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Effectiveness of interventions to improve hand motor function in individuals with moderate to severe stroke: a systematic review protocol

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ABSTRACT

Introduction: The human hand is extremely involved in our daily lives. However, the rehabilitation of hand function after stroke can be rather difficult due to the complexity of hand structure and function, as well as neural basis that supports hand function. Specifically, in individuals with moderate to severe impairment following a stroke, previous evidence for effective treatments that recovers hand function in this population is limited, and thus has never been reviewed. With the progress of rehabilitation science and tool development, results from small clinical trials have been available. The newly accumulated evidence drives the aim of this systematic review: to identify interventions that has potential to effectively increase hand function in individuals with moderate to severe stroke.

Methods and analysis: This systematic review protocol is consistent with the methodology recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols and the Cochrane handbook for systematic reviews of interventions. Electronic searches will be carried out in the PubMed, CINAHL, Physiotherapy Evidence Database (PEDro) and Cochrane Library databases, along with manual searches in the reference lists from included studies and published systematic reviews of interventions to improve upper limb or hand motor function in individuals with moderate to severe stroke. Two reviewers will screen all retrieved titles, abstracts and full texts, perform the evaluation of the risk bias and extract all data independently. In case of any unsolved disagreements after discussion, a third reviewer will be referred to as an arbitrator. The risk of bias of the included random controlled trials (RCTs) will be evaluated by the Cochrane Collaboration's tool. A qualitative synthesis will be provided in text and table, to summarize the main results of the selected publications. The quality of the included publications will be evaluated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system from the Cochrane Handbook for Systematic Reviews of Interventions.

Ethics and dissemination: No ethical approval is needed, and the results of this review will be disseminated via peer-reviewed publications and conference presentations.

Trial registration number: The protocol has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) on 10 April 2019 (registration number: CRD42019128285).

Strengths and limitations of this study

- To the best of our knowledge, this is the first systematic review for the effectiveness of interventions to improve hand function in individuals with moderate to severe stroke.
- The results of this systematic review will provide a detailed summary of the current progress of evidence for interventions to improve hand motor function, which will contribute to offering valuable information for therapeutists to help stroke survivors with moderate to severe impairment and identifying the gaps in the literature for further research.
- There may be significant heterogeneity because of wide range of outcome measures, types of intervention and duration and frequency of training.

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INTRODUCTION

Stroke is one of the main causes of long-term disabilities among adults[1]. Up to 85% of stroke survivors have hemiparesis that affects the upper extremity on one side[2], and less than half of them can regain proper arm function 6 months after stroke[3 4]. Generally, hemiparesis impacts the movement function of hand and wrist more than shoulder and elbow[3 5]. As we know, the hand movements play a core role in upper limb function because of its indispensable and sophisticated function in human daily lives[6]. Many vital activities of daily living, such as using a fork, buttoning a shirt, and opening a door handle, require various hand function[7]. The losses in hand function can seriously affect patients' functional independence and quality of life[8].

Currently, for mildly impaired stroke survivors (about 20-25%)[9], constraint-induced movement therapy (CIMT) has been reported to produce significantly greater gains in hand/arm function compared to conventional therapy[10 11]. However, for stroke survivors who have moderate to severe impairment and do not meet the inclusion criteria of CIMT[12 13], intervention options for hand function recovery are limited. The complexity of hand structure and function together with the neural basis that supports hand function might contribute to the great difficulty of hand function rehabilitation after stroke. Enormous biomechanical complexity makes the hand extensively represented in a large region of the motor cortex of the brain[14], which suggests that fine control of hand movement depends heavily on the intact corticospinal tract. When the ipsilesional corticofugal tract was serious damaged due to stroke, contralesional motor-related cortical recruitment becomes the main neural compensatory model for these moderate to severe stroke patients according to previous studies[15]. Evidence to support such opinion includes that inhibition of contralesional motor cortex using transcranial magnetic stimulation[16] or tDCS[17] can lead to more disrupted performance of a simple motor task in patients with poorer motor outcome. The contralesional cortical recruitment may rely on contralesional corticobulbospinal tract such as the corticoreticulospinal tract to control the affected upper limb[18]. However, the compensatory corticoreticulospinal tract branches at multiple segments in spinal cord, and innervates proximal muscles more than distal ones, and prefers the flexors but lacks comparable resolution and innervation to hand and finger extensor muscles[19 20]. Above features results in the abnormal involuntary coupling between shoulder abduction and wrist/finger flexion, which is also known as the "flexion synergy", as well as muscle weakness especially at extensors of distal joints, thus further constrains functional hand movements especially hand opening[21 22]. In short, it seems that extension at distal joints, like hand opening, depends more on the function of corticospinal track, primarily projected from the lesioned hemisphere, and lacks compensatory neural system to provide 'backup' driving. This neural basis makes effective restoration of hand function in moderate to severe stroke patients become extremely challenging. Furthermore, the resulted 'none-use-decay' can cause further decrease of the hand function. Although full of challenges, some of the research findings demonstrate that hand function recovery in this population is still feasible with evidence showing both feasibility in intervention-induced changes in behavior[23 24] and neural plasticity measures[20]. We therefore focus on hand function recovery in the group of stroke survivors with moderate to severe impairment in this systematic review.

According to our knowledge of the literature, ample summary of the efficacy of various interventions for upper limb function rehabilitation in stroke patients can be found in published systematic reviews. Most of these reviews evaluate the efficacy of a single category of therapeutic technique, such as CIMT[25-29], robot-assisted therapy[30-35], bilateral training[36 37], task-oriented training[38], exercise therapy[39], functional electrical stimulation(FES)[40 41], orthotics[42 43], mental practice[44 45], mirror therapy[46 47], action observation[48], non-invasive cerebral stimulation[49-52], brain-computer interface[53 54], virtual reality[42], home-based therapy programmes[55], etc. There are also found some comprehensive systematic reviews on general function treatment of upper limb after stroke[56-58] or other specific problems, such as motor dysfunction[59 60], sensory impairment[61], spasticity[62 63], decreased quality of life [64], and shoulder pain and subluxation[65-67]. In addition, other important issues of upper limb rehabilitation after stroke, like timing of intervention[68], dose of training[69], effects of severity on motor recovery[24], outcome measures[70-75] and predictors of functional restoration[76 77] were systematically reviewed as well. However, much less attention has been paid to the systematic review of hand function rehabilitation after moderate to severe stroke[78-83]. Fortunately, with growing attention to this research field in recent decades, increased number of clinical trials that focus on moderate to severe stroke patients are available now, involving various intervention methods, like EMG-triggered electrical stimulation[84], transcranial direct current stimulation[85], robot-assisted movement training, repetitive transcranial magnetic stimulation[86], and mirror therapy[87]. Although with relatively small sample size, a review of these reported work will provide insight for the future direction alone this line of research and thus may further impact future clinical practice for this large population.

Comprehensive overview of hand motor function rehabilitation in individuals with moderate to severe stroke has long been neglected not only in systematic reviews but also in the main guidelines for stroke rehabilitation. In the most recent *Guidelines for Adult Stroke Rehabilitation and Recovery* released by the American Heart Association and the American Stroke Association in 2016, we can only locate recommendations for the treatment of upper extremity activity but hardly find any evidence-based suggestions for hand function training[88]. The 2015 update of the *Canadian Stroke Best Practice Recommendations: Stroke Rehabilitation Practice Guidelines* has provided a series of recommends on the management of upper extremity following stroke, including the restore of sensorimotor function, and relief of spasticity and pain. Regarding the hand function rehabilitation after stroke, limited recommendations are scattered among evidence for upper extremity, such as FES and CIMT for hand motor function, botulinum toxin for hand spasticity and range of motion, and exercise and massage for hand edema[89]. Similar problems can be found in stroke rehabilitation guidelines in UK and Australia, which mainly provide recommendations on upper extremity management while lack a detailed description of the current evidence on hand function recovery[90 91]. The absence of systematic evidence in guidelines for hand rehabilitation following stroke greatly increases the difficulty of clinical work.

In short, a standardized systematic review on the effectiveness of interventions is warranted to improve hand motor function in individuals with moderate to severe stroke. Therefore, the aim of this review is to provide an overview of the following:

1. to identify which interventions that have been employed to increase hand function in individuals with moderate to severe stroke;
2. to verify the effectiveness of these interventions;
3. to identify the gaps in the literature.

METHODS AND ANALYSES

Study design

The review protocol was written and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) (see the PRISMA checklist)[92 93]. For the results of this systematic review, we will publish it following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement[94 95].

Eligibility criteria

Types of study

We will include all randomized controlled trials published in English that investigated the efficacy of rehabilitation interventions to improve hand motor function in individuals with moderate to severe stroke. The random allocation process should be performed in a standard way. Quasi-RCTs or trails without control group such as case series and case reports will be excluded.

Participants

We will include all RCTs which have recruited adult patients (≥18 years of age) with first or recurrent stroke. Stroke is defined 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 World Health Organization[96]. The diagnosis of stroke should be confirmed by CT or MRI. The participants in all trails should be assessed as moderate to severe unilateral hand dysfunction as indicated by hand functional assessments such as the Fugl-Meyer Upper Extremity Scale (<45) and Chedoke-McMaster Stroke Assessment (≤stage 4). Patients with subarachnoid hemorrhage or subdural hematoma will be excluded. Studies with participants with transient ischemic attack will be excluded since all neurological symptoms would disappear.

Types of interventions

We will select all trials assessing a rehabilitation method (PT/OT) that targets on the post-hand hand function regaining in stroke survivors that have moderate to severe impairment. Trials focusing only on the training of elbow and shoulder will be excluded.

The PT is defined as 'services to individuals and populations to develop, maintain and restore maximum movement and functional ability throughout the lifespan' and 'physical therapy is concerned with identifying and maximizing quality of life and movement potential within the spheres of promotion, prevention, treatment/ intervention, habilitation and rehabilitation' by the World Confederation for Physical Therapy (WCPT) (http://www.wcpt.org/policy/ps-descriptionPT).

The OT is defined by the American Occupational Therapy Association as the profession that 'helps people across the lifespan to do the things they want and need to do through the therapeutic use of daily activities (occupations)'. Occupational therapy services typically include: 1) an individualized evaluation, during which the client/family and occupational therapist determine the person's goals, 2) customized intervention to improve the person's ability to perform daily activities and reach the goals, and 3) an outcomes evaluation to ensure that the goals are being met and/or make changes to the intervention plan (https://www.aota.org/About-Occupational-Therapy.aspx).

Type of outcome measures

The primary outcomes of this systematic review will focus on changes in patients' hand function using various assessments from baseline to the last available follow-up. The assessments can be divided into two groups[72]: body functions measures (targeting impairments of hand function, such as Fugl-Meyer Assessment hand part, Chedoke-McMaster Stroke Assessment, Motricity Index etc.) and activity measures (assessing limitations of activities, such as Action Research Arm Test, Box and Block Test, Wolf Motor Function Test, etc.).

Secondary outcome measures will include kinematic analysis of hand movement, possible improvements of quality of life and possible mental health improvements related to the practice of interventions. The adverse events associated with interventions and adherence to treatment will also be considered.

Search strategy for the identification of relevant studies

Electronic searches will be performed for potentially eligible RCTs in the PubMed, CINAHL, Physiotherapy Evidence Database (PEDro) and Cochrane Library databases with restriction in articles with full texts in English. All databases will be searched between January 1999 and January 2019. Searches will combine terms from medical subject headings (MeSH) and keywords in title, abstract and text for the population, intervention and outcomes. The Cochrane Library Database search strategy in the table below will be adapted for other databases. Furthermore, RCTs will also be obtained from the reference lists of included studies and published systematic reviews of interventions to improve upper limb or hand motor function in individuals with moderate to severe stroke.

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
#3	#1 OR #2
#4	MeSH descriptor: [Hand] explode all trees
#5	(Hand* OR Palm* OR Finger* OR Thumb* OR Wrist*):ti,ab,kw
#6	#4 OR #5
#7	MeSH descriptor: [Rehabilitation] explode all trees
#8	MeSH descriptor: [Exercise] explode all trees
#9	MeSH descriptor: [Therapeutics] explode all trees
#10	(Rehab* OR Exercis* OR Therap* OR Treat*):ti,ab,kw
#11	#7 OR #8 OR #9 OR #10
#12	#3 AND #6 AND #11 in Trials

Screening of the studies

The reference management software, Endnote (version X9; Thomson Reuters, NY, USA), will be used to help upload, store and select the literature results. For each database, a separate library group will be created to keep all original search results. 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 dialog box in the Endnote. Two independent reviewers (HWW, RA) will screen all the retrieved titles and abstracts according to the previously determined inclusion and exclusion criteria and 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 search strategy. In case of any disagreements, a third reviewer (JY) will be referred to make a final decision. All reasons for exclusion of any publications will be noted. 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[94 95].

Data extraction

The two independent reviewers (HWW, RA) will carry out the data extraction following recommendations from the PRISMA statement[94 95]. Disagrees between the two reviewers will be solved by a third reviewer (JY) to reach a consensus. The extracted data will include general study information (authors, year of publication and ethics), characteristics of participants (sample size, inclusion/ exclusion criteria, random process and allocation, age, gender, type and time since the onset of the stroke), interventions (type of intervention, dose, duration, frequency, supervision and comparison/control group), outcome measures (observation time points, hand function assessments, hand movement kinematic analysis, quality of life changes, possible mental improvement, dropout, length of follow up, adverse events and conflict of interest). If necessary, the corresponding authors of the selected publications will be contacted for missing data and further information.

Risk of bias

The risk of bias of the included RCTs will be evaluated by the Cochrane Collaboration's tool (Table 8.5.a in the Cochrane Handbook for Systematic Reviews of Interventions)[97]. The Cochrane Collaboration's tool is a 6-item checklist, which includes sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias not issued in other domains mentioned above. For each item in the checklist, the risk of bias will be categorized as low (meet all criteria), unclear (insufficient detail reported in the publications) or high risk of bias (meet none of the criteria). Two independent reviewers (HWW, RA) will perform these judgements of risk of bias and disagreements will be resolved first by discussion and then by referring to a third reviewer author (JY) as an arbitrator when necessary.

Strategy for data synthesis

We will provide a qualitative synthesis, in text and table, to summarize the main results of the selected publications. A narrative synthesis will be included to demonstrate the findings, structured around the type of intervention, target population characteristics, intervention content and types of outcome. We anticipate that there will be limited scope for meta-analysis because of the range of different outcomes measured and heterogeneity of interventions across the existing trials based on initial screening.

Analyses of subgroups or subsets

We will perform the subgroups analyses if sufficient data are available. These analyses will involve differences between the stroke phases (i.e. acute/subacute/chronic), the main therapeutic goal of treatment (i.e. aiming at the recovery of hand function/aiming at the recovery of arm and hand function), the measurement tools (e.g. activity measures/body function measures), intervention details (type, duration and delivery of the intervention), participation of patients in trails (active movement training/passive training) and quality and risk of bias.

Quality of evidence

According to the recommendations from the Cochrane Handbook for Systematic Reviews of

Interventions[97], the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used to assess the body of the evidence for all outcomes[98]. This system involves consideration of within-study risk of bias, consistency, directness of evidence, precision of effects estimates and publication bias. The overall quality of evidence will be adjudicated at four levels: high, moderate, low and very low (table 2).

Table 2 Quality of evidence and definitions

High quality	Further research is very unlikely to change the confidence in the estimate of effects.
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 effect and is likely to change the estimate
Very low quality	Any estimate of the effect is very uncertain

Ethics and dissemination

This systematic review does not need ethical approval and informed consent. Findings of this review will be disseminated via peer-reviewed publications and conference presentations.

DISCUSSION

Rehabilitation of hand motor function after stroke is different from other parts of the body like the lower extremity, truck and even the proximal part of the upper limb, which recover faster and more completely [99]. The neural basis underlying the hand rehabilitation in moderate to severe stroke patients makes effective restoration of hand motor function extremely challenging, therefore, currently this cohort of stroke survivors are largely ignored for hand function rehabilitation. To date, there is also no systematic review or guideline that focuses extensively on the effectiveness of interventions to improve hand motor function in individuals with moderate to severe stroke. To the best our knowledge, this is the first systematic review that attempts to sort out the hand rehabilitation approaches and make a comprehensive analysis of the existing evidence to fill in the gaps in this field.

This systematic review has several strengths. First, the preparation of this protocol is consistent with the methodology recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols and the Cochrane handbook for systematic reviews of interventions. Second, we only include RCTs which have recruited participants with moderate to severe hand function after stroke. This is because publications have provided us with convincing evidence that patients with baseline ability to control wrist and finger extension can achieve improvements in hand function and quality of life after receiving treatment procedures like modified CIMT[12 13]. However, there is no consensus on the effectiveness of intervention methods for stroke patients with more severely damaged hand. Third, more and more clinical trials on this topic have been published in recent decades, and it is time for a systematic review now.

The results of this systematic review will provide a detailed summary of the current progress of evidence for interventions to improve hand motor function in individuals with moderate to severe stroke. Such a review can contribute to not only identifying the gaps thus providing a guidance for further research, but also offering valuable information for therapeutics to help stroke survivors with impaired hand function.

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Contributors JY is the lead and the guarantor of this review. HWW and RA conceptualized the review and drafted the manuscript. HWW and RA developed the search strategy included in the protocol. JJ, LD and SGC revised the protocol critically. All authors read and provided feedback on the draft and approved the final manuscript.

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Effectiveness of interventions to improve hand motor function in individuals with moderate to severe stroke: a systematic review protocol

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ABSTRACT

Introduction: The human hand is extremely involved in our daily lives. However, the rehabilitation of hand function after stroke can be rather difficult due to the complexity of hand structure and function, as well as neural basis that supports hand function. Specifically, in individuals with moderate to severe impairment following a stroke, previous evidence for effective treatments that recover hand function in this population is limited, and thus has never been reviewed. With the progress of rehabilitation science and tool development, results from more and more clinical trials are now available, thereby justifying conducting a systematic review.

Methods and analysis: This systematic review protocol is consistent with the methodology recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols and the Cochrane handbook for systematic reviews of interventions. Electronic searches will be carried out in the PubMed, CINAHL, Physiotherapy Evidence Database (PEDro) and Cochrane Library databases, along with manual searches in the reference lists from included studies and published systematic reviews. The date range parameters used in searching all databases is between January 1999 and January 2019. Randomized controlled trials (RCTs) published in English, with the primary outcome focusing on hand motor function, will be included. Two reviewers will screen all retrieved titles, abstracts and full texts, perform the evaluation of the risk bias and extract all data independently. The risk of bias of the included RCTs will be evaluated by the Cochrane Collaboration's tool. A qualitative synthesis will be provided in text and table, to summarize the main results of the selected publications. A meta-analysis will be considered if there is sufficient homogeneity across outcomes. The quality of the included publications will be evaluated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system from the Cochrane Handbook for Systematic Reviews of Interventions.

Ethics and dissemination: No ethical approval is needed, and the results of this review will be disseminated via peer-reviewed publications and conference presentations.

Trial registration number: The protocol has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) on 10 April 2019 (registration number: CRD42019128285).

Strengths of this study

- To the best of our knowledge, this is the first systematic review for the effectiveness of interventions to improve hand motor function in individuals with moderate to severe stroke.
- The results of this systematic review will provide a detailed summary of the current progress of evidence for interventions to improve hand motor function, which will contribute to offering valuable information for therapeutists to help stroke survivors with moderate to severe impairment and identifying the gaps in the literature for further research.

Limitations of this study

- We anticipate that a limited meta-analysis is likely to be conducted because there may be significant heterogeneity owing to wide range of outcome measures, types of intervention and duration and frequency of training.
- There is always a possibility that the review does not identify all evidence or limitations relevant to the research question, such as the introduction of language bias due to the selection

of studies published only in English.

INTRODUCTION

Stroke is one of the main causes of long-term disabilities among adults[1]. Up to 85% of stroke survivors have hemiparesis that affects the upper extremity on one side[2], and less than half of them can regain proper arm function 6 months after stroke[3 4]. Generally, hemiparesis impacts the movement function of the hand and wrist more than shoulder and elbow[3 5]. As we know, hand movement plays a core role in upper limb function because of its indispensable and sophisticated function in human daily lives[6]. Many vital activities of daily living, such as using a fork, buttoning a shirt, and opening a door handle, require various hand functions[7]. The losses in hand function can seriously affect patients' functional independence and quality of life[8].

Currently, for mildly impaired stroke survivors (about 20-25%)[9], constraint-induced movement therapy (CIMT) has been reported to produce significantly greater gains in hand/arm function compared to conventional therapy[10 11]. However, for stroke survivors who have moderate to severe impairment and do not meet the inclusion criteria of CIMT[12 13], intervention options for hand motor function recovery are limited. The complexity of hand structure and function together with the neural basis that supports hand function might contribute to the great difficulty of hand function rehabilitation after stroke. Enormous biomechanical complexity makes the hand extensively represented in a large region of the motor cortex of the brain[14], which suggests that fine control of hand movement depends heavily on an intact corticospinal tract. When the ipsilesional corticofugal tract is serious damaged due to stroke, contralesional motor-related cortical recruitment becomes the main neural compensatory model for these moderate to severe stroke patients, according to previous studies[15]. That the inhibition of contralesional motor cortex using transcranial magnetic stimulation[16] or tDCS[17] can lead to more disrupted performance of a simple motor task in patients with poorer motor outcome serves as evidence to support such opinion. The contralesional cortical recruitment may rely on contralesional corticobulbospinal tract such as the corticoreticulospinal tract to control the affected upper limb[18]. However, the compensatory corticoreticulospinal tract branches at multiple segments in spinal cord, and innervates proximal muscles more than distal ones, and prefers the flexors but lacks comparable resolution and innervation to hand and finger extensor muscles[19 20]. The aforementioned features result in the abnormal involuntary coupling between shoulder abduction and wrist/finger flexion, which is also known as the "flexion synergy", as well as muscle weakness especially at extensors of distal joints, thus further constrains functional hand movements especially hand opening[21 22]. In short, it seems that extension at distal joints, like hand opening, depends more on the function of corticospinal track, primarily projected from the lesioned hemisphere, and lacks compensatory neural system to provide 'backup' driving. This neural basis makes effective restoration of hand function in moderate to severe stroke patients become extremely challenging. Furthermore, the resulting 'none-use-decay' can cause further decrease of the hand function. Although full of challenges, some of the research findings demonstrate that hand function recovery in this population is still feasible, with evidence showing both feasibility in intervention-induced changes in behavior[23 24] and neural plasticity measures[20]. We therefore focus on hand function recovery in the group of stroke survivors with moderate to severe impairment in this systematic review.

According to our knowledge of the literature, ample summary of the efficacy of various interventions for upper limb function rehabilitation in stroke patients can be found in published systematic reviews. Most of these reviews evaluate the efficacy of a single category of therapeutic technique, such as CIMT[25-29], robot-assisted therapy[30-35], bilateral training[36 37], task-oriented training[38], exercise therapy[39], functional electrical stimulation(FES)[40 41], orthotics[42 43], mental practice[44 45], mirror therapy[46 47], action observation[48], non-invasive cerebral stimulation[49-52], brain-computer interface[53 54], virtual reality[42], home-based therapy programmes[55], etc. There are also some comprehensive systematic reviews on general function treatment of upper limb after stroke[56-58] or other specific problems, such as motor dysfunction[59 60], sensory impairment[61], spasticity[62 63], decreased quality of life [64], and shoulder pain and subluxation[65-67]. In addition, other important issues of upper limb rehabilitation after stroke, like timing of intervention[68], dose of training[69], effects of severity on motor recovery[24], outcome measures[70-75] and predictors of functional restoration[76 77] were systematically reviewed as well. However, much less attention has been paid to the systematic review of hand function rehabilitation after moderate to severe stroke[78-83]. Fortunately, with growing attention to this research field in recent decades, an increased number of clinical trials that focus on moderate to severe stroke patients is now available, involving various intervention methods, like EMG-triggered electrical stimulation[84], transcranial direct current stimulation[85], robot-assisted movement training, repetitive transcranial magnetic stimulation[86], and mirror therapy[87]. Although with relatively small sample sizes, a review of these reported works will provide insight for the future direction along this line of research and thus may further impact future clinical practice for this large population.

Comprehensive overview of hand motor function rehabilitation in individuals with moderate to severe stroke has long been neglected not only in systematic reviews but also in the main guidelines for stroke rehabilitation. In the most recent *Guidelines for Adult Stroke Rehabilitation and Recovery* released by the American Heart Association and the American Stroke Association in 2016, we can only locate recommendations for the treatment of upper extremity activity but can hardly find any evidence-based suggestions for hand function training[88]. The 2015 update of the *Canadian Stroke Best Practice Recommendations: Stroke Rehabilitation Practice Guidelines* has provided a series of recommendations on the management of upper extremity following stroke, including the restoration of sensorimotor function, and relief of spasticity and pain. Regarding the hand function rehabilitation after stroke, limited recommendations are scattered among evidence for other forms of upper extremity interventions, such as FES and CIMT for hand motor function, botulinum toxin for hand spasticity and range of motion, and exercise and massage for hand edema[89]. Similar problems can be found in stroke rehabilitation guidelines in UK and Australia, which mainly provide recommendations on upper extremity management while lacking a detailed description of the current evidence on hand function recovery[90 91]. The absence of systematic evidence in guidelines for hand rehabilitation following stroke greatly increases the difficulty of clinical work.

In short, a standardized systematic review on the effectiveness of interventions is warranted to improve hand motor function in individuals with moderate to severe stroke. Therefore, the aim of this review is to provide an overview of the following:

1. to identify which interventions that have been employed to increase hand function in individuals with moderate to severe stroke;
2. to verify the effectiveness of these interventions;
3. to identify the gaps in the literature.

METHODS AND ANALYSES

Study design

The review protocol was written and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) (see the PRISMA checklist in *supplementary table 1*)[92 93]. For the results of this systematic review, we will publish it following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement[94 95].

Eligibility criteria

Types of study

We will include all randomized controlled trials published in English that investigated the efficacy of rehabilitation interventions to improve hand motor function in individuals with moderate to severe stroke. The random allocation process should be performed in a standard way. Quasi-RCTs or trials without control group such as case series and case reports will be excluded. Preliminary and pilot studies, abstracts published in congress and conferences will also be excluded.

Participants

We will include all RCTs which have recruited adult patients (≥18 years of age) with first or recurrent stroke. Stroke is defined 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 World Health Organization[96]. The diagnosis of stroke should be confirmed by CT or MRI. The participants in all trials should be assessed as moderate to severe unilateral hand dysfunction as indicated by hand functional assessments such as the Fugl-Meyer Upper Extremity Scale (<45) and Chedoke-McMaster Stroke Assessment (≤stage 4) [97 98]. Patients with subarachnoid hemorrhage or subdural hematoma will be excluded. Studies with participants with transient ischemic attack will be excluded since all neurological symptoms would disappear.

Types of interventions

We will select all trials assessing interventions that at least have one of the treatment goals targeting the regaining of post-hand hand function in individuals with moderate to severe stroke. These interventions should be compared with a control intervention (e.g. no treatment, standard care, conventional training or the same intervention method with different parameters). Trials focusing only on the training of elbow and shoulder will be excluded. The interventions here encompass many different, individual interventions, such as FES, mirror therapy, robot training, CIMT, brain-computer interface, repetitive transcranial magnetic stimulation, etc. Interventions can either be one-to-one or in group setting, hospital-based or home-based (under the supervision of professional), supervised by therapists or self-training. No limits will be placed 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' hand function using various assessments from baseline to the last available follow-up. The assessments can be divided into two groups[72 74]: body functions measures (targeting impairments of hand function, such as Fugl-Meyer Assessment hand part, Chedoke-McMaster Stroke Assessment, Motricity Index etc.) and activity measures (assessing limitations of activities, such as Action Research Arm Test, Box and Block Test, Wolf Motor Function Test, etc.).

Secondary outcome measures will include kinematic analysis of hand movement, possible improvements of quality of life, and mental health improvements related to the hand motor function recovery. The adverse events associated with interventions and adherence to treatment will also be considered.

Search strategy for the identification of relevant studies

Electronic searches will be performed for potentially eligible RCTs in the PubMed, CINAHL, Physiotherapy Evidence Database (PEDro) and Cochrane Library databases with restriction in articles with full texts in English. The date range parameters used in all databases will be between January 1999 and January 2019. Searches will combine terms from medical subject headings (MeSH) and keywords in title, abstract and text for the population, intervention and outcomes. The Cochrane Library Database search strategy in the table below (table 1) will be adapted for other databases. Furthermore, RCTs will also be obtained from the reference lists of included studies and published systematic reviews of interventions to improve upper limb or hand motor function in individuals with moderate to severe stroke.

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
#3	#1 OR #2
#4	MeSH descriptor: [Hand] explode all trees
#5	(Hand* OR Palm* OR Finger* OR Thumb* OR Wrist*):ti,ab,kw
#6	#4 OR #5
#7	MeSH descriptor: [Rehabilitation] explode all trees
#8	MeSH descriptor: [Exercise] explode all trees
#9	MeSH descriptor: [Therapeutics] explode all trees
#10	(Rehab* OR Exercis* OR Therap* OR Treat*):ti,ab,kw
#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	#7 OR #8 OR #9 OR #10 OR #11
#13	#3 AND #6 AND #12 in Trials

Screening of the studies

The reference management software, Endnote (version X9; Thomson Reuters, NY, USA), will be used to help upload, store and select the literature results. For each database, a separate library group will be created to keep all original search results. 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 dialog box in the Endnote. Two independent reviewers (HWW, RA) will screen all the retrieved titles and abstracts according to the previously determined inclusion and exclusion criteria and 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 search strategy. In case of any disagreements, a third reviewer (JY) will be referred to make a final decision. All reasons for exclusion of any publications will be noted. 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[94 95].

Data extraction

Two independent reviewers (HWW, RA) will carry out the data extraction following recommendations from the PRISMA statement[94 95]. Disagrees between the two reviewers will be solved by a third reviewer (JY) to reach a consensus. The extracted data will include general study information (authors, year of publication and ethics), characteristics of participants (sample size, inclusion/ exclusion criteria, random process and allocation, age, gender, type and time since the onset of the stroke), interventions (type of intervention, dose, duration, frequency, supervision and comparison/control group), outcome measures (observation time points, hand function assessments, hand movement kinematic analysis, quality of life changes, possible mental improvement, dropout, length of follow up, adverse events and conflict of interest). If necessary, the corresponding authors of the selected publications will be contacted for missing data and further information.

Risk of bias

The risk of bias of the included RCTs will be evaluated by the Cochrane Collaboration's tool (Table 8.5.a in the Cochrane Handbook for Systematic Reviews of Interventions)[99]. The Cochrane Collaboration's tool is a 6-item checklist, which includes sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias not issued in other domains mentioned above. For each item in the checklist, the risk of bias will be categorized as low (meet all criteria), unclear (insufficient detail reported in the publications) or high risk of bias (meet none of the criteria). Two independent reviewers (HWW, RA) will perform these judgements of risk of bias and disagreements will be resolved first by discussion and then by referring to a third reviewer author (JY) as an arbitrator when necessary.

Strategy for data synthesis

We will provide a qualitative synthesis, in text and table, to summarize the main results of the selected publications. A narrative synthesis will be included to demonstrate the findings, structured around the type of intervention, target population characteristics, intervention content and types of outcome. We will check the heterogeneity of included studies by performing the χ^2 test (significant level: 0.1) and the I^2 statistic (high levels of heterogeneity: $I^2 \geq 50\%$). For studies that have sufficient data, and are homogeneous regarding the interventions and outcome measures, we will synthesize the results in meta-analysis using the Review Manager software (RevMan, Version 5.3). In case of substantial heterogeneity, only qualitative synthesis will be performed.

Analyses of subgroups or subsets

We will perform the subgroups analyses if sufficient data are available. These analyses will involve differences between the stroke phases (i.e. acute/subacute/chronic), the main therapeutic goal of treatment (i.e. aiming at the recovery of hand function/aiming at the recovery of arm and hand function), the measurement tools (e.g. activity measures/body function measures), intervention details (type, duration and delivery of the intervention), participation of patients in trials (active movement training/passive training), and quality and risk of bias.

Quality of evidence

According to the recommendations from the Cochrane Handbook for Systematic Reviews of Interventions[99], the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used to assess the body of the evidence for all outcomes[100]. This system involves consideration of within-study risk of bias, consistency, directness of evidence, precision of effects estimates and publication bias. The overall quality of evidence will be adjudicated at four levels: high, moderate, low and very low (table 2).

Table 2 Quality of evidence and definitions

High quality	Further research is very unlikely to change the confidence in the estimate of effects.
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 effect and is likely to change the estimate
Very low quality	Any estimate of the effect is very uncertain

Ethics and dissemination

This systematic review does not need ethical approval and informed consent. Findings of this review will be disseminated via peer-reviewed publications and conference presentations.

Patient and public involvement

No patient involved.

DISCUSSION

Rehabilitation of hand motor function after stroke is different from other parts of the body like the lower extremity, trunk and even the proximal part of the upper limb, which recover faster and more completely [101]. The neural basis underlying the hand rehabilitation in moderate to severe stroke patients makes effective restoration of hand motor function extremely challenging, therefore, currently this cohort of stroke survivors is largely ignored for hand function rehabilitation. To date, there is also no systematic review or guideline that focuses extensively on the effectiveness of interventions to improve hand motor function in individuals with moderate to severe stroke. To the best our knowledge, this is the first systematic review that concentrates on hand rehabilitation approaches in moderate to severe stroke patients and attempts to make a comprehensive analysis of the existing evidence to fill in the gaps in this research field.

This systematic review has several strengths. First, the preparation of this protocol is consistent with the methodology recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols and the Cochrane handbook for systematic reviews of interventions. Second, we only include RCTs which have recruited participants with moderate to severe hand function after stroke. This is because publications have provided us with convincing evidence that patients with baseline ability to control wrist and finger extension can achieve improvements in hand function and quality of life after receiving treatment procedures like modified CIMT[12 13]. However, there is no consensus on the effectiveness of intervention methods for stroke patients with more severely impaired hand function. Third, more and more clinical trials on this topic have been published in recent decades, and the time for a systematic review is now.

The results of this systematic review will provide a detailed summary of the current progress of evidence for interventions to improve hand motor function in individuals with moderate to severe stroke. Such a review can contribute by not only identifying the gaps, thus providing guidance for further research, but by also offering valuable information for therapeutics to help stroke survivors with impaired hand function.

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Contributors JY is the lead and the guarantor of this review. HWW and RA conceptualized the review and drafted the manuscript. HWW and RA developed the search strategy included in the protocol. JJ, LD and SGC revised the protocol critically. All authors read and provided feedback on the draft and approved the final manuscript.

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Supplementary Table 1 PRISMA checklist

Section and topic	Item No	Checklist item
Administrative information		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
Introduction		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
Methods		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

Item No	***1a***	***1b***	***2***	***3a***	***3b***	***4***	***5a***	***5b***	***5c***	***6***	***7***	***8***	***9***
Page	*1*	*/*	*1*	*9*	*9*	*/*	*9*	*/*	*/*	*3*	*4*	*5*	*6*
Line	*6*	*/*	*41*	*14*	*19*	*/*	*23*	*/*	*/*	*15*	*46*	*7*	*7*
Item No	***10***	***11a***	***11b***	***11c***	***12***	***13***	***14***	***15a***	***15b***	***15d***	***15c***	***16***	***17***
Page	*6*	*6*	*6*	*7*	*7*	*5*	*7*	*7*	*7*	*7*	*7*	*/*	*8*
Line	*19*	*51*	*56*	*10*	*14*	*48*	*26*	*47*	*45*	*50*	*53*	*/*	*9*