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Does cycling induced by functional electrical stimulation enhance motor recovery in the subacute phase after stroke? a systematic review and meta-analysis

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Abstract

Objective: To investigate the effects of cycling with functional electrical stimulation on walking, muscle power and tone, balance and activities of daily living in subacute stroke survivors.

Data Sources: Ten electronic databases were searched from inception to February 2020.

Review methods: Inclusion criteria were: subacute stroke survivors (<6 months since stroke), an experimental group performing any type of cycling training with electrical stimulation, alone or in addition to usual care, and a control group performing usual care alone. Two reviewers assessed eligibility, extracted data and analyzed the risks of bias. Standardized Mean Difference (SMD) or Mean Difference (MD) with 95% Confidence Intervals (CI) were estimated using fixed- or random-effects models to evaluate the training effect.

Results: Seven randomized controlled trials recruiting a total of 273 stroke survivors were included in the meta-analyses. There was a statistically significant, but not clinically relevant, effect of cycling with electrical stimulation compared to usual care on walking (six studies, SMD [95% CI] = 0.40 [0.13, 0.67]; $P = 0.004$), capability to maintain a sitting position (three studies, MD [95% CI] = 7.92 [1.01, 14.82]; $P = 0.02$) and work produced by the paretic leg during pedaling (2 studies, MD [95% CI] = 8.13 [1.03, 15.25]; $P = 0.02$). No significant between-group differences were found for muscular power, tone, standing balance, and activities of daily living.

Conclusions: Cycling training with functional electrical stimulation cannot be recommended in terms of being better than usual care in subacute stroke survivors. Further investigations are required to confirm these results, to determine the optimal training parameters and to evaluate long-term effects.

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Stroke, rehabilitation, functional electrical stimulation, cycling, meta-analysis

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Introduction

Functional electrical stimulation is a well-established intervention for motor recovery after stroke.[1,2] Lower limb functional electrical stimulation has been applied in different modalities, multichannel or single-channel to the peroneal nerve, overall showing a positive effect on gait performance.[3–5] In the last decade, cycling induced by functional electrical stimulation has been proposed as an alternative treatment for gait recovery after stroke.[6,7] Indeed, cycling entails an asymmetric coordinated activation of the two legs similar to locomotion,[8,9] but can be safely applied soon after stroke, since it does not require the capability to maintain upright posture. A recent systematic review with meta-analysis has quantitatively summarized the current evidence about the effects of cycling with and without functional electrical stimulation on functional mobility after stroke.[10] The Authors concluded that cycling has a positive effect on walking speed, walking ability and balance, and benefits on balance were increased when functional electrical stimulation was added to cycling training. However, this review was mainly focused on cycling training in general, and just one single-outcome meta-analysis, including only two studies, was conducted to compare the effects of cycling induced by functional electrical stimulation to usual care. Furthermore, a mixed population, including both subacute and chronic stroke survivors, was considered. The only reviews specifically focused on cycling induced by functional electrical stimulation were qualitative and targeted on individuals with spinal cord injury.[11–13]

This systematic review with meta-analyses aimed at gathering and synthetizing the current evidence about the effects of cycling induced by functional electrical stimulation in the subacute phase after stroke. The primary aim was to analyze whether cycling induced by functional electrical stimulation represents an effective alternative or integrative treatment to usual care for promoting walking abilities over short distances in these patients. Different secondary outcome measures were also appraised, including muscle strength, spasticity, balance, cycling performance and basic activities of daily living.

Methods

This study was undertaken in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statements.[14]

Identification of the studies

The following electronic databases Cochrane Library, Pubmed, Embase, Google Scholar, IEEExplore, PsychINFO, Scopus, Web of Science, ClinicalTrial.gov, WHO International Clinical Trials Registry, OpenGrey database were searched for their inception up to February 2020. Methodological search filters by study designs and outcomes were not applied to minimize incomplete retrieval of identified research. No language, date and document format restrictions were applied to reduce reporting bias. The following keywords were combined in the search strategy: *electrical stimulation, neuromuscular stimulation, Functional Electrical Stimulation (FES), Neuro-Muscular Electrical Stimulation (NMES), Functional Neuro-muscular Stimulation (FNS), cycling, pedaling, ergometry, cycle ergometry, cycle training, stroke, cerebrovascular accident (CVA).* The full search strategy is available in Supplemental Appendix 1. Reference lists of all potentially eligible articles identified from the search strategy were also screened to identify any further studies for inclusion.

Eligibility criteria

Studies were included if they implemented an intervention based on cycling induced by functional electrical stimulation alone or in addition to usual care

and if they compared its effects to usual care and/or any other treatments involving no types of electrical muscle stimulation. Randomized, quasi-randomized or crossover trials with a longitudinal design were considered. Studies were excluded if only abstract was available or numerical scores of outcomes were not reported. Case reports, editorials, letters, commentaries, and review articles were also excluded.

Participants of included studies were adult patients (age 18+ years) with a diagnosis of single ischemic or hemorrhagic stroke in the subacute phase (i.e. less than six months since first stroke). No eligibility criteria were defined based on outcome measures, which were classified based on the International Classification of Functioning, Disability and Health[15] to facilitate content comparisons and interpretations.

Titles and abstracts of the identified papers were independently evaluated by two review authors (EA, MP). Full texts of all potentially relevant articles were then obtained and assessed by each review author (EA, MP). After full text review, study eligibility was determined. Data from eligible studies were extracted by one review author (MP) using a structured form, including study design, number of patients, patient's demographic and clinical characteristics, intervention protocol, comparison groups, and results of the outcomes. A second review author (EA) confirmed the data extraction accuracy and any disagreement was resolved by discussion. When relevant information was missing, authors of primary studies were contacted.

Risk of bias assessment

The risk of bias of each study was assessed using a domain-based evaluation tool and different criteria from each domain were separately evaluated: (1) selection bias (random sequence generation; allocation concealment; group similarity at baseline); (2) performance bias (blinding of participants; blinding of personnel; co-interventions; compliance); (3) detection bias (blinding of outcome assessment; timing of outcome assessment); (4) attrition bias (incomplete outcome data; intention-to-treat analysis); (5) reporting bias (selective reporting). Two review authors (EA, MP) independently assessed the risk of bias of each included studies using the revised extension[16] of the criteria described by Cochrane Handbook for Systematic Reviews of Interventions.[17] For each criterion, a "low risk," "high risk" or "unclear risk" of bias was assigned. Each study was classified as "low risk" of bias, if at least six of the appraised criteria were considered as "low risk," whereas if more than six criteria were assessed as "high" or "unclear risk," the study was considered at "high risk" of bias.

Measures of treatment effects

The results of individual studies were collected and combined when possible through meta-analysis techniques,[18] to evaluate the effect of cycling induced by functional electrical stimulation with respect to usual care at short- and/or intermediate-term follow-up.

Outcome data were pooled in categories of outcome measures based on the sub-domains of the International Classification of Functioning, Disability and Health classification, as reported in Supplemental Appendix 2. Outcomes measured closest to four weeks were considered short-term follow-up, outcomes measured closest to six months were considered intermediate-term follow-up.[17]

For continuous outcome measures the intervention effects were evaluated through the Mean Difference (MD) or the Standardized Mean Difference (SMD) based on Hedges' *g*, along with the 95% Confidence Interval (CI), of post-intervention values.[19] However, if there was a baseline imbalance, which was defined as a between-group difference at baseline higher than the minimal clinically important difference, in at least one study, the meta-analysis for that specific outcome was conducted on change values.[17]

Heterogeneity among studies was assessed using the I^2 statistic and the Chi^2 test.[20] In case of high heterogeneity, that is, $I^2 > 50\%$, a random-effect model was applied, otherwise a fixed-effect model was preferred.[21]

All analyses were performed using Review Manager 5.3 software.[22] The null hypothesis of no statistical difference was rejected if the *P*-value was <0.05.

Missing standard deviations or mean values were retrieved by contacting the authors of primary studies or estimated by means of imputation from available data.[23]

Data synthesis

The overall quality of the evidence for each category of outcome measures was evaluated by means of the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system.[24] For each outcomes category, the following factors were assessed: limitations in study design (if the majority of the studies was considered at "high risk" of bias), inconsistency (if there was an unexplained high heterogeneity among studies, e.g. $I^2 > 25\%$), and imprecision (overall sample size lower than 300). The quality started as "high" when all the studies included in the meta-analysis were randomized controlled trials and was reduced by one level for each of the unmet factors.

The main results of this systematic review were reported in the "Summary of findings table" following the guidelines of the Cochrane collaboration.[18,24]

Results

Study selection

Figure 1 reports the PRISMA flowchart of the study: 7 independent studies from 10 published articles[25–34] met the eligibility criteria and were included in this systematic review. The list of included studies in alphabetic order is reported in Supplemental Appendix 3.

Characteristics of included studies

The main characteristics of the included studies are summarized in Table 1.

In summary, they are all randomized controlled trials set in inpatient rehabilitation units. They recruited a total of 273 subjects with a mean (SD) age of 62 (6) years, ranging from 53 to 74 years and mean (SD) time after stroke at recruitment of 40 (18) days, in the range of 15 to 60 days.

In five studies, the experimental group performed active cycling augmented by functional electrical stimulation, delivered to both legs (S2) or only to the paretic leg (S3,S4,S6,S7); in the two remaining studies (S1,S5), the experimental group performed passive cycling augmented by functional electrical stimulation delivered to both legs. The control groups principally received usual care (S1–S5,S7) and active or passive cycling (S1,S3,S6,S7). When reported, both experimental and control groups were trained for an equal amount of time. The duration of the intervention ranged from three to eight weeks, while the frequency varied from three to six times per week. The total number of training sessions ranged between 12 (S3) and 48 (S7). The drop-out rate varied between 0% to 17% at the end of the intervention. The reasons for drop-out were reported in all studies and were not correlated to the intervention group.

Methodological quality

Supplemental Figure S1 shows the summary of the risk of bias assessment. Overall, four studies (S1–S4) were evaluated as "low risk" of bias. The most frequent source of bias was performance bias, because no studies provided blinding of personnel, as expected, since it is unfeasible for this type of training, and only one study (S1) provided an adequate blinding of participants, implementing a cycling training with placebo functional electrical stimulation.

Treatment Effects at short-term follow-up

Figure 2 reported the results of the meta-analyses at short-term follow-up.

Six studies were included in the meta-analysis of the primary outcome, that is, walking short distances, and a significant effect (SMD [95% CI] = 0.40 [0.13, 0.67]; $P = 0.004$; 221 patients) was found in favor of the experimental group (Figure 2(a)) with a moderate quality of the evidence. Since a baseline imbalance was found in one study (S6, between-group difference of 0.27 m/s[35,36] at baseline), this meta-analysis was conducted on change values.

For secondary outcome measures, no baseline imbalance was found, and thus meta-analyses were

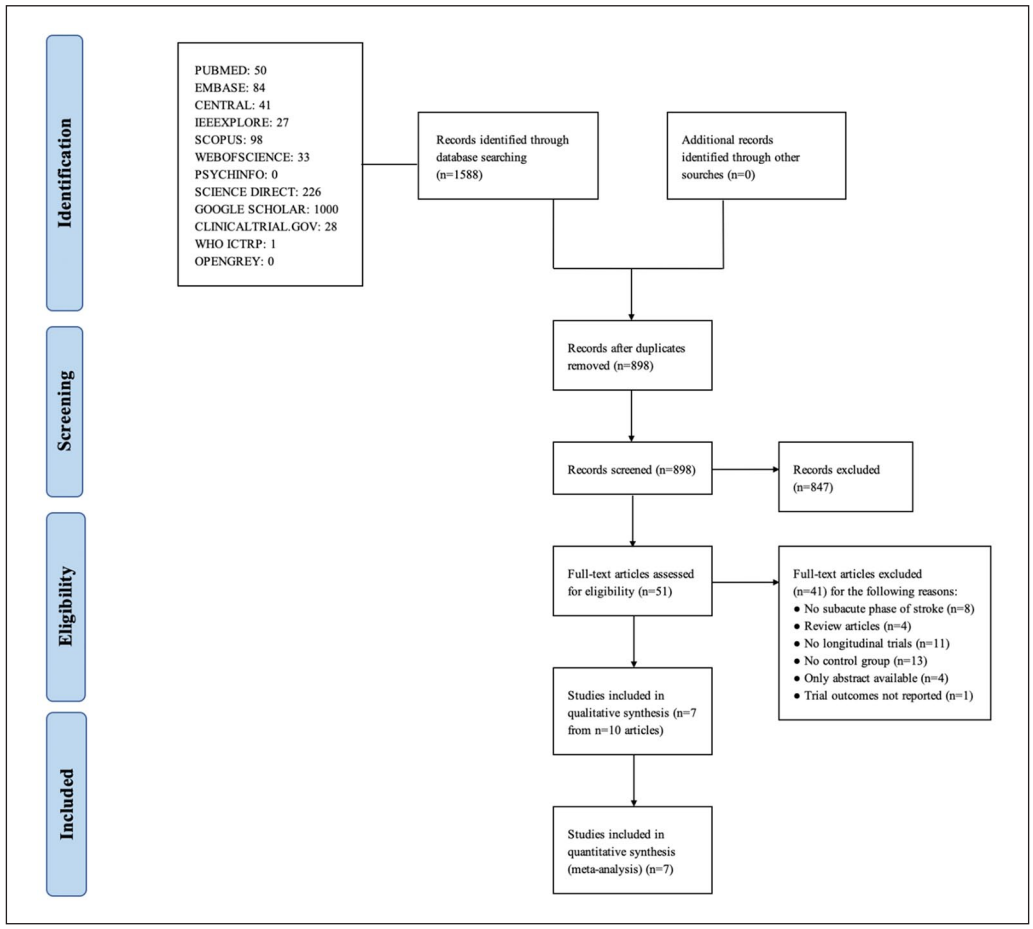

Figure 1. PRISMA flowchart of the literature search process.

performed on post-treatment values. Muscle power functions of the lower limbs showed a tendency, not statistically significant, in favor of the experimental group (SMD [95% CI] = 0.23 [−0.05, 0.51]; $P = 0.11$; 194 patients; five studies) with a moderate quality of the evidence (Figure 2(b)). Muscle tone (SMD [95% CI] = 0.49 [−1.74, 2.71]; $P = 0.67$; 91 patients; two studies) and capability to maintain a standing position (SMD [95% CI] = 0.52 [−0.41, 1.45]; $P = 0.28$; 173 patients; four studies) revealed no significant differences between groups with a low quality of the evidence (Figure 2(c) and (d)). A significant difference in favor of the experimental group was found for the capability to maintain a sitting position (MD [95% CI] = 7.92 [1.01, 14.82]; $P = 0.02$; 118 patients; three studies) (Figure 2(e)) with a moderate quality of the evidence. Two studies evaluated the performance during cycling (S1,S2). The mean work produced by the affected leg (Figure 2(f)) at the end of the intervention was significantly superior in the experimental group with respect to the control group (MD [95% CI] = 8.13 [1.03, 15.25]; $P = 0.02$; 46 patients) with a moderate quality of the evidence. The unbalance between the work produced by the two legs during pedaling (Figure 2(g)) showed instead a positive but not statistically significant trend (MD [95% CI] = 7.80 [−3.69, 19.29]; $P = 0.18$; 46 patients) in favor of the experimental group with a low quality of the evidence.

Table 1. Main characteristics of the included studies.

Study	Design, country and setting	Participants	Intervention and dosage	Control and dosage	Relevant outcome measures
S1 - Ambrosini et al. and Ambrosini[25–27]	• RCT • Italy • Rehabilitation unit (inpatient)	• 35 enrolled (17 Exp / 18 Con), • 30 analyzed (15 Exp / 15 Con) • 19 ischemic / 8 hemorrhagic / 3 TBI • Age: 57.5 (12.2)* years • TSI: 48.0 (39.7)* days	• Passive FES-cycling + usual care • (25 minutes + 180 minutes) × 5/weeks × 4 weeks • Bilateral stimulation: Q, H, GM, TA • Stimulation frequency: 20 Hz; PW: 300 μs; current: above motor threshold • Cadence = 20 rpm	• Passive cycling with placebo FES + usual care • (25 minutes +180 minutes) × 5/weeks × 4 weeks	• 50 Meter Walk Test • Motricity Index • Trunk Control Test • Upright Control Test • Work of the paretic leg • Pedaling unbalance • EMG of rectus femoris and biceps femoris
S2 – Ambrosini et al. and Peri et al.[28,29]	• RCT • Italy • Rehabilitation unit (inpatient)	• 68 enrolled (34 Exp / 34 Con) • 68 analyzed (34 Exp / 34 Con) • 55 ischemic / 9 hemorrhagic / 4 hematoma • Age: 74.3 (12.2)* years • TSI: 16.0 (10.8)* days	• Active FES-cycling + UC • (25 minutes + 50 minutes) × 5/weeks × 3 weeks • Bilateral Stimulation: Q, H, TA, GL • Stimulation frequency: 20 Hz; PW: 400 μs; current: above motor threshold • Cadence = 20 rpm	• Usual care • 75 minutes × 5/weeks × 3 weeks	• Gait Speed • 6 Minute Walk Test • Functional Independence Measure • Motricity Index • Trunk Control Test • Fall Efficacy Scale • Gait Spatial and temporal parameters • Work of the paretic leg • Pedaling unbalance
S3 - Bauer et al.[30]	• RCT • Austria; • Rehabilitation unit (inpatient)	• 40 enrolled (21 Exp / 19 Con), • 37 analyzed (19 Exp /18 Con) • 25 ischemic / 12 hemorrhagic • Age: 61.4 (12.6)* years • TSI: 52.3 (44.0)* day	• Active FES-cycling + usual care • (20 minutes + N.A.) × 3/weeks × 4 weeks • Unilateral stimulation: Q, H • Stimulation frequency: 25 Hz; PW: 250 μs; current: maximal comfortably tolerated • Cadence = 20 rpm	• Active cycling + usual care • (20 minutes + N.A.) × 3/weeks × 4 weeks	• Functional Ambulation Category • Performance-Oriented Mobility Assessment (balance sub-scale) • Motricity index • Modifies Ashworth Scale
S4 - De Sousa et al.[31]	• RCT • Australia • 2 Rehabilitation unit (inpatient)	• 40 enrolled (20 Exp / 20 Con), • 39 analyzed (19 Exp / 20 Con) • 22 ischemic / 9 hemorrhagic / 7 TBI / 2 others • Age: 61.0 (15.5)* years • TSI: 36.0 (28.8)* days	• Active FES-cycling + usual care • (17–32 minutes + N.A.) × 5/weeks × 4 weeks • Unilateral Stimulation: Q, H, TA, GL • Stimulation frequency: 50 Hz; PW: 450 μs; current: maximal comfortably tolerated • Cadence = 30 rpm	• Usual care >60 minutes + 5/weeks × 4 weeks	• Mobility • Strength of the knee extensors • Strength of the key muscles

(Continued)

Table 1. (Continued)

Study	Design, country and setting	Participants	Intervention and dosage	Control and dosage	Relevant outcome measures
S5 - Ferrante et al.[32]	• RCT • Italy • Rehabilitation unit (inpatient)	• 20 enrolled (10 Exp / 10 Con), • 20 analyzed (10 Exp / 10 Con) • 15 ischemic / 5 hemorrhagic • Age: 53.5 (10.7)* years • TSI: 53.3 (23.7)* days	• Passive FES-cycling + usual care • (35 minutes + 145 minutes) × 5/ weeks × 4 weeks • Bilateral Stimulation: Q, H, GM, TA • Stimulation frequency: N.A; PW: N.A; current: N.A. • Cadence = 40 rpm	• Usual care • 180 min × 5/weeks × 4 weeks	• Trunk Control Test • Motricity Index • Upright Motor Control Test • 50 Meter Walk Test • Sit To Stand Trial • Maximal Voluntary Contraction
S6 - Lee et al.[33]	• RCT • Korea • Rehabilitation unit (inpatient)	• 16 enrolled (8 Exp / 8 Con), • 16 analyzed (8 Exp / 8 Con) • 10 ischemic / 6 hemorrhagic • Age: 63.3 (14.6)* years • TSI: 59.9 (44.3)* days	• Active FES-cycling • 30 minutes × 5/weeks × 4 weeks • Unilateral Stimulation: Q, H, GM, TA • Stimulation frequency: 60 Hz; PW: 300 μs; current: above motor threshold • Cadence = 30 rpm	• Active cycling • 30 minutes × 5/ weeks × 4 weeks	• 6 Minute Walk Test • Berg Balance Scale • Korean-Modified Barthel Index • Exercise Tolerance Test
S7 - Li et al.[34]	• RCT • China • Rehabilitation unit (inpatient)	• 54 enrolled • 52 analyzed (18 Exp / 17 Con C1 / 17 Con C2) • 30 ischemic / 22 hemorrhagic • Age: 60.5 (12.9)* years • TSI: 14.9 (5.7)* days	• Active FES-cycling + usual care • (30 minutes + 120 minutes) × 6/ weeks × 8 weeks • Unilateral Stimulation: TA, GL • Stimulation frequency: 25 Hz; PW: 250 μs; current: above motor threshold • Cadence = N.A.	• C1: Active cycling + usual care • (30 minutes + 120 minutes) × 6/ weeks × 8 weeks • C2: usual care • 120 minutes × 6/ weeks × 8 weeks	• Composite Spasticity Scale • Berg Balance Scale • 10-m Walking Speed • Modified Fugl-Meyer, lower limbs sub-scale

*Mean (standard deviation).
FES: Functional Electrical Stimulation; GL: Gastrocnemius Lateralis; GM: Gluteus Maximum; H: Hamstrings; N.A.: Not Available; Q: Quadriceps; PW: pulse width; RCT: Randomized controlled trial; TA: Tibialis Anterior; TBI: Traumatic Brain Injury; TSI: Time since injury. Exp: Experimental group; con: Control group.

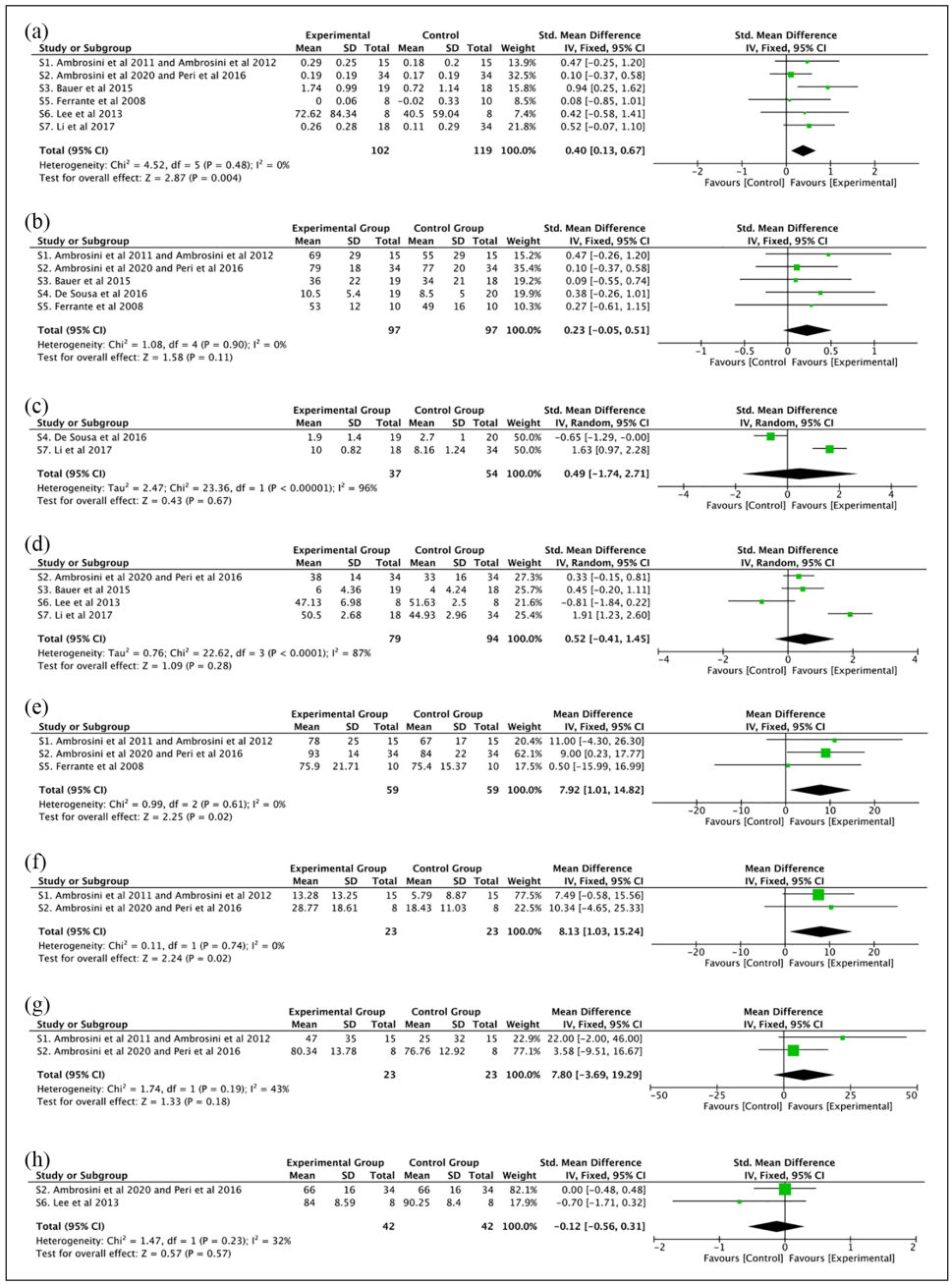

Figure 2. Forest plots of comparison at the short-term follow-up: Experimental (FES-cycling training (plus usual care)) versus Control Group (cycling alone and/or usual care). The training effects were computed starting from change from baseline for outcome a (Walking short distances) and post-intervention data for outcomes from b to h. (a) Walking short distances, (b) Muscle power functions of the lower limbs, (c) Tone of muscles of lower half of body§, (d) Maintaining a standing position, (e) Maintaining a sitting position, (f) Mobility other specified, mean work produced by the paretic leg, (g) Mobility other specified, pedaling unbalance§, and (h) Basic activities of daily living. **[AQ: 1]**
§For outcomes with a negative direction of improvement, values in the meta-analysis were reported as superior value of the range minus the actual value of the outcome.

Functional Electrical Stimulation (FES) cycling training compared to other physiotherapy for sub-acute post-stroke patients at short-term follow-up

Patient or population: sub-acute post-stroke patients
Intervention: functional electrical stimulation (FES) cycling
Comparison: other types of physiotherapy

Outcomes	Illustrative comparative risks (95% CI)		No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Other types of physiotherapy	FES-cycling training			
[d4500] Walking short distances Gait Speed (m/s)	* The mean change after training at short-term follow-up for the most representative study (S2.Ambrosini et al. 2020 and Peri et al. 2016) was 0.17 m/s (SD 0.19 m/s)	The estimated mean walking speed over short distances in the FES-cycling group was **0.08 m/s higher** (0.02 to 0.13 m/s higher)	221 (6 studies)	⊕⊕⊕⊙ **moderate (1)**	The effect was not clinically relevant. (<0.16 m/s which is considered the clinical important treatment effect for gait speed in stroke patients (Tilson et al. 2010)).
[b7303] Power of muscles in lower half of the body Motricity Index [0-100]	* The mean at short-term follow-up for the most representative study (S2.Ambrosini et al. 2020 and Peri et al. 2016) was 77 (SD 20)	The estimated mean power of muscles in lower half of the body in the FES-cycling group was **4.6 higher** (1.00 lower to 10.2 higher)	194 (5 studies)	⊕⊕⊕⊙ **moderate (1)**	No effect was found.
[d4154] Maintaining a standing position Berg Balance Scale [0-56]	* The mean at short-term follow-up for the most representative study (S2.Ambrosini et al. 2020 and Peri et al. 2016) was 33 (SD 16)	The estimated mean of maintaing a standing position in the FES-cycling group was **8.32 higher** (6.56 lower to 23.2 higher)	173 (4 studies)	⊕⊕⊙⊙ **low (1,2)**	No effect was found.
Basic ADL, combination of [d510] Washing oneself, [d520] Caring for body parts, [d530] Toileting, [d540] Dressing, [d550] Eating Functional Indipendence Measure motor subscale [13-91]	* The mean at short-term follow-up for the most representative study (S2.Ambrosini et al 2020 and Peri et al. 2016) was 66 (SD 16)	The estimated mean of basic ADL in the FES-cycling group was **4.66 lower** (32.32 lower to 22.73 higher)	84 (2 studies)	⊕⊕⊙⊙ **low (1,2)**	No effect was found.

* Of the included trials for this outcome, the study with the lowest risk of bias and the highest number of participants was chosen. The reported data represent the short-term follow-up value in the control group of this study.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change the confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.
Very low quality: There are very uncertainty about the estimate

1 Serious imprecisions.
2 Unexplained heterogeneity.
3 Serious risk of bias.

Figure 3. Summary of findings for the main comparisons.

Finally, no significant difference, with a low quality of the evidence, was found between the two intervention groups in the capability to perform activities of daily living: (SMD [95% CI] = −0.12 [−0.56; 0.31], $P = 0.57$; 84 patients; two studies).

Figure 3 summarizes the main findings of this systematic review on the effect at short-term follow-up. When the results of the meta-analysis for the primary outcome was transformed in gait speed, a significant between-group difference of 0.08 m/s [0.02; 0.13] was found in favor of patients performing cycling induced by functional electrical stimulation. No significant difference was found for muscle power, capability to maintain a standing position and activities of daily life. The quality of the evidence ranged from low to moderate: it was only downgraded due to serious imprecision (total number of participants <300) and in two cases also for unexplained heterogeneity ($I^2 > 25\%$).

Treatment Effects at intermediate-term follow-up

Two studies (S1,S2) assessed the treatment effects on walking short distances, muscle power functions and capability to maintain a sitting position at

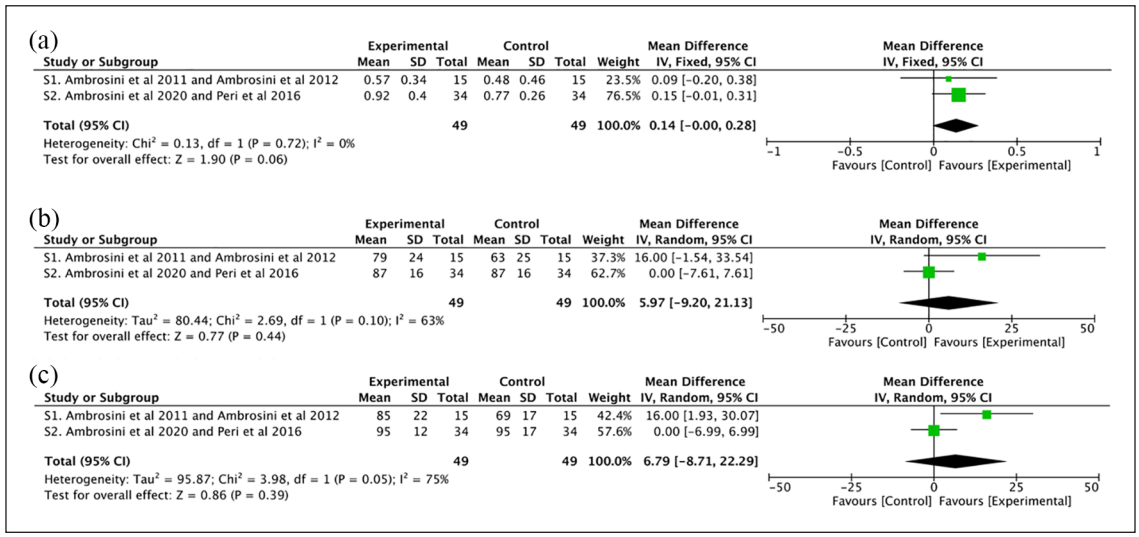

Figure 4. Forest plots of comparison at the intermediate-term follow-up: Experimental (FES-cycling training (plus usual care)) versus Control Group (cycling alone and/or usual care). The training effects were computed starting from intermediate-term follow-up data. (a) Walking short distances, (b) Muscle power functions of the lower limbs, and (c) Maintaining a sitting position. **[AQ: 2]**

intermediate-term follow-up on a total of 98 patients. No baseline imbalance was found, and meta-analyses were performed on intermediate-term follow-up values (Figure 4). Regarding walking short distances (Figure 4(a)), a near-threshold significant difference with a moderate quality of the evidence was found between the two intervention groups (MD [95% CI] = 0.14 [0.00, 0.28], $P = 0.06$). No significant differences (Figure 4(b–c)) were found, with a low quality of the evidence, for muscle power (MD [95% CI] = 5.97 [−9.20, 21.13], $P = 0.44$) and capacity of maintaining a sitting position (MD [95% CI] = 6.79 [−8.71, 22.29]; $P = 0.39$).

Adverse events and patients' satisfaction

In the only study (S2) which reported information about adverse events, no adverse events were highlighted for neither intervention groups. No studies evaluated the patients' satisfaction with the intervention.

Discussion

This systematic review, gathering information from seven randomized controlled trials recruiting a total of 273 subacute stroke patients, showed that cycling training augmented by functional electrical stimulation induces a significant improvement on walking ability, work produced by the paretic leg during pedaling and capability to maintain a sitting position with respect to other treatments not involving the use of functional electrical stimulation at short term follow-up. For what concerns other secondary outcome measures, for example, muscle power functions and tone of the lower limbs, capability to maintain a standing position, and to perform activities of daily living, no difference was found. Finally, no significant differences were found at intermediate-term follow-up in terms of walking, muscle power and capability to maintain a sitting position. Overall, the quality of the evidence ranged from low to moderate.

Due to the crucial role of locomotion recovery for independence and home return after stroke,[36] the capability of walking short distances was chosen as the primary outcome of this systematic review. Six out of 7 included studies evaluated this outcome and could be pooled in a meta-analysis, which showed a statistically significant difference between the two interventions (SMD [95% CI] = 0.40 [0.13, 0.67]; Figure 2(a)). When transformed

in gait speed, a difference of 0.08 m/s was found in favor of the experimental group (Figure 3), below the minimal clinically important difference estimated in subacute stroke survivors for gait speed (e.g. 0.16 m/s[36]). Therefore, despite statistically significant improvements, cycling training induced by functional electrical stimulation is not clinically superior to usual care based on gait-related outcome measures. A similar result was achieved by a recent systematic review,[10] which evaluated the effects of cycling training (with no electrical stimulation) on the 10-m walking speed in stroke survivors (SMD [95% CI] = 0.30 [0.05, 0.50]). It is important to mention that in our meta-analysis, 4 out of 6 included studies explicitly performed cycling training without electrical stimulation in the control group, and therefore our results might show the additional benefits, on the top of cycling training alone, of using functional electrical stimulation synchronized to the cycling movement. These additional benefits might be explained by the enhanced afferent feedback evoked by electrical stimulation, which favors neural plasticity.[37]

Previous systematic reviews with meta-analyses evaluated the general effects of functional electrical stimulation (not necessarily combined with cycling training) on walking compared to usual care or no intervention.[1,5,38] Two of these reviews[5,38] were focused on chronic stroke survivors and showed small to moderate effects on gait speed and walking distance. The third review[1] included studies whose participants were affected by a stroke with any chronicity and showed a small significant effect of gait speed (SMD [95% CI] = 0.08 [0.02, 0.15]). However, none of these reviews was focused neither on subacute stroke survivors nor on the specific effects of cycling training combined with functional electrical stimulation.

Regarding muscle power functions of the lower limb and capability to maintain a standing position, only positive trends in favor of the experimental group was found, but the meta-analyses did not find significant between-group differences. This suggests that the improvement of walking was not strictly correlated nor to higher muscle strength neither to an improved balance. However, the effect on balance (SMD [95% CI] = 0.52 [−0.41, 1.45]; $P = 0.28$; 173 patients; 4 studies) has to be considered with caution, since it was based on a low number of studies and was affected by a high heterogeneity. In a previous review,[10] cycling with functional electrical stimulation revealed a significant effect on balance (SMD [95%] = 1.48[0.99, 1.97]) compared with cycling alone. Nevertheless, that result was based only on two[30,33] out of the four currently available studies assessing the effects of cycling induced by functional electrical stimulation on balance.

Cycling training induced by functional electrical stimulation showed to improve the capability to maintain a sitting position and to increase the work produced by the paretic leg during pedaling, two aspects which are specific of the type of training performed.

Finally, the benefits for muscle tone and activities of daily living remained controversial, with only two studies, characterized by a high heterogeneity, evaluating these outcomes. Outcome measures evaluating the capability of performing daily self-care activities should be included in future randomized controlled trials, due to the crucial role of this domain for the quality of life of stroke survivors.

The improvements achieved at the end of the intervention were not maintained at intermediate-term follow-up. Indeed, only a positive trend, but not a significant difference, was found in favor of cycling with functional electrical stimulation for what concerns walking short distances and no differences were found for muscle power and capability to maintain a sitting position. However, these results have to be interpreted with caution since they were based on only two studies (S1, S2). Therefore, we advocate for future studies to foresee follow-up visits evaluating the effects of cycling with functional electrical stimulation at intermediate and long term.

In terms of methodological quality, four out of seven studies were judged as at low risk of bias. The main source of bias was related to the blinding procedure: in four out of seven studies the assessors were blind, but in almost all studies both participants and personnel were aware of group assignment. In only one study (S1), the control group was involved in a cycling training with placebo functional electrical stimulation in order to assure the blindness of participants. However, this

limitation is widespread among rehabilitation studies in which the training requires the use of specific equipment. Other potential sources of bias derived from the lack of intention-to-treat analysis, which characterized three out of seven studies, and the poor evaluation of the compliance to the intervention, reported in only two studies (S2, S4).

Overall, the quality of the evidence ranged from low to moderate and therefore all the results should be interpreted carefully. Indeed, all meta-analyses included an overall sample size lower than 300, with a maximum of 221 patients for the primary outcome, and in many cases, there was a high heterogeneity between the studies.

Based on the available results, cycling training with functional electrical stimulation can be considered a safe and well-accepted intervention for stroke survivors; indeed, none of the included studies reported adverse events due to the training, and the drop-out rates were balanced between intervention groups.

A common limitation in all the included studies but one (S2) was the mean age of the participants, between 53 (S5) to 63 (S6) years old, below the mean age of stroke survivors (e.g. 73 years).[39] To increase the generalizability of the results, we strongly advocate clinical researchers to carry out randomized controlled trials with no limitation on the age of the participants.

This systematic review has some limitations. First, although unlikely, we could have lost some studies and we did not search through unpublished literature. Second, the included studies were characterized by a high heterogeneity: they differed from the type of cycling training delivered to the experimental group (e.g. passive versus active pedaling; electrical stimulation delivered to both legs or only to the affected leg; electrical stimulation provided to different muscle groups; different stimulation parameters; etc.), from the types of intervention delivered to the control group (only usual care versus usual care plus cycling training), from the outcome measures and from the number of training sessions. The low number of included studies did not allow to perform sub-group analyses, preventing us to derive any conclusions about the best training parameters. Third, the meta-analysis evaluating the effect on walking short distances was based on change values since one study was characterized by a baseline imbalance. Fourth, the effects at intermediate-term follow-up have to be considered with caution since they were based only on two studies. Lastly, many of the included studies had small sample sizes, overall decreasing the quality of the evidence.

Based on our results, cycling training with functional electrical stimulation cannot be recommended in terms of being better than usual care. However, this type of intervention might be used as a labor-efficient alternative to usual care. Indeed, due to the low supervision required, cycling training with functional electrical stimulation can be safely performed in group sessions. Furthermore, it could be a valid option for home training. High-quality randomized controlled trials, recruiting larger sample sizes with no limitation on the participants' age, including long-term follow-up and assessing activities of daily living, are needed to drive final conclusions about the effectiveness of cycling training with functional electrical stimulation. Future research should also attempt to identify the optimal training regimen in order to maximize the therapeutic outcomes.

Clinical messages

- Patients with subacute stroke performing cycling training induced by functional electrical stimulation achieved a significant but not clinically relevant improvement in walking ability.
- Current evidence of the effect of cycling training induced by functional electrical stimulation relies on a limited number of studies.
- Further investigations are required to determine the optimal training parameters and to evaluate long-term effects.

Authors' Contribution

- EA was responsible for conceiving and designing the study, literature search, study selection, data extraction, risk of bias assessment, data synthesis and interpretation, drafting and

critically revising the article, and approving the final version of the article.
- MP was responsible for literature search, study selection, data extraction, risk of bias assessment, analysis of treatment effects, data synthesis and interpretation, drafting and critically revising the article, and approving the final version of the article.
- GF was responsible for interpreting the data, critically revising the article, and approving the final version of the article.
- AP was responsible for conceiving and designing the study, critically revising the article, and approving the final version of the article.
- SF was responsible for conceiving and designing the study, critically revising the article, and approving the final version of the article.

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Supplemental material

Supplemental material for this article is available online.

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