NOVEL DEVICES IN THE REHABILITATION OF CHILDREN WITH CEREBRAL PALSY

Ph.D. Thesis

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„A person who never made a mistake

never tried anything new."

Albert Einstein

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1. LIST OF ABBREVIATIONS

BOS	base of support
CI	confidence interval
CIMT	Constraint-Induced Movement Therapy
COM	center of mass
CP	Cerebral palsy
CT	conventional treatment
ET	exercise therapy
GMFM	Gross Motor Function Measure
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HABIT	Hand Arm Bimanual Intensive Therapy
LMC	Leap motion controlled
MD	mean difference
MOS	margin of stability
NDT	neurodevelopmental training
OT	Occupational Therapy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUEST	Quality of upper extremity skills test
RAGT	robotic-assisted gait training
RCT	randomized controlled trial
RoB	Risk of Bias
RT	resistance training
SD	standard deviations
SMD	standardized mean difference
VGBT	Video Game-based Therapy

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to strengthen the faith that the quality of life of children suffering from Cerebral palsy can be improved by novel rehabilitation methods.

My mission is to clarify the indications and roles of innovative methods in the rehabilitation of children with cerebral palsy.

My specific goals include evaluating the effectiveness of new devices in the rehabilitation of disabled children and assessing their impact on daily rehabilitation therapy.

2.2. Scientometrics

Number of all publications:	7
Cumulative IF:	8.20
Av IF/publication:	1.17
Ranking Scimago:	Q1: 3, Q3: 1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	5.2
Av IF/publication:	2.6
Ranking Scimago:	Q1: 2
Number of citations on Google Scholar:	8
Number of citations on MTMT (independent):	3
H-index:	1

2.3.Future plans

My future goals involve integrating my passion for research with front-line patient care. To me, understanding healthcare means a lot more than just the theory of it, and I am excited to become more skilled by working directly with patients. In treating patients, I hope to grasp how patients experience their daily struggles and what they need. My overarching goal is to bring together research and clinical practice, allowing me to forge a career that not only contributes to scientific advancement but also has a real, positive effect on patient health and healthcare delivery.

3. SUMMARY OF THE PH.D.

Advances in technology have led to the emergence the new therapeutic opportunities in rehabilitation medicine. These new types of devices not only offer novel opportunities, but also a kind of obligation to explore whether these devices are truly innovative and useful, whether they can replace today's devices, or whether their complementary therapeutic application can become part of the daily routine.

In the first part of the research we have chosen to evaluate the effect robotic-assisted gait training that uses robotic technology and external energy to aid individuals with movement impairment. We tried to assess and determine its possible current and future places and potential indications in everyday rehabilitation. In order to get more insight into the effect of robotic-assisted gait training on gait function in everyday rehabilitation practice we made a systematic review and meta-analysis which consist only of randomized controlled trials.

In the subsequent stage of our work, we decided to assess the effect of Video Game-Based therapy on upper limb function compared to conventional therapy with systematic review and meta-analysis study design.

Our results showed that when we compared robotic-assisted gait training to usual therapy or treadmill training we found significant gait speed improvement in favor of the intervention group and insignificant betterment in the next gait parameters: cadence, Step length, single leg support time, step width. Gross motor function measurement (GMFM) D and E scores purpose to measure standing and postural stability (GMFMD) and walking, jumping, and running showed insignificant improvement after Robotic-assisted gait training.

According to upper extremity rehabilitation, we noted that video game-based therapy was significantly superior in grasp function, upper limb motor function, and hand function questionnaires compared to control groups, and insignificant improvement was observed in the following outcomes: grip strength, manual dexterity, Self-care function (weefim), Abilhand-Kids and Jebsen Taylor Hand Function tests.

Our results suggest that however these novel devices do not have a clearly better rehabilitation efficiency compared to traditional forms of therapy.

4. GRAPHICAL ABSTRACT (including all studies)

NOVEL DEVICES IN THE REHABILITATION OF CHILDREN WITH CEREBRAL PALSY

Context: Advances in technology have led to the emergence the new therapeutic opportunities in rehabilitation medicine. These techniques attempt to improve impaired function by leveraging the neuroplasticity of the brain, however, the therapeutic impact and possibilities of these new methods are still need clarification

Evidence for gait improvement with robotic-assisted gait training of children with cerebral palsy remains uncertain

Effectiveness of Video Game-Base to Improve Hand Function in Children with Cerebral Palsy: A Systematic Review and Meta-Analysis

Significant improvement:

- Gait speed: 0,1m/s

No significant differences:

- GMFM D
- GMFM E
- Step length
- Cadence
- Single leg support time

Significant improvement:

- Grasp function
- Hand function tests
- Hand motor function questionnaires

No significant differences:

- Grip strength
- Manual dexterity
- Self Care (WeeFim)
- ABILHAND-Kids
- Jebsen Taylor Hand Function

Implication: It is worth to consider to integrate it in the daily routine and to combine these tools with standard techniques. Although the expectations are understandable contrary to these demands, their breakthrough beneficial effects do not significantly overtake the traditional forms.

CENTRE FOR TRANSLATIONAL MEDICINE

5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

Our aim is to evaluate the efficacy and clarify the role of novel devices in the rehabilitation in children with cerebral palsy.

5.1.2. What is the problem to solve?

The main purpose in cerebral palsy children rehabilitation is to mitigate the loss of function caused by (the origin of the disease) the brain injury, however, the primarily neuromotor disorder is non-progressive in the greater part of cases, the motor function and the physical condition deteriorates with age (1). The rehabilitation for disabled children can take a considerable part of their lives. Although the usual rehabilitation techniques achieve good results, the need for new innovative tools has naturally arised, but their effectiveness has not yet been proven. These techniques attempt to improve impaired function by leveraging the neuroplasticity of the brain, however, the therapeutic impact and possibilities of these new methods still need clarification (1).

5.1.3. What is the importance of the topic?

Cerebral palsy occurs by damage to the developing brain, which may cause movement disorders. The incidence of the disease is 2-3 out of 1000 live birth (2). Continuous rehabilitation plays a prominent role in the lives of these children in order to prevent the loss of those functions. From that standpoint finding the adequate rehabilitation tools with the appropriate indication circle is crucial and increases the efficacy which offers a chance to decrease the unnecessary time spent on rehabilitation and make decisions easier for therapists and clinicians. From an economic point of view, the therapy becomes more target-oriented thereby easing the situation of parents worldwide.

5.1.4. What would be the impact of our research results?

The pressure from parents and therapists is understandable to use these modern tools in the rehabilitation of children with cerebral palsy, however, this investigation helps to push our knowledge towards showing reality. The objective determination of the therapeutic possibilities of the new devices thereby improves the quality of life of children with CP. By assigning a more precise range of indications, it is possible to make the therapeutic programs more targeted and to use them in a more target-oriented manner thereby increasing the cost-effectiveness and reducing the time spent on unnecessary therapy.

5.2. Cerebral palsy

Cerebral palsy is a neuromotor disease, which can influence posture, muscle tone, and motor development (3-5). The pathophysiology background starts with the damage to the developing brain in the uterus or during the neonatal period (3-5). However the lesion is non-progressive, due to the development of secondary conditions, deterioration is observed with advancing age (2). The neuromotor disease can be categorized based on clinical findings as dyskinetic, spastic, hypotonic, or mixed (2).

Based on the extent of involvement, CP can be classified as bilateral when both body sides are affected and unilateral when only one side is impaired (6).

Spastic diplegia can be seen in 35% of the cases, which originate from immature oligodendroglia injury between the 20 and 34 weeks of gestation. Usually, the thalamocortical and corticospinal pathways are damaged and on neuroimaging most commonly periventricular leukomalacia can be seen (3, 4, 7). Most of the spastic diplegic children can have a chance for independent ambulation (2).

In a quadriplegic condition, PVN and multicystic cortical encephalomalacia can be seen in neuroimaging and 20% of the cases are associated with premature birth and it is associated with severe cognitive deficit, epilepsy, visual and functional disability (2, 4, 7, 8). The chance of independent ambulation in severe cases is poor.

Due to the utero or perinatal stroke in 25 % of the cases unilateral (hemiplegic) alteration can be seen. They have usually normal cognitive functioning and have the ability to independently walk (2-4, 9, 10).

Dystonic, dyskinetic, or choreoathetosis phenotypes occur in 15% of cerebral palsy, the cause in the background usually kernicterus, neurometabolic or neurogenetic disorder, or hypoxic-ischemic encephalopathy.

The extrapyramidal CP is often associated with the following: cognitive, visual, and hearing disabilities, seizures, sleeping, and behavioral problems (2-4, 7).

At Children with cerebral palsy functional classification systems are mostly used for mobility and hand function. The Gross Motor Function Classification System (GMFCS) describes self-initiated and device-assisted movements. The scale to describe the upper extremity function in children with CP (from 4 to 18 age) is the Manual Ability Classification System (MACS) (2).

5.3. Prevention, treatment interventions and physiotherapy

The most effective prevention aiming to diminish the incidence of CP should focus on the main risk factors which are low birthweight and premature birth. It has been shown that magnesium-sulfate administration for women at risk of imminent preterm labor (before the 32nd week) has a neuroprotective effect and diminishes the risk of CP (8, 11). In the case of hypoxic-ischemic encephalopathy in term and late term periods therapeutic hypothermia, which initiated within 6 hours after birth can have a positive effect (8, 12, 13). The specific types of interventions, like constraint-induced movement therapy or task-specific training-based therapy, can be an effective way to improve neuromotor function, based on the developing brain's neuroplasticity (14). Considering that the underlying disease causes wide-ranging symptoms and secondary changes, the multidisciplinary team approach is the most optimal way in the treatment (2).

In the case of spasticity, the intervention can differ depending on the goal of the treatment (8, 15-18). A patient-related treatment plan should be carefully considered. In some cases reducing generalized spasticity or eliminating focal spasticity may lead to better functional outcomes (2).

According to the previously discussed nature of the disease, physiotherapy and occupational therapy at the age of 4-5 are relatively more effective than starting later (19, 20). The physiotherapy in CP is suitable to increase muscle strength, joint mobility, and muscle endurance (21, 22). The physiotherapy for children with CP usually includes exercises, which aim to improve postural control, balance, and mobility. The constraint-induced therapy focuses mainly on strengthening the upper limb in children with CP (10, 14, 23-25).

The main goal of occupational therapy in children with cerebral palsy is to improve upper limb fine motor function and to help improve the effectiveness of daily activities.

6. OBJECTIVES

6.1. Study I. – Evidence for gait improvement with robotic-assisted gait training of children with cerebral palsy remains uncertain

Walking for healthy individuals doesn't mean any difficulties however for the population of children with cerebral palsy it can require significant effort due to the impaired gait pattern (26-28). Although the underlying disease is not progressive the primary injury may lead to loss of function with advancing age (2). Most of the cases this injury resulted in inadequate posture control and impaired balance with weak stability (2).

Robotic-assisted gait training (RAGT) is a novel method that aims to improve posture control, stability, and balance. It has the potential effect to promote the neural circuits with forced walking movement on high intensity in order to reach gait improvement through the spinal cord and brain plasticity (29, 30).

Numerous authors reported that RAGT can be an effective tool in the rehabilitation of children with CP, but the roles and guidelines for this therapy remained undetermined (29, 31-33). This meta-analysis aimed to estimate the RAGT effect on gait parameters and function in contrast to usual therapy or treadmill training in children with cerebral palsy.

6.2. Study II. – Effectiveness of Video Game-Based Therapy to Improve Hand Function in Children with Cerebral Palsy: A Systematic Review and Meta-Analysis

The main goal of rehabilitating the upper limb in children with CP is to reduce the impairment of function resulting from brain injury. The possible advantages of video game-based therapy can be the relatively low prices of gaming consoles, the opportunity to perform functional tasks multiple times, the alterable of the virtual environment with different levels of difficulty, the promise of sensory and cognitive stimulation through auditory, and visual and tactile signals with feedback and the ability to increase patient motivation (1).

Although VGBT theoretically contains all the essential components needed to promote or stimulate neuroplasticity, it is still uncertain whether this leads to successful practical application. Several authors found the benefits of video game-based therapy in the rehabilitation of neurological disorders, however, only a few studies have investigated the effectiveness of this therapy in children with cerebral palsy (34, 35).

7. Methods

These systematic reviews and meta-analyses were conducted in accordance with the Cochrane Handbook (36) and the PRISMA 2020 guidelines followed (37). The protocols of the studies were registered on PROSPERO: Study I.: CRD 42022312513, Study II.: CRD42021284957.

7.1. Search strategy

During the systematic searches, the following five databases were used: MEDLINE (via PubMed), Cochrane CENTRAL, Embase, Scopus, and Web of Science. In the databases, all fields were used during the investigations except in study II. (VGBT), where Scopus search was limited to only titles, abstracts, and keywords. The search date for Project I. and Project II. was 2021.10.14. and 2024.01.26. respectively. The used search key was "Cerebral palsy AND robot* AND random* „ when we assessed the effect of robotic-assisted gait training and in the second meta-analysis the key was "Cerebral palsy AND (virtual reality OR game OR nintendo OR playstation OR xbox)".

7.2. Study Selection

After duplicate articles were removed, two authors (OG and MV) conducted the selection process independently first titles and abstracts were screened. When a paper met the eligibility criteria or if there was any uncertainty about the concordance of inclusion criteria, the authors (OG and MV) assessed the full text of the articles. The full texts that remained were reviewed using the same approach. Cohen's kappa values are employed to assess the degree of agreement. If any discrepancies arose it was resolved by a third author (TT).

7.3. Inclusion/Exclusion Criteria

According to the study types the main inclusion criteria was that only randomized controlled trials published in peer-reviewed journals were considered in the two meta-analyses, any other study types meant exclusion. The assessed population had to include children with cerebral palsy under the age of 18, additionally, at least one investigation arm had to take VGBT or RAGT with or without accompanying traditional physical therapies, and any other studies that meet these eligibility criteria partially were excluded.

7.4. Data Extraction

The authors created the standardized data collection sheet in Microsoft Excel. One author (MV) collected the data, while another author (OG) reviewed it. The outcomes that were extracted are indicated in **Table 1**. Any discrepancies were resolved by discussion. We extracted data which aim to evaluate the upper extremity function for assessing the video game-based therapy effect. For assessing the effect of robotic-assisted gait training analyzed gait and posture data were used.

Table 1. Data was extracted from each eligible study.

Data related to	-
1. the article	study name, first author, publication year, Digital Object Identifier (DOI), language, contact details, study design, study duration
2.the intervention	randomization, blinding, country, number of participating centers, concomitant interventions in both treatment arms, total duration of intervention, method and frequency of therapeutic intervention
3.the population	total number of participants, number of patients who were randomized and the number of those who completed the study, age, gender, description of enrolled patients, patient characteristics such as hemiplegia, diplegia, triplegia, tetraplegia

7.5. Assessment of Evidence Quality and Risk of Bias

To evaluate the risk of bias the Cochrane risk-of-bias tool for randomized trials (ROB2) (38), and for the quality of evidence assessment, the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) scale was used (39). Two independent reviewers (OG and MV) did the assessment if any discrepancies arose they were resolved by discussion.

7.6. Statistical analysis

The authors (OG & MV) completed the meta-analysis for each outcome only when information from at least three studies was available and they provided the meta-analysis findings with the help of Forest plots. When pooled studies were available for continuous outcomes of robotic-assisted gait training, Pooled Mean Differences (MD and 95 % Confidence Intervals were calculated to investigate the differences between the compared treatments. The control intervention was applied in certain subgroup analyses. For the meta-analyses, a random effects model was used. The average improvement was computed by deducting the mean score before treatment from the mean score after treatment. A conservative approximation was used to calculate the standard deviation of change when correlation data was not available for example: we assumed a correlation of -1.

To compare the outcomes of the trial groups in the VGBT study, the Standardised Mean Difference (SMD) and the 95 % confidence intervals were calculated for continuous outcome measures (40).

The mean value of change was achieved by calculating the difference between the means before and after the treatment. Because the correlation data was not supplied, the standard deviation of change was estimated in a rather conservative way taking a correlation of minus one. Different studies measure the same outcomes using different rating scales, thus making it impossible to carry out a mean difference analysis of more than one RCT. As reported by our group, the SDs were used to normalize the outcomes whereby the respective results were divided by the SDs in order to calculate an effect size referred to as the SMD. These SMD results can be pooled in the meta-analysis due to the equivalence of the unit across all the studies. It has been observed that an SMD of 0.2 is small, 0.5 medium, and 0.8 large (40).

The Q-profile approach also suggested the tau-squared estimate in Projects One and Two. The Cochrane Q test and I2 index values were used to evaluate the presence of heterogeneity between the studies with the cut-off at 0.1 for the P value. Because of the small number of studies, it was not possible to perform Egger's test for small-study effects. The presence of publication bias was examined using funnel plots. Statistical analyses were performed using R language software, in particular the 'meta' package (version 5.2.0) authored by Schwarzer in 2022 and the 'dmetar' package (version 0.0.9000) authored by Cuijpers, Furukawa, and Ebert in 2020 (41, 42).

8. RESULTS

8.1. Search and selection, characteristic of the included studies

8.1.1. Study I. – Evidence for gait improvement with robotic-assisted gait training of children with cerebral palsy remains uncertain

A total of 7,363 articles were screened (see Fig.1.). Forty-one papers were left for the full-text selection. After the selection process, thirteen full texts (43-54) were suitable. Seven articles (44, 45, 47, 49, 53-55) were eligible for meta-analysis, and the other five studies for qualitative analysis due to the inadequate reported form of outcome (50, 51) and due to the crossover study design (43, 46, 48). The values of Cohen's kappa result were 0.89 at the abstract and title and 1.00 during the full-text selection. The PRISMA flow is presented in **Fig. 1.**

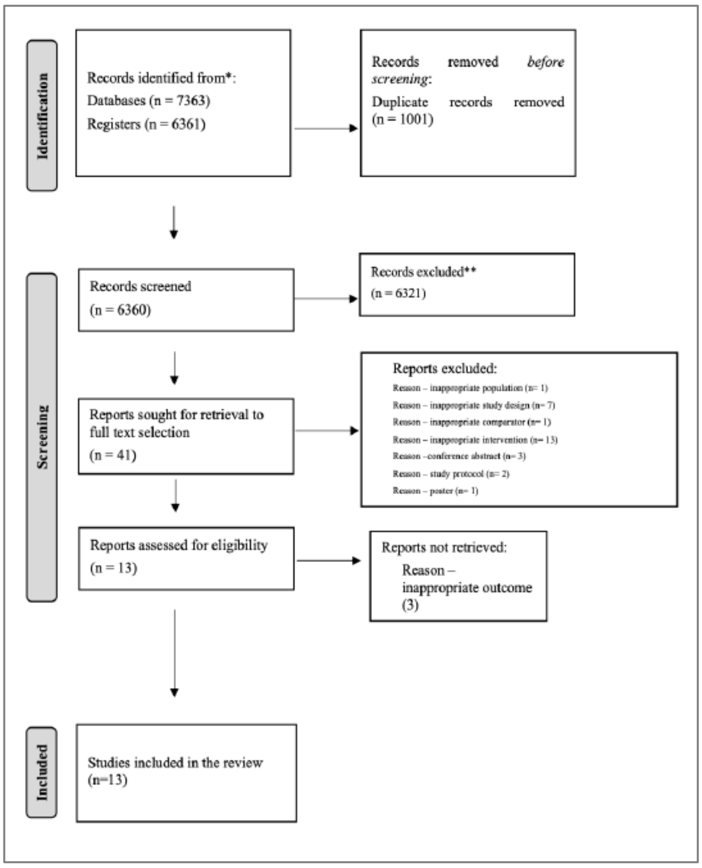

Figure 1. The PRISMA flow chart detailing the selection process.

Table 2. The baseline characteristic from the included papers.

First author	Year of publication	Country	Patient number	GMFCS	Age of patients	Duration	Type of CP	Study groups	Intervention time
C. AmmannReiffer	2020	Switzerland	16	II-IV.	6–18	1.25 (mos)	bilateral spastic	Lokomat system	15 × 45 min
B. Aras	2019	Tukey	20	II-III.	6–14	5 (mos)	mixed	Lokomat system, Hocoma AG	20 × 45 min
M. Druzbicki	2013	Poland	35	II-III.	6–13	12 (mos)	bilateral spastic	Lokomat system	20 × 45 min
L. H. Jin	2020	South Korea	20	II-IV.	3–11	9 (mos)	mixed	Walkbot K	18 × 30 min
S. Kawasaki	2020	Japan	10	I-III.	5–16	2 days	mixed	Honda walking assist	11 × 0,5 min
M. S. E. Mahgoub	2020	Egypt	30	-	7–14	9 (mos)	hemiplegia	Lokomat system	12 × 45 min
D. Pool	2020	Australia	40	III-V.	5–12	39 (mos)	-	(RT600)+ locomotor training	18 × 60 min
N. Smania	2011	Italy	18	II-IV.	10–18	10 (mos)	bilateral spastic	Lokomotor Gait trainer (GTI)	10 × 30 min
L. Wallard	2017	France	30	II.	8–10	-	bilateral spastic	Lokomat	20 × 40 min
L. Wallard	2018	France	30	II.	8–10	36 (mos)	bilateral spastic	Lokomat system, Hocoma AG	20 × 40 min
M. Wu	2017	USA	23	I-IV.	4–16	36 (mos)	bilateral spastic	Robot assisted "3dcalt"	18 × 30–40 min
L. H. Jin	2012	China	32	-	4–16	12 (mos)	-	LokoHelp system	48 × 20 min
A.Martinez	2013	Mexico	14	II.	4–16	-	hemiplegia	Lokomat system	10 × 30 min

The characteristics of the baseline from the included studies are presented in **Table 2**. The revised Risk of Bias 2 (RoB 2) tool was used to analyze the included RCTs.
The overall risk of bias, resulted in ’some concerns’, neither high nor low risk of bias was observed. A high level of evidence was detected in four outcomes (GMFM D and E, gait speed, and step length), the other two remained outcomes had a low level of evidence due to the patient numbers.

8.1.2. Study II. – Effectiveness of Video Game-Base to Improve Hand Function in Children with Cerebral Palsy: A Systematic Review and Meta-Analysis

During the investigation, 1605 papers were observed, and 63 were eligible for full-text selection, in the end, 24 papers were left as suitable. The Cohen’s kappa values were 0.96 for the title and abstract and 1 for the full-text selection. The flow of the selection process is presented in the PRISMA diagram in **Figure 2.**

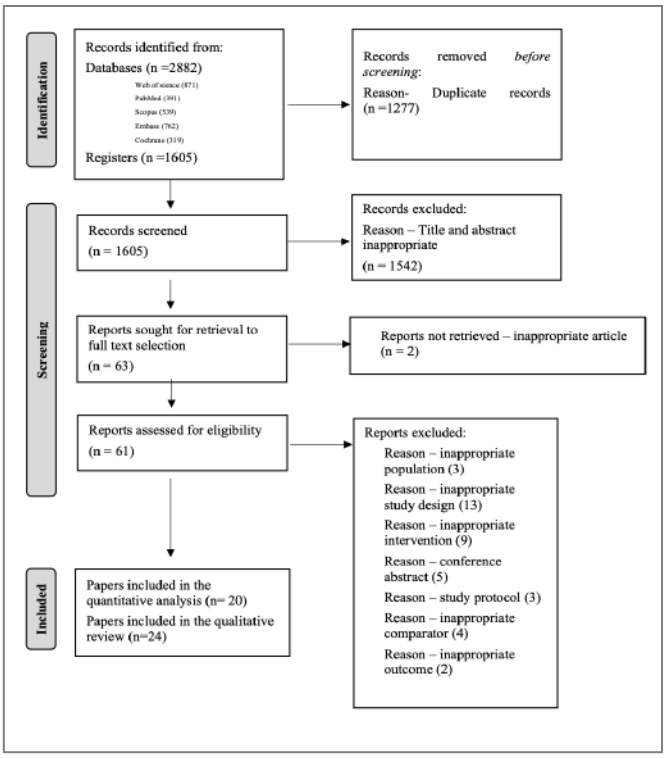

Figure 2. PRISMA 2020 flow diagram detailing the selection process.

The participant's age was 5-20 years in one of the papers (56). We have tried to contact the authors of the article to ask for further information about how many children were above the age of 18, but no feedback was received. Taking into account that the average age of the control group was 12.4±4.93 years and it was 10.6±3.78 years in the investigated group with 10-10 participants in both groups, in the case of a normal distribution only one participant would be older than 18 years. We decided that since this was within a reasonable margin of error, it would have been a bigger mistake to exclude it.

From the 24 papers (1, 56-78) four could not be included in the study half of them (71, 75) due to the reported outcome were out of our interest and the remained half (1, 59) were suitable only for the review section: the limiting factors were the cross over study design (1), and not adequately comparable reported self-care scores used (59).

The baseline characteristics of the included investigations presented in **Table 3**. The investigation included 785 children aged from 3 years to 20 years. The types of cerebral palsy were diplegic in two (57, 59), hemiplegic in ten (57, 59, 61, 62, 66, 69, 70, 73, 74, 78), mixed in five (56, 60, 63, 65, 76) and unknown in the remained four articles (63, 67, 68, 77). The applied intervention was Nintendo Wii in ten, VR therapy in eight, and Leap motion-controlled (LMC) games or computer game-based systems in the remaining cases alone or in combination with other therapies. The control groups received conventional treatment (CT), CIMT and Hand Arm Bimanual Intensive Therapy (HABIT), OT, exercise therapy (ET), neurodevelopmental training (NDT), resistance training (RT), or absence of treatment. The applied therapy intensity was increased in the study groups in five cases (57, 61, 64, 66, 70) while in the remained others the applied therapy intensity was similar.

Based on the risk of bias two articles were evaluated as 'high risk'(69, 77), 4 papers as 'some concerns'(57, 58, 61, 72), and 14 were 'low risk' (56, 60, 62-68, 70, 73, 77-79). The results of risk of bias are detailed in.

The evidence was 'very low' in three (self-care, grip strength, and upper limb fine motor function), 'low' in the other three (grasp function, manual dexterity, and Abilhand-Kids), and 'moderate' in two articles with the GARDE assessment tool.

Table 3. The baseline characteristic and results from each article.

F. Author/Pub. Year	Country	Patient N.	Mean Age (Years)	Female %	Duration/ Intensity	Study Groups	comparator	Outcome	Other information
S.Sahin/2019	Turkey	60	I:10.5 +-3.62 C: 10.06+- 3.24	38,3%	45min.x2d.x8w	VR + (TOT)	TOT	WeeFim Selfcare	Game:Air challenge,Boxing trainer,Wall breaker,Jet run,Super kick.
G.Acar/2016	Turkey	30	I:9,53+-3,04 C:9,73+-2,86	46,6%	45min.x2dx6 w.	N.Wii + NDT	NDT	QUEST Grasp,JTHFT,ABILHAND-Kids,WeeFim	Games:tennis, baseball, and boxing.
A.Alsaif/2015	Saudi Arabia	40	6-10	Ni.	20min.x7d.x12w.	N.Wii	No training	m-ABC-2	Games (20) :goal-directed arm. movements, balancing, and jumping
S. Atasavun/2016	Turkey	24	I:9,13+-2,57 C:10,11+-2,62	58,3%	30min.x2d.x12w.	N.Wii + Physio Th.	Physio Th.	PEDI	Games: basketball, tennis, boxing.
E. Avcil/2020	Turkey	30	I:10,93+-4,09 C:11,07+-3,24	43,4%	24 session/8 w.	N.Wii + LMC	NDT	Grip Strength	Games: Fizyosoft®CatchAPet, Leapball.
H. C. Chiu/2014	Taiwan	62	I:9,4+-1,9 C:9,5+-1,9	54,8%	40min.x3d.x6 w	N.Wii + Usual Th.	Usual Th.	JTHFT,Grip strength	Game: Wii Sports Resort.
S. M. El-Shamy/2018	Egypt	40	I:9,5+-1,2C:9,8+-1,4	35%	40min.x3d.x12 w.	N.Wii + Usual Th.	Usual Th.	PMDS-2,Grip strength, PMDS-2 grasp	Games:tennis;boxing;bowling; basketball.
J. Y. Choi/2021	Korea	78	5,66+-2,83	51,28%	60min.x5d.x4 w.	VR+OT	OT	ULPRS	Game: RAPAEL Smart Kids.
C. Kassee/2017	Canada	6	9,33	0%	40min.x5d.x6w.	N.Wii	Resistance tr.	Grip strength,ABILHAND-Kids, Melbourne Assesment II.	Games: Wii Nunchuck,Wii Sports Resort.
T. N. Wang/2021	Taiwan	18	I:8,55+-2,09C:8,56+-2,15	61%	135min.x2d.x8w.	N.Wii + CIT	Const.-ind. Th.	ABILHAND-Kids	Games: e.g.,Sports Resort, Wii Sports, Mario Sports Mix, Cooking Mama: Cook Off, Let's Tap, and Happy Dance Collection.
J. E. Sajan/2016	India	18	I:12,4+-3,78C:12,4+-4,93	45%	45min.x6dx3w.	N.Wii	CT	Quest,BBT	Games: boxing, tennis.
D. Tarakci/2016	Turkey	30	I:10,46+-2,69C:10,53+-2,79	36,6%	50min.x2d.x12w.	N.Wii + NDT	CT	WeeFim	Games: walking on rope,skiing,Tilt Table-Balance Board,Heading
D. Tarakci/2019	Turkey	30	I:10,93+-4,09C:11,06+-33,23	43,3%	60min.x3d.x8w.	LMC	CT	Grip strength, JTHFT,Duruoz Hand index	Fizyosoft Games: CatchAPet,Leapball.
K. Ren/2016	China	35	I:4,75+-0,83C:4,5+-1,16	42,8%	40min.x5d.x12w.	VR + (OT)	CT+OT	PMDS-2,Grip strength, PMDS-2 grasp	-
O.Fidan/2023	Turkey	52	I:9,2+-2,08 CT:9,4+-2,25	40,38%	45min.x2dx8 w.	VR	NDT	QUEST	Games:fruits Ninja,tennis game, soccer,bowling.
A. K. Menekseoglu/2023	Turkey	36	I:8,2+-1,8C:8,3+-1,4	47,2%	60min.x2d.x6w.	VR + Exercise th.	Exercise th.	QUEST, ABILHAND-Kids	Games: butterfly,bee,eagle game.
A. Kanitkar/2023	India	63	I:7,3+-2,1C:7,8+-1,9	-	45min.x3d.x16w.	PC games-based e.	CIMT + HABIT	PMDS-2	Games:arcade-style.
R.Bedair/2016	Egypt	40	I:7,05+-0,99C:7,25+-0,96	42,5%	60min.x3d.x16w.	VR + Physical Th.	Physio Th.	ABILHAND-Kids, PMDS-2	Games: tennis, bowling, golf, space pop, bubbles,boat driving.
G. Saussez/2023	Belgium	38	I:9+-3,1C:9,1+-2,9	50%	90h/2w	REAtouch +HABIT-ILE	HABIT-ILE	ABILHAND-Kids, JTHFT	Regular Games: (e.g., board games, card, building activities, etc.)
M. Daliri/2023	Iran	20	I:6,4+-1,07C:6,1+-1,1	25%	60min.x2d.x16w.	LMC	OT	QUEST, Grip Strength	Games:cube grasping, flower petal,removal,Kyoto.
J. Y. Choi/2023	Italy	35	I:8,1+-3,2C:7,3+-2,6	48,6%	30min.x5.dx6w.	VR + (OT)	OT	ABILHAND-Kids, Melbourne Assesment II.	Game: RAPAEL Smart Kids.
L.Zoccolio/2016	Italy	18	6,89+-1,91	-	90min.x2d.x8 weeks	Xbox kinect+ Usual Th.	CT	QUEST, ABILHAND-Kids	Game:Xbox kinect adventure package.

[1] I.[2] C.[3]min.[4]d.[5]w.[6]VR[7]TOT[8]N.Wii[9]NDT[10]Physio th.[11]LMC[12]Usual Th.[13]OT[14]CIT[15]exercise th.[16]PC games-based e.[17] Physical Th.[18]HABIT-ILE[19]Resistance tr.[20]Const-ind Th.[21]CT[22]CIMT[23]HABIT[24]WeeFim[25]QUEST[26]JTHFT[27]m-ABC-2[28]PEDI[29]PMDS-2[30]ULPRS[31]BBT

[1] Intervention
[2] Control group
[3] Minute
[4] Day
[5] week
[6] Virtual reality
[7] Traditional occupational therapy
[8] Ninetendo Wii
[9] Neurodevelopmental treatment
[10] Physio therapy
[11] Leap motion controller
[12] Usual therapy
[13] Occupational therapy
[14] constraint-induced therapy
[15] exercise therapy
[16] Computer game-based therapy
[17] Physical therapy
[18] Hand Arm Bimanual Intensive Training Including Lower Extremity
[19] Resistance training
[20] Constraint induced therapy
[21] Conventional therapy
[22] Constraint induced movement therapy
[23] Hand Arm Bimanual Intensive Training
[24] Functional Independence Measure for Children
[25] Quest quality of upper extremity skills test
[26] Jebsen Taylor Hand Function Test
[27] Movement Assessment Battery for Children-2
[28] Pediatric Evaluation of Disability Inventory
[29] Peabody Developmental Motor Scales-2
[30] Upper Limb Physician's Rating Scale
[31] Box and Block Test

8.2. Results of the qualitative and quantitative analysis

8.2.1. Robotic-assisted gait training qualitative analysis

The scores of GMFM-D were evaluated in four articles (44, 47, 53, 54). Half of them used physiotherapy (47, 53), and the other half treadmill training (44, 54) as a control group. The RAGT group reached an insignificant improvement of 5.78 %, (95 % CI − 7.46, 19.03) compared to the control group (see **Fig.3.**). The intervention group was inferior with − 3.48 %, (95 % CI − 26.8, 19.90) contrast to the treadmill subgroup. RAGT was superior with 10.15 %, (95 % CI − 5.92, 26.22) compared to the physio-only subgroup. None of the findings were statistically significant. The evidence according to the GRADE assessment was high. Based on the risk of bias assessment, all included studies resulted in some concerns (44, 47, 53, 54). Among the two crossover trial articles (43, 46) that could not be included in the meta-analysis, one (46) reported a significant improvement in favor of the intervention group, while the other (43) found no significant changes.

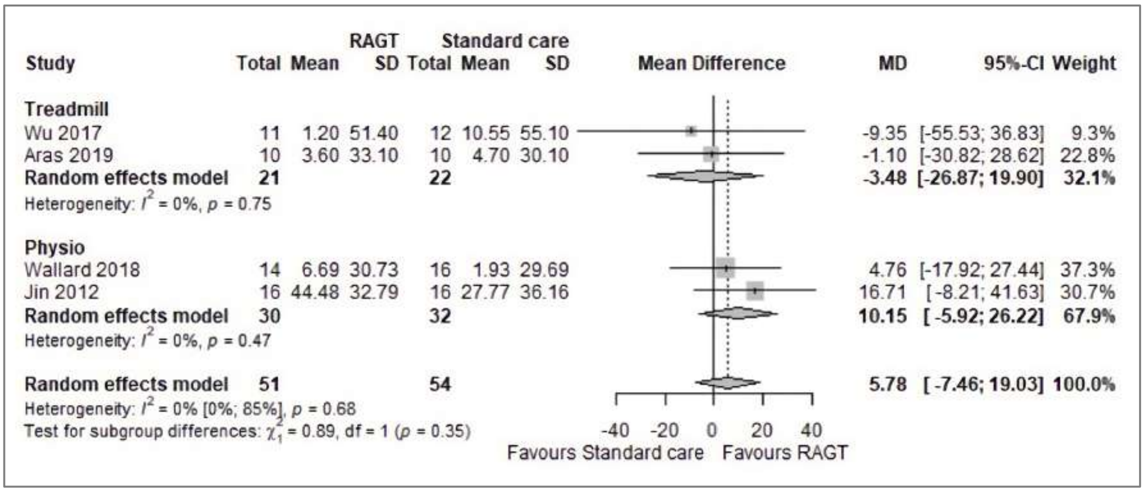

Figure 3. Forest Plot of Mean Differences of Gross Motor Function Measurement "D" improvement in percentage, comparing the intervention of robotic-assisted gait training to either physiotherapy or treadmill training. Subgroups formed on the basis of the comparison group.

GMFM E was evaluated in four papers (44, 47, 53, 54) (**Fig.4.**), two of them used physiotherapy (47, 53), and the remaining two (44, 54) treadmill training was used in the control group. The whole effect was a 5.67 % (95 % CI − 6.13, 17.47) greater increase in the RAGT group compared to the control group. The RAGT group was superior by 7.77

% (95 % CI − 5.95, 21.50) in contrast to the physio subgroup, while underperformed the treadmill group by 0.28 % (95 % CI − 23.38, 22.83). None of the results were found to be statistically significant. The evidence was high with the GRADE assessment. The whole risk of bias indicates some concerns (44, 47, 53, 54). One (43) from two cross-over studies (43, 46), which could be implemented only in the systematic review part of the study not find any differences between the groups, while the other (46) showed significant betterment for RAGT compared to physiotherapy (P=0.021).

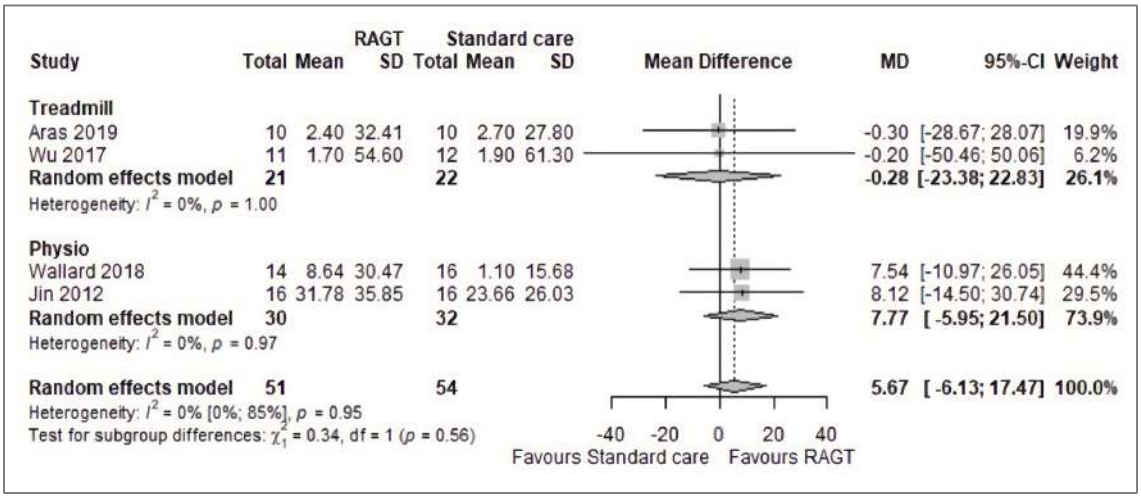

Figure 4. Forest plot of Mean Differences of Gross Motor Function Measurement ”E” improvement in percentage, comparing the intervention of robotic-assisted gait training to either physiotherapy or treadmill training. Subgroups formed based on comparison arm.

Six investigations evaluate the gait speed pre- and post-intervention (44, 45, 49, 53-55). Four applied physiotherapy (45, 49, 53, 55), and two used treadmill training (44, 54) in the comparator groups. Robotic-assisted gait training was found to be significantly more effective with 0.10 m/s, 95 % CI [0.02, 0.19] in contrast to the control group (**Figure 5.**). When we compared the study group to physio subgroup the difference was (0.11 m/s, 95 % CI [− 0.02, 0.24]) and in case of treadmill subgroup (0.04 m/s, 95 % CI [− 0.33, 0.11]) difference was seen in favor to RAGT. The overall risk of bias indicates ’some concerns’ and the GARDE assessment was ’high’. From the studies which could not be used in the meta-analysis section one (51) reported significant gait velocity improvement in favor to RAGT and the other four (43, 46, 48, 50) articles found insignificant changes as a result of RAGT when compared to physio or treadmill training.

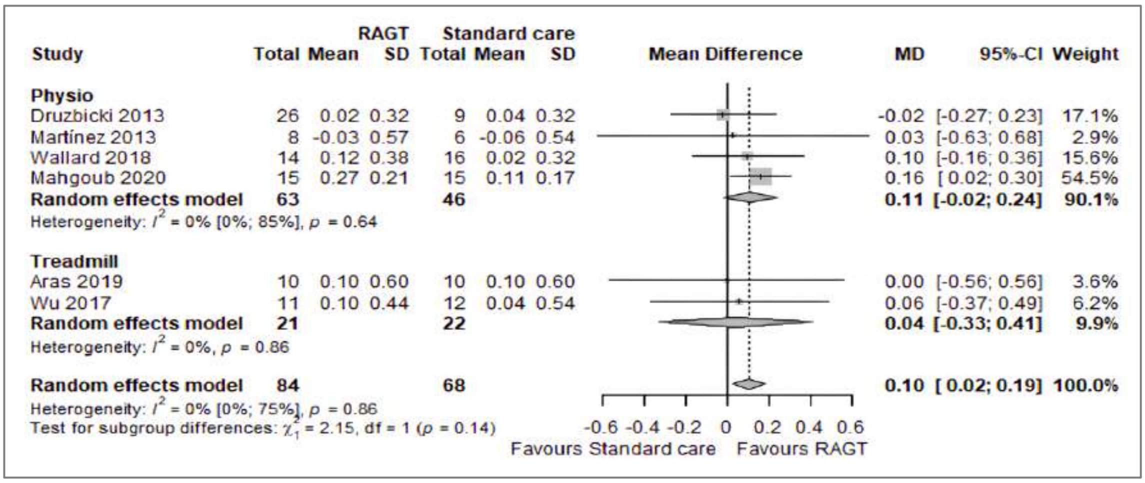

Figure 5. Forest plot of Mean Differences of gait speed improvement in m/sec, comparing the intervention of robotic-assisted gait training to either physiotherapy or treadmill training. Subgroups formed on the basis of comparison arm.

Cadence as steps per minute was assessed by three-dimensional gait analysis, in four articles (44, 49, 53, 54) (**Figure 6.**) Half of them applied physiotherapy (49, 53) and the other two (44, 54) used treadmill training as a control. The RAGT changed steps number by 5.45 (95 % CI − 11.65, 0.76) in contrast to the control group. The treadmill training subgroup resulted in an average of 9.80 steps, (95 % CI − 26.22, 45.83) number decrease per minute in contrast to the study group. In the physiotherapy subgroup (5.91 steps/min, (95 % CI − 12.21, 0.38)) an increase was seen compared to the RAGT group. These results were statistically insignificant. While the risk of bias showed 'some concerns' and the level of GRADE was 'low'.

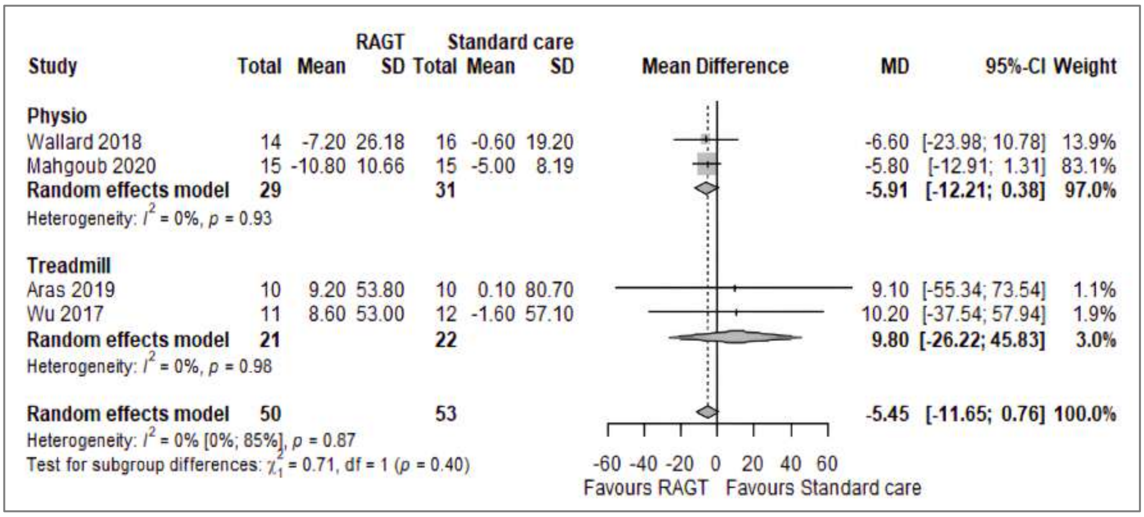

Figure 6. Forest plot of Mean Differences of step number/min. decrease, comparing the intervention of robotic-assisted gait training to either physiotherapy or treadmill training. Subgroups formed on the basis of comparison arm.

Four (44, 45, 53, 54) out of the included papers analyzed step length (**Fig.7.**). Half of them (44, 54) used treadmill training and two applied physiotherapy (45, 53) as a control. The study group increased the step length with 0.03 m, (95 % CI − 0.03, 0.10) compared to controls. The differences were statistically insignificant. The evidence was 'high' with the GRADE assessment and the risk of bias resulted in 'some concerns'. A study (51) which we were unable to include in the metanalysis part due to the form of outcome reporting, indicates a significant increase in step length in favour of the experimental group in contrast to the control.

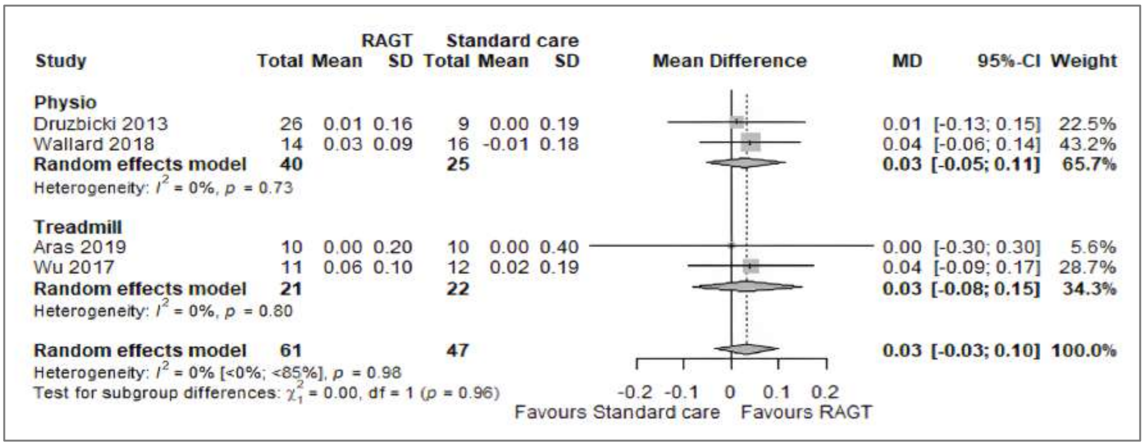

Figure 7. Forest plot of Mean Differences of step length improvement in meter, comparing the intervention of robotic-assisted gait training to either physiotherapy or treadmill training. Subgroups formed on the basis of comparison arm.

Single leg support time was assessed in three papers (44, 53, 54) (**Fig.8.**). The RAGT groups were found to be more effective compared to physiotherapy with an insignificant change of 0.04 s (95 % CI − 0.03, 0.11). The risk of bias assessment indicates 'some concerns' in all studies, while the GRADE resulted in 'low' evidence.

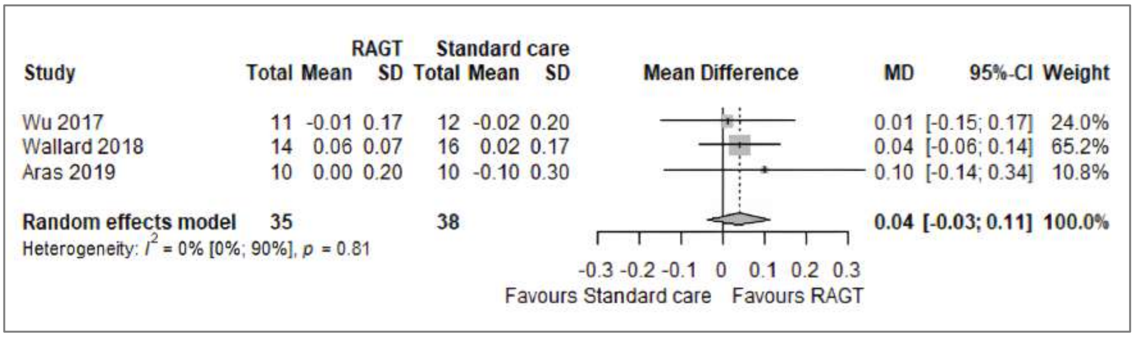

Figure 8. Forest plot of Mean Differences of single leg support time improvement in seconds, comparing the intervention of robotic-assisted gait training to either physiotherapy or treadmill training. Subgroups formed on the basis of comparison arm.

Two articles by (45, 53) evaluated the step width changes after RAGT. The control groups used physiotherapy in both papers. In one of them (45) an insignificant improvement was seen after the RAGT in the other (53) a statistically significant decrease was detected between the groups (P=0.022). The evidence was found to be 'low' by the GARDE tool.

8.2.2. Quantitative analysis Robotic-assisted gait training

The meta-analysis includes seven papers. The results are presented in Forest plots, as shown in Figures 3. - Figures 8. Gait speed was assessed with 3d gait analysis or 10m walking test in six studies (see Fig.5.). Four articles used Gross Motor Function Measure (GMFM) domains D and E (see Fig 3,4.). Temporo-spatial gait parameters were measured with 3D gait analysis in five articles (see Figs.6-8.).

8.2.3. VGBT on upper limb function qualitative analysis

Grip strength was assessed by six of the selected papers (**Fig.9.**). From them two articles (65, 66) found significant-, and two other (62, 69) an insignificant improvement in the experimental group. One investigation (77) results in an insignificant increase for the control group and the other indicates no differences between groups (60). In five articles (60, 62, 65, 66, 77) the risk of bias was found to be 'low risk' and the remaining one (69) was 'high risk.

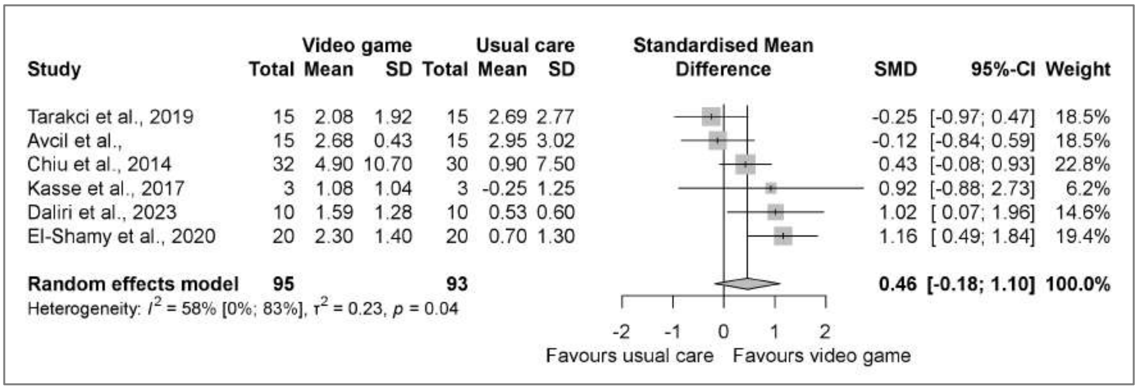

Figure 9. Forest plot of standardized mean differences in grip strength, comparing the intervention video-game-based therapy to other rehabilitation forms (usual therapy, neurodevelopmental treatment, resistance training, and Occupational Therapy).

Nine papers evaluated the grasp function (56, 57, 65-68, 70, 72) after video game-based therapy (**Fig.10.**). An improvement was seen in seven (56, 57, 65, 66, 68, 70, 72) out of eight cases, from them four were significant (65, 66, 68, 72). Risk of bias resulted in ‘low risk’ in six papers (56, 65-68, 70) the remaining two were ‘some concerns’ (57, 72). One study (1) which we were unable to include in the meta-analysis part due to the crossover study design detected a significant improvement in the VGBT group.

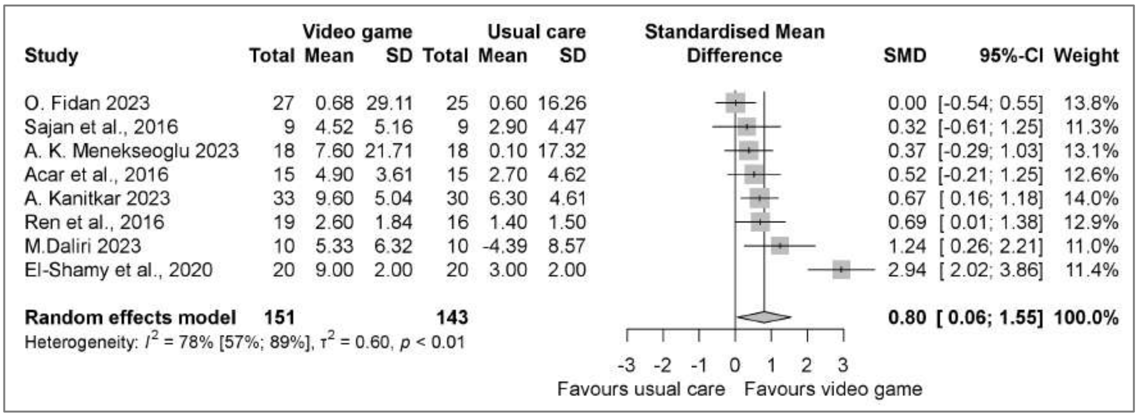

Figure 10. Forest plot of standardized mean differences in grasp function, comparing the intervention video-game-based therapy to other rehabilitation forms (conventional and neurodevelopmental therapy, Occupational Therapy, CIMT, HABIT, and exercise therapy).

The video game-based effect on manual dexterity (manual dexterity physical test) was assessed in ten articles (56, 57, 61, 62, 64, 69, 70, 74, 77, 78) (**Fig.11.**). Six articles (56, 62, 64, 74, 77, 78) indicated no any differences between the groups, three (57, 69, 70) other found minimal differences, in two (69, 70) of them VGBT was superior compared to control group. Only one (61) was statistically significant in favor of the experimental group. The risk of bias assessment showed ‘low risk’ in seven papers (56, 62, 64, 70, 74, 77, 78), one resulted in ‘high risk’ (69), and the remaining two (57, 61) ‘some concerns’.

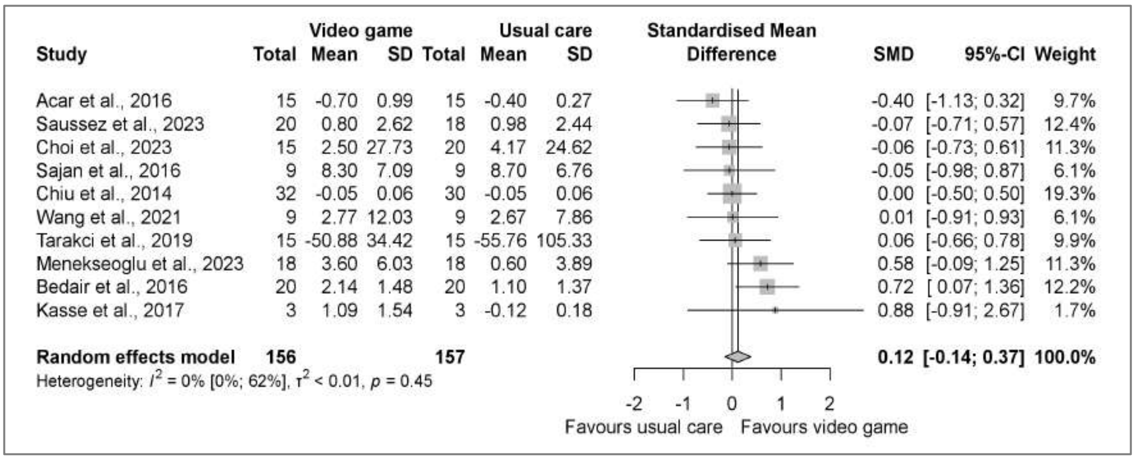

Figure 11. Forest plot of standardized mean differences in manual dexterity physical tests, comparing the intervention video-game-based therapy to other rehabilitation forms (conventional, neurodevelopmental, resistance training and constraint-induced therapy, occupational, HABIT, and exercise therapy).

17 articles (1, 56-58, 61-70, 72, 74, 77) assessed the upper limb fine motor function change after video game-based therapy (**Fig.12.**). Eight studies (58, 61, 65, 66, 68-70, 72) reported an improvement after VGBT, from them, five were mathematically significant (58, 65, 66, 68, 72), seven further articles (56, 62-64, 67, 74, 77) found no any differences between the groups and one paper (57) detected an insignificant improvement in favor to control. The risk of bias showed ‘low risk’ in 11 cases (56, 62-68, 70, 74, 77) ‘high risk’ in 1 investigation (69) and in the remaining 4 (57, 58, 61, 72) ‘some concerns’. The one article (1), in which we could include only the systematic review part of the research indicates a significant improvement in favor of the experimental group with the Quality of Upper Extremity Skills Test (QUEST) score.

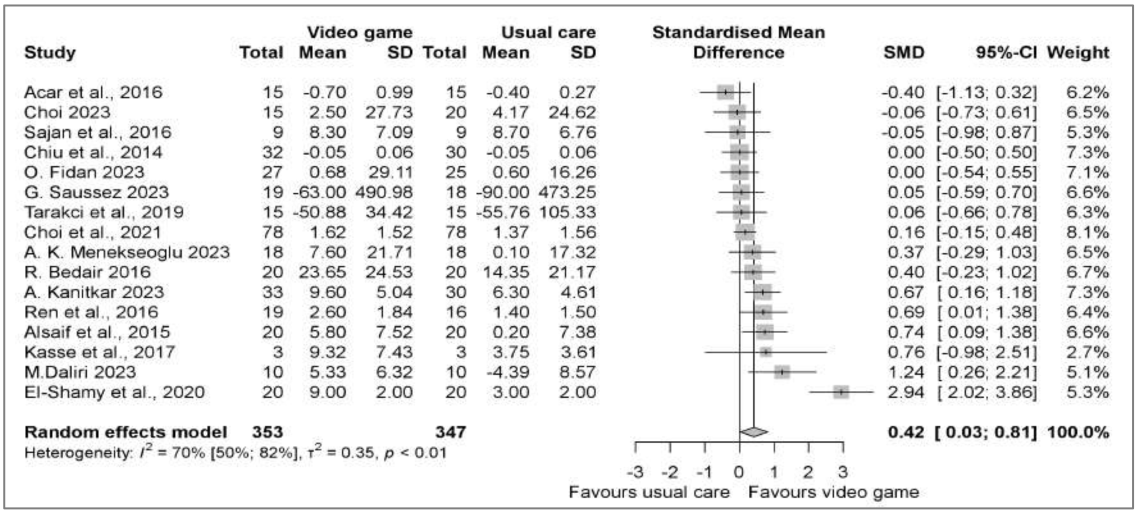

Figure 12. Forest plot of standardized mean differences in upper limb fine motor function tests, comparing the intervention video-game-based therapy to other rehabilitation forms (conventional, neurodevelopmental, resistance training and Occupational Therapy, HABIT, exercise therapy or absence of treatment).

Hand function was assessed with questionnaires in seven investigations (57, 61, 69, 70, 74, 77, 78) (**Fig.13.).** One of them (61) found a significant and three of them (69, 70, 77) insignificant improvement in favor to the study group, while the other three (57, 74, 78) indicate no any differences between the examined groups. The risk of bias resulted in 'low risk' at four papers (70, 74, 77, 78), two (57, 61) categorized as 'some concerns' and the remained one (69) was 'high risk'.

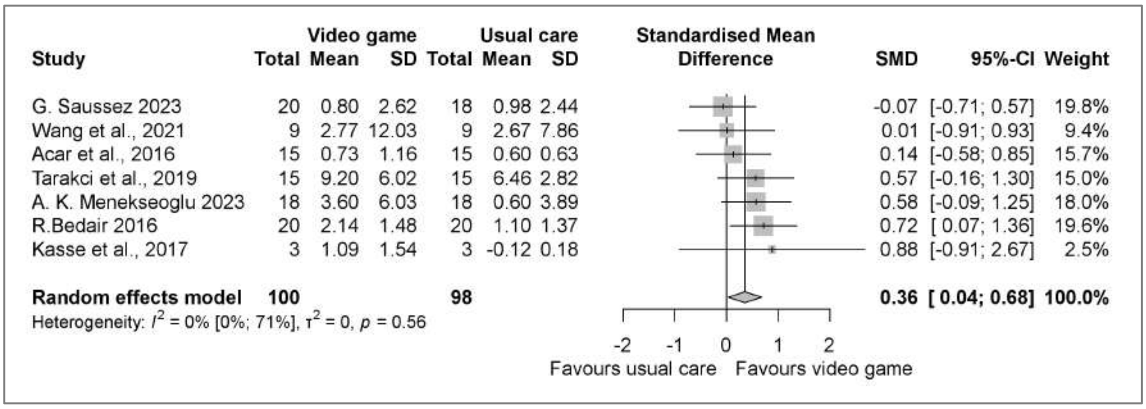

Figure 13. Forest plot of standardized mean differences in hand function questionnaires, comparing the intervention video-game-based therapy to other rehabilitation forms (conventional, neurodevelopmental, resistance training, constraint-induced therapy, HABIT, and exercise therapy).

Three papers (57, 73, 76) evaluated the VGBT effect on the WeeFim self-care subdomain (**Fig.14.).** All the publications found improvement in the study group, but only one (57) was statistically significant. The risk of bias showed 'high risk' (76), 'low risk' (73), and 'some concerns' (57). One investigation (59) in the review part observed an insignificant improvement in favor of the experimental group with the Paediatric Evaluation of Disability Inventory self-care subdomain.

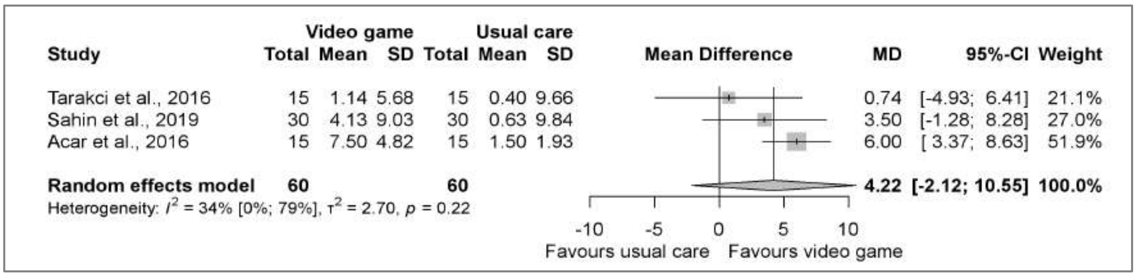

Figure 14. Forest plot of Mean Differences in Self-Care (WeeFim), comparing the intervention video game-based therapy to other rehabilitation forms (conventional therapy, neurodevelopmental therapy, and occupational therapy).

Seven papers assessed the effectiveness of VGBT on hand function with Abilhand-kids (1, 57, 61, 69, 70, 74, 78) (**Fig.15.)**. Two articles (69, 70) reported insignificant and one other (61) significant improvement for the study group and the remained three investigations (57, 74, 78)indicated no any differences between the examined groups. The Risk of bias was rated as 'low' in half of the cases (70, 74, 78) and the other half resulted in 'high risk' (69) and in 'some concerns' (57, 61). One study (1) was suitable only for the systematic review and detected a statistically significant improvement for the controls.

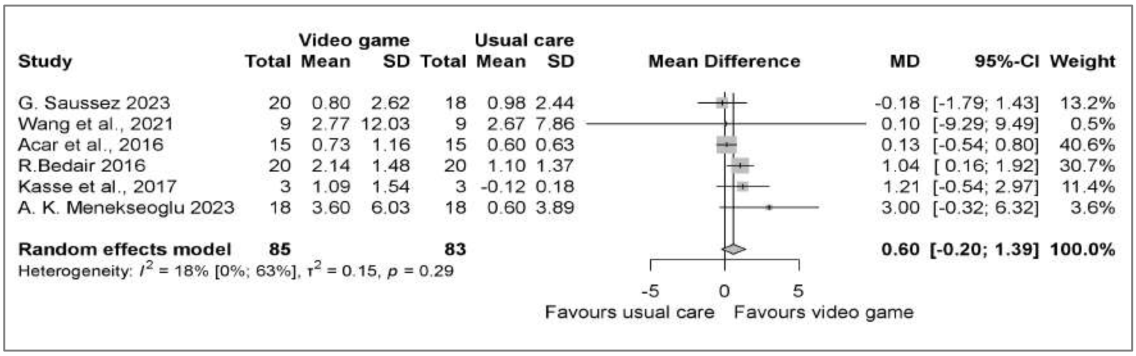

Figure 15. Forest plot of Mean Differences in Abilhand-Kids, comparing the intervention video game-based therapy to other rehabilitation forms (conventional, neurodevelopmental, resistance training, constrain induced therapy, and exercise therapy).

The Hand Function assessment with Jebsen Taylor test was used in four articles (57, 62, 74, 77) (**Fig.16.)**. Two of the included studies (74, 77) reported no differences and the remained papers (57, 62) resulted in an insignificant improvement for the treatment group. Three-quarters of it rated as 'low risk' (62, 74, 77) and the remained one (57) was 'some concerns'.

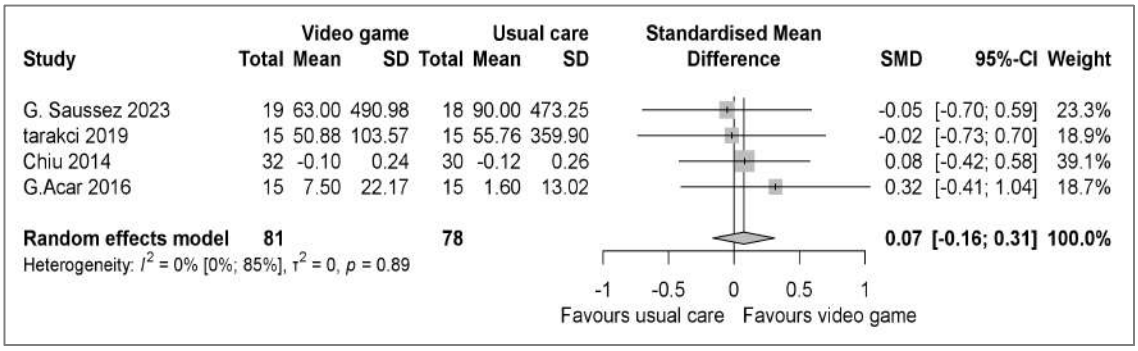

Figure 16. Forest plot of Standardized Mean Differences in the Jebsen Taylor Hand Function, comparing the intervention video game-based therapy to other rehabilitation forms (conventional, neurodevelopmental, and HABIT.

8.2.4. Quantitative analysis of VGBT

The meta-analysis used 20 papers to assess the effectiveness of VGBT on upper limb function with 8 outcomes.

Grip strength assessment showed an insignificant increase in the study group with an SMD of 0.46 (95% CI -0.18, 1.10), as shown in **Fig.9.**

VGBT improved grasp function statistically significantly with the SMD 0.80 (95% CI 0.06, 1.55) **(Figure 10.).** When we assessed the manual dexterity with physical tests, the SMD was 0.12 (95% CI -0.14, 0.37), which, means an insignificant change in favor of the treatment group **(Fig.11.).** According to hand function questionnaires and upper limb fine motor function we found a statistically significant improvement in both cases, the result in the questionnaires was SMD 0.36 (95% CI 0.04, 0.68) and in the motor function the SMD was 0.42 (95% CI 0.03, 0.81) (see in **Fig.12. and Fig.13.**)

The WeeFim (self-care) score increased with a Mean Difference (MD) of 4.22 (95% CI -2.12, 10.55) in favor of the intervention group (**Fig.14.**). When the Abilhand-Kids and Jebsen Taylor Hand Function was evaluated separately a non-significant improvement was seen in the experimental groups compared to control groups, the Jebsen Taylor Hand function showed an SMD of 0.07 95% CI -0.16, 0.31) (**Fig.15.),** while the in Abilhand-Kids the MD was 0.60 (95% CI -0.20, 1.39) (**Fig.16.)**.

9. DISCUSSION

9.1. Summary of findings, international comparisons

These studies were performed to evaluate the effectiveness of novel methods in the rehabilitation of children with cerebral palsy. To get a complete insight into the effect of these rehabilitation tools, two systematic reviews and meta-analyses were conducted. In order to ensure the high quality only randomized controlled trials were included.

Among the innovative devices, our investigation initially focused on robotic-assisted gait training. To estimate the effect of RAGT the functional and temporo-spatial gait data from the articles were pooled.

When the functional effect of RAGT was assessed a notable (absolute) therapeutic effect in improving postural stability (GMFM-D) and walking abilities (GMFM-E) was observed, but the changes in comparison to the control groups were statistically insignificant.

Comparing the intervention group to the physiotherapy subgroup the difference was larger, but when the RAGT effect was investigated as opposed to treadmill training the impact on functional outcome was nearly negligible (close to zero).

Consistent with earlier research (80, 81) our results in GMFM D and E exceeded the minimal clinically important differences estimated by Oeffinger et al. (82) (GMFM D 5.78 %, GMFM E 5.67 %).

The different ages of the examined population in the articles may have a potential bias effect due to the natural improvement of GMFM with ages (83). Our investigation results are based on randomized controlled studies, which means the natural improvement of GMFM would affect both groups equally, moreover, the included studies were brief (4–12 weeks) enough not to have any difference in the appearance of the disease related to the natural history. Additionally, in all of the papers, the patient's mean ages were similar in both groups. According to these mentioned considerations, we think that the impact of natural improvement on our result was negligible (83).

Although the implemented papers and further non-RCT articles also assumed that RAGT can have a positive impact on walking quality through posture stability in children with cerebral palsy, we found that the effect of RAGT was only comparable to the control groups (80, 81).

To get some insight into the mechanisms behind this result, which was estimated as a 6% greater enhancement in gait function in our evaluation, we also assessed the alteration of temporo-spatial gait parameters. Through these gait parameters, we can get some insight into the gait phases and how they relate to each other and the RAGT effect in the stability or the energy consumption during walking. However, in healthy individuals, the step-to-step transitions occur efficiently along the whole range of walking, in patients who suffer from central nervous system disorder muscle weakness and coordination can lead to an abnormal walking pattern through impaired walking balance and decreased energy efficiency (28).

Based on the dynamic walking models, energy efficiency can be achieved by decreasing the collision speed of the heel through the adequate strength and timing of plantarflexion during the pre-swing phase. The plantarflexion tends to be weaker compared to healthy individuals, and this diminished power causes a large contralateral collision, which requires increased compensation efforts (28, 84). In the investigated population impaired walking stability can be observed both in the mediolateral and in the antero-posterior axis resulting from the inability to apply the appropriate movements in the gait phases.

The larger collision, in addition to instability, ended in a decreased step length and in a greater step width. Numerous researchers determined that robotic-assisted gait training had a positive impact on balance, step length, and gait speed in contrast to conventional or treadmill training (32, 33, 80, 85, 86), while others, indicated that training with the novel device was not more effective compare to equal amount of balance or treadmill training (29, 31, 32, 87, 88).

Despite the high standard deviation of the data and an insignificant change observed, our findings in step length indicate that the intervention group is at least as effective in step length improvement as treadmill training or physiotherapy (80).

Gait velocity represents an important element of temporo-spatial gait parameters, which can provide some insight into the robotic-induced gait alterations and is often recognized as the sixth vital sign due to its significant relationship with mobility efficiency (89).

Walking speed increasement in cerebral palsy may reflect enhanced gait performance and improved walking quality. It is difficult to discuss the clinical importance of those minor increases in gait velocity. Regarding the degree of involvement of the underlying disease (CP), the gait speed can be variable, however, the change we detected showed an advantage for RAGT over controls which represents one-fifth of the original values. As in other non-RCT studies, we also found a statistically significant increase in gait speed in favor of the intervention group (80, 81).

The time when only a single foot is in contact with the ground is called single leg support time, it is extended from the opposite toe-off until the contralateral initial contact. Our results showed that RAGT did not increase the single leg support time when we compared it to controls. In terms of single leg support time, the same result was found in a non-RCT study, which assessed 26 children with (bilateral spastic) cerebral palsy (41).

The fact that the time of the swing phase stayed unaltered, in addition to the greater walking speed, strengthens our theory that the step length enlarged since the greater gait velocity and the increased distance had to be achieved over a single step if the swing phase time stayed unvaried. „The finding that the time of the swing phase remained unchanged together with the increased gait speed supports our theory that the step length increased, as the faster the gait is, the longer the distance has to be covered during one step if the time of the swing phase remains unchanged"(90). Although the variability of the number of steps can also be experienced in children with CP, and they reached higher walking speed by increasing the number of steps, we found a decrease in the required step number in favor of the intervention group, which might demonstrate an enhancement. The theory of increased step length is further reflected in the tendency of cadence decrease, despite the fact that this result was statistically insignificant (91, 92). A meta-analysis that assessed the robotic-assisted gait training effect on cadence in adult patients after subacute stroke similar to our results, could not detect any significant differences (93).

An increased gait velocity can be reached through an accelerated swing phase with the help of greater „contralateral plantarflexion in the pre-swing phase"(90). As we discussed above, gait speed improvement with unaltered swing phase time can enhance the tendency of step length increase. These results indicate that the contralateral faster swing phase may have been caused by a stronger plantarflexion. The stronger plantarflexion requires additional energy consumption, but it can decrease the collision power in the contralateral heel strike, and the diminished compensatory work can cover this extra energy demand (28). Single leg support time, which is the most unstable part of the walking cycle followed by the toe-off period. Step length increasement at this point is only achievable with enhanced stability.

The base of support (BOS), the center of mass (31), and their relationship can be used to evaluate the postural stability. In a standing position when the COM above the BOS results in the most energy-efficient and the most stable condition.

To understand the dynamic stability (the stability during gait), the margin of stability (49) needs to be assessed (94). From the temporo-spatial gait parameters, step length and step width are predictive parameters for mediolateral stability (95). Data about step width were reported by only two RCTs, from them one found no differences between the groups, while the other detected a significant decrease in favor of the study group compared to the control group or the baseline data of the treatment group. Another paper, which evaluates the RAGT effect on balance found a diminished step width after intervention (81). According to the non-significant step length change and the step width data we could not do a summarized calculation therefore the improvement in gait stability with this new device compared to physiotherapy or treadmill training could not be demonstrated.

In the second part of our investigation, our focus shifted to another new rehabilitation form which uses video games to improve upper limb function in children with cerebral palsy (96). In the second meta-analysis, we were able to analyze the following eight different outcomes: grasp function, grip strength, the Jebsen Taylor hand function, manual dexterity, Abilhand-Kids results, self-care, hand function questionnaire, and upper limb fine motor function. In all outcomes, an improvement in the investigated groups was detected, but only three of them were statistically significant (grasp function, hand function questionnaire, and upper limb fine motor function).

The understanding of standardized mean differences (SMDs) is often difficult, but the change we detected in the grasp function can be categorized as a large effect. The result of upper limb fine motor function, Weefim self-care, grip strength, AbilHand Kids, and hand function questionnaires can be interpreted as a moderate effect, and in the remained outcomes (the Jebsen Taylor hand function, manual dexterity) the effects were small.

In daily activities, grip strength is crucial to perform different functional tasks and it can provide an objective evaluation of hand function (97). In the case of spasticity, muscle weakness can be seen as the result of decreased strength of muscle agonists and imbalance in muscle tone (98).

The relationship between grip strength and daily activity performance is still unclear, some articles reported that activity can be directly influenced by grip strength, while other studies find that the grip strength of the non-dominant hand plays a key role in holding objects stable (99). The grip strength assessment is a widespread method to evaluate impaired hand function but it has not got any specific cut-off point, because of the age diversity and the different degrees of involvement (of the disease) resulted in various grip strengths in CP (98). In the included papers hand dynamometers were used to assess the grip strength. In a study Yildirim et al. (100) found a statistically significant increase in grip strength in children with CP after the VGBT therapy in contrast to Structured-Neurodevelopmental-Therapy-based hand rehabilitation. In 2022 a meta-analysis, which used three RCTs to assess the effect of Nintendo Wii alone or in combination with other therapies, detected a statistically significant improvement in grip strength compared to other rehabilitation methods (101). Regarding the fact that in all included articles, both groups improved in grip strength (except one study (77)), we believe that the insignificant change in favor of the intervention group indicates that VGBT is not superior to the control group.

Although there is no clear relationship between functional activities and grip strength children with cerebral palsy commonly suffer also from spasticity, muscle weakness, and coordination problems, that cause impaired grasping and reaching function (98, 102). A recently published meta-analysis, which evaluated the effect of Nintendo Wii found an improvement in grip strength and grasp function due to the continuous grip of the joystick. A potential limitation of that investigation could be that VGBT was applied as a supplementary therapy (Nintendo Wii + conventional therapy) in contrast to conventional therapy alone (101). To assess the grasping abilities we pooled QUEST grasp subdomains and Peabody grasp function statistically. Consistent with other articles, we also detected a significant improvement in grasp function in favor of VGBT alone or in combination with other therapies, suggesting that VGBT alone or use in combination can have some advantages over traditional forms of rehabilitation alone. Taking into consideration that there is no clear direct relationship between maximal voluntary contraction and muscle coordination, they can be equally crucial in daily activities (98).

With the aim to better understand the effect of this therapy and how it can influence daily activities through coordination improvement, we decided to analyze the manual dexterity tests. In children with cerebral palsy impaired manual dexterity at the involved upper limb is often seen. In an investigation, (non-RCT) which used the Jebsen-Taylor hand function test, to assess manual dexterity authors found a significant improvement in favor of VGBT (100). Consistent with a previous meta-analysis that evaluated the effect of Nintendo Wii on manual dexterity alone or as an adjunctive therapy, we also observed a non-significant change between the groups even when we used Jebsen Taylor Hand function tests (101).

For the purpose of evaluating the effect of VGBT a single physical test was chosen from each paper, and the results were combined and the SMD between the groups was determined. The authors reviewed and chose a single test from each paper that represented upper limb motor function. In the case of multiple tests, we selected the one that included the highest number of cases. With this method, we detected a significant improvement for the intervention group, which can indicate that VGBT as a supplementary therapy may offer advantages over conventional therapy alone.

In order to get a more accurate picture of the therapy, we decided to separate the functional tests of the upper extremity questionnaires. The two used questionnaires (Duruoz hand index, Abilhand kids) focus mainly on daily activity (1). An article (crossover trial), which we could not use in the meta-analysis part found an improvement in Abilhand-Kids favoring the conventional therapy group over the VGBT group (1).

In contrast, another paper that assessed hand function with Duruoz hand index in patients with juvenile idiopathic arthritis found an improvement for the intervention group (VBGT) compared to the control group (103). When we assessed the questionnaires that aimed to evaluate hand function we found that VGBT alone or in combination with other forms proved to be superior (significantly) in contrast to other rehabilitation therapy. If we evaluate the Abilhand-Kids questionnaire separately, the result is the same with statistical significance.

We analyzed the self-care function with the WeeFim score to see the impact of VGBT on everyday activities (104). In a crossover investigation, an insignificant improvement was seen in favor of the study group in everyday activities (1). In line with the meta-analysis, which analyzed the effect of Nintendo Wii on self-care function, we detected that VGBT alone or as an adjunctive therapy was as showed the same level of effectiveness as the control groups.

However, an article by El-Shamy (66) found significant improvements in three outcomes out of eight, when evaluating the results. Worth considering that the intervention group got an increased amount of time (additional 24 h Nintendo Wii+ usual care) in contrast to the control. It is crucial to note that in our effort to thoroughly summarize and analyze the existing data in the literature, we had to acknowledge some clinical and methodological heterogeneity among the included studies.

The investigations used different types of VGBT with varied types of video games and it is also important to take into account the heterogeneity of the applied interventions in the control group. Despite these factors, we decided to make a meta-analysis because of various reasons:

One reason was our intention to identify potential sources of heterogeneity through visual inspection of Forest plots, which could then serve as a basis for further sensitivity testing and subgroup analysis, should a hypothesis emerge (for example, observing the superiority of VGBT over certain comparators, but not others).

In order to get an even more accurate picture of the novel rehabilitation methods and give an opportunity to assess these therapeutic forms in a new aspect, we adapt a parent-reported outcome measurements tool into Hungarian (105). Therefore we recommend the use of the validated form of the CP CHILD in our institutional protocol to assess the role of innovative therapeutic forms.

9.2. Strengths

Our meta-analyses, are the most comprehensive and newest study of these novel rehabilitation techniques and are based on the articles currently available in the literature. We included only RCTs, making it the highest level of evidence to date.

Given the large number of patients and the diverse demographics, the findings can be broadly applied to children diagnosed with cerebral palsy (CP).

9.3. Limitations

Our main research limitation could be the small number of high-quality investigations in both meta-analyses. A further limiting factor that could potentially influence our results should be emphasized: most of the studies applied short investigation periods (3-12 weeks). An extended investigation period could ensure better insight into the effect of these novel methods. In the investigation of VGBT, a more homogeneous intervention should be used in the study groups and in the control groups.

In the meta-analysis, which assesses the effect of robotic-assisted gait training on the gait speed result a statistical predominance can be seen in one study (Mahgoub (49)). We think that in the RAGT meta-analysis, patient-reported outcomes should be used to assess the real functional change besides the parametrical differences we observed.

It can be considered as a limiting factor that, despite the fact that in the VGBT study the age range was determined below 18 in both groups, we included an investigation (56), which used an age range of 5-20, according to the low number of cases and that the mean age with SD was below 18 years we decided to include it.

A further distorting factor could be the different treatment times used in some articles between the study and the comparator groups. When we evaluate the VGBT effect on grasp function and upper limb fine motor function we should consider a potential bias factor in one of the articles (El-Shamy et al.) (66) the intervention group received 40% more treatment time in contrast to the control, therefore these changes should be critically treated.

10. CONCLUSIONS

Our results suggest that these novel methods which are supposed to take advantage of using the brain's neuroplasticity through forced repetitive movements (RAGT) or leveraging neuroplasticity of the brain (VGBT) are at least as effective as other usual methods for rehabilitation in upper and lower limb function in children with cerebral palsy. It is worth considering to integrate it into the daily routine and combining these tools with standard techniques. Although the expectations are understandable contrary to these demands, their breakthrough beneficial effects do not significantly overtake the traditional forms.

11. IMPLEMENTATION FOR PRACTICE

We developed an internal protocol to evaluate the results of the novel devices with a before and after questionnaire and we recommend considering its application in other institutions as well. Although both devices can be recommended for everyday use as additional therapy, we draw the attention of patients and their parents to these results and the fact that robotic-assisted walking training requires a significant financial sacrifice together with questionable additional benefits. In this way, it is worthwhile to reduce the expectations about these therapies.

12. IMPLEMENTATION FOR RESEARCH

Based on the result of our analyses, we suggest that further investigations with more direct patient-related outcomes, and longer-lasting randomized controlled trials, especially with homogenized patient groups are needed in the future. For robotic-assisted gait training studies patient or parent-reported outcomes should be included to prove whether this therapy is superior in improving balance and gait stability than other conventional therapies.

For the second study further, only VGBT included investigation should have taken to estimate its independent effect. It is necessary to distinguish between leap motion video game-based therapy and controller-based video games and also the type of videogame should be taken into account. Investigators should take care to mitigate biasing factors such as increased intervention time in the intervention group or combination therapy.

We propose that in forthcoming times, further health-economy studies should be conducted to determine whether the benefits of the therapies outweigh the expenses when compared to conventional forms of rehabilitation.

13. IMPLEMENTATION FOR POLICYMAKERS

The timely application of scientific results at the bedside is of paramount importance. Due to the potential benefits of video game-based therapy and robotic-assisted gait training and the absence of reported harmful effects, it may be worth considering the use of this treatment as an additional tool to other traditional therapies. The establishment of guidelines or at least institutional protocols for the integration of VGBT into upper extremity rehabilitation in children with CP may lead to better compliance, and therefore, improved therapeutic outcomes. Moreover, a new therapy of real interest to children with cerebral palsy could be introduced.

14. FUTURE PERSPECTIVES

While robot-assisted walking training may become a wider alternative in the future as it becomes cheaper. In the field of video game-based therapy, with the development of technology, there may be future opportunities for the creation of video games that improve targeted functions and their widespread distribution among children with cerebral palsy.

15. REFERENCES

1. Zoccolillo L, Morelli D, Cincotti F, Muzzioli L, Gobbetti T, Paolucci S, et al. Video-game based therapy performed by children with cerebral palsy: a cross-over randomized controlled trial and a cross-sectional quantitative measure of physical activity. Eur J Phys Rehabil Med. 2015;51(6):669-76.

2. Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: a clinical overview. Transl Pediatr. 2020;9(Suppl 1):S125-s35.

3. Colver A, Fairhurst C, Pharoah PO. Cerebral palsy. Lancet. 2014;383(9924):1240-9.

4. Graham HK, Rosenbaum P, Paneth N, Dan B, Lin JP, Damiano DL, et al. Cerebral palsy. Nat Rev Dis Primers. 2016;2:15082.

5. 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;109:8-14.

6. Hospital NCs. Cerebral Palsy (CP) 2024 [Available from: https://www.nationwidechildrens.org/conditions/cerebral-palsy-cp.

7. Korzeniewski SJ, Slaughter J, Lenski M, Haak P, Paneth N. The complex aetiology of cerebral palsy. Nat Rev Neurol. 2018;14(9):528-43.

8. Michael-Asalu A, Taylor G, Campbell H, Lelea LL, Kirby RS. Cerebral Palsy: Diagnosis, Epidemiology, Genetics, and Clinical Update. Adv Pediatr. 2019;66:189-208.

9. Horridge K. Children and Youth with Complex Cerebral Palsy: Care and Management Edited by Laurie J Glader and Richard D Stevenson. London: Mac Keith Press, 2019 £39.95 (Softback), pp 384 ISBN: 978-1-909962-98-9. Developmental Medicine & Child Neurology. 2019;61.

10. Liptak GS, Murphy NA. Providing a primary care medical home for children and youth with cerebral palsy. Pediatrics. 2011;128(5):e1321-9.

11. Shepherd E, Salam RA, Middleton P, Makrides M, McIntyre S, Badawi N, et al. Antenatal and intrapartum interventions for preventing cerebral palsy: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev. 2017;8(8):Cd012077.

12. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009;361(14):1349-58.

13. Shepherd E, Salam RA, Middleton P, Han S, Makrides M, McIntyre S, et al. Neonatal interventions for preventing cerebral palsy: an overview of Cochrane Systematic Reviews. Cochrane Database Syst Rev. 2018;6(6):Cd012409.

14. Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, et al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy: Advances in Diagnosis and Treatment. JAMA Pediatr. 2017;171(9):897-907.

15. Blumetti FC, Wu JCN, Barzi F, Axt MW, Waugh MC, Selber P. Orthopaedic Surgery in Dystonic Cerebral Palsy. J Pediatr Orthop. 2019;39(4):209-16.

16. Nahm NJ, Graham HK, Gormley ME, Jr., Georgiadis AG. Management of hypertonia in cerebral palsy. Curr Opin Pediatr. 2018;30(1):57-64.

17. Novak I, McIntyre S, Morgan C, Campbell L, Dark L, Morton N, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. Dev Med Child Neurol. 2013;55(10):885-910.

18. Patel DR, Soyode O. Pharmacologic interventions for reducing spasticity in cerebral palsy. Indian J Pediatr. 2005;72(10):869-72.

19. EE HHB. Orthopaedic Management in Cerebral Palsy. 2nd ed. ed. London: Mac Keith Press; 2007.

20. Rubin I, Greydanus DE, Merrick J, Patel DR. Health Care for People with Intellectual and Developmental Disabilities across the Lifespan2016. 1-2307 p.

21. Das SP, Ganesh GS. Evidence-based Approach to Physical Therapy in Cerebral Palsy. Indian J Orthop. 2019;53(1):20-34.

22. NF DKICT. Physiotherapy and Occupational Therapy for People with Cerebral Palsy. London: Mac Keith Press; 2010.

23. AH JTCEH. In: L BMRNP, editor. Children with Disabilities. 8th ed. ed. Baltimore: Paul Brookes; 2019. p. 423–56.

24. Chiu HC, Ada L. Constraint-induced movement therapy improves upper limb activity and participation in hemiplegic cerebral palsy: a systematic review. J Physiother. 2016;62(3):130-7.

25. Jamali AR, Amini M. The Effects of Constraint-Induced Movement Therapy on Functions of Cerebral Palsy Children. Iran J Child Neurol. 2018;12(4):16-27.

26. Kim HY, Shin J-H, Yang SP, Shin MA, Lee SH. Robot-assisted gait training for balance and lower extremity function in patients with infratentorial stroke: a single-blinded randomized controlled trial. Journal of NeuroEngineering and Rehabilitation. 2019;16(1):99.

27. Nardon M, Ruzzante F, O'Donnell L, Adami A, Dayanidhi S, Bertucco M. Energetics of walking in individuals with cerebral palsy and typical development, across severity and age: A systematic review and meta-analysis. Gait Posture. 2021;90:388-407.

28. Kuo AD, Donelan JM. Dynamic Principles of Gait and Their Clinical Implications. Physical Therapy. 2010;90(2):157-74.

29. Picelli A, Melotti C, Origano F, Waldner A, Fiaschi A, Santilli V, et al. Robot-Assisted Gait Training in Patients With Parkinson Disease: A Randomized Controlled Trial. Neurorehabilitation and Neural Repair. 2012;26(4):353-61.

30. Yun SJ, Lee HH, Lee WH, Lee SH, Oh B-M, Seo HG. Effect of robot-assisted gait training on gait automaticity in Parkinson disease: A prospective, open-label, single-arm, pilot study. Medicine. 2021;100(5):e24348.

31. Carda S, Invernizzi M, Baricich A, Comi C, Croquelois A, Cisari C. Robotic Gait Training Is not Superior to Conventional Treadmill Training in Parkinson Disease: A Single-Blind Randomized Controlled Trial. Neurorehabilitation and Neural Repair. 2012;26(9):1027-34.

32. Picelli A, Melotti C, Origano F, Neri R, Waldner A, Smania N. Robot-assisted gait training versus equal intensity treadmill training in patients with mild to moderate Parkinson's disease: A randomized controlled trial. Parkinsonism & Related Disorders. 2013;19(6):605-10.

33. Picelli A, Melotti C, Origano F, Waldner A, Gimigliano R, Smania N. Does robotic gait training improve balance in Parkinson's disease? A randomized controlled trial. Parkinsonism & Related Disorders. 2012;18(8):990-3.

34. Cano-Mañas MJ, Collado-Vázquez S, Rodríguez Hernández J, Muñoz Villena AJ, Cano-de-la-Cuerda R. Effects of Video-Game Based Therapy on Balance, Postural Control, Functionality, and Quality of Life of Patients with Subacute Stroke: A Randomized Controlled Trial. J Healthc Eng. 2020;2020:5480315.

35. Kim JH. Effects of a virtual reality video game exercise program on upper extremity function and daily living activities in stroke patients. J Phys Ther Sci. 2018;30(12):1408-11.

36. VA HJTJCJCMLTPMW. Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition ed. Chichester (UK): John Wiley & Sons; 2019.

37. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

38. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

39. G. GDT. GRADEpro Guideline Development Tool. McMaster University and Evidence Prime; 2022.

40. Faraone SV. Interpreting estimates of treatment effects: implications for managed care. P t. 2008;33(12):700-11.

41. Manikowska F, Brazevic S, Krzyżańska A, Jóźwiak M. Effects of Robot-Assisted Therapy on Gait Parameters in Pediatric Patients With Spastic Cerebral Palsy. Front Neurol. 2021;12:724009.

42. RC T. R: A Language and Environment for Statistical Computing. 2021.

43. Ammann-Reiffer C, Bastiaenen CHG, Meyer-Heim AD, van Hedel HJA. Lessons learned from conducting a pragmatic, randomized, crossover trial on robot-assisted gait training in children with cerebral palsy (PeLoGAIT). J Pediatr Rehabil Med. 2020;13(2):137-48.

44. Aras B, Yaşar E, Kesikburun S, Türker D, Tok F, Yılmaz B. Comparison of the effectiveness of partial body weight-supported treadmill exercises, robotic-assisted treadmill exercises, and anti-gravity treadmill exercises in spastic cerebral palsy. Turk J Phys Med Rehabil. 2019;65(4):361-70.

45. Drużbicki M, Rusek W, Snela S, Dudek J, Szczepanik M, Zak E, et al. Functional effects of robotic-assisted locomotor treadmill thearapy in children with cerebral palsy. J Rehabil Med. 2013;45(4):358-63.

46. Jin LH, Yang SS, Choi JY, Sohn MK. The Effect of Robot-Assisted Gait Training on Locomotor Function and Functional Capability for Daily Activities in Children with Cerebral Palsy: A Single-Blinded, Randomized Cross-Over Trial. Brain Sci. 2020;10(11).

47. Jin X, Meng Z, Yin Z. The effects of robot-aided walking training on the walking ability in children with cerebral palsy. Chinese Journal of Rehabilitation Medicine. 2012;27:822-4.

48. Kawasaki S, Ohata K, Yoshida T, Yokoyama A, Yamada S. Gait improvements by assisting hip movements with the robot in children with cerebral palsy: a pilot randomized controlled trial. J Neuroeng Rehabil. 2020;17(1):87.

49. Mostafa M, Serag M, Amin W, Zahran S. Effect of Locomotor Training with A Robotic-Gait Orthosis (Lokomat) in Spasticity Modulation Of Spastic Hemiplegic Children: A Randomized Controlled Trial. Fizjoterapia Polska. 2020;20.

50. Pool D, Valentine J, Taylor NF, Bear N, Elliott C. Locomotor and robotic assistive gait training for children with cerebral palsy. Dev Med Child Neurol. 2021;63(3):328-35.

51. Smania N, Bonetti P, Gandolfi M, Cosentino A, Waldner A, Hesse S, et al. Improved gait after repetitive locomotor training in children with cerebral palsy. Am J Phys Med Rehabil. 2011;90(2):137-49.

52. Wallard L, Dietrich G, Kerlirzin Y, Bredin J. Robotic-assisted gait training improves walking abilities in diplegic children with cerebral palsy. Eur J Paediatr Neurol. 2017;21(3):557-64.

53. Wallard L, Dietrich G, Kerlirzin Y, Bredin J. Effect of robotic-assisted gait rehabilitation on dynamic equilibrium control in the gait of children with cerebral palsy. Gait Posture. 2018;60:55-60.

54. Wu M, Kim J, Arora P, Gaebler-Spira DJ, Zhang Y. Effects of the Integration of Dynamic Weight Shifting Training Into Treadmill Training on Walking Function of Children with Cerebral Palsy: A Randomized Controlled Study. Am J Phys Med Rehabil. 2017;96(11):765-72.

55. Arellano-Martínez IT, Rodríguez-Reyes G, Quiñones-Uriostegui I, Arellano-Saldaña ME. Análisis espacio temporal y hallazgos clínicos de la marcha. Comparación de dos modalidades de tratamiento en niños con parálisis cerebral tipo hemiparesia espástica. Reporte preliminar. Cirugía y Cirujanos. 2013;81(1):14-20.

56. Sajan JE, John JA, Grace P, Sabu SS, Tharion G. Wii-based interactive video games as a supplement to conventional therapy for rehabilitation of children with cerebral palsy: A pilot, randomized controlled trial. Dev Neurorehabil. 2017;20(6):361-7.

57. Acar G, Altun GP, Yurdalan S, Polat MG. Efficacy of neurodevelopmental treatment combined with the Nintendo(®) Wii in patients with cerebral palsy. J Phys Ther Sci. 2016;28(3):774-80.

58. AlSaif AA, Alsenany S. Effects of interactive games on motor performance in children with spastic cerebral palsy. J Phys Ther Sci. 2015;27(6):2001-3.

59. Atasavun Uysal S, Baltaci G. Effects of Nintendo Wii(™) Training on Occupational Performance, Balance, and Daily Living Activities in Children with Spastic Hemiplegic Cerebral Palsy: A Single-Blind and Randomized Trial. Games Health J. 2016;5(5):311-7.

60. Avcil E, Tarakci D, Arman N, Tarakci E. Upper extremity rehabilitation using video games in cerebral palsy: a randomized clinical trial. Acta Neurol Belg. 2021;121(4):1053-60.

61. Bedair R, Al-Talawy H, Shoukry K, Abdul-Raouf E. Impact of virtual reality games as an adjunct treatment tool on upper extremity function of spastic hemiplegic children. 2016;9:1-8.

62. Chiu HC, Ada L, Lee HM. Upper limb training using Wii Sports Resort for children with hemiplegic cerebral palsy: a randomized, single-blind trial. Clin Rehabil. 2014;28(10):1015-24.

63. Choi JY, Yi SH, Ao L, Tang X, Xu X, Shim D, et al. Virtual reality rehabilitation in children with brain injury: a randomized controlled trial. Dev Med Child Neurol. 2021;63(4):480-7.

64. Choi JY, Yi SH, Shim D, Yoo B, Park ES, Rha DW. Home-based virtual reality-enhanced upper limb training system in children with brain injury: a randomized controlled trial. Front Pediatr. 2023;11:1131573.

65. Daliri M, Moradi A, Fatorehchy S, Bakhshi E, Moradi E, Sabbaghi S. Investigating the Effect of Leap Motion on Upper Extremity Rehabilitation in Children with Cerebral Palsy: A Randomized Controlled Trial. Dev Neurorehabil. 2023;26(4):244-52.

66. El-Shamy Sm PhD PT, El-Banna Mf PhD PT. Effect of Wii training on hand function in children with hemiplegic cerebral palsy. Physiother Theory Pract. 2020;36(1):38-44.

67. FİDan Ö, Genc A. EFFECT OF VIRTUAL REALITY TRAINING ON BALANCE AND FUNCTIONALITY IN CHILDREN WITH CEREBRAL PALSY: A RANDOMIZED CONTROLLED TRIALSEREBRAL PALSİLİ ÇOCUKLARDA SANAL GERÇEKLİK EĞİTİMİNİN DENGE VE FONKSİYONELLİK ÜZERİNE ETKİSİ: RANDOMİZE KONTROLLÜ ÇALIŞMA. Türk Fizyoterapi ve Rehabilitasyon Dergisi. 2022;34.

68. Kanitkar A, Parmar ST, Szturm TJ, Restall G, Rempel GR, Sepehri N, et al. Evaluation of a computer game-assisted rehabilitation program for manual dexterity of children with cerebral palsy: Feasibility randomized control trial. Pm r. 2023;15(10):1280-91.

69. Kassee C, Hunt C, Holmes MWR, Lloyd M. Home-based Nintendo Wii training to improve upper-limb function in children ages 7 to 12 with spastic hemiplegic cerebral palsy. J Pediatr Rehabil Med. 2017;10(2):145-54.

70. Menekseoglu AK, Capan N, Arman S, Aydin AR. Effect of a Virtual Reality-Mediated Gamified Rehabilitation Program on Upper Limb Functions in Children With Hemiplegic Cerebral Palsy: A Prospective, Randomized Controlled Study. Am J Phys Med Rehabil. 2023;102(3):198-205.

71. Metin Ökmen B, Doğan Aslan M, Nakipoğlu Yüzer GF, Özgirgin N. Effect of virtual reality therapy on functional development in children with cerebral palsy: A single-blind, prospective, randomized-controlled study. Turk J Phys Med Rehabil. 2019;65(4):371-8.

72. Ren K, Gong XM, Zhang R, Chen XH. [Effects of virtual reality training on limb movement in children with spastic diplegia cerebral palsy]. Zhongguo Dang Dai Er Ke Za Zhi. 2016;18(10):975-9.

73. Şahin S, Köse B, Aran OT, Bahadır Ağce Z, Kayıhan H. The Effects of Virtual Reality on Motor Functions and Daily Life Activities in Unilateral Spastic Cerebral Palsy: A Single-Blind Randomized Controlled Trial. Games Health J. 2020;9(1):45-52.

74. Saussez G, Bailly R, Araneda R, Paradis J, Ebner-Karestinos D, Klöcker A, et al. Efficacy of integrating a semi-immersive virtual device in the HABIT-ILE intervention for children with unilateral cerebral palsy: a non-inferiority randomized controlled trial. Journal of NeuroEngineering and Rehabilitation. 2023;20(1):98.

75. Shih T-Y, Wang T-N, Shieh J-Y, Lin S-Y, Ruan S-J, Tang H-H, et al. Comparative effects of kinect-based versus therapist-based constraint-induced movement therapy on motor control and daily motor function in children with unilateral cerebral palsy: a randomized control trial. Journal of NeuroEngineering and Rehabilitation. 2023;20(1):13.

76. Tarakci D, Ersoz Huseyinsinoglu B, Tarakci E, Razak Ozdincler A. Effects of Nintendo Wii-Fit(®) video games on balance in children with mild cerebral palsy. Pediatr Int. 2016;58(10):1042-50.

77. Tarakci E, Arman N, Tarakci D, Kasapcopur O. Leap Motion Controller-based training for upper extremity rehabilitation in children and adolescents with physical disabilities: A randomized controlled trial. J Hand Ther. 2020;33(2):220-8.e1.

78. Wang TN, Chen YL, Shieh JY, Chen HL. Commercial Exergaming in Home-Based Pediatric Constraint-Induced Therapy: A Randomized Trial. OTJR (Thorofare N J). 2021;41(2):90-100.

79. Saussez G, Bailly R, Araneda R, Paradis J, Ebner-Karestinos D, Klöcker A, et al. Efficacy of integrating a semi-immersive virtual device in the HABIT-ILE intervention for children with unilateral cerebral palsy: a non-inferiority randomized controlled trial. J Neuroeng Rehabil. 2023;20(1):98.

80. Bayón C, Martín-Lorenzo T, Moral-Saiz B, Ramírez Ó, Pérez-Somarriba Á, Lerma-Lara S, et al. A robot-based gait training therapy for pediatric population with cerebral palsy: goal setting, proposal and preliminary clinical implementation. Journal of NeuroEngineering and Rehabilitation. 2018;15(1):69.

81. Yazıcı M, Livanelioğlu A, Gücüyener K, Tekin L, Sümer E, Yakut Y. Effects of robotic rehabilitation on walking and balance in pediatric patients with hemiparetic cerebral palsy. Gait Posture. 2019;70:397-402.

82. Oeffinger D, Bagley A, Rogers S, Gorton G, Kryscio R, Abel M, et al. Outcome tools used for ambulatory children with cerebral palsy: responsiveness and minimum clinically important differences. Dev Med Child Neurol. 2008;50(12):918-25.

83. Hanna SE, Bartlett DJ, Rivard LM, Russell DJ. Reference curves for the Gross Motor Function Measure: percentiles for clinical description and tracking over time among children with cerebral palsy. Phys Ther. 2008;88(5):596-607.

84. Armand S, Decoulon G, Bonnefoy-Mazure A. Gait analysis in children with cerebral palsy. EFORT Open Rev. 2016;1(12):448-60.

85. Cherni Y, Ballaz L, Lemaire J, Dal Maso F, Begon M. Effect of low dose robotic-gait training on walking capacity in children and adolescents with cerebral palsy. Neurophysiol Clin. 2020;50(6):507-19.

86. Žarković D, Šorfová M, Tufano JJ, Kutílek P, Vítečková S, Ravnik D, et al. Gait changes following robot-assisted gait training in children with cerebral palsy. Physiol Res. 2021;70(S3):S397-s408.

87. Picelli A, Melotti C, Origano F, Neri R, Verzè E, Gandolfi M, et al. Robot-assisted gait training is not superior to balance training for improving postural instability in patients with mild to moderate Parkinson's disease: a single-blind randomized controlled trial. Clin Rehabil. 2015;29(4):339-47.

88. Conner BC, Remec NM, Lerner ZF. Is robotic gait training effective for individuals with cerebral palsy? A systematic review and meta-analysis of randomized controlled trials. Clin Rehabil. 2022;36(7):873-82.

89. Fritz S, Lusardi M. White paper: "walking speed: the sixth vital sign". J Geriatr Phys Ther. 2009;32(2):46-9.

90. Vezér M, Gresits O, Engh MA, Szabó L, Molnar Z, Hegyi P, et al. Evidence for gait improvement with robotic-assisted gait training of children with cerebral palsy remains uncertain. Gait & Posture. 2024;107:8-16.

91. Abel MF, Damiano DL. Strategies for increasing walking speed in diplegic cerebral palsy. J Pediatr Orthop. 1996;16(6):753-8.

92. Kuo YL, Culhane KM, Thomason P, Tirosh O, Baker R. Measuring distance walked and step count in children with cerebral palsy: an evaluation of two portable activity monitors. Gait Posture. 2009;29(2):304-10.

93. Nedergård H, Arumugam A, Sandlund M, Bråndal 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.

94. Hof AL, Gazendam MG, Sinke WE. The condition for dynamic stability. J Biomech. 2005;38(1):1-8.

95. Rethwilm R, Böhm H, Haase M, Perchthaler D, Dussa CU, Federolf P. Dynamic stability in cerebral palsy during walking and running: Predictors and regulation strategies. Gait Posture. 2021;84:329-34.

96. Vezér M, Gresits O, Engh MA, Szabó B, Molnár Z, Hegyi P, et al. Effectiveness of Video-Game-Based Therapy to Improve Hand Function in Children with Cerebral Palsy: A Systematic Review and Meta-Analysis. Journal of Clinical Medicine. 2024;13(24):7524.

97. Klingels K, Demeyere I, Jaspers E, De Cock P, Molenaers G, Boyd R, et al. Upper limb impairments and their impact on activity measures in children with unilateral cerebral palsy. Eur J Paediatr Neurol. 2012;16(5):475-84.

98. van Meeteren J, van Rijn RM, Selles RW, Roebroeck ME, Stam HJ. Grip strength parameters and functional activities in young adults with unilateral cerebral palsy compared with healthy subjects. J Rehabil Med. 2007;39(8):598-604.

99. Krumlinde-Sundholm L, Eliasson A-C. Development of the Assisting Hand Assessment: A Rasch-built Measure intended for Children with Unilateral Upper Limb Impairments. Scand J Occup Ther. 2009;10:16-26.

100. Yildirim Y, Budak M, Tarakci D, Algun ZC. The Effect of Video-Based Games on Hand Functions and Cognitive Functions in Cerebral Palsy. Games Health J. 2021;10(3):180-9.

101. Montoro-Cárdenas D, Cortés-Pérez I, Ibancos-Losada MDR, Zagalaz-Anula N, Obrero-Gaitán E, Osuna-Pérez MC. Nintendo(®) Wii Therapy Improves Upper Extremity Motor Function in Children with Cerebral Palsy: A Systematic Review with Meta-Analysis. Int J Environ Res Public Health. 2022;19(19).

102. Agarwal A, Verma I. Cerebral palsy in children: An overview. J Clin Orthop Trauma. 2012;3(2):77-81.

103. Arman N, Tarakci E, Tarakci D, Kasapcopur O. Effects of Video Games-Based Task-Oriented Activity Training (Xbox 360 Kinect) on Activity Performance and Participation in Patients With Juvenile Idiopathic Arthritis: A Randomized Clinical Trial. Am J Phys Med Rehabil. 2019;98(3):174-81.

104. You SH, Jang SH, Kim YH, Kwon YH, Barrow I, Hallett M. Cortical reorganization induced by virtual reality therapy in a child with hemiparetic cerebral palsy. Dev Med Child Neurol. 2005;47(9):628-35.

105. Molnár-Hevér D BZ, Domos Gy, Firnigel B, Horváth N,Kiss S, L'Auné G, Skaliczki G, Szakály N, Szőke Gy, Vezér M, Unni G. N,Terebessy T. . Cerebralis paresisben szenvedő gyermekek egészségindexe. Orvosi Hetilap. 2023;164(16):610–8.

16. BIBLIOGRAPHY

16.1. Publications related to the thesis

Vezér M, Gresits O, Engh M. A, Szabó L, Molnar Zs, Hegyi P, Terebessy T. (2024) Evidence for gait improvement with robotic-assisted gait training of children with cerebral palsy remains uncertain.
Gait & Posture.
Q1, IF: 2,20

Vezér M, Gresits O, Engh M. A, Szabó L, Molnar Zs, Hegyi P,Terebessy T. (2024). Effectiveness of Video-Game-Based Therapy to Improve Hand Function in Children with Cerebral Palsy: A Systematic Review and Meta-Analysis
Journal of Clinical Medicine
Q1, IF: 3,00

16.2. Publications not related to the thesis

Molnár-Hevér D, Bejek Z, Domos Gy, Firnigel B, Horváth N,Kiss S, L'Auné G, Skaliczki G, Szakály N, Szőke Gy, **Vezér M**, Unni G. N,Terebessy T. (2023).
Hungarian adaptation of the Caregiver Priorities and Child Health Index of Life with Disabilities questionnaire
Orvosi Hetilap
Q3, IF: 0,8

Gresits O, **Vezér M**, Engh M. A, Szabó L, Molnár Zs, Hegyi P. Terebessy T, (2025).
Limited Evidence of Functional Benefit After Upper Limb Botulinum Toxin Treatment in Children With Cerebral Palsy: Systematic Review and Meta-analysis.
American Journal of Physical Medicine & Rehabilitation
Q1, IF: 2,2

<u>Vezér M</u>, Domos Gy, Horváth N, Kiss S, Terebessy T, Szőke Gy, (2018).
Antibiotikus rezisztencia kialakulása MRSA okozta osteomyelitisben.
Magyar Traumatológia Ortopédia Kézsebészet Plasztikai Sebészet

Domos Gy, Kiss S, Terebessy T, Horváth N, Kovács P. M, **<u>Vezér M</u>**, Szőke Gy, (2019).
Gyermekkori poszttraumás komplex femurdeformitás kezelése időbeli eltolással végzett nyolcas lemezes temporer epiphyseodesissel.
Magyar Traumatológia Ortopédia Kézsebészet Plasztikai Sebészet

Hevér D, Domos Gy, Horváth N, Kiss S, Szakály N, Szőke Gy,
<u>Vezér M</u>, Terebessy T (2020).
A cerebralis paresises gyermekek ortézissel történő ellátásának vizsgálata
Gyermekgyógyászati Továbbképző Szemle

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