Title: Physical Therapy in Down Syndrome: Systematic review and Meta-analysis

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Word count: 6343

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ABSTRACT

Aim: Down syndrome is the most common chromosomal abnormality, with a worldwide incidence around 0.1% in newborns. This syndrome requires a multidisciplinary approach, where Physical Therapy plays an important role. The aim of this study is to evaluate the effectiveness of Physical Therapy in Down syndrome. To know and compare the effectiveness of different Physical Therapy interventions in this population.

Method: A systematic review and meta-analysis of randomized controlled trials was conducted. The literature search was performed during April 2017 in the databases: Pubmed, WoS, PEDro, and Scopus. The studies were selected using predefined inclusion and exclusion criteria. The quality of the methods used in the studies was evaluated by the PEDro scale. Subsequently, the data were extracted and statistical analysis was performed when it was possible.

Results: A total of 25 articles were included, of which 15 contributed information to the meta-analysis. Statistical analysis showed favorable results for the strength (Standardized mean difference (SMD)=1,86; CI95%:(0,98;2,74) and SMD=2,74; CI95%:(1,44;4,03)), balance (SMD=4,80; CI95%:(2,72;6,89) and SMD=-3,30; CI95%:(-5,17;-1,44)), and body mass index (SMD=-0,45; CI95%:(-0,81;-0,10)).

Interpretation: The results show the potential benefit of certain types of Physical Therapy interventions in people with Down syndrome. There are still many aspects to clarify and new lines to research.

Running head: Physical Therapy in Down Syndrome: Meta-analysis.

Keywords: Down Syndrome, Physical Therapy Specialty, Physical Therapy Modalities, Systematic review, Meta-analysis.

ABBREVIATIONS

BMI: Body Mass Index.
CG: Control Group.
CI: Confidence Interval.
CoG: Center of Gravity.
DS: Down syndrome.
H: Hours.
HR: Heart Rate.
ICF: International Classification of Functioning, Disability and Health.
IG: Intervention Group.
IQ: Intellectual Quotient.
Max: Maximum.
Min: Minutes.
ND: Not Described
PEDro: Physiotherapy Evidence Database.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
PT: Physical Therapy.
RCT: Randomized Controlled Trial.
RER: Respiratory Exchange Ratio.
RM: Repetition Maximum.
SMD: Standardized Mean Difference.
VM: Minute ventilation.
VO2: Oxygen consumption.
W: Weeks.
WoS: Web of Science.

WHAT THIS PAPER ADDS

- Physical Therapy interventions in Down Syndrome are different and varied.
- Improvements are evidenced in strength, balance, and body mass index.
- Inconclusive data for cardiovascular function and bone mineral content.

INTRODUCTION

Down syndrome (DS) is the most common chromosomal abnormality[1–4]. The estimated global incidence of this chromosomopathy is around 0.1% in newborns[5]. It is characterized by a variable degree of intellectual disability, some effects on health and development, as well as peculiar physical features[2,6]. A wide range of comorbidities can be present in these people, affecting the respiratory, cardiovascular, sensory, gastrointestinal, hematological, immunological, endocrine, musculoskeletal, renal and genitourinary systems, as well as at the neurological level[7].

The lives of people with DS have changed considerably in the last 50 years[8]. Despite the many comorbidities that may coexist in individuals with DS, the survival rate has increased dramatically from less than 50% in the mid-1990s to 95% in the early 2000s[7]. These data are accompanied by an increase in longevity of this population[7–11], which has a life expectancy of approximately 60 years nowadays[7,11].

The improvement in the survival rate can be attributed to factors such as the advancement of medicine in general. Advances in detection and prenatal diagnosis that have enabled early intervention and adequate health care in an early way[7–9], as well as changes in attitude in society toward the normalization of the lives of people with DS[7]. These improvements have made it possible to achieve a better state of health, a higher degree of autonomy and integration in the community of this population in the last two decades[12].

It should not be forgotten that a comprehensive approach and treatment are required in this group. Therefore, in the care of these people, we must consider medical-health aspects, such as psycho-pedagogical and socio-cultural dimensions[13]. Within the multidisciplinary team is the figure of the physiotherapist, who begins to intervene from the first days of life[13,14]. Physical Therapy (PT) starts from the movement as the basis of the whole development process, without separating it from the sensory and psychic aspects[13].

The limited reviews studying the efficacy of PT[15–20] in this population focus on a specific type of intervention. Likewise, there are no known clinical practice guidelines that support the physiotherapeutic intervention in this collective. All this requires a reflection on the need for further research in this area of action, the idea from which this article is born. The general objective of the present paper is to evaluate the effectiveness of PT in DS. As secondary objectives, we aim to know and compare the effectiveness of different PT interventions in people with DS, obtain a global view of the current situation of PT in this syndrome, and facilitate the creation of new lines of research on this subject.

METHODS

The present review was conducted and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines on systematic reviews of randomized controlled trials (RCTs)[21].

Search strategy

The search of the literature for the present review was made during April 2017 using the databases and the searches detailed in Table I. Filters were not applied in relation to publication dates, nor language. A total of 566 potential articles were found.

<< INSERT TABLE I HERE>>

Eligibility criteria

Studies included in this review met the following inclusion criteria: (I) the participants were children and adults diagnosed with DS; (II) a physical intervention was performed according to the World Confederation for Physical Therapy statement[22], such as therapeutic exercise, manual therapy techniques, patient-related instructions and orthotic devices; (III) an intervention was compared to a control group; (IV) the study design was a randomized controlled trial (RCT); and (V) the outcomes were within the measured dimensions of the International Classification of Functioning, Disability and Health (ICF)[23]. Specifically, our target were the outcomes related to *body functions* (such as, vestibular, cardiovascular and respiratory, weight maintenance and movement-related functions), and *activities and participation* (such as, motor skills, carrying out tasks, mobility and walking indices). On the other hand, the studies were excluded from this review if: (I) a sample including people with DS was selected, but the outcome data were not shown separately for participants with DS; (II) an intervention that was not considered within the competencies of PT was performed; (III) more than one intervention were compared at the same time. Two reviewers independently assessed the titles and abstracts according to the criteria established above, and full-text versions of eligible papers were retrieved.

Assessment of the risk of bias

For the evaluation of the quality of the methods used in the studies included in this review, the PEDro scale was used. This scale has a total of 11 items, which include: (1) notification of selection criteria, (2) allocation of subjects to groups at random, (3) concealment of allocation, (4) similarity among groups at baseline in relation to the most important prognostic indicators, (5) blinding of participants, (6) blinding of researchers/therapists, (7) blinding of researchers measuring at least one key outcome, (8) proportion of initial participants that contribute measures to the key results, (9) compliance of the intervention assigned by the participants, (10) presentation of statistical comparisons between the groups, (11) presentation of specific measures and variability of the key results . When the criterion of each category is met, a point is awarded, except for criterion number 1, which is not used for the calculation of the total score of the scale. Therefore, the possible score on the scale ranges from 0 to 10, with a higher score indicating a higher quality in the methods used in the study.

Data extraction

Two researchers independently reviewed and extracted the data of each document in a systematic way and arriving at a consensus on all the items. The following information was extracted from the studies: author; year of publication; characteristics of the participants (number of participants in both groups, average age, gender, severity of intellectual disability, average weight, average height and presence of comorbidity); in addition to the characteristics of the intervention carried out (type, frequency, duration of the session, measures of results, measurement instrument and results).

Statistical analysis

The statistical analysis was carried out with the statistical software EPIDAT 3.1 (General Directorate of Public Health of Galicia, Galicia, Spain). Heterogeneity was determined by the Dersimonian and Laird test with the Cochran Q statistic. When homogeneity was observed, a fixed-effect model was used. Instead, in case of heterogeneity, a random effects model was used. This model includes the variability due to the differences between the studies. The results of all the subgroups included in this meta-analysis were represented in Forest plots. The Forest plots show the differences observed between the mean values of the effect size between the intervention group and the control group, as well as the overall measure, including all the corresponding confidence intervals. In turn, the publication bias was analyzed through the Begg (Z statistic) and Egger (t statistic) tests. The effect sizes compared were: bench press; leg press; total balance score, anteroposterior and mediolateral displacement of the center of gravity (CoG); bone mineral content at the lumbar level; maximum oxygen consumption (VO_2); maximum heart rate (HR); and body mass index (BMI). A meta-analysis was applied comparing changes in the effect size (post and pre-intervention) between the intervention group and the control group. As these were continuous variables, the standardized mean differences and 95% confidence intervals were used. The significance level was set to $p<0.05$.

RESULTS

As stated in Figure 1, the search was carried out through the combination of keywords in the databases, retrieving a total of 566 documents. Subsequently, duplicated articles were excluded. After this first selection, the titles and summaries of the articles found were reviewed, and a second exclusion was made of those studies that did not meet the proposed selection criteria. The articles obtained after this last selection were evaluated more accurately. After excluding those that did not meet the specified criteria, the studies that are part of this review were finally obtained. In this way, a total of twenty-five studies were reviewed, which used a wide variety of interventions in the search for actions that improve the quality of life of this population. Due to the plurality of the parameters measured and the diversity of instruments and scales used in the assessment, out of the total of twenty-five studies, only fifteen could be included in the meta-analysis for statistical comparison.

<<INSERT FIGURE 1 HERE>>

Risk of bias

Table II shows the scores of the PEDro scale for each article included in the review. It was considered that eleven of the studies have a high methodological quality, with results on this scale equal to or higher than 6[24]. Four studies used a method of concealment of group assignment. Given that the studies analyze physical interventions versus control groups, neither the participants nor the therapists could be blinded in any of the studies. The lowest score reached was 3, obtained by two articles. The maximum score was 8, and it was obtained by a total of four articles.

<<INSERT TABLE II HERE>>

Data extraction

As shown in Table III, a total of 786 subject participated in the studies included in this review. The study that used the smallest sample size was Millar et al.[25], with 14 participants. On the other hand, the study with the largest sample size was Lin and Wuang[26], with a total of 92 participants . Regarding the age of the participants, most of the studies[27–29] analyzed subjects of average age less than 18 years. However, the rest of the studies[25,30–36] carried out their interventions with participants whose average age exceeded 18 years. Only two studies[34,33] conducted their research with participants over thirty years of age, standing up the study of Carmeli et al.[34] for being the study with older participants. According to the studies detailing the gender of the participants, 55.5% were men and 44.5% were women.

<<INSERT TABLE III HERE>>

In Table IV the studies were classified in four groups according to the similarity between the interventions. In this way, the most used was therapeutic exercise[25,26,29–35,37–45]. On the other note, other interventions were based on full-body vibration[46,47], early intervention techniques such as infant massage[36] or treadmill training[28,48], as well as orthotic devices such as the supramalleolar orthosis[48,49].

<<INSERT TABLE IV HERE>>

Next, Table V shows the main characteristics of the interventions carried out in the different studies of this review. The duration of the interventions ranged from one day[30] to twelve months[44]. Other interventions did not have a defined duration. That is the case of three studies[28,48,49] in which the intervention ended when the subject acquired the ability to walk. The frequency of the intervention ranged from only one day[30] to every day[29]. Different methods were used to measure outcomes: scales[26–29,36,37,40,41,43,48], dynamometer[26,30,33,34,40,44,47], balance platform[42,45–47], anthropometric measurements[28,39], physical and functional tests[25,31–35,38,39,43,44], bone densitometry[41,44] , video recording[49], activity monitors[31,39] , electrocardiogram[25,33,35,43], heart rate monitor[35], and gas consumption control[25,33,35,43]. In the assessment of motor skills, 1-Repetition Maximum (1RM) test[31–33,38] and Bruininks-Oseretsky test of motor proficiency[26,29,37] were the most used.

<<INSERT TABLE V HERE>>

Study subgroups included in the meta-analysis

For the statistical comparison, the outcome measure, the type of intervention carried out, as well as the measurement instrument were taken into account. In order to be able to compare the studies, it was necessary that they measured the same concept with the same instrument, in addition to having made an intervention with similar characteristics. Table VI shows the subgroups formed for the meta-analysis, revealing the particularities for which they were grouped.

<<INSERT TABLE VI HERE>>

Table VII shows the characteristics of the subgroups included in the meta-analysis. Different subgroups has been established according to the measurement of the effect. The results show that five of the subgroups (1, 1B, 2, 3, 6) presented favorable results in a significant way. In contrast, the results were inconclusive for four of the subgroups (3B, 4, 5, 5B).

<<INSERT TABLE VII HERE>>

Next, Table VIII presents the results related to the meta-analyses of the subgroups.

<<INSERT TABLE VIII HERE>

Muscle strength

People with DS usually have low strength levels[50]. For that reason, the strength has been object of study in various studies. In the meta-analysis performed in this work, muscle strength was assessed in the different studies through tests for maximum strength generation, such as 1RM. The generation of maximum muscular strength was tested by establishing the amount of weight that each participant could lift in a bench press and a sitting leg press[32]. The meta-analysis for bench and leg press was performed independently in two subgroups.

Bench press muscle strength in upper limb valued by 1RM, was measured by four studies[31–33,38] in this review. Both the individual results and the overall result obtained show that the interventions performed had a positive effect on the maximum strength bench press 1RM test. In the lower limb, muscle strength was also assessed using the 1RM leg press test in the same studies, obtaining a positive overall result of the interventions on improvement in this muscle test.

The study by Rimmer et al.[33] stands out for its greater effect in both subgroups. This study is characterized by the older participants (average 39.4 years), a higher frequency of sessions per week (three times instead of two as the other studies), and two more weeks of intervention compared to the other studies included in this subgroup. The study by Shields et al.[33] had a positive effect on the upper limbs strength, but on the other hand, no significant improvements were obtained on the lower limbs.

In another study by Shields et al.[31], two post-intervention measurements were taken, one at week eleven, and the other at week twenty-four. In the meta-analysis, the effect of the intervention on muscle strength at week twenty-four, although diminished, is maintained for both the upper and lower extremities, being higher in the lower limbs.

Previously, the main findings have been exposed based on the meta-analysis performed in this work, but other aspects of these previously mentioned studies that may have relevance and that are not included in the statistical analysis should be commented. This is the case of the lack of impact of the interventions carried out in three of the studies on functionality[31,32,38].

Balance

The decrease in balance is a characteristic present in people with DS[15]. A total of four studies on the balance were included in the statistical analysis. One of the subgroups consisting of two studies[29,37] evaluated the effect of the interventions (both physical exercise programs) on the score of the balance subscale of the Bruininks Oseretsky Test of Motor Proficiency scale. After the interventions, the participants of both studies improved their total balance, being greater the effect of the study by Rahman[37]. A notable difference is the variation in age between the studies. In Rahman and Shaheen[29], the age of the participants comprised between 2 and 5 years, whereas in the study by Rahman[37] the age range was 10 to 13 years.

In relation to the characteristic balance deficit, people with DS had a greater number of center of gravity oscillations in anteroposterior and mediolateral direction[45]. Two studies[46,47] analyzed the effects of their interventions on displacements of the center of gravity in the stabilometry platform. The oscillations in the mediolateral direction were reduced after the intervention in both studies. However, the anteroposterior oscillations were not reduced in the work of Villarroya et al.[46], and in this case the global effect of the meta-analysis did not provide conclusive data.

Bone mineral content

Two studies[41,44] analyzed the effect that their training programs had on bone mineral content at the lumbar spine level. The study by Ferry et al.[44] presented favorable results in the improvement of the parameter studied, while the study by González-Agüero et al.[41] showed contradictory results. Therefore, the final results of the meta-analysis in this subgroup were not conclusive.

Cardiovascular function

The effects of exercise on maximum absorption of VO_2 (VO_2max) were studied in four of the reviewed trials[25,33,35,43]. The results of the meta-analysis revealed that the data provided by the studies were inconsistent in order to show a positive overall result on VO_2max. Of the four studies, the intervention of Rimmer et al.[33] was highlighted, showing notable improvements on this cardiovascular indicator. There are relevant differences in this study, in which the average age of the participants exceeded twice the age (39.4 years) of the other studies included in the subgroup (over 18 years). Another difference to highlight is that in the work of Rimmer et al.[33], the stress test was performed on a cycle ergometer, while in the other studies the test was performed on a treadmill. The duration of the session is also a noteworthy aspect, since the duration of the session by Rimmer et al.[33] ranged from 45 to 65 minutes, while that of the remaining three studies ranged from 15 to 30 minutes. In addition, the sample size of the study by Rimmer et al.[33] was higher (n=52) compared to the other three studies (Millar et al.[25] n=14, Varela et al.[35] n=16, González Agüero et al.[43] n=27). In relation to the type of intervention, the study by Rimmer et al.[33] includes in its training program strength exercises, something that it has in common with the study by González-Agüero et al.[43].

The maximum heart rate (HR max) is also a cardiovascular variable that provides information when evaluating the cardiovascular condition in a physical test[51]. This variable was measured by the same researches that studied VO_2max. The aim of the HR max study was to determine if there were changes in the effort and intensity of the exercise that the participants could reach after carrying out the intervention. The overall result of the meta-analysis for this subgroup was not conclusive, although there were studies whose interventions did have a favorable effect on this parameter[33,43]. In the study by Varela et al.[35], despite having obtained some improvement on this parameter, their data were not precise. The best results obtained were again those of Rimmer et al.[33], despite the difference in age with respect to the participants of the other studies already mentioned. The data resulting from the statistical analysis of the two cardiovascular variables suggest that the intervention of Millar et al.[25] was not effective in improving cardiovascular capacity in people with DS.

Body Mass Index

In the study by Ulrich et al.[39], participants were taught to ride a bicycle with the intention of improving their activity level. After seven weeks of intervention, body mass indexes (BMI) were reduced, although their data were inconclusive. In the study by Rimmer et al.[33], a favorable effect on the BMI of the participants of adult age was obtained after the training of cardiovascular exercises and strength. The two studies in this subgroup are very different: while one conducted a five-day punctual intervention[39], the other applied a twelve-week training program[33].

Additional evidence

From our systematic review, not all the studies were included in the meta-analysis. Nevertheless, several comments should be highlighted in relation to their findings. Therefore, this information is gathered in the present section.

The study by Harris[27] proposed individual treatments based on neurodevelopmental therapy for its participants (approximately 10 months old). After the intervention, no statistically significant differences were found between the groups, although there were differences in favor of the intervention group for the achievement of individual treatment objectives.

Another trial framed in the context of early care was the study of Hernandez-Reif[36], in which the effects of an additional half hour of massage therapy during two months in children around two years old are studied. The results revealed significant improvements in development (gross and fine) and tone.

Ulrich et al.[28] asked what would happen if children at a young age (around 10 months) trained on a treadmill with partial support of their body weight. This intervention was carried out until the child acquired the gait, showing how the intervention group learned to walk with help and independently significantly faster than the control group.

The authors Looper and Ulrich considered in two studies the benefits of the use of supramalleolar orthotic in addition to the early intervention on treadmill on motor development[48], and on the support of upper extremities during play[49]. The results obtained showed that one month after the intervention, the group that did not use the supramalleolar orthotic obtained better scores, and no significant differences were found in the support of the hands during the game in the vertical position.

In the trials, programs were proposed that sought to improve balance through sensorimotor training[42], through training that includes jumping and balance tests[40] or with core stability training[45]. The study by Carmeli et al.[34] could also be linked to this group of studies, who performed an intervention on treadmill and assessed its effects on leg strength and dynamic balance. This study differs from the rest because the participants are older, with an average age above 63 years. The results obtained after the six months of the program conclude that the intervention can provide improvements in muscle strength at the level of lower limbs, balance and functionality in walking.

Another trial included in this review (Chen et al.[30]) had a different objective. In this study, the influence of a single intervention of twenty minutes on the treadmill on manual grip strength in a group of young men was checked. The greater strength entered in the intervention group was explained by the brain changes stimulated by the exercise that cause effects in other muscle groups different from those exercised.

The trial by Lin and Wuang[26] is the one that gathered the largest sample of all those included in this review. A total of 92 participants underwent a treadmill training program and Wii Sports® games for a total of six weeks. Both the agility and muscle strength of all the muscle groups evaluated showed significant improvements after the intervention. Another study, previously mentioned and included in the meta-analysis (Rahman[37]), also made use of the Wii Fit® games in its intervention.

DISCUSSION

The main aim of the present paper is to synthesize the existing evidence and research the effect of PT interventions in DS population. Therefore, the results of the systematic review and meta-analysis are discussed in the following paragraphs.

Muscle strength

The findings on strength levels highlight the benefits that exercise programs can have on the improvement of muscle strength in people with DS. Considering the results of Rimmer et al.[33], we could state that increasing frequency and duration of interventions offer better results on strength training, besides being a safe and beneficial activity in adults with DS. Another interesting difference is that while in the other works the intervention is based on a progressive resistance training, in Rimmer et al.[33] the progressive resistance training is combined with aerobic exercise, suggesting that combining both exercise modalities offers better results in muscle strength training.

The study by Shields et al.[32] had a positive effect on the upper limbs strength, but no significant improvements on the lower limbs. The explanation for those facts could be that the participants had a greater potential to develop muscle strength at the level of the upper extremities. This is due to the fact that, at the beginning of the study, the difference of 1RM calculation on lower limbs was much higher than those of the upper limbs. Another explanation proposed in this research is that these people exercise the lower limb muscles in their daily life activities more frequently than their upper limb musculature, being therefore more effective an intervention in these last muscle groups.

The fact that the effect of the intervention in Shields et al.[31] persists in the long term after the intervention is finished is a valuable outcome. In the study, it is explained by the possibility that the participants trained during the intervention period continued to train voluntarily after the end of the program. The contributions of this study suggest that the training programs obtain long-term effects on the improvement of strength in people with DS, either due to the intervention characteristics or to motivation to a more active lifestyle.

In spite of not being studied in the statistical analysis of the data, the lack of repercussion of some of the programs[31,32,38] on the functionality is an important aspect to mention. These studies carried out a program of progressive resistance in which activities that represent natural and representative contexts for the participants were not included. The fact that the actions we take in the approach of people with DS include functional activities could be an important aspect in improving the basic daily life activities in these people, and therefore strengthen their autonomy and independence.

Balance

In terms of global balance, two studies that based their intervention on physical exercise programs were analyzed[29,37]. Despite studying groups of young subjects of different ages, the results were favorable for both studies, especially in the study by Rahman[37]. The maturative development between both groups of participants is not the same, and this factor may influence the results. In view of them, it could be suggested that exercise programs on balance are effective, even in young children with SD.

Two studies[46,47] evaluated the effects of vibration on the number of center of gravity oscillations in anteroposterior and mediolateral direction in the stabilometry platform. Although the intervention was a vibration in both studies, the Eid[47] research had better results in the reduction of the center of gravity oscillations in both directions. This remarkable difference could be due to the fact that the study by Eid[47] combines a PT program plus the vibration intervention and, instead, that of Villarroya et al.[46] is based solely on vibration. These data suggest that vibration is effective in improving balance in children and adolescents with DS and its effects are greater when this therapeutic modality is incorporated into a PT program.

Bone mineral content

Previous studies have observed lower levels of bone mineral content in people with DS, finding this characteristic not only in adults, but also in children and adolescents[41]. Promoting an improvement of bone mass during childhood and adolescence can be a determining factor for good skeletal health later[44]. Under this idea, two studies[41,44] measured the effect of training programs on bone mineral content at the lumbar spine level. The reason why the control group in the work of González-Agüero et al.[41] was the one that presented improvements in bone mineral content after the intervention is unclear. This fact is not discussed in this study, which leads to the idea that it could have been an error in the introduction of post-test information in the data tables.

Cardiovascular function

Cardiovascular exercises are essential for the maintenance of optimal cardiovascular health[24]. VO2max is commonly used as a key indicator of cardiovascular training[17]. The effects of exercise on maximum absorption of VO2 were studied in four of the reviewed trials[25,33,35,43] . The results of the meta-analysis were inconclusive for this cardiovascular indicator, but the study of Rimmer et al.[33] stands out for its results on VO_2max. In Rimmer et al.[33] the subjects are older, the stress test is performed on a cycle ergometer, the duration of the session is longer, the sample number is greater and the program includes strength exercises.

Taking into account the early aging suffered by people with DS and the recent life expectancy increase of this population[7], it is an important finding in the search of the improvement of quality of life for these people that an intervention with subjects around the age of 40 is capable of producing significant improvements upon maximum oxygen consumption. However, in turn, it should be mentioned that the improvements in the cardiovascular capacity of this group of people may also be influenced by the lower baseline state they presented at the beginning of the study. The performance of the stress test in the study by Rimmer et al.[33] could not be performed on a treadmill, due to the risk of falling of the participants, and therefore it was performed on a cycle ergometer. The test mode used results in lower VO2max values compared to the treadmill stress test in a range of 5% to 25%[33], this aspect should also be taken into account. In view of the data, the longer duration of the training session seems to be related to improvements at the cardiovascular level. The results also suggest that the combination of a program of progressive resistance and aerobic exercise may have a greater impact at cardiovascular level in people with DS than an aerobic exercise program alone. Lastly, it is worth mentioning the higher possibility of observing significant changes when working with larger sample sizes.

The maximum heart rate is also a key indicator for evaluate the cardiovascular condition[51]. This variable was measured by the same researches that studied VO2max. The overall result of the meta-analysis for this subgroup was not conclusive, but two studies[33,43] have a favorable effect on this parameter, highlighting again the study of Rimmer et al.[33]. The statistical analysis of the two cardiovascular variables suggest that the intervention of Millar et al.[25] was not effective in improving cardiovascular capacity in people with DS. The intervention based on walking / jogging proposed by these authors may not be sufficiently motivating or may become monotonous, thus affecting performance and effort on the part of the participants.

Body Mass Index

The overweight and obesity prevalence in people with DS is a common problem, which is why the health promotion through initiatives that encourage greater participation in physical activities can be an important pillar when working with this population[20,33,39]. In the study by Ulrich et al.[39] participants were taught to ride a bicycle with the intention of improving their activity level. After seven weeks of intervention, body mass indexes were reduced, although their data were inconclusive. It would be interesting to know the statistical analysis of the long-term indices, in order to know in this way if the intervention causes or does not affect the BMI over time. In the study by Rimmer et al.[33] a favorable effect on the BMI of the participants of adult age was obtained after the training of cardiovascular exercises and strength. The two studies in this subgroup are very different. Despite the differences, and the scarcity of studies in this meta-analysis subgroup, the overall result suggests that interventions that promote greater physical activity also have an impact on body mass indexes in this population.

Additional evidence

As mentioned in the results section, the different findings about the documents not included in the meta-analysis are now discussed.

PT will be present from the first days in the lives of children with DS. The aim of the intervention at such young ages is to stimulate the psychomotor development of the child, as well as to carry out preventive physical activities[13,52]. In this line of research, we find the study by Harris[27], the oldest one included in this review. The reason for the absence of statistical significance in the differences between groups was justified in the lack of assessment tools capable of detecting the changes.

Another trial framed in the context of early care was the study of Hernandez-Reif[36], suggesting that the massage therapy intervention improves the early stimulation of children with DS. These data should be taken with caution because the used tools were not validated.

Continuing in the pediatric stage, it is well known that walking is an especially important skill for young children. Its impact is multidimensional, affecting motor, cognitive and social development[28,53–55]. Children with DS begin to walk approximately one year later than children without disabilities[28]. The finding by Ulrich et al.[28] reveals the opportunity offered by the treadmill intervention on the development of children with DS. Subsequently, other studies not included in this review have focused on studying the most optimal intensity of this type of intervention for motor development and gait in these children[56–58].

Moreover, it is also very common to provide children with SD orthoses in order to improve the functionality of the gait[49]. The results obtained by Looper and Ulrich[48] make it necessary to reflect on the possible negative effects on the development that the use of supramalleolar orthotic seems to have in children who have not yet reached the gait, for this reason more research is necessary before a generalized recommendation of this type of technical aid in this population.

Although not included in the meta-analysis due to incompatibility for statistical comparison, three of the studies included in this review have also studied the balance in the population with DS[40,42,45]. The three obtained some improvement on the balance of their participants after the intervention, strengthening the previously commented idea that the exercise programs are effective for improving the balance in this population. In the trials, programs that sought to improve balance through sensorimotor training[42], through training that includes jumping and balance tests[40] or with core stability training[45] were proposed. We highlight the essay by Aly and Abonour[45] for the results obtained and the differences in the characteristics of their intervention. In this study, core stability exercises were proposed, based on the fact that the stability of the core can help to improve the dynamic balance and muscle coordination between the lower and upper extremities, as well as reduce the risk of injuries and muscle imbalances[45]. The results of the trial invite us to consider this type of exercise as part of a program to improve balance in children with DS. The study by Gupta et al.[40] also combined the balance exercise with the strength exercise, obtaining significant improvements in the strength of lower limbs.

On the other hand, the findings by Carmeli et al.[34] are remarkable. First of all, because they are a group of people of such advanced age, taking into account that the current life expectancy of this population is around 60 years[7]. Secondly, it is also striking that the severity of intellectual disability was mild in the whole group, given the usual characteristics of the aging process in this group. Another question to comment could be the suitability of the intervention given the risk of falling of the participants, although all the subjects completed the program and the presence of problems was not notified. Findings like those of this study imply significant progress in search of interventions that improve the independence and, in general, the improvement of the quality of life of these people.

Within the variety of studies covered in this review, we find the study of Chen et al.[30] that emphasizes the importance of maintaining an active lifestyle in DS people for the realization of the activities of daily life. In this study, the exercise can cause an effect in other muscle groups different from those exercised, explaining these changes by brain changes. An interesting aspect would be to check if these effects are maintained in the long term or are just temporary.

Some studies of this review incorporated the use of new technologies as a form of therapy. This is the case of Lin and Wuang [26] and Rahman[37], who used Nintendo Wii® games in their interventions. Given the good results obtained in both studies in children and adolescents, the use of new technologies could be a useful tool in the PT treatment of people with DS. The advantages of the use of videogames include the prevention of monotony and boredom, the increase of motivation, the ability to provide direct feedback, and allow the execution of a second task[59].

Despite being an extensive revision collecting works of different interventions, other types of PT interventions are not present in the works found. That is the case of respiratory PT, which may be of potential use if we take into account that respiratory problems have a high morbidity and contribute to the reduction of the quality of life of this group[3]. Another example would be the PT approach to orofacial stimulation and swallowing disorders, with oral problems also being characteristic of this population[7]. In addition, further research is needed on essential aspects that, despite having been studied previously, have not been clarified yet.

All this leads to highlight the clear need for more research in PT in the DS.

Limitations

Next, we will comment on the main limitations of this study. Despite careful selection of keywords and search strategies, it is possible that potentially useful literature has been excluded from the review. Also, an exhaustive search of unpublished literature could provide interesting articles to consider.

The present study was limited by the heterogeneity of the included studies, making comparison difficult. For this reason, from the total of twenty-five articles included, only fifteen provide information to the meta-analysis. Additionally, despite evaluating the same parameter, the difference in scales or instruments used for the assessment makes statistical comparison impossible. Another remarkable aspect is the sample size, small in most of the studies; and the lack of long-term follow-up of the interventions. Finally, due to the small number of studies that composed some subgroups, the data provided by the statistical analysis should be taken with caution.

CONCLUSIONS

PT is effective in the improvement of the maximum strength of upper and lower limbs; in the increase of the total balance, as well as in the reduction of mediolateral displacements of the CoG; in addition to the decrease of the body mass index. In regards to the anteroposterior displacements of the CoG, cardiovascular capacity or bone mineral content, the evidence of improvement was less conclusive or limited.

Programs that combine strength training with aerobic exercise obtain better results on strength and cardiovascular capacity than those that only use one of these two types of training. The actions based only on walking or jogging do not seem to be enough to achieve improvements at the cardiovascular level in people with DS. The therapeutic exercise programs, as well as the whole body vibration, are beneficial in the improvement of the balance in children and adolescents with DS, the effects of the intervention being greater by vibration when it is incorporated into a PT program instead of being performed isolated. The initiatives that encourage greater participation in physical activities have an influence on the reduction of body mass index in both adult and children subjects. The findings of this review reinforce the importance of the PT in the treatment of people with DS.

REFERENCES

1. Megarbane A, Ravel A, Mircher C, Sturtz F, Grattau Y, Rethore MO, et al. The 50th anniversary of the discovery of trisomy 21: the past, present, and future of research and treatment of Down syndrome. Genet Med. 2009;11:611-6.
2. Asim A, Kumar A, Muthuswamy S, Jain S, Agarwal S. «Down syndrome: an insight of the disease». J Biomed Sci. 2015;22:1-9.
3. Colvin KL, Yeager ME. What people with Down Syndrome can teach us about cardiopulmonary disease. Eur Respir Rev. 2017;26:1-16.
4. Kazemi M, Salehi M, Kheirollahi M. Down Syndrome: Current Status, Challenges and Future Perspectives. Int J Mol Cell Med. 2016;5:125-33.
5. United Nations. World Down Syndrome Day. New York: United Nations, 2017.
6. Haydar TF, Reeves RH. Trisomy 21 and early brain development. Trends Neurosci. 2012;35:81-91.
7. Arumugam A, Raja K, Venugopalan M, Chandrasekaran B, Kovanur Sampath K, Muthusamy H, et al. Down syndrome. A narrative review with a focus on anatomical features. Clin Anat. 2016;29:568-77.
8. Glasson E, Sullivan S, Hussain R, Petterson B, Montgomery P, Bittles A. The changing survival profile of people with Down's syndrome: implications for genetic counselling. Clin Genet. 2002;62:390-3.
9. Lott IT, Dierssen M. Cognitive deficits and associated neurological complications in individuals with Down's syndrome. Lancet Neurol. 2010;9:623-33.
10. Glasson EJ, Dye D., Bittles A. The triple challenges associated with age-related comorbidities in Down syndrome. J Intellect Disabil Res. 2014;58:393-8.
11. Holmes G. Gastrointestinal disorders in Down syndrome. Gastroenterol Hepatol Bed Bench. 2014;7:6-8.
12. Schapira IT, Ferrari AM, Aspres N, Guardiol AB, Antoniutti AI, Bedacarratz R. Down Syndrome: An Assessment of Infant Psychomotor Development and Its Impact on Social and Familial Integration. Int Med Rev Down Syndr. 2007;11:2-8.
13. Martínez NB, García MM. Psychomotor development in children with Down syndrome and physiotherapy in early intervention. Int Med J Down Syndr. 2008;12:28-32.
14. Caballero Blanco JA, Moreno Cabezas A, Ortiz Garrido M V., Marín Padilla C. Postural analysis: prevention from physical therapy. Int Med Rev Down Syndr. 2011;15:41-4.
15. Sugimoto D, Bowen SL, Meehan WP, Stracciolini A. Effects of Neuromuscular Training on Children and Young Adults with Down Syndrome: Systematic Review and Meta-Analysis. Res Dev Disabil. 2016;55:197-206.
16. Shields N, Dodd K. A systematic review on the effects of exercise programmes designed to improve strength for people with Down syndrome. Phys Ther Rev. 2004;9:109-15.
17. Dodd KJ, Shields N. A systematic review of the outcomes of cardiovascular exercise programs for people with Down syndrome. Arch Phys Med Rehabil. 2005;86:2051-8.

18. Andriolo R, Dib R El. Aerobic exercise training programmes for improving physical and psychosocial health in adults with Down syndrome. Cochrane Libr. 2009;2:1-25.
19. Hardee JP, Fetters L. The effect of exercise intervention on daily life activities and social participation in individuals with Down syndrome: A systematic review. Res Dev Disabil. 2017;62:81-103.
20. Bertapelli F, Pitetti K, Agiovlasitis S, Guerra-Junior G. Overweight and obesity in children and adolescents with Down syndrome - prevalence, determinants, consequences, and interventions: A literature review. Res Dev Disabil. 2016;57:181-92.
21. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions : Checklist and Explanations. Ann Intern Med. 2015;162:777-84.
22. World Confederation for Physical Therapy. Policy statement: Description of physical therapy. London, United Kingdom: WCPT; 2017.
23. World Health Organization. International Classification of Functioning, Disability and Health. Geneva, Switzerland: WHO; 2001.
24. Li C, Chen S, Meng How Y, Zhang AL. Benefits of physical exercise intervention on fitness of individuals with Down syndrome. Int J Rehabil Res. 2013;36:187-95.
25. Millar LA, Fernhall B, Burkett LN. Effects of aerobic training in adolescents with Down syndrome. Off J Am Coll Sport Med. 1993;25:270-4.
26. Lin HC, Wuang YP. Strength and agility training in adolescents with Down syndrome: A randomized controlled trial. Res Dev Disabil. 2012;33:2236-44.
27. Harris SR. Effects of Neurodevelopmental Therapy on Motor Performance of Infants with Down's Syndrome. Dev Med Child Neurol. 1981;23:477-83.
28. Ulrich DA, Ulrich BD, Angulo-kinzler RM, Yun J. Treadmill Training of Infants With Down Syndrome: Evidence-Based Developmental Outcomes. Pediatrics. 2001;108:1-7.
29. Abdel Rahman SA, Shaheen AAM. Efficacy of weight bearing exercises on balance in children with down syndrome. Egypt J Neurol Psychiatry Neurosurg. 2010;47:37-42.
30. Chen CCJJ, Ringenbach DRS, Snow M. Treadmill walking effects on grip strength in young men with Down syndrome. Res Dev Disabil. 2014;35:288-93.
31. Shields N, Taylor NF, Wee E, Wollersheim D, O'Shea SD, Fernhall B. A community-based strength training programme increases muscle strength and physical activity in young people with Down syndrome: A randomised controlled trial. Res Dev Disabil. 2013;34:4385-94.
32. Shields N, Taylor NF, Dodd KJ. Effects of a Community-Based Progressive Resistance Training Program on Muscle Performance and Physical Function in Adults With Down Syndrome: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2008;89:1215-20.

33. Rimmer JH, Heller T, Wang E, Valerio I. Improvements in Physical Fitness in Adults With Down Syndrome. Am J Ment Retard. 2004;109:165-74.
34. Carmeli E, Kessel S, Coleman R, Ayalon M. Effects of a treadmill walking

program on muscle strength and balance in elderly people with Down syndrome. J Gerontol A Biol Sci Med Sci. 2002;57:M106-10.
35. Varela AM, Sardinha LB, Pitetti KH. Effects of an Aerobic Rowing Training Regimen in Young Adults With Down Syndrome. Am J Ment Retard. 2001;106:135-44.
36. Hernandez-Reif M, Field T, Largie S, Mora D, Bornstein J, Waldman R. Children with Down syndrome improved in motor functioning and muscle tone following massage therapy. Early Child Dev Care. 2006;176:395-410.
37. Abdel Rahman Abdel Rahman S. Efficacy of Virtual Reality-Based Therapy on Balance in Children with Down Syndrome. World Appl Sci J. 2010;10:254-61.
38. Shields N, Taylor NF. A student-led progressive resistance training program increases lower limb muscle strength in adolescents with Down syndrome: a randomised controlled trial. J Physiother. 2010;56:187-93.
39. Ulrich DA, Burghardt AR, Lloyd M, Tiernan C, Hornyak JE. Physical Activity Benefits of Learning to Ride a Two-Wheel Bicycle for Children With Down Syndrome: A Randomized Trial. Phys Ther. 2011;91:1463-77.
40. Gupta S, Bhamini K, Kumaran S. Effect of strength and balance training in children with Down’s syndrome: a randomized controlled trial. Clin Rehabil. 2011;25:425-32.
41. González-Agüero A, Vicente-Rodríguez G, Gómez-Cabello A, Ara I, Moreno LA, Casajús JA. A 21-week bone deposition promoting exercise programme increases bone mass in young people with Down syndrome. Dev Med Child Neurol. 2012;54:552-6.
42. Jankowicz-Szymanska A, Mikolajczyk E, Wojtanowski W. The effect of physical training on static balance in young people with intellectual disability. Res Dev Disabil. 2012;33:675-81.
43. González-Agüero A, Gómez-Cabello A, Matute-Llorente A, Gómez-Bruton A, Vicente-Rodríguez G, Casajús JA. Effects of a circuit training including plyometric jumps on cardiorespiratory fitness of children and adolescents with Down syndrome. Int Med Rev Down Syndr. 2014;18:35-42.
44. Ferry B, Gavris M, Tifrea C, Serbanoiu S, Pop AC, Bembea M, et al. The bone tissue of children and adolescents with Down syndrome is sensitive to mechanical stress in certain skeletal locations: A 1-year physical training program study. Res Dev Disabil. 2014;35:2077-84.
45. Aly SM, Abonour AA. Effect of core stability exercise on postural stability in children with Down syndrome. Int J Med Res Heal Sci. 2016;5:213-22.
46. Villarroya MA, González-Agüero A, Moros T, Gómez-Trullén E, Casajús JA. Effects of whole body vibration training on balance in adolescents with and without Down syndrome. Res Dev Disabil. 2013;34:3057-65.
47. Eid MA. Effect of Whole-Body Vibration Training on Standing Balance and Muscle Strength in Children with Down Syndrome. Am J Phys Med Rehabil. 2015;94:633-43.
48. Looper J, Ulrich DA. Effect of Treadmill Training and Supramalleolar Orthosis Use on Motor Skill Development in Infants With Down Syndrome: A Randomized Clinical Trial. Phys Ther. 2010;90:382-90.
49. Looper J, Ulrich D. Does Orthotic Use Affect Upper Extremity Support During Upright Play in Infants With Down Syndrome? Pediatr Phys Ther. 2011;23:70-7.
50. Lotan M. Quality Physical Intervention Activity for Persons with Down

Syndrome. Sci World J. 2007;7:7-19.
51. Cordova A, Villa G, Sureda A, Rodriguez-Marroyo JA, Sánchez-Collado MP. Physical Activity and Cardiovascular Risk Factors in Spanish Children Aged 11-13 Years. Rev Esp Cardiol. 2012;65:620-6.
52. Guzmán-Muñoz EE, Gutiérrez-Navarro LB, Miranda-Díaz SE. Postural control in children , adolescents and adults with Down syndrome. Rev Med Int Sindr Down. 2017;21:12-6.
53. Agulló IR, González BM. Original Factors influencing motor development in children with Down syndrome. Int Med J Down Syndr. 2006;10:18-24.
54. Malak R, Kostiukow A, Krawczyk-Wasielewska A, Mojs E, Samborski W. Delays in motor development in children with Down syndrome. Med Sci Monit. 2015;21:1904-10.
55. Jung H, Chung E, Lee B. A comparison of the balance and gait function between children with Down syndrome and typically developing children. J Phys Ther Sci. 2017;29:123-7.
56. Wu J, Looper J, Ulrich BD, Ulrich DA, Angulo-barroso RM. Exploring effects of different treadmill interventions on walking onset and gait patterns in infants with Down syndrome. Dev Med Child Neurol. 2007;49:839-945.
57. Wu J, Looper J, Ulrich D a, Rosa M, Angulo-barroso RM. Effects of Various Treadmill Interventions on the Development of Joint Kinematics In Infants With Down Syndrome. Phys Ther. 2010;90:1265-75.
58. Ulrich DA, Lloyd MC, Tiernan CW, Looper JE, Angulo-Barroso RM. Effects of Intensity of Treadmill Training on Developmental Outcomes and Stepping in Infants With Down Syndrome: A Randomized Trial. Phys Ther. 2008;88:114-22.
59. Bonnechère B, Jansen B, Omelina L, Van Sint Jan S. The use of commercial video games in rehabilitation: a systematic review. Int J Rehabil Res. 2016;39:277-90.

FIGURES AND TABLES

Figure 1. Information flow diagram of the different phases of the systematic review.

Table I. Search strategy.

Table II. PEDro scale score for clinical trials included in the review.

Table III. Main characteristics of participants in the studies.

Table IV. Classification of the studies according to the type of intervention.

Table V. Main characteristics of the study interventions.

Table VI. Groups created for the meta-analysis.

Table VII. Characteristics of the subgroups included in the meta-analysis.

Table VIII. Meta-analysis results.

TABLES

Table I. Search strategy.		
Databases	Total found articles	Search
Pubmed	129	("Down Syndrome"[Mesh]) AND ("Physical Therapy Specialty"[Mesh] OR "Physical Therapy Modalities"[Mesh])
PEDro	90	Down syndrome
WoS	98	(Physiotherapy OR physical therapy) AND “Down syndrome”
Scopus	249	(Physiotherapy OR physical therapy) AND “Down syndrome”

Table II. PEDro scale score for clinical trials included in the review												
		PEDro scale										
Study	**Total score**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Harris (1981)[27]	6	–	×		×			×	×		×	×
Millar et al. (1993)[25]	3	–	×								×	×
Varela et al. (2001)[35]	5	–	×		×				×		×	×
Ulrich et al. (2001)[28]	5	–	×		×				×		×	×
Carmeli et al. (2002)[34]	6	–	×		×			×	×		×	×
Rimmer et al. (2004)[33]	5	–	×		×				×		×	×
Hernandez-reif et al. (2006)[36]	6	–	×		×			×	×		×	×
Shields et al. (2008)[32]	8	–	×	×	×			×	×	×	×	×
Rahman and Shaheen (2010)[29]	4	–	×		×						×	×
Rahman (2010)[37]	4	–	×		×						×	×
Looper and Ulrich (2010)[48]	4	–	×		×						×	

Shields and Taylor (2010)[38]	8	–	×	×	×			×	×	×	×	×
Looper and Ulrich (2011)[49]	4	–	×		×						×	×
Ulrich et al. (2011)[39]	4	–	×		×						×	×
Gupta et al. (2011)[40]	6	–	×	×	×				×		×	×
González-Agüero et al. (2012)[41]	5	–	×		×				×		×	×
Jankowicz – Szymanska et al (2012)[42]	3	–	×								×	×
Lin and Wuang (2012)[26]	7	–	×		×			×	×	×	×	×
Shields et al. (2013)[31]	8	–	×	×	×			×	×	×	×	×
Villarroya et al. (2013)[46]	4	–	×		×						×	×
Chen et al. (2014)[30]	6	–	×		×				×	×	×	×
González-Agüero et al. (2014)[43]	5	–	×		×				×		×	×
Ferry et al (2014)[44]	4	–	×		×						×	×
Eid (2015)[47]	8	–	×	×	×			×	×	×	×	×
Aly and Abonour (2016)[45]	6	–	×		×				×	×	×	×

The "×" symbol indicates that the item where it is found has been punctuated.

Table III. Main characteristics of participants in the studies.

Study	Groups	Average age	Females : Males	Severity of intellectual disability	Average weight (kg)	Average height (cm)	Comorbidity among the participants
Harris (1981)[27]	IG (n=10) CG (n=10)	10.91 (7.64) 9.45 (6.66) Months	5:5 6:4	ND	ND	ND	2 participants with serious heart defects
Millar et al. (1993)[25]	IG (n=10) CG (n=4)	18.4 (2.9) 17.0 (2.8) Years	3:11	IQ between 30-70 Mild to severe	66.5 (12.5) 58.4 (25.3)	153.7(7.1) 150.0 (15.8)	ND
Varela et al. (2001)[35]	IG (n=8) CG (n=8)	22.0 (3.8) 20.8 (2.3) Years	0:8 0:8	IQ = 39.4 (12.2) IQ = 38.4 (7.4) Mild to moderate	62.2 (10.7) 60.1 (7.4)	153.6 (21.5) 157.3 (4.1)	ND
Ulrich et al. (2001)[28]	IG (n=15) CG (n=15)	302.6 (52.6) 312.1 (66.1) Days	ND	ND	8.2 (0.90) 8.1 (0.92)	69.2 (2.62) 69.6 (2.74)	9 participants were born with heart disease and required surgery (of which 7 were in the intervention group)
Carmeli et al. (2002)[34]	IG (n=16) CG (n=10)	63.5 (2.0) 63.3 (4.8) Years	10:6 6:4	IQ between 56-75 Mild	ND	ND	15% of the participants had heart disease. Other conditions of comorbidity were depression and possible adverse reactions to the drugs
Rimmer et al. (2004)[33]	IG (n=30) CG (n=22)	38.6 (6.2) 40.6 (6.5) Years	16:14 13:9	ND	80.5 (20.0) 76.0 (18.2)	151.0 (9.0) 151.0 (4.0)	4 participants were diagnosed with heart disease
Hernandez-reif et al. (2006)[36]	IG (n=11) CG (n=10)	24.36 (10.57) 25.1(7.95) Months	5:6 3:7	ND	ND	ND	ND
Shields et al. (2008)[32]	IG (n=9) CG (n=11)	25.8 (5.4) 27.6 (9.5) Years	2:7 5:6	Mild to severe (20% mild, 80% moderate to severe)	78.4 (13.5) 61.2 (6.7)	158.8 (7.12) 152.0 (10.0)	ND

Rahman and Shaheen (2010)[29]	IG (n=13) CG (n=13)	4.56 (0.44) 3.92 (1.16) Years	8:5 7:6	IQ between 36 to 67 Mild to moderate	ND	ND	ND
Rahman (2010)[37]	IG (n=15) CG (n=15)	10.92 (1.16) 11.56 (0.44) Years	8:7 9:6	IQ between 36 to 67 Mild to moderate	ND	ND	ND
Looper and Ulrich. (2010)[48]	IG (n=10) CG (n=7)	642 (121) 578 (188) Days	ND	ND	10.26 (0.61) 9.41 (1.39)	78.67 (2.74) 75.81 (7.93)	ND
Shields and Taylor (2010)[38]	IG (n=11) CG (n=12)	15.9 (1.5) 15.3 (1.7) Years	3:8 3:9	Mild to severe (26% mild, 65% moderate, 9% severe)	63 (6) 58 (7)	159 (11) 156 (7)	ND
Looper and Ulrich. (2011)[49]	IG (n=10) CG (n=7)	642 (121) 578 (188) Days	ND	ND	10.26 (0.61) 9.41 (1.39)	78.67 (2.74) 75.81 (7.93)	ND
Ulrich et al. (2011)[39]	IG (n=19) CG (n=27)	12.0 (1.9) 12.4 (2.2) Years	10:9 16:11	ND	ND	ND	ND
Gupta et al. (2011)[40]	IG (n=12) CG (n=11)	13.0 (ND) 13.5 (ND) Years	4:8 5:6	IQ of 36-52 IQ of 38-49 Mild to moderate	28.5 (ND) 23.9 (ND)	132.2 (ND) 137.3 (ND)	ND
González-Agüero et al. (2012)[41]	IG (n=13) CG (n=14)	13.8 (2.6) 15.5 (2.6) Years	8:6 5:9	ND	40.1 (9.6) 48.7 (10.7)	141.9 (12.5) 146.8 (10.7)	7 participants (4 from the control group and 3 from the intervention group) took medication during the study (Levothyroxine sodium)
Jankowicz-Szymansk et al. (2012)[42]	IG (n=20) CG (n=20)	16.8 (ND) Years	20:20	Moderate	63.69 (7.97) 61.43 (10.6)	170 (0.4) 168 (0.3)	ND

Lin and Wuang (2012)[26]	IG (n=46) CG (n=46)	15.6 (3.6) 14.9 (3.9) Years	25:21 24:22	IQ= 52 (ND) IQ= 53 (ND) Mild to moderate	57.2 (10.2) 58.8 (20.0)	153.0 (8.0) 151.0 (9.0)	ND
Shields et al. (2013)[31]	IG (n=34) CG (n=34)	17.7 (2.4) 18.2 (2.8) Years	15:19 15:19	Mild to moderate (50% mild, 50% moderate)	65 (9) 64 (14)	155 (8) 153 (10)	ND
Villarroya et al. (2013)[46]	IG (n=16) CG (n=13)	15.93 (2.48) 15.64 (2.93) Years	11:19	ND	48.44 (8.83) 51.93 (14.10)	148.75 (8.2) 147.57 (12.6)	ND
Chen et al. (2014)[30]	IG (n=12) CG (n=8)	21.76 (4.79) 17.77 (3.49) Years	0:20	Moderate to severe	80.30 (22.92) 70.96 (24.25)	145.86 (11.6) 151.40 (7.8)	ND
González-Agüero et al. (2014)[43]	IG (n=14) CG (n=13)	13.7 (2.6) 15.6 (2.5) Years	8:6 4:9	ND	40.1 (9.6) 47.9 (10.7)	141.9 (12.5) 146.7 (11.1)	ND
Ferry et al (2014)[44]	IG (n=20) CG (n=22)	16.0 (1.8) 16.9 (1.5) Years	10:10 8:14	ND	59.8 (16.9) 65.4 (16.1)	153.9 (8.4) 155.3 (8.9)	ND
Eid (2015)[47]	IG (n=15) CG (n=15)	8.93 (0.7) 9.26 (0.79) Years	7:8 6:9	IQ= 57.6 (3.08) IQ= 57.06 (2.98) Mild	29.2 (3.4) 29.53 (3.22)	118 (2.27) 119.06 (2.81)	ND
Aly and Abonour (2016)[45]	IG (n=15) CG (n=15)	8.11 (1.26) 8.34 (1.07) Years	4:11 5:10	IQ= 48.33 (6.38) IQ= 50.33 (4.70) Mild to moderate	21.46 (2.44) 22.06 (2.4)	120.46 (5.46) 119.26 (4.35)	ND

Mean (standard deviation); IG intervention group; CG control group; IQ intellectual quotient; ND not described.

Table IV. Classification of the studies according to the type of intervention.

Intervention group	**Number of studies**	**Examples of type of therapy**
Therapeutic exercise	18[25,26,29–35,37–45]	Walking/jogging, cardio and strength exercises, progressive resistance training, weight-bearing exercises, strength and balance training, conditioning and jumping training, sensorimotor training, circuit training including plyometric jumps, training of physical qualities, core-stability exercises, treadmill training, training with Wii games, learning to ride a bike, exercise with an ergometer
Vibration	2[46,47]	Full body vibration
Early stimulation	3[27,28,36]	Neurodevelopment therapy, massage therapy, treadmill training with partial body weight support
Technical aid	2[48,49]	Supramalleolar orthosis

Table V. Main characteristics of the study interventions.

Study	Intervention	Frequency	Session duration	Intervention duration	Outcome measure	Measuring instrument	Results
Harris (1981)[27]	IG: Neurodevelopment Therapy CG: No additional intervention	3 times/ week	40 min	9 weeks	Motor development	-The Bayley Scales of Infant Development -Peabody Developmental Motor Scales	No statistically significant difference was found between the groups. But there was a significant difference in favor of IG in achieving individual treatment goals ($P = 0.05$).
Millar et al. (1993)[25]	IG: Aerobic training (walking / jogging) CG: No regular physical training	3 times/ week	30 min	10 weeks	VO2 max., VM, HR, RER, time and degree of exhaustion.	- Treadmill exercise test with gas consumption control and electrocardiogram	There were no statistically significant differences for any of the parameters of aerobic capacity. However, there was a significant improvement over time (and grade) in the treadmill exercise test after the intervention in the IG ($P < 0.00089$).
Varela et al. (2001)[35]	IG: Exercise in an ergometer CG: No regular physical activity	3 times/ week	15-25 min	16 weeks	VO2 max., VM max., HR max., RER, distance covered, working level, body weight, and percentage of body fat	- Stress tests in treadmill and rowing-ergometer with gas consumption control, heart rate monitor, and electrocardiogram	Training did not improve the cardiovascular capacity of the participants. However, exercise resistance and work capacity were improved in both tests ($P < 0.01$ for treadmill, $P < 0.05$ for rowing-ergometer) after the intervention in comparison with the CG.

Ulrich et al. (2001)[28]	IG: Training on treadmill with partial weight support CG: No training	5 times/ week	8 min	Until the child learned to walk	Motor development and growth	-The Bayley Scales of Infant Development -Battery of 11 anthropometric measurements	The IG learned to walk with help ($P = 0.03$) and to walk independently ($P = 0.02$) significantly faster than the CG. There were no significant differences in any of the anthropometric variables.
Carmeli et al. (2002)[34]	IG: Training on treadmill CG: No training	3 times/ week	10-45 min	6 months	Leg strength and dynamic balance	-Dynamometer -Functional test: "Time-up and go".	After the intervention there was a significant improvement in the isokinetic strength of knee flexion and extension (P values <0.01), as well as in the dynamic equilibrium ($P < 0.05$) in the IG.
Rimmer et al. (2004)[33]	IG: Cardiovascular training and strength training CG: No training	3 times/ week	30-45 min aerobic exercise. 15-20 min strength exercises	12 weeks	Cardiovascular capacity, strength (upper and lower limbs), and body composition (weight, BMI, skin folds).	-Exercise test on a cycle ergometer with control of gas consumption and electrocardiogram. -1RM bench press, and seated leg press machine. Hand grip dynamometer.	Results showed that IG significantly improved cardiovascular fitness: VO_2 max. ($ml.min^{-1}$); VO_2 max. ($ml.kg^{-1}.min^{-1}$); HR max.; time of exhaustion; and maximum workload (all values $P<0.01$). Also the strength of the extremities ($P<0.0001$), and slightly the body weight ($P<0.01$).
Hernandez-reif et al. (2006)[36]	IG: Massage therapy CG: Reading	2 times/ week	30 min	2 months	Motor development and muscle tone.	-Developmental programming for infants and Young children scale. -The Arms, Legs and Trunk Muscle Tone Score.	Results after the intervention revealed significant improvements in gross and fine motor development (Both $P < 0.05$). In addition, the tone of the limbs also improved (less hypotonia) significantly ($P \leq 0.05$).

Shields et al. (2008)[32]	IG: Progressive resistance training CG: Continued daily activities	2 times/ week	ND	10 weeks	Strength muscle function and functionality upper and lower extremities.	- 1RM repetition maximum tests. - Number of repetitions complete to 50% of a 1RM. - Time up and down stairs test; The grocery shelving task	Results showed that the intervention significantly improved the muscular resistance of the upper extremities (P <0.01) compared to the CG. The rest of the measures did not show significant differences between the groups.
Rahman and Shaheen (2010)[29]	IG: Traditional PT + Weight-bearing exercises CG: Traditional PT	Daily	IG: 80min CG: 60min	6 weeks	Static, dynamic and total balance.	- Subscale of the scale The Bruininks-Oseretsky Test of Motor Proficiency	The results showed significant improvements in the static (P = 0.006), dynamic (P = 0.002) and total (P = 0.002) balance in the IG after the intervention.
Rahman (2010)[37]	IG: Traditional training + Wii games CG: Traditional PT	2 times/ week	Conventional program 60 min IG + 30min Wii-Fit games	6 weeks	Balance	- Subscale of the scale The Bruininks-Oseretsky Test of Motor Proficiency	The results revealed a significant improvement on the balance (P = 0.000) when the IG was compared with the CG.
Looper and Ulrich. (2010)[48]	IG: Treadmill training + supramalleolar orthosis CG: Treadmill training	5 times/ week	8 h / day use of the orthosis 8 min / day	Until the child learned to walk	Gross Motor Function	-The Gross Motor Function Measure	All children showed significant improvements in the Gross Motor scores over time (P <0.001). One month after the intervention, the CG had higher scores in total than the IG (P = 0.01), as well as the standing subscale (P = 0.01)

			treadmill training				and walking, running and jumping subscale (P=0.02).
Shields and Taylor (2010)[38]	IG: Progressive resistance training CG: Continued his usual activities	2 times/ weeks	ND	10 weeks	Muscle strength and functionality upper and lower extremities.	- 1RM repetition maximum tests. - Time up and down stairs test. -The grocery shelving task.	The results showed improvement in muscle strength of the lower extremities compared to the CG. There were no significant differences between the groups for the rest of the measurements.
Looper and Ulrich. (2011)[49]	IG: Treadmill training + supramalleolar orthosis CG: Treadmill training	5 times/ weeks	8 h / day use of the orthosis 8 min / day treadmill training	Until the child learned to walk	Support of the child's upper extremities during play in an upright position	-Video recording	Significant group differences were not found in the support of the hands during the game in the vertical position. All the children decreased the support on both hands with the passage of time (P = 0.05)
Ulrich et al. (2011)[39]	IG: Learning to ride a bicycle CG: No intervention	5 consecutive days	75 min	5 days	Lower extremities muscle strength, balance, height, weight, skin folds and physical activity.	- Manual muscle tester - Keep balance on one leg - Scale, meter, plicometer. - Monitor with accelerometers	The participants who learned to ride spent significantly less time in sedentary activity at 7 weeks (P = 0.035) and at 12 months (P = 0.004) after the intervention and more time in moderate to vigorous physical activity at 12 months (P = 0.023) compared to CG participants. Body fat also seemed to be positively influenced over time by the subjects who learned to ride (P = 0.047).

Gupta et al. (2011)[40]	IG: Strength and balance physical training CG: They continued their normal activities	3 times/ weeks	ND	6 weeks	Lower limb strength and balance	-Dynamometer - Subscale of the The Bruininks-Oseretsky scale Test of Motor Proficiency	After the training, the IG participants showed a statistically significant improvement ($P < 0.05$) in the strength of the lower limbs of all the muscle groups evaluated. The score on the balance subscale also improved in the IG significantly ($P = 0.001$).
González-Agüero et al. (2012)[41]	IG: Conditio-ning and jumping training CG: No intervention	2 times/ weeks	25 min	21 weeks	Bone mineral content, pubertal development, and anthropo-metric measurements	-Dual-energy X-ray absorptiometry -Five stages by Tanner and Whitehouse	After the intervention, increments were observed in total and hip bone mineral content, and total lean mass in the IG (All $p < 0.05$). An interaction between time and exercise was found for total lean mass ($p < 0.05$). The increase of the lean total mass, the height and Tanner's stage represented almost 60 % in the increase of mineral bone total content in the group of intervention ($P < 0,05$).
Jankowicz-Szymanska et al. (2012)[42]	IG: Sensorimotor training CG: No intervention	2 times/ weeks	45 min	12 weeks	Static balance	Balance platform	After the training sessions, the tests improved in the intervention group, but the differences were not statistically significant. Except for the time in the maintenance of the CoG within the circle of 13 mm at the beginning and at the end in the intervention subjects ($P = 0.0014$).

Lin and Wuang (2012)[26]	IG: Treadmill training + Wii Sports games CG: Everyday activities	3 times/ week	25 min	6 weeks	Lower limb strength and agility	-Dynamometer -Subtests of the Bruininks-Oseretsky Test of Motor Proficiency-Second Edition	IG had significant improvements in agility (P = 0.02) and muscle strength of all muscle groups evaluated (P <0.05).
Shields et al. (2013)[31]	IG: Progressive resistance training CG: Social activities	IG: 2 times / week CG: 1 time / week	IG: 45-60 min CG:90 min	10 weeks both groups	Execution of work tasks, muscular strength, and physical activity	-Weighted box stacking test and a weighted pail carry test - Tests of maximum force of a repetition (1RM) - Activity monitor	There was no difference between the groups for the execution of work tasks. IG increased muscle strength in upper and lower limb at week 11 compared with CG. In week 24, only the lower limb muscle strength was increased. Physical activity levels were significantly higher in the IG at week 24 but not at 11. (All values P <0.05).
Villarroya et al. (2013)[46]	IG: Vibration CG: No vibration	3 times/ week	15-20 min	20 weeks	Static balance	- Pressure platform	Significant decrease in condition 4 (closed eyes surface unstable / open eyes stable surface) of the mid-lateral displacement and average velocity of the CoG in the group of SD who performed the intervention (P <0.05)
Chen et al. (2014)[30]	IG: Treadmill exercise CG: Viewing a video	Only 1 time	20 min	1 session	Gripping strength	-Dynamometer	The post-test between both groups were significantly different. The IG obtained greater strength in the post test compared to the CG (P = 0.03).

González-Agüero et al. (2014)[43]	IG: Circuit training that includes plyometric jumps CG: No increase in daily activities	2 times /week	20-25 min	21 weeks	Working time, VO2 max, RER max, HR max., VM max Anthropometric measurements and puberty state	- Test of effort in treadmill with control of gas consumption and electrocardiogram -Scale of Tanner	After 21 weeks of training, the IG improved its cardiorespiratory parameters (VO2 max, HR max, RER max, VM max, and work time) (all values P <0.05). In addition, improvements in cardiorespiratory parameters (VO2max, HRmax, and VMmax) were significantly higher compared to the CG (all values P <0.05).
Ferry et al (2014)[44]	GI: Physical qualities training GC: No intervention	2 times/ week	60 min	12 months	Bone mineral content, density, attenuation of ultrasound and speed. Motor skills	-Dual X-ray absorpsiometry -QUS device -Physical tests: Standing broad jump; Sit-and-reach test; Sit-ups; manual dynamometry	The year of intervention increased the values of bone mineral content in the lumbar spine (P <0.005) and in the hip (P <0.05). Bone mineral density was only increased in the lumbar spine (P <0.05). The punctuations of the physical tests increased significantly compared to the CG.
Eid (2015)[47]	IG: PT + Vibration Program GC: PT Program	3 times/ week	Both groups 1 hour, the GI plus 5-10 min of full body vibration	6 months	Balance and muscle strength of knee flexors and extensors	-Biodex Stability System - Manual dynamometry	There was a statistically significant improvement in favor of the IG in terms of strength: knee flexors (P = 0.04) and knee extensors (P = 0.01). There were also improvements on the balance of the IG compared to CG: mediolateral stability (P = 0.001); anteroposterior (P = 0.0001); Stability in general (P = 0.004).

Aly and Abonour (2016)[45]	GI: Conventional PT program + core-stability exercises GC: Conventional Physical Therapy Program	3 times/ weeks	45-60 min	8 weeks	Balance (postural stability)	-Biodex balance system	There was a significant decrease in the anteroposterior (P = 0.0001), mediolateral (P = 0.002) and general stability (P = 0.0001) indices of the IG participants compared to the CG after the intervention. Both groups showed a significant decrease in the three stability indices in the post treatment compared to the pre-treatment.

IG intervention group; CG control group; ND not described; Min minutes; H hours; VO_2 oxygen consumption; HR heart rate; RER respiratory exchange ratio; VM minute ventilation; Max. maximum; BMI body mass index; RM repetition maximum; CoG centre of gravity.

Table VI. Groups created for the meta-analysis.

Group	Studies	Measured concept	Type of intervention	Instrument
1	Rimmer et al. (2004)[33]	Strength	Therapeutic exercise	1RM Test
	Shields and Taylor (2010)[38]			
	Shields et al. (2008)[32]			
	Shields et al. (2013)[31]			
2	Rahman and Shaheen (2010)[29]	Balance	Therapeutic exercise	Bruininks-Oseretsky Test of Motor Proficiency
	Rahman (2010)[37]			
3	Eid (2015)[47]	Balance	Vibration	Stabilometry platform
	Villarroya et al. (2013)[46]			
4	Ferry et al. (2014)[44]	Bone mineral content	Therapeutic exercise	Dual X-ray absorpsiometry
	González-Agüero et al. (2012)[41]			
5	González-Agüero et al. (2014)[43]	Cardiovascular function	Therapeutic exercise	Gas consumption analyzer / electro-cardiogram
	Rimmer et al. (2004)[33]			
	Varela et al. (2001)[35]			
	Millar et al. (1993)[25]			
6	Ulrich et al. (2011)[39]	Body mass index	Therapeutic exercise	Weight and height
	Rimmer (2004)[33]			

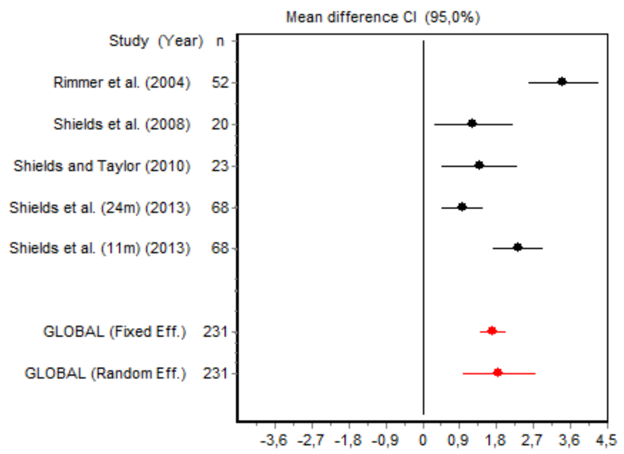
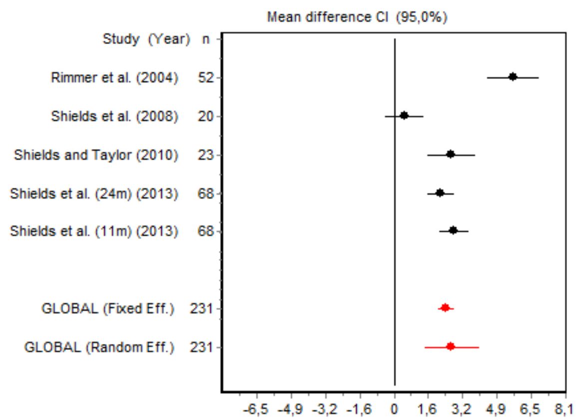
RM repetition maximum.

Table VII. Characteristics of the subgroups included in the meta-analysis.

Sub-groups	Included studies	Measurement of the effect	Heterogeneity test	Type of model	Publication bias *	Favour
1	Rimmer et al. 2004[33] Shields and Taylor. 2010[38] Shields et al. 2013 (24w)[31] Shields et al. 2013 (11w)[31] Shields et al. 2008[32]	Bench press	There is heterogeneity Q=28.7241; gl=4; p<0.001	Random effects	Non-existent Z=-0.2449; p=0.8065 T=0.7088; p=0.5296	Intervention
1B	Rimmer et al. 2004[33] Shields and Taylor. 2010[38] Shields et al. 2013 (24w)[31] Shields et al. 2013 (11w)[31] Shields et al. 2008[32]	Leg press	There is heterogeneity Q=46.6937; gl=4; p<0.001	Random effects	Non-existent Z=0.7348; p=0.4624 T=0.6842; p=0.5430	Intervention
2	Rahman and Shaheen 2010[29] Rahman 2010[37]	Total balance	There is heterogeneity Q=3.9407; gl=1; p=0.0471	Random effects	--	Intervention
3	Eid 2015[47] Villarroya et al. 2013[46]	CoG mediolateral displacement	There is heterogeneity Q=5.3302; gl=1; p=0.0210	Random effects	--	Intervention
3B	Eid 2015[47] Villarroya et al. 2013[46]	CoG anterolateral displacement	There is homogeneity Q=2.3964; gl=1; p=0.1216	Fixed effects	--	Inconclusive
4	Ferry et al 2014[44] González-Agüero et al 2012[41]	Bone mineral content lumbar spine	There is heterogeneity Q=32.0516; gl=1; p<0.001	Random effects	--	Inconclusive
5	González-Agüero et al. 2014[43] Rimmer et al. 2004[33] Varela et al. 2001[35] Millar et al. 1993[25]	VO_2 max.	There is heterogeneity Q=49.6632; gl=3; p<0.001	Random effects	Non-existent Z=0.3397; p=0.7341 T=0.0244; p=0.9828	Inconclusive
5B	González-Agüero et al. 2014[43] Rimmer et al. 2004[33] Varela et al. 2001[35] Millar et al. 1993[25]	HR max.	There is heterogeneity Q=54.1798; gl=3; p<0.001	Random effects	Non-existent Z=1.6984; p=0.0894 T=-2.8319; p=0.1054	Inconclusive
6	Ulrich et al. 2011[39] Rimmer 2004[33]	BMI	There is homogeneity Q=0.5365; gl=1; p=0.4639	Fixed effects	--	Intervention

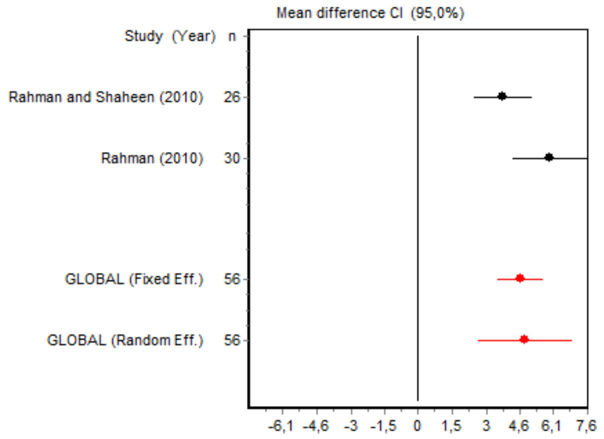
-- Results of this test are not shown for groups formed by two studies exclusively; BMI body mass index; VO2 max maximum oxygen consumption; HRmax maximum heart rate; CoG centre of gravity; W weeks.

Table VIII. Meta-analysis results.

Subgroup	Results				Forest plot
1	**Study**	**n**	**Standardized mean difference (CI95%)**	**Weights (%)**	
	Rimmer et al. 2004[33]	52	3,4245 (2,5667;4,2824)	19,3501	
	Shields et al. 2008[32]	20	1,2422 (0,2808;2,2035)	18,4775	
	Shields and Taylor 2010[38]	23	1,3898 (0,4784;2,3012)	18,9009	
	Shields et al. 2013 (24w)[31]	68	0,9750 (0,4722;1,4778)	22,0156	
	Shields et al. 2013 (11w)[31]	68	2,3211 (1,7061;2,9360)	21,2559	
	Random effects	**231**	**1,8629 (0,9843;2,7415)**		
1B	**Study**	**n**	**Standardized mean difference (CI95%)**	**Weights (%)**	
	Rimmer et al. 2004[33]	52	5,6554 (4,4372;6,8736)	18,6069	
	Shields et al. 2008[32]	20	0,5083 (-0,3866;1,4032)	20,1337	
	Shields and Taylor 2010[38]	23	2,7359 (1,5982;3,8737)	19,0068	
	Shields et al. 2013 (24w)[31]	68	2,2286 (1,6234;2,8338)	21,2426	
	Shields et al. 2013 (11w)[31]	68	2,8387 (2,1652;3,5122)	21,0101	
	Random effects	**231**	2,7445 (1,4498;4,0392)		

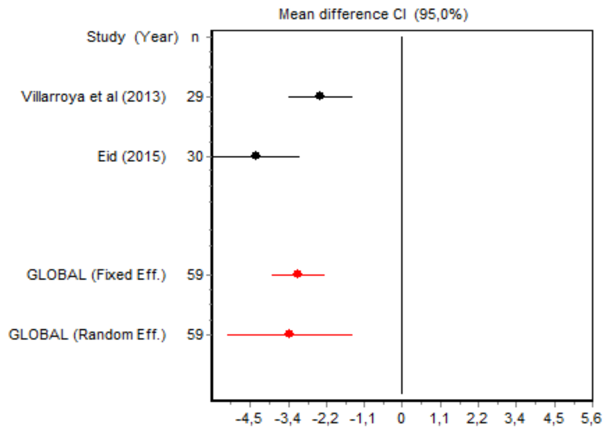
2

Study	n	Standardized mean difference (CI95%)	Weights (%)
Rahman and Shaheen 2010[29]	26	3,8077 (2,5185;5,0969)	53,1749
Rahman 2010[37]	30	5,9403 (4,2755;7,6050)	46,8251
Random effects	**56**	**4,8063 (2,7206;6,8920)**	



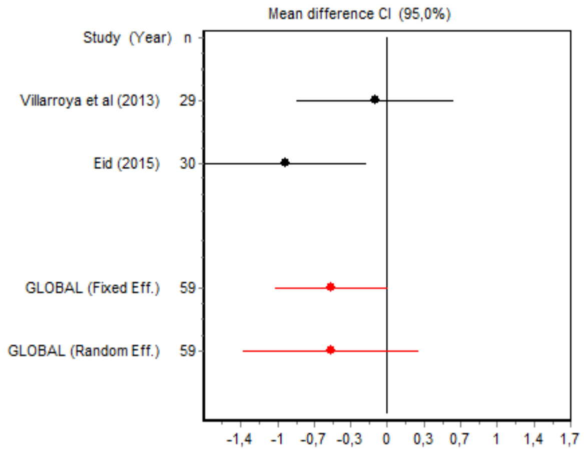
3

Study	n	Standardized mean difference (CI95%)	Weights (%)
Villarroya et al. 2013[46]	29	-2,4088 (-3,3679;-1,4497)	52,8074
Eid 2015[47]	30	-4,3175 (-5,6235;-3,0115)	47,1926
Random effects	**59**	**-3,3096 (-5,1771;-1,4420)**	



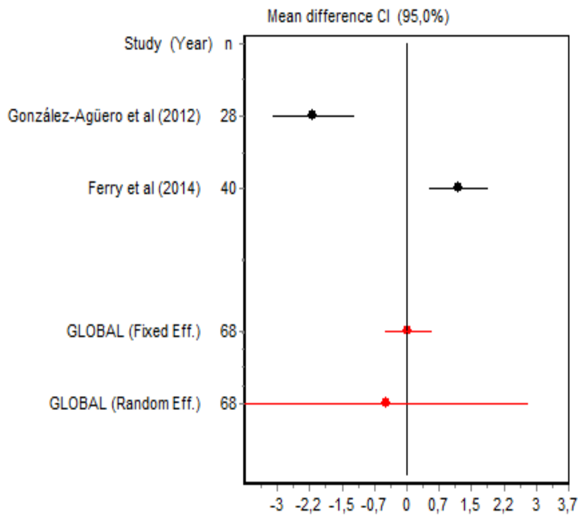
3B

Study	n	Standardized mean difference (CI95%)	Weights (%)
Villarroya et al. 2013[46]	29	-0,1116 (-0,8440;0,6208)	51,4745
Eid 2015[47]	30	-0,9420 (-1,6964;-0,1877)	48,5255
Fixed effects	**59**	**-0,5146 (-1,0401;0,0109)**	



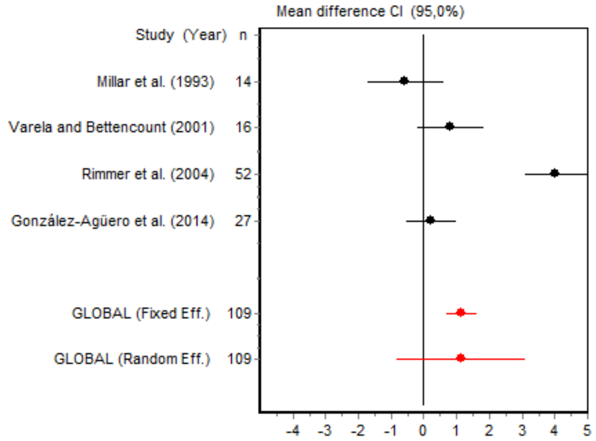
4

Study	n	Standardized mean difference (CI95%)	Weights (%)
González-Agüero et al. 2012[41]	28	-2,1208 (-3,0468;-1,1949)	49,5162
Ferry et al. 2014[44]	40	1,1837 (0,5118;1,8555)	50,4838
Random effects	**68**	**-0,4526 (-3,6908;2,7856)**	



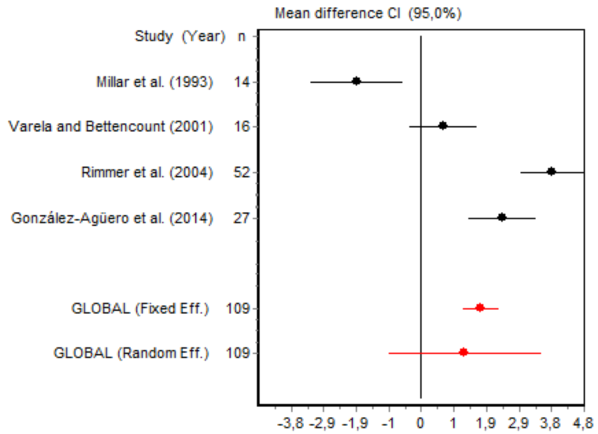
5

Study	n	Standardized mean difference (CI95%)	Weights (%)
Millar et al. 1993[25]	14	-0,5505 (-1,7279;0,6268)	24,3388
Varela et al. 2001[35]	16	0,8329 (-0,1887;1,8545)	24,8828
Rimmer et al. 2004[33]	52	4,0434 (3,0913;4,9955)	25,1075
González-Agüero et al. 2014[43]	27	0,2192 (-0,5379;0,9764)	25,6709
Random effects	**109**	**1,1447 (-0,8078;3,0972)**	



5B

Study	n	Standardized mean difference (CI95%)	Weights (%)
Millar et al. 1993[25]	14	-1,8995 (-3,2558;-0,5432)	24,1784
Varela et al. 2001[35]	16	0,6510 (0,3546;1,6566)	25,1932
Rimmer et al. 2004[33]	52	3,8665 (2,94194;7911)	25,3945
González-Agüero et al. 2014[43]	27	2,3994 (1,40973;3890)	25,2339
Random effects	**109**	**1,2921 (-0,93753;5217)**	



6

Study	n	Standardized mean difference (CI95%)	Weights (%)
Rimmer 2004[33]	52	-0,6217 (-1,1847;-0,0587)	40,6035
Ulrich et al. 2011[39]	72	-0,3487 (-0,8142;0,1168)	59,3965
Fixed effects	**124**	**-0,4596 (-0,8183;-0,1008)**