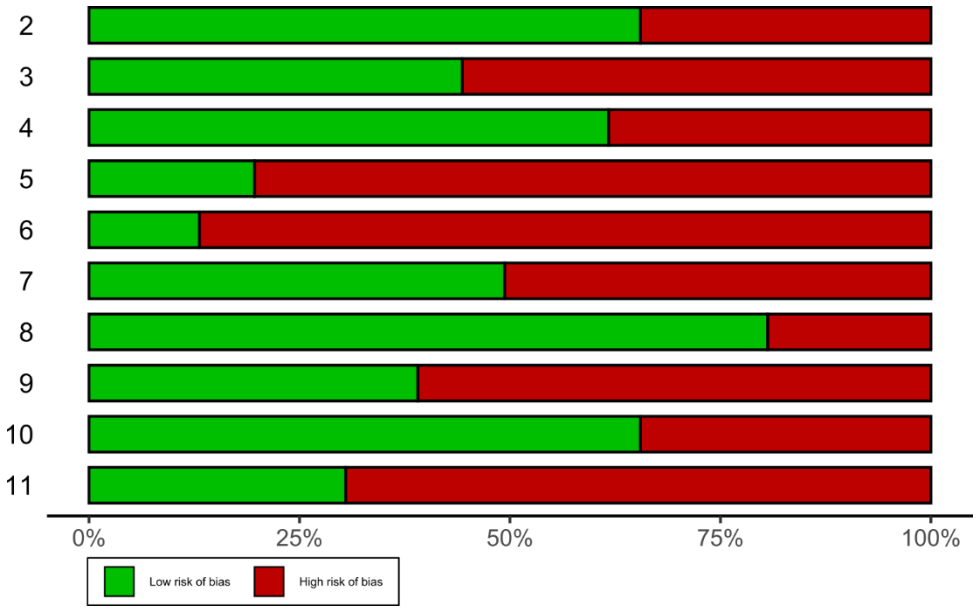

Figure 2. Risk of bias for the included studies. Items are: 2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received), 3. Allocation was concealed, 4. The groups were similar at baseline regarding the most important prognostic indicators, 5. There was blinding of all subjects, 6. There was blinding of all therapists who administered the therapy, 7. There was blinding of all assessors who measured at least one key outcome, 8. Measures of at least one key outcome were obtained from >85% of the subjects initially allocated to groups, 9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analyzed by intention to treat, 10. The results of between-group statistical comparisons are reported for at least one key outcome, 11. The study provides both point measures and measures of variability for at least one key outcome.

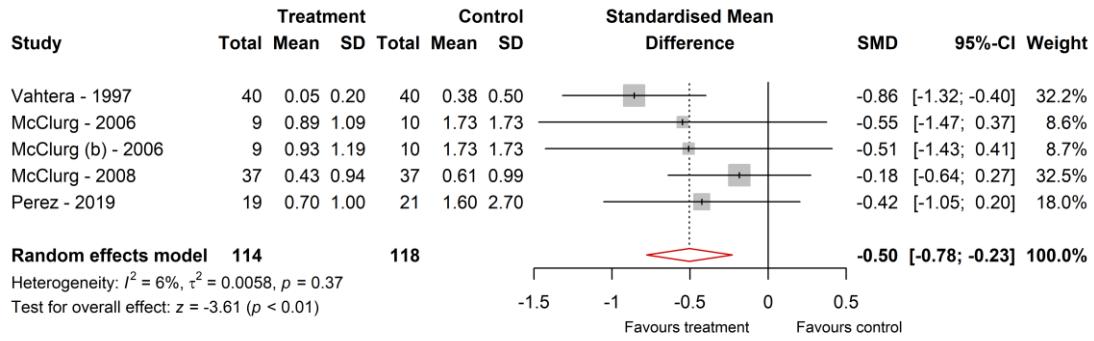

Figure 3. Forest plot for the primary outcome leakage

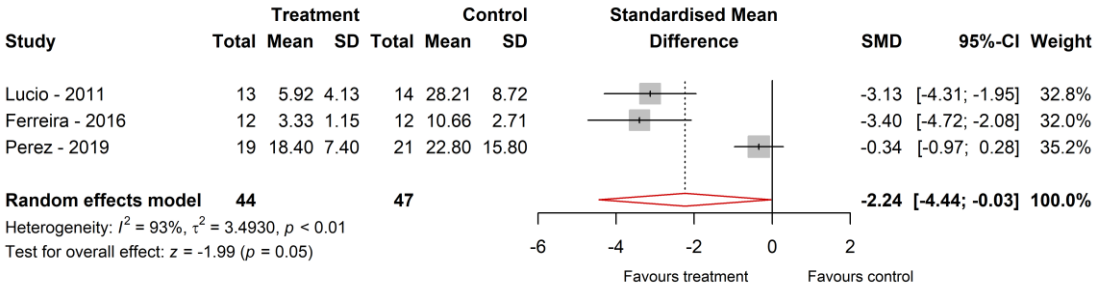

Figure 4. Forest plot for the secondary outcome OAB

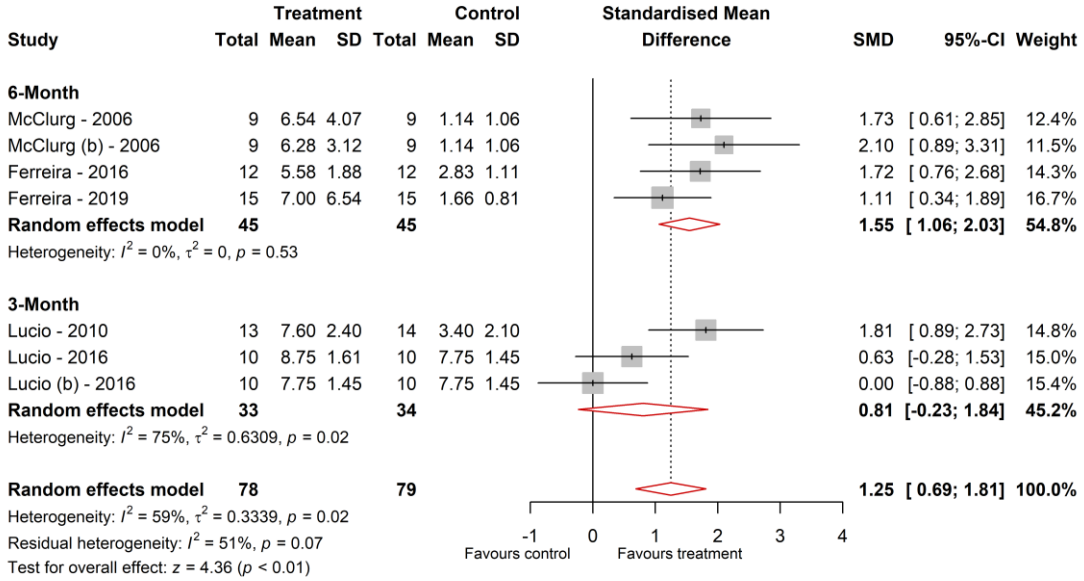

Figure 5. Subgroup analysis based on duration of treatment for the outcome PERFECT (Endurance)

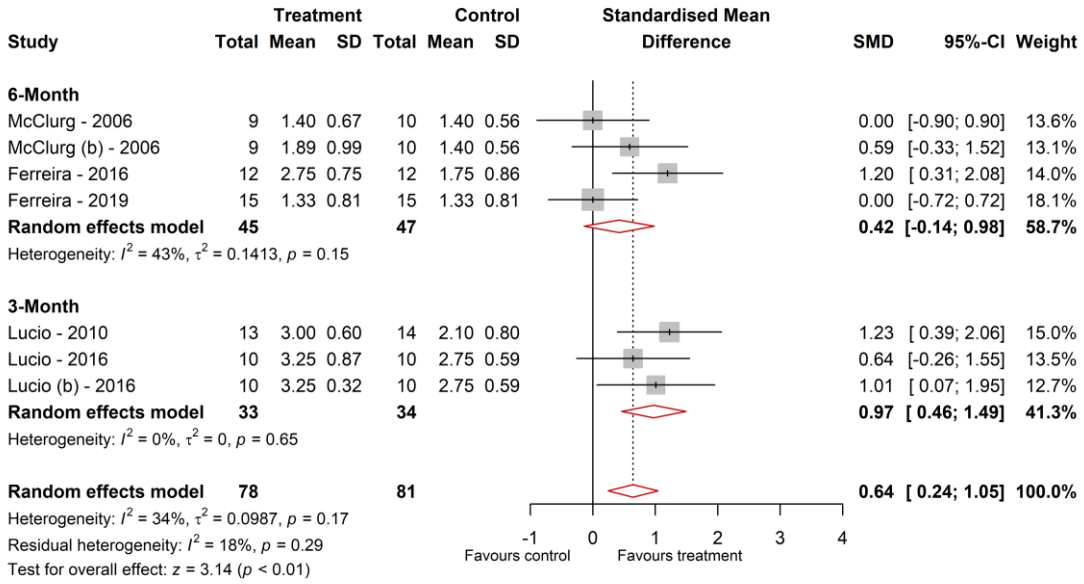

Figure 6. Subgroup analysis based on duration of treatment for the outcome PERFECT (Power)

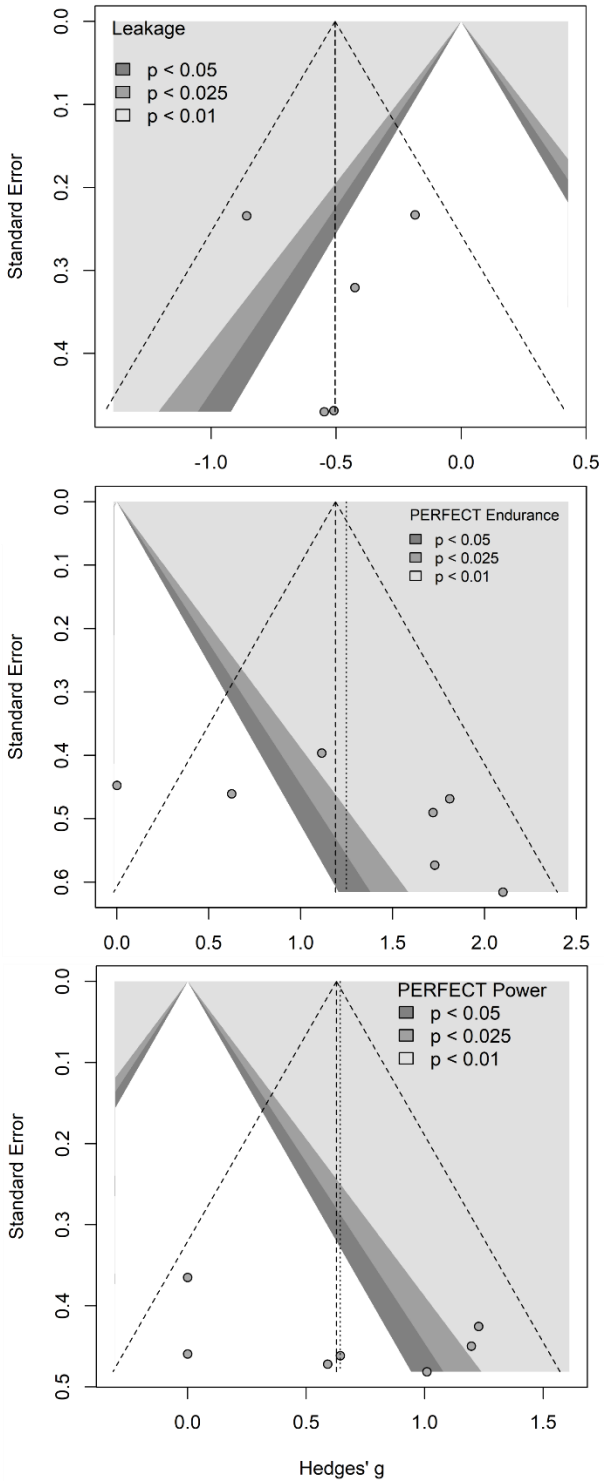

Figure 7. Funnel plot for publication bias for the outcomes leakage, PERFECT (Endurance), and PERFECT (Power)