SM Vascular Medicine

Research Article

Effectiveness of physiotherapy to promote motor recovery in individuals with stroke: a systematic review protocol

Shehong Zhang[1], Hongyu Xie[3], Chuanjie Wang[4], Fengfeng Wu[1]* and Xin Wang[2]*

[1]Department of Rehabilitation Medicine, affiliated Huzhou Central Hospital, Zhejiang University School of Medcine, Huzhou Central Hospital. Huzhou, Zhejiang, China

[2]Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, 60 Fenwood Road, Boston, MA 02115, USA

[3]Department of Rehabilitation Medicine, Huashan Hospital, Fudan University, Shanghai, China

[4]Department of Rehabilitation Medicine, Jinshan Hospital, Fudan University, Shanghai, China

Abstract

Introduction: Motor function is essential in our daily lives. Over 70% of stroke survivors have motor or other neurological functional disabilities. However, rehabilitation of motor function suffered from a stroke is rather difficult due to various reasons. Moreover, previous evidence for the effectiveness of physiotherapy for people with stroke that recover motor function is varied and limited in the chronic phase and therefore has never been reviewed systematically. With the progress of study in neurology and development of novel tools for rehabilitation, we can easily collect data from clinical trials now, so justifying conducting a systematic review.

Methods and analysis: This systematic review protocol is developed in accordance with the methodology recommended by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols, as well as the Cochrane handbook for systematic reviews of interventions. Relevant studies,including Randomized controlled trials (RCTs) published in English, published between January 2001 and January 2021, will be identified by searching the databases. We will perform searches for relevant studies in databases, including PubMed, Embase, CINAHL, and Web of Science, Physiotherapy Evidence Database and Cochrane Library databases. The reference lists of included articles and reviews will be searched manually. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation system from the Cochrane Handbook for Systematic Reviews of Interventions) approach will be used to systematically appraise the quality of methodology. We will assess the risk of bias of the RCTs included using the Cochrane Collaboration's tool and provide a qualitative synthesis and consider conducting a meta-analysis if the final data across outcomes shows sufficient homogeneity.

Ethics and dissemination: No ethical approval is needed as the proposed study does not involve the collection of primary data, and the results of this review will be disseminated via peer-reviewed publications and conference presentations.

Trial registration number: CRD42021267069.

Strengths and limitations of this study

- The main strength of the present study is that this is the first systematic review that different commonly used types of physiotherapy were included, which makes a big difference from the other trials that mostly focused on specific areas of physiotherapy.
- By systematic review, all relevant high-quality evidence will be identified and effect of interventions to promote motor recovery, including recovery of impairment or related function, after stroke will be investigated. Such that we can identify areas for which interventions show promise of efficacy according to the results of this review.
- It is anticipated that a limited meta-analysis may be conducted since there may be significant heterogeneity among the identified trials due to a wide range of outcome measures, the amount and methods of intervention, and the duration and frequency of training.
- It's possible that the current review does not identify all evidence or limitations relevant to the research question because there are restrictions on both language and year of the articles included.

Submitted: 06 May 2022 | **Accepted:** 01 June 2022 | **Published:** 04 June 2022

***Corresponding author:** Professor Xin Wang, Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, 60 Fenwood Road, Boston, MA 02115, USA.

Professor Fengfeng Wu, Department of Rehabilitation Medicine, affiliated Huzhou Central Hospital, Zhejiang University School of Medcine, Huzhou Central Hospital. Huzhou, Zhejiang, China

Citation: Zhang S, Xie H, Wang C, Wu F, Wang X (2022) Effectiveness of physiotherapy to promote motor recovery in individuals with stroke: a systematic review protocol. SM Vasc Med 4: 6.

Introduction

Stroke is the leading cause of long-term even permanent disability and a second leading cause of death worldwide[1]. Moreover, the incidence of stroke occurred as an increasing trend in the young[2]. In the long term, 25–74% of patients have to rely on human assistance for basic ADLs like feeding, self-care, and mobility[3]. Because of declining fatality, together with the aging population and improvements in acute care[4], the prevalence of stroke is likely to increase in the future, and a growing number of individuals will have to deal with stroke-related disability[5]. The most widely recognized impairment caused by stroke is motor impairment, which restricts function in muscle movement or mobility[6]. Over 70% of stroke survivors have motor or other neurological functional disabilities[7], almost 64% cannot walk independently, even after rehabilitation[8], up to 85% of stroke

survivors have hemiparesis that affects gait speed, among a hardy group of stroke survivors, much of the improvement in impairment and disability occurs during the first month and then reaches a plateau[9]. And thus handicap continues to be the main issue that results in difficulties in daily life, greater dependence and social isolation, as well as poorer quality of life. As we know, motor function plays a critical role in human daily lives. Stroke is a serious health issue that requires both immediate and long-term medical attention. It is expected that the burden of stroke further increases until effective stroke prevention strategies are more widely implemented. Most people (83%) survive but experience damage to their motor skills[10]. Physiotherapy (PT) is one of the key disciplines in interdisciplinary poststroke rehabilitation. Complementary to pharmacotherapy and neurosurgical treatments, the aim of physiotherapy is to improve multiple damaged-function, including physical capacity or activity, gait, posture, strength, transfers, coordination, endurance, balance and flexibility and so on[11-17].

It is assumed that interdisciplinary complex rehabilitation interventions[18, 19] would play a role as the mainstay of poststroke care[20, 21]. Physical therapy, as one of the key disciplines in interdisciplinary stroke rehabilitation[21]. Physiotherapy is composed of many different modalities and novel physiotherapy interventions are continuously being developed and applied in the clinic. Examples include Tai Chi[22] and Yoga[23] .We can found many small, randomized, clinical trials (RCT) that have studied interventions in the acute rehabilitation phase, but can barely read the reports focused on the chronic recovery phase in people with stroke[24, 25]. The recommendations in the first Dutch evidence-based 'Clinical Practice Guideline for physical therapy in patients with stroke were based on meta-analyses of 123 randomized controlled trials (RCTs) and date back to 2004, in none of the studies was blinding possible for patient or therapist, and only 72 of the 123 RCTs had blinded the observer[26]. In view of the tremendous growth in the number of RCTs in this field and the methodological quality for RCTs is markedly improved, therefore, it is now necessary to update the ''state of the art'' concerning the evidence for physical therapy interventions in stroke rehabilitation. This aim is in line with the 2006 Helsingborg Declaration on European Stroke Strategies, which states that stroke rehabilitation should be based on evidence as much as possible[27, 28] .

During the past few decades, numerous studies have evaluated the effectiveness of the various physiotherapy modalities[17], in comparisons across different interventions on different limbs. For example, Electromechanical-assisted gait training for walking[6, 29] and Task-oriented physical fitness training for walking[30, 31] have been reported to be beneficial for the lower paretic limb. However, the methodologies applied in these studies were highly variable and many different even controversial outcomes for motor function were delivered in the program of different timing and intensity of acute rehabilitation. Due to these inconsistencies, it is necessary to up-to-date the understanding of this field for interpreting the available evidence and providing clear and concise treatment recommendations to people with stroke, which would help to refine strategies for primary intervention and to inform the design of future clinical trials.

Here, we aim to evaluate the effectiveness of multiple physiotherapy modalities, conventional physiotherapy, resistance training, treadmill training, strategy training, dance, martial arts, environmental enrichment, aerobic exercises, hydrotherapy, balance and gait training, dual tasking, exergaming, and Nordic walking by means of a meta-analysis and focus on motor function recovery of the motor function of stroke survivors.

According to our knowledge of the literature, ample summary of the efficacy of various interventions in stroke patients can be found in published systematic reviews and meta-analysis. In addition, since 2014 the most comprehensive meta-analysis so far was published[17], many new studies have been reported, creating a much larger body of evidence. We can find some guidelines of different physical activities for stroke servivors, however, the guideline of Physiotherapy for stroke in the chronic recovery phase cannot be found so far. Even in the most recent Guidelines for Adult Stroke Rehabilitation and Recovery released by the American Heart Association and the American Stroke Association in 2016[32], we cannot find the recommendation in the subacute recovery phase following stroke which greatly increased the difficulty of clinical work.

In short, the goal of our comprehensive review is to provide an overview involving: (1) To evaluate the effectiveness of various physiotherapy interventions on motor function; (2) To identify which areas require further research.

Methods and analysis

Study design

The systematic review protocol was written and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) (see the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA-P) checklist in online supplementary table 1) [33, 34]. For the results of this systematic review, we will publish it following the PRISMA statement[35, 36].

Eligibility criteria

Identification of study: The findings from randomised controlled trial (RCT) is likely to be closer the true effect than the ones from the other research methods[37] because the unique characteristics of RCT[38], so we will include all randomized controlled trials (RCTs)[39] that studied the efficacy of a physiotherapy intervention on the motor function in individuals with stroke who experienced a stroke, before 6 months, named as the chronic phase[17], and only articles written in English were include for this review. Quasi-RCTs or trials without control group such as case series and case reports will be excluded. Preliminary and pilot studies as well as abstracts published in congress and conferences will also be excluded. All trials that published from 2010 to 2021 were included.

Participants: We will include all RCTs which have recruited adult patients aged 18 years or over who had a single, mono-

hemispheric stroke over 6 months and were confirmed by neuroimages. The definition of stroke is described as 'a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin' by WHO[40]. Participants in all trials should be evaluated as meet either higher- or lower-functioning motor criteria derived from the recognized assessments related to motor function, such as Fugl-Meyer and the streamlined Wolf Motor Function Test (WMFT)[41, 42]. This systematic review does not need Patient and Public involvement statement as the proposed study does not involve the collection of primary data.

Types of interventions

We will select all trials assessing a physiotherapy intervention that aimed to improve motor functions and/or activities in people with stroke. These interventions should be compared with a control intervention (*e.g.* no intervention, sham therapy, active therapy, standard care, conventional training or the same intervention method with different parameters).

Based on the previous report[17], we modified mildly and then divided the physiotherapy interventions for stroke rehabilitation into the following categories: (1) interventions related to gait and mobility-related functions and activities, including the strategy training for complex motor sequences and cueing interventions, exercise or training interventions with a therapeutic goal; (2) interventions related to arm-hand activities; (3) interventions related to activities of daily living; (4) interventions related to physical fitness; and (5) other interventions which could not be classified into one of the other categories. We will not place limitation on the timing, frequency and duration of interventions.

Type of outcome measures

The primary outcomes of this systematic review will focus on changes in patients' motor function using various assessments from baseline to the last available follow-up. According to the International Classification of Functioning, Classification, and Health (ICF), the following outcome domains were selected: (1) muscle and movement functions: such as muscle power functions[43],muscle tone functions[44]; (2) arm-hand activities: including hand and arm use[25]; (3) Balance outcomes: including kinematic balance and static balance; (4) Gait outcomes: including gait speed and gait pattern[45].

Secondary outcome assessments will include the following outcome domains: (1) Activities of daily living (ADL): including basic ADL(*e.g.* toileting, eat and drink unassisted) [46-48] and extended ADL(*e.g.* preparing meals)[49]; (2) Mental health improvements associated with the motor function recovery. We will also consider and analyze the adverse events related to the indicated interventions.

Search strategy for relevant studies

For this review, we will perform electronic searches for relevant publications with full texts written in English in the PubMed, Wiley/Cochrane Library, EMBASE, CINAHL and Physiotherapy Evidence Database. The articles published from January 2001 to January 2021 in the database will be included.

We also searched grey literature and clinical trials registers. This will be performed by two independent researchers after all of the researchers developed the search string. The databases will be searched by indexing terms and free-text terms used with synonyms and related terms in the title or abstract, we list these terms in Table 1.

Table 1: Search strategy in Cochrane Library Database.

#1 MeSH descriptor: [Stroke] explode all trees
#2 Stroke:ti OR Cerebrovascular Accident:ti OR CVA:ti OR Cerebrovascular Event:ti OR Cerebrovascular Insult:ti OR Brain:ti Vascular Accident:ti OR Apoplexy:ti OR Brain Infraction:ti OR Poststroke:ti
#3 MeSH descriptor: [Hemiplegia] OR [Paresis] explode all trees
#4 (Hemiplegia OR Paresis OR hemipleg OR hemipar OR paresis OR paretic):ti,ab,kw
#5 search #1OR #2OR #3OR #4
#6 MeSH descriptor: [Rehabilitation] explode all trees
#7 MeSH descriptor: [physiotherapy] explode all trees
#8 MeSH descriptor: [Exercise Therapy] explode all trees
#9 (Rehabilitati* OR physiotherap* OR (physical AND (therapy OR therapies OR activity OR activities[tiab])) OR exercis* OR training):ti, ab, kw
#10 search #6 OR #7 OR #8 OR #9
#11 ((electrical stimulation) OR FES OR (mirror therapy) OR (constraint-induced movement therapy) OR CIMT OR robot OR (brain-computer interface) OR BCI OR (repetitive transcranial magnetic stimulation) OR rTMS OR (transcranial direct current stimulation) OR tDCS OR (task-oriented training) OR (task-based training) OR acupuncture OR (bilateral treatment) OR (motor relearning) or (manual therapy) OR orthosis OR stretch OR biofeedback OR (virtual reality) OR VR OR (motor imagery) OR (action observation)):ti,ab,kw
#12 (randomized controlled trial) OR (controlled clinical trial) OR (systematic review) OR (guideline):ti,ab
#13 search (#11 OR #12)
#14 search (#10 AND #11 AND #13
MeSH, medical subject headings

Screening of the studies

Data management: The reference management software, Endnote (V.X9; Thomson Reuters, New York, USA), will be used to help upload and keep the literature search results and relevant PDF files. Duplicate records will be automatically removed by the EndNote software. A separate library group will be created to store all original search results from one database. All separate library group copies will then merge into a new library group and duplicate checking will be carried out in the new library group using a Find Duplicates dialogue box in the Endnote. Two independent reviewers (SHZ, HYX) will screen all the retrieved titles and abstracts according to the previously determined inclusion and exclusion criteria and the full text will be screened to further confirm the final selection of the publications. Additional articles might be included by reference list check of the selected studies and relevant published systematic reviews mentioned in the search strategy. In case of any difference among reviewers, all the reviewers will discuss the discrepancies and/or send them

to the authors of the articles. The PRISMA flow of information through the different phases of a systematic review will be filled in, to record the whole screening process in detail[50, 51]. Full-text articles, published abstracts, and conference proceedings were included. In addition, reference lists were hand searched to identify further relevant articles.

We will also identify randomized controlled trials of a physical therapy intervention (compared with no intervention or standard care/practice) where people with stroke practiced activities of daily living, or where performance in activities of daily living was the focus of the physical therapy intervention.

Data extraction

According to the recommendations from the PRISMA statement[52], data extraction will be conducted by two independent reviewers (SHZ and HYX). A third reviewer (XW) will be response to the discrepancies between the former two reviewers and make the final decision during the review. We will contact the corresponding authors for further information, if the required data are missing from the selected publications.

Data items

The extracted data from incorporated studies will include the following information: 1) general study information (first author, year of publication, title of journal), 2) characteristics of participants (types, sample size, inclusion/ exclusion criteria, random process and allocation, age, gender, ethnic group and the onset time), 3) interventions (type of intervention, study design and setting, supervision and comparison/control group), 4) consequences (primary and secondary outcome measures).

Risk of bias in included studies

The checklist of the Cochrane Collaboration's tool will be used to evaluate the risk of each RCT included[53]. The checklist contains six items of bias, which are as follows: 1) selection bias, 2) performance bias, 3) detection bias, 4) attrition bias, 5) reporting bias, and 6) other bias. The risk of bias in each item will be categorized as low (meet all criteria), high (meet none of the criteria) risk of bias, or unclear (insufficient detail reported in the publications). The information for each potential source of bias will be reported to demonstrate the results and details of the assessment. The same two researchers (SHZ and HYX) will conduct an assessment for the risk of bias of each included study independently. If there is any disagreement, we will discussion and make a conclusion. A third reviewer (Fengfeng Wu) will be response to resolve the disagreement if consensus is still not reached after discussion.

Strategy for data synthesis

We will assess heterogeneity between studies included using the Cochran Q statistic and the I^2 test. The data with the P-value of the Q statistic < 0.1 or an I2 > 50% will be considered as statistically significant heterogeneity between included studies[54]. We will only perform a qualitative synthesis if there is substantial heterogeneity. We will use the Review Manager software (RevMan, V.5.3) to synthesize the results from the studies with sufficient data and homogeneous features about the interventions and outcome measures. The main results of the publications selected will be summarized and presented as a qualitative synthesis.

Quality of evidence

According to the recommendations from the Cochrane Handbook for Systematic Reviews of Interventions[55], the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used to evaluate the body of the scientific evidence and outcome[56]. GRADE system involves rating evidence for a given outcome, including two main domains: 1) indications for upgrading the evidence (having a large effect size and dose–response gradient), 2) indications for downgrading the evidence (serious risk of bias, serious inconsistency between studies, serious indirectness, serious imprecision of effects and likely publication bias).

The overall quality of scientific evidence will be classified into the following four levels: high, moderate, low, or very low (Table 2).

Table 2 Quality of evidence and definitions.

(1)	High quality: Very confident that the estimate of effects is as close as possible to the true effect and is almost impossible changed by further research.
(2)	Moderate quality: Moderately confident that the estimate of effects is likely to be close to the true effect but there is a possibility that it is substantially different and is possible changed by further research.
(3)	Low quality: Limited confidence that the estimate of effect may be substantially different from the true effect and is very likely to be changed by further research.
(4)	Very low quality: Very little confidence that any estimate of effect is very uncertain.

Ethics and dissemination

Ethics considerations: This systematic review does not need ethical approval because that the proposed study does not involve the collection of primary data. Findings of this review will be disseminated via peer-reviewed publications and conference presentation(s).

Dissemination plan

This systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on 01 July 2021 (registration number CRD42021267069).

Findings of this review will be disseminated through peer-reviewed publications and conference presentations.

Patient and public involvement

No patient involved.

Contributors Xin Wang is the leader and the guarantor of this review. SHZ conceptualized the study protocol and drafted the manuscript. SHZ and HYX developed the search strategy, data management, and methodological appraisal of the studies. FFW, XW and CJW revised the protocol and provided critical insights.

All authors provided feedback on the draft and approved the final written manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not- for- profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer-reviewed.

ORCID iDs

Shehong Zhang https://orcid.org/0000-0002-7635-8004

Fengfeng Wu http://orcid.org/0000-0003-2629-082X

REFERENCES

1. GBD 2016 Stroke Collaborators. *Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016.* The Lancet Neurology, 2019. **18**(5): p. 439-458.
2. Ekker MS, Verhoeven JI, Vaartjes I, et al. *Stroke incidence in young adults according to age, subtype, sex, and time trends.* Neurology, 2019. **92**(21): p. e2444-e2454.
3. Miller EL, Murray L, Richards L, et al. *Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient: a scientific statement from the American Heart Association.* Stroke, 2010. **41**(10): p. 2402-48.
4. Govan L, Langhorne P, Weir CJ, et al. *Does the prevention of complications explain the survival benefit of organized inpatient (stroke unit) care?: further analysis of a systematic review.* Stroke, 2007. **38**(9): p. 2536-40.
5. Roger VL, Go AS, Lloyd-Jones DM, et al. *Heart disease and stroke statistics--2011 update: a report from the American Heart Association.* Circulation, 2011. **123**(4): p. e18-e209.
6. Langhorne P, Coupar F, Pollock A. *Motor recovery after stroke: a systematic review.* Lancet Neurol 2009. **8**: p. 741-54.
7. Richards CL, Malouin F, and Nadeau S. *Stroke rehabilitation: clinical picture, assessment, and therapeutic challenge.* Prog Brain Res, 2015. **218**: p. 253-80.
8. Jørgensen HS, Nakayama H, Raaschou HO, et al. *Recovery of Walking Function in Stroke Patients: The Copenhagen Stroke Study.* Arch Phys Med Rehabil, 1995. **76**(1):p. 27-32.
9. Mayo NE, Wood-Dauphinee S, Ahmed S, et al. *Disablement following stroke.* disability and rehabilitation 1999. **21**(5/6): p. 258-68.
10. Ontario Health (Quality). *Continual Long-Term Physiotherapy After Stroke: A Health Technology Assessment.* ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES, 2020. **20**(7): p. 1-70.
11. Cleland BT and Madhavan S. *Ipsilateral Motor Pathways and Transcallosal Inhibition During Lower Limb Movement After Stroke.* Neurorehabil Neural Repair, 2021. **35**(4): p. 367-78.
12. Pang TY, Hannan AJ, and Lawrence AJ. *Novel approaches to alcohol rehabilitation: Modification of stress-responsive brain regions through environmental enrichment.* Neuropharmacology, 2019. **145**(Pt A): p. 25-36.
13. Laver KE, Lange B, George S, et al. *Virtual reality for stroke rehabilitation.* Cochrane Database Syst Rev, 2017. **11**: p. CD008349.
14. Corbetta D, Sirtori V, Castellini G, at al. *Constraint-induced movement therapy for upper extremities in people with stroke.* Cochrane Database Syst Rev, 2015(10): p. CD004433.
15. Weber LM and Stein J. *The use of robots in stroke rehabilitation: A narrative review.* NeuroRehabilitation, 2018. **43**(1): p. 99-110.
16. Liu YC, Yang YR, Tsai YA, et al. *Cognitive and motor dual task gait training improve dual task gait performance after stroke - A randomized controlled pilot trial.* Sci Rep, 2017. **7**(1): p. 4070.
17. Veerbeek JM, van Wegen E, van Peppen R, et al. *What is the evidence for physical therapy poststroke? A systematic review and meta-analysis.* PLoS One, 2014. **9**(2): p. e87987.
18. Corry M, Clarke M, While AE, et al. *Developing complex interventions for nursing: a critical review of key guidelines.* J Clin Nurs, 2013. **22**(17-18): p. 2366-86.
19. Langhorne P, Legg L. *EVIDENCE BEHIND STROKE REHABILITATION.* J Neurol Neurosurg Psychiatry, 2003. **74**: p. 18-21.
20. Le Danseur M. *Stroke Rehabilitation.* Crit Care Nurs Clin North Am, 2020. **32**(1): p. 97-108.
21. Langhorne P, Bernhardt J, and Kwakkel G. *Stroke rehabilitation.* The Lancet, 2011. **377**(9778): p. 1693-702.
22. Wu S, Chen J, Wang S, et al. *Effect of Tai Chi Exercise on Balance Function of Stroke Patients: A Meta-Analysis.* Med Sci Monit Basic Res, 2018. **24**: p. 210-5.
23. Lawrence M, Celestino Junior FT, Matozinho HH, et al. *Yoga for stroke rehabilitation.* Cochrane Database Syst Rev, 2017. **12**: p. CD011483.
24. Duncan PW, Sullivan KJ, Behrman AL, et al. *Body-weight-supported treadmill rehabilitation after stroke.* N Engl J Med, 2011. **364**(21): p. 2026-36.
25. Wolf SL, Winstein CJ, Miller JP, et al. *Effect of Constraint-Induced Movement Therapy on Upper Extremity Function 3 to 9 Months After Stroke: The EXCITE Randomized Clinical Trial.* JAMA, 2006. **296**(17): p. 2095-104.
26. Van Peppen RP, Kwakkel G, Wood-Dauphinee S, et al. *The impact of physical therapy on functional outcomes after stroke: what's the evidence?* Clin Rehabil, 2004. **18**(8): p. 833-62.

27. Kjellstrom T, Norrving B, and Shatchkute A. *Helsingborg Declaration 2006 on European stroke strategies.* Cerebrovasc Dis, 2007. **23**(2-3): p. 231-41.

28. Norrving B. *The 2006 Helsingborg Consensus Conference on European Stroke Strategies.* International Journal of Stroke, 2007. **2**: p. 139-43.

29. Mehrholz J, Thomas, S, Werner C, et al., *Electromechanical-assisted training for walking after stroke.* Cochrane Database Syst Rev, 2017. **5**: p. CD006185.

30. English C, Hillier SL, and Lynch EA. *Circuit class therapy for improving mobility after stroke.* Cochrane Database Syst Rev, 2017. **6**: p. CD007513.

31. Wevers L, van de Port I, Vermue M, et al. *Effects of task-oriented circuit class training on walking competency after stroke: a systematic review.* Stroke, 2009. **40**(7): p. 2450-9.

32. Winstein CJ, Stein J, Arena R, et al. *Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association.* Stroke, 2016. **47**(6): p. e98-e169.

33. Moher D, Shamseer L, Clarke M, et al. *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Systematic Reviews, 2015. **4**(1):p. 1.

34. Shamseer L, Moher D, Clarke M, et al. *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation.* BMJ, 2015. **350**: p. g7647.

35. Liberati A, Altman DG, Tetzlaff J, et al. *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* PLoS Med, 2009. **6**(7): p. e1000100.

36. Liberati A, Altman DG, Tetzlaff J, et al. *The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration.* Annals of Internal Medicine, 2009. **151**(4): p. 65-94.

37. Evans D. *Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions.* Journal of Clinical Nursing, 2003. **12**: p. 77-84.

38. Akobeng AK. *Understanding randomised controlled trials.* Arch Dis Child, 2005. **90**(8): p. 840-4.

39. Sibbald B, Roland M. *Understanding controlled trials Why are randomised controlled trials important?* BMJ, 1998. **316**(7126):201.

40. Hatano S. *Experience from a multicentre stroke register: a preliminary report.* BULL. WORLD HEALTH ORGAN, 1976. **54**: p. 541-53.

41. Thickbroom GW, Cortes M, Rykman A, et al. *Stroke subtype and motor impairment influence contralesional excitability.* Neurology, 2015. **85**(6): p. 517-20.

42. Wu CY, Fu T, Lin KC, et al. *Assessing the streamlined Wolf motor function test as an outcome measure for stroke rehabilitation.* Neurorehabil Neural Repair, 2011. **25**(2): p. 194-9.

43. Lee J and Stone AJ. *Combined Aerobic and Resistance Training for Cardiorespiratory Fitness, Muscle Strength, and Walking Capacity after Stroke: A Systematic Review and Meta-Analysis.* J Stroke Cerebrovasc Dis, 2020. **29**(1): p. 104498.

44. Persson CU, Holmegaard L, Redfors P, et al. *Increased muscle tone and contracture late after ischemic stroke.* Brain Behav, 2020. **10**(2): p. e01509.

45. Beyaert C, Vasa R, and Frykberg GE. *Gait post-stroke: Pathophysiology and rehabilitation strategies.* Neurophysiol Clin, 2015. **45**(4-5): p. 335-55.

46. Andersen HE, Eriksen K, Brown A, et al. *Follow-up services for stroke survivors after hospital discharge--a randomized control study.* Clin Rehabil, 2002. **16**(6): p. 593-603.

47. Legg, L.A., et al., *Occupational therapy for adults with problems in activities of daily living after stroke.* Cochrane Database Syst Rev, 2017. **7**: p. CD003585.

48. Vloothuis JD, Mulder M, , Veerbeek JM, et al. *Caregiver-mediated exercises for improving outcomes after stroke.* Cochrane Database Syst Rev, 2016. **12**: p. CD011058.

49. Langhorne P, Collier JM, Bate PJ, et al., *Very early versus delayed mobilisation after stroke.* Cochrane Database Syst Rev, 2018. **10**: p. CD006187.

50. Liberati A, Altman DG, Tetzlaff J, et al. *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* J Clin Epidemiol, 2009. **62**(10): p. e1-34.

51. Moher D, Liberati A, Tetzlaff J, et al. *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* PLoS Med, 2009. **6**(7): p. e1000097.

52. Moher D, Shamseer L, Clarke M, et al. *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015statement.* Systematic Reviews, 2015. **4**(1): p. 1.

53. Higgins JP, Altman DG, Gøtzsche PC, et al. *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* BMJ, 2011. **343**: p. d5928.

54. Shen Y, Fang L, Ye B, et al. *Meta-analysis of diagnostic accuracy of nucleic acid amplification tests for abdominal tuberculosis: A protocol.* PLoS One, 2020. **15**(12): p. e0243765.

55. Cumpston M, Li T, Matthew J Page MJ, et al. *Updated guidance for trusted systematicreviews: a new edition of the CochraneHandbook for Systematic Reviews ofInterventions.* Cochrane Library, 2019. **10**.

56. Guyatt GH, Oxman AD, Vist GE, et al. *GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.* BMJ, 2008. **336**(7650): p. 924-6.