SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3340.

GRESITS ORSOLYA ZSUZSANNA

A támasztó- és mozgató szervrendszer működésének fiziológiája

című program

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FUNCTIONAL EFFECTS OF COMMON CEREBRAL PALSY TREATMENT METHODS

Ph.D. Thesis

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Translational Medicine Program

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2025

“If I had to sum up the reason for my success in the end, I'd simply say that I was always the one who wanted it more.”

Tibor Benedek

“Ha legvégül össze kellene foglalnom a sikereim okát, csak annyit mondanék, hogy mindig én akartam jobban.”

Benedek Tibor

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1. LIST OF ABBREVIATIONS

AHA	Assisting Hand Assessment
BoNT-A	botulinum toxin A
CI	confidence interval
COPM	Canadian Occupational Performance Measure
CP	Cerebral palsy
FDRO	femoral derotation osteotomy
GAS	Goal Attainment Scaling
GDI	Gait Deviation Index
GGI	Gillette Gait Index
GPS	Gait Profile Score
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
MA	Melbourne Assessment of Unilateral Upper Limb Function
MCID	Minimal Clinically Important Difference
MD	mean difference
MINORS	Methodological Index for Non-randomized Studies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RoB	Risk of Bias
SD	standard deviations
SMD	standardized mean difference

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is that scientific research results are implemented more quickly in daily clinical practice to provide the best possible treatment for our patients.

As a mother and an orthopedic trainee with a strong interest in pediatric orthopedics, my mission is to contribute to high-quality research to improve the treatment of neuromuscular patients.

To contribute to my mission and vision, my specific goals during my PhD studies were to evaluate the functional effects of two commonly performed procedures in children with cerebral palsy: upper-limb botulinum-toxin injections and femoral derotation osteotomies.

2.2. Scientometrics

Number of all publications:	7
Cumulative IF:	10.6
Av IF/publication:	1.5
Ranking Scimago:	D1:1, Q1:3, Q4:1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	5.4
Av IF/publication:	2.7
Ranking Scimago:	D1:1, Q1:1
Number of citations on Google Scholar:	15
Number of citations on MTMT (independent):	7
H-index:	2

2.3. Future plans

I intend to complete my orthopedic training, which I have started at Semmelweis University, and continue my scientific career here. Following my primary focus of interest, my hoped-for future research topic will be neuromuscular disease pathology and treatment. I wish to honor the legacy of our distinguished predecessor, Professor Tibor Vízkelety, by helping Hungarian pediatric orthopedics regain its international recognition.

3. SUMMARY OF THE THESIS

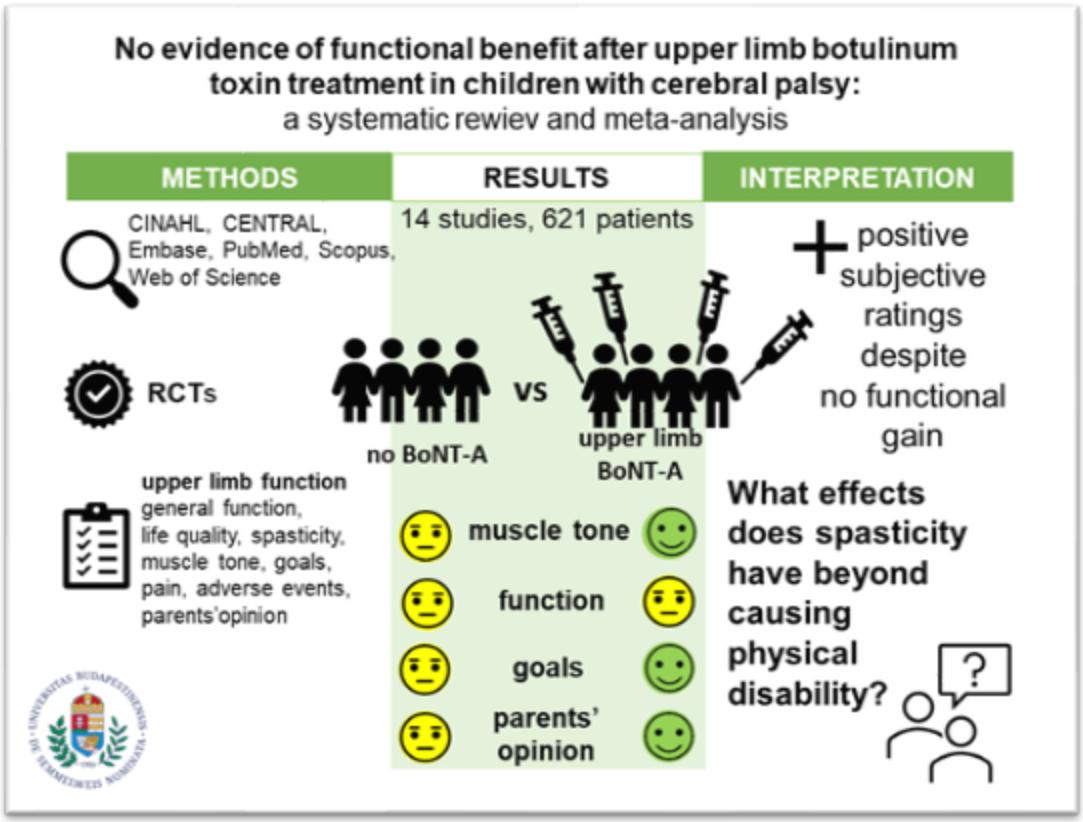
Cerebral palsy (CP) is the most frequent neuromuscular disease; patients with this condition are presented in large numbers in pediatric orthopedic clinics requesting care. The management of CP presents complex clinical challenges due to its heterogeneous manifestations and lifelong impact.

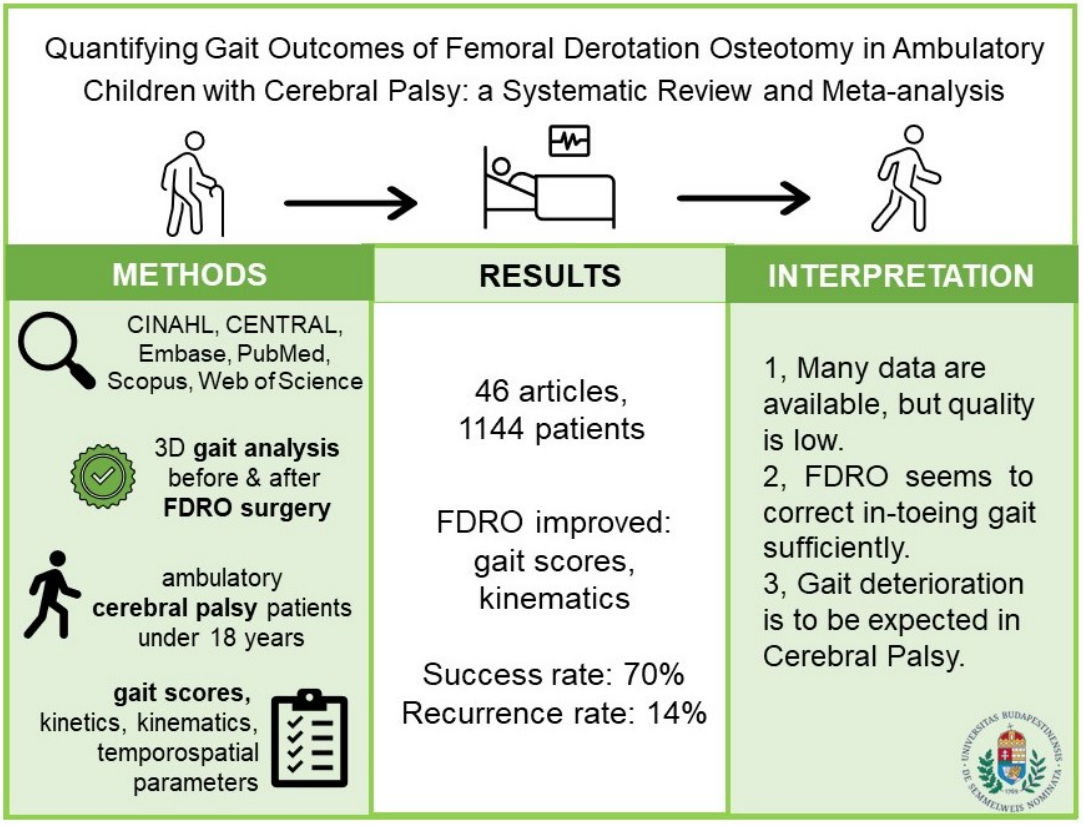
This thesis critically investigates the functional outcomes of two commonly applied interventions in children with CP, upper-limb botulinum toxin A (BoNT-A) injections and femoral derotation osteotomy (FDRO) surgeries. The main aim was to aid individual decisions regarding these interventions, which is sometimes challenging, particularly in patients with moderate motor impairment.

The first systematic review and meta-analysis assessed the added value of BoNT-A injections beyond standard non-invasive therapies on upper-limb function. While BoNT-A significantly reduced muscle tone and increased goal achievement and client satisfaction, no functional benefit was observed. The second systematic review and meta-analysis evaluated the effect of FDRO on gait in ambulatory children. Patients with associated hip conditions were excluded to prevent distortion from FDROs performed to resolve hip (sub)luxation. Results of the FDRO study demonstrated significant improvements in rotation kinematics (e.g., hip rotation and foot progression angle), as well as in composite gait scores. Long-term benefits were less robust, presumably because of the natural course of gait deterioration in CP. Evidence on kinetic changes and patient-reported outcomes (e.g., quality of life, client satisfaction, pain) is largely unreported.

Despite the widespread use of these interventions, findings revealed substantial knowledge gaps, particularly regarding long-term effectiveness, real-life functional gains, and patient-reported outcomes. These insights underscore the necessity for longitudinal studies, harmonized outcome measures, and broader inclusion of subjective data in CP research. By clarifying what is known and unknown, this work aims to support shared decision-making among patients, families, and clinicians of different fields while contributing to a more evidence-based, patient-centered approach to CP care.

4. GRAPHICAL ABSTRACTS





5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

This work aimed to evaluate the effects, particularly functional effects, and the magnitude of changes of two commonly performed procedures in children with cerebral palsy: upper-limb botulinum toxin injections (BoNT-A) and femoral derotation osteotomy (FDRO) surgeries.

5.1.2. What is the problem to solve?

Although there is no definitive cure for cerebral palsy (CP), several orthopedic interventions are used to limit the secondary musculoskeletal consequences. Safety, short-term, and direct effects of the common interventions are usually well-documented; however, changes in body function, pain levels, participation, life quality, and patient satisfaction are lacking.

CP is a very diverse condition, and even similarly categorized patients may present remarkable individual differences. Optimal care, therefore, should always be tailored to the individual. Deciding what is the best treatment, however, can be challenging.

Among the many available interventions, we investigated two commonly performed procedures to aid personal decisions about them: upper-limb BoNT-A injections and FDRO surgeries.

5.1.3. What is the importance of the topic?

Cerebral palsy is the leading cause of physical disability in childhood. (1) The prevalence has remained unchanged for decades; approximately 1 in every 500 children is affected by CP. (2, 3) Except for the very severe cases, life expectancy with CP remains similar to that of typically developing children. Therefore, reaching the best possible life quality and function is crucial in this population, not just for medical ethics, but also for economic reasons.

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

A better understanding of what to expect from upper-limb BoNT-A injections and orthopedic surgeries containing FDROs will help patients and caregivers to decide

whether to undergo these invasive interventions. We hope the results will help professionals from different fields of CP care (surgeons, physiotherapists, neurologists, rehabilitation specialists, etc.) develop similar expectations and facilitate understanding and shared decision-making about BoNT-A and FDRO, and their optimal timing. Furthermore, the identified lack of knowledge in the literature can direct future CP research.

5.2. Cerebral palsy

Due to the complex nature of Cerebral Palsy, the introduction is strictly limited to presenting only the topics closely related to the topics of this thesis.

5.2.1. Overview

Cerebral Palsy (CP) is a condition caused by a non-progressive injury to the developing brain, occurring prenatally, during birth, or in the early stages of life. (4)

From the neuromuscular perspective, the injury of the upper motor neurons is important. One typical consequence is the loss of corticospinal tract connections to lower motor neurons, hence to skeletal muscles, causing paresis or partial paralysis. Paresis is typically more serious for distal muscles than proximal muscles. Another typical consequence of the upper-motoneuron lesion is hypertonia. Hypertonia is hypothesized to be caused by the loss of inhibitory descending input to the lower motoneurons. This keeps the stretch reflex in the peripheral neuromuscular system from being overactive, resulting in hypertonia and hyperreflexia.

Clinical presentations of CP vary depending mainly on the primary lesion; however, this work focuses solely on the musculoskeletal issues. Common symptoms include inhibition of longitudinal growth in muscle–tendon units and long bones, muscle imbalance and hypertonia, altered gait biomechanics, weakness, and loss of selective motor control, resulting in reduced activity. (3, 5)

Although the brain lesion is stationary, motor impairments tend to deteriorate as the body grows. (6). In addition to musculoskeletal issues, individuals with CP might have further disorders, such as seizures, mental impairments, poor eyesight, hearing difficulties, drooling, impaired chewing and swallowing, gastrointestinal problems, bowel or bladder difficulties, problems with communication, and many other issues.

5.2.3. Classifications

CP can be classified according to several aspects. From our perspective, the following are important.

Based on clinical presentation, spastic, dyskinetic, ataxic, or mixed types can be distinguished. (6) The vast majority, 80% patients, belong to the spastic subtype. (7) This condition can be painful, bothersome, and contribute to physical disability.

Based on topographical distribution, bilateral (diplegia, triplegia, or quadriplegia) or unilateral (monoplegia or hemiplegia) involvements exist. (8)

The most commonly used functional classification system is the Gross Motor Function Classification System (GMFCS), where the grouping is based on walking function. (9) GMFCS I indicates the least impaired, and GMFCS V indicates the most serious patients. The studied interventions are mostly performed in GMFCS II-III.

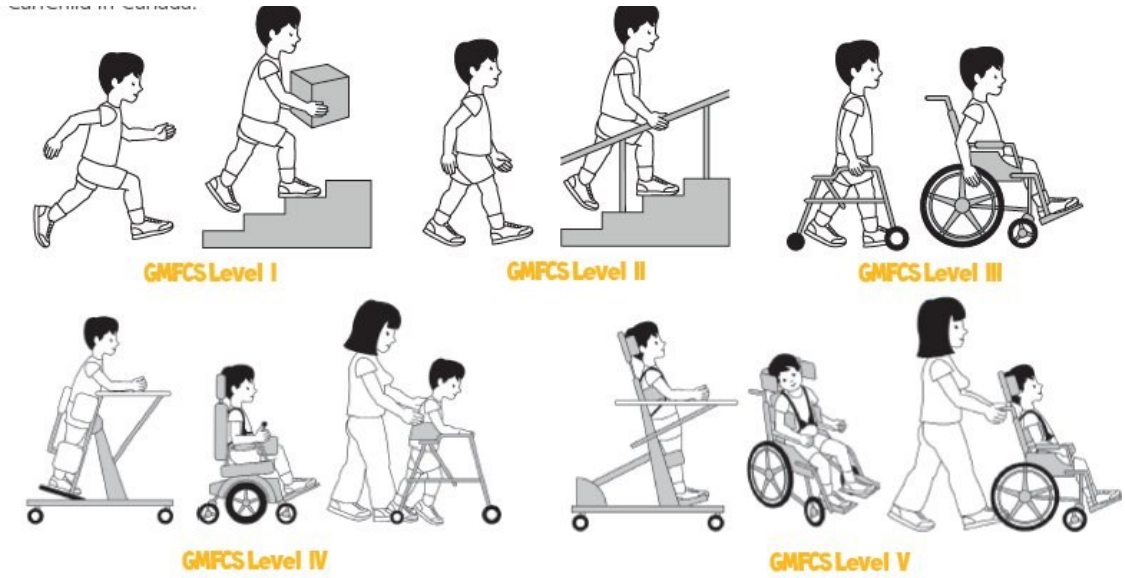


Figure 1. Gross Motor Function Classification System (GMFCS) sourced from © Palisano et al. (1997) Dev Med Child Neurol 39:214-23 CanChild: www.canchild.ca.

5.3. Interventions in CP examined in this thesis

Cerebral palsy is a highly heterogeneous condition, always requiring an individualized treatment approach. (10) Given that the primary condition leads to diverse symptoms and additional complications, the multidisciplinary team approach is the most optimal and recommended way of treatment. (6) Affected children typically receive developmental care from multiple specialty providers simultaneously. (11)

A pediatric orthopedic surgeon is usually present in the treating team, as most individuals with CP have orthopedic surgeries at some point.

Efforts to manage CP's motor disabilities in most cases are directed to normalizing tone (like BoNT-A injections) and promoting healthy motor patterns (like gait-improving surgeries with FDRO).

5.3.1. BoNT-A

The currently used definition of spasticity – characterized by a velocity-dependent stretch reflex - was introduced by Lance. (12) The most commonly used interventions to manage spasticity in CP are oral baclofen, intrathecal baclofen pumps, selective dorsal rhizotomy surgery, and intramuscular BoNT-A injections. (5) 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. (6)

Intramuscular botulinum toxin (BoNT-A) injections have been proven to decrease muscle tone temporarily, (13) and has been routinely administered for three decades in CP. [14] Since then, the administration of BoNT-A has become a routine procedure; both upper and lower extremities are commonly treated. Usually, multiple muscles are injected in one session, and treatment can be repeated. (15) BoNT-A exerts its effects by blocking the acetylcholine release at the neuromuscular junction, causing focal paresis. Neuromuscular blockade disappears at three months on average after the injection. (16) BoNT-A injections have, therefore, temporary, and dose-dependent effects. It is advised that BoNT-A should not be used as a stand-alone treatment but as a part of a rehabilitation program. (17-19)

5.3.2. FDRO

After contractures, the second major component of musculoskeletal pathology in cerebral palsy is torsion of long bones. (5) Femoral neck anteversion is around 30 degrees at birth. In typically developing children, it remodels with growth and normal motor development, reaching the value of 15 degrees by adulthood. (20) However, in children with cerebral palsy, remodelling often does not happen, and increased anteversion frequently persists. Ambulatory children with increased femoral anteversion typically develop an in-toeing gait as compensation. (21, 22) Beyond aesthetics, in-toeing is often associated with functional problems, like tripping over one's feet and rubbing the knees.(23) Therefore, a surgical correction is usually advised.(21, 24, 25) Soft-tissue surgeries are considered

ineffective in resolving internal rotation gait (26); however, emerging evidence questions this belief.(27-29)

The gold-standard treatment method is femoral derotation osteotomy (FDRO). It is often part of single-event multilevel surgery, aiming to correct lever arms and improve gait.(26)

FDROs can be performed in the subtrochanteric localization ('proximal') or in the supracondylar localization ('distal'). (30) They are invasive procedures associated with potential risks and challenges: a need for general anesthesia, surgical complications, such as bleeding, non-union, under- or over-correction, fixation failure, (31) and a long rehabilitation period. (32)

Short-term effects of FDRO have been widely reported: significant improvements in hip rotation and foot progression angle in bilateral and unilateral CP patients and an improved pelvic rotation in unilateral children, but no change in bilaterally involved ones.(33) Restoring lever arms has the potential consequence of preventing secondary deformities, resulting in improved function in the long term. For all that, a surgical approach is usually favored. However, uncertainties remain around the exact indication and results of FDROs.(13)

5.3.3. Gait analysis

Since its introduction in the 1970s, clinical gait analysis has evolved from a largely research-focused tool into a vital component of clinical decision-making for CP-related gait disorders. (5) To perform gait analysis, a specialized laboratory is required, equipped with a three-dimensional motion capture system. The most common systems use 3D passive-marker systems with infrared cameras, traditional video cameras, and force plates built into the walking surface or treadmill. First, the markers are placed on the individual, and then, after a calibration period, the movement is captured. The recorded data needs to be processed and imported into a biomechanical model. The standard output consists of a certain number of gait cycles analysed, commonly depicted in a graphical format in the sagittal, coronal, and transverse planes. A gait analysis captures tempospatial, kinematic, kinetic, and sometimes neuromuscular data.

Temporospatial parameters refer to measurements of how a person walks, specifically focusing on the time and space aspects of their gait cycle, for example, gait speed, velocity, step width, stride length, single leg support time, etc.

Kinematic gait parameters describe the movement patterns of the body during walking. In practice, kinematics describes the movement of individual segments of the applied biomechanical model relative to each other or the laboratory, thus approximating the movement of real joints.

Kinetic gait parameters refer to the forces and moments acting on the body during walking. They are calculated from gait cycles, in which the examined individual contacts the force plate. Similarly to kinematics, real forces and moments acting on joints can only be estimated.

Gait scores (34, 35) are single scores representing the quality of patient kinematics during gait. Their calculation methods and scales differ; therefore, distinct gait scores cannot be directly compared.

The Gait Deviation Index (GDI)(36) is calculated from 15 standard kinematic graphs of the pelvis, hips, knees, and ankles. Ranges 0-100 points. Higher values indicate better gait: 100 points (and above) represent a normal gait. Every 10-point decrease means one standard deviation distance from the mean of the healthy individuals.

The Gait Profile Score (GPS) (37) represents the root mean square difference between the patient's kinematic data and the average of healthy subjects measured in degrees. Healthy subjects' GPS is around 5-6°. Higher GPS scores mean more deviation from the normal gait. The minimal clinically important difference is 1.6°. (38)

The Gillette Gait Index (GGI) (39) uses 13 kinematic values of the pelvis, hip, knee, ankle, and three temporospatial parameters (percentage of stance phase, normalized velocity, and cadence). Lower scores represent better gait. An average GGI score is reported to be 15 for healthy subjects and 900 for the affected side of Type IV hemiplegics. (40) The square root of GGI correlates well with GPS.

6. OBJECTIVES

6.1. Study I. – No Evidence of Functional Benefit after Upper limb Botulinum Toxin Treatment in Children with Cerebral Palsy: Systematic Review and Meta-analysis

The aim of this study was to assess what upper limb BoNT-A treatment can add to the non-invasive physical therapies in children with spastic cerebral palsy. The primary outcome of interest was upper-limb function; secondary outcomes were muscle tone, activity, participation, health-related quality of life, and client satisfaction. Our overall goal with this study was to provide clarification and a critical appraisal equally to treating physicians and policymakers.

6.2. Study II. – Impact of Femoral Derotation Osteotomy on Gait in Ambulatory Children with Cerebral Palsy: A Systematic Review and Meta-Analysis

We aimed to systematically review, synthesize, and contextualize the results of orthopedic surgeries with FRDOs in ambulatory children with CP with centralized hips, where the surgery aimed to improve gait function. The goals of this study were to aid orthopedics in setting up correct indications for this major surgery and to aid clients in reaching informed decisions. Furthermore, to facilitate understanding among professionals involved in CP care, in order to 'maximize potential outcomes and minimize risk.' (41)

7. METHODS

The conducted systematic reviews and meta-analyses were performed in accordance with the Cochrane Handbook (42) and the PRISMA 2020 guidelines were followed (43). The protocols of the studies were registered on PROSPERO, under No. CRD42021283865 and No. CRD42022312486.

7.1. Search strategy

The systematic search for the BoNT-A study was conducted in October 2022 with the search key cerebral palsy AND (botox OR botulinum OR botulotoxin OR BoNT OR BoNT-A or btx), and for the FDRO study in May 2023 with the search key "Cerebral Palsy" AND osteotomy. The following six databases were searched: CINAHL, Cochrane CENTRAL, Embase, PubMed, Scopus, and Web of Science. No filters or restrictions were applied, except for the FRDO study, where Scopus search was limited to only titles, abstracts, and keywords.

7.2. Study Selection

After the removal of duplicates, two authors (MV and GO) conducted the selection process independently according to the criteria defined by the preregistered protocol. First, titles and abstracts were screened. When a paper met the eligibility criteria or if there was a doubt about eligibility, the authors (OG and MV) assessed the full text of the articles. Full texts were obtained when an article met the inclusion criteria or when there was doubt about eligibility. Retrieved full texts were screened similarly. To quantify agreement, Cohen's kappa values were calculated. An agreement of more than 0.8 was sought to judge whether the selection criteria were sufficiently reproducible. Disagreements were resolved by a third reviewer (TT) in the BoNT-A study and by discussion in the FDRO study.

7.3. Inclusion/Exclusion Criteria

To define inclusion criteria, the PICO (population, intervention, comparator, outcomes) framework was used, as recommended by the PRISMA guidelines.

7.3.1. Criteria for the BoNT-A study: randomized controlled trials (RCTs) comparing upper-limb BoNT-A-treated and no-BoNT-A groups of children with spastic cerebral

palsy. A study was included if it had at least one intervention and one control group that completely matched our criteria.

Population: children with spastic cerebral palsy.

Intervention: upper limb botulinum toxin (BoNT-A) treatment followed by a non-invasive rehabilitation program.

Comparator: no BoNT-A. Any combination of placebo, sham procedure, or any non-invasive rehabilitation method was accepted.

Outcome measures: upper limb function, body function, health-related life quality, muscle tone, spasticity, individual goals, pain, adverse events, and client satisfaction.

7.3.2. Criteria for the FDRO study: studies comparing the results of instrumented 3D gait analysis of patients with cerebral palsy before and after an FDRO surgery.

Population: cerebral palsy patients with the ability to walk, under 18 years at the time of surgery.

Intervention: FDRO, performed either alone or as a part of complex surgery. Both proximal (intertrochanteric or subtrochanteric level) and distal (supracondylar level) localization are accepted.

Outcomes: Gait scores, temporospatial gait parameters, pelvic, hip, knee, and ankle kinetics and kinematics, foot progression angle, pain, quality of life, patient or family satisfaction, adverse event(s).

7.4. Data Extraction

The first author created the standardized data collection sheet in Microsoft Excel. One author (GO) collected the data, while another author (MV) reviewed it. Besides characteristics of the included articles (first authors, the year of publication, country of study, digital object identifiers, study design, population, study period, follow-up time, intervention details, procedures in the control group, main findings) all outcomes of the authors' interests were extracted, regardless the measurement. Any discrepancies were resolved by discussion.

7.5. Assessment of Evidence Quality and Risk of Bias

For the BoNT-A study, the Cochrane risk-of-bias tool for randomized trials (RoB 2) (44), and for the quality of evidence assessment, the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) scale was used (45) For the FRDO study, the Methodological Index for Non-randomized Studies (MINORS) (46) tool was used. Two reviewers (MV and GO) independently performed the assessments. Discrepancies were resolved by discussion. Potential publication bias was assessed by visual inspection of Funnel-plots, and in case the presence of at least 10 separate data points, classical Egger's test p-values for MD effect size were calculated. (47) Small study bias was assumed if the p-value was less than 10%.

7.6. Statistical analysis

A meta-analysis was carried out for each outcome when data from at least three independent studies were available. As considerable between-study heterogeneity was assumed in all cases, a random-effects model was used to pool effect sizes.

If the mean and standard deviation of the change were available, they were used for the analysis; in all other cases, the baseline and after-intervention data were used to calculate the change. As the correlation was not available, the standard deviation of change was calculated by using an upper approximation, i.e., we assumed a correlation of -1.

Results were displayed in forest plots. In the BoNT-A study, analyses show the difference between the changes observed in the BoNT-A groups versus in the control groups. In the FDRO study, however, analyses show the change before and after surgery.

For continuous outcomes, pooled Mean Differences (MDs), and for dichotomous variables, pooled Odds Ratios (ORs) along with their 95% Confidence Intervals (CI) were calculated. For gait scores, standardized mean differences (SMD) were used as an effect size measure with 95% CIs, due to the use of different scales. Hedges' g was used as SMD. (48) The inverse variance weighting method was used to calculate the pooled MDs and SMD. SMDs were retransformed into all the utilized original scales used as additional information to facilitate interpretation. We multiplied the resulting SMD point estimation by the calculated pooled SD for the respective scale to perform this retransformation. (49)

For the correction rate and recurrence, proportions were used as an effect size measure with 95% CIs. To calculate study proportions and pooled proportions, the total number of patients and those with the event of interest were extracted from each study. A random intercept logistic regression model was used to pool these outcomes. (50, 51)

Data were grouped as predefined in the protocol: in the BoNT-A study, measurements within 3 months of injections are marked 'during BoNT-A', while after 3 months as 'after BoNT-A'. In the FDRO study, the first two years after surgery were considered short-term, 3-4 years were considered mid-term, and at least five years were considered long-term. Where the data pool was large enough to be meaningful, osteotomy location and CP topography were also analysed.

To estimate the heterogeneity, the variance measure $\tau 2$ was applied. In the BoNT-A study, it was estimated with the Q profile method, and in the FDRO study, with the maximum likelihood method. Between-study heterogeneity was assessed by means of the Cochrane Q test and the I2 values. (52) I2 values of 25 %, 50 %, and 75 % were considered the cutting points between low, moderate, and high levels of heterogeneity. All statistical analyses were performed with R (53) using the meta (54) and dmetar (55) packages.

8. RESULTS

8.1. Search and selection, characteristic of the included studies

8.1.1. Study I. – No Evidence of Functional Benefit after Upper Limb Botulinum Toxin Treatment in Children with Cerebral Palsy

Altogether 4862 publications were screened (Cohen's kappa 0.91 for abstract and title screening), and 51 full texts were obtained (Cohen's kappa 0.92 for full-text screening). Results of the search and screening process are detailed in the PRISMA flowchart, in Figure 2. The baseline characteristics of the enrolled studies are detailed in Table 1. 20 reports of 14 studies qualified for final inclusion (56-75), containing data from a total of 621 patients. 83% had unilateral, 17% bilateral involvement. Five studies (61, 63, 65, 66, 73) reported data of repeated BoNT-A. However, we could only assess the effects of single injections, due to the following cofunding factors: differences in measurement methods, timing of injections, the way of data reporting, or because patients in the control group also received BoNT-A injections in the meantime.

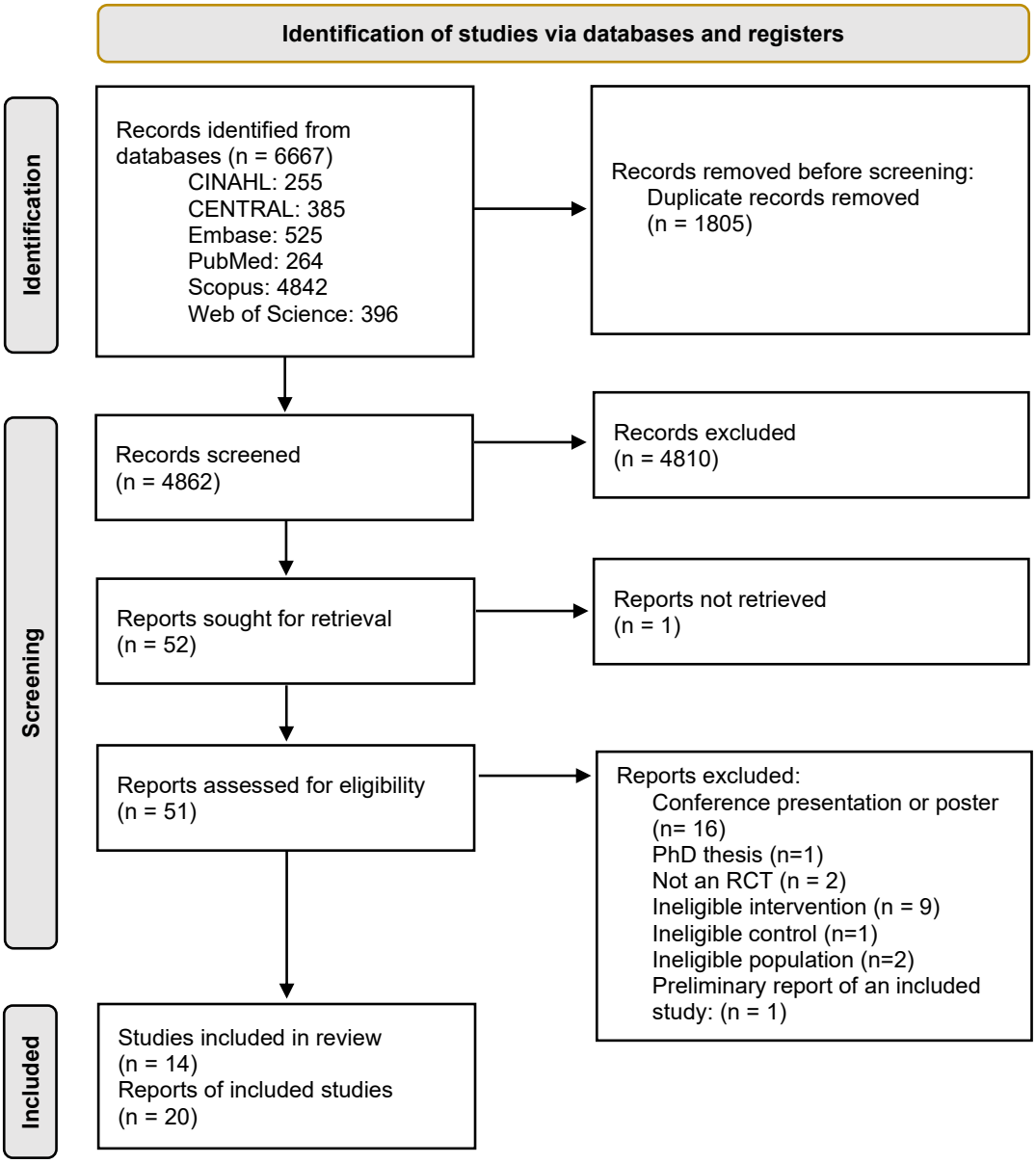


Figure 2. PRISMA flow diagram of study selection (BoNT-A study)

Table 1. Baseline characteristics of studies included in the BoNT-A study

Study	Study groups	Patient number	Main findings	Outcomes used
Corry (56)	BoNT-A vs placebo	14	BoNT-A decreased tone, increased ROM, and had better subjective change results.	AS; aROM; wrist resonance frequency (tone); grasp&release; coin transfer; subjective change
Dimitrova (57)	BoNT-A + OT vs placebo + OT	157	BoNT-A decreased tone and the dynamic component of spasticity and had better GAS scores for passive goals during the toxin effect.	MAS-B, Tardieu, CGI, GAS, QUEST
Elnaggar (58)	1: BoNT-A 2: rNMES 3: BoNTA + rNMES 4: control	60	Increased MA, AHA, PMAL scores in 1-3. study groups. The BoNT-A + rNMES group had the highest improvement.	MA; AHA; PMAL
Fehlings (59)	BoNT-A + OT vs OT	29	BoNT-A: significant improvement on QUEST, PEDI. Modest improvement on mAS, pROM. Decrease on grip strength.	QUEST; PEDI; pROM; grip; MAS elbow, wrist, forearm, thumb
Ferrari (60)	BoNT-A vs placebo	27	BoNT-A: significant increase in AHA and GAS. Modest increase in other measurements. Decrease in grip strength. House 4-5	MAS ‡ grip strength,‡ PRS UL,‡ AHA, PEDI, ABIHAND-Kid, GAS‡

			classification improved the most with BoNT-A.	
Koman (61)	BoNT-A vs placebo	73	BoNT-A: greater improvement in MA and wrist aROM. No between-group difference in UERS and HRQL.	UERS,‡ ROM,‡ MA, HRQL‡
Lidman (62, 63)	BoNT-A (repeated 2x) + OT vs OT	20	AHA revealed a superior effect in the BoNT-A/OT group at 12 months. aROM and COPM improved in both groups.	AHA; aROM elbow, forearm; pROM elbow, forearm; COPM
Lowe (64, 65)	BoNT-A (repeated 2x) + OT vs OT	42	BoNT-A: greater improvement on QUEST, GAS, COPM, PEDI and goals. Decreased tone.	QUEST, COPM, PEDI, GAS, AS
Olesch (66)	BoNT-A (repeated 3x) + OT vs OT	22	BoNT-A: COPM performance and GAS improved, decreased spasticity.	COPM, GAS, Tardieu, QUEST, PDMS-FM
Rameckers, Speth (67-69, 72)	BoNT-A + OT vs OT	20	BoNT-A: increased wrist aROM and decreased tone during effect, but no functional benefit. Greater satisfaction. Control: improved aROM, decreased tone with 6 months of PT/OT. No evidence was found for an added	aROM wrist, forearm, thumb; pROM, AS, MA, PEDI, subjective judgement, stretch resisted angle, grip strength, 9-hole peg test, kinematic aiming task,

			benefit of BTX on function and strength.	
Russo (70)	BoNT-A + OT, OT	43	BoNT-A: significant improvement in body structure, activities, participation, and improved self-conception during the toxin effect.	MAS elbow, wrist; Tardieu elbow, wrist; PEDI, PEDsQL, AMPS, self-concept, GAS
Speth (71)	1: BoNT-A, 2: BITT, 3: BoNT-A+BITT, 4: control	24	During BoNT-A effect: positive effect on the quality of movement and amount of use of the affected UL. But no additional effect of BoNT-A on bimanual performance and goal achievement. BITT: positive effect on goal achievement and bimanual performance.	AHA, ABIHAND-Kid, OSAS, GAS, COPM
Van Heest (73)	1: surgery, 2: BoNT-A (repeated 3x), 3: ongoing therapy	18	At 12 months, the surgery group had the greatest improvement, BoNT-A had a minor improvement, and regular therapy had no improvement. BoNT-A group had decreased grip strength.	aROM, pinch&grip strength, Visual analog scale of appearance of UL, SHUEE, box&block, AHA, PODCI, PedsQL, CAPE, COPM
Wallen (74, 75)	1: BoNT-A + OT, 2: BoNT-A, 3: OT,	72	BoNTA+OT enhances the self-reported, individualized,	COPM, GAS, MA,‡ PEDI,‡, CHQ,‡ Tardieu, aROM,‡

	4: control		functional outcomes of children with CP.	pROM,‡ parent satisfaction

For outcomes marked with ‡, no numerical results were reported.

Abbreviations: AHA Assisting Hand Assessment, aROM active range of motion, AS Ashworth-scale, BITT bimanual task-oriented therapy, BoNT-A botulinum neurotoxin, CAPE Children's Assessment of Participation and Enjoyment, CGI Clinical Global Impression of Change, CHQ Child Health Questionnaire, COPM Canadian Occupational Performance Measure, GAS Goal Attainmetn Scaling, HRQL Health related quality of life, MA Melbourne Assessment, , mAS modified Ashworth-scale, MCP metacarpophalangeal joint, OSAS Observational Skills Assessment Score, OT occupational therapy, PDMS-FM Peabody Developmental Motor Scale – Fine motor, PEDI Pediatric Evaluation of Disability Inventory, PedsQL Pediatric Quality of Life, PODCI Pediatrics Outcomes Data Collection Instrument, PRS UL Physician Ratings Scale of upper limb, MAL Pediatric Motor Acitvity Log, rNMES reciprocal neuromuscular electrical stimulation, pROM passive range of motion, QUEST Quality of Upper Extremity Skills Test, SHUEE Shriners Hospital Upper Extremity Evaluation, UERS upper extremity rating scale

8.1.2. Study II. – Impact of Femoral Derotation Osteotomy on Gait in Ambulatory Children with Cerebral Palsy

Altogether, 1,427 publications were screened, and 75 full texts were obtained. 46 articles qualified for final inclusion. (30, 76-120) Eligible articles are from 26 separate studies or databases. The Cohen's kappa values were 0.9 for the title and abstract and 0.98 for the full-text selection. Results of the search and screening process are detailed in Figure 3. The baseline characteristics of the enrolled studies are presented in Table 2. Altogether, 1,144 patients were reviewed, the vast majority belonging to GMFCS II-III. One study (86) assessed the results of isolated FDROs. All the other studies simultaneously performed soft tissue procedures, bony corrections, or both.

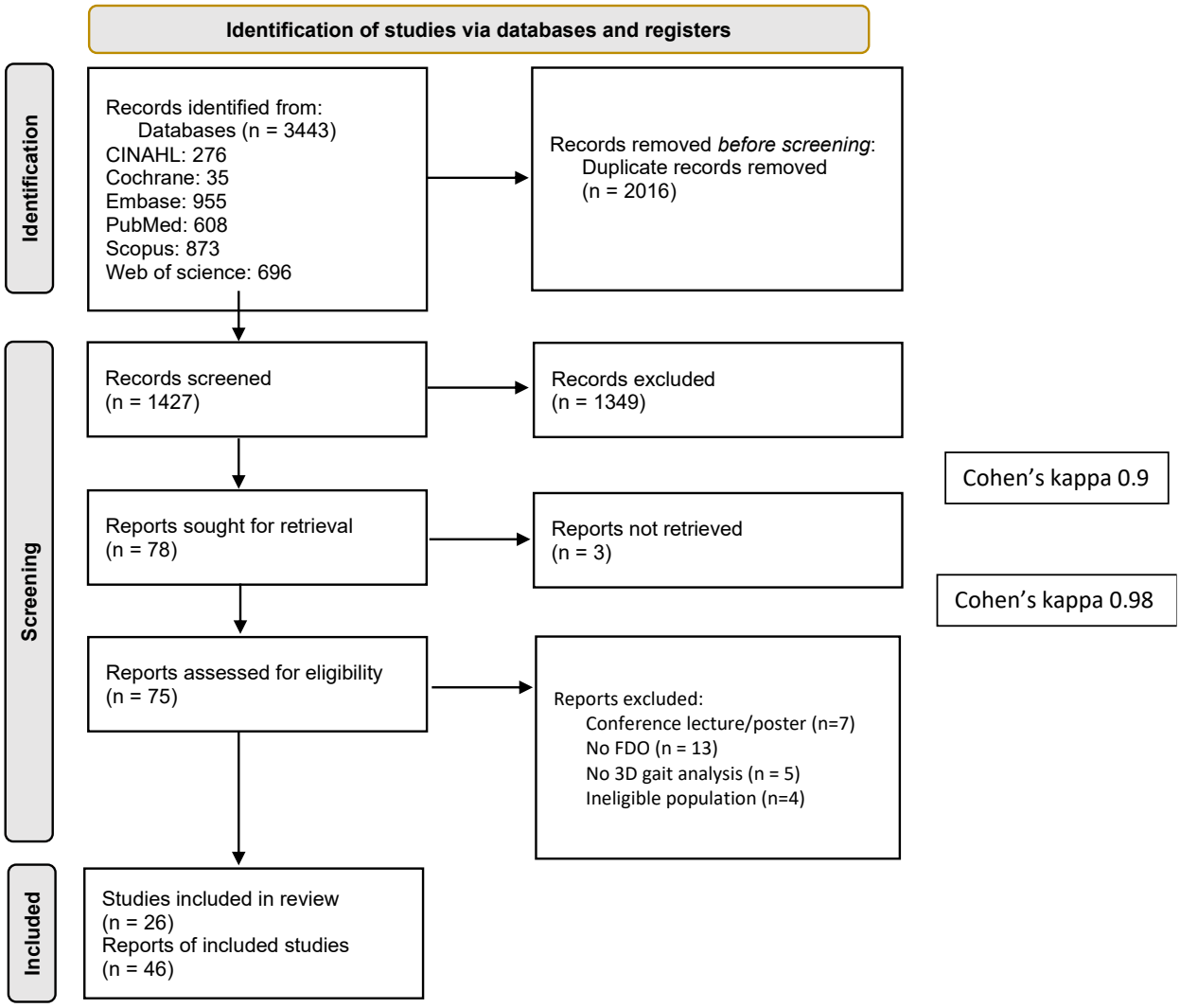


Figure 3. PRISMA flow diagram detailing the selection process (FDRO study)

Table 2. Baseline characteristics of studies included in the FDRO study

Study	Study design ‡	Number of FDRO	GMFCS	Mean age at surgery	FDRO location	Concomitant interventions	Control group	Follow-up time
Aminian 2003	R	9	NA	8,5	proximal	soft tissue procedures	Age-matched typically developing children	avg. 1 year (13 mo)
Böhm 2015	R	45	I-III.	12,5	distal	25% tibia rotation, 27% femoral extension, 40% foot correction procedures	-	avg 2 years (21 mo)
Boyer 2016	R	131	NA	8	proximal	SEMLS	age-matched CP patients, excessive anteversion (>30°), but no FDRO	short-term: avg. 1,5 years, long-term: avg 4,5 years
Boyer 2017	R	140	I-III.	9	proximal	7% had simultaneous varization	-	avg. 1 year
Boyer 2021	P	NA	I-IV.	NA	proximal	SEMLS	age-matched CP patients, excessive anteversion (>30°), but no FDRO	

Schwartz 2014	R	795	NA	NA	NA	SEMLS	SEMLS without FDRO	9 to 36 months
Braatz 2013	P	56	I-III.	11,5	73% distal, 27% proximal	Proximal FDROs had pelvic osteotomies as well	-	1 year
Braatz 2018	R	72	I-II.	10,5	72% distal, 28% proximal	SEMLS	-	1 year
Braatz 2015	P	85	I-III.	11	50% distal, 50% proximal	25% tibia rotation, further soft tissue and/or bone surgeries	-	2-4 years
Chung 2008	R	34	I-II.	8	NA	SEMLS	SEMLS without FDRO; normal foot progress angle and hip rotations	1 year
Church 2015	R	99	I-IV.	10	4% distal, 96% proximal	SEMLS	-	5 years
Perotti 2019	R	19	I-III.	10	NA	SEMLS	-	avg 8 years

Cimolin 2011	P	24	I-II.	12	proximal	isolated FDRO	-	10 months
de Morais 2012, 2013	R	71	I-III.	10	proximal	SEMLS	-	avg 4,5 years
Desailly 2020	R	34	I-II.	12,5	50% distal, 50% proximal	SEMLS	-	avg 1,5 years
Dreher 2007	P	57	I-IV.	10	80% distal, 20% proximal	SEMLS	-	1 year
Dreher 2012	R	59	I-III.	10,5	46% distal, 54% proximal	SEMLS	-	1, 3, 9 years
Niklash 2015	R	44	I-III.	11	NA	SEMLS	-	1 year
Niklash 2015	R	138	I-III.	11	67% distal, 33% proximal	SEMLS	-	1 year
Niklash 2015	R	NA	I-III.	9,5	NA	SEMLS	-	avg 8 years
Niklash 2018	R	29	I-III.	10	NA	SEMLS	-	avg 8 years
Niklash 2018	R	119	I-III.	NA	NA	SEMLS	-	1 year

Thielen 2019	R	134	I-III.	11	distal	SEMLS	SEMLS without FDRO; normal foot progress angle and hip rotations	1 year
El Barbary 2020	P	75	I-III.	10,5	distal	SEMLS	-	avg 2 years
Givon 2022	R	115	I-III.	9	proximal	SEMLS	-	1 year
Hayford 2021	R	NA	I-III.	9	NA	SEMLS	-	avg 2,5 years
Kay 2003	R	33	I-III.	9	65% distal, 35% proximal	SEMLS	-	avg 1,5 years
Kay 2004	R	19	I-III.	10	NA	SEMLS	SEMLS without FDRO; normal foot progress angle and hip rotations	avg 1,5 years
Wren 2013	P	7	I-IV.	10	NA	SEMLS	children with CP who had an indication for FDRO, but it was	1 year

							not performed.	
Wren 2022	R	103	I-IV	8,5	Majority distal	SEMLS	-	3 years
Kim 2005	R	45	NA	9	distal	SEMLS	-	6,5 years
Kim 2018	R	28	I-II.	13	distal	SEMLS	-	1 year
Kuo 1998	R	18	I-III.	11	proximal	60% of patients had hamstring lengthening, 25% tibia rotation	-	2 years
Kwon 2013	R	50	I-II.	7	proximal	SEMLS	SEMLS without FDRO; normal foot progress angle and hip rotations	1 year
Sung 2018	R	53	I-II.	8	proximal	SEMLS	-	avg. 13 years (min 10)
Mc Mulkin 2016	R	98	I-III.	12	NA	16% had just FDRO, the others had soft tissue surgeries, some patients	children with CP who had an indication for FDRO, but the	1 year

						had bony foot or tibia correction.	osteotomy was not performed	
Moisan 2022	R	10	I-II.	11	proximal	SEMLS	-	1.5 years
Ounpuu 2002, 2017	P	27	NA	8	30% distal, 70% proximal	rectus femoris transfer, hamstring lengthening, gastrocnemius lengthening in all children	-	1 year, 5 years, 11 years
Pirpiris 2003	P	56	NA	12	50% distal, 50% proximal	SEMLS	-	1 year
Saglam 2016	R	175	I-III.	6,2	NA	SEMLS	-	2 years
Saraph 2002	P	22	I-II.	12	distal	SEMLS; tibia rotation	-	mean 3 years
Thomp-son 2010	P	36	I-III.	11	proximal or metaphyseal minimal-invasive	SEMLS	-	1 year

Van Campen-hout 2019	R	NA	I-II.	9	proximal	SEMLS; SDR	-	3 years
Vermuy-ten 2021	R	55	I-III.	10,5	proximal	SEMLS	-	3 years, 5 years

‡: P stands for a prospective, R for a retrospective study design. Abbreviations: avg: average, CP: cerebral palsy, FDRO: femoral derotation osteotomy, GMFCS: Gross Motor Function Classification System, SEMLS: Single Event Multilevel Surgery,

8.2. Effect of Upper Limb BoNT-A Therapy

8.2.1. Primary outcome: upper limb function

Although all eligible studies assessed upper-limb function, the methods and reporting varied. The following measurement methods were u: ed:

- ABILHAND-Kids (60, 71),
- active range of motion (56, 62, 72, 73),
- Assisting Hand Assessment (AHA) (58, 60, 62, 71, 73),
- Melbourne Assessment of Unilateral Upper Limb Function (MA) (58, 61, 72),
- Quality of Upper Extremity Skills Test (QUEST) (56, 59, 64, 66),
- Shriners Hospital Upper Extremity Evaluation (73).

Among them, AHA and MA (Figure 4**)** scores had enough properly reported datasets to be meta-analysed. Both analyses revealed a between-group difference that is statistically not significant and is below the reported smallest detectable change. For MA, the smallest detectable change is 7.2% (121), and the mean difference of 3.13 units corresponds to a change of approximately 5%. The smallest detectable change for AHA is 5 points (105). The Minimal Clinically Important Difference (MCID) is unknown for AHA for MA. Heterogeneity was low. Certainty of evidence was moderate for MA, low for AHA due to the limited patient numbers.

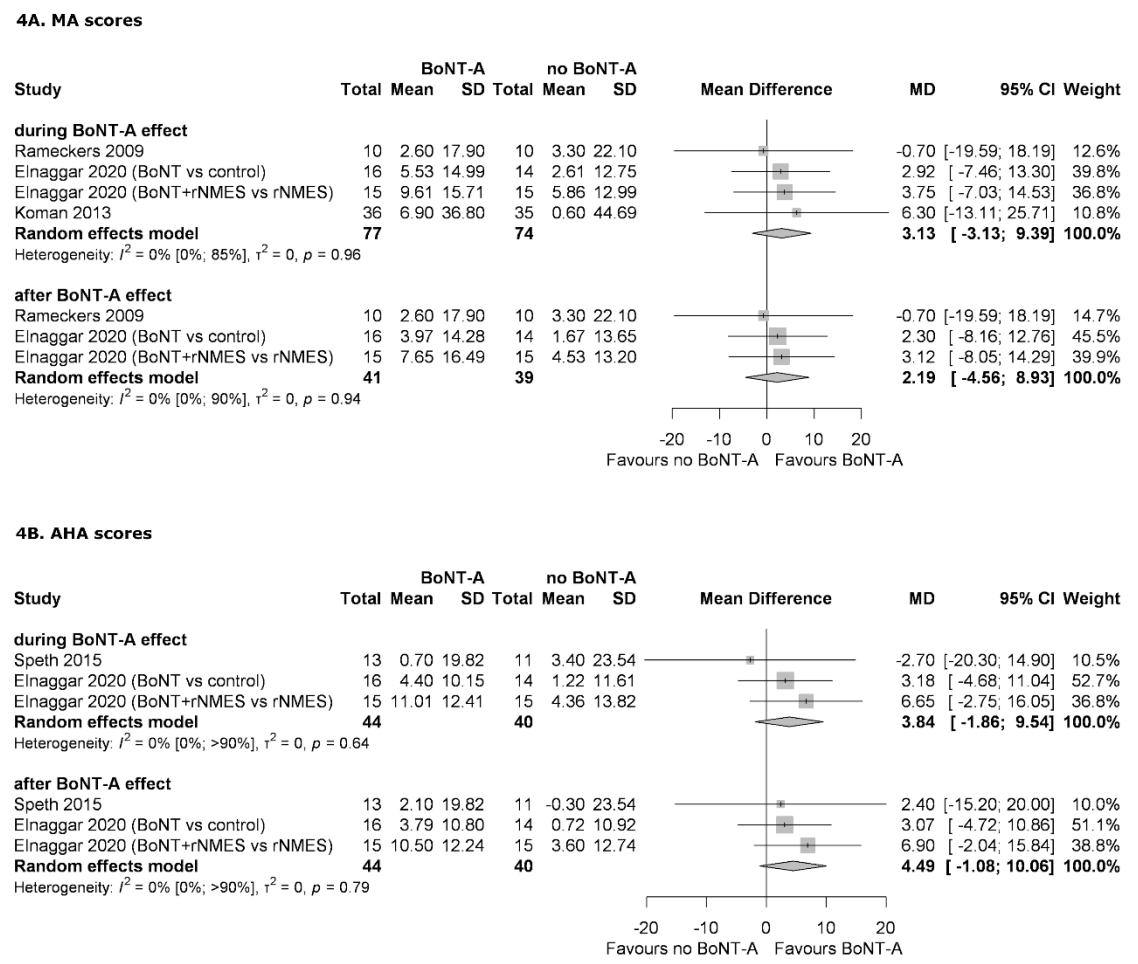


Figure 4. Forest plot representing results of meta-analyses on upper-limb function, comparing the changes observed in the BoNT-A versus no-BoNT-A groups. The pooled results represent mean differences (MDs) with their 95% confidence intervals (CIs). Melbourne Assessment of Unilateral Upper Limb (MA) scores are presented in 4A, Assisting Hand Assessment (AHA) scores in 4B.

8.2.2. Secondary outcomes

Grip strength (59, 60, 69, 73) data were not able to be statistically analysed. A decrease in grip strength was revealed during the pharmacological effect of injections. Fehlings et al (4) reported that weakness resolved completely after the BoNT-A effect. Ferrari et al (5) and Rameckers et al (14), however, report that although it improved, but was not completely resolved at six months, nor at nine months after injection.

Muscle tone and spasticity

The Ashworth scale was used in the six articles reporting muscle tone. (56, 57, 59, 64, 67, 72) The pooled analysis confirms a decrease in muscle tone during the BoNT-A effect, with both the elbow and wrist scores reaching statistical significance. (Figure 5)

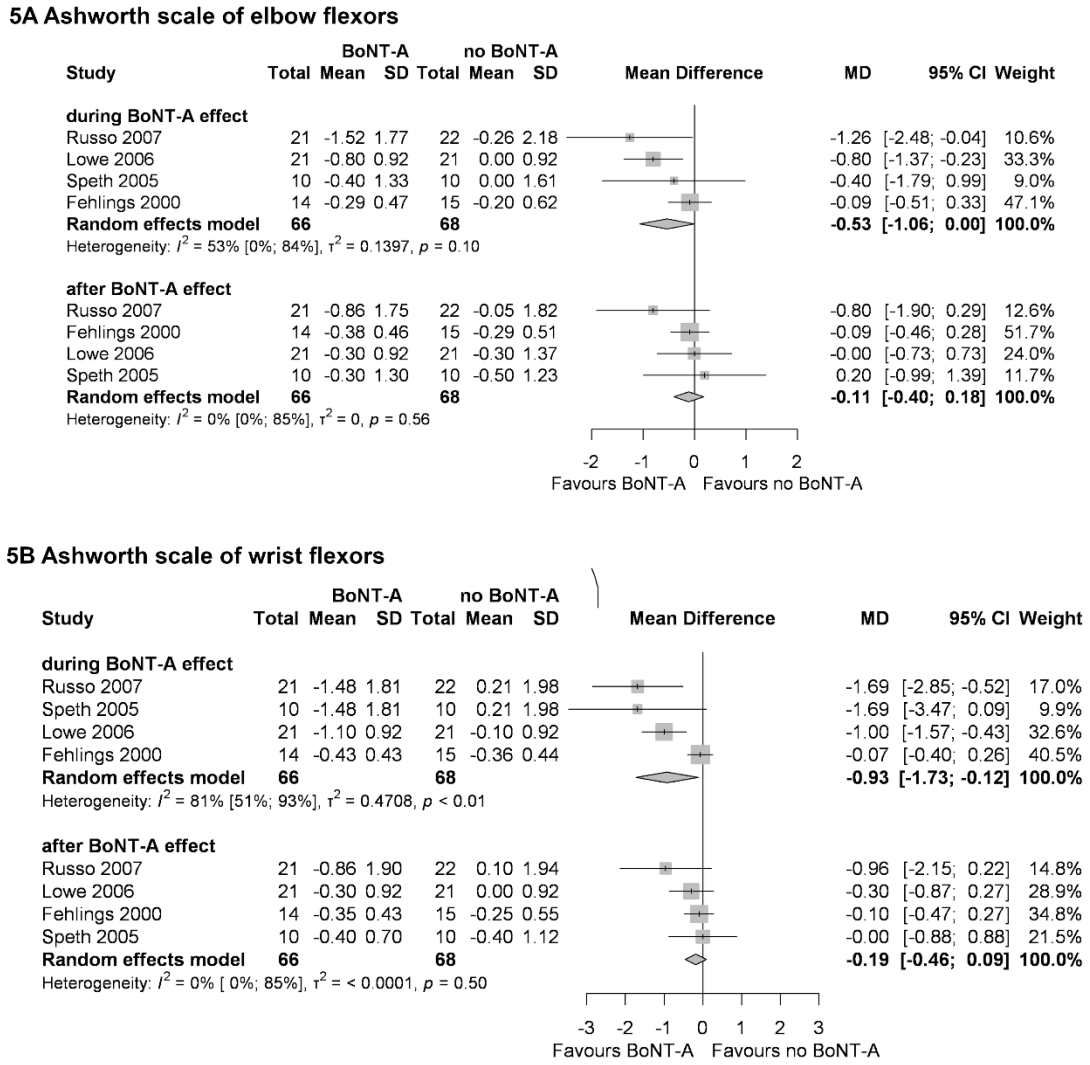


Figure 5. Forest plot representing results of meta-analyses on muscle tone measured by the Ashworth scale (AS), comparing the changes observed in the BoNT-A versus no-BoNT-A groups.

Spasticity was assessed in four articles (57, 66, 70, 75), all using the Tardieu scale. This represents the dynamic component of spasticity, measured as the difference in degrees between the spastic catch and the full range of motion. Pooled results demonstrate a statistically significant decrease in elbow spasticity during the BoNT-A effect (Figure 6).

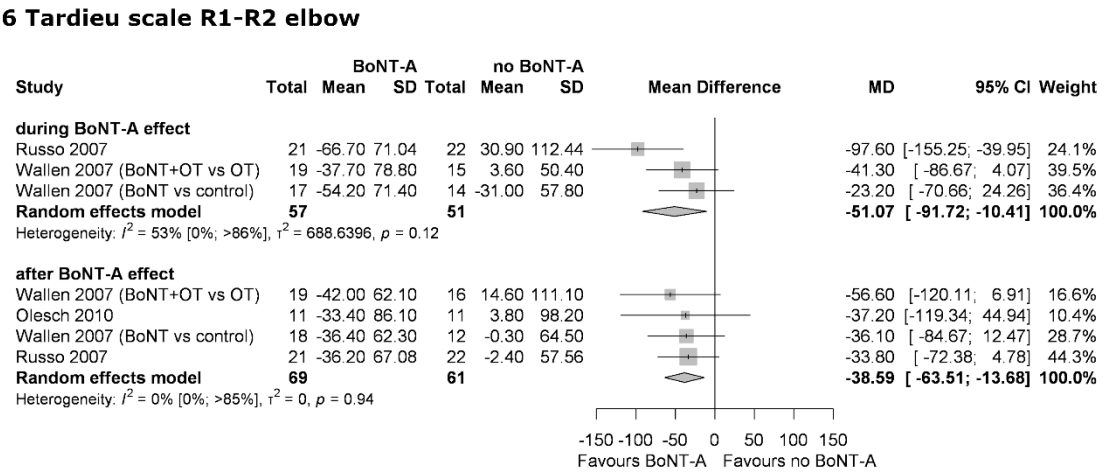


Figure 6. Forest plot representing results of meta-analyses on the dynamic component of spasticity, comparing the changes observed in the BoNT-A versus no-BoNT-A groups. The Tardieu scale was utilized, measured in degrees as the difference between the full range of motion and the spastic catch.

Goal attainment

Goal Attainment Scaling (GAS) was used in five studies. (56, 65, 66, 71, 74) The pooled analysis of GAS T scores revealed significantly higher scores in the BoNT-A groups during BoNT-A (Figure 7).

The Canadian Occupational Performance Measure (COPM) was reported in six studies. (62, 65, 66, 71, 73, 74) The pooled analysis showed some improvement with BoNT-A. Change in COPM performance was statistically significant (Figure 8A, during BoNT-A, while the change in COPM satisfaction scores was not significant (Figure 8B)

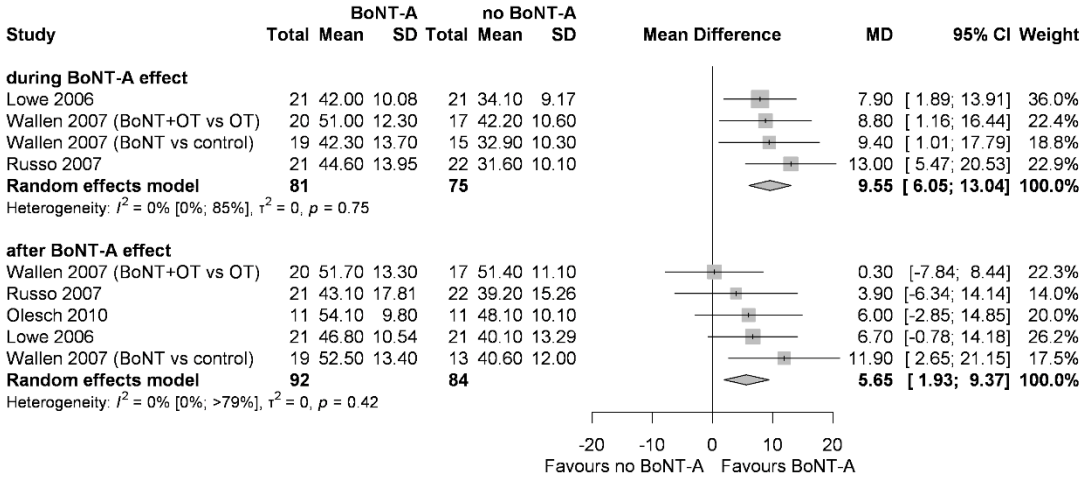
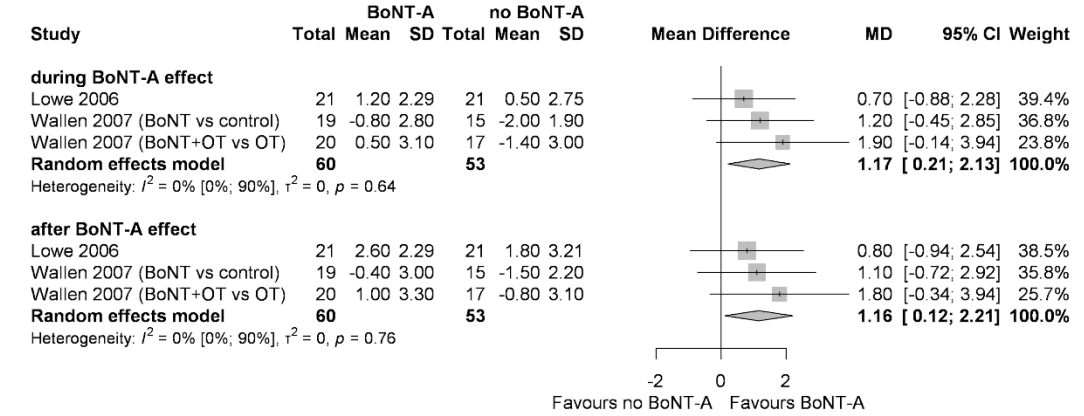


Figure 7. Results of meta-analyses on Goal Attainment Scaling T-scores

8A Canadian Occupational Performance Measure performance



8B Canadian Occupational Performance Measure satisfaction

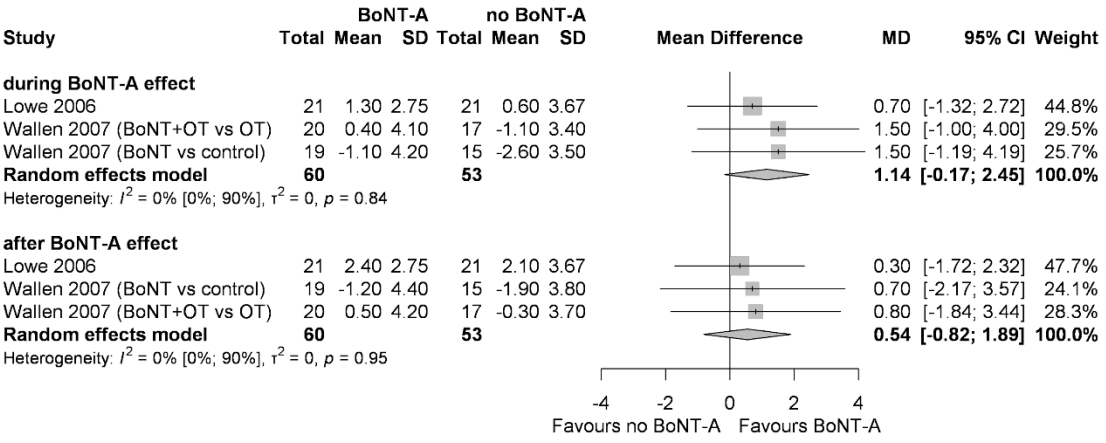


Figure 8. Results of meta-analyses on the Canadian Occupational Performance Measure. 8A represents COPM performance subscores, 8B satisfaction subscores.

Client satisfaction

Parental opinions on treatment results were reported in 4 studies (56, 70, 72, 75) To make them comparable, we dichotomized data into 'improvement' and 'no improvement' and calculated odds ratios (OR). Figure 9 shows significantly better ORs for BoNT-A-treated groups at all three timepoints.

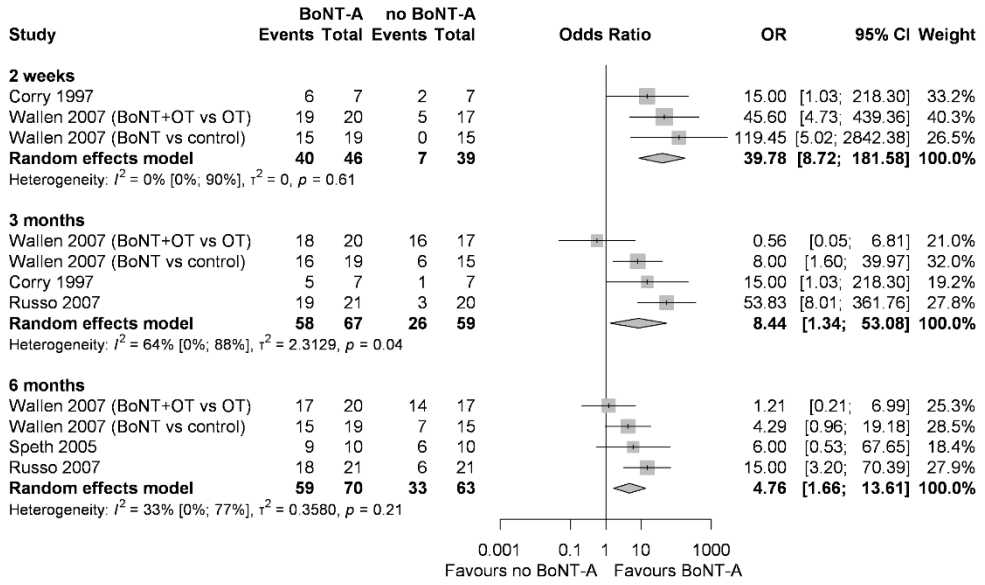


Figure 9. Forest plot representing the results of meta-analyses on client satisfaction 2 weeks, 3 months, and 6 months after BoNT-A injection to the spastic upper limb. Values represent the total number of patients in the BoNT-A versus the no BoNT-A groups, and 'events' represent the ones with improvement among them. The pooled results are odds ratios (OR) and their 95% confidence intervals (CI).

Pain

Russo et al. (70) was the only study reporting data on pain; no difference was noted between the BoNT-A and control groups.

Adverse Events

Almost all of the eligible studies reported on adverse events, (56-62, 64, 66, 69-74) which are detailed in the supplementary material of the BoNT-A article. None of the studies revealed a difference in frequency or seriousness of adverse events between the BoNT-A and the non-BoNT-A groups.

Risk of bias

Patient-reported outcomes were rated 'some concern' due to their subjective nature. The study of Speth et al. (71) was rated as 'high concern' as randomization problems were reported. GAS and COMP scores in Olesch et al were rated as of high concern, because the assessor was not blinded to patient allocation. For all other outcomes, the rating was low risk of bias.

8.3. Effects of FDRO, Results of Analyses

8.3.1. Primary outcome: gait scores

The following gait scores were used in the eligible articles:

- Gait Deviation Index (80, 107, 114)
- Gait Profile Score (94, 102, 117, 118)
- Gillette Gait Index (81, 116)

All individual articles reported a significant improvement in the gait score following FDRO.

Pooled gait scores (Figure 10) (80, 81, 102, 107, 114, 116) In the short-term analysis (220 patients), a significant improvement was revealed after FDRO. The long-term analysis (103 patients) also reveals a tendency for improvement, but the results are not significant. Overall heterogeneity (I2 value of 77%) is high, presumably because of the large individual differences observed in Cerebral Palsy. Prediction intervals (i.e., the expected range of effects of future studies) suggest that future studies will likely have similar results. The retransformed SMD of 0.99 was roughly 10.1 on the GDI scale, -1.6 on the GPS scale, and -394.1 on the GGI scale. The retransformed long-term SMD of 0.68 was roughly 6.9 on the GDI scale, -1 on the GPS scale, and -270.7 on the GGI scale.

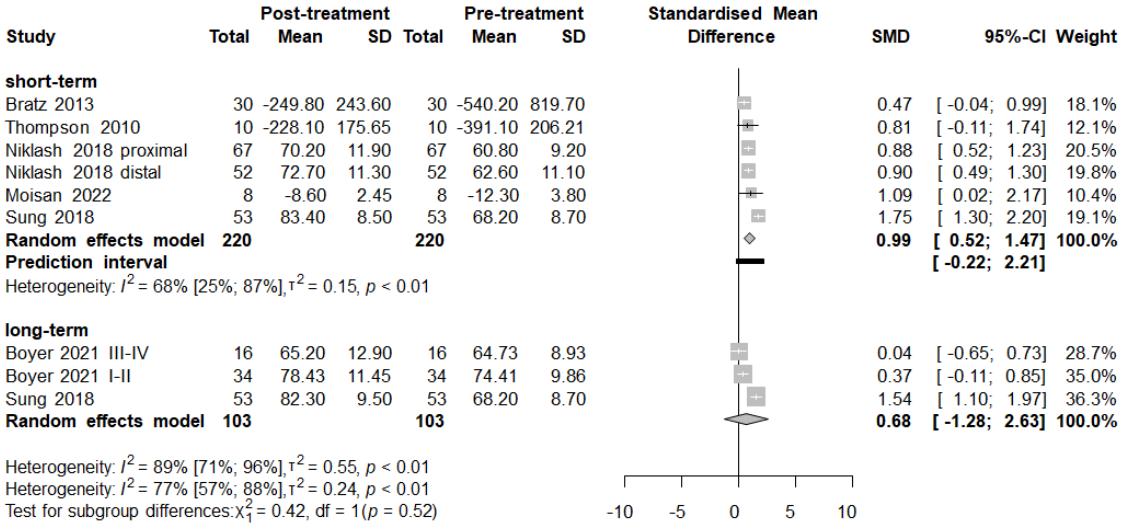


Figure 10: Result of meta-analyses on gait scores, due to different scales utilized (GDI, GPS, and GGI), the method of the standardized mean differences (SMD) was used.

8.3.2. Secondary outcomes

Transverse plane kinematics (rotations)

Pooled pelvic rotation (Figure 11) results are presented in degrees. Data were grouped post-hoc according to preoperative asymmetry. The asymmetrical group (more than 5 degrees of rotation preoperatively, 109 patients) had a significant improvement of 6.64 degrees. Heterogeneity was moderate. The symmetrical group (238 patients) had a minimal mean change of 1 degree. Heterogeneity was high. The test for subgroup difference confirms a statistically significant difference between the two groups.

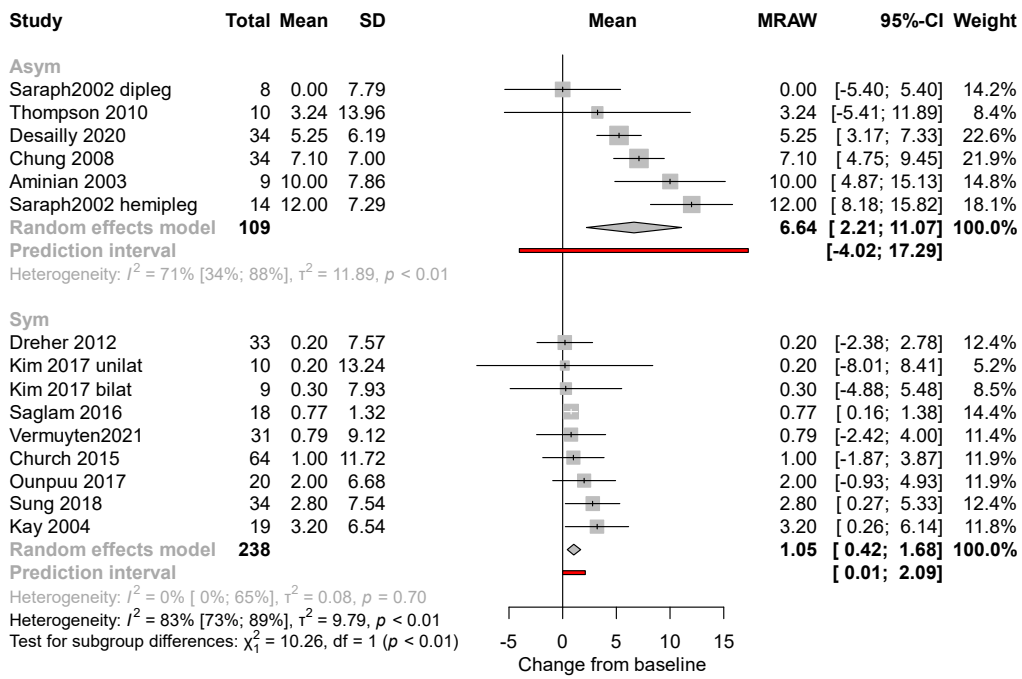


Figure 11: Meta-analysis results on pelvic rotation. Data were grouped post-hoc based on preoperative pelvic asymmetry in gait analysis.

Pooled hip rotation (Figure 12) results are presented in degrees; negative values represent internal rotation. All included studies reported improvements, with a magnitude between -32 and -5 degrees. Short-term analysis (1-2 years after the operation; 1075 patients) revealed a significant improvement in internal hip rotation with a mean change of -14 degrees. Mid-term analysis (3-4 years after the operation; 372 patients) revealed a similar, significant improvement of -16 degrees. Long-term analysis (more than 5 years after the operation, 258 patients) also showed a significant improvement of -12 degrees. Heterogeneity was high in all analyses. Prediction intervals (i.e., the expected range of

effects of future studies) suggest that future studies will likely have similar results.

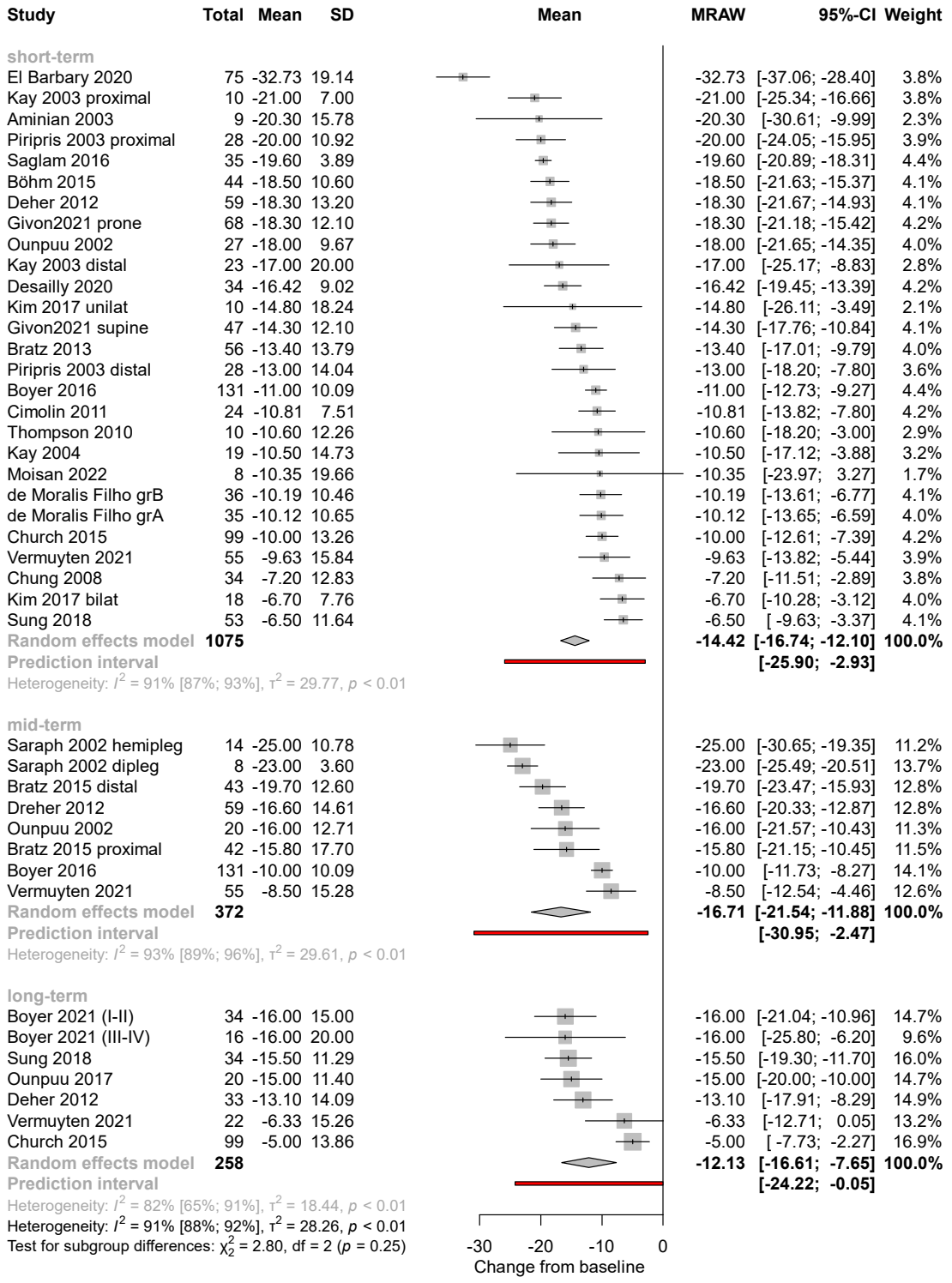


Figure 12: Meta-analysis results on hip rotation.

Pooled foot progression angle (Figure 13) results are presented in degrees; negative values represent internal rotation. All included studies reported improvements, with a

magnitude between -25 and -6.5 degrees. Short-term analysis (1-2 years after the operation; 744 patients) revealed a significant improvement with a mean change of -16 degrees. Mid-term analysis (3-4 years after the operation; 171 patients) revealed a similar, significant improvement of -16 degrees. Long-term analysis (more than 5 years after the operation, 356 patients) also showed a significant improvement of -15 degrees. Heterogeneity was high in all analyses. Prediction intervals (i.e., the expected range of effects of future studies) suggest that future studies will likely have similar results.

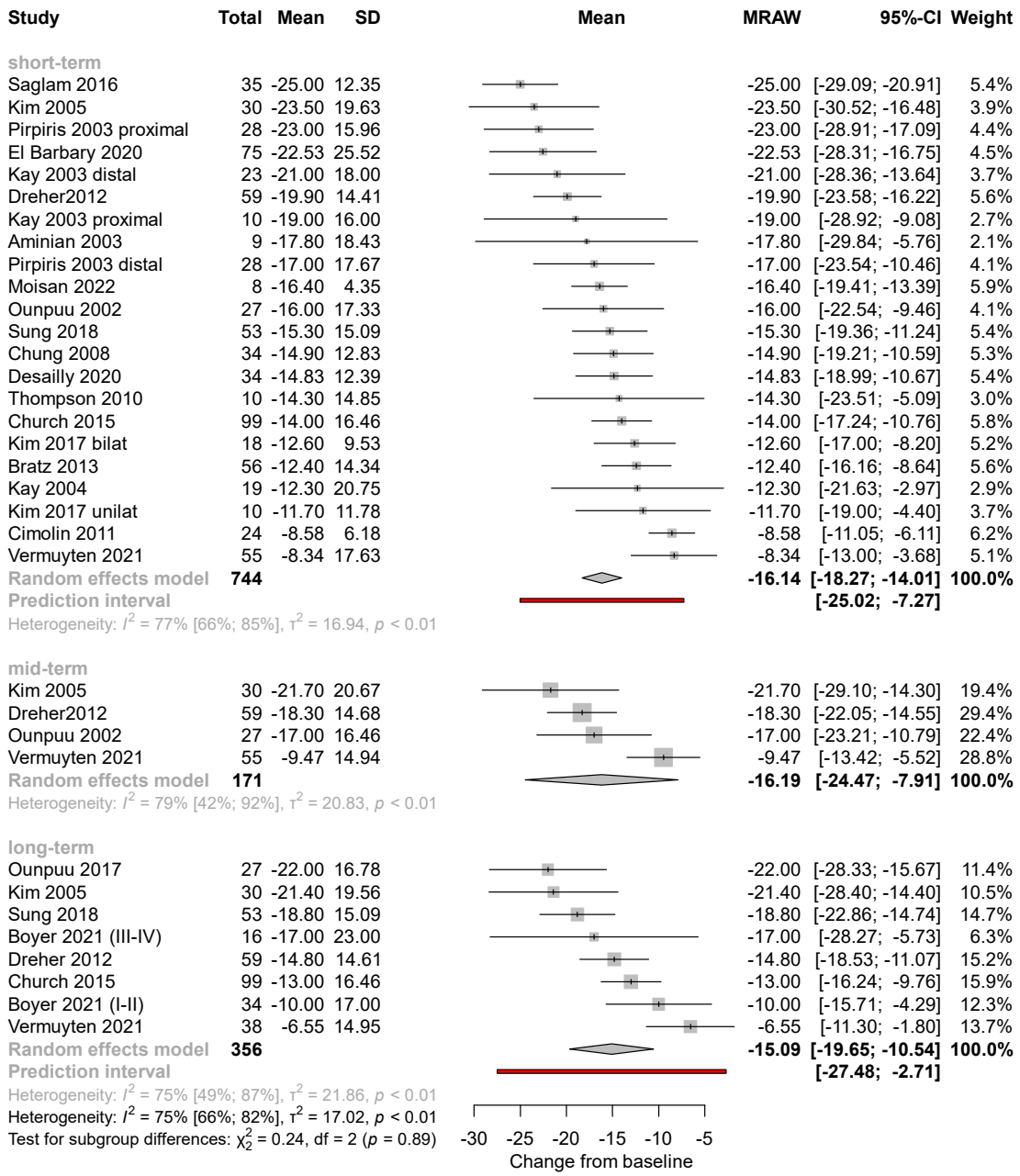


Figure 13: Meta-analysis results on foot progression angle.

Sagittal plane kinematics (flexion-extension)

Pelvic tilt was assessed in seven studies, revealing mixed but small changes (-4 to 3 degrees). Negative values represent posterior tilt. Only short-term results were present. 405 patients were included. MD was -1.39 ° (CI -2.8 to 0.02) in the short term. (Figure 14.) Heterogeneity was moderate.

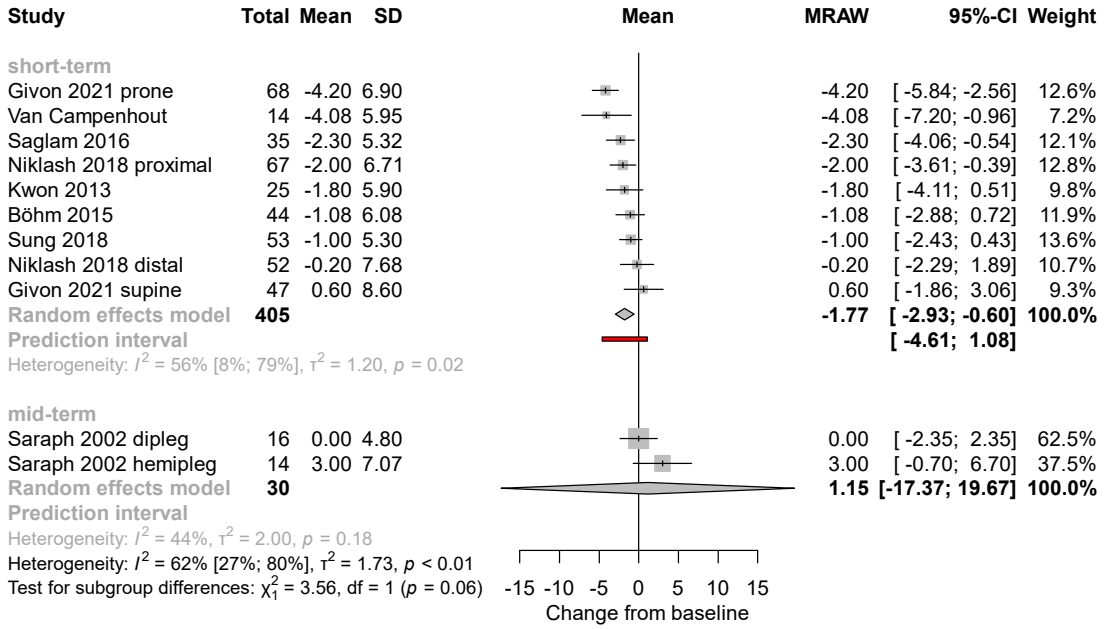


Figure 14: Meta-analysis results on pelvic tilt.

Knee flexion-extension results are presented in degrees; negative values represent a more extended knee. Six studies with 284 patients were meta-analysed, short-term MD was -8.63 (CI -13.01 to -4.24) (Figure 15). Heterogeneity was moderate.

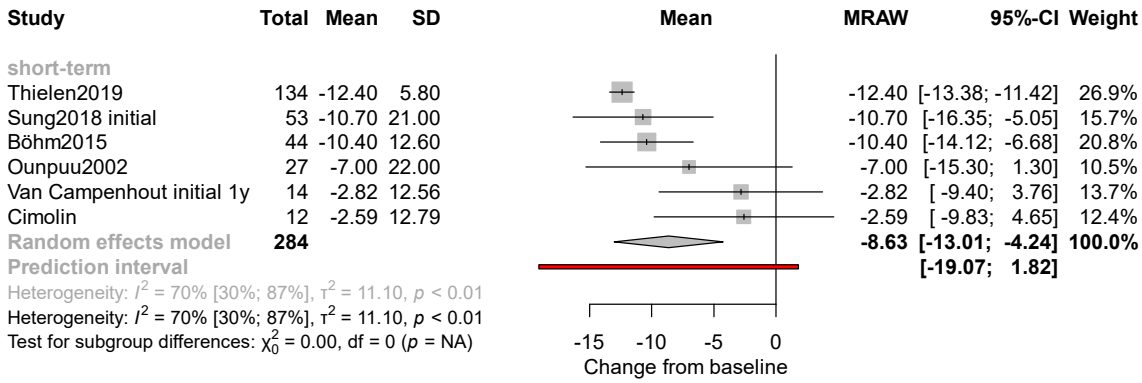


Figure 15: Meta-analysis results on knee flexion-extension.

Frontal plane (ab-adduction)

We were able to analyse the data of the hip ab-adduction from three studies, including 259 patients altogether. Results are presented in degrees; negative values represent adduction. MD was -4.32° (CI -11.36 to 2.72). (Figure 16)

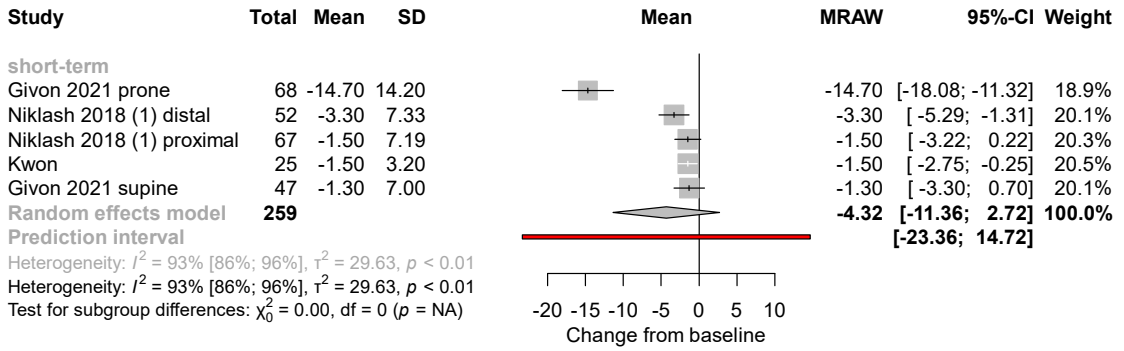


Figure 16: Meta-analysis results on hip abduction-adduction.

Kinetics

The number of kinetic data points was very limited, and pooling was not possible. Boyer et al.(80) reported a minimal reduction in hip abduction moment over ten years after surgery. Niklasch et al.(105) attempted to identify factors associated with recurrence. Patients who later developed a recurrence of internal rotation gait had a significantly smaller hip joint impulse before surgery. Thielen et al.(115) described increased frontal hip moments one year after supracondylar FDRO. Patient numbers were small.

Temporospatial gait parameters

Minimal changes were detected in the pooled results of cadence, step length, stride length, step width, and velocity in the short term. Analyses are presented in the supplementary material of the FDRO study.

Impact of FDRO localization: comparing distal and proximal osteotomy localizations, we found no subgroup differences in hip rotation or foot progress angle. Analyses are presented in the supplementary material of the FDRO study.

FDRO vs no FDRO Controlled studies offer the highest possible evidence for FDRO efficacy, as randomized controlled trials are not feasible. Nine articles of seven independent studies had control groups. All except the one by Kay (96) reported better outcomes when FDRO was performed. However, only three studies (78, 101, 119) had adequate control groups with age-matched CP patients with internal hip rotation gait, but no FDRO was performed. Pooled results of hip rotation had an MD of -10.13 (CI -21.8 to 1.54) in the short term (Figure 17), and pooled results of foot progress had an MD of -7.18 (CI -17.5 to 3.14) in the short term (Figure 18)

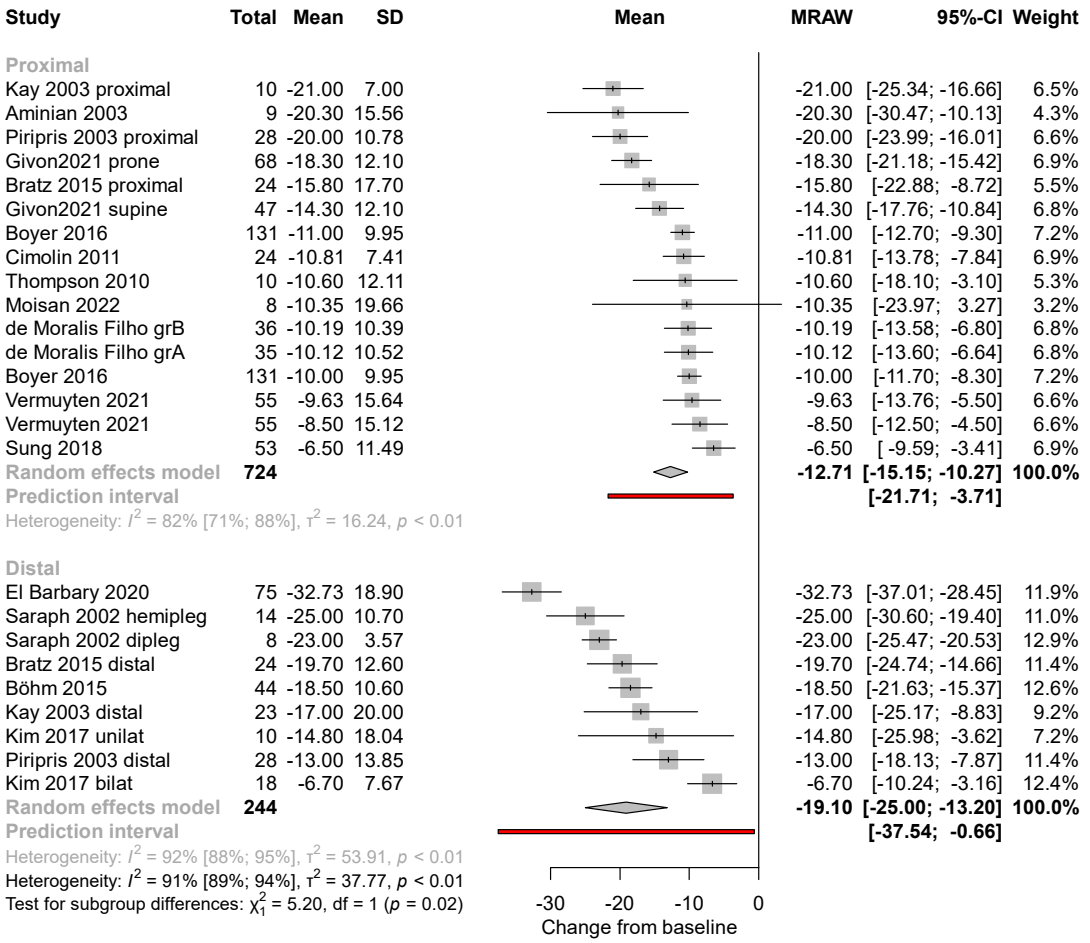


Figure 17. Hip rotation subgroups distal vs. proximal FDRO localization (mean changes in degrees)

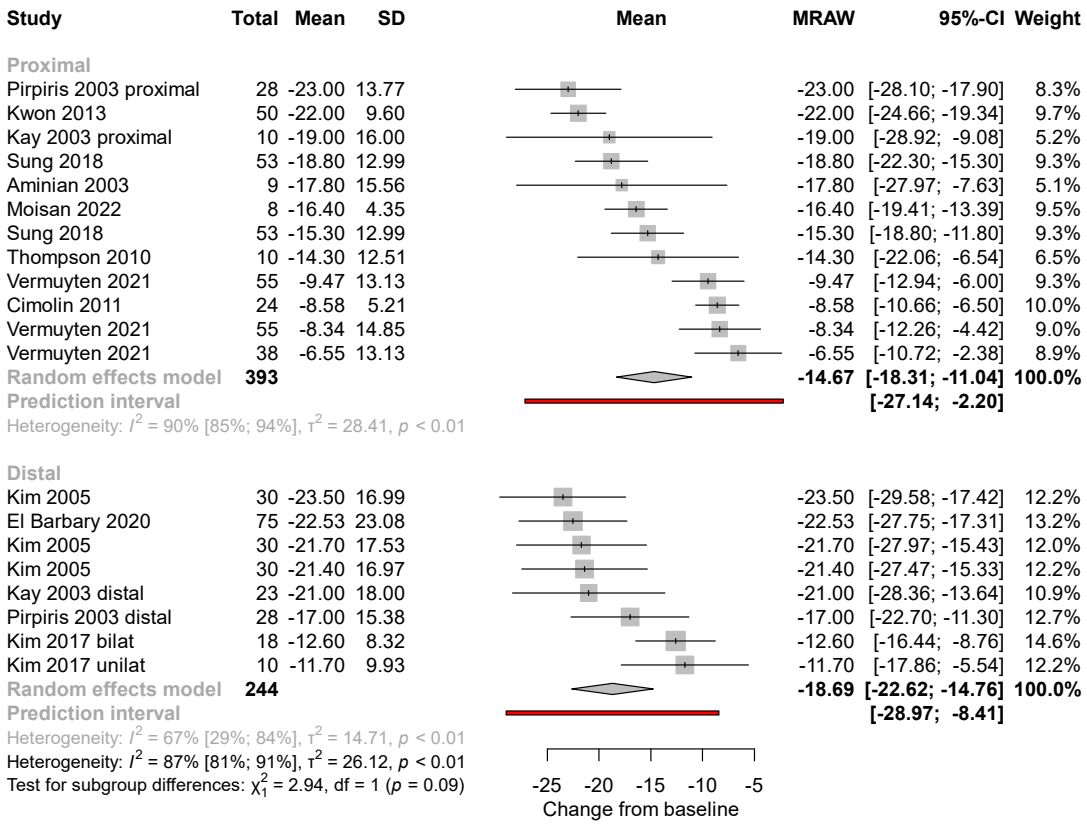


Figure 18. Foot progression angle subgroups: distal vs proximal FDRO localization (mean changes in degrees)

Pain

Only McMulkin et al. (101) assessed pain levels, reporting significantly lower pain levels in the GMFCS I/II group one year after FDRO. The GMFCS III group also showed some improvement one year after FDRO.

Adverse events

Altogether, 11 out of the 46 articles reported adverse events. All were surgical complications, such as the need for revision due to non-union of the osteotomy. No anesthesia-related complications and no major or life-threatening events were reported. More details are presented in the supplementary material of the FDRO study.

Correction rate

The success of FDRO was measured as the proportion of patients with 'corrected' hip rotation. The definition of correction varied slightly between the articles, the ones with lower correction rates applied more rigorous criteria. Results are presented as proportions: total patient numbers and the number of patients reported to be reaching a good correction are presented on the forest plot. Short-term analysis (749 patients) revealed a pooled correction rate of 74%. Long-term analysis (119 patients) shows a rate of 69%. Heterogeneity was high in all analyses**.** (Figure 19) One author (Ounpuu)(109) assessed the correction rate at both time points, reporting 59% at one year and 52% at ten years.

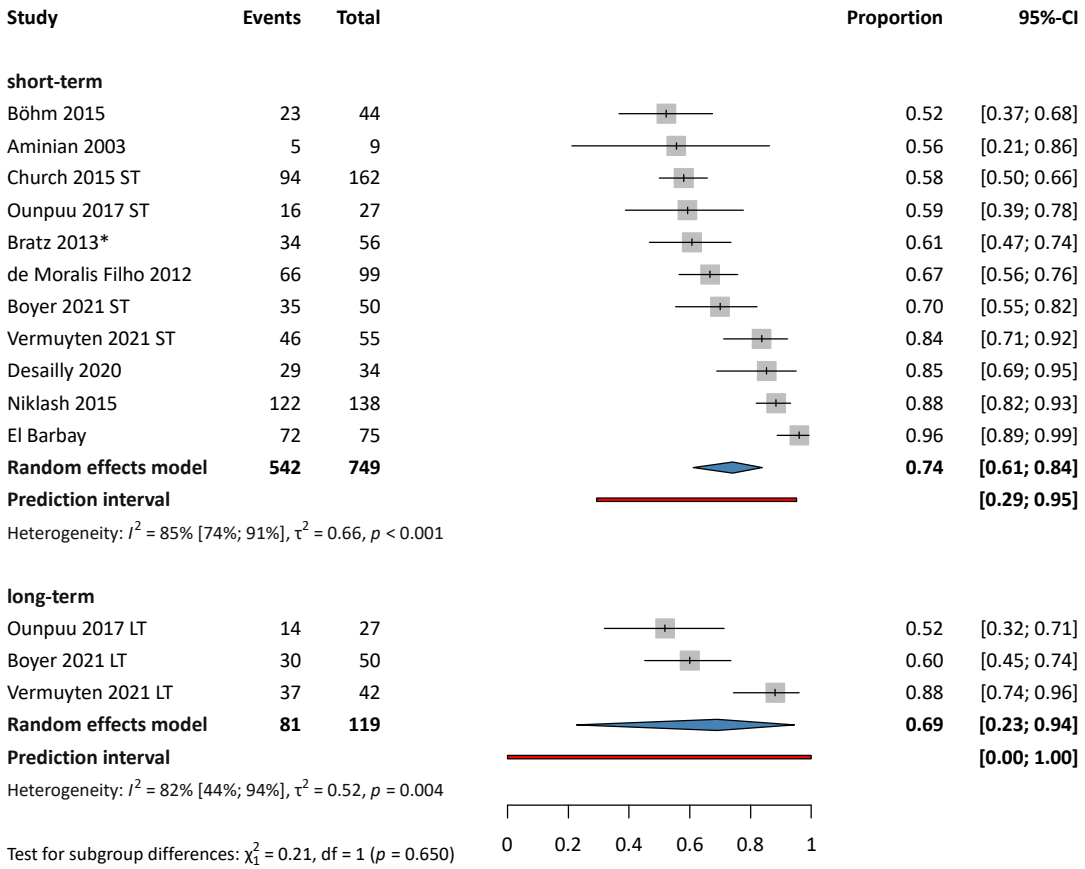


Figure 19: Meta-analysis results on correction rate (proportions)

Recurrence

Reappearance of in-toeing gait after a successful FDRO ranged from 3% to 33%, with an average of 13%. (Figure 20) Results are presented as proportions: total patient numbers

and the number of patients showing a recurrence are presented. The first row shows the mean age of patients at the surgery in each study. Analysis of 531 patients revealed a pooled recurrence rate of 13%. Heterogeneity was moderate.

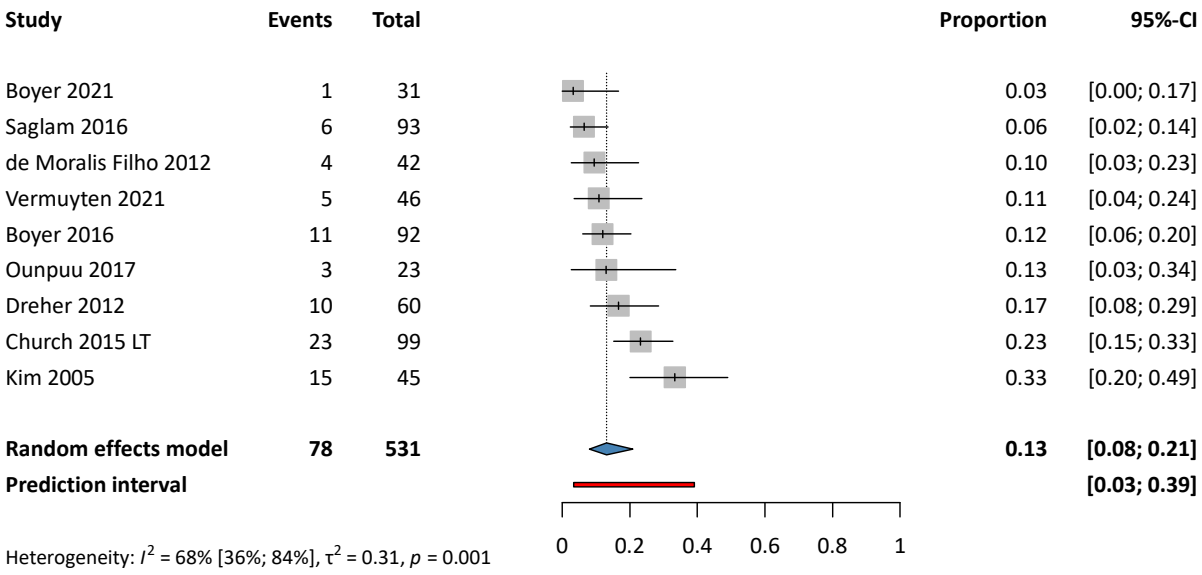


Figure 20: Meta-analysis results on recurrence rate (proportions)

Life quality and client satisfaction: no data were found.

9. DISCUSSION

9.1. Summary of findings and international comparisons

9.1.1. BoNT-A study

Findings of this study can be summarised in three main points. Firstly, all the RCTs found a significant reduction in muscle tone using standard outcome measures. Secondly, no unequivocal evidence was found for improvement in body function, despite the broad variety of outcomes analyzed. Thirdly, client satisfaction was strongly supportive of upper-limb BoNT-A injections.

The most robust difference observed between the BoNT-A and the non-BoNT-A groups was in the caregivers' subjective opinion: BoNT-A-treated groups scored much better. No doubt, this question is highly subjective and potentially biased due to blinding problems in BoNT-A studies. Blinding is challenging, as in most cases, both parents and therapists guess patient allocation correctly during the pharmacological effect of BoNT-A.(56, 121) However, we have reasons to believe that better parents' ratings with BoNT-A are not purely due to the placebo effect. First, the first-ever RCT on upper limb BoNT-A (56) reached the highest possible level of blinding by using placebo injections in the control group. Authors of this study report high parental satisfaction with BoNT-A, noting that every patient in the control group requested BoNT-A after the study period. Second, Chin et al (122) report that 74% of their BoNT-A-treated children had a clinical improvement. This rate is similar to the summarised results of this study, three months after injection. Third, the pattern of difference in time seems to follow the pattern of pharmacological effect of BoNT-A, suggesting that the explanation of positive parental rating might be directly related to BoNT-A.

The second most robust difference observed was in goal achievement. Individualized goals were measured by two scales across the eligible articles: GAS focuses directly on the achievement of pre-defined goals, whereas COPM assesses the change in two aspects (function and satisfaction) of previously identified problems. Pooled GAS scores and pooled COPM scores suggest that BoNT-A brings treated children closer to their goals, similarly to the findings of Sakzewsli et al (19) and Mathevon et al(18). Both reviews concluded that BoNT-A and occupational therapy together improve goal achievement. In

contrast, Speth et al (71) found no improvement on raw GAS scores. Nevertheless, results should be treated cautiously because of the limited knowledge on the nature of goals and the highly subjective nature of this outcome. The second one is particularly problematic in BoNT-A studies, as families most likely are aware of their group allocation at the time of assessment, leading to high chances of bias.

Third significant difference found was the well-known temporary decrease in muscle tone and spasticity. Similarly, to previous reviews (17, 19, 123) a decrease in grip strength was found due to BoNT-A treatment. Very limited available data on fine motor skills revealed no to minimal change.

Upper limb function measured by MA and AHA tests revealed minor changes. Although pooled results were slightly in favour of BoNT-A, mean differences remained below the smallest detectable change and were minimal in amount, suggesting that no functional improvement could be established. This finding is also identical with the findings of Farag et al (123). Individual patient data on upper limb function (59, 62) was available in two articles: changes spread greatly from mild decrease through no change to great improvement. All studies within the pooled results present with wide confidence intervals crossing the line of 0, suggesting similarly diverse personal changes.

Bodily function and health-related life quality revealed conflicting results in accordance with previous reviews. A minimal decrease was observed with BoNT-A on Pediatric Quality of Life Inventory and Assessment of Motor and Process Skills 'motor' score. No change was found in PEDI and life quality of parents, and a modest improvement in PMAL. Pain was reported only in one article in which both the BoNT-A and the control group were receiving occupational therapy, showing remarkable improvement in both groups. No data was found on participation and activity.

Adverse events were scarce and mild to moderate in severity. This supports previous findings that BoNT-A injections are generally safe and reliable.

9.1.2. FDRO study

Overall results support the general belief that FDROs improve gait function in the study population. An improvement in gait quality was revealed, as indicated by significant

short-term improvements in gait scores, hip rotation, and foot progression angle. The benefits appear to persist over time, although the long-term effects are less robust, with wider confidence intervals and greater heterogeneity between studies. Additional studies are needed to examine other kinematic changes, kinetics, and walking energy.

Changes in kinematic results

The most significant change is the direct impact of FDRO on transverse plane kinematics. A consistent improvement in internal hip rotation was observed, with an average of -14 degrees, twice the Minimal Clinically Important Difference (MCID). Consequently, in-toeing improved as the progression angle changed with an average of -16 degrees. Comparable magnitudes suggest that femoral anteversion was indeed a major contributor to in-toeing. The improvements are likely significant enough to lead to a meaningful enhancement in the functional problems as well.(109) Favorable results were maintained over more than five years. The results indicate that patients with functional issues related to internal rotation gait presumably experience benefits from surgery.

Pelvic rotation is problematic in 30-60% of children with CP.(124-126) Articles with symmetric baseline data revealed a pooled minor mean change of 1°, while it was 6.6° for asymmetric ones. FDRO presumably improves pelvic malrotation with 1.5 times the MCID. This finding is consistent with Hara et al,(127) who also found that greater pre-operative asymmetry was linked to more correction of pelvic rotation following FDRO.

Pooled results confirmed a hip varisation of -4 degrees. The authors of this study consider this change to be mainly the direct effect of FDRO, as it also changes the projection of the femur in the frontal plane, even if the osteotomy was purely rotational. (20)

Pelvic tilt results were too heterogeneous to draw a clear conclusion. However, all studies reporting improvements performed FDROs in proximal localization; the others were distal(107, 112), mixed(111), or no data.(93) This supports the assumption that proximal FDOs may amend increased anterior pelvic tilt, but distal FDOs do not.(100, 101, 107) The authors of this study attribute the favorable change of 8.6° toward more extended knees mainly to be the consequence of simultaneously performed hamstring lengthenings. However, contrary opinions exist. Akalan et al.(128) report that peak knee extension is influenced by femoral anteversion, both in typically developing children and children with CP. The lever-arm change can also have some knee-extension effects. As the foot

progress angle normalizes, the center of pressure of application of the ground reaction force moves closer to normal, which lengthens the knee-extensor moment arm.(129)

Changes in kinetic results

Studies describing gait kinetics were scarce, although the primary goal of orthopedic surgeries is to restore lever arms.(129) In anatomic models, changes in anteversion directly influence hip kinetics (20, 130), although no direct change in the proximal bony geometry is performed.(115) Boyer(80) described an unexpected lack of improvement in hip abductor moment in the short term, but the improvement was seen three years after FDRO. Further studies are required to confirm whether the theoretically favorable kinetic changes are actually observed in real life.

Changes in temporospatial parameters

As expected, surgery did not influence temporospatial gait parameters.

Changes in gait function

A consistent improvement was observed across all articles reporting gait scores. Results are heterogeneous, probably because even a cleaned CP population varies significantly. The magnitude of improvement in the short term was approximately 10-point GDI, which is two times as large as the MCID and represents a change equal to 1 SD in the gait of healthy subjects.(35) Some deterioration was observed in the long-term function. This observation supports the belief that gait function in CP tends to deteriorate with growth. (131, 132) The results suggest that more severe categories either show less improvement, have a higher rate of deterioration, or both. Furthermore, that the improvement will be maintained in the long term, in accordance with the observation of Saisongcroh et al.(133) However, the only study with long-term results and a proper control group was by Boyer et al.(80) reported that the FDRO group had a significant advantage only in the short term, but not 10 years after surgery. Lennon et al.(134) also propose that short-term superior gait results of orthopedic surgeries might no longer be present in adulthood.

It is difficult to determine the real-life impact of gait score improvement, as there is limited data on quality of life or client satisfaction. Theoretically, it should be significant. McMulkin et al.(101) examined multilevel surgical patients with and without FDROs.

The FDRO group had slightly better gait outcomes, with an average GDI improvement of 13 points and a 15% reduction of net oxygen cost. However, they were unable to demonstrate that the improved kinematics led to lower metabolic power. Gill et al.(135) However, they concluded that the gait pattern of a child, as indicated by the GDI, affected metabolic power approximately twice as much as the next most significant contributor. According to their calculations, a 13-point improvement in GDI would be equivalent to a 10–22% reduction in metabolic power. Similarly, Gagnat et al.(136) described that increased gait deviation contributed to the increased energy cost of walking in children with GMFCS I and II.

Additional studies are needed to clarify whether and to what extent improved gait function after FDROs is linked to real-life benefits, such as reduced walking energy, less fatigue, or longer walking distance.

Correction, recurrence

The self-reported rate of successful FDROs was between 52% and 96%. The difference lies mainly in how success is defined. Articles with lower success rates applied more rigorous criteria; hip rotation had to fall in the normal range of typically developing children. Results confirm that perfect correction was achieved in over half of the cases. The exact rate of under-correction was stated only in 2 articles, which were 4%(92) and 11%(104).

The overall recurrence rate of 13% can be considered low, but it also had significant heterogeneity (3% to 33%). The identification of underlying causes is beyond this work. Reported risk factors for recurrence include pre-operatively reduced hip joint impulse, increased ankle plantar flexion, internal foot progression(105) and younger age at surgery (<10 years).(33),(97)

Previous systematic reviews of FDRO

In 2014, a meta-analysis was performed on the topic(33); however, it has several limitations to note. It did not exclude patients with hip problems; not all patients involved had FDRO, only hip and pelvic rotation kinematics were described, and the follow-up time was also limited, with a maximum of 3.1 years.

In 2024, a new meta-analysis was published (23) reporting only long-term (5+ years) results of hip rotation kinematics, foot progression, and hip rotation passive range of motion. Statistical results show only SMDs, so the magnitudes of changes are unknown.

9.2. Strengths

To the best of our knowledge, both studies are the most recent and most comprehensive meta-analyses in their field. The pre-registered protocol was followed, and a rigorous methodology was applied.

Although more reviews (17-19, 123) have already assessed the effects of upper limb BoNT-A, our work had a novel approach as we wanted to study solely the added effect of BoNT-A and did not attempt to distinguish between accompanying therapies.

Similarly, more reviews (23, 33) have been made on FDRO in children and adolescents with Cerebral Palsy, our study could achieve the most cleaned population and the highest patient numbers among them.

9.3. Limitations

In the BoNT-A study, different upper limb or hand function measurements were used in the eligible articles. Reporting or providing data was insufficient in a not negligible number, that made the statistical synthesis and interpretation of the results difficult or even beyond possibility. Available data did not allow us to separate unilateral or bilateral involvement. That is problematic, as the use of the upper extremity is substantially different in the two groups. Unilaterally involved children usually have a perfect and a seriously impaired upper extremity, contrary to bilateral involvement, where both upper extremities have somewhat impairment.

The main limitations of the FDRO study are the quality of available data. Among the eligible studies, only three studies had adequate control groups, all with limited numbers of patients and short follow-up times. Of the 46 articles included, only six were of high quality. A large proportion of our data came from retrospective cohort analyses - these studies do not represent all operated patients – as would be desirable - only the ones who had gait analyses before and after FDRO; hence, they are subject to numerous biases, systematic errors, and missing results. Similarly, the concomitant procedures performed

with FDRO are heterogeneous but also represent the individual needs of involved patients.

10. CONCLUSIONS

10.1. BoNT-A study

The significant decrease in spasticity and muscle tone caused by the upper-limb botulinum toxin injections was not associated with functional improvement; however, better goal attainment and caregiver satisfaction were noted.

10.2. FDRO study

FDRO surgeries demonstrate statistically and clinically meaningful improvements in gait quality, hip rotation, and foot progression angle. Long-term results are less robust, presumably because of the natural course of CP-related gait deterioration

11. IMPLEMENTATION FOR PRACTICE

The following should be considered before upper-limb BoNT-A treatment in children and adolescents with spastic CP: injections reduce muscle tone and decrease spasticity, but simultaneously reduce grip strength. No functional benefit should be anticipated, but client feedback is generally positive, and it might increase goal achievement.

And the following should be considered at indicating femoral rotational osteotomy in ambulatory children and adolescents presenting with in-toeing gait: FDROs should presumably be avoided in patients without significant internal hip rotation in gait analysis and increased femoral anteversion, as described by Schwartz et al. (113) Therefore, gait analysis and measurement of anteversion should always be performed before considering surgery.

Patients experiencing significant functional or aesthetic problems due to internal rotation gait may benefit from FDRO.

For younger patients, presumably, a conservative treatment approach should be favoured over surgery. This allows for observation of the problem's progression (or improvement) and might help avoid a higher relapse rate associated with younger age.

12. IMPLEMENTATION FOR RESEARCH

Regarding BoNT-A, further studies are needed to evaluate the long-term effects of repeated injections and to clarify the influence of BoNT-A treatment on all disability domains (body function, activities, and participation). More homogeneous outcomes should be used. We recommend focusing more research activity on spasticity itself to better understand the cause of highly positive parental feedback after BoNT-A.

Regarding FDRO, future studies are needed to clarify kinetics and walking energy changes. It is advisable to follow reporting guidelines to achieve higher quality; longer follow-up times and prospective designs are recommended. Proper maintenance and analysis of CP registers would also be beneficial to clarify whether improvements from childhood orthopedic surgeries last through adolescence or adulthood. Collecting subjective outcomes is also recommended.

13. IMPLEMENTATION FOR POLICYMAKERS

BoNT-A study: Strong scientific evidence supports the safety and efficacy of BoNT-A treatment in managing spasticity in children. Regulations, however, are usually very restrictive; only off-label usage is possible in this population and indication in several countries. We recommend updating protocols and local regulations to synchronize them with ongoing clinical practice and to make BoNT-A treatment more accessible for spastic children.

FDRO study: efforts should be made to make gait analysis more accessible and highlight the importance of gait analysis in surgical protocols.

We urge policymakers to facilitate clinical research and data collections regarding cerebral palsy, as despite the frequency of this condition, so little is still known about the optimal management.

14. FUTURE PERSPECTIVES

The findings of this work highlight the significant gaps in our understanding of commonly used interventions for cerebral palsy, despite it being the most prevalent neuromuscular disorder. Long-term follow-up of individuals with CP is likely essential to address these knowledge deficits. Moreover, greater emphasis on systematically collecting patient-reported outcomes is needed, as they offer critical insights into the lives of individuals and families with CP. Patients' perspectives should play a more prominent role in guiding future research and clinical practice.

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16. BIBLIOGRAPHY

16.1. Publications related to the thesis.

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American Journal of Physical Medicine & Rehabilitation Q1, IF: 2,4

Gresits O, Vezér M, Engh M A, Szabó B, Molnár Zs, Hegyi P, Terebessy T (2026). Impact of Femoral Derotation Osteotomy on Gait in Ambulatory Children with Cerebral Palsy: A Systematic Review and Meta-analysis
Brazilian Journal of Physical Therapy D1, IF: 3.2

16.2. Publications not related to this 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: 2,2

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: 2,9

Kiss S, Terebessy T, Horváth N, Domos Gy, **Gresits O**, Szőke Gy (2014). Treatment of clubfoot with Ponseti
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Hungarian Trauma/Magyar Traumatológia Ortopédia Kézsebészet Plasztikai Sebészet

Szabó M, Ökrös K, **Gresits O**, Szeverényi Cs (2024)

Internet use by parents of children with clubfoot and analysis of clubfoot-related content on the Internet

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