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A systematic review of the efficacy of conservative interventions on the gait of ambulant adults with cerebral palsy

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A systematic review of the efficacy of conservative interventions on the gait of ambulant adults with cerebral palsy

Aim: To identify, appraise and synthesize evidence regarding efficacy of conservative interventions (physiotherapeutic, pharmacological) to improve walking in ambulant adults with cerebral palsy (CP).

Method: Standard search and extraction methods were utilised. A descriptive synthesis was performed with additional limited meta-analysis where the same outcome measurements were used and clinical heterogeneity was low. Interventions were considered according to target domain (International Classification of Functioning, Disability and Health).

Results: From 1571 papers identified, 10 met inclusion criteria. Study exclusion was predominantly due to gait not being a target of the intervention, or non-adult age range. Five randomised controlled trials were identified. Interventions were diverse and included strength training, sensory cueing, neurodevelopmental training, whole body vibration and spasticity medication. A small between-group effect on gait speed was found, weighted mean difference 0.09 (95% CI 0.03 to 0.16).

Conclusion: Evidence to support efficacy of one physiotherapeutic or pharmacological intervention over another to improve gait in adults with CP is currently limited. Further research is required using standardised gait outcome measures, longer follow up periods and higher quality trial designs.

Key words:

Gait, rehabilitation, cerebral palsy, physiotherapy

A systematic review of the effect of conservative interventions on the gait of ambulant adults with cerebral palsy

Cerebral palsy (CP) is the most common cause of childhood physical disability, affecting around 3 in every 1000 live births (Odding et al. 2006). It is a lifelong condition, with more than 70% of individuals surviving into adulthood following improvements in neonatal and childhood care (Odding et al. 2006). For example, around 34,000 Australians (Access Economics 2008) and at least 700,000 people living in the USA (Goldstein 2009) are estimated to have CP, with most being adults, not children (Tosi et al. 2009). Adults with CP have complications that have been described as 'under-recognized, undocumented, and undertreated' (Cerebral Palsy International Research Foundation 2013). Accumulating evidence suggests that 25% or more of ambulant adults with CP experience premature age-related changes, resulting in a functional decline in early to middle adulthood (Morgan and McGinley 2014). Characteristics associated with accelerated mobility decline have been identified, such as bilateral motor impairment, worse initial gait ability, older age, (Opheim et al. 2012), Jahnsen, Olsson, & Stanghelle 2012) and higher levels of pain and fatigue (Opheim et al. 2009).

Recent governmental and organisational directives have now acknowledged the need to provide appropriate health care for those living with a developmental disability that extends beyond childhood (Goldstein 2009). For example, a recent Australian government reform (National Disability Insurance Scheme, NDIS 2013) has acknowledged the requirement for a 'lifelong approach' to providing care and support for those living with a disability, such as CP. This means that funding assessment will look beyond the immediate need, and across the course of a person's life. Furthermore, such schemes acknowledge the necessity to focus on funding intensive intervention, 'particularly for people where there is good evidence that it will substantially improve functioning or delay or lessen a decline in functioning' (NDIS 2013). The challenge for health professionals is to identify evidence-based interventions that will enable

adults with CP to maintain or improve their functional abilities, where that evidence does not yet exist, or is only just emerging (Tosi et al. 2009).

Ambulant adults with CP may experience disordered movement arising from primary or secondary neurological and musculoskeletal dysfunction such as movement disorder (e.g. spasticity, dystonia), bony mal-alignment and contracture, muscle weakness, and reduced motor dexterity (Tosi et al. 2009). All of these factors may contribute to reduced selective motor control and impact on walking ability. A recent systematic review synthesised evidence on physiotherapeutic interventions for a broad range of ambulant and non-ambulant adolescents and young adults with CP (Jeglinsky et al. 2010). A small range of studies delivering, for example, strength training (Unger et al. 2006), aquatic exercise (Vogtle et al. 1998), task oriented training (Choy et al. 2003), vibration exercise (Kwam 1997) and stretches (Cadenhead et al. 2002) were described. However few directly reported objective measures of gait as an outcome of an intervention, nor did most specifically identify gait improvement as a goal of the intervention in the cohort. Furthermore, those targeted at ambulant adults alone were not clearly identified, often being reported within mixed age groups (adolescents through to adults) and/or mixed ambulatory ability. As a result, there is no clear evidence regarding efficacy of interventions to guide physiotherapists in treatment selection.

In contrast, reviews of interventions to improve walking in children and adolescents with CP have reported a wide range of effective interventions, such as botulinum toxin type A (BTX-A), orthotic, electrical stimulation and surgical management (Boyd and Hays 2001; Cauraugh et al. 2010; Gannotti et al. 2010; McGinley et al. 2012; Rodda et al. 2006). These reviews identified interventions that are generally targeted at specific functional level subgroups and recommended for selected age groups. However these findings are unlikely to be directly generalisable to adults who have reached neurological and musculoskeletal maturity. A preliminary review of the adult CP literature readily identifies a selection of studies of focused surgical interventions for defined secondary conditions or symptoms at an impairment level.

For example, ambulant adults with athetoid CP may develop cervical myelopathy as an adverse consequence of the prolonged movement disorder (Guettard et al. 2012) and benefit from specific surgical interventions (Haro et al. 2002; Onari et al. 2002). However, the efficacy of conservative interventions, such as physiotherapy or pharmacological to address more generic gait decline in ambulant adults with CP has not yet been clearly established. Given that nonsurgical or conservative interventions are arguably regarded as more accessible first line treatment options, there is a need to synthesise information relevant to the ambulant group of adults with CP. Physiotherapists need information regarding effective interventions targeted at gait rehabilitation for ambulant adults with CP. The aim of this study was therefore to identify, appraise and synthesise the evidence regarding the efficacy of conservative interventions to address walking dysfunction in ambulant adults with CP.

Method

The search strategy was developed, reviewed and refined by the authors, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Moher et al. 2009). Electronic searches of published reports indexed on health related electronic databases from MEDLINE (from 1970), EMBASE (from 1980), CINAHL (from 1982), SPORTDISCUS (from 1985) and Cochrane were performed in August 2013. The search terms were customised to each database and included the following keywords: cerebral palsy, gait disorders (neurologic), walking, mobility, physical mobility, ambulation, functional mobility, Botox, botulinum toxin, physiotherapy, exercise, rehabilitation, orthotics. The search was restricted to adults (≥18 years). Of note, for studies that included both children and adults, and provided individual data, only the subset 18 years and older was included where this data extraction was possible. Targeted hand-searching of reference lists and key journals supplemented electronic searching. An example search strategy is outlined in Appendix 1.

The titles and abstracts identified by the initial search strategy were screened by the first named author (PM) to identify potentially eligible reports and retrieve full-text reports. When

the title or abstract did not clearly indicate whether an article should be included, the complete article was retrieved and reviewed. Full-text reports were then independently evaluated by two authors (JM and PM) for the following inclusion criteria: (1) all participants with a diagnosis of cerebral palsy or able to extract data for subset of participants with diagnosis of cerebral palsy; (2) mean age of participants at the time of the intervention was 18 years or older, or able to extract individual data to subset 18 years and older; (3) participants were ambulant immediately prior to the intervention; (4) primary aim, or one of primary aims of intervention was to improve gait; (5) data detailing pre and post-intervention objective measures of gait available; (6) full text reports published in English. Studies were excluded if the intervention was of a surgical nature. Any trial design was included in the review except for single case reports. Any disagreements on eligibility were discussed and resolved with a third reviewer (FD).

Data extraction and quality appraisal

Data extraction was conducted independently by two reviewers (PM and JM) using a customized data extraction form that was generated and piloted to identify key details for each study including study design, population characteristics, intervention type and conduct, proposed mechanistic target and the type and estimates of the gait outcome reported. Using the International Classification of Functioning (ICF) framework (Rosenbaum and Stewart 2004) and methodology reported in McGinley et al. (2012), the gait outcome tool was classified as either addressing impairments of body structure and function, or activity limitations. This was considered important so as to consider the impact of the intervention on the interactive relationship between the health condition (cerebral palsy) and contextual factors. Studies were also independently evaluated for risk of bias by two reviewers (PM and FD) using published quality appraisal tools appropriate for each study design. The Physiotherapy Evidence Database (PEDro) tool (Maher et al. 2003) was used for randomised controlled study designs; the Newcastle-Ottawa quality assessment scale for case-control study designs (NOS)(Wells et al. 2005); and a tool designed by the Institute of Health Economics (Moga et al. 2012) for case-series designs. Key items were selected from each tool to systematically

appraise selection, detection/performance and attrition bias according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (Balshem et al. 2011; Guyatt et al. 2011). Selection bias was evaluated using PEDro items 2-3, NOS items 1-4 and case-series items 3,5,6 for studies with corresponding designs. Detection/performance bias was evaluated using PEDro items 5-7, NOS item 5 and case-series item 11-12. Attrition bias was evaluated using PEDro items 8-9, NOS item 9 and case-series item 16. Each study was required to fulfil the criteria corresponding to its design for each type of bias to be rated as high quality (i.e. low risk of bias). Any disagreements on quality criteria were checked against the original article to ascertain the correct scoring according to a pre-defined procedure, in accordance with established and recommended protocols (Moher et al. 2009).

Evidence synthesis

Evidence synthesis was conducted using a modified GRADE system (Balshem et al. 2011; Guyatt et al. 2011) to determine the overall strength of a recommendation. This approach enables the synthesis of both randomized controlled trials, which begin as high level of evidence, and observational studies, which begin as low level of evidence. The risk of bias is then considered to determine the overall strength of the recommendation of the evidence from each study as being high, low or very low as outlined in table 1. This system recognises that, depending on the associated risk of bias, evidence from randomised controlled trials (RCTs) can be regarded as either high or downgraded to low, whilst evidence from observational studies can only be regarded as low or downgraded to very low. Further upgrading and downgrading of this strength can also be applied depending on the consistency of findings from multiple studies.

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Between-group effect sizes (ES) were calculated where suitable data was available. Limited meta analysis was considered possible when the same methods of measurement were used and clinical heterogeneity was low (<30%, Higgins and Thompson, 2002). The size of the effect was reported as a weighted mean difference (95% CI). The analyses were performed using Review Manager 5.2. When data were not considered appropriate or able to be included in the pooled analysis, a descriptive analysis was performed.

Results

The electronic searches and hand-search of bibliographies, following removal of duplicates, yielded a total of 1572 articles. The search process and yield is outlined in figure 1. The majority of records excluded from initial data screening were rejected as gait rehabilitation was not the primary aim of the intervention (n= 612), or the intervention was targeted at subjects <18 years, or data relevant to the subset over 18 years were unable to be extracted (n=322).

Fig. 1 PRISMA flow diagram

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Following the application of the inclusion/exclusion criteria, ten studies were identified for inclusion. These included two small studies with identified adult subjects within broader age samples (Baram and Lenger, 2012; Brochard et al. 2009). Key descriptive details regarding study cohort, target of intervention, outcome measures used, study design and quality are provided in table 2.

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Studies varied widely in design, intervention type, duration and length of follow-up. Eight studies explored the efficacy of 'physiotherapeutic' interventions (Ahlborg et al. 2006; Andersson et al. 2003; Baram and Lenger, 2012; Dickin et al. 2013; Kim et al. 2011; Kim et al. 2012; Maeland et al. 2009; Taylor et al. 2013), and two studies evaluated spasticity medication efficacy (Brochard et al. 2009; Maanum et al. 2011). There were five randomised controlled trials (Ahlborg et al. 2006; Kim et al. 2012; Maanum et al. 2011; Maeland et al. 2009; Taylor et al. 2013), three non-randomised case-controlled studies (Andersson et al. 2003; Baram and Lenger 2012; Kim et al. 2011) and two case-series (Brochard et al. 2009; Dickin et al. 2013). Three studies (Baram and Lenger 2012; Dickin et al. 2013; Kim et al. 2011) evaluated only the immediate effect of a single session of an exercise intervention. Five studies evaluated the effect of an exercise training program delivered twice (Ahlborg et al. 2006; Andersson et al. 2003; Kim et al. 2012; Maeland et al. 2009; Taylor et al. 2013) weekly, for a total of three, ten or twelve weeks. Length of follow up for these exercise interventions was typically short (predominantly immediately post intervention), with the exception of Taylor et al. (2013) who reported outcomes of a follow up assessment 12 weeks following the conclusion of the intervention. One study reported the effects of a single dosage of medication (BTX-A) on gait after eight weeks (Maanum et al. 2011). One study (Brochard et al. 2009) examined the effects of continuous medication (Baclofen) delivery on gait outcomes over a mean of 16 months after intrathecal baclofen implantation.

Study samples

The majority of studies were conducted in Europe and Asia. Study samples were generally small convenience samples, ranging from a case series of two (auditory training subset; Baram and Lenger, 2012) up to 66 (33 intervention, 33 control) in a double blind RCT (Maanum et al. 2011). Participants were recruited via hospital and rehabilitation facilities records (Ahlborg et

al. 2006; Kim et al. 2011; Kim et al. 2012; Maanum et al. 2011; Maeland et al. 2009; Taylor et al. 2013), community services such as CP organisations, newspapers and websites (Maanum et al. 2011), from previous involvement in research studies (Andersson et al. 2003), and from a CP register (Taylor et al. 2013). Only three studies (Maanum et al. 2011; Maeland et al. 2009; Taylor et al. 2013) reported *a priori* calculation of required sample sizes.

Participants' gait ability prior to intervention was described using a range of methods. Six studies used the Gross Motor Function Classification System (GMFCS, Palisano et al. 2007) (Ahlborg et al. 2006; Brochard et al. 2009; Kim et al. 2011; Maanum et al. 2011; Maeland et al. 2009; Taylor et al. 2013) to report pre-intervention gait status and one used the Cerebral Palsy – International Sports and Recreation Association classification, (CP-ISRA, 2005) (Dickin et al. 2013). The remaining studies used descriptive terminology to report the subject's ambulation capacity (with or without aids)(Andersson et al. 2003; Baram and Lenger 2012; Kim et al. 2012). Not surprisingly, given the inclusion requirement for participants to be ambulant pre-intervention, there was a higher proportion of individuals with diplegia and hemiplegia than quadriplegia, where this topographical information was reported.

The mean age of participants with CP in the identified studies ranged from 18 years (Taylor et al. 2013) to 41 years (Maeland et al. 2009). The maximum age of a participant in the reported studies was 69 years (Maeland et al. 2009). In almost all studies the mean age was around 30 or less, reflecting the need to develop, deliver and evaluate interventions for adults with CP in their early adult years.

Gait outcome measures

A wide range of gait measurement scales/tools were utilised to evaluate intervention efficacy. These ranged from instrumented kinematic analysis (Dickin et al. 2013; Kim et al. 2011; Maanum et al. 2011; Taylor et al. 2013) and spatial-temporal measures (step and stride length, cadence, velocity) (Andersson et al. 2003; Baram and Lenger 2012; Brochard et al. 2009; Dickin

et al. 2013; Kim et al. 2011; Kim et al. 2012; Maeland et al. 2009; Taylor et al. 2013), through to other recognised and validated performance-based mobility outcome measures: Timed up and go (Podsiadlo and Richardson, 1991); the 6 minute walk test (American Thoracic Society 2002); the Gross Motor Function Measure – Domain E: walking, running, jumping (Russell et al. 1989) and the Functional Mobility Scale (Graham et al. 2004)(Ahlborg et al. 2006; Andersson et al. 2003; Maanum et al. 2011; Maeland et al. 2009; Taylor et al. 2013). Only two studies (Brochard et al. 2009; Taylor et al. 2013) used a carer or participant-reported questionnaire (Gillette Functional Assessment Questionnaire; Novachek et al. 2000). Walking outcomes were classified using the ICF model as either measuring impairments of body structure and function, or activity limitations (Rosenbaum and Stewart, 2004). Figure 2 illustrates the relationship of these outcome measures within the overall functional context of a person with CP. Four studies included gait outcome measures at the ICF level of body function and structure (Baram and Lenger 2012; Dickin et al. 2013; Kim et al. 2011; Kim et al. 2012), two studies used gait outcome measures at the ICF level of activities (Ahlborg et al. 2006; Andersson et al. 2003) and four used both (Brochard et al. 2009; Maanum et al. 2011; Maeland et al. 2009; Taylor et al. 2013).

Fig. 2 International Classification of Functioning illustrating the alignment of gait measurement outcomes with ICF domains

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Details of the outcome measures are summarized in Table 3.

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Efficacy of interventions

Within each ICF domain, the results of statistical analyses were identified for within-group and between-group efficacy (where available) on gait outcomes (table 3). Where more than one intervention was examined within a study, both study arms are described. No statistical analyses were available for the subset of adults in studies by Brochard et al. (2009) and Baram and Lenger (2012) due to small data sets.

Body structures and function

The greatest volume of evidence supported by statistical analysis was around the effect on gait speed from a diverse range of physiotherapeutic strategies (Andersson et al. 2003; Dickin et al. 2013; Kim et al. 2012; Maeland et al. 2009; Taylor et al. 2013). Three studies demonstrated a within-group statistically significant improvement in gait speed post treatment (Andersson et al. 2003; Dickin et al. 2013; Kim et al. 2012). These findings are consistent with the trend towards improvement after visual cue training evident in the data from the adult subgroup reported by Baram and Lenger (2012). Notably, one sample (Kim et al. 2012) demonstrated a within-group significant decline in gait speed after neurodevelopmental therapy (NDT). There was also a variable outcome from intrathecal baclofen, with two participants increasing in gait speed post treatment, and another declining in gait speed (Brochard et al. 2009). Where data were available, the within-group effects (pre and post intervention) have been illustrated in a forest-plot in figure 3a, providing an indication of the trend and direction of gait speed change as a result of an individual intervention. Of note, the small sample sizes and very wide confidence intervals indicate that caution is needed with interpretation. Meta analysis was not performed due to sample heterogeneity (I^2 >30%; Higgins and Thompson, 2002), interventional heterogeneity and varied research design.

Fig. 3a Forest plot illustrating within-group outcomes of interventions on gait speed (m/s); pre and post intervention comparison, according to first named author. Total = number of participants in each study

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Two studies reported a between-group significant effect on gait speed, with superior outcomes for RAS training compared to NDT training (ES 0.27; Kim et al. 2012), and for strength training compared to no intervention (Andersson et al. 2003)(table 3). However, Andersson et al. (2003) calculated gait speed from 6MWT data, which may warrant caution with interpretation of results. Neither of the RCTs by Taylor et al. (ES 0.13, Taylor et al. 2013) or Maeland et al. (2009) found a significant effect on gait speed when comparing intervention and control groups (table 3). Of note, Maeland et al. (2009) reported baseline differences in their two groups, with faster gait speed recorded in the training group prior to intervention, precluding confident calculation of effect size.

Data was pooled from RCTs reporting gait speed (m/s) as an outcome measure (Kim et al. 2012; Maeland et al. 2009; Taylor et al. 2013), calculated from 10m walk tests, after low between-study statistical heterogeneity was demonstrated (I^2 <30%; Higgins and Thompson, 2002) permitting meta analysis. A forest plot of the individual studies and pooled data is illustrated in figure 3b. In the analysis of Kim et al.'s data (2012), the RAS group was considered the intervention, and the NDT group was considered the control. Pooled data demonstrated an overall increase in gait speed of 0.09 (95% CI 0.03 to 0.16) post intervention compared to comparison groups.

Fig. 3b Mean Difference (95% CI) of effects of between group interventions on gait speed (m/s) from pooled data (n=42) of three RCTs of ambulant adults with CP (first named author). Total = number of participants in each study

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Relatively few studies evaluated the effect of interventions on kinematic walking patterns. Two studies demonstrated a significant within-group improvement in walking quality, with greater normalisation post rhythmical auditory stimulation (RAS) (Kim et al. 2011; Kim et al. 2012). Kim et al. (2012) also reported a between-group significant effect post RAS, with improvement in selected kinematic outcomes (Gait deviation index, GDI) in comparison to NDT training (ES 0.30). Neither strength training (Taylor et al. 2013) nor BTX-A (Maanum et al. 2011) were found to statistically improve walking pattern quality with only small effect sizes derived (e.g. knee initial contact, ES 0.19, Maanum et al. 2011; e.g. gait profile score, ES 0.16, Taylor et al. 2013).

Activity outcomes

Efficacy of interventions on the ICF subdomain of activity was also variable (Table 3). While an early study of strength training showed significant improvement in gross motor function compared to controls (Andersson et al. 2003), no effect was found in subsequent studies (Ahlborg et al. 2006; Maeland et al. 2009). Most recently, Taylor et al. (2013) reported an improvement in Functional Mobility Scale (5m category only; ES 0.36) and patient-reported Functional Ambulation Questionnaire (ES 0.40) both within and between groups. Vibration therapy also led to a within-group improvement in functional measures, but no between-group difference (Ahlborg et al. 2006). A statistically significant within-group improvement occurred as a result of BTX-A intervention (Maanum et al. 2011), however there was no

significant between-group effect relative on function compared to a placebo (TUG, ES 0.17; 6MWT, ES 0.12). In Brochard and colleague's case series (2009), one participant did not change function post intrathecal baclofen, and two subjects improved post treatment.

Adherence to intervention and adverse events

Information about adherence rates and the occurrence of adverse events can provide clinicians with indirect evidence about the clinical feasibility and acceptability of a training programme to participants. Of the five studies that delivered physiotherapy interventions across more than one session, three reported adherence rates which generally were 75% or higher (Ahlborg et al. 2006; Maeland et al. 2009; Taylor et al. 2013). Reporting of the monitoring or occurrence of adverse events was infrequent and lacked detail, with only four studies (Brochard et al. 2009; Maanum et al. 2011; Maeland et al. 2009; Taylor et al. 2013) noting the type and incidence of adverse events.

Study design and quality

For the purposes of study design and quality analysis, Baram and Lenger's (2012) two different interventions applied were considered as two different studies (Table 2). The majority of study cohorts (7/11) were rated as being at risk of selection bias (Ahlborg et al. 2006; Andersson et al. 2003; Baram and Lenger 2012; Brochard et al. 2009; Dickin et al. 2013; Kim et al. 2011). The majority of studies (9/11) were rated as having low risk of performance bias (Baram and Lenger 2012; Brochard et al. 2009; Dickin et al. 2013; Kim et al. 2011; Kim et al. 2012; Maanum et al. 2011; Maeland et al. 2009; Taylor et al. 2013) and attrition bias (7/11) (Ahlborg et al. 2006; Andersson et al. 2003: Dickin et al. 2013; Kim et al. 2011; Kim et al. 2012; Maanum et al. 2011; Taylor et al. 2013). Three of the RCTs (Kim et al. 2012; Maanum et al. 2011; Maeland et al. 2009) were rated as being at risk of bias which contributed to the downgrading of the strength of recommendations from these studies.

Evidence synthesis

Results are presented in descriptive format in Table 3, with strength of recommendations outlined in Table 2. Meta analysis was not considered appropriate for the majority of study outcomes other than gait speed because of wide variation in study samples, study designs and outcome measures, with high levels of clinical heterogeneity. Using the modified GRADE approach, a high strength of recommendation was given to evidence from four of the RCTs (Kim et al. 2012; Maanum et al. 2011, Maeland et al. 2009; Taylor et al. 2013), while a low strength of recommendation was given to one study (Ahlborg et al. 2006) and a very low recommendation to the remaining five studies (Andersson et al. 2003; Baram and Lenger 2012; Brochard et al. 2009; Dickin et al. 2013; Kim et al. 2011). An upgrading or downgrading of the recommendation based on consistency of results from multiples studies was not considered appropriate due to study heterogeneity.

Discussion

This systematic review synthesised the available evidence from interventions that aim to improve gait in ambulant adults with CP. A range of physiotherapeutic and pharmacological studies of varying design and quality were identified. The interventions were diverse, ranging from whole body vibration techniques and auditory and visual cueing, to more traditional strengthening programs, with wide variation in dosage. Subsequently, there have been limitations in the ability to synthesize the outcomes and make clear recommendations regarding efficacy of interventions.

Disappointingly, the strength of evidence revealed by around half of the studies was very low, limiting confidence in the outcomes. Only five RCTs were included in the review, of which four were allocated a high strength of recommendation. Small sample sizes further hindered the likelihood of statistically significant findings. All but three studies (Maanum et al. 2011; Maeland et al. 2009; Taylor et al. 2013) failed to report determination of *a priori* sample sizes

to be able to demonstrate a statistically significant result, although some explored the clinical significance of outcomes in discussion (e.g. Andersson et al. 2003). It is likely that small numbers of participants contributed to the no-effect outcome found in some studies. Very few studies from the initial search were exclusively targeted at adults (over 18 years), resulting in exclusion of a large number of papers or only a small subset of participants being included. Only studies published in the last ten years i.e. from 2003-2013 were retrieved with our search terms despite not specifying a date range. It is surprising that although there are now a considerable number of adults living with CP, many of whom are over the age of 45 (Tosi et al. 2009), with an increasing awareness of the effects of premature mobility decline in ambulant adults with CP (Morgan and McGinley 2013; Opheim et al. 2012), there are still so few published adult interventional studies available in comparison to paediatric studies.

A range of measures were used to document mobility. Andersson et al. (2003) the earliest study in the review, predated the development of the GMFCS and its use in adults to identify differing levels of performance in gross motor function (Palisano et al. 2007; Sandstrom et al. 2004). More recent studies were generally of higher quality and used standardized descriptors including the GMFCS to define their sample characteristics (Ahlborg et al. 2006; Brochard et al. 2009; Kim et al. 2011; Maanum et al. 2011; Maeland et al. 2009; Taylor et al. 2013), and validated outcome measures such as the TUG, 6MWT and kinematic and temporal measures. Despite the increased usage of the GMFCS in adult CP literature, this classification system was surprisingly lacking in some very recent studies, impacting on the readers' ability to consider how representative the sample is of their own clinical practice (Baram and Lenger 2012; Kim et al. 2012).

The ICF model provided structure to the analysis of the efficacy of interventions against walking ability-related outcome measures. The ICF provides a common language for describing health, functioning, and disability (Rosenbaum and Stewart 2004). The theoretical mechanism underpinning the interventions applied to impairments within this review can broadly be classified as targeting muscle weakness (n=4; Ahlborg et al. 2006; Andersson et al. 2003;

Maeland et al. 2009; Taylor et al. 2013), spasticity (n=2; Brochard et al. 2009; Maanum et al. 2011) and/or motor dexterity (n=5; Baram and Lenger 2012; Ahlborg et al. 2006; Dickin et al. 2013; Kim et al. 2011; Kim et al. 2012).

Muscle weakness

Four studies (Ahlborg et al. 2006; Andersson et al. 2003; Maeland et al. 2009; Taylor et al. 2013) investigated the efficacy of a lower limb strengthening program on gait outcomes. Although Andersson et al.'s case-control study (2003) was able to demonstrate an improvement in a range of gait outcomes (GMFM, TUG, 6MWT, gait velocity) post 10 weeks of biweekly exercise sessions, more recent RCTs failed to demonstrate an effect with no gait improvement post 8 weeks (Ahlborg et al. 2006; Maeland et al. 2009), or 12 weeks of exercise (Taylor et al. 2013). These differences in outcomes may relate to study design, but may also be attributable to the marked variation across studies in the training protocols and participant characteristics. Study protocols varied in training parameters with respect to muscle groups targeted, training intensity, training frequency, equipment usage and session design. Cohorts in the studies by Andersson et al. (2003) and Taylor et al. (2013) were also around 10 or more years younger than those in the study by Maeland et al. (2009). A recent systematic review of the efficacy of strengthening interventions in children and youth with CP suggests that greater efficacy may be experienced by those who are younger (Park and Kim 2014). Andersson et al.'s participants (2003) were also at a higher level of mobility (GMFCS I and II) compared to those described by Taylor et al. (2013) and Maeland et al. (2009) (GMFCS II and III). Mobility decline is more likely to be experienced in middle age by adults with CP who are less independently mobile (Strauss et al. 2004). It may be that benefits from lower limb strengthening programs are more likely to occur in those with greater ambulatory ability pre-intervention.

In order for strengthening interventions to be recommended for adoption by this population, it is also important to identify the maintenance of any gains after cessation of the program. Scianni and colleague's review of strengthening interventions in children and adolescents with

CP suggested that any effects on the GMFM may not be maintained after program completion (Scianni et al. 2009). Only Taylor et al.'s study (2013) in this review reported a follow up assessment to identify the longevity of effects on their selected outcome measures.

Spasticity

Both pharmacological studies explored the impact of medication (BTX-A, Maanum et al. 2011]; baclofen, Brochard et al. 2009) to reduce the effect of spasticity on gait outcomes. Both intervention and control participants in Maanum et al.'s study (2011) improved in 6MWT scores, and the intervention group improved in TUG score, with greater variability in gait outcomes apparent in the case series reported by Brochard et al. (2009). No clear recommendations can be made regarding the efficacy of medication on spasticity in ambulant adults with CP as a result.

Motor dexterity

Most studies in this review explored the efficacy of an intervention that targeted motor dexterity either through driving coordinated motor output, or by optimising sensory input, or both (Ahlborg et al. 2006; Baram and Lenger 2012; Dickin et al. 2013; Kim et al. 2011; Kim et al. 2012). Baram and Lenger (2012) and the two studies by Kim's groups (2011; 2012) reported the effect of enhanced sensory input through auditory or visual mechanisms. There is some evidence of efficacy of an auditory cueing strategy on improving body structure and function measures. Improved kinematic quality was demonstrated in both of Kim et al.'s studies (2011; 2012), and temporospatial parameters improved in Kim's (2012) subsequent RCT. The results of Baram and Lenger's auditory cueing case series (2012) were more variable, with a stronger trend demonstrated in the visual cueing case series. The efficacy of sensory cueing on gait outcomes has been previously demonstrated in those with acquired neurological disease (Arias and Cudeiro 2008; Thaut et al. 2007) and in children with CP (Ruck et al. 2010), however is typically not sustained. The longevity of any changes as a result of this intervention in adults with CP is important to identify before this intervention can be recommended.

The clinical importance and magnitude of the effect needs to be considered when interpreting the efficacy of interventions. Few studies interpreted outcome data with respect to minimally clinically important differences (MCID). No MCID in gait speed is available for adults with CP, however data from a geriatric sample suggests a small meaningful change requires a gain of at least 0.05 m/sec in gait speed (Perera et al. 2006). Only three studies exceeded this MCID in gait speed from a mixture of interventions (strength training , Andersson et al. 2003, visual cueing, Baram and Lenger 2012, and RAS, Kim et al. 2012). Maeland et al. (2009) proposed a MCID of 50m for the 6MWT, based upon clinical and functional community task requirements. Based on this estimate, only the participants in the study by Andersson et al. (2003) achieved a MCID post strengthening program intervention. In general, effect sizes were small (Cohen 1988). The nature of 'improvement' in gait speed should also be considered. Although low gait speed (<1m/sec) identifies persons at high risk of health-related outcomes in well-functioning older people (Cesari et al. 2005), increasing gait speed may not be desirable in those with CP, as an increase may result in excessive energy expenditure (Fonseca et al. 2004). It is likely that self-selected gait speed is optimised by those with CP to balance environmental demands, available dynamic resources and task requirements, and hence other qualitative measures of mobility may be more valuable. Of interest, although participants in the study by Taylor and colleagues did not improve in gait speed, significant improvement relating to gains in self-rated perceptions of gait improvement occurred (Taylor et al. 2013). Given that measures of ambulatory self confidence and falls efficacy are recognised as important components of older adult balance and mobility programs due to the relationship between self-efficacy and participation, it is recommended that these aspects are included in future trials.

A number of limitations should be acknowledged when interpreting the findings of this review. This review applied rigorous inclusion/exclusion criterion to identify ambulant samples and thus may have excluded studies of participants who had recently become non ambulant. It is possible that this resulted in the exclusion of studies with individuals who may have been able to regain ambulation as a result of a gait training intervention. However, we would argue that adults with CP, frequently reluctant to re-engage with health services (Ng et al. 2003), may

typically access community based therapies as first contact to address mobility decline. It is not unreasonable therefore to explore what evidence exists to underpin conservative therapies for this cohort. It is also possible that some potentially relevant studies were excluded as a result of the application of our stringent age criterion. We selected 18 years in order to ensure that participants had reached musculo-skeletal maturity, and that any school-based therapy interventions would have ceased. We also considered that the nature and design of interventions aimed at adults may differ from those developed for children. In addition, we only identified studies that were published in English. All eligible papers were retained in the review regardless of study quality, in order to provide a comprehensive overview of the few studies that were available. Publication bias was not assessed, and the uncontrolled studies may present an overestimation of treatment efficacy.

McGinley et al. (2012) have proposed a number of recommendations for consideration when planning or reporting future surgical interventional studies in CP that are also relevant to future studies of conservative gait interventions in adults with CP. The use of GMFCS Level to describe and stratify participants, description of movement disorder and topographical distribution, adequate reporting of the intervention, RCT methodology wherever possible, appropriate selection of valid and reliable standardized outcome measures described in relation to ICF domains, and relating to MCID and/or reporting of clinical significance are advised (McGinley et al. 2012).

Conclusion

Ambulant adults with CP may benefit from conservative interventions to address age-related gait decline. The greatest amount of evidence currently available supports improvement in gait speed, although the effect size is small. The evidence to support strength training as a strategy to improve gait in adults with CP is currently inconsistent. Evidence to support the efficacy of one specific intervention over another on a gait-related impairment or activity limitation is

currently limited. Further research is required using higher quality trial designs, standardised gait outcome measures, and longer term measurement of effects to enable clearer evaluation of interventional efficacy.

Declaration of interest

The authors report no declarations of interest.

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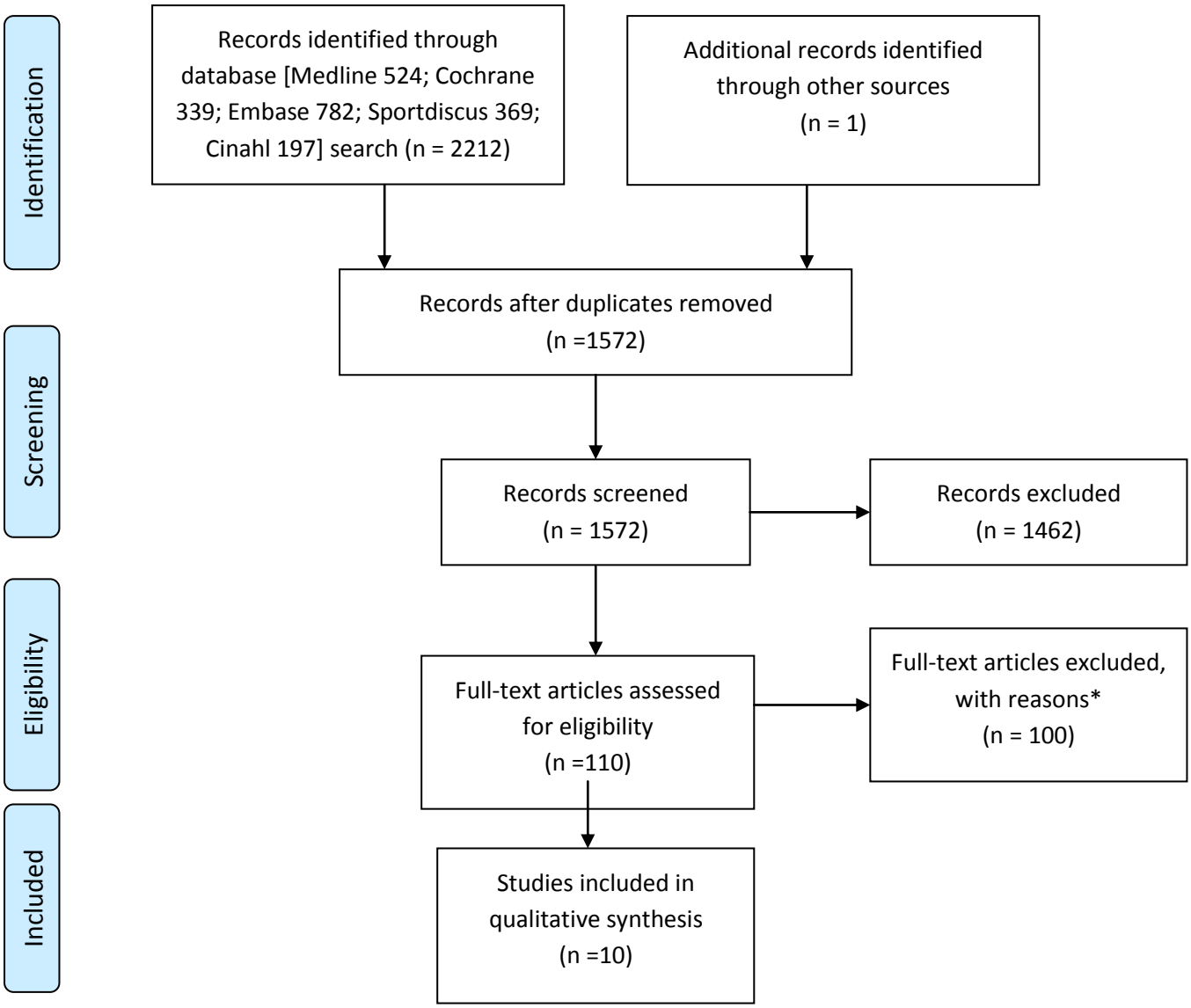
Appendix 1		
	EMBASE SEARCH	
#	Searches	Results
1	Cerebral palsy.mp. or Cerebral Palsy/	28571
2	Exercise Therapy/ or Physical therapy Modalities/ or or physical therapy.mp.	80116
3	Rehabilitation	58106
4	Gait/ or locomotion/	69916
5	2 or 3 or 4	201202
6	Muscle Relaxants, Central/or Baclofen/ or intrathecal baclofen pump.mp.	17901
7	Botulinum toxin.mp. or Botulinum Toxins/	22708
8	Phenols/	34412
9	6 or 7 or 8	75021
10	5 or 9	244687
11	1 and 10	6025
12	Limit 11 to (English language and humans)	3781
13	Limit 12 to (adult <18 to 64 years> or aged <65+ years>)	782

Figure 1: PRISMA flow diagram



*full text exclusion reason in order of application of inclusion criteria

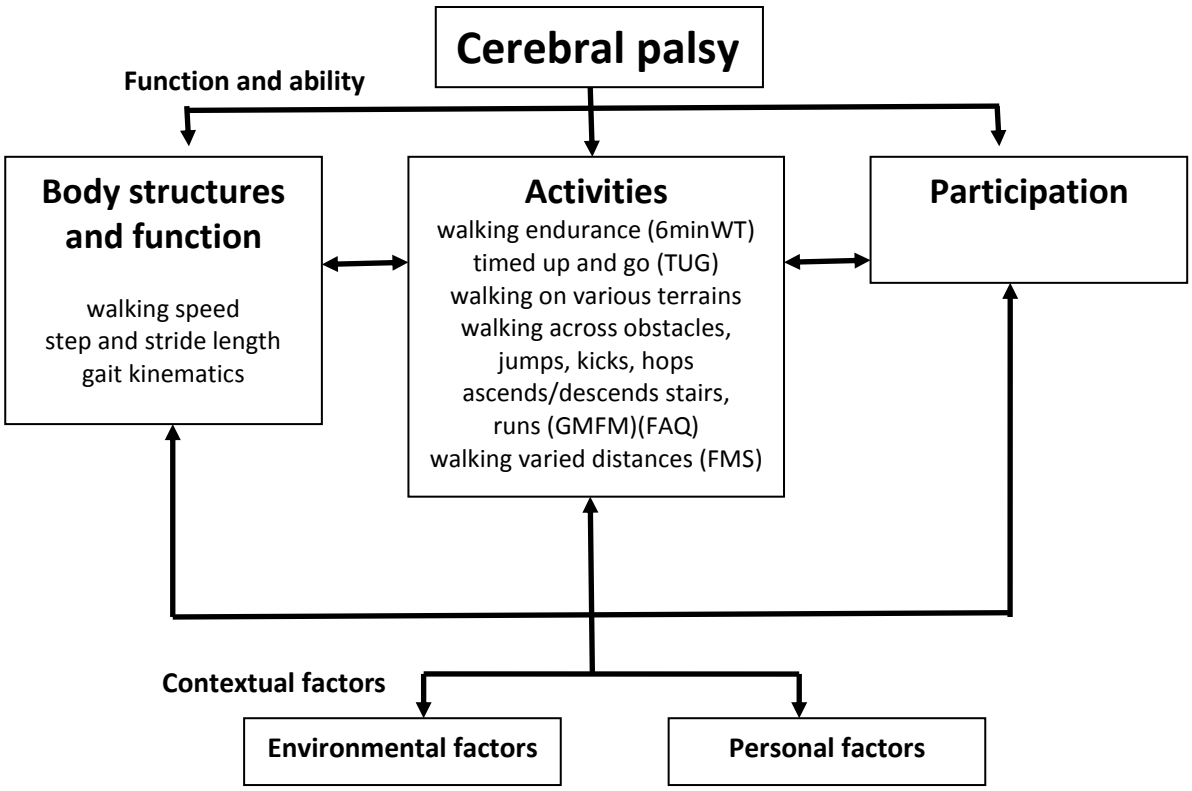
(1) Mean age < 18 years, or unable to extract data for subjects >18 years, n=73

(2) Participants not ambulant prior to intervention, or unable to extract ambulant subgroup, n=14

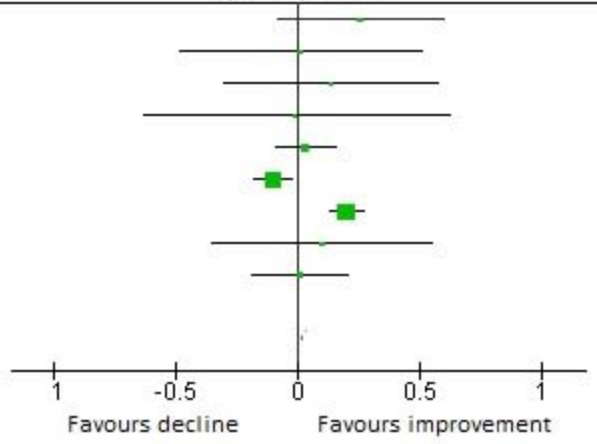
(3) Gait not a primary aim of intervention, n=4

(4) No objective measure of gait used, n=9

Figure 2: International Classification of Functioning illustrating the alignment of gait measurement outcomes with ICF domains.



Study or Subgroup	Post intervention Mean	SD	Total	Pre intervention Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Andersson	1.01	0.405	10	0.754	0.372	10	1.8%	0.26 [-0.08, 0.60]
Baram auditory	1.087	0.244	2	1.077	0.262	2	0.8%	0.01 [-0.49, 0.51]
Baram visual	1.378	0.285	3	1.242	0.259	3	1.1%	0.14 [-0.30, 0.57]
Brochard	0.473	0.306	3	0.48	0.462	3	0.5%	-0.01 [-0.63, 0.62]
Dickin	0.993	0.128	8	0.961	0.121	8	13.9%	0.03 [-0.09, 0.15]
Kim NDT	0.6	0.1	13	0.7	0.1	13	35.0%	-0.10 [-0.18, -0.02]
Kim RAS	0.7	0.1	15	0.5	0.1	15	40.4%	0.20 [0.13, 0.27]
Maeland	1.1	0.4	6	1	0.4	6	1.0%	0.10 [-0.35, 0.55]
Taylor	0.95	0.34	23	0.94	0.34	23	5.4%	0.01 [-0.19, 0.21]



NDT = neurodevelopmental therapy; RAS = rhythmic auditory stimulation

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kim 2012	0.7	0.1	13	0.6	0.1	15	84.2%	0.10 [0.03, 0.17]
Maeland	1.1	0.4	6	0.8	0.6	6	1.4%	0.30 [-0.28, 0.88]
Taylor	0.95	0.34	23	0.91	0.29	25	14.4%	0.04 [-0.14, 0.22]
Total (95% CI)			**42**			**46**	**100.0%**	**0.09 [0.03, 0.16]**

Heterogeneity: Chi² = 0.86, df = 2 (P = 0.65); I² = 0%

Test for overall effect: Z = 2.71 (P = 0.007)

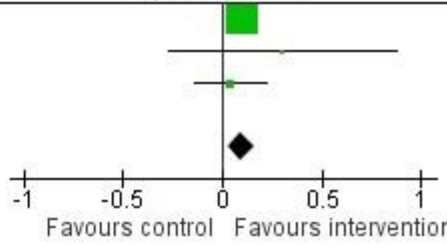


Table 1. Strength of recommendations using the GRADE approach

Starting level of evidence based on study design	Quality of evidence (key criteria for selection, detection, performance and attrition risk of bias)	Overall strength of recommendation
High: Randomised controlled trials	High	High
	Low	Low
Low: Observational (case-controlled and case-series)	High	Low
	Low	Very low

Table 2. Key descriptive study details, study design and quality scores from the 10 studies included in the systematic review

Study ID	**Population**		**Intervention**		**Outcome**	**Study quality**		
Author (first named) Year Country	**Intervention characteristics**	**Comparison characteristics**	**Proposed target of intervention**	**Intervention type** (Additional interventions)	**Gait outcome**	**Study design** (level of evidence)	**Quality of Evidence** Selection Performance Attrition	**Strength of evidence**
Physiotherapy Studies								
Ahlborg 2006 Sweden	N =7 (I: WBV) Age 32 (24-41) M:F 4,3 Diplegia GMFCS: I-III	N = 7 (CP: PRE) Age 30 (21-39) M:F 4,3 Diplegia GMFCS I-III	WBV: Motor dexterity PRE: Muscle weakness	WBV: 8 week training period, 3x/week PRE: (leg press) 8 week training period, 3x/week (Nil)	GMFM (E) 6MWT, TUG	RCT (High)	Low Low High	Low
Andersson 2003 Sweden	N=10 (I) Age 31 (23-44) M:F 7,3 Diplegia GMFCS*:I, II	N=7 (CP) Age 33 (25-47) M:F 4,3 Diplegia GMFCS*:I, II	PRE: Muscle weakness	I: 1 hour, 2x/week for 10 weeks 10 leg strengthening exercises plus 15 mins leg stretches (Nil)	GMFM (E), 6MWT TUG	Case control (Low)	Low Low High	Very low
Baram (visual) 2012 Israel	N= 3[1] (I) Age: 21 (18-26) M:F 1,2 NR	N=7 (Healthy) Age: 12 (12-13) M:F: 4,3	Motor dexterity (via sensory feedback)	Single training session of visual cueing	Spatial temporal	Case control (Low)	Low High Low	Very low

	GMFCS*: I, II							
Baram (auditory) 2012 Israel	N=2[1] (I) Age: 22 (18-26) M:F 1,1 NR GMFCS*:I, II	N=8 (Healthy) Age: 13 (12-14) M:F 4,4	Motor dexterity (via sensory feedback)	Single training session of auditory cueing	Spatial temporal	Case control (Low)	Low High Low	Very Low
Dickin 2013 USA	N=8 (I) Age: 30 (10, 20 -51) M:F 6,2 Diplegia (4) Hemi(4) GMFCS*:I, II	N/A	Motor dexterity	Single session of WBV (1 min WBV; 1 min rest) x 5 applied in semi squat position	Kinematic Spatial temporal	Case series (Low)	Low High High	Very low
Kim 2011 Korea	N=14 (I) Age: 26 (15-38, 7.31) M:F 9,5 Diplegia GMFCS: I, II	N=30 (Healthy) Age: 22 (1.74) M:F 15,15	Motor dexterity (via sensory feedback)	I: Single session intervention of individualised RAS	Kinematic Spatial temporal	Case control (Low)	Low High High	Very low
Kim 2012 Korea	N= 15 (I: RAS) Age:I: 27.3 (SD 2.4) M:F 10,5 Diplegia GMFCS*: I	N= 13 (CP: NDT) C: 27.3 (SD 2.5) M:F 7,6 Diplegia GMFCS*: I	RAS: Motor dexterity (via sensory feedback) NDT: motor dexterity, movement disorder	3 weeks of 3 x 30 minute sessions/week of either individualised RAS or NDT delivered by trained physiotherapists (Nil)	Kinematic Spatial temporal	RCT (High)	High High High	High

			normalisation					
Maeland 2009 Norway	N=6 (I) Age: 41 (32-69), M:F 2,4 Diplegia GMFCS: II, III	N= 6 (CP) Age: 45 (27-65) M:F 2,4 Diplegia GMFCS: II, III	Muscle weakness	I: 8-week PRE (10 min warm up stationary bike or treadmill followed by seated leg press) 3 days/wk (Nil)	Spatial - Temporal GMFM (E: items 84 & 87) 6MWT	RCT (High)	High High High	High
Taylor 2013 Australia	N=23(I) Age: 18 (1.9) M:F 13,10 NR GMFCS: II, III	N=25(CP) Age: 18 (2.9) M:F 13,12 NR GMFCS: II, III	PRE: Muscle weakness	I: 12 weeks of 2 x/week 4-6 individualised leg exercises (usual care including physio, no PRE)	Spatial-Temporal Kinematic GMFM (D, E) 6MWT FMS Gillette FAQ	RCT (High)	High High High	High
Pharmacology Studies								
Brochard 2009 France	N= 3[1] (I) Age: 21 (19-22) M:F NR Diplegia (1), Quad (2) GMFCS: II, III	N/A	Movement disorder (spasticity)	Intrathecal baclofen pump Pre and post test – mean 16 (SD 9) months post (NR)	Spatial-Temporal Kinematic, Gillette FAQ	Case series (Low)	Low High Low	Very low
Maanum 2011 Norway	N=33 (I) Age: 36.2 (10.6) M:F 14,19	N=33 (CP) Age: 38.4 (12.1) M:F 16,17	Movement disorder (spasticity)	I: Botox (BoNT-A) CP: saline injections Pre-test and post test at 8	Kinematic 6MWT TUG	RCT (High)	High High High	High

	Diplegia (17) Hemi (16) GMFCS: I-III	Diplegia (19) Hemi (14) GMFCS: I-III	weeks (I and CP: usual physio)		

I: intervention group; CP = cerebral palsy control group; NR: not reported; N/A: not applicable

WBV: whole body vibration; PRE: progressive resistance exercise; RAS: rhythmic auditory stimulation; NDT: neurodevelopmental therapy; GMFCS: Gross Motor Function Classification System; GMFM: Gross Motor Function Measure; 6MWT: six minute walk test; TUG: timed up and go; FMS: functional mobility scale; FAQ: functional ambulation questionnaire; RCT: randomised controlled trial;

*author estimate from description; [1]: subset of cohort ≥18 years

Table 3. Response to intervention: Within-group treatment effect, and between-group treatment effect of cohorts reporting statistical analysis (first author and year of publication)

ICF domain	**Outcome tool/measure**	**Within group treatment effect**			**Between group treatment effect**	
		Improved	**No effect**	**Declined**	**Improved**	**No Difference**
Physiotherapy interventions:						
Body structure and function	Speed	Vibration (Dickin, 2013) Auditory Cue (Kim, 2012) Strength Training (Anderson, 2003)[1]	Strength Training (Maeland, 2009; Taylor, 2013) Auditory Cue (Kim, 2011)[2]	NDT (Kim, 2012)	Strength Training vs control (Anderson, 2003)[1] Auditory Cue vs NDT (Kim, 2012)	Strength Training vs control (Maeland, 2009; Taylor, 2013)

	Step/stride length	Auditory Cue (Kim, 2012) Vibration (Dickin, 2013)	Auditory Cue (Kim, 2011)[2]	NDT (Kim, 2012)	Auditory Cue vs NDT (Kim, 2012)	
	Kinematic (including GDI, GGI, GPS)	Auditory Cue (Kim, 2011; Kim, 2012)	NDT (Kim, 2012) Strength Training (Taylor, 2013)		Auditory Cue vs NDT (Kim, 2012)	Strength training vs control (Taylor, 2013)
Activity	GMFM (D & E)	Strength Training (Anderson, 2003)[3] Vibration (Ahlborg, 2006)	Strength Training (Ahlborg, 2006; Maeland, 2009[4]; Taylor, 2013)		Strength Training vs control (Anderson, 2003)[3]	Strength Training vs vibration (Ahlborg, 2006) Strength Training vs control (Maeland,

						2009[4])
	6MWT	Strength Training (Anderson, 2003)	Vibration (Ahlborg, 2006) Strength Training (Ahlborg, 2006; Maeland, 2009; Taylor, 2013)		Strength Training vs control (Anderson, 2003)	Strength Training vs vibration (Ahlborg, 2006) Strength Training vs control (Maeland, 2009)
	TUG	Strength Training (Anderson, 2003)	Vibration (Ahlborg, 2006) Strength Training (Ahlborg, 2006)		Strength Training vs control (Anderson, 2003)	Strength Training vs vibration (Ahlborg, 2006)
	FAQ	Strength Training (Taylor, 2013)			Strength Training vs control (Taylor, 2013)	
	FMS	Strength Training (Taylor, 2013[5])			Strength Training vs control (Taylor, 2013[5])	
Pharmacology interventions:						

Body structure and function	Kinematic		BTX-A (Maanum, 2011)			BTX-A vs placebo (Maanum, 2011)
Activity	6MWT	BTX-A (Maanum, 2011)				BTX-A vs placebo (Maanum, 2011)
	TUG	BTX-A (Maanum, 2011)				BTX-A vs placebo (Maanum, 2011)

BTX-A : botulinum toxin type A

GDI: gait deviation index; GGI: Gillette gait index ; GPS: Gait profile score ; GMFM: gross motor function measure ; 6MWT : six minute walk test ; TUG : timed up and go ; FAQ : functional ambulation questionnaire

[1]calculated from distance covered in six minutes; [2]expressed as a percentage of side to side asymmetry; [3]total of Domains D and E; [4]Items 84 and 87 only of domain E; [5]FMS 5m only