Neuromuscular Exercise in Children with Down Syndrome. A Systematic Review

Eliana-Isabel Rodríguez-Grande (eliana.rodriguez@urosario.edu.co)
Universidad del Rosario

Olga-Cecilia Vargas-Pinilla
Universidad del Rosario

Martha-Rocio Torres-Narvaez
Universidad del Rosario

Nelcy Rodríguez-Malagón
Pontificia Universidad Javeriana

Research Article

Keywords: effectiveness, therapeutic exercise, physical exercise, physical rehabilitation, physiotherapy, childhood

Posted Date: January 5th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1164740/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Objective
to evaluate the effects of neuromuscular exercise, specifying the parameters and characteristics of effective interventions to improve balance, muscle strength and flexibility in children with DS between the ages of 4 and 18 years.

Data Sources:
A search was carried out on PubMed, PEDro, EMBASE, SCIELO, Lilacs, Cochrane library.

Study Selection:
The search yielded 1384 eligible articles. Randomized clinical trials were selected, and that would have reported the effectiveness in the outcomes.

Data Extraction:
The methodology and results of the studies were critically appraised in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Data Synthesis:
Ten studies were included. The interventions included mechanotherapy, vibration, and use of different unstable surfaces. The exercise frequency ranged from three days to five days a week, and the duration of each session was between six and 15 minutes. The frequency was between two and three times a week for 6 and 12 weeks and the intensity was between 60% and 80% of maximum resistance (MR).

Conclusion
neuromuscular exercise appears to be effective for the improvement of both lower limb and chest muscle strength and balance in children over 8 years of age.

Introduction
Children with Down syndrome (DS) exhibit delayed motor development compared with typically developing children. DS involves alterations in balance, strength, and muscular endurance, which affect postural control and generate atypical motor development in addition to cognitive disability. Approximately 10% of children with DS are able to sit in an upright position and exhibit an independent walking pattern before the age of 3 years, and approximately 95% exhibit these abilities between 3 and 6 years of age.

In general, children with DS retain the typical sequence of motor development, but basic motor skills are attained late in childhood. The hypotonia and muscle weakness that are characteristic of DS interfere with intermuscular coordination, which affects balance and the processing of proprioceptive information and results in alterations in postural control, functionality and quality of life of the child. These characteristics restrict independence in mobility, which increases the demand for monitoring and support by caregivers, a situation that becomes more evident in the adolescent stage because of the new relationships established with friends and the school environment in which the child interacts.

To promote mobility and independence in daily activities, children and adolescents with DS can participate in therapeutic physiotherapy interventions that aid the development of motor skills and improve functional performance through the use of therapeutic exercise, among other intervention alternatives. Therapeutic exercise involves the application of physical exercise parameters such as intensity, frequency, and duration for therapeutic purposes. Therapeutic exercise categories include aerobic, anaerobic, resistance, and neuromuscular exercise. Neuromuscular exercise activates neurophysiological processes of intermuscular coordination that, together with increased muscle strength and postural responses, contribute to stability in the execution of motor patterns within the functional repertoire of children and adolescents with DS. There are different ways to perform neuromuscular exercise, including the use of unstable surfaces such as balls or mats, mechanotherapy equipment, isokinetic techniques, and bodyweight resistance exercises.

To the best of our knowledge, no systematic reviews have addressed the effects of neuromuscular exercise in the pediatric population with DS. However, several primary studies have examined the effects of neuromuscular interventions in children and adolescents with DS. Although some published reviews on the effects of physical therapy interventions have included neuromuscular exercise in their analysis, the inclusion of recent primary studies may improve the certainty of the evidence.

Previous systematic reviews of evidence regarding muscle exercise have included randomized controlled trials (RCTs) and quasi-experimental studies, making comparisons between studies despite the differences in their methodological quality. In addition, previous systematic reviews have examined different research questions, different populations, and different therapeutic interventions.
The aim of the current study was to synthesize the existing research evidence on the effects of neuromuscular exercise, specifying the parameters and characteristics of effective interventions to improve balance, muscle strength and flexibility in children with DS between the ages of 4 and 18 years. This synthesis of the best available evidence may help to facilitate the inclusion of these interventions in therapeutic approaches for this population and facilitate the development of motor skills and functional performance in children with DS.

**Methods**

**Methods** We adhered to the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) guidelines.  

**Eligibility criteria**

**Design:** A systematic review of the literature was conducted to identify RCTs.

**Type of participants:** Children with DS between the ages of 4 and 18 years.

**Type of interventions:** All neuromuscular interventions of therapeutic exercise with specific prescription parameters in terms of intensity, frequency, duration, among others were included.

**Outcomes:** For inclusion, studies identified in the literature search had to include results for at least one of the outcomes included in the review: muscle strength, balance, and flexibility.

**Search and identification of studies**

Search terms were generated from the Population, Intervention, Comparison and Outcome (PICO) components of the following question: What is the effect of neuromuscular therapeutic exercise on strength, balance, and flexibility in children with DS? These terms were adapted according to the different databases explored. A systematic search was conducted in the Pubmed, EMBASE, SCIELO, Lilacs, Cochrane Library and Epistemonikos databases. In addition, other sources of evidence were consulted to allow the identification and analysis of published or unpublished literature (gray literature) that had not been detected by the systematic search. This process was carried out through manual searches in reference lists of documents found in the review of databases. This process was developed over 7 months.

The terms used included: down syndrome/ exp, Down syndrome, mongolism, trisomy (infancy/ exp OR infancy) child/ exp, therapeutic exercise/exp, exercise, neuromuscular, exercise, resistance training, physical, activity, therapeutic, resistance, training, stretching, balance, rehab* OR kinesiotherap*.

**Selection of the studies**

The final selection of the studies was made independently by two reviewers who were both physiotherapists, one with training as an epidemiologist and the other with a Master's degree in Exercise and Sports Rehabilitation (MRTN and OCVP). The reviewers reviewed all titles and abstracts and excluded those that were considered irrelevant to the review because they did not meet the eligibility criteria of RCT design and inclusion of at least one of the prioritized outcomes.

Subsequently, the reviewers reviewed the full text of the studies verifying the eligibility criteria. Each reviewer generated Bib Tex files of the studies they considered eligible, and identified duplicates were eliminated using a bibliographic manager. The choice of each study was determined by consensus after independent review by the two reviewers. In cases where there was no consensus, a third reviewer decided on eligibility.

**Extraction and management of variables**

All variables considered relevant for the comparison of the studies and measurement of outcomes were extracted. Data on the type, mode, frequency, intensity, duration of the interventions, location in which the interventions were performed (e.g., outpatient clinic, home), person in charge of applying the intervention (e.g., physical therapist, other professional, family member or caregiver) were extracted from predesigned forms.

For the population, data were obtained regarding age, sex, sample size of each group and cognitive engagement.

Data were extracted for muscle strength, balance, and flexibility outcomes. For balance, data were obtained on center of mass displacement or time to maintain a balanced posture. For muscle strength, data were reported in pounds, kilograms of force, or Newtons. For flexibility, data on muscle elongation were obtained.

**Evaluation of study quality**

Two independent assessors (MRTN and OCVP) assessed the risk of bias of each included study using the Cochrane Collaboration's risk of bias assessment tool. The assessors rated each study as having a "low risk of bias," "high risk of bias," or "unclear risk of bias," taking into account six domains: random sequence generation (selection bias), allocation masking (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data, and selective reporting (reporting bias). The risk of bias rating was analyzed using Revman 5.1 software.

Disagreements in bias assessment were resolved by a third-party evaluator (EIRG).
Evaluation of the certainty of the evidence

Evaluation of the certainty of the evidence found was carried out using the GRADE approach\textsuperscript{22}. In this approach, the evaluation of evidence goes beyond the evaluation of the methodological quality, because the evidence found for each outcome was graded considering the risk of bias, inconsistency, directness or indirectness of the evidence and imprecision, risk of selective publication of outcomes, and dose-response gradient. The first four criteria were rated using a three-level ordinal scale: \textit{very serious, serious and not serious}. The classification options for risk of selective publication of outcomes were: \textit{not detected, strong suspicion}. The classification options for effect size were: \textit{no, large, very large}. The classification options for presence of confounding factors were: \textit{no, will reduce the demonstrated effect, suggests spurious effect}. The classification options for dose-response gradient were: \textit{no, yes, no}\textsuperscript{23}.

Synthesis of data

The selected body of evidence was organized by prioritized outcomes. Within each outcome, we described the characteristics of the population, the parameters of the interventions including the mode of exercise applied, the frequency, intensity and duration of the interventions applied in these studies, and the quantitative results achieved with their level of significance. This information is presented in Table 1.

Meta-analysis was performed when similarities were found in the components of the PICO question in at least two studies, as well as in the instruments used for the measurement of the outcome and the qualification of the risk of bias. When the measurement instruments were different, the data were converted to common units.

For meta-analyses, data on population characteristics, randomization methods, outcome measures, duration of follow-up and methods of analysis were extracted from each study in a database previously designed in Excel. Direct comparisons made between the intervention and a control group defined as educational activities, recreational activities, or continuity with activities of daily living or another intervention of interest for this review were considered.

For the prioritized outcomes, averages and standard deviations were extracted from the available data. Standardized differences from the mean (SMD) and 95% confidence intervals (95% CI) were calculated to allow comparability of data. Heterogeneity between trials was assessed using the chi-square test, a statistical significance level of $p < 0.05$ and the value of statistic $I^2$. When the data exhibited heterogeneity with an $I^2$ greater than 70\%, the results were combined using the random effects model and the 95\% CI was calculated\textsuperscript{24,25}. All the analysis above was performed using Revman 5 software\textsuperscript{26}.

Results

Study selection

A total of 1,384 studies were identified in the systematic literature search. From other sources, including the bibliographic references of the studies found in the systematic search, 239 additional studies were identified, resulting in a total of 1,623 identified studies. Of these studies, 88 were excluded because of duplication and 1,159 were excluded on the basis of reviewing the titles and abstracts. In total, 376 studies were reviewed in full text by two reviewers, of which 366 were excluded for not meeting the eligibility criteria. Finally, 10 primary studies were included. Figure 1 shows a flow chart of studies identified and included in the body of evidence.

Assessment of the risk of bias of included studies

Allocation (selection bias)

Six studies\textsuperscript{10,11,27-30} presented a low risk of bias because they reported masking of randomization, whereas four studies\textsuperscript{31-34} presented a high risk of bias because they did not report the methods by which participants were assigned, and the personnel in charge of maintaining random assignment were not masked.

Blinding

Because of the nature of the interventions used, the risk of bias assessment of each study took into account the blinding of the outcome assessors in each study. Three studies\textsuperscript{28,31,32} presented a high risk of bias, while seven\textsuperscript{10,11,27,29,30,32,34} presented a low risk of bias.

Outcomes with incomplete data

Three studies presented a high risk of bias because they reported incomplete data by not including data from participants who did not achieve the expected results\textsuperscript{33} or did not indicate the number of participants included in the reported results\textsuperscript{29,32}. The remaining studies reported all data from the study sample.

Selective report

Eight studies presented a low risk of selective reporting because they included all of the outcomes that were measured; one study had high risk\textsuperscript{22} and one more had unclear risk of bias\textsuperscript{29}.

This information is summarized in Figures 2 and 3.

Modes of application of neuromuscular exercise in physiotherapy interventions in children aged 4 to 18 years.
Two studies involved the use of mechanotherapy equipment available in gyms for muscle strength training\(^{10,27}\). Three studies applied therapeutic vibration\(^{11,28,31}\), which was combined with conventional physiotherapy interventions in two studies\(^{11,28}\). Two studies used different unstable surfaces for balance training\(^{29,32}\), and one study used Nintendo Wii and virtual reality\(^{33}\). One study used isokinetic exercise\(^{30}\) and another used bicycle training\(^{33}\).

**Frequency, intensity and duration of neuromuscular exercise**

In the two studies that examined muscle strengthening exercises using mechanotherapy equipment, the frequency was twice a week for 10 weeks\(^{10,27}\). In the studies that applied vibration\(^{11,28,31}\), the frequency was between three times per week for 24 weeks\(^{11}\) and three sessions every month for 20 weeks\(^{31}\) to 12 weeks\(^{28}\).

Exercise using unstable surfaces was applied with a frequency between two and three times a week for 8 and 12 weeks and a volume of three sets of 12 repetitions for each muscle group that was exercised\(^{29,32}\).

Lin et al.\(^{34}\) applied exercise three times a week for 6 weeks, whereas Eid et al.\(^{29}\) applied a frequency of three times a week for 6 months. The duration of the sessions varied between 35 and 75 minutes and the intensity, a parameter mentioned in few of the selected studies, was between 60% and 80% of maximum resistance (MR) in the studies that included exercise using mechanotherapy equipment\(^{10,27}\). Lin et al.\(^{34}\) used the speed and inclination of the treadmill as intensity criteria, which started at 2.0 kph (0% inclination) and ended with an average speed of 3.0 kph (58° elevation).

**Outcomes assessed in the studies included in the review**

Of the proposed outcomes to be evaluated, no evidence was found for the outcome of flexibility in this population. Table 1 shows the characteristics of the studies included in this review.

**Quantitative results by outcome and assessment of the certainty of the evidence**

Neuromuscular exercise in the different modes of application presented in this review was associated with significant increases in chest (8.51 [2.35, 14.67]) and lower limb (21.54 [1.64, 41.43]) muscle strength (Table 2 and Appendix 1). Interventions with neuromuscular exercise were associated with significant improvement in balance when their mode of application was isokinetic training and core stability exercises (−0.20 [−0.29, −0.12]) (Table 2 and Appendix 1). The certainty of the evidence for the outcome of muscle strength was between moderate and high. In contrast, the certainty of evidence for balance was highly variable, ranging from very low to high, mainly because of the imprecision of the results obtained in the primary studies. The information is presented in Table 2.

**Discussion**

The modalities of therapeutic exercise include neuromuscular exercise and neuromotor exercise. Although these two types of exercise can be similar, they are used in different training scenarios, some of which are therapeutic and some of which are focused on increasing performance in athletes\(^{35}\). Neuromuscular exercise aims to improve sensorimotor control (i.e., the ability to produce controlled movement through coordinated muscle activity) and to facilitate neuromuscular control. Thus, neuromuscular exercise seeks to improve the unconscious response of muscles to signals related to dynamic joint stability, which is the ability of the joint to remain stability during movement execution. To achieve this goal, neuromuscular exercise improves variables such as muscle strength, flexibility, and balance\(^{36,37}\).

The present review included articles reporting neuromuscular exercise with outcomes including muscle strength, balance, and flexibility. According to the American College of Sport Medicine (ACSM), some neuromotor exercise interventions incorporate other motor skills, such as coordination and agility\(^{36}\). That is, neuromotor exercise combines resistance and flexibility training with activities such as Tai chi and Yoga. Thus, the characteristics of these two types of exercise are treated as interchangeable in the literature reviewed\(^{37}\).

The evidence identified was scarce regarding the interventions and outcomes selected, and the quality of the evidence was found to be low–moderate. Although the studies included in the present review were RCTs, they presented high risk and unclear risk in aspects that affect the internal validity of the study and certainty in the measurement of the effect. These risks were related to the masking of randomized allocation\(^{31,34}\), the masking of outcome assessment\(^{28,31,32}\), and selective data reporting\(^{32}\). In addition, the sample sizes of the studies were small, which may explain the wide confidence intervals\(^{27,28,30,32,33}\). The loss to follow-up and the impact on statistical power could be related to the non-significant differences found in the equilibrium outcome\(^{32}\), which may have been the result of systematic type 2 error\(^{38}\).

No evidence was found for the outcome of flexibility. However, muscle stretching exercises were included as part of the training plan in two of the studies that examined muscle strength as the main outcome\(^{30,34}\). A previous study reported that the simultaneous training of flexibility and muscular strength improved muscular performance and the maintenance of improvements in muscular elongation\(^{39}\). Thus, flexibility may not have been included as a primary outcome in studies of the DS population because it was considered as a means to promote another outcome (such as muscle strength) and, in turn, as an indispensable element for effective and safe training\(^{39,40}\).

Another potential reason for the outcome of flexibility to not have been included as a therapeutic objective in previous studies is that children with DS exhibit characteristic muscle hypotonia, which is a decrease in the residual tension of the muscles at rest\(^{41}\). Hypotonia is in turn associated with decreased muscle strength, increased joint laxity, and increased flexibility in these children\(^{42}\). Therefore, improvement in flexibility may not be a primary objective of therapeutic
exercise, particularly when there is controversy regarding whether increased flexibility directly promotes strength gains or, on the contrary, limits muscle strength gains.\(^{43}\)

Regarding the parameters examined in the application of neuromuscular therapeutic exercise to improve muscle strength, the most common were frequency, intensity, and duration. The proposed therapeutic windows for the frequency of neuromuscular exercise in previous studies ranged from between two to three times per week, to 8 weeks \(^{10,27,27}\), to 24 weeks \(^{11}\). The approximate volume in this therapeutic window was three sets of 12 repetitions for each muscle group, the duration of each session varied between 35 and 75 minutes with an intensity between 60% and 80% of maximum resistance (MR) \(^{10,27}\).

Evidence regarding the use of neuromuscular exercise to improve balance reported the use of progressive muscle training 2–3 times per week in 45–60 minute sessions for 10–24 weeks. These studies included isometric and isokinetic exercises and muscle stretching, as well as therapeutic vibration, exercise bikes and virtual reality with devices such as Nintendo Wii \(^{27,28,30,31,33}\).

The therapeutic window proposed in this review is related to the ACSM's proposed guidelines for the evaluation and prescription of physical exercise \(^{40}\). The ACSM guidelines recommend a frequency greater than or equal to 2 or 3 days a week, a duration greater than or equal to 20 minutes, and an accumulated duration per week equal to or greater than 60 minutes, for the training of motor skills such as balance, coordination, gait, agility and proprioception in older adults and young people \(^{40}\).

The ACSM recommendations regarding prescription parameters are focused on physical exercise for potentially healthy adults \(^{40}\). There are no recommendations regarding parameters for the pediatric population because of the absence of supporting evidence in that age group. Future studies should evaluate the dose of neuromuscular exercise in potentially healthy children to define clear recommendations in this population. These can be extracted from the synthesis and analysis of scientific evidence or from the adaptation of existing scientific evidence regarding physical exercise in populations with specific conditions. Thus, future studies on therapeutic exercise should include the prescription parameters to get closer to a therapeutic dose of exercise in children with DS.

Despite the scarcity of evidence regarding the effects of neuromuscular exercise in the pediatric population with DS, an effect has been reported in a population of adults with DS. Sugimoto et al. \(^{12}\), reported significant changes in muscle strength, and functional task performance in adults and youth with DS when they performed neuromuscular exercise. To the best of our knowledge, the current study is the first systematic review to evaluate the effect of neuromuscular exercise in a pediatric population with DS from RCTs, contributing to the robustness of current evidence.

Future experimental studies should explore the effects of neuromuscular exercise in the pediatric population in early childhood (under 5 years of age) through play, given that the studies reported in the present review include the pediatric population from 8 years of age onwards. In children under 5 years of age, it is possible that the improvement of sensorimotor control favors the appearance of fundamental motor patterns \(^{44}\) that appear late in children with DS compared with typically developing children \(^{45}\).

**Conclusion**

Despite the limited number of RCTs available in previous literature, neuromuscular exercise appears to be effective for the improvement of both lower limb and chest muscle strength in children over 8 years of age when isometric and isokinetic training is used as a mode of exercise in addition to other strategies, such as treadmill training. There is also evidence for a positive effect on balance improvement when unstable surfaces and balance platforms, as well as lower limb muscle strength training, are used as modes of application. Future research is needed to investigate the effects of neuromuscular exercise in early childhood in more detail, as well as its effects on outcomes such as flexibility.

**Declarations**

**Acknowledgments**

We thank Benjamin Knight, MSc., from Edanz (https://www.edanz.com/ac) for editing a draft of this manuscript.

**Author contributions**

ERG, OVP and MTN designed the study, ERG and a research assistant searched and selected the evidence, extracted, and synthesized data. NRM advised the methodology and collaborated in the data analysis. All authors prepared and reviewed the manuscript.

**Funding**

This is a non-funded study

**Competing interests**

The authors declare that they have no competing interests.

**References**
1. Capio C. M., Mak, T. C. T., Tse, M. A. & Masters, R. S. W. Fundamental movement skills and balance of children with Down syndrome. *J. Intellect. Disabil. Res.* 62(3), 225–236 (2018).

2. Malak, R., Kostiukow, A., Krawczyk-Wasielewska, A., Mojs, E. & Samborski, W. Delays in motor development in children with Down syndrome. *Med. Sci. Monit. Int. Ed.* 21, 1904–1910 (2015).

3. Frank, K. & Esbensen, A. J. Fine motor and self-care milestones for individuals with Down syndrome using a Retrospective Chart Review. *J. Intellect. Disabil. Res.* 59(8), 719–729 (2015).

4. Lauteslager, P. E. M., Vermeer, A. & Holders, P. J. M. Disturbances in the motor behaviour of children with Down’s syndrome: the need for a theoretical framework. *Physiotherapy* 84(1), 5–13 (1998).

5. Maiano, C. et al. Static postural control among school-aged youth with Down syndrome: a systematic review. *Gait Posture* 62, 426–433 (2018).

6. Ruiz-González, L., Lucena-Antón, D., Salazar, A., Martín-Valero, R. & Moral-Munoz, J. A. Physical therapy in Down syndrome: systematic review and meta-analysis. *J. Intellect. Disabil. Res.* 63(8), 1041–1067 (2019).

7. Kinsner, C. & Colby, L. A. *Ejercicio terapéutico: fundamentos y técnicas.* Editorial Paidotribo. 638 p. (2005).

8. Filipa, A., Byrnes, R., Paterno, M. V., Myer, G. D. & Hewett, T. E. Neuromuscular training improves performance on the Star Excursion Balance Test in young female athletes. *J. Orthop. Sports Phys. Ther.* 40(9), 551–558 (2010).

9. Gupta, S., Rao, B. Effect of strength and balance training in children with Down’s syndrome: a randomized controlled trial. *Clin. Rehabil.* 25(5), 425–432 (2011).

10. Shields, N. et al. A community-based strength training program increases muscle strength and physical activity in young people with Down syndrome: a randomised controlled trial. *Res. Dev. Disabil.* 34(12), 4385–4394 (2013).

11. Eid, M. A. Effect of whole-body vibration training on standing balance and muscle strength in children with Down syndrome. *Am. J. Phys. Med. Rehabil.* 94(8), 633–643 (2015).

12. Sugimoto, D., Bowen, S. L., Meehan, W. P. & Straccioli, A. Effects of neuromuscular training on children and young adults with Down syndrome: systematic review and meta-analysis. *Res. Dev. Disabil.* 55, 197–206 (2016).

13. Maiano, C. et al. Static postural control among school-aged youth with Down syndrome: A systematic review. *Gait Posture* 62, 426–433 (2018).

14. Ruiz-González, L., Lucena-Antón, D., Salazar, A., Martín-Valero, R. & Moral-Munoz, J. A. Physical therapy in Down syndrome: systematic review and meta-analysis. *J. Intellect. Disabil. Res.* 63(8), 1041–1067 (2019).

15. Moher, D., Liberati, A., Tetzlaff, J. & Altman D. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* [Internet]. [cited 2021:11](6)(7). Available from: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.100097

16. *Epistemonikos: database of the best evidence-based health care.*

https://www.epistemonikos.org/en/documents/3e07214980ff84a2c03884055427aae6642e5945/matrix?current=5e050f0c6ec0d638046c4982

17. LILACS. https://lilacs.bvsalud.org/es/

18. SciELO.org https://scielo.org/es/

19. PubMed. PubMed. https://pubmed.ncbi.nlm.nih.gov/

20. Cochrane Reviews. Cochrane Library. https://www.cochranelibrary.com/

21. Cochrane Handbook for Systematic Reviews of Interventions. http://handbook.cochrane.org/

22. GRADE handbook. https://gdt.gradepro.org/app/handbook/handbook.html

23. About GRADEpro Informatics & Knowledge Management Department. http://tech.cochrane.org/revman/other-resources/gradepro/about-gradepro

24. Higgins, J. P. T. Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. *Int. J. Epidemiol.* 37(5), 1158–1160 (2008).

25. Huedo-Medina, T. B., Sánchez-Meca, J., Marín-Martínez, F. & Botella, J. Assessing heterogeneity in meta-analysis: Q statistic or I² index? *Psychol. Methods.* 11(2), 193–206 (2006).

26. RevMan. online-learning/core-software-cochrane-reviews/revman

27. Shields, N. Student-led progressive resistance training program increases lower limb muscle strength in adolescents with Down syndrome: a randomised controlled trial. *J. Physiotherapy.* (2010).

28. Emara, H. Effects of whole body vibration on body composition and muscle strength of children with Down syndrome. (2016).

29. Aly, S. M. & Abonour, A. A. Effect of core stability exercise on postural stability in children with Down syndrome. *Int. J. Med. Res. Health Sci.* 5(10), 213–222 (2016).

30. Eid, M. A., Aly, S. M., Huneif, M. A. & Iismai, D. K. Effect of isokinetic training on muscle strength and postural balance in children with Down’s syndrome. *Int. J. Rehabil. Res.* 40(2), 127–133 (2017).

31. Villarroya, M. A., González-Aguero, A., Moros, T., Gómez-Trullén, E. & Casajús, J. A. Effects of whole body vibration training on balance in adolescents with and without Down syndrome. *Res. Dev. Disabil.* 34(10), 3057–3065 (2013).

32. Jankowicz-Szymanska, A., Mikolajczyk, E. & Wojtanowski, W. The effect of physical training on static balance in young people with intellectual disability. *Res. Dev. Disabil.* 33(2), 675–681 (2012).

33. Ulrich, D. A., Burghardt, A. R., Lloyd, M., Tieman, C. & Hornyak, J. E. Physical activity benefits of learning to ride a two-wheel bicycle for children with Down syndrome: a randomized trial. *Phys. Ther.* 91(10), 1463–1477 (2011).

34. Lin, H.-C. & Wang, Y.-P. Strength and agility training in adolescents with Down syndrome: a randomized controlled trial. *Res. Dev. Disabil.* 33(6), 2236–2244 (2012).
35. Therapeutic exercise: foundations and techniques, 6th edition: 9780803625747: Medicine & Health Science Books @ Amazon.com. https://www.amazon.com/Therapeutic-Exercise-Foundations-Techniques-6th/dp/080362574X#reader_B00HYHBAVU

36. Bushman, B. Neuromotor exercise training. *ACSMs Health Fit. J.* **16**(6), 4–7 (2012).

37. Taulaniemi, A., Kankaanpää, M., Tokola, K., Pärkkäri, J. & Suni, J. H. Neuromuscular exercise reduces low back pain intensity and improves physical functioning in nursing duties among female healthcare workers: secondary analysis of a randomised controlled trial. *BMC Musculoskelet. Disord.* **20**(2019). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6626624/

38. Barlow, R. Systematic errors: facts and fictions. ArXivhep-Ex0207026. (2002). http://arxiv.org/abs/hep-ex/0207026

39. Simão, R. *et al.* The influence of strength, flexibility, and simultaneous training on flexibility and strength gains. *J. Strength Cond. Res.* **25**(5), 1333–1338 (2011).

40. ACSM’s guidelines for exercise testing and prescription. https://shop.lww.com/ACSM-s-Guidelines-for-Exercise-Testing-and-Prescription/p/9781975150181

41. Martin, K., Kaltenmark, T., Lewallen, A., Smith, C. & Yoshida, A. Clinical characteristics of hypotonia: a survey of pediatric physical and occupational therapists. *Pediatr. Phys. Ther.* **19**(3), 217–226 (2007).

42. Foley, C. & Killeen, O. G. Musculoskeletal anomalies in children with Down syndrome: an observational study. *Arch. Dis. Child.* **104**(5), 482–487 (2019).

43. Leite, T. *et al.* Influence of strength and flexibility training, combined or isolated, on strength and flexibility gains. *J. Strength Cond. Res.* **29**(4), 1083–1088 (2015).

44. Malak, R., Kotwicka, M., Krawczyk-Wasielewska, A., Mojs, E. & Samborski, W. Motor skills, cognitive development and balance functions of children with Down syndrome. *Ann. Agric. Environ. Med.* **20**(4), 803–806 (2013).

45. Cardoso, A., Campos, A., Santos, M., Santos, D., & Rocha, N. Motor performance of children with Down syndrome and typical development at 2 to 4 and 26 months. *Pediatr. Phys. Ther.* **27**(2), 135–141 (2015).

**Tables**

**Table 1. Characteristics of the included studies**
| Reference   | Participants | Interventions                        | Outcomes, measuring instrument                  | Application parameters: intensity, frequency, duration, therapeutic exercise mode | Results (for each outcome evaluated in the study). Presented here are the initial and final measurements for each group and the p-value reported by the study |
|-------------|--------------|--------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Shield N, 2013 | Number of participants: 68  
Boys: 38  
Girls: 30  
Age: 17.9±2.6 years  
Severity of intellectual disability: Mild–moderate. | Group 1: Progressive resistance training  
Group 2: Social program | Muscle strength: 1 MR  
Type: Anaerobic  
Mode: Gym machines  
Frequency: 2 days a week for 10 weeks  
Duration: 45–60 minutes  
Intensity: 60%–80% of 1 MR, 3 sets of 12 repetitions  
Intervention applied by: Physiotherapy student | Chest press (kg) 1 MR, Group 1: pre: 35.9±15.0; after week 11: 43.6±16.0; after week 24: 42.7±18.4.  
Chest press (kg) 1 MR, Group 2: pre: 30.0±14.0; after week 11: 32.0±11.7; after week 24: 35.0±14.0  
Leg press (kg) 1 RM, Group 1: pre: 92.0±45.2; after week 11: 128.1±46.8; after week 24: 133.3±59.5  
Leg press (kg) 1 MR, Group 2: pre: 79.4±47.7; after week 11: 92.4±49.9; after week 24: 101.3±48.3 | |
| Shield N, 2010 | Number of participants: 23  
Boys: 17  
Girls: 6  
Age: 15±1.6 years  
Severity of intellectual disability: Mild: 6 children; moderate: 15 children; severe: two children. | Group 1: Progressive resistance training  
Group 2: Usual recreational and leisure activities | Muscle strength: 1 MR  
Type: Anaerobic  
Mode: Gym machines  
Frequency: 2 days a week for 10 weeks  
Duration: 45–60 minutes  
Intensity: 60%–80% of 1 MR, 3 sets of 12 repetitions  
Intervention applied by: Physiotherapy student | Chest press (kg): Group 1: pre: 44±18; after week 10: 55±24  
Chest press (kg) Group 2: pre: 40±9; after week 10: 44±12  
Leg press (kg): Group 1: pre: 87±46; after week 10: 132±50  
Leg press 1 MR (kg) Group 2: pre: 89±44; after week 10: 97±43 | |
| Eid MA, 2017 | Number of participants: 31  
Boys: 17  
Girls: 14  
Age: 10.26±0.79 years  
Severity of intellectual disability: Mild | Group 1: Conventional physiotherapy and isokinetic training  
Group 2: Conventional physiotherapy | Muscle strength: Isokinetic dynamometer (maximum peak torque)  
Balance: Biodex platform  
Type:  
Mode: Isokinetic Machines and Balance Training  
Frequency: 3 days a week for 12 weeks  
Duration: 60 minutes  
Intensity: Speeds 90–120°/sec  
Intervention applied by: Physiotherapists | Maximum peak torque (Nm) Group 1: Right knee flexors: pre: 24.38±2.16; after week 10: 29.06±2.46; Right knee extensors: pre: 39.66±3.43; after week 10: 45.06±2.86; Left knee flexors: pre: 20.13±2.19; after week 10: 25.22±3.28; Left knee extensors: pre: 36.2±3.14; after week 10: 40.73±3.03  
Group 2: Right knee flexors: pre: 25.43±2.22; after week 10: 27±2.47; Right knee extensors: pre: 40.43±3.28; after week 10: 42±3.46; Left knee flexors: pre: 20.93±1.69; after week 10: 22.18±1.88; Left knee extensors: pre: 36.68±3.32; after week 10: 37.93±3.47 | Group 1: Anteroposterior stability index pre: 1.42±0.3; post: 1.19±0.18; Mediolateral stability index pre: 1.67±0.17; post: 1.23±0.08; Total stability index pre: 1.69±0.21; post: 1.43±0.13  
Group 2: Anteroposterior stability index pre: 1.43±0.13; post: 1.34±0.09; Mediolateral stability index pre: 1.68±0.15; post: 1.54±0.13; Total stability index pre: 1.71±0.09, post: 1.6±0.08 |
| Jankowicz A, 2012 | Number of participants: 40  
Boys: 20  
Girls: 20  
Age: 16.8 years | Group 1: Balance training  
Group 2: No exercise | Static one-legged balance. Using Duo Balance. Centre Of Gravity (COG) trajectory length and time frame in which the vertical projection of COG remained within the 13 mm radius circle  
Type:  
Mode: Unstable surfaces (ball and foam)  
Frequency: 2 days a week for 12 weeks | COG trajectory length (mm) Group 1: OA pre: 2083.26±1220.8; post: 1615.62±694.6; OC pre: 3440.04±1308.01; post: 2591.46±1166.6  
COG trajectory length (mm) Group 2: OA pre: 1858.15±774.24; post: 1871.19±1531.8; OC pre: 3169.9±1351.3; post: 3107.5±2215.0 | Percentage of time (seconds) circle radius 13 mm: Group 1: OA pre: 55.91±24.81, post: 53.68±24.84; Group 2: OA pre: 50.3±24.81, post: 51.6±24.84 |
| Study | Number of Participants | Group 1 | Group 2 | Muscle Strength | Type | Mode | Frequency | Duration | Intensity | Intervention | Maximum Muscular Force | Balance (seconds) |
|-------|------------------------|--------|--------|---------------|------|------|-----------|----------|-----------|--------------|----------------------|-------------------|
| Lin H, 2012 | 92 | Exercise program based on virtual reality with Wii, treadmill | No exercise | Manual dynamometer (lbs) | Type: | Mode: Unstable surfaces (ball and foam) | Frequency: 3 days a week for 6 weeks | Duration: 45 minutes | Intensity: NR | No activity | Group 1: Right knee extension: pre: 15.8±10.01, after week 7: 19.7±9.8, after 1 year: 15.6±4.4; Left knee extension: pre: 15.4±10.3, after week 7: 20.1±10.2, after 1 year: 14.7±4; Right knee flexion: pre: 13.6±11.2, after week 7: 17.5±9.1, after 1 year: 15±4.4; Left knee flexion: pre: 13.3±8.3, after week 7: 17.2±11.2, after 1 year: 13±4.4 | Group 1: Lower left leg: pre: 5.3±4.9, after week 7: 6.6±5.7, after 1 year: 8.3±8.2; Lower right leg: pre: 4.7±4.8, after week 7: 7.0±7.8, after 1 year: 7.3±8.3 |
| Villaroya MA, 2013 | 57 | Vibration training | No exercise | Unipedal static equilibrium time (seconds) | Type: | Mode: Bicycle | Frequency: 5 days | Duration: 75 minutes | Intensity: NR | No activity | Maximum muscle force (kgs): Group 2: Right knee extension: pre: 12.9±6.6, after week 7: 15±5.4, after 1 year: 12±4.9; Right knee flexion: pre: 11.1±4.3, after week 7: 12±4.1, after 1 year: 12±5.1, left knee flexion: pre: 11±4.7, after week 7: 12±4.4, after 1 year: 10.2±4.4 |
| Eid MA, 2017 | 57 | Conventional | No exercise | Bipedal balance and gait training with muscle | Type: | Mode: Vertical vibration platform Power Plate Pro 5 | Frequency: 3 days a week for 20 weeks | Duration: 18 minutes | Intensity: 28-Hz frequency, 29-mm amplitude, and 2.2-g vibration dose | No activity | No significant p-values. They report the difference, not the values of the measured outcomes. |
| Group | Exercise | Equipment | Type | Mode | Frequency | Duration | Intensity | Intervention applied by |
|-------|---------|-----------|------|------|-----------|----------|-----------|-------------------------|
| 1     | Exercise and vibration | Manual dynamometer (N) | Type | Mode | Frequency | Duration | Intensity | Intervention applied by |
|       | Group 1: Exercise | Group 2: Exercise | | | | | | Physiotherapist |
| 2     | Conventional physiotherapy | Balance and gait training | | | | | | Physiotherapist |

### Group 1: Intervention
- Type: Physiotherapy and vibration
- Mode: Bipedal postures and gait
- Frequency: 3 days a week for 24 weeks
- Duration: 60 minutes
- Intensity: Vibration amplitude of 2 mm and frequency of 25 to 30 Hz
- Intervention applied by: Physiotherapist

### Group 2: Control group
- Type: Conventional physiotherapy
- Mode: Bipedal postures and gait
- Frequency: 3 days a week for 24 weeks
- Duration: 60 minutes
- Intensity: Vibration amplitude of 2 mm and frequency of 25 to 30 Hz
- Intervention applied by: Physiotherapist

**Table 2. Evaluation of the certainty of the evidence presented for each outcome**
| No. of studies | Study design | Risk of bias | Inconsistency | Indirect evidence | Imprecision | Other considerations | Neurmuscular Exercise | Control | Relative (95% CI) | Absolute (95% CI) | Certainty |
|----------------|--------------|--------------|---------------|-------------------|-------------|----------------------|-----------------------|---------|------------------|------------------|-----------|
| Chest muscle strength. Intervention: Mechanotherapy. Measuring instrument: Maximum resistance (MR) (Shield 2010 and 2013) (Follow-up: Mean 11 weeks; (kg)) | 2 randomized trials | not serious | not serious | not serious | serious \(^a\) | none | 45 | 46 | MD 8.51 higher. (2.35 to 14.67) | ⨁⨁ MO |
| Muscle strength of the lower limbs. Intervention: Mechanotherapy. Measuring instrument: Maximum resistance (MR) (Shield 2010 and 2013) (Follow-up: Mean 12 weeks; evaluated torque (Newton)) | 2 randomized trials | not serious | not serious | not serious | serious \(^a\) | none | 45 | 46 | MD 21.54 higher. (1.64 to 41.43) | ⨁⨁ MC |
| Muscle strength of the lower limbs. Intervention: Isokinetic training. Instrument: Maximum peak torque (Newton) (Eid 2017) (Follow-up: 12 weeks) | 1 randomized trials | not serious | not serious | not serious | not serious | none | 16 | 15 | MD 2.68 higher. (1.68 to 3.68) | ⨁ HIG |
| Hip and knee muscle strength. Intervention: Exercise with treadmill and Wii. Instrument: Manual dynamometry (Lbs) (Lin 2012) (Follow-up: 18 weeks) | 1 randomized trials | not serious | not serious | not serious | not serious | none | 46 | 46 | MD 1.08 higher. (0.8 higher to 1.36 higher) | ⨁ HIG |
| Knee muscle strength. Intervention: Isometric training. Instrument: Manual dynamometer (kg) (Ulrich 2011) (Follow-up: weekly for 12 months) | 1 randomized trials | very serious \(^b\) | not serious | not serious | not serious | none | 19 | 27 | MD 3.18 higher. (1.87 higher to 4.5 higher) | ⨁ LÖV |
| Knee muscle strength. Intervention: Conventional physiotherapy and therapeutic vibration (Eid 2015 and Emara 2016) Instrument: Manual dynamometry (Newtons) (Follow-up: 12 weeks) | 2 randomized trials | serious | not serious | not serious | serious \(^c\) | none | 32 | 30 | MD 2.53 higher. (1.89 higher to 3.16 higher) | ⨁ LÖV |
| Balance. Intervention: Conventional physiotherapy plus isokinetic training/core stability exercises (Eid 2017 and Sobhy 2016). Instrument: Stability Index (Bic up: 12 weeks) | 2 randomized trials | not serious | not serious | not serious | not serious | none | 16 | 15 | MD 0.2 lower. (0.29 lower to 0.12 lower) | ⨁ HIG |
| Balance. Intervention: Neuromuscular exercise using unstable surfaces and balloons (Jankowics 2012). Instrument: Path length center of gravity (mm) (Follow-up: 12 weeks) | 1 randomized trials | very serious \(^d\) | not serious | not serious | very serious \(^e\) | none | 20 | 20 | MD 336.54 lower. (948.52 lower to 275.44 higher) | ⨁ VEF |
| Unipedal balance. Intervention: Isometric training and unipedal balance (Ulrich 2011). Instrument: Unipedal balance maintained (seconds) (Follow-up: 12 months) | 1 randomized trials | very serious \(^d\) | not serious | not serious | serious | none | 17 | 27 | MD 2.54 higher. (0.62 higher to 4.45 higher) | ⨁ VEF |
CI: Confidence Interval; MD: Mean Difference

Explanations

a. Very wide confidence intervals. In one of the studies, the change is not statistically significant
b. The trend is high risk 5/7
c. Large confidence intervals
d. High risk 5/7
e. Very large confidence intervals

Figures

Figure 1
Flow chart of studies included in the body of evidence on the effect of neuromuscular exercise on muscle strength and balance in children with DS between the ages of 4 and 18 years. Adapted from: Moher, D et al. PLoS Med. 6(7), (2009). e1000097. doi:10.1371/journal.

Figure 2
Risk of bias summary: review authors’ judgments about each risk of bias item for each included study.

Figure 3
Risk of bias graph: review authors’ judgments about each risk of bias item presented as percentages across all included studies.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- Appendix11.docx