

Effectiveness of Treadmill Training on Walking Ability in Adults with Cerebral Palsy: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Patients with cerebral palsy (CP) may necessitate long-term treatment and monitoring of their condition, not only during the period of development but also during adulthood. **Objectives:** This systematic review aimed to analyze evidence from randomized controlled trials (RCTs) that have investigated the effect of treadmill training on walking ability in adults with cerebral palsy. **Methods:** RCTs were identified and selected systematically, with appropriate keywords applied in four scientific databases (Medline, Scopus, the Cochrane Library, and the Physiotherapy Evidence Database) and one bibliographic search engine (Google Scholar) from January 1980 to September 2021. Two assessors extracted and analyzed data from relevant RCTs published in English and then independently rated those studies for risk of bias with the Risk of Bias (RoB 2) tool. **Results:** Out of the 96 studies that were initially identified, 93 were excluded, as these either did not meet the inclusion criteria or were duplicates. Three clinical trials were finally included, characterized by some concerns and a high risk of bias (RoB 2). Meta-analysis was only performed for the maximum distance in the '6-minute walk for distance test', due to differences in the remaining outcomes utilized between studies. Overall, there was evidence of some concerns and high risk of bias that treadmill training did not significantly improve the walking ability in adult patients with CP relative to the control conditions. **Conclusion:** More high-quality RCTs are required, examining the effectiveness of treadmill training on different aspects of walking ability such as gait speed, endurance, and energy expenditure.

Key words: Cerebral Palsy, Adults, Treadmill, Exercise, Physical Therapy, Walking, Gait

INTRODUCTION

The term cerebral palsy (CP) refers to a group of disorders caused by non-progressive damage to the immature brain resulting in motor and postural disorders. Motor control disturbances, abnormal muscle tone, poor sensation, and coordination may promote abnormal movement patterns during the development period causing contractions and deformities (Graham, Paget & Wimalasundera, 2019). These disturbances may worsen in adulthood, restricting walking ability and activities of daily living (Jahnsen et al., 2004; Tosi et al., 2009). Furthermore, primary arthritis, pain, and chronic fatigue may contribute to the deterioration of the functional ability of adults with CP (Tosi et al., 2009).

In general, individuals with CP experience a series of decrements in several psychosocial aspects (e.g., social support, self, and social acceptance), considered critical factors for successful involvement in a life situation, as described by the ICF framework (Horsman et al., 2010). These aspects

affect functional independence and successful engagement in several social activities and have been reported in the literature (Tosi et al., 2009; Verhoef et al., 2014). Specifically, adults with CP exhibit reduced participation in recreation activities, difficulties in intimate relationships and lower rates of employment compared to the typically developed adults (van der Slot., 2010; Maestro-Gonzalez et al., 2018). Further, the economic burden of CP on parents/carers can be significant (Tonmukayakul et al., 2018). Health care of CP patients involves expenses for home modification, special equipment, transport, assistance with daily living, therapy, and rehabilitation. Improvements in walking ability, occupational skills, and behavior may emerge through strength and treadmill training, counseling programs, and lifestyle interventions conducted at rehabilitation centers or at home, which are considered feasible and cost-effective for adolescents and young adults with CP (Slaman et al., 2015; Shih et al., 2018).

Treadmill training, an intervention based on motor learning theories, has been widely used for the restoration of components of mobility according to the International Classification of Functioning, Disability and Health (ICF), such as the walking ability of individuals with CP (Willoughby et al., 2010; Chrysagis et al., 2012; Johnston et al., 2011). Treadmill with or without support promotes task-specific training that in turn may cause nervous system neuroplastic changes, improving walking ability and independence (Hesse, 2001; Hadders-Algra, 2000). These changes are more likely to occur in children below the age of 10-12 years of age, which have not developed a mature motor pattern yet (Ericsson, Krampe, & Heizmann, 1993; Petersen et al., 2010). On the other hand, the walking patterns have already been developed in adults with cerebral palsy, although secondary connective tissue abnormalities tend to remain (Morgan et al., 2014).

Previous systematic reviews examined the effectiveness of treadmill training with or without body weight support in children and young adults with cerebral palsy. Multu et al. (2009) stated that body weight supported treadmill training (BWSTT) may have positive benefits to gross motor function and gait parameters of children with cerebral palsy, taking into account the small number of participants, the heterogeneity of participants' gross motor ability, and the low quality of the studies included. Similarly, two previous systematic reviews concluded that BWSTT is a treatment approach that is both safe and feasible, demonstrating positive results in gross motor function and walking parameters for children with CP, however in parallel underlying the importance of further high-quality research in this field (Damiano et al., 2009; Willoughby et al., 2009).

Recently published systematic reviews and meta-analyses (Moreau et al., 2016; Booth et al., 2018; Han & Yun, 2020) reported positive effects of gait training (overground, treadmill with or without body weight support) on the walking ability of children and adolescents with CP. Specifically, Moreau et al. (2016) stated that children with CP can benefit from gait training interventions regarding gait speed. Booth et al. (2018) also looked into the impact of functional gait training (treadmill training with or without body weight support and overground gait training) on measures relating to gait in children and young adults with CP. A moderate effect for gait speed was reported, while gait endurance and gross motor function demonstrated a smaller effect (Booth et al., 2018). Finally, Han & Yun, (2020) reported a significant improvement in gait endurance, gait speed, and limb support time due to treadmill training in eight studies included in this review. Therefore, summarizing previous research, gait training is superior on walking ability compared to conventional physical therapy, is safe in general and may be conducted in clinical and community settings.

Overall, published systematic reviews with or without meta-analyses examined the effectiveness of gait training in groups of participants with cerebral palsy ranging from children to young adults. Given that adults with CP have shown a decline in mobility and activity levels during their life

span, it is timely to explore the effect of gait interventions on the walking ability of that population. Therefore, the present systematic review and meta-analysis aimed to examine the effect of treadmill training on the walking ability of adults with CP over the age of 18.

METHODS

The present systematic review and meta-analysis was conducted according to updated PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations (Page et al., 2021) and has been previously registered at the PROSPERO international database (CRD42021271826). Risk of bias assessment was performed by the revised Cochrane risk-of-bias tool (RoB 2) for randomized trials (Higgins et al., 2019).

Inclusion and Exclusion Criteria

The inclusion criteria for the present review were as follows: (a) randomized controlled trials or non-randomized controlled trials examining the effects of treadmill training with or without support, (b) engagement of adults with cerebral palsy over 18 years of age, (c) studies with outcomes related to walking ability and (d) studies written in English.

Studies that did not include a comparison group, used gait training without treadmill as an intervention, that included children or adolescents with cerebral palsy, and did not utilize at least one outcome variable concerning walking ability, such as walking speed or endurance, were excluded.

Search Strategy

The sources searched were: Medline (via PubMed), Scopus, Cochrane Library, and the PEDro Databases, as well as the Google Scholar search engine. The search was conducted within a certain timeframe, from January 1980 to September 2021. The search strategy was carried out using the PICO format. For example, in the PubMed: (a) for the population the terms 'adults' AND 'cerebral palsy', (b) for the intervention, the terms 'treadmill training' OR 'treadmill' OR 'functional training' OR 'gait training' c) for the outcome the terms 'gait speed' OR 'gait function' OR 'walking' OR 'spatiotemporal' OR 'locomotion'.

The selection of the studies was performed by two reviewers of the research (NC and GT) team applying the eligibility criteria. One of the two reviewers screened the records, and the other checked the decisions.

Data Extraction

Participant demographics, baseline characteristics, study design and methodology, intervention, duration, adverse effects, outcome data were extracted in custom-made data extraction tables. The data was extracted by one reviewer and was reviewed by another reviewer. Disagreements between individual judgments were resolved by a third reviewer (GAK) member of the research team.

Risk of Bias Assessment

Two assessors conducted the risk of bias assessment using the revised Cochrane Risk-of-Bias tool (RoB 2) (Higgins et al., 2019). The tool examines five bias domains referring to randomization procedure, intervention, outcome data, and the reported result. The overall judgment of risk of bias is classified as either 'low risk of bias', 'unclear risk of bias', and 'high risk of bias'.

Data Synthesis-Statistical Analysis

Data were examined to ensure the comparability between populations, interventions, and outcome types and their assessment time-points before these could be combined in a meta-analysis. Guidance was provided by the "Cochrane Handbook for Systematic Reviews of Interventions", chapters 6, 10 and 23 (Higgins et al., 2019).

If certain data were not amenable to meta-analysis, a qualitative synthesis approach was followed. If data could be quantitatively combined, the random effects method for meta-analysis was applied, with a variation on the inverse-variance method, under the assumption that the different studies reported different yet related intervention effects. The RevMan 5.4 statistical package, freely available from the Cochrane Systematic Reviews site was used for relevant comparisons and construction of the forest plots of the outcomes selected.

RESULTS

A bibliographic search of the five databases revealed 96 articles. After the removal of duplicates, 58 studies remained for the title and abstract screening. From 58 records screened, 53 were excluded due to various reasons such as ineligible population, intervention, methodical design or they were books chapters or review studies. Five reports were retrieved and checked for eligibility, and finally, three of them were included in the review. A flow chart (Figure 1) presents in detail the procedure that was followed.

Characteristics of Studies

All studies included were RCTs, however, with relatively low sample size. All studies had at least one group performing treadmill training compared to a control group. Outcomes of the same kinematic domain (distance or speed), measured in at least two studies, with the same test before and immediately after the exercise period, were included in a meta-analysis. The three eligible studies were conducted in Iran (Bahrami et al., 2019), Denmark (Lorenzen et al., 2017), and Korea (Kim et al., 2015). A treadmill was used at home (Lorenzen et al., 2017) or in an educational and rehabilitation charity center (Bahrami et al., 2019). In contrast, Kim et al. (2015) did not report the intervention setting.

All studies included adults with CP, classified as either GMFCS I-III level (Bahrami et al., 2019; Lorenzen et al., 2017) or those that could ambulate independently indoors without a gait aid (Kim et al., 2015). The mean(SD) age of the participants ranged from 24.43(9.07) to 38.5(12.5) years

in all studies, whereas an age range of 18-45 was reported by Bahrami, Noorizadeh Dehkordi, & Dadgoo (2019) and an age range of 19-59 by Lorenzen et al. (2017). All included studies reported participants' demographic details (age, sex, and the number of participants) separately for the experimental and control groups.

Experimental group interventions comprised treadmill training (Bahrami, Noorizadeh Dehkordi, & Dadgoo, 2019; Lorenzen et al., 2017) or treadmill training combined with conventional physical therapy (Kim et al., 2015), lasting for six weeks (Lorenzen et al., 2017), eight weeks (Bahrami, Noorizadeh Dehkordi, & Dadgoo, 2019), or between 1-2 months (Kim et al., 2015). During that intervention period, participants trained for 30 minutes per session and completed a total of 16 and 20 sessions in the studies of Bahrami, Noorizadeh Dehkordi, & Dadgoo (2019) and Kim et al. (2015) respectively, while Lorenzen et al. (2017) reported a mean(SD) of 34.3(8.8) days of daily training.

As far as the training progression details provided, all three studies reported speed and distance progression (Bahrami, Noorizadeh Dehkordi, & Dadgoo, 2019; Lorenzen et al., 2017; Kim et al., 2015), whereas progression in velocity and incline was reported by Lorenzen et al. (2017) as mean(SD) values.

Bahrami, Noorizadeh Dehkordi, & Dadgoo (2019) described the traditional therapy provided to the control group in detail, consisting of static stretching sport biking, strengthening exercises and proprioceptive neuromuscular facilitation. The control group received conventional therapy in the study of Kim et al. (2015), whereas Lorenzen et al. (2017) described the control group as 'non-training' with no other details (Table 1).

Outcomes

Walking ability was measured with the 10-meter walk test (10MWT) (Bahrami, Noorizadeh Dehkordi, & Dadgoo, 2019), 6-minute walk for distance test (6MWD) (Bahrami, Noorizadeh Dehkordi, & Dadgoo, 2019; Kim et al., 2015), and gait analysis kinematic data (Lorenzen et al., 2017). However, the data collected with the 10MWT and the gait analysis kinematic data were derived from a single study each; therefore these measures could not be included in a meta-analysis (Table 2).

Risk of Bias Assessment

Concerning the risk of bias assessment of the studies included, two were rated as having 'some concerns' (Lorenzen et al., 2017; Bahrami, Noorizadeh Dehkordi, & Dadgoo, 2019) and one (Kim et al., 2015) as 'high risk of bias' (Figure 2). All the studies were evaluated as 'low risk of bias' at the domains of 'missing outcomes data' and 'selection of the reported result' as presented in Figures 2 and 3.

Functional Performance Meta-Analysis of 6MWD

The 6MWD, as a functional performance/capacity and an indirect aerobic capacity measure, was reported in 2 of the included studies of the present systematic review (Bahrami,

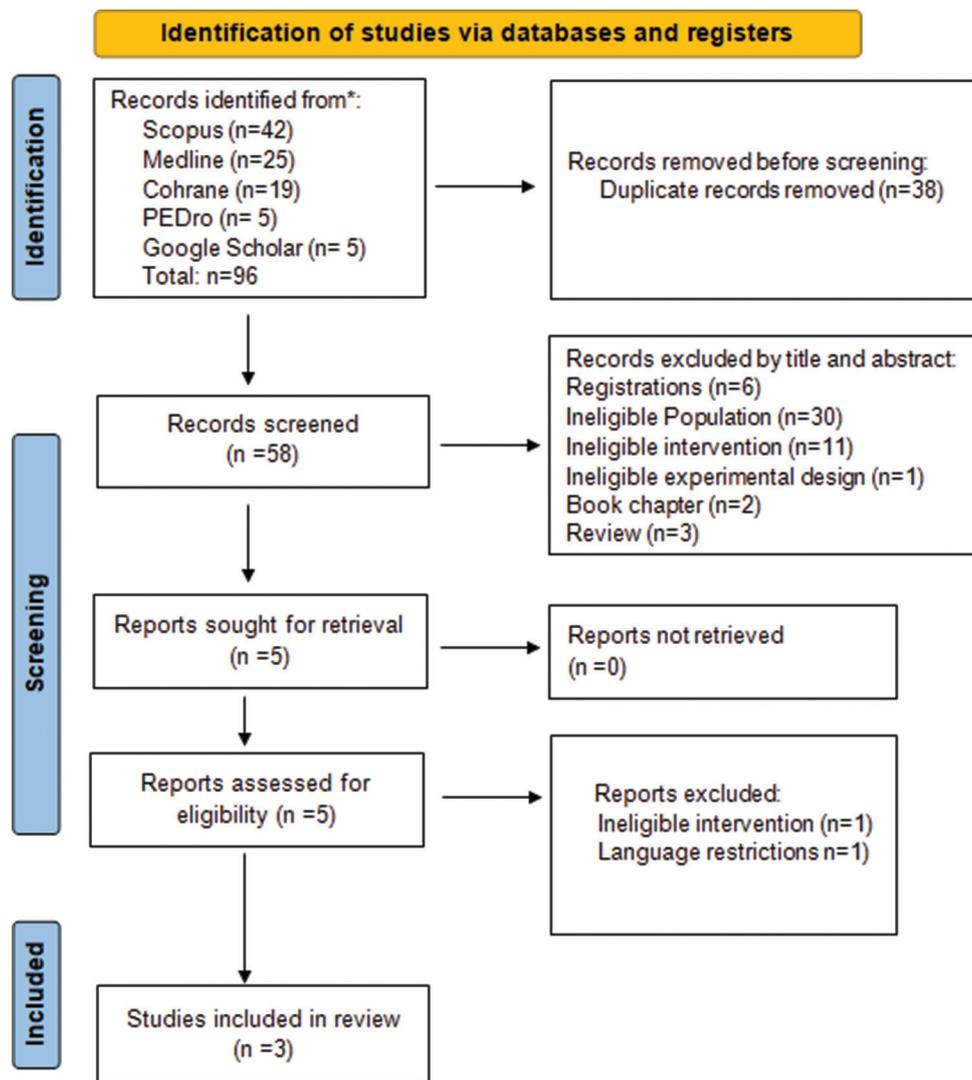


Figure 1. PRISMA flowchart outlining the identification and selection procedure for studies in this systematic review

Noorizadeh Dehkordi, & Dadgoo, 2019; Kim et al., 2015). The imputed values of within-group mean and standard deviation pre-post intervention differences for the 6MWDT were inserted in a forest-plot and a meta-analysis was performed. Overall, 31 participants receiving the experimental treadmill training exercise intervention were compared with 25 participants in the control groups.

As shown in Figure 4, the total effect was not statistically significant ($p=0.44$), although an overall between-group mean difference (95% CI) of 22.74 (-35.25, 80.74) m was registered. From visual inspection, the overlap of CIs between the results of individual studies was evident, as these were quite broad for both studies. The chi-square test was non-significant ($p=0.94$) and the I^2 statistic denoted an 0% of variability in effect estimates due to non-significant heterogeneity between the results of the two studies.

DISCUSSION

After a comprehensive bibliographic search in four databases and one search engine, including studies reported in English, from 1980 onwards, only three relevant articles were retrieved and included in the present review.

The included studies used various tests to evaluate the walking ability of the participants, such as the 10MWT, the 6MWDT, and kinematic data. As mentioned earlier, in the meta-analysis performed, only outcomes measuring the same kinematic domain with the same outcome were included; therefore this requirement was fulfilled only for 6MWDT used by Kim et al. (2015) and Bahrami, Noorizadeh Dehkordi, & Dadgoo (2019). In the study of Lorenzen et al. (2017), although mentioned within their methodology that walking ability was examined by the 6MWDT and 10MWT, no relevant data were subsequently reported. Further, we attempted to contact via e-mail the primary authors of all included studies in this systematic review, to provide data not included in the original reports (mean difference and SD mean difference per group). However, since no response was received, data imputation methods were followed according to recommendations (Higgins, Eldridge, & Li, 2019).

Meta-analysis for 6MWDT showed no significant statistically total effect, although an overall between-group difference was observed. The results disagree with the findings of Han & Yun (2020), who reported a large effect size on walking endurance of treadmill training in children with

Table 1. Characteristics of included studies

Study	Study Design	Age range M(SD)	Functional status	Group E/C	Experimental group intervention	Control group intervention
Bahrami, Noorizadeh, Dehkordi, & Dadgoo, 2019	RCT	18-45 E 25.9 (7.7) C 25.1 (4.3)	I-III GMFCS 15/4/11	15/14	Treadmill training 30 min (3X10 with 2 min interval and 10 min warm up (8 weeks, 16 sessions) Treadmill speed progression (Km/h) 1.17 (0.39) to 2.7 (1.56) Treadmill distance progression (Km) 0.5 (0.27) to 1.23 (0.65)	Traditional physiotherapy (strengthening, balance, PNF) and 10 min warm up
Lorentzen et al., 2017	RCT	19–59 E 37.4 (2.6) C 38.5 (12.5)	I-III GMFCS 10/7/15	16/16	Treadmill training 30 min (6 Weeks, 34.3(8.8) days of training Treadmill speed (km/h) Average: 3.1 (1.4) Progression at 1.3 (0.9) & Treadmill incline (%) Average: 5.5 (2.4) Progression at 5.4 (2.2) (only figure provided)	Details not reported
Kim et al., 2015	RCT	- E 28.6 (8.5) C 24.4 (9.1)	Ability to ambulate independently indoors without a gait aid	14/7	Treadmill training and conventional therapy 30 min (1-2 months, 20 sessions) Treadmill speed progression (met/min) 20.36 (11.34) to 20.71(11.30) Treadmill distance progression (met) 117.14 (60.26) to 120.71(58.50)	Conventional therapy

Table 2. Outcome measures and results of included studies

Study	Outcomes	Pre-intervention	Post-intervention	Results Between groups	Results Within groups
Bahrami, Noorizadeh, Dehkordi, & Dadgoo, 2019	10MWT (m/s) Experimental Control	1.08(0.47) 0.99(0.56)	1.22(0.50) 1.02(0.61)	Non-significant difference (p=0.42)	p=0.00 p=0.51
	6MWDT (m) Experimental Control	291.13(160.28) 276.10(167.19)	342.63(174.62) 308.57(181.22)	Non-significant difference (p=0.61)	p=0.00 p=0.03
Lorentzen et al., 2017	Gait speed kinematic data ----- 6MWDT (m) 10MWT (s)	Only figure provided ----- No data provided		Significant difference (p<0.001) No significant interaction (p>0.6)	
Kim et al., 2015	6MWDT (m) Experimental Control	151.29 (91.79) 162.14 (81.85)	193.93 (79.01) 180.71 (61.40)	Not reported	p<0.05
	Gait velocity (6MWDT) m/min Experimental Control	28.09(14.29) 29.88 (9.96)	33.49(12.69) 31.43 (9.40)	Not reported	p<0.05

cerebral palsy in a meta-analysis including 3 RCTs. However, Han & Yun (2020) included three studies examining walking endurance by different tests such as 6MWDT or 10MWT. Additionally, in the previous review, the mean age of the participants ranged from 6.8-10.3 years, while in our meta-analysis, the mean age of the participants was 24.4-28.6 years. Similarly, Booth et al. (2018), in their systematic

review, argued that gait training might have positive effects on walking endurance in children and young adults with CP, however, without a meta-analysis, due to the variety of the tests used (2-minute walk, 6MWDT, and 10MWT). The researchers concluded that there is weak evidence concerning the effectiveness of treadmill training on gait endurance of children and young adults with cerebral palsy. In agreement

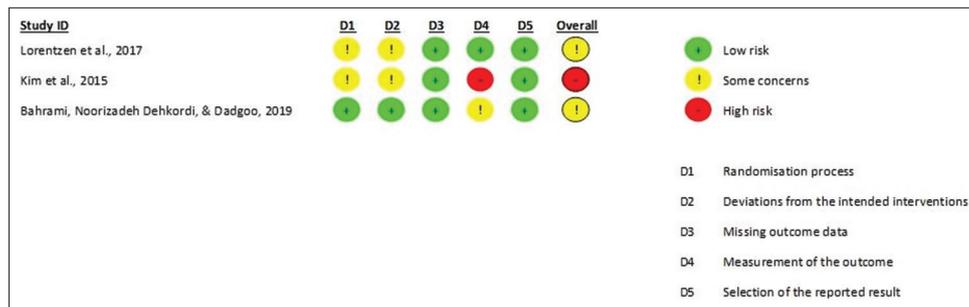


Figure 2. Resulting risk of bias per methodological quality item assessed with the Risk of Bias (RoB 2) Tool

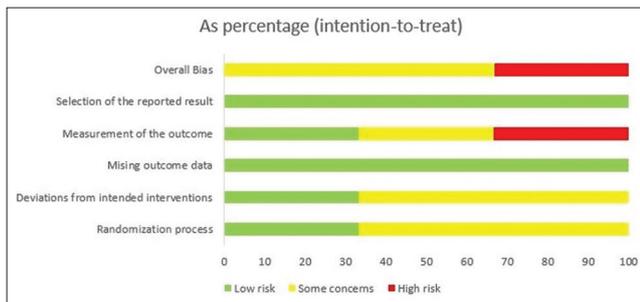


Figure 3. Resulting risk of bias assessed with the Risk of Bias (RoB 2) Tool per methodological quality item expressed as percentage

with our study, Willoughby et al. (2009) and Multu et al. (2009), in their systematic reviews without meta-analysis, reported no significant effect on walking endurance due to treadmill training in children with cerebral palsy with partial body weight support.

Physiological changes occurring during adulthood in individuals with cerebral palsy may explain the results of our study. Specifically, the development of atypical walking patterns accompanying problems such as fatigue, pain, and arthritis limits the functional capacity of adults with cerebral palsy (Jahnsen et al., 2004; Gjesdal et al., 2020).

Additionally, abnormal forces in joints of the lower limbs may contribute to overuse syndromes and poor postural control (Opheim et al., 2009). Finally, increased passive stiffness accompanied with spasticity deteriorates walking ability, negatively affecting daily life activities (Geertsen et al., 2015).

The two studies in our meta-analysis reported a within-group significant effect of the intervention on walking endurance of adults with cerebral palsy as evaluated by 6MWD. A between-group comparison showed no statistical difference in the study of Bahrami, Noorizadeh Dehkordi, & Dadgoo (2019), while Kim et al. (2015) provided no results. No significant heterogeneity was detected between the results of the 6MWD regarding those two studies. However, slight differences or limited information were evident regarding the experimental and control groups' interventions. Specifically, the experimental group in the study of Bahrami, Noorizadeh Dehkordi, & Dadgoo (2019) conducted 16 sessions at eight weeks while the participants in the experimental group of Kim et al. (2015) completed 20 sessions in 1-2 months. Additionally, Bahrami, Noorizadeh Dehkordi, & Dadgoo (2019) provided detailed information

for the traditional therapy of the control group while Kim et al. (2015) described the control treatment group only as 'conventional'.

The three studies in our systematic review reported walking ability parameters that could not be included in meta-analysis. Specifically, Bahrami, Noorizadeh Dehkordi, & Dadgoo (2019) used the 10MWT to examine the effect of a treadmill program on gait speed in adults with cerebral palsy. The researchers stated that there was a non-significant statistical difference between the experimental and the control group that received conventional physical therapy. Similarly, Lorentzen et al. (2017) examined the effectiveness of a treadmill program in adults with cerebral palsy and found no significant interaction between group and time for gait speed as examined by the 10MWT. However, the researchers reported a significant between-group effect for gait speed as examined by three-dimensional gait analysis, although a figure was only provided without numerical data. Finally, Kim et al. (2015) could not identify any between-group differences, comparing the effects of treadmill training relative to conventional physical therapy, concerning energy expenditure as evaluated by the KB1-C oximeter.

Regarding the risk of bias of the included studies in the present systematic review, two showed some concerns and one high risk of bias. Additionally, the 'measurement of the outcome' domain showed high risk and some concerns in the studies included in our meta-analysis.

Treadmill training constitutes a task-specific exercise intervention that may be used according to the principles of motor learning to improve the walking ability of children and young adults with physical disabilities (Moreau et al., 2016; Booth et al., 2018; Han & Yun, 2020). However, studies so far failed to provide a significant effect of treadmill training compared to conventional therapy in adults with CP (Bahrami, Noorizadeh Dehkordi, & Dadgoo, 2019; Kim et al., 2015). However, promising findings have been reported in studies performed in adults with other neurological disorders, such as spinal cord injuries (Yu et al., 2019) and stroke (Polese et al., 2013; Nascimento et al., 2021), following treadmill training programs. Possibly, in order to demonstrate an effect with this type of training alone or in combination with other motor learning-based activities (Hüche Larsen et al., 2021), the specific characteristics of the adults with CP involved have to be registered, and programs of various training dosage (intensity and duration) have to be examined, to match patient capability with the appropriate training dosage. According to the present systematic review and the absence of signifi-

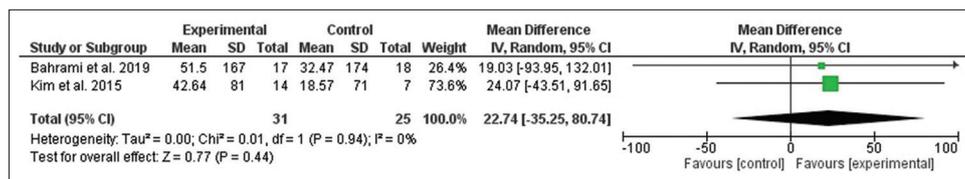


Figure 4. Meta-analysis of studies for 6MWDT

cant effect on walking endurance, we have to acknowledge that the treadmill training is still a safe and feasible intervention which may promote an active lifestyle in adults with CP and increase their participation in meaningful activities, according to the ICF principles (Horsman et al., 2010). The repetitive (recurring) movements of the lower limbs during treadmill training may activate central pattern generators, promoting neuroplasticity and facilitating the reorganization of the central nervous system (Steuer and Guertin, 2019). Further, recent findings in mammalian models have reported increases in the hypoxia-inducible transcription factor (HIF-1 α), a mediator of several genes involved in metabolism, synaptogenesis, and blood flow, occurs with intensive treadmill exercise, suggesting a regulatory role of this factor in exercise-enhanced neuroplasticity (Halliday et al., 2019). Also, improvement in Diffusion Tensor Imaging and Motor Evoked Potential measurements were demonstrated in children with CP involved in antigravity treadmill training (Azizi et al., 2018). Overall, treadmill training, being feasible and cost-effective, may be used by clinicians and researchers interchangeably with other available interventions in the field of rehabilitation in adults with CP.

A number of limitations could have affected the results of the present study. Firstly, the small number of the included studies limits the generalizability of the results. Secondly, there was limited information of the control intervention and the reported results. Finally, there were insufficient data for the walking ability parameters such as gait speed and energy expenditure which could be included in future work. Future studies including sufficient populations and an array of relevant outcome measures are necessary for this population.

CONCLUSION

According to our results, treadmill training is a viable and safe treatment, although not superior to conventional physical therapy concerning the walking endurance of adults with cerebral palsy. There is limited scientific evidence regarding the use of treadmill training in adults with cerebral palsy; therefore, this is still an open area for research, requiring more high-quality randomized trials in the field.

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