Journal of Physiotherapy 67 (2021) 243–251

Journal of PHYSIOTHERAPY

journal homepage: www.elsevier.com/locate/jphys

Invited Topical Review

Physiotherapy management of Down syndrome

Nora Shields

Department of Physiotherapy, Podiatry and Prosthetics and Orthotics, La Trobe University, Melbourne, Australia

KEY WORDS

Down syndrome, Exercise
Meta-analysis
Physical therapy

[Shields N (2021) Physiotherapy management of Down syndrome. *Journal of Physiotherapy* 67:243–251]

Introduction

Over the past century, the life expectancy of people born with Down syndrome has increased from 9 to 60 years,[1] with data indicating that it could match the general population within a generation.[2] This rapid increase in survival is largely due to earlier surgical correction of heart defects, better treatment of infections and improved general healthcare.[3] This success, however, is tempered by the substantially higher risk and early onset of several chronic health conditions in adults with Down syndrome, particularly cognitive decline commencing in their early 40s.

Evidence-based clinical guidelines for the medical care of adults with Down syndrome were recently published, with one strong recommendation that screening for Alzheimer-type dementia start after the age of 40 years.[4] By comparison, there are no known clinical practice guidelines to support physiotherapy management.[5] The physiotherapy profession has much to offer people with Down syndrome: a wide breadth of practice spanning early infancy through to old age, unique contributions as part of a multidisciplinary team in managing chronic health conditions and, specifically, expertise in exercise and physical activity. Therefore, it is timely to review the available evidence to guide physiotherapists in their management of Down syndrome. This review focuses on the most recent evidence (published since 2000) from randomised controlled trials involving people with Down syndrome across their lifespan. It provides an evaluation of interventions that are either currently within the scope of, or could become part of, physiotherapy practice.

What is Down syndrome?

Down syndrome (or trisomy 21) is the most common genetic cause of intellectual disability,[6] occurring in an estimated 1 in 800 births worldwide.[6] Approximately 11,000 people with Down syndrome live in Australia[7] and 250,000 in the USA.[8] Down syndrome is caused by the over-expression of normal genetic material, usually an extra chromosome 21. Trisomy 21 occurs by meiotic nondisjunction, when the egg or sperm carries an extra copy of chromosome 21.[6] The risk of trisomy 21 increases with parental age. In translocation Down syndrome, which can be inherited, an additional chromosome 21 is attached to another chromosome. Mosaic Down syndrome or partial trisomy 21 is the result of a mutation during mitosis, where the embryo has a combination of typical cells, as well as cells with a third copy of chromosome 21. People with mosaic Down syndrome usually have fewer clinical features than those with other types of Down syndrome, but this depends on how early in development the mutation occurs.

Burden of Down syndrome

Down syndrome has whole-of-genome and epigenetic effects, with consequences to the structure and function of the nervous, cardiovascular, musculoskeletal and endocrine systems. The primary clinical feature of Down syndrome is intellectual disability, which is usually moderate but can range from mild to severe. Central nervous system structural differences include a smaller cerebrum, cerebellum and brain stem. Adults with Down syndrome are at ultra-high risk of experiencing early cognitive decline, with a cumulative risk of dementia of 45% by 55 years and 80% by 65 years[9] compared with 20 to 35% by 75 years in the general population. Common structural differences in the cardiovascular system are congenital heart defects, affecting 40 to 55% of infants with Down syndrome.[10] Although the limited available evidence suggests a reduced risk of atherosclerotic cardiovascular disease,[4] cardiovascular functioning is usually compromised in people with Down syndrome who have very low cardiorespiratory fitness,[11] altered physiology (such as autonomic dysfunction),[12] and are at higher risk of stroke across all age groups than the general population.[13] Respiratory illness is the most common reason for hospitalisation of children,[14] and pneumonia is a leading cause of death in older people with Down syndrome.[15] Obstructive sleep apnoea is also more common and more severe in adolescents and adults with Down syndrome than in the general population.[16]

Down syndrome is associated with extensive musculoskeletal sequelae, including muscle weakness, hypermobility, ligamentous laxity and skeletal deformities. Musculoskeletal conditions such as atlantoaxial instability, scoliosis, foot deformities, and hip and

https://doi.org/10.1016/j.jphys.2021.08.016

patellar instability are common. Prevalence estimates of atlantoaxial instability from population-based studies are 4 to 8%,[17,18] although less than 1 to 2% of people with Down syndrome develop symptoms of spinal cord compression,[19] and permanent or sudden damage to the spinal cord rarely occurs without previous neurological symptoms.[20] Annual health screening to check for signs and symptoms of cervical myelopathy using targeted history and physical examination are recommended instead of routine cervical spine x-rays in asymptomatic people with Down syndrome.[4] Prevalence estimates of scoliosis rise from 2% in children[18] to 7% in adolescents and young adults,[17] and increase after thoracotomy for the treatment of congenital heart disease.[21] The risk of major complications after surgical correction of scoliosis is greater among those with Down syndrome than those with idiopathic scoliosis,[22] likely due to more concurrent comorbidities in those with Down syndrome. Prevalence estimates for hip and patellar instability among children with Down syndrome are 1 to 7% and 1 to 4%, respectively. These conditions are usually due to bony anomalies[23,24] and can interfere with walking. Young people with Down syndrome have a high incidence of foot deformities, such as flat feet (76%),[25] and many complain of foot problems that interfere with daily life.[17] Recent research shows that children with Down syndrome have shorter and wider feet with greater girth,[26] which can make shoe fitting problematic.

The endocrine system is adversely impacted by Down syndrome, with increased incidence of osteoporosis, thyroid disease, diabetes and obesity. Six studies (n = 796),[4] rated as poor quality by recent clinical guidelines, have reported wide-ranging prevalence estimates for osteoporosis (1 to 45%) among adults with Down syndrome. Higher rates of osteoporosis in this cohort are likely related to lower bone mineral density, early menopause, thyroid disease, low physical activity and muscle weakness. However, there is some evidence that triplication of certain genes on chromosome 21 itself confers a risk.[15] Prevalence estimates for diabetes are also higher among adults with Down syndrome compared with the general population across all age groups: 3.5% versus 0.7% for young adults and 5.5% versus 2.7% for adults aged $\geq$ 30 years.[27] The prevalence of hypothyroidism is high (27% across 19 cohort and case-control studies),[28] placing people with Down syndrome at higher risk of depression.[29] Indeed, population-based data indicate that about one-third of young people with Down syndrome have a mental health condition[17] such as anxiety (22%) or depression (11%). Being overweight and obese is another major problem in adolescents (61%)[30] and adults (72%)[31] with Down syndrome. These rates of mental health conditions and obesity are substantially higher than in the general population. Other common co-occurring impairments among people with Down syndrome are vision impairment, hearing impairment, speech and language disabilities and behavioural conditions.[4]

Physiotherapy management of Down syndrome

A physiotherapist's role when working with a person with Down syndrome depends on life-stage and usually relates to facilitating physical activity. Depending on individual presentation, early in life the focus is on optimising motor skills and minimising development of abnormal compensatory movement patterns. During adolescence and young adulthood, the focus is on maximising physical and mental health. In adulthood, the focus is on maintaining function, slowing physical deterioration due to early ageing and delaying the onset of Alzheimer's disease.

Early intervention

Typically, infants with Down syndrome learn to walk but are delayed in attaining this milestone. The probability that a child with Down syndrome will walk by 24 months is 40%, by 30 months it is 74% and by 36 months it is 92%.[32] Delayed and abnormal motor development can include reduced movement, especially against gravity; an inability to initiate weight shift; ineffective postural control; the tendency to become stuck in a position; and difficulty developing fine motor skills. In many countries, infants with Down syndrome would expect to receive early intervention support from a physiotherapist. Despite this, six trials (n = 144) supporting evidence-based early intervention practice by physiotherapists have been published; these trials investigated parent-delivered treadmill training and massage therapy.

Parent-delivered treadmill training

Treadmill training aims to promote earlier independent walking among infants with Down syndrome and the development of a more typical walking pattern. Achieving the fundamental skill of walking is desirable, as it provides opportunities to interact with the environment, facilitating motor, social and cognitive development. Three trials (n = 77),[33–42] completed by one research group, found immediate and longer-term benefits for infants with Down syndrome from home-based, parent-delivered treadmill training in terms of developmental milestone attainment, movement efficacy and physical activity levels.

An initial trial[39] (n = 30) found that infants with Down syndrome who commenced treadmill training in addition to their usual care when able to sit independently at around 10 months walked on average 3 months earlier than those who received usual care only (MD 101 days, 95% CI 18 to 184). A subsequent trial (n = 30), reported across seven articles,[33–35,38,40–42] found that infants with Down syndrome completing high-intensity treadmill training, incorporating progression via belt speed, duration and resistance, also achieved motor milestones earlier,[38] displayed more typical walking patterns,[34] more advanced maturation of joint kinematics,[41] earlier adoption of mature strategies to walk over obstacles[42] and spent more time in higher-intensity physical activity[33] than those receiving lower-intensity training. A third trial (n = 17)[36,37] reported that supramalleolar orthoses may have a detrimental effect on gross motor skills development of infants with Down syndrome. Although the effect on time to onset of walking was unclear, the infants who had worn orthotics in addition to treadmill training, from the time they could pull themselves to standing at around 20 months, had lower gross motor function measure (GMFM) total scores and lower standing and walking scores (D subscale) and running and jumping scores (E subscale) 1 month after walking onset[37] compared with those who did not wear orthotics. The effect on the amount of hand support used by infants when standing upright, as a proxy for perceived stability, was unclear.[36] Therefore, orthotics should not be prescribed for infants with Down syndrome prior to the onset of walking. Future studies are needed to determine if orthotics confer a beneficial or detrimental effect on young children with Down syndrome when prescribed after the onset of walking.

Despite the favourable evidence, a recent US-based survey of current practice[43] found that only 6.5% of physiotherapists implemented treadmill training, with almost a third indicating that this was because of the requirement for specialist equipment (a customised treadmill operating at 0.2 m/s). This intervention also requires substantial parental effort, time commitment and training, and ongoing therapist support. While some families may like the program structure, knowing what to do, how to do it and for how long, it may be impractical for others implementing this training at home for 8 minutes a day, 5 days per week for approximately 10 months. Indications of difficulty adhering to the intended training protocol have been reported;[37,40] however, data on how families felt about the intervention are unavailable.

Massage therapy

Massage therapy is not typically prescribed for children with developmental motor disorders, as it is a passive intervention requiring minimal physical demand from the recipient.[44] However, there is some evidence that massage therapy can support developmental growth in preterm infants,[45] and early intervention treatments for children at risk of, or with, developmental motor disorders

often incorporate sensory elements such as tactile stimulation.[46] Three trials[44,47,48] (n = 67) have reported positive short-term effects on development (global, motor, visual-motor, language, social) in favour of massage therapy as an adjunct to early intervention for infants aged 4 to 8 months[47] and young children (mean age 2 years) with Down syndrome.[44,48] Massage therapy was delivered in two trials[47,48] by trained staff weekly and at home by (trained) parents daily for 10 to 15 minutes for 1 month[47] or 5 months,[48] and in one trial exclusively by a massage therapist for 30 minutes, twice a week for 2 months.[44] Only the latter trial[44] controlled for attention to account for the increase in contact, communication and dedicated time spent with the infant with Down syndrome.

Summary of trials relating to early intervention

Early developmental intervention is frequently used by physiotherapists to improve overall functional outcomes for infants at risk of developmental delay and is supported by growing evidence. However, most early intervention trials systematically exclude infants with chromosomal conditions, intellectual disability and/or congenital heart defects. As shown, the evidence about early intervention specifically for infants with Down syndrome is sparse, but (with the caveat that these trials lack methodological rigour) they support parent-delivered interventions with a primary focus (repetition of movement or sensory stimulation) and daily application to promote earlier developmental milestone attainment.

Task-specific training interventions

The gap in gross motor skills abilities between children with and without Down syndrome widens with age.[49] Task-specific training involves massed practice of participant-relevant, context-specific tasks, where the intervention focuses on the skills needed for a task.[50] The effect of task-specific training on gross motor abilities among children with Down syndrome has been investigated in two trials[49,51] (n = 73); both showed benefits when implemented during early adolescence. A 5-day program for learning to ride a two-wheel bicycle,[49] in a summer camp setting and comprising intensive individualised instruction for 75 minutes per day, enabled 19 of 36 (56%) participants (mean age 12 years) to achieve independent cycling over 9 m. Participants commenced training on adapted bicycles and progressed to their own standard two-wheel bicycle by the last day of the program. Compared to a wait-list control group, at 12 months those who completed the program spent less time sedentary, spent more time in moderate to vigorous physical activity and had lower subcutaneous fat.[49] Similarly, nine 45-minute sessions of throwing instruction over 3 weeks improved throwing accuracy, but not coordination, compared with everyday activities in adolescents with Down syndrome (mean age 13 years).[51]

Summary of trials relating to task-specific training

Most children with Down syndrome eventually learn a basic repertoire of motor skills[49] and continue to develop motor proficiency into adolescence.[52] Although evidence-based motor interventions involving task specificity are frequently applied by physiotherapists in adult neurological rehabilitation, the emphasis on motor development in clinical programs for children and adolescents with Down syndrome usually declines once they can walk. Based on two trials, task-specific training appears beneficial for children and adolescents with Down syndrome to learn and develop proficiency in motor skills at doses (6.25 to 6.75 hours) lower than children with cerebral palsy require to achieve upper limb individual goals (14 to 25 hours) or general function goals (30 to 40 hours).[53] Continued focus by clinicians on motor skills beyond walking is especially important for those with Down syndrome, given the consequences for their participation in education and recreational settings, but also because motor ability better predicts functional limitations in this population than cognitive performance.[54]

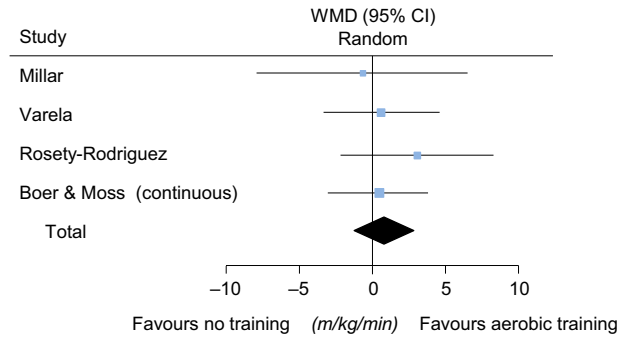

Figure 1. Mean difference (95% CI) in effect of continuous aerobic exercise on relative VO_2peak (ml/kg/min), estimated by pooling data from four studies (n = 78). WMD = weighted mean difference.

Exercise

Aerobic training

People with Down syndrome have very low cardiorespiratory fitness (relative VO_2peak); the average relative VO_2peak of adolescents and young adults with Down syndrome is equivalent to that of a 60-year-old with heart disease.[55] Low cardiorespiratory fitness negatively impacts participation in daily and recreational activities of people with Down syndrome.[56] It is also likely associated with the high rates of secondary health conditions in people with Down syndrome (eg, stroke, cancer), given the strong associations between relative VO_2peak and chronic disease in the general population.[57,58] Aerobic training (including walking, swimming, cycling, rowing and exergaming) increases relative VO_2peak in the general population when implemented at sufficient intensity, frequency and time.[59] It is the exercise intervention most studied in Down syndrome, with 20 trials[60–83] investigating outcomes related to cardiovascular fitness, body size, functional activities, low-grade inflammation and cognition. There is substantial heterogeneity within these trials in terms of participant age (range 4 to 63 years), program duration (6 to 36 weeks) and training intensity (low to high intensity) but all trials incorporated supervision in the intervention design.

A Cochrane review,[84] published in 2010, was inconclusive about the effects of aerobic training on cardiovascular fitness outcomes for adults with Down syndrome. The addition of two subsequent trials[62,66] of continuous aerobic training to their forest plots shows similar inconclusive findings for relative VO_2peak (Figure 1) and pulmonary ventilation, but there was a between-group difference for maximum test time (time to exhaustion) in favour of continuous aerobic training compared with no exercise, based on data from two trials[62,67] (Table 1); for a more detailed forest plot, see Figure 2 on the eAddenda. A single trial[62] reported a between-group difference in favour of interval training compared with continuous aerobic exercise for relative VO_2peak, pulmonary ventilation and time to exhaustion. When data from five trials that implemented any exercise training (ie, interval or continuous aerobic and/or strengthening training) were combined, between-group differences in favour of exercise were found for relative VO_2peak (Figure 3) and pulmonary ventilation; for more a detailed forest plot, see Figure 4 on the eAddenda. The lower cardiorespiratory fitness of people with Down syndrome may be partially explained by lower muscle quantity and quality.[85] This may explain why programs including aerobic and strengthening exercise have a positive effect on cardiorespiratory fitness, when aerobic training alone have not.

Meta-analyses show that aerobic training has positive effects on physical function (6-minute walk distance, sit-to-stand test, Timed Up and Go), waist circumference and body mass index (BMI) compared with no exercise (Table 1). One trial[80] also reported between-group differences in favour of swim training (three times a week for 50 minutes, in groups of up to eight, for 36 weeks) compared with recreational water games (twice a week) on waist circumference, BMI, percentage body fat and some skinfold

Table 1
Summary of findings.

Outcome	Trials (*n*)	Participants (*n*)		MD (95% CI)	Certainty
		Ex	Con		
Continuous aerobic training versus no exercise					
VO_2peak, *(ml/kg/min)*	4	41	37	0.84 (−1.38 to 3.06)	low[a,b]
Pulmonary ventilation, *(l/min)*	3	30	28	6.46 (−0.81 to 13.73)	low[a,b]
Time to exhaustion, *(min)*	2	21	24	2.23 (1.11 to 3.35)	low[a,b]
Body weight, *(kg)*	6	100	104	−1.1 (−2.4 to 0.1)	low[a,b]
Percentage body fat, *(%)*	4	44	46	−1 (−3 to 2)	low[a,b]
Waist circumference, *(cm)*	4	44	46	−2.7 (−5.3 to −0.1)	low[a,b]
Body mass index	5	95	94	−1.8 (−3.3 to −0.3)	very low[a,b,c]
Timed Up and Go, *(s)*	5	60	58	−1.7 (−2.4 to −0.9)	very low[a,b]
Six-minute walk distance, *(m)*	5	52	56	51 (26 to 75)	low[a,b]
Sit-to-stand, *(n)*	3	32	35	1.8 (0.4 to 3.1)	very low[a,b,c]
Hand-grip strength, *(kg)*	2	25	29	1.2 (−2.6 to 4.9)	low[a,b]
Any exercise training versus no exercise					
VO_2peak, *(ml/kg/min)*	5	71	59	2.93 (1.25 to 4.62)	low[a,b]
Pulmonary ventilation, *(l/min)*	3	30	28	9.67 (1.49 to 17.85)	low[a,b]

Con = control, ex = exercise.
[a] Downgraded due to limitations of studies: < 75% of studies were rated at low risk of bias overall.
[b] Downgraded due to imprecision: there were very large confidence intervals with the higher end indicating appreciable benefit and the lower end indicating either a little effect or worse outcome.
[c] Downgraded due to inconsistency: there was statistical heterogeneity (I^2 values > 40%).

measurements (suprailiac, triceps) in 45 adolescents with Down syndrome (mean age 14 years). The Cochrane review[84] reported data from a single trial showing no effect of aerobic training on two anthropometric outcomes (weight, percent body fat) for people with Down syndrome. The addition of five subsequent trials[61,62,75,77,78] on body weight, and three subsequent trials[62,66,77] on percentage body fat to their forest plot shows similar findings (Figures 5 and 6). For more detailed forest plots, see Figures 7 and 8 on the eAddenda. A meta-analysis of two trials[62,77] also found no effect on handgrip strength test when compared with no exercise (Table 1).

More recent trials have investigated the effects of aerobic training on low-grade systematic inflammation and cognitive function. One trial,[64–66] reported across three articles and involving 20 premenopausal women with Down syndrome (mean age 25 years), found that aerobic training had positive effects on low-grade systematic inflammation. Reported between-group differences after 10 weeks of aerobic exercise, three times per week, for 30 to 40 minutes at 55 to 65% peak heart rate indicated reduced levels of pro-inflammatory cytokines (TNF-α, IL6),[65] some acute phase proteins (CRP and fibrinogen but not α1-antitrypsin),[65] and leptin but not adiponectin[64] immediately after training; however, these changes were mostly not retained at follow-up 3 months later. Three small trials have reported mixed results on the effect of aerobic training on cognitive function. One trial (n = 12)[81] found no between-group differences in short-term working memory or selective attention for exergaming compared with regular activities in older adults with Down syndrome (mean age 50 years). Another trial[70,71] (n = 27), reported across two articles, found no differences in cognitive function between groups exercising on 2 days compared with 1 day per week for 12 weeks in adults with Down syndrome (mean age 28 years) in a program delivered by videoconference.[70] A third trial (n = 34)[68,69] involving young adults with Down syndrome (mean age 18 years) reported between-group differences after 8 weeks of training in favour of assisted cycling compared with voluntary cycling for cognitive planning,[68] some executive function outcomes (reaction time and response inhibition) but not others (set shifting and language fluency)[69] and for manual dexterity (which was shown to be strongly associated with cognitive planning ability and verbal working memory in adolescents with Down syndrome).[68]

Five trials have reported effects of aerobic training on balance outcomes in children and adolescents (three trials, n = 165) and adults (two trials, n = 53) with Down syndrome. Two trials,[76,82] involving children with Down syndrome, found positive changes in balance in favour of exergaming compared with 6 weeks of strengthening and walking activities[82] but no difference compared with 24 weeks of sensory integration, neurodevelopmental therapy and perceptual motor activities.[76] A third trial[79] reported between-group differences in overall balance stability in favour of exercising using a 'suspension system' compared with treadmill walking and balance training in young children with Down syndrome (4 to 9 years). In adults with Down syndrome, a between-group difference in favour of 8 weeks of swim training compared with no training for dynamic balance (walking on a balance beam) was reported[61] in one trial but a second trial found no difference when exergaming was compared with usual activities.[77]

The effect of aerobic training on a range of other outcomes has been investigated in at least one trial. Four months of aerobic training plus a calcium supplement had a greater effect on femoral neck bone density than either aerobic training alone, or calcium supplement alone in one trial[73] of 48 children with Down syndrome (mean age 9 years). Compared to no training, small positive changes in muscle strength have been reported after exergaming, swim training and treadmill training in adolescents,[75] adults[61] and older adults[63] with Down syndrome. Ten weeks of Nordic walking for adults with Down syndrome (mean age 31 years) resulted in improvements in spatiotemporal gait parameters compared with no training. One trial[72] (n = 29) in children with Down syndrome (mean age 9 years) found no differences in pulmonary function tests for those who completed rowing training (12 weeks) compared with positioning, breathing exercises, postural drainage and incentive spirometry. Two trials[61,77] reported between-group differences for aerobic capacity (modified shuttle tests) in favour of 8 weeks of exergaming or swim training compared with usual activities or no training. No between-group differences were found for gait speed, physical activity levels, or wellbeing in a feasibility trial[78,86] involving 16 young adults with Down syndrome (mean age 21 years) allocated to 8 weeks of 150 minutes of walking per week compared with sedentary social activities.

Progressive resistance training

Muscle strength in the upper and lower limbs is up to 50% less in people with Down syndrome compared with those without disability,[87,88] negatively impacting the ability to perform everyday activities.[56] Progressive resistance training is regarded as the best way to improve muscle strength in almost all populations, when completed with sufficient intensity and progression of load.[59] Four trials[89–93] (n = 151) have investigated the effects of this type of training in adolescents and young adults with Down syndrome, implementing similar exercises, but with differences in intensity, duration, group size (individual versus small group), and qualification of the supervisor. Three trials[91–93] of moderate-to-vigorous intensity

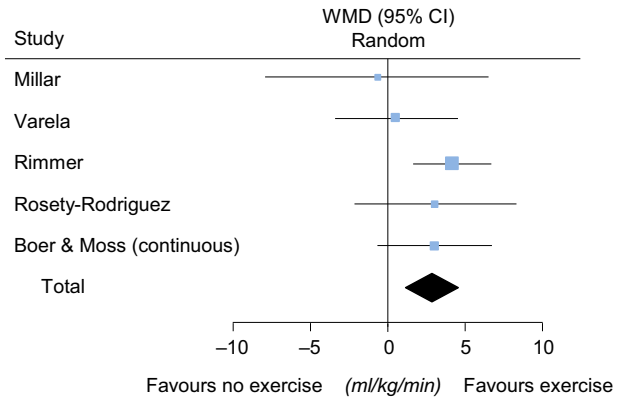

Figure 3. Mean difference (95% CI) in effect of any exercise on relative VO_2peak (ml/kg/min), estimated by pooling data from five studies (n = 130).
WMD = weighted mean difference.

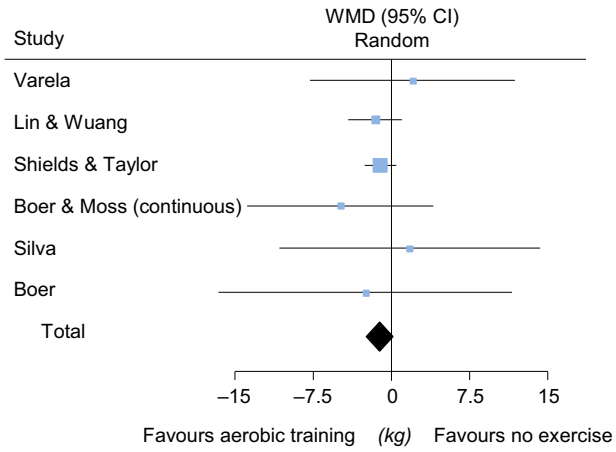

Figure 5. Mean difference (95% CI) in effect of aerobic exercise on body weight (kg), estimated by pooling data from six studies (n = 204).
WMD = weighted mean difference.

training (60 to 80% of 1RM) led to increases in muscle strength and lower limb function (measured using the timed stair climb) but not upper limb function (measured using grocery shelving task) compared with no exercise immediately after a 10-week program.[94] Changes in leg but not arm muscle strength were maintained at the 3-month follow-up.[93] A between-group difference in physical activity levels also favoured progressive resistance training at the 6-month follow-up. Compared to no training, low-intensity to moderate-intensity progressive resistance training (40 to 65% of 8RM) led to a reduction in low-grade systemic inflammation, indicated by between-group differences in leptin, TNF-α and IL-6 levels,[90] and to reduced susceptibility to infection, indicated by between-group differences in IgA levels,[89] in men with Down syndrome.

Progressive resistance training was incorporated into the exercise protocols of an additional four trials[95–98] (n = 136). The largest of these trials,[98] involving 52 adults with Down syndrome (mean age 39 years), found between-group differences in cardiovascular fitness, muscle strength and body weight in favour of 12 weeks of combined training (30 to 45 minutes of continuous aerobic training at 50 to 70% $V0_2$peak, 15 to 20 minutes of progressive resistance training at 70% of 1RM; 3 days per week) compared with no exercise. Two trials[95,96] involving adolescents with Down syndrome reported improvement in leg muscle strength and balance after either 6 weeks of a combined low-intensity to moderate-intensity progressive resistance and balance training compared with usual activity or 12 weeks of lower limb isokinetic training and balance/isotonic strengthening program compared with a balance/isotonic strengthening program only. One trial[97] found that a 12-week program of positioning, breathing exercises and incentive spirometry in 30 children with Down syndrome (mean age 12 years) had positive effects on pulmonary function (forced expiratory volume in 1 second and maximum voluntary ventilation, but not for forced vital capacity and peak expiratory flow rate) compared with a low-intensity lower limb strengthening program.

Combined aerobic and non-progressive strengthening exercise programs

People with Down syndrome have low bone mineral density, which confers a higher risk of osteoporosis in adulthood.[15] Exercise is important for bone formation during childhood and to maintain bone mass in adulthood, as a mechanical stimulus to encourage bone modelling and re-modelling.[99] Three trials[100–103] (n = 100) have studied the effects of 'conditioning' exercise programs (comprising non-progressive strengthening and aerobic training two or three times weekly for 21 to 52 weeks) on bone or muscle mass compared with no exercise in adolescents and young adults with Down syndrome. One trial[102] reported between-group differences for total lean mass and lower limb lean mass in favour of conditioning exercise. No effect on bone mineral content[100,103] or bone mineral density[100] was reported in two trials implementing a 6-month program, but a larger trial[101] implementing a 12-month program reported positive effects in favour of exercise on lumbar spine and hip bone mineral content, and in lumbar spine bone mineral density. This trial[101] also reported improvements in physical fitness in favour of conditioning exercise but no between-group differences in physical activity at 12 months.

Inspiratory muscle training

Respiratory disorders are a common cause of illness and death in children and adults with Down syndrome.[6] Upper, lower and general respiratory tract conditions and infections account for 40% of all hospital admissions in children with Down syndrome.[14] Those with congenital heart disease are at an even higher risk of hospitalisation for respiratory infections than those without.[104] Inspiratory muscle training[105] and incentive spirometry[106] are two interventions targeting pulmonary function to have been investigated in trials involving children with Down syndrome (n = 50). Positive effects on pulmonary function and respiratory muscle strength were reported in one trial[105] involving 16 children with Down syndrome (aged 11 years), half of whom trained 5 days per week for 4 weeks with an inspiratory muscle training device set at 40% maximal inspiratory pressure compared with a control group training at 0% maximal inspiratory pressure. However, the addition of incentive spirometry to an oromotor exercise program had no effect on either pulmonary or oromotor function in a trial[106] of 34 children with Down syndrome (mean age 8 years). One trial[83] investigating respiratory aspects of speech production reported a between-group difference in favour of swim training (12 weeks, three times a week, for 60 minutes) for maximum phonation duration, but not initiation volume or expired mean airflow, in adolescents with Down syndrome (n = 28) compared with no training.

Balance training

Limitations to balance and postural control among children and adolescents with Down syndrome are well documented[107] and show the slowest development longitudinally.[52] The primary impairment in the postural control system is reduced muscle tone. Related secondary issues are insufficiency of muscular co-contractions, insufficiency of balance reactions, reduced proprioception and hypermobility. As a result, children with Down syndrome experience problems in achieving and maintaining posture and movement, and inadequate development of their motor abilities.[108] Six trials[60,109–113] (n = 187) have investigated the effect of exercise on balance in children and adolescents with Down syndrome. In three trials,[60,109,110] (n = 91) core stability exercise training for 8 weeks was found to have beneficial effects on static balance compared with either no training[110] or in addition to strength, balance and postural control exercises[60,109] in children with Down syndrome (mean ages 4 and 9 years). One of these trials[60] also reported between-group differences for functional balance (Berg balance scale). Between-group differences were also reported in static and dynamic balance after 6 weeks

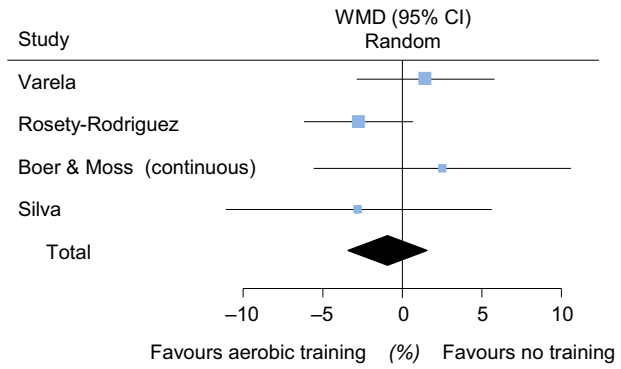

Figure 6. Mean difference (95% CI) in effect of aerobic exercise on percentage body fat (%), estimated by pooling data from four studies (n = 90).
WMD = weighted mean difference.

of strengthening and balance exercise compared with strengthening and aerobic exercise in young children with Down syndrome (mean age 4 years).[113] However, another trial[112] found that 6 weeks of vestibular stimulation activities had a superior effect on functional balance compared with strengthening and balance exercise in children with Down syndrome aged 6 to 9 years. The only trial[111] involving adolescents with Down syndrome (mean age 17 years) found no between-group difference in static balance between those who completed balance exercises for 45 minutes, twice a week, for 12 weeks, compared with no training. A systematic review[107] of 11 randomised and non-randomised clinical trials reached similar conclusions.

Summary of trials relating to exercise

Exercise (aerobic training, progressive resistance training, combined programs, balance training) appears to have similar effects on people with Down syndrome as the general population. Provided that physiotherapists implement exercise in accordance with the recommended guidelines (ie, sufficient dose and intensity), it can improve cardiovascular fitness, muscle strength and reduce activity limitations. Uncertainty remains about the specific role of exercise in addressing the issue of cognitive decline in people with Down syndrome and, more generally, the long-term benefits of exercise on the prevention of chronic diseases, particularly those associated with low-grade inflammation.

Health education and behaviour change interventions

High levels of obesity and low levels of physical activity are key issues throughout life for people with Down syndrome. Health education and behavioural change interventions play an important role in addressing these problems in the general population. However, only two trials[114,115] (n = 74) have investigated the benefits of these interventions for adults with Down syndrome. Compared with no intervention, a 12-week health promotion program, comprising 1 hour of exercise and 1 hour of health education delivered three times per week, improved attitudes towards exercise and psychological wellbeing, but not community integration or depression, immediately after the intervention among 53 adults with Down syndrome (mean age 40 years).[115] The second trial[114] involving 21 participants with BMI $\geq$ 85th percentile (mean age 20 years) reported between-group differences in body weight (MD −3.2 kg, 95% CI −1 to −5.5 kg) sustained at 1 year (MD −3.6 kg, 95% CI −1.4 to −5.9 kg) in favour of parent training in behavioural strategies (diet and activity monitoring, modification of stimulus control conditions, goal setting and positive reinforcement) in addition to a 6-month nutrition and activity education program (16 sessions of 90-minutes duration each). Between-group differences in favour of the experimental group were also reported for moderate to vigorous physical activity levels immediately post intervention (25 minutes, 95% CI 6 to 43 minutes) but not at 1 year (15 minutes, 95% CI −3 to 34 minutes).

Summary of trials relating to health education and behaviour change interventions

Healthy eating and physical activity are complex health behaviours impacted by capability, motivation and opportunity. Having an intellectual disability and limitations in literacy further impact these health behaviours. Based on two trials, health education and behaviour change interventions, which physiotherapists could implement as part of a multidisciplinary team, have benefits for adults with Down syndrome in improving attitudes towards exercise, participation in physical activity and weight loss. Indeed, the level of weight loss achieved with a group-based intervention (24 hours total duration per four to five participants) delivered by a multidisciplinary team (dietitian and therapeutic recreation specialist) was commensurate with that achieved by an individual intervention (3.5 hours total duration) delivered by a primary care practitioner to members of the general population.

Whole-body vibration

Whole-body vibration training exposes the entire body to mechanical vibrations as an individual stands (static) on a platform that oscillates at a particular frequency and amplitude.[116] Based on piezoelectric theory, the interaction of the mechanical vibrations with the structures of the body stimulates bone formation.[117] Two trials[95,118] of whole-body vibration implemented the same protocol of standing in a squat position on a vertical platform for 15 to 20 minutes, three times a week, for 6 months, while a third[119] implemented a shorter 3-month program. Compared with either no training[118,120,121] or as an adjunct to exercise,[95,119] these trials (n = 90) found short-term positive effects on static standing balance in children and adolescents with Down syndrome,[118] on lower limb muscle strength in children with Down syndrome[95,119] and subtotal bone mineral density (ie, total body except the head) and subtotal bone mineral content in adolescents with Down syndrome.[121] No short-terms effects were found on either body fat in children[119] or adolescents[120] or on lean body mass in adolescents.[120] The longer-term effects of whole-body vibration training have not been tested.

Summary of trials relating to whole-body vibration

Although the primary aim of applying whole-body vibration is to stimulate bone formation, only one trial, with methodological limitations, found positive between-group changes in subtotal bone mineral content (3%) and bone mineral density (1.6%) for this passive intervention after 20 weeks. Further, these effects are lower than those found for an (active) exercise intervention, reported from a similar-sized trial with similar methodological limitations, albeit over a longer duration (1 year). Given the additional benefits of exercise on muscle mass and physical fitness, it seems prudent for physiotherapists to choose to implement exercise interventions over whole-body vibration.

Future directions for research and practice

A recent consensus initiative involving invited scientific experts identified research gaps relating to almost every aspect of Down syndrome (cognition, behaviour, communication, sleep, the various body systems and community engagement), including general research needs (research training, research inclusion, open access data and robust trial designs).[122] From a physiotherapy perspective, the most pressing health concern that people with Down syndrome face is their ultra-high risk of cognitive decline with an onset in their early 40s. Only recently have trials, albeit with methodological limitations, investigated the effect of exercise on cognitive function in people with Down syndrome; although evidence from animal[123,124] and longitudinal studies[125] suggests that regular, long-term, moderate-intensity to high-intensity exercise has the potential to reduce their risk of cognitive decline. Rigorous trials are urgently needed to determine if exercise is effective in maintaining cognitive function and delaying the onset of dementia in adults with Down syndrome.[125] As the meta-analyses presented as part of this review show,

there is preliminary evidence that exercise has positive short-term effects on physical function and may have positive short-term effects on cognitive function. Therefore, new trials of long-term exercise interventions are urgently needed to better understand if exercise is effective and cost-effective in reducing the ultra-high risk of cognitive decline in people with Down syndrome and, if effective, whether a dose-response relationship exists. Aligned with this is the need for studies to understand how best to support the long-term implementation of exercise in clinical and community practice, given the needs of many people with Down syndrome for supervision to facilitate exercise, particularly at higher intensities.

A second area of need, within both research and practice, is the effect of interventions implemented by physiotherapists on participation outcomes. As shown, most research has focused on changes in body structure (eg, weight, waist circumference and percentage body fat), body function (eg, muscle strength, cardiovascular fitness and balance) and activities (eg, 6-minute walk distance and sit-to-stand). What is missing are data related to participation: involvement in life situations, describing attendance (being there) and involvement (experience of participation). Participation is arguably the most important outcome for people with Down syndrome, and physiotherapy research and practice need to adapt to better reflect this.

eAddenda: Figures 2, 4, 7 and 8 can be found online at https://doi.org/10.1016/j.jphys.2021.08.016.

Ethics approval: Nil.

Competing interests: Nil.

Source(s) of support: Nil.

Acknowledgements: The author thanks Natalie Pearse, Senior Library Research Advisor at La Trobe University, for her assistance in completing the database searches that supported this review.

Provenance: Invited. Peer reviewed.

Correspondence: Nora Shields, Department of Physiotherapy, Podiatry and Prosthetics and Orthotics, La Trobe University, Melbourne, Australia. Email: n.shields@latrobe.edu.au

References

1. Carfì A, Brandi V, Zampino G, Mari D, Onder G. Care of adults with Down syndrome: gaps and needs. *Eur J Intern Med*. 2015;26:375–376.
2. Bittles A, Glasson E. Clinical, social, and ethical implications of changing life expectancy in Down syndrome. *Dev Med Child Neurol*. 2004;46:282–286.
3. Glasson E, Dye D, Bittles AH. The triple challenges associated with age-related comorbidities in Down syndrome. *J Intellect Disabil Res*. 2014;58:393–398.
4. Tsou AY, Bulova P, Capone G, Chicoine B, Gelaro B, Harville TO, et al. Medical care of adults with Down syndrome: a clinical guideline. *JAMA*. 2020;324:1543–1556.
5. Ruiz-González L, Lucena-Antón D, Salazar A, Martín-Valero R, Moral-Munoz J. Physical therapy in Down syndrome: systematic review and meta-analysis. *J Intellect Disabil Res*. 2019;63:1041–1067.
6. Bull MJ. Down syndrome. *N Engl J Med*. 2020;382:2344–2352.
7. National Disability Insurance Agency. *NDIS Quarterly Report to disability ministers 31 March 2021*. 2021. Canberra.
8. Presson AP, Partyka G, Jensen KM, Devine OJ, Rasmussen SA, McCabe LL, et al. Current estimate of Down syndrome population prevalence in the United States. *J Pediatr*. 2013;163:1163–1168.
9. McCarron M, McCallion P, Reilly E, Mulryan N. A prospective 14-year longitudinal follow-up of dementia in persons with Down syndrome. *J Intellect Disabil Res*. 2014;58:61–70.
10. Santoro SL, Steffensen EH. Congenital heart disease in Down syndrome–a review of temporal changes. *J Congenit Cardiol*. 2021;5:1–14.
11. Roizen N, Patterson D. Down's syndrome. *Lancet*. 2003;361:1281–1289.
12. Hilgenkamp TI, Wee SO, Schroeder EC, Baynard T, Fernhall B. Peripheral blood flow regulation in response to sympathetic stimulation in individuals with Down syndrome. *Artery Res*. 2018;24:16–21.
13. Sobey CG, Judkins CP, Sundararajan V, Phan TG, Drummond GR, Srikanth VK. Risk of major cardiovascular events in people with Down syndrome. *PLoS One*. 2015;10:e0137093.
14. Fitzgerald P, Leonard H, Pikora TJ, Bourke J, Hammond G. Hospital admissions in children with Down syndrome: experience of a population-based cohort followed from birth. *PLoS One*. 2013;8:e70401.
15. Torr J, Strydom A, Patti P, Jokinen N. Aging in Down syndrome: morbidity and mortality. *J Policy Pract Intellect Disabil*. 2010;7:70–81.
16. Lal C, White DR, Joseph JE, van Bakergem K, LaRosa A. Sleep-disordered breathing in Down syndrome. *Chest*. 2015;147:570–579.
17. Pikora TJ, Bourke J, Bathgate K, Foley K-R, Lennox N, Leonard H. Health conditions and their impact among adolescents and young adults with Down syndrome. *PLoS One*. 2014;9:e96868.
18. Thomas K, Bourke J, Girdler S, Bebbington A, Jacoby P, Leonard H. Variation over time in medical conditions and health service utilization of children with Down syndrome. *J Pediatr*. 2011;158:194–200.e1.
19. Tomlinson C, Campbell A, Hurley A, Fenton E, Heron N. Sport preparticipation screening for asymptomatic atlantoaxial instability in patients with Down syndrome. *Clin J Sport Med*. 2020;30:293–295.
20. Lagan N, Huggard D, Mc Grane F, Leahy TR, Franklin O, Roche E, et al. Multiorgan involvement and management in children with Down syndrome. *Acta Paediatr*. 2020;109:1096–1111.
21. Milbrandt TA, Johnston CE. Down syndrome and scoliosis: a review of a 50-year experience at one institution. *Spine*. 2005;30:2051–2055.
22. Chung AS, Renfree S, Lockwood DB, Karlen J, Belthur M. Syndromic scoliosis: national trends in surgical management and inpatient hospital outcomes: a 12-year analysis. *Spine*. 2019;44:1564–1570.
23. Maranho D, Fuchs K, Kim Y-J, Novais EN. Hip instability in patients with Down syndrome. *J Am Acad Orthop Surg*. 2018;26:455–462.
24. Dugdale TW, Renshaw T. Instability of the patellofemoral joint in Down syndrome. *J Bone Joint Surg Am*. 1986;68:405–413.
25. Lim PQ, Shields N, Nikolopoulos N, Barrett JT, Evans AM, Taylor NF, et al. The association of foot structure and footwear fit with disability in children and adolescents with Down syndrome. *J Foot Ankle Res*. 2015;8:1–10.
26. Hassan NM, Buldt AK, Shields N, Landorf KB, Menz HB, Munteanu SE. Differences in foot dimensions between children and adolescents with and without Down syndrome. *Disabil Rehabil*. 2021:1–8.
27. Alexander M, Petri H, Ding Y, Wandel C, Khwaja O, Foskett N. Morbidity and medication in a large population of individuals with Down syndrome compared to the general population. *Dev Med Child Neurol*. 2016;58:246–254.
28. Capone GT, Chicoine B, Bulova P, Stephens M, Hart S, Crissman B, et al. Co-occurring medical conditions in adults with Down syndrome: a systematic review toward the development of health care guidelines. *Am J Med Genet A*. 2018;176:116–133.
29. Walker J, Dosen A, Buitelaar J, Janzing J. Depression in Down syndrome: a review of the literature. *Res Dev Disabil*. 2011;32:1432–1440.
30. Maïano C, Hue O, Morin AJ, Moullec G. Prevalence of overweight and obesity among children and adolescents with intellectual disabilities: a systematic review and meta-analysis. *Obes Rev*. 2016;17:599–611.
31. Stancliffe R, Lakin K, Larson S, Engler J, Bershadsky J, Taub S, et al. Overweight and obesity among adults with intellectual disabilities who use services in 20 US states. *Am J Intellect Dev Disabil*. 2011;116:401–418.
32. Palisano RJ, Walter SD, Russell DJ, Rosenbaum PL, Gémus M, Galuppi BE, et al. Gross motor function of children with Down syndrome: creation of motor growth curves. *Arch Phys Med Rehabil*. 2001;82:494–500.
33. Angulo-Barroso R, Burghardt AR, Lloyd M, Ulrich DA. Physical activity in infants with Down syndrome receiving a treadmill intervention. *Infant Behav Dev*. 2008;31:255–269.
34. Angulo-Barroso RM, Wu J, Ulrich DA. Long-term effect of different treadmill interventions on gait development in new walkers with Down syndrome. *Gait Posture*. 2008;27:231–238.
35. Lloyd M, Burghardt A, Ulrich DA, Angulo-Barroso R. Physical activity and walking onset in infants with Down syndrome. *Adapt Phys Active Q*. 2010;27:1–16.
36. Looper J, Ulrich D. Does orthotic use affect upper extremity support during upright play in infants with Down syndrome? *Pediatr Phys Ther*. 2011;23:70–77.
37. 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;90:382–390.
38. 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;88:114–122.
39. Ulrich DA, Ulrich BD, Angulo-Kinzler RM, Yun J. Treadmill training of infants with Down syndrome: evidence-based developmental outcomes. *Pediatrics*. 2001;108:E84.
40. 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;49:839–845.
41. Wu J, Looper J, Ulrich DA, Angulo-Barroso RM. Effects of various treadmill interventions on the development of joint kinematics in infants with Down syndrome. *Phys Ther*. 2010;90:1265–1276.
42. Wu J, Ulrich DA, Looper J, Tiernan CW, Angulo-Barroso RM. Strategy adoption and locomotor adjustment in obstacle clearance of newly walking toddlers with Down syndrome after different treadmill interventions. *Exp Brain Res*. 2008;186:261–272.
43. Johnson R, Looper J, Fiss A. Current Trends in pediatric physical therapy practice for children with Down syndrome. *Pediatr Phys Ther*. 2021;33:74–81.
44. 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.
45. Field TM, Schanberg SM, Scafidi F, Bauer CR, Vega-Lahr N, Garcia R, et al. Tactile/kinesthetic stimulation effects on preterm neonates. *Pediatrics*. 1986;77:654–658.
46. Blauw-Hospers CH, Hadders-Algra M. A systematic review of the effects of early intervention on motor development. *Dev Med Child Neurol*. 2005;47:421–432.
47. Pinero-Pinto E, Benítez-Lugo M-L, Chillón-Martínez R, Rebollo-Salas M, Bellido-Fernández L-M, Jiménez-Rejano J-J. Effects of massage therapy on the development of babies born with Down syndrome. *Evid Based Complement Altern Med*. 2020. Article ID 4912625.
48. Silva LM, Schalock M, Garberg J, Smith CL. Qigong massage for motor skills in young children with cerebral palsy and Down syndrome. *Am J Occup Ther*. 2012;66:348–355.
49. 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;91:1463–1477.
50. Hubbard IJ, Parsons MW, Neilson C, Carey LM. Task-specific training: evidence for and translation to clinical practice. *Occup Ther Int*. 2009;16:175–189.

51. Noghondar NV, Sohrabi M, Taheri HR, Kobravi HR, Khodashenas E. The effect of training on variability and accuracy of overhand throwing in children with Down syndrome. *Int J Dev Disabil*. 2019. https://doi.org/10.1080/20473869.2019.1574388.
52. Jobling A. Motor development in school-aged children with Down syndrome: a longitudinal perspective. *Int J Disabil Dev Educ*. 1998;45:283–293.
53. Jackman M, Lannin N, Galea C, Sakzewski L, Miller L, Novak I. What is the threshold dose of upper limb training for children with cerebral palsy to improve function? A systematic review. *Aust Occup Ther J*. 2020;67:269–280.
54. Volman MJ, Visser JJ, Lensvelt-Mulders GJ. Functional status in 5 to 7-year-old children with Down syndrome in relation to motor ability and performance mental ability. *Disabil Rehabil*. 2007;29:25–31.
55. Baynard T, Pitetti KH, Guerra M, Unnithan VB, Fernhall B. Age-related changes in aerobic capacity in individuals with mental retardation: a 20-yr review. *Med Sci Sports Exerc*. 2008;40:1984–1989.
56. Cowley PM, Ploutz-Snyder LL, Baynard T, Heffernan KS, Young JS, Hsu S, et al. The effect of progressive resistance training on leg strength, aerobic capacity and functional tasks of daily living in persons with Down syndrome. *Disabil Rehabil*. 2011;33:2229–2236.
57. Schmid D, Leitzmann MF. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. *Ann Oncol*. 2015;26:272–278.
58. Wang Y, Li F, Cheng Y, Gu L, Xie Z. Cardiorespiratory fitness as a quantitative predictor of the risk of stroke: a dose–response meta-analysis. *J Neurol*. 2020;267:491–501.
59. Liguori G, American College of Sports Medicine. *ACSM's guidelines for exercise testing and prescription*. Philadelphia, USA: Lippincott Williams & Wilkins; 2020.
60. Alsakhawi RS, Elshafey MA. Effect of core stability exercises and treadmill training on balance in children with Down syndrome: randomized controlled trial. *Adv Ther*. 2019;36:2364–2373.
61. Boer PH. The effect of 8 weeks of freestyle swim training on the functional fitness of adults with Down syndrome. *J Intellect Disabil Res*. 2020;64:770–781.
62. Boer P, Moss S. Effect of continuous aerobic vs. interval training on selected anthropometrical, physiological and functional parameters of adults with Down syndrome. *J Intellect Disabil Res*. 2016;60:322–334.
63. 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 Geront A: Biol Sci Med Sci*. 2002;57:M106–M110.
64. Ordonez FJ, Fornieles-Gonzalez G, Camacho A, Rosety MA, Rosety I, Diaz AJ, et al. Anti-inflammatory effect of exercise, via reduced leptin levels, in obese women with Down syndrome. *Int J Sport Nutr Exerc Metab*. 2013;23:239–244.
65. Ordonez FJ, Rosety MA, Camacho A, Rosety I, Diaz AJ, Fornieles G, et al. Aerobic training improved low-grade inflammation in obese women with intellectual disability. *J Intellect Disabil Res*. 2014;58:583–590.
66. Rosety-Rodriguez M, Diaz AJ, Rosety I, Rosety MA, Camacho A, Fornieles G, et al. Exercise reduced inflammation: but for how long after training? *J Intellect Disabil Res*. 2014;58:874–879.
67. Varela AM, Sardinha LB, Pitetti KH. Effects of an aerobic rowing training regimen in young adults with Down syndrome. *Am J Ment Retard*. 2001;106:135–144.
68. Holzapfel SD, Ringenbach SD, Mulvey GM, Sandoval-Menendez AM, Cook MR, Ganger RO, et al. Improvements in manual dexterity relate to improvements in cognitive planning after assisted cycling therapy (ACT) in adolescents with down syndrome. *Res Dev Disabil*. 2015;45-46:261–270.
69. Ringenbach SD, Holzapfel SD, Mulvey GM, Jimenez A, Benson A, Richter M. The effects of assisted cycling therapy (ACT) and voluntary cycling on reaction time and measures of executive function in adolescents with Down syndrome. *J Intellect Disabil Res*. 2016;60:1073–1085.
70. Ptomey LT, Szabo AN, Willis EA, Gorczyca AM, Greene JL, Danon JC, et al. Changes in cognitive function after a 12-week exercise intervention in adults with Down syndrome. *Disabil Health J*. 2018;11:486–490.
71. Ptomey LT, Szabo AN, Willis EA, Greene JL, Danon JC, Washburn RA, et al. Remote exercise for adults with Down syndrome. *Transl J Am Coll Sports Med*. 2018;3:60.
72. El Kafy EM, Helal OF. Effect of rowing on pulmonary functions in children with Down syndrome. *Pediatr Phys Ther*. 2014;26:437–445.
73. Reza SM, Rasool H, Mansour S, Abdollah H. Effects of calcium and training on the development of bone density in children with Down syndrome. *Res Dev Disabil*. 2013;34:4304–4309.
74. Skiba A, Marchewka J, Skiba A, Podsiadło S, Sulowska I, Chwała W, et al. Evaluation of the effectiveness of Nordic walking training in improving the gait of persons with Down syndrome. *BioMed Res Int*. 2019. Article ID 6353292.
75. Lin HC, Wuang YP. Strength and agility training in adolescents with Down syndrome: a randomized controlled trial. *Res Dev Disabil*. 2012;33:2236–2244.
76. Wuang YP, Chiang CS, Su CY, Wang CC. Effectiveness of virtual reality using Wii gaming technology in children with Down syndrome. *Res Dev Disabil*. 2011;32:312–321.
77. Silva V, Campos C, Sa A, Cavadas M, Pinto J, Simoes P, et al. Wii-based exercise program to improve physical fitness, motor proficiency and functional mobility in adults with Down syndrome. *J Intellect Disabil Res*. 2017;61:755–765.
78. Shields N, Taylor NF. The feasibility of a physical activity program for young adults with Down syndrome: A phase II randomised controlled trial. *J Intellect Dev Disabil*. 2015;40:115–125.
79. El-Meniawy GH, Kamal HM, Elshemy SA. Role of treadmill training versus suspension therapy on balance in children with Down syndrome. *Egypt J Med Hum Genet*. 2012;13:37–43.
80. Suarez-Villadat B, Luna-Oliva L, Acebes C, Villagra A. The effect of swimming program on body composition levels in adolescents with Down syndrome. *Res Dev Disabil*. 2020;102:103643.
81. Perrot A, Maillot P, Le Foulon A, Rebillat A-S. Effect of exergaming on physical fitness, functional mobility, and cognitive functioning in adults with Down syndrome. *Am J Intellect Dev Disabil*. 2021;126:34–44.
82. Rahman SA, Rahman A. Efficacy of virtual reality-based therapy on balance in children with Down syndrome. *World Appl Sci J*. 2010;10:254–261.
83. Casey AF, Emes C. The effects of swim training on respiratory aspects of speech production in adolescents with down syndrome. *Adapt Phys Active Q*. 2011;28:326–341.
84. Andriolo RB, El Dib R, Ramos L, Atallah ÁN, da Silva EM. Aerobic exercise training programmes for improving physical and psychosocial health in adults with Down syndrome. *Cochrane Database Syst Rev*. 2005.
85. Beck V, Baynard T, Lefferts E, Hibner B, Fernhall B, Hilgenkamp TI. Anthropometry does not fully explain low fitness among adults with Down syndrome. *J Intellect Disabil Res*. 2021;65:373–379.
86. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=363104.
87. Croce RV, Pitetti KH, Horvat M, Miller J. Peak torque, average power, and hamstring/quadriceps ratios in nondisabled adults and adults with mental retardation. *Arch Phys Med Rehabil*. 1996;77:369–372.
88. Pitetti KH, Climstein M, Mays MJ, Barrett PJ. Isokinetic arm and leg strength of adults with Down syndrome: a comparative study. *Arch Phys Med Rehabil*. 1992;73:847–850.
89. Fornieles G, Rosety MA, Elosegui S, Rosety JM, Alvero-Cruz JR, Garcia N, et al. Salivary testosterone and immunoglobulin A were increased by resistance training in adults with Down syndrome. *Braz J Med Biol Res*. 2014;47:345–348.
90. Rosety-Rodriguez M, Camacho A, Rosety I, Fornieles G, Rosety MA, Diaz AJ, et al. Resistance circuit training reduced inflammatory cytokines in a cohort of male adults with Down syndrome. *Med Sci Monit*. 2013;19:949–953.
91. 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;56:187–193.
92. 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;89:1215–1220.
93. 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;34:4385–4394.
94. Wentz EE, Looper J, Menear KS, Rohadia D, Shields N. Promoting participation in physical activity in children and adolescents with Down syndrome. *Phys Ther*. 2021;101:pzab032.
95. 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;4:633–643.
96. Gupta S, Rao BK, Kumaran SD. Effect of strength and balance training in children with Down's syndrome: a randomized controlled trial. *Clin Rehabil*. 2011;25:425–432.
97. Hussein ZA. Strength training versus chest physical therapy on pulmonary functions in children with Down syndrome. *Egypt J Med Hum Genet*. 2017;18:35–39.
98. Rimmer JH, Heller T, Wang E, Valerio I. Improvements in physical fitness in adults with Down syndrome. *Am J Ment Retard*. 2004;109:165–174.
99. Specker B, Thiex NW, Sudhagoni RG. Does exercise influence pediatric bone? A systematic review. *Clin Orthop Relat Res*. 2015;473:3658–3672.
100. Dilek G, Öztürk C, Hepgüler S, Özkınay F, Dilek M. The effect of exercise on bone mineral density in patients with Down syndrome. *J Pediatr Res*. 2018;5:1.
101. 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;35:2077–2084.
102. González-Agüero A, Vicente-Rodríguez G, Gómez-Cabello A, Ara I, Moreno LA, Casajús JA. A combined training intervention programme increases lean mass in youths with Down syndrome. *Res Dev Disabil*. 2011;32:2383–2388.
103. González-Agüero A, Vicente-Rodríguez G, Gómez-Cabello A, Ara I, Moreno LA, Casajus JA. A 21-week bone deposition promoting exercise programme increases bone mass in young people with Down syndrome. *Dev Med Child Neurol*. 2012;54:552–556.
104. So S, Urbano R, Hodapp R. Hospitalizations of infants and young children with Down syndrome: evidence from inpatient person-records from a statewide administrative database. *J Intellect Disabil Res*. 2007;51:1030–1038.
105. Vural M, Özdal M, Pancar Z. Effects of inspiratory muscle training on respiratory functions and respiratory muscle strength in Down syndrome: a preliminary study. *Isokinet Exerc Sci*. 2019;27:283–288.
106. Ibrahim AF, Salem EE, Gomaa NE, Abdelazeim FH. The effect of incentive spirometer training on oromotor and pulmonary functions in children with Down's syndrome. *J Taibah Univ Med Sci*. 2019;14:405–411.
107. Maïano C, Hue O, Lepage G, Morin AJS, Tracey D, Moullec G. Do exercise interventions improve balance for children and adolescents with Down syndrome? A systematic review. *Phys Ther*. 2019;99:507–518.
108. Lauteslager P, Vermeer A, Helders P. Disturbances in the motor behaviour of children with Down's syndrome: the need for a theoretical framework. *Physiotherapy*. 1998;84:5–13.
109. Aly SM, Abonour AA. Effect of core stability exercise on postural stability in children with Down syndrome. *Int J Med Res Health Sci*. 2018;5:213–222.
110. Ghaeeni S, Bahari Z, Khazaei AA. Effect of core stability training on static balance of the children with Down syndrome. *Phys Treat*. 2015;5:49–54.
111. Jankowicz-Szymanska A, Mikolajczyk E, Wojtanowski W. The effect of the degree of disability on nutritional status and flat feet in adolescents with Down syndrome. *Res Dev Disabil*. 2013;34:3686–3690.
112. Kamatchi K, Balachandar V, Kaviraja N. Comparative evaluation of weight bearing exercise and vestibular stimulation on balance in children with Down syndrome. *Int J Pharma Bio Sci*. 2018;9:227–234.
113. Rahman SAA, Shaheen A. Efficacy of weight bearing exercises on balance in children with Down syndrome. *Egypt J Neurol Psychiatr Neurosurg*. 2010;47:37–42.
114. Curtin C, Bandini LG, Must A, Gleason J, Lividini K, Phillips S, et al. Parent support

improves weight loss in adolescents and young adults with Down syndrome. *J Pediatr*. 2013;163:1402–1408.
115. Heller T, Hsieh K, Rimmer JH. Attitudinal and psychosocial outcomes of a fitness and health education program on adults with down syndrome. *Am J Ment Retard*. 2004;109:175–185.
116. Bidonde J, Busch AJ, van der Spuy I, Tupper S, Kim SY, Boden C. Whole body vibration exercise training for fibromyalgia. *Cochrane Database Syst Rev*. 2017.
117. Weber-Rajek M, Mieszkowski J, Niespodziński B, Ciechanowska K. Whole-body vibration exercise in postmenopausal osteoporosis. *Menopause Rev*. 2015;14:41.
118. Villarroya MA, Gonzalez-Aguero A, Moros T, Gomez-Trullen E, Casajus JA. Effects of whole body vibration training on balance in adolescents with and without Down syndrome. *Res Dev Disabil*. 2013;34:3057–3065.
119. Emara HA. Effects of whole body vibration on body composition and muscle strength of children with Down syndrome. *Int J Ther Rehabil Res*. 2016;5:1–8.
120. Gonzalez-Aguero A, Matute-Llorente A, Gomez-Cabello A, Casajus JA, Vicente-Rodriguez G. Effects of whole body vibration training on body composition in adolescents with Down syndrome. *Res Dev Disabil*. 2013;34:1426–1433.
121. Matute-Llorente A, Gonzalez-Aguero A, Gomez-Cabello A, Olmedillas H, Vicente-Rodriguez G, Casajus JA. Effect of whole body vibration training on bone mineral density and bone quality in adolescents with Down syndrome: a randomized controlled trial. *Osteoporos Int*. 2015;26:2449–2459.
122. Hendrix JA, Amon A, Abbeduto L, Agiovlasitis S, Alsaied T, Anderson HA, et al. Opportunities, barriers, and recommendations in Down syndrome research. *Transl Sci Rare Dis*. 2020;5:99–129.
123. Kida E, Rabe A, Walus M, Albertini G, Golabek AA. Long-term running alleviates some behavioral and molecular abnormalities in Down syndrome mouse model Ts65Dn. *Exp Neurol*. 2013;240:178–189.
124. Walus M, Kida E, Rabe A, Albertini G, Golabek AA. Widespread cerebellar transcriptome changes in Ts65Dn Down syndrome mouse model after lifelong running. *Behav Brain Res*. 2016;296:35–46.
125. Pape SE, Baksh RA, Startin C, Hamburg S, Hithersay R, Strydom A. The Association between Physical Activity and CAMDEX-DS Changes Prior to the Onset of Alzheimer's Disease in Down Syndrome. *J Clin Med*. 2021;10:1882.