# Body-weight-supported gait training for mobility and quality of life in adults with acquired and congenital, non-progressive brain injuries: a systematic review

Bøgelund Pedersen, Morten; Esmann Fonvig, Christina; Aagaard, Per; Hansen, Gunhild Mo; Jørgensen, Karsten Juhl; Holsgaard-Larsen, Anders

*Publication date:*
2021

*Document version:*
Accepted manuscript

*Citation for pulished version (APA):*
Bøgelund Pedersen, M., Esmann Fonvig, C., Aagaard, P., Hansen, G. M., Jørgensen, K. J., & Holsgaard-Larsen, A. (2021). Body-weight-supported gait training for mobility and quality of life in adults with acquired and congenital, non-progressive brain injuries: a systematic review. PROSPERO. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=282642&VersionID=1614753

# Body-weight-supported gait training for mobility and quality of life in adults with acquired and congenital, non-progressive brain injuries: a systematic review

**Collaborators/authors:**
Morten Bøgelund Pedersen, MSc[1,2], Christina Esmann Fonvig, MSc[1,2], Per Aagaard, MSc, PhD, Professor[3], Gunhild Mo Hansen, MSc, PhD[4], Karsten Juhl Jørgensen, MSc, Professor[5], Anders Holsgaard Larsen, MSc, PhD, Professor[1,2]

**Affiliations:**
[1] Orthopaedic Research Unit, Department of Clinical Research, University of Southern Denmark, Odense, Denmark.
[2] Department of Orthopaedics and Traumatology, Odense University Hospital, Odense, Denmark.
[3] Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark.
[4] Hammel Neurorehabilitation Centre and University Research Clinic, Hammel, Denmark.
[5] Centre for Evidence-Based Medicine Odense, Odense University Hospital, Odense, Denmark.

**Corresponding author:**
Morten B. Pedersen, MSc; Orthopaedic Research Unit, Department of Clinical Research, University of Southern Denmark, Campusvej 55 DK-5230 Odense, Denmark.
E-mail: mlyngpedersen@health.sdu.dk / ORCiD: 0000-0001-5691-5734

**Funding:**
This work was supported by a core grant from the University of Southern Denmark through the SDU-Trinity research group and the Region of Southern Denmark (Grant nr: A965 - 10240367). No financial support or other benefits were obtained from commercial sources.

# Abstract

## Objective

To evaluate potential effects and harms associated with body-weight-supported gait training in adults with acquired or congenital, non-progressive brain injuries based on its effects on mobility, quality of life and adverse events.

## Methods

The systematic review will comprise randomised controlled trials of body-weight-support (BWS) gait training for adults with non-progressive brain injuries, identified through electronic searches of Cochrane CENTRAL, Medline and Embase. Any type of comparator will be considered. Reports will be restricted to English, French, or German languages. No restrictions will be imposed on type of BWS, methods of implementation, experimental setting, or content of the intervention. Two independent reviewers will select studies, extract data, and assess risk of bias and certainty of the evidence, using Covidence online tool, Cochranes Risk of Bias tool for randomised trials 2 (RoB-2), and the Grading of Recommendations Assessment, Development and Evaluation (GRADE), respectively. The primary outcome will be gait function (measured objectively using functional scales). Secondary measures will be walking speed, walking capacity, gait pathology and quality of life. The primary outcome for harm will be total number of withdrawals, with adverse events and serious adverse events as secondary outcomes. Extracted data will be synthesised using restricted maximum likelihood based (REML) random-effects meta-analyses. To explore possible causes of heterogeneity, subgroup analyses of the primary outcome (gait function) will be carried out for selected key study characteristics. To explore the impact of systematic errors, sensitivity analyses will be performed by applying subgroup analyses of RoB-2 domains as well as comparing a fixed-effect analysis to the result of the random-effects model.

## Perspectives and dissemination

The findings from this systematic review and meta-analysis are anticipated to have an impact on clinical practice both directly through knowledge dissemination and indirectly by helping clinical professionals and decision makers establish and employ guidelines and recommendations on the use of body-weight-supported gait training in adults with non-progressive brain injury. The results of this study will be disseminated through international peer-reviewed publication channels, scientific meetings, and presented for public outreach via suitable sources of social media.



## Keywords

Body-weight-support, gait training, rehabilitation, robotics, acquired brain injuries, congenital brain injuries, traumatic brain injuries.

# Introduction

## Background

Acquired and congenital non-progressive brain injuries (ABI, CBI), including stroke, traumatic brain injuries (TBI), and cerebral palsy (CP), can lead to motor impairments, often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour (1). Injuries can be focal or diffuse, with varying severity and location, ensuing a multitude of possible changes in functioning. Dependent on location and type, the injuries often affect motor function through spasticity, ataxia, or dyskinesia, limiting an independent lifestyle and leading to impairments in social life and employment opportunities (2-4). Compared to healthy peers, individuals with ABI or CBI typically lead a sedentary lifestyle (5, 6) with increased risk of chronic diseases, such as diabetes, hypertension, and cardiovascular conditions (7, 8). Altogether resulting in a reduced quality of life as well as higher risks of depression, and anxiety (9-11). Management strategies have been focused on increasing or maintaining physical performance with a life-course perspective that facilitates participation in everyday activities and preventing secondary complications (12, 13). More specific, current clinical practice has typically focused on improving gait performance and lower limb motor function through exercise and assisted resistance training.

Evolving technologies such as body-weight-support (BWS) training could have the potential to increase participation and quality of life by improving gait and motor function. During BWS the users are supported by a mechanism, such as an overhead suspension system, providing a reduction in apparent body weight while supporting vertical alignment and lateral stability of the trunk throughout the gait cycle (14, 15). This enables people with functional disabilities to perform complete gait cycles and engage in locomotor activities beyond their habitual functional capabilities (14, 16). The degree (% unloading in body mass) of BWS affects a number of kinetic, kinematic and spatio-temporal parameters of ambulation, most notably manifested as a reduction in lower limb joint moments, muscle activity, energy cost of walking, and reduced ground reaction forces (14, 17).

## Rationale and evidence-based research

To avoid scientific redundancy and ensure that the objective of the present study is overlapping with other current or planned systematic reviews, a pragmatic review of existing evidence has been performed (search date: 12 August 2021) in accordance to the Evidence-Based Research principles (18).

A pragmatic search of MEDLINE, EMBASE, Cochrane CENTRAL and PROSPERO was performed with the intent of uncovering existing and planned systematic reviews regarding BWS training in adults with non-progressive brain injury. Keywords for the PICO search strategy was derived from previous systematic reviews on exercise for patients with cerebral palsy (19), BWS for walking after stroke (20) and robot-assisted gait training for paediatric gait disorders (21), which were modified to include the target population and intervention (**Appendix 1**). The included keywords in the search strategy aimed to increase specificity, rather than sensitivity. The search strategies for all the databases are listed in **Appendix 2**. The search identified 425 citations, whereof 15 systematic reviews were deemed relevant (20-34). An overview of the systematic reviews is presented in **Appendix 3**.

The 15 systematic reviews identified as described above focused on robotic or mechanically assisted interventions, more specifically robotic-assisted gait training (21, 23, 27-32, 34), mechanically assisted gait training with or without BWS (24, 26), robotics in rehabilitation (22, 33) and BWS treadmill training (20, 25, 29). Only a limited number of patient groups were investigated, with 9 studies investigating stroke, 1 for neurological disorders, and 5 for cerebral palsy. The studies regarding stroke and general neurological disorder included older adults with a mean age of around 60 years, whereas all the studies on cerebral palsy included children only (<18 years). For the studies on cerebral palsy, the full range of Gross Motor Function Classification Scale (GMFCS) was represented, with grades I to IV included in 4 out of 5 studies.

Tefertiller et al. (32) were the only single study investigating neurological disorders as a patient group, with the remaining studies focusing on either adults with stroke or children with CP. No studies investigated the effect of BWS on non-progressive ABI or CBI, therefore

its effect could not be determined. For stroke and CP, most studies reported inconclusive effects, however with Lefmann et al. (21) reporting significant positive effects of BWS training on some subcategories of Gross Motor Function (GMFM), Garcia et al. (22) reporting major advantages for gait rehabilitation, and Mehrholz et al. (34) reporting increased odds for regaining independent walking ability. In general, the included reviews reported clinically insignificant or inconclusive effects on selected gait parameters, other mobility measures, physical activity, participation, and quality of life, spanning low-to-high certainty of evidence. When reported, no significant increase in adverse events were observed.

As the use of assistive devices for gait training are gaining widespread acceptance in the clinical practice, there is a growing need to confirm its credibility. A systematic review of the current literature could prove useful for healthcare practitioners and future guideline panels, enabling to make informed decisions on whether to encourage BWS gait training or not. Further, the present systematic review is intended to identify important key areas of BWS research, investigating the effect of different types of unloading protocols, which potentially could provide a supportive framework for future trials.

### Objectives

To evaluate the potential effects and harms associated with body-weight-supported gait training in adults with non-progressive brain injuries based on its effects on mobility, quality of life and adverse events.

## Methods

This protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for protocols (PRISMA-P) (35). Subsequently, the PRISMA 2020 statement and the guidelines put forward by Cochrane will be used to guide the reporting of the final systematic review and meta-analysis (36, 37). The present protocol has been registered at the International Prospective Register of Systematic Reviews (PROSPERO).

## Eligibility criteria

Randomised controlled trials (RCT) will be considered for inclusion. Reports must be peer-reviewed and published as full-text, thus excluding reports such as manuscripts and conference abstracts. Only reports written in English, French or German language will be included.

For a study to be considered eligible for inclusion, it must examine the benefits and/or harms of BWS gait training in adults diagnosed with acquired or congenital, non-progressive brain injury.

Participants must be adults with a reduced function of gait following an acquired or congenital non-progressive brain injury including stroke, traumatic brain injuries (TBI), and cerebral palsy (CP). For a study population to be considered adult, it must have a mean age of 18 or higher, with no participants younger than 15 years. This age limit was set as gait is considered matured at 15 years and to avoid excluding CBI trials, which often includes adolescents (38). Gait disabilities of any clinical manifestations are considered for inclusion, including changes in muscle tonus (e.g., spasticity and hypo-/hypertonicity), ataxia, or dyskinesia. ABI trials are expected to primarily include participants affected by stroke and traumatic brain injuries, with cerebral palsy being a dominant condition in CBI trials. No restrictions will be imposed on time since stroke onset or trauma event. For both ABI and CBI, any location and severity of brain damage will be considered eligible.

Interventions may use any type of BWS (e.g., static, dynamic) with or without the use of any assistive device (e.g., treadmill, Lokomat, gait trainer). No restrictions will be imposed on the setting (e.g., one-to-one, group), delivery (e.g., therapist, healthcare professional, self-training), structure (e.g., frequency, intensity), or method of follow-up (e.g., questionnaire, group discussion, telephone). Aquatic interventions will be excluded.

BWS gait training is defined as exercise that employ body-weight unloading during concurrent gait training using a mechanical device, provided through either an upwards pressure (e.g., weight reducing treadmill using positive air pressure to lift users), hoisting mechanism (e.g., equipping a user with a harness and providing an upwards lift through a ceiling mounted robot) or other types of mechanisms (e.g., Lokomat, exoskeleton). Non-

weight-bearing interventions, such as devices that deliver continuous passive motions only, will not be considered eligible.

Control comparisons of any type will be considered, including no intervention, sham gait training, alternative levels of unloading or an equal dose of gait training without BWS (with or without the help of therapists or walking aids). Sham gait training is defined as training for less than 30% of the duration, frequency or volume that the intervention group spent gait training. Studies providing usual care as a comparison also will be eligible as long as both groups are receiving equal amounts of training.

Eligible studies will be included independent of the outcome measures reported. Studies presenting insufficient data to be included in the quantitative analysis will be included in the qualitative evidence synthesis.

## Information sources

A search for relevant studies will be conducted in CENTRAL (Cochrane Library), MEDLINE (Ovid) and EMBASE (Ovid). Completed, withdrawn, or terminated studies will be identified through ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP). References cited in the included study reports and the systematic reviews uncovered in the preliminary search will be examined for relevant trials. Backwards and forward citation searches of study reports included in the systematic review will be performed through Web of Science. In addition, hand searching of relevant references will be performed.

## Search strategy

The search strategies for the databases were developed by the research group, then peer-reviewed by a research librarian not otherwise associated with the project. All search strategies were generated using PICO as presented in **Appendix 4**. The choice of keywords and Medical Subject Headings (MeSH) were based on the aim to increase sensitivity of the search, rather than specificity.

Adhering to the PICO guidelines, keywords and MeSH terms for the individual categories (Patient, Intervention, Comparison and Outcome) were derived from the systematic reviews uncovered in the preliminary search as well as a previous systematic review on

exercise for patients with cerebral palsy (19) and non-progressive brain injuries (39). The search strategy was modified to increase sensitivity by adding synonyms and keywords deemed relevant by the authors. Furthermore, the Ovid MeSH search engine was used to explore and specify MeSH terms.

To filter the search results for RCTs, The Cochrane Highly Sensitive Search Strategy for identifying randomised trials will be applied for the searches in MEDLINE and Embase, while CENTRAL will be filtered using the sites functions. The filter was modified to reduce the risk of excluding relevant records by removing the boolean operator "NOT" for filtering animal studies and unwanted study designs. Further, to reduce noise the keywords "open adj label" and "volunteer or volunteers" were removed from the Embase filter.

## Selection process

Duplicates between the searches in MEDLINE and EMBASE will be removed using Ovid's functions. Additionally, duplicates between the search results from all sources will be removed using EndNote's duplicate removal tool.

After removal of duplicates, the literature search results will be transferred to Covidence software, allowing reviewers to perform the selection process in a standardised manner. The initial screening of title and abstract and subsequent full text assessment will be performed independently by two reviewers (MBP, CEF) based on the inclusion and exclusion criteria. Any discrepancies between the two reviewers will be resolved through discussion or consultation with a third reviewer (AHL). In case that records contain insufficient data or lack transparency regarding their methods, the investigators will be contacted to in- or exclude the record.

Records published in languages not stated in the eligibility criteria will be excluded.

## Data collection

Data will be collected from included records by two reviewers (MBP, CEF) using standardised forms in Covidence, allowing reviewers to collect data independently. Any discrepancies will be resolved through discussion or consultation with a third reviewer (AHL).

Outcomes of interest reported as ordinal or continuous data will be collected as mean change scores with their corresponding measures of dispersion, with dichotomous outcomes being collected as number of events and number of participants. Records reporting their data only as final scores will have the data converted to change scores, following the methods for conversion described in Cochrane Handbook. If a record contains insufficient data for conversion to change scores, the corresponding author will be contacted by email to obtain additional data. Should contacted investigators fail to respond or supply sufficient data, means and measures of dispersion will be approximated from figures. If a change score cannot be obtained from figures, differences in mean values at the end of the treatment will be used (40).

## Data items

Eligible records will be assigned an ID number and have data extracted for general information, study methodology, demographic information, and details of the intervention as specified in **Appendix 5**.

The primary outcome of the present analysis will be gait function, examining the participants ambulation ability. Gait function will be measured using objective functional scales (e.g., Functional Ambulation Category, Gross Motor Function Measure, and Motor Assessment Scale) (**Table 1**). Secondary outcomes will be walking speed (measured in metres per second), walking capacity (measured in distance covered in a given time period, e.g., 6-minute walk test), gait pathology (measured using 3-dimensional gait analysis) and quality of life.

The primary measure for harm will be total number of withdrawals from respective studies. Secondary measures for harm will be adverse events and serious adverse events.

Data for outcomes will be collected at baseline and at 6 months follow-up. If outcomes are measured at multiple time-points, measurements obtained 6 months after intervention or at the closest possible time point, will be prioritised for the respective measures. Cross-over trials will have their data extracted from the first intervention period to avoid carry-over effects, regardless of the use of washout periods (41).

| Outcome domain | Outcome measure hierarchy |
|---|---|
| Gait function | FAC > GMFM-88 (E) > GMFM-66 (E) > MAS (walking item) > FIM (walking item) > Barthel Index (ambulation item) > FMS |
| Walking speed | 10-metre walk test > 8-metre walk test > other |
| Walking capacity | 6-minute walk test > other |
| Gait pathology | GDI > GPS > GVI > Other |
| Quality of life | EQ5D > HRQOL > SF-36 > other (e.g., MQOL, QOLS) |
| Harm | Ratio of participants experiencing events in three categories:<br>• Total number of withdrawals<br>• Adverse events<br>• Serious adverse events |

**Table 1**: Prioritised list of outcome domains with a corresponding hierarchical list of outcome measures.
EQ5D, European Quality of life 5-Dimensions; FAC, Functionel Ambulation Classificiation; FMS, Functionel Mobility Scale; GDI, Gait Deviation Index; GPS, Gait Pathology Score; GVI, Gait Variability Index; MAS, Motor Assessment Scale; FIM, Functional Independence Measure; GMFM, Gross Motor Function Measure 88 or 66 items (dimension E, walking running and jumping); HRQOL, Health Related Quality of Life; MQOL, McGill Quality of Life; SF-36, Short Form 36; QOLS, The Quality of Life Scale.

Should a record contain multiple results eligible for inclusion within an outcome domain, the outcome measures presented in the majority of records will be prioritised. If the records show heterogeneity in the choice of outcome measures, then the result will be prioritised based on the outcome measure hierarchy presented in **Table 1**. If the reported outcome measures are not listed in the outcome measure hierarchy, the study investigators will choose the most fitting outcome measure based on its contents and ability to measure the construct at hand.

## Risk of bias assessment

The risk of bias of included studies will be assessed by two independent reviewers (MBP, CEF) using Cochranes Risk of Bias tool for randomised trials 2 (RoB-2), which covers five domains: bias arising from the randomisation process, bias due to deviations from intended intervention, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result (42). Each domain will receive a risk of bias judgement of either **low risk of bias**, **some concerns** or **high risk of bias** based on the algorithms provided by RoB-2.

The included studies will receive an overall risk of bias, reflecting the trustworthiness of the presented results. A judgment of **low risk of bias** will be given if the study is judged to be at **low risk of bias** for all domains. A judgment of **some concerns** will be given if one or more domains of the study has been judged to raise **some concerns** but haven't been judged to be at **high risk of bias** for any domain. A judgement of **high risk of bias** will be

given if one or more domains has been judged to be at **high risk of bias**. If a study receives judgements of **some concerns** for multiple domains in a way that both reviewers consider having substantially lowered the confidence in the result, the overall risk of bias will be judged as **high risk of bias**.

Risk of bias will be assessed at the outcome level. If the study presents insufficient details for the review authors to determine the risk of bias for a given domain, the study investigators will be contacted by email for clarification. Any discrepancies between the two reviewers will be solved through discussion or by consultation with a third reviewer (AHL).

## Effect measures

Outcome domains examining benefits will be summarised using ordinal or continuous measures. Due to an anticipated heterogeneity in the outcome measures of the included records, data will be synthesised as standardised mean differences (SMDs) with corresponding 95% confidence intervals (CI). Should all the included records use the same measure for reporting, weighted mean differences (WMDs) with their corresponding 95% CI will be reported instead. Harm will be summarised as dichotomous data using relative risk (RR) with 95% confidence intervals.

To ease interpretation of the present analysis, outcome domains summarised as SMDs will be re-expressed as WMDs. The re-expressed estimates of effect will be calculated from the SMDs using standard deviations of baseline scores from studies investigating the minimal clinical important differences (MCID) in the target population. If no such studies can be located, standard deviations of baseline scores from studies included in the analyses will be used. Further, measures of harm reported as risk ratios will be re-expressed as absolute measures (e.g., risk difference). To evaluate the estimates importance for clinical decision makers, re-expressed effect estimates will be compared to available values for the minimal clinical important differences (MCID) of the reported outcome measure.

## Synthesis methods

*Eligibility for each synthesis* – Any record meeting the eligibility criteria will be included in the quantitative syntheses if the reported data are sufficiently detailed. To be included in a

synthesis, a record must report a mean difference with its corresponding variance, or present other types of data allowing for conversion into group mean differences and related variances. Records will be excluded from quantitative analysis if the intervention and control therapies are deemed to be too similar, making it difficult to discern the true benefit of the target intervention (e.g., 30% unloading of body weight compared to 20% unloading of body weight).

*Data for presentation or synthesis* – Records reporting data as mean differences and variance between baseline and final scores will have their data extracted and synthesised directly. Any other type of reported data will be converted into group mean differences with corresponding variances as recommended by Cochrane (43). Records only reporting a variance for baseline and final scores, omitting variance for change scores, will have the variance for change imputed following Cochrane recommendations, using a correlation coefficient calculated from other included studies. In case a correlation coefficient cannot be established, a r-value of 0.75 will be applied. Due to an anticipated low occurrence of adverse events, the dichotomous measures for harm will be adjusted using the continuity correction by Sweeting et al. (44). To avoid double counting of participants, any trials having more than one eligible intervention group will have its control group divided by the number of comparison groups.

*Data used to tabulate or visually display results* – In general, all tables and figures displaying the included records will be structured alphabetically based on the authors names. A flowchart will depict the undertaken process of identifying records for inclusion in the review and meta-analysis. Forest plots will be presented for the primary outcome of benefit (gait function) and harm (total number of withdrawals), displaying the effect estimates and confidence intervals of each record. Additional forest plots and funnel plots will be attached as supplementary files. A table will display the key characteristics of the individual records included in the qualitative synthesis. This will include the author name, year published, participant characteristics (e.g., age), number of participants included, gender distribution, intervention details (e.g., BWS method, primary technology used, dosage/intensity, educational background of trial personnel), and comparison details (e.g., method of comparison, description). The Grading of Recommendations Assessment,

Development and Evaluation (GRADE) evidence profile will be presented through a summary of findings table (SoF). For each outcome, the SoF table will display the number of trials and patients included in the synthesis, an overview of the individual levels of risk of bias, relative effect estimates, evaluation of certainty of the evidence, absolute effect size, and GRADE assessment per outcome. Stratified analyses will be tabulated. For each stratification, the table will display the number of records included in the analysis, estimated effect and measures for variance ($T^2$) and inconsistency ($I^2$). The risk of bias assessment will be tabulated on the trial level and presented in a supplementary file.

*Synthesis of results* – Data will be synthesised using restricted maximum likelihood (REML) based random-effects meta-analyses (45). The heterogeneity across studies will be assessed and interpreted using the $Tau^2$ and $I^2$ inconsistency index. $I^2$ values of less than 25% will be interpreted as having a low between trial heterogeneity, with values above 75% being interpreted as substantial. Due to the potential difference in study characteristics, some clinical heterogeneity is anticipated. Therefore, random effects meta-analysis will be used per default to synthesize the results of the included studies (46). All statistical analyses will be conducted using Stata version 16 or newer.

*Subgroup analyses* – Meta-analyses is likely to be inconclusive due to the observed heterogeneity between trials. To explore the possible causes of heterogeneity among study results and further investigate the impact of population and intervention characteristics, stratified analyses of the primary outcome (gait function) will be performed using REML-based random-effects meta-analysis at the single-study level (each study is included in one subgroup only). Studies will be categorised based on the majority (≥70%) of patient or intervention characteristics at baseline of the following:

Ambulatory status; The achieved effect of an intervention may be affected by the participants ambulatory status at baseline:

- Ambulatory participants (FAC score ≥4, or other indicators)
- Non-ambulatory participants (FAC score ≤3, or other indicators)
- Mixed participants

Type of condition; participants type of condition may reflect their ability to participate in gait related activities, thereby affecting the outcome of the study:

- Acquired brain injury (non-traumatic)
- Traumatic brain injury
- Congenital brain injury

Condition phase; participants in the acute phase of their condition may experience a higher amount of spontaneous recovery than participants in the chronic phase:

- Acute (within three months)
- Chronic (longer than three months)
- Mixed

Extent of condition; participants type of condition may reflect their ability to participate in gait related activities, thereby affecting the outcome of the study:

- Unilateral (e.g., hemiplegia)
- Bilateral (e.g., paraplegia, tetraplegia)
- Mixed

Method of delivery; interventions make use of varying methods when applying body-weight-unloading mechanisms, some technologies may affect the participants differently:

- Treadmill (e.g., Alter G)
- Stationary platforms (e.g., Lokomat)
- Mobile platforms (e.g., LiteGait, Andago)
- Ceiling mounted systems (e.g., Ergo-Trainer, Bioness Vector)
- Other (e.g., exoskeleton)

Unloading mechanism; the type of body-weight-unloading mechanism applied may affect the quality of the content of the intervention:

- Positive air pressure (e.g., Alter G)
- Static unloading (e.g., LiteGait)
- Pneumatic unloading (e.g., Ergo-Trainer, LiteGait)
- Dynamic unloading (e.g., Bioness vector)
- Total body unloading (e.g., lokomat)
- Other (e.g., exoskeleton)

Comparator/control; the type of control group may affect the outcome of the study:

- Usual care
- Waitlist
- Sham therapy
- Comparison therapy (e.g., gait training without BWS)
- Other

Approach in delivery; the personnel applying the intervention may have varying types of educational backgrounds, affecting the measured effect of the intervention:

- Physical therapist
- Other personnel (e.g., nurse, occupational therapist, exercise physiologist)
- Self-applied
- Other

REML-based meta-regression-analyses will be conducted to explore the relationship between the following variables and the effect size of BWS training in the included studies:

- Mean age at baseline
- Gait function at baseline
- Walking capacity at baseline (measured in metres)
- Health related quality of life at baseline (normalised to VAS units)
- Extent of intervention (the total number of hours spent on training)
- Length of intervention (the total length of the intervention in days)

*Sensitivity analysis* –Sensitivity analysis will be performed to estimate the potential impact of systematic errors from risk of bias across studies. Analyses will be performed on the domain level of RoB-2 as well as the overall risk of bias, stratifying studies based on their received judgment of low risk of bias, some concerns or high risk of bias. As random-effects meta-analyses can appear more effective when including small studies (small-study bias), a fixed-effect meta-analysis will be applied to investigate the sensitivity of the random-effects analysis. Should the point estimate of the fixed-effect meta-analysis not be included in the 95% CI of the random-effects model, the certainty of the evidence will be rated down. To adjust for small-sample bias, Hedge's g value will be applied to meta-analyses (47, 48).

## Assessment of reporting bias

To assess publication bias, funnel plots and Egger's test will be applied for meta-analyses including at least 10 trials. Two study authors (MBP, CES) will independently assess the

funnel plots for asymmetry. Should either the funnel plot or Egger's test indicate the presence of reporting bias, the certainty in evidence in the effect measure will be rated down. Outcome reporting bias will be investigated through comparing the outcomes specified in the trial protocols with the reported outcomes in the corresponding record. If no protocol is available, the outcomes reported in the method section will be compared to the results section of the record.

### Certainty assessment

The certainty of the evidence will be assessed using the GRADE tool, assessing each outcome domain for risk of bias, imprecision, inconsistency, indirectness, and other consideration (e.g., publication bias) (49). Each outcome will receive an overall judgment of whether the evidence supporting the reported data is of high, moderate, low, or very low certainty. The GRADEpro GDT software will be used to prepare the SoF table.

## Ethical considerations and dissemination

The findings and conclusions from the present systematic review and meta-analysis are anticipated to have an impact on clinical practice both directly through knowledge dissemination and indirectly by helping discission makers shape guidelines and recommendations on the use of body-weight-unloading gait training for adults with acquired and congenital, non-progressive brain injuries. The results of this study will be disseminated through a peer-reviewed article, scientific meetings, and presented for public outreach via suitable sources.

In accordance with ICMJE standards, this study will be drafted by the primary investigator (MBP) and revised critically by collaborators, who will be co-authors after providing a substantial contribution through; design or conception of the work, drafting the work or revising it critically for important intellectual content, and approving the final version to be published. All authors agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Contributors

MBP and AHL conceived and designed the study; MBP, CES and AHL contributed to the development of the protocol. MBP, CES, GMH, PAA, KJJ and AHL assisted in the final protocol and agreed to its final approval before submission.


## Funding

This work was supported by a core grant from the University of Southern Denmark through the SDU-Trinity research group and the Region of Southern Denmark (Grant nr: A965 - 10240367). No financial support or other benefits were obtained from commercial sources.


## Competing interests

This study has no financial or commercial interests to declare.

## References


1. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007;49(6):480.
2. Michelsen SI, Uldall P, Hansen T, Madsen M. Social integration of adults with cerebral palsy. Dev Med Child Neurol. 2006;48(8):643-9.
3. Michelsen SI, Uldall P, Kejs AMT, Madsen M. Education and employment prospects in cerebral palsy. Dev Med Child Neurol. 2005;47(8):511-7.
4. Ashman T, Gordon W, Cantor J, Hibbard M. Neurobehavioral consequences of traumatic brain injury. Mt Sinai J Med. 2006;73(7):999-1005.
5. Aviram R, Harries N, Rabani AS, Amro A, Nammourah I, Al-Jarrah M, et al. Comparison of Habitual Physical Activity and Sedentary Behavior in Adolescents and Young Adults With and Without Cerebral Palsy. Pediatr Exerc Sci. 2018;31(1):60-6.
6. Wondergem R, Veenhof C, Wouters EMJ, de Bie RA, Visser-Meily JMA, Pisters MF. Movement Behavior Patterns in People With First-Ever Stroke. Stroke. 2019;50(12):3553-60.
7. Peterson MD, Ryan JM, Hurvitz EA, Mahmoudi E. Chronic Conditions in Adults With Cerebral Palsy. JAMA. 2015;314(21):2303-5.
8. Shavelle R, Strauss D, Whyte J, Steven D, Yuk L. Long-Term Causes of Death After Traumatic Brain Injury. Am J Phys Med Rehabil. 2001;80(510-516).
9. Smith KJ, Peterson MD, O'Connell NE, Victor C, Liverani S, Anokye N, et al. Risk of Depression and Anxiety in Adults With Cerebral Palsy. JAMA Neurol. 2019;76(3):294-300.
10. Colver A, Rapp M, Eisemann N, Ehlinger V, Thyen U, O Dickinson H, et al. Self-reported quality of life of adolescents with cerebral palsy: a cross-sectional and longitudinal analysis. Lancet. 2015;385(9969):705-16.
11. Scholten A, Haagsma J, Cnossen M, Olff M, van Beeck E, Polinder S. Prevalence of and Risk Factors for Anxiety and Depressive Disorders after Traumatic Brain Injury: A Systematic Review. J Neurotrauma. 2016;33(22):1969-94.
12. Morris T, Tormos Muñoz JM, Cattaneo G, Solana-Sánchez J, Bartrés-Faz D, Pascual-Leone A. Traumatic Brain Injury Modifies the Relationship Between Physical Activity and Global and Cognitive Health: Results From the Barcelona Brain Health Initiative. Front Behav Neurosci. 2019;13:135.
13. Stroke Foundation. Clinical Guidelines for Stroke Management. Melbourne Australia. 2021.
14. Apte S, Plooij M, Vallery H. Influence of body weight unloading on human gait characteristics: a systematic review. Journal of NeuroEngineering and Rehabilitation. 2018;15(1):53.
15. Dragunas AC, Gordon KE. Body weight support impacts lateral stability during treadmill walking. J Biomech. 2016;49(13):2662-8.
16. Klobucká S, Klobucký R, Kollár B. Effect of robot-assisted gait training on motor functions in adolescent and young adult patients with bilateral spastic cerebral palsy: A randomized controlled trial. NeuroRehabilitation. 2020;47(4):495-508.

17. Sousa CO, Barela JU, Prado-Medeiros CL, Salvini TF, Barela AMF. The use of body weight support on ground level: an alternative strategy for gait training of individuals with stroke. J Neuroeng Rehabil. 2009;6:43.
18. Lund H, Brunnhuber K, Juhl C, Robinson K, Leenaars M, Dorch BF, et al. Towards evidence based research. BMJ. 2016;355:i5440.
19. Ryan JM, Cassidy EE, Noorduyn SG, O'Connell NE. Exercise interventions for cerebral palsy. Cochrane Database Syst Rev. 2017;6(6).
20. Mehrholz J, Pohl M, Elsner B. Treadmill training and body weight support for walking after stroke. Cochrane Database Syst Rev. 2014;2014(1):CD002840.
21. Lefmann S, Russo R, Hillier S. The effectiveness of robotic-assisted gait training for paediatric gait disorders: systematic review. J Neuroeng Rehabil. 2017;14(1).
22. Garcia LL, González YG, Carrera IDC, Calvete AA. [Benefits of robotics in gait rehabilitation in cerebral palsy: A systematic review]. Rehabilitacion (Madr). 2020;54(2):128-36.
23. Colomera JA, Nahuelhual P. [Effectiveness of robotic assistance for gait training in children with cerebral palsy. a systematic review]. Rehabilitacion (Madr). 2020;54(2):107-15.
24. Chiu H-C, Ada L, Bania TA. Mechanically assisted walking training for walking, participation, and quality of life in children with cerebral palsy. Cochrane Database Syst Rev. 2020;11:CD013114.
25. Mutlu A, Krosschell K, Spira DG. Treadmill training with partial body-weight support in children with cerebral palsy: a systematic review. Dev Med Child Neurol. 2009;51(4):268-75.
26. Ada L, Dean CM, Vargas J, Ennis S. Mechanically assisted walking with body weight support results in more independent walking than assisted overground walking in non-ambulatory patients early after stroke: a systematic review. J Physiother. 2010;56(3):153-61.
27. Calabrò RS, Sorrentino G, Cassio A, Mazzoli D, Andrenelli E, Bizzarini E, et al. Robotic-assisted gait rehabilitation following stroke: a systematic review of current guidelines and practical clinical recommendations. Eur J Phys Rehabil Med. 2021;57(3):460-71.
28. Nedergård H, Arumugam A, Sandlund M, Brändal A, Häger CK. Effect of robotic-assisted gait training on objective biomechanical measures of gait in persons post-stroke: a systematic review and meta-analysis. J Neuroeng Rehabil. 2021;18(1):64.
29. Schröder J, Truijen S, Van Criekinge T, Saeys W. Feasibility and effectiveness of repetitive gait training early after stroke: A systematic review and meta-analysis. J Rehabil Med. 2019;51(2):78-88.
30. Swinnen E, Beckwée D, Meeusen R, Baeyens JP, Kerckhofs E. Does robot-assisted gait rehabilitation improve balance in stroke patients? A systematic review. Top Stroke Rehabil. 2014;21(2):87-100.
31. Tedla JS, Dixit S, Gular K, Abohashrh M. Robotic-Assisted Gait Training Effect on Function and Gait Speed in Subacute and Chronic Stroke Population: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Eur Neurol. 2019;81(3-4):103-11.
32. Tefertiller C, Pharo B, Evans N, Winchester P. Efficacy of rehabilitation robotics for walking training in neurological disorders: a review. J Rehabil Res Dev. 2011;48(4):387-416.

33. Zheng QX, Ge L, Wang CC, Ma QS, Liao YT, Huang PP, et al. Robot-assisted therapy for balance function rehabilitation after stroke: A systematic review and meta-analysis. Int J Nurs Stud. 2019 95:7-18.
34. Mehrholz J, Thomas S, Kugler J, Pohl M, Elsner B. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2020;10(10):CD006185.
35. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1).
36. Page M, McKenzie J, Bossuyt P, Boutron I, Hoffmann T, Mulrow C. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
37. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2021.
38. Froehle AW, Nahhas RW, Sherwood RJ, Duren DL. Age-related changes in spatiotemporal characteristics of gait accompany ongoing lower limb linear growth in late childhood and early adolescence. Gait Posture. 2013;38(1):14-9.
39. Longley V, Hazelton C, Heal C, Pollock A, Woodward-Nutt K, Mitchell C, et al. Non-pharmacological interventions for spatial neglect or inattention following stroke and other non-progressive brain injury. Cochrane Database Syst Rev. 2021;7(7):CD003586.
40. Costa BRd, Nüesch E, Rutjes AW, Johnston BC, Reichenbach S, Trelle S, et al. Combining follow-up and change data is valid in meta-analyses of continuous outcomes: a meta-epidemiological study. J Clin Epidemiol. 2013;66(8):847-55.
41. Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. Int J Epidemiol. 2002;31(1):140-9.
42. Sterne J, Savović J, Page M, Elbers R, Blencowe N, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366(l4898).
43. Higgins JPT, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021.
44. Sweeting M, Sutton A, Lambert P. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23(9):1351-75.
45. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7(3):177-88.
46. Riley R, Higgins J, Deeks J. Interpretation of random effects meta-analyses. BMJ. 2011;342(d549).
47. Hedges L. Distribution Theory for Glass's Estimator of Effect Size and Related Estimators. Journal of Educational Statistics. 1981;6(2):107-28.
48. Murad M, Wang Z, Chu H, Lin L. When continous outcomes are measured using different scales: guide for meta-analysis and interpreation. BMJ. 2019;364.
49. Guyatt GH, Oxman A, Akl E, Kunz R, Vist G, Brozek J. GRADE guidelines: 1. Introduction-Grade evidence profiles and summary of findings tables. J Clin Epidemiol.64(4):383-94.

# Appendix

## Appendix 1: PICO search strategy

| Population | Intervention | Comparison | Outcome |
|---|---|---|---|
| Brain injury<br>Brain damage<br>Stroke<br>Cerebral palsy | Body-weight-unloading<br>Robotic exercise<br>Gravity supported exercise<br>Gravity reduced exercise<br>Aquatic exercise | Any | Gait quality<br>Gait speed<br>Quality of life<br>Functional performance and activity |

# Appendix 2: Search strategies for uncovering current systematic reviews

## (search date: 12 August 2021)

**Search strategy of individual keywords for MEDLINE through Ovid**

| Nr. | Keyword |
|---|---|
| #1 | stroke/ |
| #2 | stroke.ti,ab. |
| #3 | (brain adj3 (damage or injury)).ti,ab. |
| #4 | cerebral palsy/ |
| #5 | OR #1-#4 |
| #6 | (weight adj3 support).ti,ab. |
| #7 | unloading.ti,ab. |
| #8 | gravity.ti,ab. |
| #9 | aquatic.ti,ab. |
| #10 | robot*.ti,ab. |
| #11 | OR #6-#10 |
| #12 | review.ti. |
| #13 | #5 AND #11 AND #12 |

**Search strategy of individual keywords for EMBASE through OVID**

| Nr. | Keyword |
|---|---|
| #1 | stroke/ |
| #2 | stroke.ti,ab. |
| #3 | (brain adj3 (damage or injury)).ti,ab. |
| #4 | cerebral palsy/ |
| #5 | OR #1-#4 |
| #6 | (weight and support).ti,ab. |
| #7 | unloading.ti,ab. |
| #8 | gravity.ti,ab. |
| #9 | aquatic.ti,ab. |
| #10 | robot*.ti,ab. |
| #11 | OR #6-#10 |
| #12 | review.ti. |
| #13 | #5 AND #11 AND #12 |

**Searchstrategy of individual keywords for CENTRAL through Cochrane Library**

| Nr. | Keyword |
|---|---|
| #1 | Stroke:ti,ab,kw |
| #2 | (brain near/3 (damage or injury)):ti,ab,kw |
| #3 | (cerebral palsy):ti,ab,kw |
| #4 | OR #1-#3 |
| #5 | (weight and support):ti,ab |
| #6 | unloading:ti,ab |
| #7 | gravity:ti,ab |
| #8 | aquatic:ti,ab |
| #9 | robot*:ti,ab |
| #10 | OR #5-#9 |
| #11 | #4 AND #10 |
| | #8 filtered for systematic reviews using the sites functions |

# Appendix 3: Overview of current systematic reviews

| | |
|---|---|
| **Title** | Mechanically assisted walking with body weight support results in more independent walking than assisted overground walking in non-ambulatory patients early after stroke: a systematic review |
| **Study type** | Systematic review of RCTs and quasi-RCTs. |
| **Participants** | Subacute, non-ambulatory, adults with stroke (mean age 65 years) |
| **Intervention** | Any type of mechanically assisted walking training (e.g. treadmill, robotic device or servomotor) with body weight support through a harness. |
| **Outcomes** | Independent walking (primary), walking speed, walking capacity. |
| **Recommendations regarding body-weight-unloading** | Effect on independent walking: Increased (RD = 0.24, 95% CI 0.13 to 0.34)<br>Effect on waling speed: Increased by 0.12 m/s (95% CI 0.02 to 0.21)<br>Effect on walking capacity: Increased by 35 m (95% CI -13 to 84)<br><br>Mechanically assisted walking results in more independent walking after 4 weeks of intervention in patients who cannot walk within the first month after stroke. Importantly, this increase is without detriment to walking speed or capacity. Further, benefits appear to be maintained at 6 months, with walking capacity and speed being superior in those who received mechanically assisted walking during inpatient rehabilitation. |
| **Evidence base for recommendation** | 6 studies included in quantitative and qualitative analysis, including a total of 549 participants.<br>Based on a PEDro assessment, the evidence is of moderate to good quality. |
| **Reference** | Ada L, Dean CM, Vargas J, Ennis S. Mechanically assisted walking with body weight support results in more independent walking than assisted overground walking in non-ambulatory patients early after stroke: a systematic review. J Physiother 2010;56(3):153-61 |

| | |
|---|---|
| **Title** | Robotic-assisted gait rehabilitation following stroke: a systematic review of current guidelines and practical clinical recommendations |
| **Study type** | Systematic review of guidelines and practical clinical recommendations. |
| **Participants** | Adults with stroke |
| **Intervention** | Robot assisted gait training |
| **Outcomes** | Independent walking (primary), walking speed, walking capacity. |
| **Recommendations regarding body-weight-unloading** | in more severely impaired people with stroke, RAGT increases the possibility to regain an independent gait, and this should be considered as either “add on” treatment or even in substitution of the traditional rehabilitation.<br>The improvement in gait recovery with electromechanically assisted gait could be explained by the fact that the intervention provides the opportunity to perform a more intensive, repetitive, and task-oriented training than would be possible with the conventional over-ground walking alone. |
| **Evidence base for recommendation** | 10 international guidelines were included in a qualitative analysis.<br>Based on an AGREE II assessment, there was a large heterogeneity of quality between the included guidelines. |
| **Reference** | Calabrò et al. Robotic-assisted gait rehabilitation following stroke: a systematic review of current guidelines and practical clinical recommendations. European Journal of Physical and Rehabilitation Medicine 2021; 57(3):460-71 |

| | |
|---|---|
| **Title** | Mechanically assisted walking training for walking, participation, and quality of life in children with cerebral palsy. |
| **Study type** | Systematic review of RCTs and quasi-RCTs. |

| | |
|---|---|
| **Participants** | Cerebral Palsy. Aged 4 to 14. GMFCS I – IV. Able to understand simple instructions. |
| **Intervention** | Any type of mechanically assisted walking training (e.g. treadmill, Lokomat, gait trainer) with or without body weight support. |
| **Outcomes** | Mobility (primary), gross motor function (primary), participation, quality of life and adverse events (primary) |
| **Recommendations regarding body-weight-unloading** | Effect on mobility: Insignificant improvements (0.07 m/s faster, 95% CI; 0.05-0.09)<br>Effect on gross motor function: No improvements (1.09% increase, 95% CI; -0.57-2.75)<br>Effect on participation: No improvements (0.33 SD higher, 95% CI; -0.27-0.93)<br>Effect on quality of life: No improvements (9.50 points higher, 95% CI; -4.03-23.03)<br>Adverse events: No difference between groups.<br><br>Mechanically assisted walking can provide high-dose, repetitive training. It may be a useful way to provide practice for younger children with poor concentration when it is hard to apply the same dose of overground walking. |
| **Evidence base for recommendation** | 17 studies included in quantitative and qualitative analysis, including a total of 451 participants.<br>Based on a GRADE assessment, the evidence is of moderate- and low-quality. |
| **Reference** | Chiu H-C, Ada L, Bania TA. Mechanically assisted walking training for walking, participation, and quality of life in children with cerebral palsy. Cochrane Database of Systematic Reviews 2020;11:CD013114 |

| | |
|---|---|
| **Title** | [Effectiveness of robotic assistance for gait training in children with cerebral palsy. a systematic review] (Spanish) |
| **Study type** | Systematic review of RCTs and quasi-RCTs. |
| **Participants** | Cerebral Palsy. Aged 4 to 17. GMFCS I – III. |
| **Intervention** | Robotic assistance systems for gait training. |
| **Outcomes** | Based on the International Classification of Functioning, Health and Disability (ICF) |
| **Recommendations regarding body-weight-unloading** | Effect on Activity (ICF): Inconclusive.<br>Included studies did not report on other ICF components. |
| **Evidence base for recommendation** | 4 studies included in qualitative analysis, including 144 participants. 0 in quantitative analysis. |
| **Reference** | Colomera JA, Nahuelhual P. [Effectiveness of robotic assistance for gait training in children with cerebral palsy. a systematic review]. Rehabilitacion (Madr) 2020;43(2):107-115 |

| | |
|---|---|
| **Title** | [Benefits of robotics in gait rehabilitation in cerebral palsy: A systematic review] (Spanish) |
| **Study type** | Systematic review of any type of study |
| **Participants** | Cerebral palsy. Aged 5 to 18. GMFCS I – IV. |
| **Intervention** | Robotics in gait rehabilitation |
| **Recommendations regarding body-weight-unloading** | The use of robotics for gait rehabilitation in cerebral palsy provides major advantages. |
| **Evidence base for recommendation** | 10 studies and 3 protocols included in analyses. |
| **Reference** | Garcia LL, González YG, Carrera IDC, Calvete AA. [Benefits of robotics in gait rehabilitation in cerebral palsy: A systematic review]. Rehabilitacion (Madr) 2020;54(2):128-136. |

| | |
|---|---|
| **Title** | The effectiveness of robotic-assisted gait training for paediatric gait disorders: systematic review |
| **Study type** | Systematic review of RCTs. |
| **Participants** | Primarily Cerebral palsy, however, some studies reported gait disorders of any aetiology (neurological, orthopaedic or developmental). Aged ≤17 (mean 9.8 years). GMFCS I – V. |
| **Intervention** | Any type of robot assisted gait training (RAGT) applied for more than 1 session. |
| **Outcomes** | Gait speed (primary), functional gross motor performance, participation, body structure and function, adverse events (primary) |
| **Recommendations regarding body-weight-unloading** | Effect on gait speed: No improvements (SMD 0.11, 95% CI -0.48-0.70)<br>Effect on functional gross motor performance: Item D and E of the GMFM showed a significant improvement. Some of the included studies showed a positive increase on 6 min walking test. (no data reported)<br>Effect on participation: Significant difference post intervention (no data reported)<br>Effect on body structure and function: Some aspects of balance was improved (no data reported)<br>Adverse events: Few mild-to-moderate adverse events were reported.<br><br>The overall evidence is considered weak and inconsistent for the effectiveness of RAGT for children with gait disorders. |
| **Evidence base for recommendation** | 17 studies included in quantitative and qualitative analysis, including a total of 486 participants.<br>Included trials were generally of high risk of bias. |
| **Reference** | Lefmann S, Russo R, Hillier S. The effectiveness of robotic-assisted gait training for paediatric gait disorders: systematic review . J Neuroeng Rehabil. 2017;14(1):1 |

| | |
|---|---|
| **Title** | Electromechanical-assisted training for walking after stroke (Review) |
| **Study type** | Systematic review of RCTs and quasi-RCTs. |
| **Participants** | Adults with stroke (mean age from 47 to 76 years) |
| **Intervention** | Electromechanical- or robot-assisted gait training, |
| **Outcomes** | Independent walking (primary), walking speed, walking capacity, adverse events. |
| **Recommendations regarding body-weight-unloading** | Effect on independent walking: 2.01 OR (95% CI 1.51 to 2.69)<br>Effect on waling speed: Increased by 0.07 m/s (95% CI -0.03 to 0.17)<br>Effect on walking capacity: Increased by 7.76 m (95% CI -21.47 to 36.99)<br><br>This Cochrane Review provides high-quality evidence that the use of electromechanical-assisted gait-training devices in combination with physiotherapy increases the chance of regaining independent walking ability among people after stroke. These results could be interpreted as preventing one participant from remaining dependent in walking after stroke for every eight treated. However, this apparent benefit for patients is not supported by our secondary outcomes. Gait-training devices were associated with improvement in walking velocity (low-quality evidence) but not in walking capacity (moderate-quality evidence). It seems that the greatest benefits with regard to independence in walking and walking speed were achieved by participants who were non-ambulatory at the start of the study and by those for whom the intervention was applied early post stroke. |
| **Evidence base for recommendation** | 62 studies included in quantitative and qualitative analysis, including a total of 2440 participants.<br>Based on a GRADE assessment, the evidence is of low to high quality. |
| **Reference** | Mehrholz J, Thomas S, Kugler J, Phol M, Elsner B. Electromechanical-assisted training for walking after stroke (Review). Cochrane Database Syst Rev 2020;(10):CD006185 |

| | |
|---|---|
| **Title** | Treadmill training and body weight support for walking after stroke (Review) |
| **Study type** | Systematic review of RCTs and quasi-RCTs. |
| **Participants** | Adults with stroke having an abnormal gait pattern (average age 60 years) |
| **Intervention** | Treadmill training and body weight support, individually or in combination, |
| **Outcomes** | Dependence on personal assistance (primary), independent walking speed (primary), independent walking endurance (primary), quality of life, ADL, death/dependency, death/institutional care. |
| **Recommendations regarding body-weight-unloading** | Effect on waling speed: Increased by 0.06 m/s (95% CI 0.03 to 0.09)<br>Effect on walking capacity: Increased by 14.19 m (95% CI 2.92 to 25.46)<br><br>People who receive treadmill training, with or without body weight support, are not more likely to improve their ability to walk independently, but their speed of walking and their walking capacity may improve. More specifically, those who are able to walk independently (but not those who are unable to walk independently) seem to benefit from this type of intervention. This review found that improvements in walking speed and endurance in people who are able to walk independently have no persisting beneficial effects. |
| **Evidence base for recommendation** | 56 studies included in quantitative and qualitative analysis, including a total of 3105 participants.<br>Based on a GRADE assessment, the evidence is of moderate quality. |
| **Reference** | Mehrholz J, Phol M, Elsner B. Treadmill training and body weight support for walking after stroke (Review). Cochrane Database Syst Rev 2014;2014(1):CD002840 |

| | |
|---|---|
| **Title** | Treadmill training with partial body-weight support in children with cerebral palsy: a systematic review |
| **Study type** | Systematic review of any study designs, including case reports. |
| **Participants** | Cerebral Palsy. Aged 1.7 to 18. GMFCS I – IV. |
| **Intervention** | Partial body-weight support treadmill training (PBWSTT) |
| **Outcomes** | Based on the International Classification of Functioning, Health and Disability (ICF) |
| **Recommendations regarding body-weight-unloading** | Effect on gross motor function: Inconclusive<br>Effect on functions other than gait: Inconclusive<br><br>Studies did not report on other ICF components.<br><br>It is unclear whether PBWSTT results in improvements for children with cerebral palsy. |
| **Evidence base for recommendation** | 7 studies included in quantitative and qualitative analysis, including a total of 41 participants.<br>The overall level of evidence was low. |
| **Reference** | Mutlu A, Krosschell K, Spira DG. Treadmill training with partial body-weight support in children with cerebral palsy: a systematic review. Dev Med Child Neurol. 2009;51(4):268-75 |

| | |
|---|---|
| **Title** | Effect of robotic-assisted gait training on objective biomechanical measures of gait in persons post-stroke: a systematic review and meta-analysis |
| **Study type** | Systematic review of RCTs. |
| **Participants** | Adults with any stage of stroke (average age 60.5 years) |
| **Intervention** | Robotic-Assisted Gait Training |
| **Outcomes** | Temporal, spatial, kinematic and kinetic parameters |
| **Recommendations regarding body-weight-unloading** | Effect on waling speed: Increased by 0.00 m/s (95% CI -0.05 to 0.05)<br>Effect on walking cadence: Increased by 1.44 steps/min (95% CI 2.34 to 5.22) |

| | |
|---|---|
| | Our findings demonstrated a very low certainty in current evidence for employing RAGT instead of non-robotic gait training to improve gait ability post-stroke. |
| **Evidence base for recommendation** | 13 studies included in quantitative and qualitative analysis, including a total of 412 participants.<br>Based on a GRADE assessment, the evidence is of very low to low quality. |
| **Reference** | Nedergård H, Arumugam A, Sandlund M, Brråndal A, Häger CK. Effect of robotic-assisted gait training on objective biomechanical measures of gait in persons post-stroke: a systematic review and meta-analysis. J NeuroEngineering Rehabil. 2021:18(64) |

| | |
|---|---|
| **Title** | Feasibility and effectiveness of repetitive gait training early after stroke: a systematic review and meta-analysis |
| **Study type** | Systematic review of RCTs. |
| **Participants** | Adults with any stage of stroke |
| **Intervention** | Robotic-Assisted Gait Training and Body weight supported treadmill training |
| **Outcomes** | Temporal, spatial, kinematic and kinetic parameters |
| **Recommendations regarding body-weight-unloading** | Repetitive gait training appears feasible and safe. Such training can lead to long-term functional improvements if provided early, but these effects are small. In sub-analyses, RAGT provided with an end-effector appears most effective and it seems that the more impaired patients benefit most. However, analyses on body function level yielded neutral effects and consequently the mechanisms underlying functional gains achieved after augmented gait training remain poorly understood. |
| **Evidence base for recommendation** | 15 studies included in quantitative and qualitative analysis, including a total of 915 participants. |
| **Reference** | Schröder J, Truijen S, Criekinge TV, Saeys W. Feasibility and effectiveness of repetitive gait training early after stroke: a systematic review and meta-analysis. J Rehabil Med. 2019;51(2):78-88 |

| | |
|---|---|
| **Title** | Does robot-assisted gait rehabilitation improve balance in stroke patients? A systematic review |
| **Study type** | Systematic review of RCTs and quasi-RCTs |
| **Participants** | Adults with any stage of stroke (average age 59.2 years) |
| **Intervention** | Robotic-Assisted Gait Training encompassing balance related outcome measures |
| **Outcomes** | Temporal, spatial, kinematic and kinetic parameters |
| **Recommendations regarding body-weight-unloading** | There is some evidence that the use of RAGT in stroke patients has positive effects on balance. No clear evidence is available about which type of rehabilitation robot produces the best results. Neither is it clear whether RAGT leads to a better outcome in balance-related outcome measurements compared with other, more conventional gait rehabilitation methods. |
| **Evidence base for recommendation** | 10 studies included in quantitative and qualitative analysis, including a total of 359 participants. |
| **Reference** | Swinnen E, Beckwée D, Meeusen R, Baeyens JP, Kerckhofs E. Does robot-assisted gait rehabilitation improve balance in stroke patients? A systematic review. Top Stroke Rehabil. 2014;21(2):87-100 |

| | |
|---|---|
| **Title** | Robotic-Assisted Gait Training Effect on Function and Gait Speed in Subacute and Chronic Stroke Population: A Systematic Review and Meta-Analysis of Randomized Controlled Trials |
| **Study type** | Systematic review of RCTs |
| **Participants** | Subacute and chronic adults with stroke |
| **Intervention** | Robotic-Assisted Gait Training |
| **Outcomes** | Walking speed (primary), muscle tone, muscle power, gait, balance, quality of life |
| **Recommendations regarding body-weight-unloading** | Effect on waling speed in sub-acute: decreased by 0.48 m/s (95% CI 0.58 to 0.35)<br>Effect on waling speed in chronic: increased by 0.04 m/s (95% CI -0.17 to 0.24)<br>Effect on waling speed combined: decreased by 0.12 m/s (95% CI -0.24 to 0.00)<br><br>The findings of the current systematic review emphasize the use of RAGT among stroke survivors, as RAGT has equal effects as conventional training in improving the functional capacity of stroke survivors. A meta-analysis of 9 studies revealed that there is no significant difference in the RAGT group versus the conventional training group regarding gait speed. However, a subanalysis of gait speed in chronic cases showed a trivial positive revelation on effect size. |
| **Evidence base for recommendation** | 9 studies included in quantitative and qualitative analysis, including a total of 298 participants. |
| **Reference** | Tedla, JS, Dixit S, Gular K, Abohashrh M. Robotic-Assisted Gait Training Effect on Function and Gait Speed in Subacute and Chronic Stroke Population: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Eur Neurol. 2019;81:103-111 |

| | |
|---|---|
| **Title** | Efficacy of rehabilitation robotics for walking training in neurological disorders: A review |
| **Study type** | Systematic review of RCTs and non-RCTs |
| **Participants** | Adults with any neurological diagnosis (average age 61.5 years) |
| **Intervention** | Robotic-Assisted Gait Training |
| **Outcomes** | Walking speed (primary), muscle tone, muscle power, gait, balance, quality of life |
| **Recommendations regarding body-weight-unloading** | Overall, this review supports that locomotor training with robotic assistance is beneficial in improving locomotor function in individuals following a stroke and SCI. The evidence in TBI and PD is insufficient to suggest the use of locomotor training with robotic assistance is of benefit in these populations. |
| **Evidence base for recommendation** | 30 studies included in quantitative and qualitative analysis. |
| **Reference** | Tefertiller C, Pharo B, Evans N, Winchester P. Efficacy of rehabilitation robotics for walking training in neurological disorders: A review. Journal of Rehabilitation Research and Development. 2011;48(4):387-416 |

| | |
|---|---|
| **Title** | Robot-assisted therapy for balance function rehabilitation after stroke: A systematic review and meta-analysis |
| **Study type** | Systematic review of RCTs |
| **Participants** | Adults with stroke |
| **Intervention** | Robotic-Assisted therapy |
| **Outcomes** | Balance (primary) |
| **Recommendations regarding body-weight-unloading** | Effect on balance: increased by 4.64 points (95% CI 3.22 to 6.06)<br><br>Robot-assisted therapy may have a significant effect on improving balance function among stroke patients compared with those without using these devices, as indicated by increases in BBS score. These findings suggest that robot-assisted |

| | |
|---|---|
| | therapy could be a complementary or alternative approach for balance function rehabilitation among stroke patients. |
| **Evidence base for recommendation** | 31 studies included in quantitative and qualitative analysis, including a total of 1249 participants. |
| **Reference** | Zheng QX, Ge L, Wang CC, Ma QS, Liao YT, Huang PP, Wang GD, Xie QL, Rask M. Robot-assisted therapy for balance function rehabilitation after stroke: A systematic review and meta-analysis. Int J Nurs Stud 2019;95:7-18 |

# Appendix 4: Planned search strategies for individual databases

## Search strategy of individual keywords for MEDLINE through Ovid

| Nr. | Keyword | Search hits (19/8-21) |
|---|---|---|
| #1 | exp brain ischemia/ or exp carotid artery diseases/ or exp cerebrovascular trauma/ or exp intracranial arterial diseases/ or exp intracranial arteriovenous malformations/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or intracranial hemorrhage, hypertensive/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/ or exp hypoxia, brain/ | 345,373 |
| #2 | cerebral palsy/ or hemiplegia/ or exp paresis/ or exp gait disorders, neurologic/ | 47,248 |
| #3 | Exp brain damage, chronic/ or brain injuries/ or exp brain concussion/ or exp brain hemorrhage, traumatic/ or brain injury, chronic/ or diffuse axonal injury/ or craniocerebral trauma/ or exp head injuries, closed/ or exp intracranial hemorrhage, traumatic/ or exp brain abscess/ or exp central nervous system infections/ or exp encephalitis/ or exp meningitis, viral/ or exp brain neoplasms/ | 432,146 |
| #4 | (stroke or poststroke or post-stroke or apoplex$ or SAH).tw,kw. | 282,035 |
| #5 | ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw,kw. | 116,009 |
| #6 | ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw,kw. | 71,744 |
| #7 | (hemipleg$ or hemipar$ or paresis or paretic).tw,kw. | 37,908 |
| #8 | ((trauma$ or acquired or congenital) adj5 brain injur$).tw,kw. | 42,442 |
| #9 | (encephalitis or meningitis).tw,kw. | 94,751 |
| #10 | ((brain or cerebr$) adj5 (neoplasm$ or lesion$ or tumor$ or tumour$)).tw,kw | 92,263 |
| #11 | (cerebral$ adj5 (pals$ or para$ or pare$ or spastic$)).tw,kw. | 30,694 |
| #12 | ((cerebral$ or CP) adj3 (spastic$ or unilateral or hemipleg$ or monoplegi$ or diplegi$ or triplegi$ or quadriplegi$)).tw,kw. | 6,297 |
| #13 | ((pals$) adj5 (spastic$ or athetoid or ataxic)).tw,kw. | 3,208 |
| #14 | or/1-13 | 1,053,657 |
| #15 | walking aid/ or gait trainer/ or electronics, medical/ or robotics/ | 49,829 |
| #16 | (unload$ adj5 (assist$ or device$ or train$ or intervention$ or therap$)).tw,kw. | 569 |
| #17 | (gravity$ adj5 (assist$ or device$ or train$ or intervention$ or therap$)).tw,kw. | 611 |
| #18 | (robot$ adj5 (assist$ or device$ or train$ or intervention$ or therap$)).tw,kw. | 11,787 |
| #19 | (mechanical$ adj5 (assist$ or device$ or train$ or intervention$ or therap$)).tw,kw. | 16,560 |
| #20 | ((electronic$ or electromechanical$) adj5 (assist$ or device$ or train$ or intervention$ or therap$)).tw,kw. | 20,283 |
| #21 | lokomat$.tw,kw. | 213 |
| #22 | ((bodyweight or body-weight) adj3 (relief$ or reliev$ or support$ or suspend$ or unload$ or unsupport$)).tw,kw. | 1,398 |
| #23 | RAGT.tw,kw. | 126 |
| #24 | (gait adj3 (assist$ or devic$ or train$ or intervention$ or therap$)).tw,kw. | 3,573 |
| #25 | (walk$ adj3 (assist$ or device$ or mechanical$)).tw,kw. | 2,025 |
| #26 | (ambulat$ adj3 (assist$ or device$ or mechanical$)).tw,kw. | 1,463 |
| #27 | or/17-33 | 80,667 |
| #28 | randomized controlled trial/ | 540,681 |
| #29 | controlled clinical study/ | 0 |
| #30 | random$.ti,ab. | 1,245,526 |
| #31 | randomization/ | 105,763 |
| #32 | placebo.ti,ab. | 226,579 |
| #33 | (compare or compared or comparison).ti. | 429,097 |
| #34 | ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. | 1,542,794 |
| #35 | ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. | 176,929 |
| #36 | double blind procedure/ | 0 |
| #37 | parallel group$1.ti,ab. | 20,167 |
| #38 | (crossover or cross over).ti,ab. | 90,209 |
| #39 | ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. | 253,244 |
| #40 | (assigned or allocated).ti,ab. | 331,073 |
| #41 | (controlled adj7 (study or design or trial)).ti,ab. | 284,037 |
| #42 | human experiment/ | 0 |

| | | |
|---|---|---|
| #43 | trial.ti. | 245,806 |
| #44 | or/28-43 | 3,366,127 |
| #45 | and/14,27,44 | 2,100 |

## Search strategy of individual keywords for EMBASE through Ovid

| Nr. | Keyword | Search hits (19/8-21) |
|---|---|---|
| #1 | exp brain ischemia/ or exp carotid artery diseases/ or exp cerebrovascular trauma/ or exp intracranial arterial diseases/ or exp intracranial arteriovenous malformations/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or intracranial hemorrhage, hypertensive/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/ or exp hypoxia, brain/ | 1,113,271 |
| #2 | cerebral palsy/ or hemiplegia/ or exp paresis/ or exp gait disorders, neurologic/ | 87,806 |
| #3 | Exp brain damage, chronic/ or brain injuries/ or exp brain concussion/ or exp brain hemorrhage, traumatic/ or brain injury, chronic/ or diffuse axonal injury/ or craniocerebral trauma/ or exp head injuries, closed/ or exp intracranial hemorrhage, traumatic/ or exp brain abscess/ or exp central nervous system infections/ or exp encephalitis/ or exp meningitis, viral/ or exp brain neoplasms/ | 963,645 |
| #4 | (stroke or poststroke or post-stroke or apoplex$ or SAH).tw,kw. | 455,511 |
| #5 | ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw,kw. | 173,929 |
| #6 | ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw,kw. | 113,137 |
| #7 | (hemipleg$ or hemipar$ or paresis or paretic).tw,kw. | 61,066 |
| #8 | ((trauma$ or acquired or congenital) adj5 brain injur$).tw,kw. | 65,618 |
| #9 | (encephalitis or meningitis).tw,kw. | 133,776 |
| #10 | ((brain or cerebr$) adj5 (neoplasm$ or lesion$ or tumor$ or tumour$)).tw,kw | 148,612 |
| #11 | (cerebral$ adj5 (pals$ or para$ or pare$ or spastic$)).tw,kw. | 47,288 |
| #12 | ((cerebral$ or CP) adj3 (spastic$ or unilateral or hemipleg$ or monoplegi$ or diplegi$ or triplegi$ or quadriplegi$)).tw,kw. | 9,219 |
| #13 | ((pals$) adj5 (spastic$ or athetoid or ataxic)).tw,kw. | 4,873 |
| #14 | or/1-13 | 2,207,875 |
| #15 | walking aid/ or gait trainer/ or electronics, medical/ or robotics/ | 48,550 |
| #16 | (unload$ adj5 (assist$ or device$ or train$ or intervention$ or therap$)).tw,kw. | 893 |
| #17 | (gravity$ adj5 (assist$ or device$ or train$ or intervention$ or therap$)).tw,kw. | 803 |
| #18 | (robot$ adj5 (assist$ or device$ or train$ or intervention$ or therap$)).tw,kw. | 21,682 |
| #19 | (mechanical$ adj5 (assist$ or device$ or train$ or intervention$ or therap$)).tw,kw. | 24,510 |
| #20 | ((electronic$ or electromechanical$) adj5 (assist$ or device$ or train$ or intervention$ or therap$)).tw,kw. | 24,388 |
| #21 | lokomat$.tw,kw. | 412 |
| #22 | ((bodyweight or body-weight) adj3 (relief$ or reliev$ or support$ or suspend$ or unload$ or unsupport$)).tw,kw. | 1,952 |
| #23 | RAGT.tw,kw. | 156 |
| #24 | (gait adj3 (assist$ or devic$ or train$ or intervention$ or therap$)).tw,kw. | 5,264 |
| #25 | (walk$ adj3 (assist$ or device$ or mechanical$)).tw,kw. | 3,141 |
| #26 | (ambulat$ adj3 (assist$ or device$ or mechanical$)).tw,kw. | 2,443 |
| #27 | or/17-33 | 121,051 |
| #28 | randomized controlled trial/ | 673,906 |
| #29 | controlled clinical study/ | 464,005 |
| #30 | random$.ti,ab. | 1,706,837 |
| #31 | randomization/ | 91,896 |
| #32 | placebo.ti,ab. | 332,754 |
| #33 | (compare or compared or comparison).ti. | 575,131 |
| #34 | ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. | 2,358,030 |
| #35 | ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. | 252,839 |
| #36 | double blind procedure/ | 189,217 |

| | | |
|---|---|---|
| #37 | parallel group$1.ti,ab. | 27,976 |
| #38 | (crossover or cross over).ti,ab. | 113,596 |
| #39 | ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. | 362,926 |
| #40 | (assigned or allocated).ti,ab. | 428,004 |
| #41 | (controlled adj7 (study or design or trial)).ti,ab. | 389,385 |
| #42 | human experiment/ | 552,499 |
| #43 | trial.ti. | 344,669 |
| #44 | or/28-43 | 5,269,838 |
| #45 | and/14,27,44 | 4,264 |

## Search strategy of individual keywords for CENTRAL through Cochrane Library

| Nr. | Keyword | Search hits (19/8-21) |
|---|---|---|
| #1 | MeSH descriptor: [brain ischemia] explode all trees | 3,770 |
| #2 | MeSH descriptor: [carotid artery diseases] explode all trees | 1,182 |
| #3 | MeSH descriptor: [cerebrovascular trauma] explode all trees | 33 |
| #4 | MeSH descriptor: [intracranial arterial diseases] explode all trees | 1,196 |
| #5 | MeSH descriptor: [intracranial arteriovenous malformations] explode all trees | 61 |
| #6 | MeSH descriptor: [intracranial embolism and thrombosis] explode all trees | 323 |
| #7 | MeSH descriptor: [intracranial hemorrhages] explode all trees | 2,048 |
| #8 | MeSH descriptor: [intracranial hemorrhage, hypertensive] explode all trees | 47 |
| #9 | MeSH descriptor: [stroke] explode all trees | 10,512 |
| #10 | MeSH descriptor: [brain infarction] explode all trees | 1,343 |
| #11 | MeSH descriptor: [stroke, lacunar] explode all trees | 45 |
| #12 | MeSH descriptor: [vasospasm, intracranial] explode all trees | 154 |
| #13 | MeSH descriptor: [vertebral artery dissection] explode all trees | 8 |
| #14 | MeSH descriptor: [hypoxia, brain] explode all trees | 329 |
| #15 | MeSH descriptor: [cerebral palsy] explode all trees | 1,496 |
| #16 | MeSH descriptor: [hemiplegia] explode all trees | 761 |
| #17 | MeSH descriptor: [paresis] explode all trees | 911 |
| #18 | MeSH descriptor: [gait disorders, neurologic] explode all trees | 714 |
| #19 | MeSH descriptor: [brain damage, chronic] explode all trees | 1,837 |
| #20 | MeSH descriptor: [brain injuries] explode all trees | 2,479 |
| #21 | MeSH descriptor: [brain concussion] explode all trees | 396 |
| #22 | MeSH descriptor: [brain hemorrhage, traumatic] explode all trees | 18 |
| #23 | MeSH descriptor: [brain injury, chronic] explode all trees | 38 |
| #24 | MeSH descriptor: [diffuse axonal injury] explode all trees | 12 |
| #25 | MeSH descriptor: [craniocerebral trauma] explode all trees | 3,780 |
| #26 | MeSH descriptor: [head injuries, closed] explode all trees | 468 |
| #27 | MeSH descriptor: [intracranial hemorrhage, traumatic] explode all trees | 180 |
| #28 | MeSH descriptor: [brain abscess] explode all trees | 48 |
| #29 | MeSH descriptor: [central nervous system infections] explode all trees | 1,419 |
| #30 | MeSH descriptor: [encephalitis] explode all trees | 320 |
| #31 | MeSH descriptor: [meningitis, viral] explode all trees | 13 |
| #32 | MeSH descriptor: [brain neoplasms] explode all trees | 2,017 |
| #33 | (stroke or poststroke or post-stroke or apoplex* or SAH):ti,ab | 55,684 |
| #34 | ((brain* or cerebr* or cerebell* or intracran* or intracerebral) near/5 (ischemi* or infarct* or thrombo* or emboli* or occlus*)):ti,ab | 8,440 |
| #35 | ((brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) near/5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)):ti,ab | 7,526 |
| #36 | (hemipleg* or hemipar* or paresis or paretic):ti,ab | 5,731 |
| #37 | ((trauma* or acquired or congenital) near/5 brain injur*):ti,ab | 4,263 |
| #38 | (encephalitis or meningitis):ti,ab | 2,152 |
| #39 | ((brain or cerebr*) near/5 (neoplasm* or lesion* or tumor* or tumour*)):ti,ab | 3,866 |
| #40 | (cerebral* near/5 (pals* or para* or pare* or spastic*)):ti,ab | 4,063 |
| #41 | ((cerebral* or CP) near/3 (spastic* or unilateral or hemipleg* or monoplegia* or diplegi* or triplegi* or quadriplegi*)):ti,ab | 1,378 |

| | | |
|---|---|---|
| #42 | ((pals*) near/5 (spastic* or athetoid or ataxic)):ti,ab | 847 |
| #43 | #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 | 83,027 |
| #44 | MeSH descriptor: [walking aid] explode all trees | 0 |
| #45 | MeSH descriptor: [gait trainer] explode all trees | 0 |
| #46 | MeSH descriptor: [electronics, medical] explode all trees | 83 |
| #47 | MeSH descriptor: [robotics] explode all trees | 956 |
| #48 | (unload* near/5 (assist* or device* or train* or intervention* or therap*)):ti,ab | 90 |
| #49 | (gravity* near/5 (assist* or device* or train* or intervention* or therap*)):ti,ab | 123 |
| #50 | (robot* near/5 (assist* or device* or train* or intervention* or therap*)):ti,ab | 3,772 |
| #51 | (mechanical* near/5 (assist* or device* or train* or intervention* or therap*)):ti,ab | 2,657 |
| #52 | ((electronic* or electromechanical*) near/5 (assist* or device* or train* or intervention* or therap*)):ti,ab | 2,223 |
| #53 | Lokomat*:ti,ab | 161 |
| #54 | ((bodyweight or body-weight) near/5 (relief* or reliev* or support* or suspend* or unload* or unsupport*)):ti,ab | 589 |
| #55 | RAGT:ti,ab | 91 |
| #56 | (gait near/5 (assist* or devic* or train* or intervention* or therap*)):ti,ab | 2,699 |
| #57 | (walk* near/5 (assist* or device* or mechanical*)):ti,ab | 929 |
| #58 | (ambulat* near/5 (assist* or device* or mechanical*)):ti,ab | 481 |
| #59 | #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 | 12,679 |
| #60 | #45 and #62 in Trials | 2,817 |

## Search strategy for ClinicalTrials.gov

| Nr. | Keyword |
|---|---|
| #1 | Stroke |
| #2 | Brain damage |
| #3 | Brain injury |
| #4 | Cerebral Palsy |
| #5 | Filter #1-#4 for “adults 18-64” and “Interventional (Clinical Trial)” using the sites functions |

# Appendix 5: Data items for extraction of eligible records

| Publication information: | Description: |
|---|---|
| Author credentials | Primary authors credentials |
| Title | Complete title of the record |
| Country | Records primary country of origin |
| Year | Year of publication |
| Publication status | Categorised as:<br>• accepted peer-reviewed manuscript<br>• published peer-reviewed article |
| Funding source | Type and source of financial support |

| Study methodology: | Description: |
|---|---|
| Trial design | Categorised as:<br>• RCT<br>• Other |
| Aim of study | Overall objective of the trial |
| Trial size | Total N of participants |
| Participant allocation | N of participants allocated to each intervention arm |
| Participant inclusion criteria | e.g., condition type, age, location or severity of brain damage |
| Participant exclusion criteria | e.g., condition type, age, location or severity of brain damage |
| Setting | Setting of the trial:<br>• Primary sector<br>• Secondary sector<br>• Tertiary sector<br>• Other |

| Demographic information: | Description: |
|---|---|
| Age | Mean age of participants |
| Gender | Percentage of participants who are female |
| Type of condition | Based on the majority of participants, records will be categorised as:<br>• Acquired brain injury (non-traumatic)<br>• Traumatic brain injury<br>• Congenital brain injury |
| Duration of disease | Time in years since first diagnosis of disease |
| Condition phase | Categorised as:<br>• Acute (within 3 months)<br>• Chronic (longer than 3 months) |
| Ambulatory status | Mean Functional Ambulation Classification score |
| Extent of condition | Based on the majority of participants, records will be categorised as:<br>• monoplegia/monoparesis<br>• diplegia/diparesis<br>• triplegia/triparesis<br>• quadriplegia/quadriparesis<br>• hemiplegia/hemiparesis<br>• paraplegia/paraparesis<br>• double hemiplegia/double hemiparesis<br>• tetraplegia/teraparesis<br>• Mixed |
| Health related quality of life at baseline | Based on the outcome hierarchy presented in table 1 |
| Walking capacity at baseline | Based on the outcome hierarchy presented in table 1 |

| Details of the intervention: | Description: |
|---|---|
| Approach in delivery | Categorised as:<br>• physical therapists<br>• other personnel<br>• self-applied<br>• other |
| Method of delivery | Categorised as:<br>• treadmill<br>• stationary platforms (e.g. lokomat)<br>• mobile platforms (e.g. litegait, andago)<br>• ceiling mounted systems (e.g. ErgoTrainer)<br>• other (e.g. exoskeleton) |
| Body-weight-unloading mechanism | Categorised as:<br>• Positive air pressure (e.g., Alter G)<br>• Static unloading (e.g., LiteGait)<br>• Pneumatic unloading (e.g., ErgoTrainer)<br>• Dynamic unloading (e.g., Bioness Vector)<br>• Total body unloading (e.g., lokomat)<br>• Other (e.g., exoskeleton) |
| Extent of intervention | Hours used on training per week |
| Length of intervention | Total length of intervention in days, from baseline to end of intervention |
| Type of comparator/control group | Categorised as:<br>• usual care<br>• waitlist<br>• sham treatment (Same content of therapy with less than 30% intensity of the intervention group)<br>• comparison therapy (e.g. regular walking training)<br>• other |
| Timing of outcome assessments | The duration between the end of intervention and the follow-up assessment in months |