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Review article

Effects of exercise programs on cardiovascular responses in individuals with down syndrome: A systematic review and meta-analysis

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ABSTRACT

The purpose of this study is to conduct a systematic review and *meta*-analysis of exercise interventions designed to improve cardiovascular responses in individuals with DS. A search for relevant articles was conducted on seven electronic databases: PubMed, PEDro, Google Scholar, Scopus, WOS, MEDLINE, and SPORT Discus. An electronic search was conducted on October 15, 2022, without applying any year constraints. The studies were chosen based on a predetermined set of inclusion and exclusion criteria. The methodology of the study was evaluated using the PEDro scale, and data analyses were conducted using the CMA v3 random effects model. In total, 625 articles were reviewed, and data from 10 randomized controlled trials (RCTs) involving DS were used in this *meta*-analysis. The results showed that exercise programs were effective in increasing VO_{2peak} (ml. kg $^{-1}$min^{-1}) (ES: 0.69; 95 % confidence interval [CI], 0.27–1.12; *P*: 0.001), time to exhaustion (ES: 0.83; CI, 0.31–1.35, *P*: 0.001), and VE_{peak} (ES: 0.76; CI, 0.32–1.20; P: 0.001). No changes were found for HR_{peak} (ES: 0.3; CI, −0.02–0.63, *P*: 0.07), VO_{2peak} (ml·min^{-1}) (ES: 0.45; CI, −0.01–0.92; *P*: 0.06), or RER (ES: 0.45; CI, −0.09–0.98, *P*: 0.10). No adverse effects were reported in any of the studies. In this *meta*-analysis and comprehensive review, exercise interventions may improve cardiovascular responses in DS; however, the association wasn't consistent across trials. RCTs with precise intervention criteria, large sample sizes, and long-term follow-up are needed in the future to demonstrate the benefits of exercise on cardiovascular responses in people with DS.

1. Introduction

Down syndrome (DS) is a genetic condition caused by trisomy of chromosome 21, has a worldwide incidence of approximately one in 1000–1100 live births, and is associated with intellectual disability (ID). More than 80 clinical characteristics have been identified in individuals with DS, including congenital cardiac disorders, which affect approximately 40 % of people with DS (S Bahiraei & Daneshmandi, 2022; Lacunza Odriozola, 2022; Mendonca, Pereira, & Fernhall, 2011; Seron et al., 2017).

Overall, individuals with DS tend to exhibit low cardiovascular fitness, as indicated by outcomes such as peak oxygen consumption (VO_{2peak}), peak minute ventilation (VE_{peak}), peak heart rate (HR_{peak}), respiratory exchange ratio (RER), and typically shorter durations in their stress tests. (Pitetti et al., 2013). VO2peak consistently shows lower values in both young people and adults with DS compared to their peers without disabilities (WOD) and those with intellectual disabilities (ID) but without DS (Baynard et al., 2008; Fernhall & Pitetti, 2001). This is accompanied by a faster time to exhaustion and a lower peak work. A study by Eberhard et al. from 1989 showed 15 % lower VO_{2peak} when bicycle ergometer was used compared with age-matched children WOD (Eberhard et al., 1989). In 1990, Fernhall et al. found that adolescents

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with DS had lower $VO2_{peak}$ when compared to adolescents with WOD using a validated treadmill protocol, and they concluded that participants with DS were not less motivated or did not understand the protocol's instructions, which could have affected their results. Following these initial contributions, the literature has consistently demonstrated lower VO_{2peak} values when individuals with DS are compared to individuals WOD and with ID but without DS (Fernhall et al., 1990). Baynard et al. reported that VO_{2peak} (absolute and relative values) is lower in children and adolescents with DS through young adulthood and into middle age, regardless of the comparison group (Baynard et al., 2008). However, In the last two decades, life expectancy for individuals with DS has increased to about 60 years, primarily due to earlier detection of cardiovascular problems and exercise interventions (Hardee & Fetters, 2017; Ruiz-González et al., 2019; Versacci et al., 2018). Cardiovascular disease should be prevented and managed more effectively in DS patients given their increasing lifespan.

Low physical activity is considered one of the most important factors in cardiovascular problems. Maintaining adequate levels of physical activity (PA) is crucial for maintaining general health and preventing chronic diseases in individuals with DS. Exercise has been found to reduce the severity and rate of cardiovascular diseases caused by physical inactivity (Cabeza-Ruiz et al., 2019). As a result, there has been an increased interest in developing and increasing PA that improves the cardiovascular fitness and health of people with DS (Dodd & Shields, 2005). In a review study conducted by Ballenger et al. in 2023, the evidence base shows that aerobic and strength training improves physical fitness variables, including maximum oxygen uptake, maximum heart rate, upper and lower body strength, body weight, and body fat percentage. Sports and play interventions improve functional mobility, performance of work tasks, and sports skills. The researchers concluded that adults with DS can derive health benefits from well-designed physical activity and exercise interventions (Ballenger et al., 2023). Therefore for DS, regular fitness training can be a useful non-pharmacological intervention. Regular exercise can also enhance quality of life and support independence maintenance throughout the lifespan by increasing work capacity and physical performance. Regular exercise training may also improve and maintain cardiovascular health through improvements in the autonomic regulation of the heart (Mendonca, Pereira, & Fernhall, 2013).

All in all, a variety of strategies and interventions have been explored, and they have shown significant improvements in cardiorespiratory fitness of people with DS, including aquatic training, water-based exercises and swimming (Naczk et al., 2021a), aerobic training using Treadmill and Stationary bikes (Seron et al., 2017), water aerobics and mix training (Boer & Moss, 2016) muscular strength and functionality upper and lower extremities (Shields et al., 2013), progressive resistance training (Cowley et al., 2011) and plyometric training (González-Agüero et al., 2014b). Nevertheless, some authors indicate that the ability to increase cardiovascular fitness levels may be limited by physiologic impairments caused by DS, including lower $VO2_{peak}$, HRpeak, RER, and time to exhaustion. On the other hand, some individuals argue that adhering to such programs could lead to notable enhancements in physiological parameters and subsequently boost cardiovascular fitness. This study aims to provide a comprehensive review and provide physicians with evidence about the advantages and risks of cardiovascular exercise programs in people with DS.

2. Methodology

2.1. Search strategy

The protocol for this systematic review was published online at the international Prospective Register of Systematic Review (PROSPERO) on January 15th, 2023 (CRD42023389385). The present study is a systematic review and *meta*-analysis carried out based on the PRISMA checklist, and all relevant articles were extracted using a search strategy. An electronic search was conducted on October 15, 2022, without any year limitation, using the following databases: PubMed, Physiotherapy Evidence Database (PEDro), Google Scholar, Scopus, WOS (Web of Science), MEDLINE, and SPORT Discus.

Three groups of search terms were used to identify the related research in the electronic databases: (group 1) 'Down * syndrome*' OR 'trisomy * 21*' OR 'intellectual* dis*' OR 'mental* retard*' OR 'mongolism *' OR 'intellectual* imp*' OR 'cognitive * imp*' OR 'developmental* dis*'; AND (group 2) cardiovascular responses* OR 'peak minute ventilation*' OR 'respiratory exchange ratio'' OR 'heart rate variability *' OR 'time to exhaustion*' OR peak oxygen consumption * OR '$_{VO2peak}$*' OR 'HR_{peak}*' OR 'RER*' OR 'VE_{peak}*; AND (group 3) intervention* OR physical trainin* OR program* OR aerobic* OR exercis* OR aerobic exercise* OR fitness OR trainin* OR improv* OR enhanc* OR therap*. English-language articles were searched in selected databases. Furthermore, AND was used between each group of keywords, while OR was used between the keywords in each group. The titles, abstracts, and keywords of the studies that were published in the journals and listed in the databases were examined for these combinations.

2.2. Eligibility criteria

The PRISMA criteria were used to guide the design of this systematic review. The following format was used to define the PICOS strategy: (Patients) Participants were DS of any age, gender, race, or ethnicity; (I: intervention) any type of exercise intervention specifically designed to improve cardio-vascular parameters; (C: comparison) at least one experimental group and one control group; (O: outcome) any measure related to cardiovascular responses to exercise programs measured directly or indirectly; (S: study type) randomized controlled trials.

The exclusion criteria were: (1) a full text of the study in English was not available; (2) the data were from reviews, conference proceedings and abstracts, editorials, dissertations, theses, and articles published in non-peer-reviewed journals; (3) the article reported only a literature review, qualitative data, or case reports; (4) the sample included people without DS. The PRISMA diagram is shown in Fig. 1.

2.3. Data extraction and quality assessment of studies

Two reviewers independently assessed the titles and abstracts according to the criteria established earlier (see Table 1): (1) Characteristics study (design, Quality, country) (2) Characteristics of participants (sample size, percentage of males, age range, mean age and intellectual disability level) (3) Type of intervention including type, duration, frequency, session length, instructors (4) Result of the measure.

The Physiotherapy Evidence Database scale was used to rate the studies that were part of this review's methodology. A point is given when a category's condition is satisfied, with the exception of criterion number 1, which is not taken into account when calculating the scale's overall score. The scale does not assess the external validity of the studies nor the effect size of the treatment. Therefore, item 1 (eligibility criteria were specified), although analyzed, is not included in the calculation of the score. This explains why 11 items generate a maximum score of 10 points. As a result, the scale's possible scores vary from 0 to 10, with a higher number denoting greater quality in the study's methodology. Studies that receive scores of 6 or higher are categorized as evidence level 1 (6–8: good; 9–10: outstanding), whereas studies that receive scores of 5 or below are categorized as evidence level 2 (4–5: acceptable; 4: poor) (Ruiz-González et al., 2019) (see Table 1). In the case of conflict between the two researchers, the methodological criteria were reassessed and discussed. Moreover, statistics of the Egger's regression intercept test and visual inspection of the funnel plot were applied to detect possible publication bias.

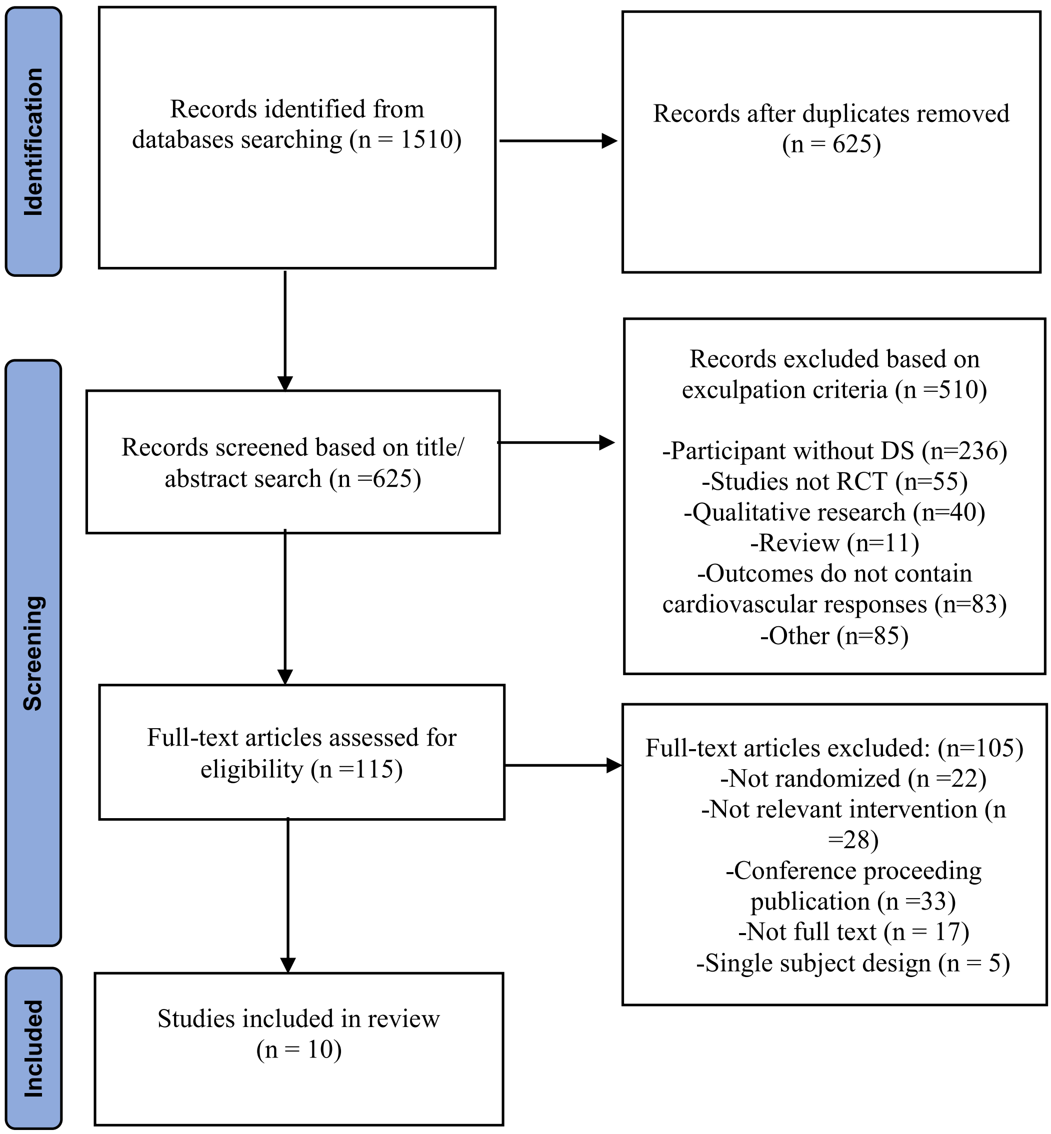


Fig. 1. PRISMA flow diagram for the systematic review and *meta*-analysis.

2.4. Statistics and data synthesis

The quantitative data were pooled using the Comprehensive Meta-Analysis (CMA) software Version 3 (Biostat, Englandwood, NJ, USA) with a random effects model, and presented with 95 % confidence intervals (CIs) for statistical *meta*-analysis. In order to represent ES, Cohen's d, weighted mean differences, heterogeneity, and forest plot were used. To control for small sample bias and prevent overestimation, Cohen's d was automatically changed to standardized mean difference g in the CMA (Borenstein et al., 2009; Littell et al., 2008). To illustrate the degree of study heterogeneity, an I^2 index was used. To further explore potential sources of heterogeneity and evaluate studies that can deviation the analysis using a funnel plot, we did sensitivity analyses by removing the studies with poor technique quality (PEDro scores) and ES (standardized mean difference). The results were presented in a descriptive manner when statistical pooling was not possible.

The summary effect of effect sizes from each outcome variable in the: VO_{2peak},VE_{peak}, HR_{peak}, RER and time to Exhaustion was classified into the following three categories: small (0.2–0.5), medium (0.5–0.8), and large (≥0.8) (Cohen, 2016). I^2 statistics were calculated to assess the heterogeneity among the included studies, and thresholds of 25 %, 50 %, and 75 % were defined as having a low, moderate, and high level of heterogeneity, respectively. An alpha level of 0.05 was defined for the statistical significance of all the tests.

3. Results

3.1. Search results

Fig. 1 shows a flow chart describing the study selection procedure. For the *meta*-analysis, reports from 10 studies (with 294 participants) were eligible. The initial searches yielded 1510 articles, of which 625 were duplicates. After the appropriateness of the article titles and abstracts was determined, 115 full texts were found. Of these, 105 did not meet the criteria for inclusion, thus the remaining 10 articles underwent analysis. The characteristics of the 10 investigations are described in Table 1.

3.2. Description of studies and participants

The final 10 articles were all RCTs. The 10 studies were performed in 7 countries, [USA (n = 3), Portugal (n = 2), Greece (n = 1), Spain (n = 1), South Africa (n = 1), Poland (n = 1), and Brazil (n = 1). The 10 articles described results for 294 participants. The average sample size

Table 1
A Summary of the results of cardiovascular responses of individuals with the DS.

Study (country)	Design	Quality (PEDro scale)	Participants n (%)	Mean Age ± SD (y)	Mean BMI	Severity of Intellectual Disability	Program Details	Training Intensity	Outcomes and Results
(Rimmer et al., 2004) (USA)	RCTs	6	**EG**: 16(53 % F) 14(47 % M) **CG**:13(59 % F) 9(41 % M)	**EG**:38.6 ± 6.2 **CG**:40.6 ± 6.5	34.5	Mild tomoderate	30 min aerobic machine based (e.g., treadmill,stationary bicycle)exercise program,15 min PRE; 3/wk for12wk	50 %–70 % $VO2_{peak}$	**EG:** VO_{2peak} ↑ HR_{peak} ↑ time to Exhaustion ↑ RER*↑
(Varela et al., 2001) (Portugal)	RCTs	6	**EG**: 8(100 % M) **CG**:8(100 % M)	**EG**:22 ± 3.8 **CG**:20.8 ± 2.3	25.4	Mean IQ 38.8	10-min warm-up, 25-min rowing program, 10-min cool down; 3/wk for 16wk	55 %–70 % VO_{2peak}	**TGE:** VO_{2peak}*↑ V_{Epeak}*↑ HR_{peak}*↓ RER*↓ **RGE:** VO_{2peak}*↑ V_{Epeak}*↓ HR_{peak}*↓ RER*↓
(Millar et al., 1993) (USA)	RCTs	4	**EG**: 7(54 % M) 2(15 % F) **CG**: 3(23 % M) 1(8 % F)	**EG**:18.4 ± 2.9 **CG**:17 ± 2.8	27.1	IQ 30–70	10-min warm-up, 30-min brisk walking/ jogging, 10-min cool down program; 3/wkfor 10wk	65 %–75 % max HR	**EG:** VO_{2peak}*↓ V_{Epeak}*↓ HR_{peak}*↓ RER*↑
(Tsimaras et al., 2003) (Greece)	RCTs	5	**EG**: 15(100 % M) **CG**:10(100 % M)	**EG**:24.5 ± 3.9 **CG**:24.7 ± 2.7	28.9	Mild to ModerateIQ 30–70	10-min warm-up, 30 min jog/ walking program; 3/wk for 12wk	65 %–75 % max HR	**EG:** VO_{2peak}↑ HR_{peak}*↑ V_{Epeak} ↑ RER* ↓
(Mendonca, Pereira, & Fernhall, 2013) (Portugal)	RCTs	7	**EG**: 10(54 % M)3(15 % F) **CG**: 9(23 % M) 3(8 % F)	**EG**:18.4 ± 2.9 **CG**:17 ± 2.8	27.95	No reported	5-min warm-up, 30-combined aerobic and resistance training, 5-min cool down program/ 3 days/week /12wk	65 % −85 % VO_{2peak}	**EG:** HR_{peak} ↑
González-Agüero, Gómez-Cabello, Matute-Llorente, Gómez-Bruton, Vicente-Rodríguez, & Casajús, 2014a) (Spain)	RCTs	5	**EG**: 6(43 % M) 8(57 % F) **CG**: 6(43 % M) 8(57 % F)	**EG**:14 ± 2.6 **CG**:15.9 ± 2.5	21.4	No reported	5-min warm-up, 10–15-plyometric training, 5-min cool down program/ 2 days/week /21wk	No reported	**EG:** VO_{2peak}↑ V_{Epeak} ↑ RER* ↑
(Boer & Moss, 2016) (South Africa)	RCTs	7	**IT**: 8(62 % M) 5(38 % F) **CAT**:7(54 % M)6(46 % F) **CG**: 10(62 % M)6(38 % F)	**IT**:30.5 ± 7.4 **CAT**:34.3 ± 9.2 **CG**:36.8 ± 8.4	30.12	No reported	5-min warm-up (4 km/h or 60 W),20 min aerobic vs. interval training,5-min cool down (4 km/h or 60 W)/ 3 days/week,12wk	70 % −80 % VO_{2peak}	**IT:** VO_{2peak}↑ V_{Epeak}↑ HR_{peak}*↑ time to Exhaustion ↑ **CAT**: VO_{2peak}↑ V_{Epeak}*↑ HR_{peak}*↑time to Exhaustion↑
(Cowley et al., 2011) (USA)	RCTs	5	**EG**: 9(43 % M) 10(57 % F) **CG**: 8(43 % M) 3(57 % F)	**EG**:29 ± 9 **CG**:27 ± 7	32.3	No reported	Progressive resistance training, 7 exercises, increasingWorkload during the programme. (8–10 x 3).,2 days/week,10wk	3 sets of 8–10 repetitions	**EG:** VO_{2peak} ↓ HR_{peak}* ↑RER↑
(Naczk et al., 2021b) (Poland)	RCTs	5	**EG**: 7(64 % M) 4(36 % F) **CG**: 7(64 % M) 4(36 % F)	**EG**:14.9 ± 2.35 **CG**:14.4 ± 1.97	25	No reported	20-min warm-up,30–50- min water-based exercise and a swimming program, 20-min cool down 3 days/week,33wk	No reported	**EG:** VO_{2peak}↑ HR_{peak}* ↑
(Seron et al., 2017) (Brazil)	RCTs	5	**ATG**: 11(69 % M)5(31 % F) **RTG**:10(67 % M)5(33 % F) **CG**: 4(40 % M) 6(60 % F)	**ATG**:15.7 ± 2.7 **RTG**:16 ± 2.8 **CG**:14.4 ± 2.5	25.96	No reported	**ATG**: aerobic training. Treadmill+ Stationary bike (15′ each,). Three times a week (50′) for 12 weeks. **RTG**: resistance training. 9 exercises (3x12 / 1′) 3′. Threetimes a week (50′) for 12 weeks.	HRR 50–70 %	**ATG:** VO_{2peak}↓ V_{Epeak}↑ HR_{peak}*↑ **RTG**: VO_{2peak} ↓ V_{Epeak}↑ HR_{peak}*↑

Abbreviations: **VO_{2peak}**: peak oxygen consumption; **V_{Epeak}**: peak minute ventilation; **HR_{peak}**: peak heart rate; **RER**: respiratory exchange ratio; **TGE**: Treadmill Graded Exercise; **RGE**: Rowing Graded Exercise; **EG:** Exercise Group; **CG:** Control Group; **IQ**: intelligence quotient; **IT**: interval training; **CAT**: continuous aerobic training; **ATG**: Aerobic Training Group; **RTG**: Resistance Training Group.
*No Significant differences with control group.

was 14.7 (range 4–31). The mean age of the participants was 22.83 years (14–40). In general, male and female participants were 190 and 104, respectively.

3.3. Exercise-training interventions

The 10 studies that met the eligibility criteria utilized twelve different types of intervention programs (Table 1). These included aerobic machine-based (e.g., treadmill, stationary bicycle), rowing, brisk walking/jogging, jog/walking, combined aerobic and resistance, plyometric, aerobic vs. interval, progressive resistance, water-based exercise, and swimming.The duration of the training periods ranged from 10 to 33 weeks, with an average of 15 weeks, and the frequency of the sessions ranged from 1 to 3 per week, with each session lasting between 25 and 90 min.

3.4. Risk of bias assessment and methodological quality

Fig. 2 shows the funnel plot, including all studies in this meta-analysis. Visual inspection of the funnel plot and Begg funnel plot identified no asymmetry, and the results of both the Begg rank correlation test and Egger linear regression were significant (Begg's test = 0.73, Egger's test = 0.27), suggesting no evidence of publication bias (Begg & Mazumdar, 1994; Egger et al., 1997). The methodological quality, as assessed with the PEDro scale, The mean PEDro scores of the included studies were 5.5 (range 4–7). The methodological quality of the four studies was good (PEDro score = 6–7). And six studies had fair quality (scores 4–5). The two assessors agreed on all 100 criteria (10 studies, 10 scores). The mismatched outcomes were discussed, and the assessors agreed on the scores presented in Table 1.

3.5. Outcome measures effects (Moderating variables)

3.5.1. Peak heart rate (HR_{peak})

HR_{peak} was measured in 11 trials (two studies had two different types of exercise programs), involving 176 participants in the intervention group and 90 participants in the control group (Fig. 3). There was a moderate degree of heterogeneity across studies for HR_{peak} (I^2 = 45.49 %, p = 0.05). Data showed that exercise training did not significantly improve HR_{peak} in DS individuals (ES = 0.3; Z = 1.82; CI (95 %) −0.02 to 0.63; p = 0.07). A sensitivity analysis was conducted, and the findings indicated that the results were consistent and stable, suggesting that the outcomes were reliable.

3.5.2. VO_{2peak} ($ml{\cdot}min^{-1}$)

VO_{2peak} ($ml{\cdot}min^{-1}$) was measured in 7 trials (one studies had two different types of exercise programs), involving 109 participants in the intervention group and 72 participants in the control group (Fig. 4). There was a moderate degree of heterogeneity across studies for VO_{2peak} ($ml{\cdot}min^{-1}$) (I^2 = 60.49 %, p = 0.02). Data showed that exercise training did not significantly improve VO_{2peak} (ml·min-1) in individuals DS (ES = 0.45; Z = 1.90; CI (95 %) −0.01 to 0.92; p = 0.06). A sensitivity analysis was conducted, and the findings indicated that the results were consistent and stable, suggesting that the outcomes were reliable.

3.5.3. VO_{2peak} ($ml{\cdot}kg^{-1}{\cdot}min^{-1}$)

VO_{2peak} ($ml.kg^{-1}{\cdot}min^{-1}$) was measured in 11 trials (two studies had two different types of exercise programs), involving 177 participants in the intervention group and 91 participants in the control group (Fig. 5). There was a high degree of heterogeneity across studies for VO_{2peak} ($ml.kg^{-1}{\cdot}min^{-1}$) ($I^2$ = 65.29 %, p = 0.00). Totally, the *meta*-analysis of all individuals showed that exercise training increased the VO_{2peak} ($ml.kg^{-1}{\cdot}min^{-1}$) (ES = 0.69; Z = 3.20; CI (95 %) 0.27 to 1.12; p = 0.00). A sensitivity analysis was conducted, and the findings indicated that the results were consistent and stable, suggesting that the outcomes were reliable.

3.5.4. Respiratory exchange ratio (RER)

Respiratory exchange ratio was measured in 6 trials, involving 95 participants in the intervention group and 69 participants in the control group (Fig. 6). There was a moderate degree of heterogeneity across studies for RER (I^2 = 61.90 %, p = 0.02). Data showed that exercise training did not significantly improve RER in individuals DS (ES = 0.46; Z = 1.66; CI (95 %) −0.08 to 1.01; p = 0.10). A sensitivity analysis was conducted, and the findings indicated that the results were consistent and stable, suggesting that the outcomes were reliable.

3.5.5. Time to Exhaustion(s)

Time to exhaustion was measured in 3 trials (one studies had two different types of exercise programs), involving 56 participants in the intervention group and 38 participants in the control group (Fig. 7). There was a low degree of heterogeneity across studies for time to exhaustion (I^2 = 38.54 %, p = 0.20). Totally, the *meta*-analysis of all individuals showed that exercise training increased the time to exhaustion (ES = 0.83; Z = 3.15; CI (95 %) 0.31 to 1.35; p = 0.00). A sensitivity analysis was conducted, and the findings indicated that the results were consistent and stable, suggesting that the outcomes were reliable.

3.5.6. Peak minute ventilation (VE_{peak})

Peak minute ventilation was measured in 8 trials (two studies had two different types of exercise programs), involving 103 participants in the intervention group and 62 participants in the control group (Fig. 8). There was a moderate degree of heterogeneity across studies for VE_{peak} (I^2 = 50.89 %, p = 0.05). Totally, the *meta*-analysis of all individuals showed that exercise training increased the VE_{peak} (ES = 0.76; Z = 3.38; CI (95 %) 0.32 to 1.20; p = 0.00). A sensitivity analysis was conducted, and the findings indicated that the results were consistent and stable, suggesting that the outcomes were reliable.

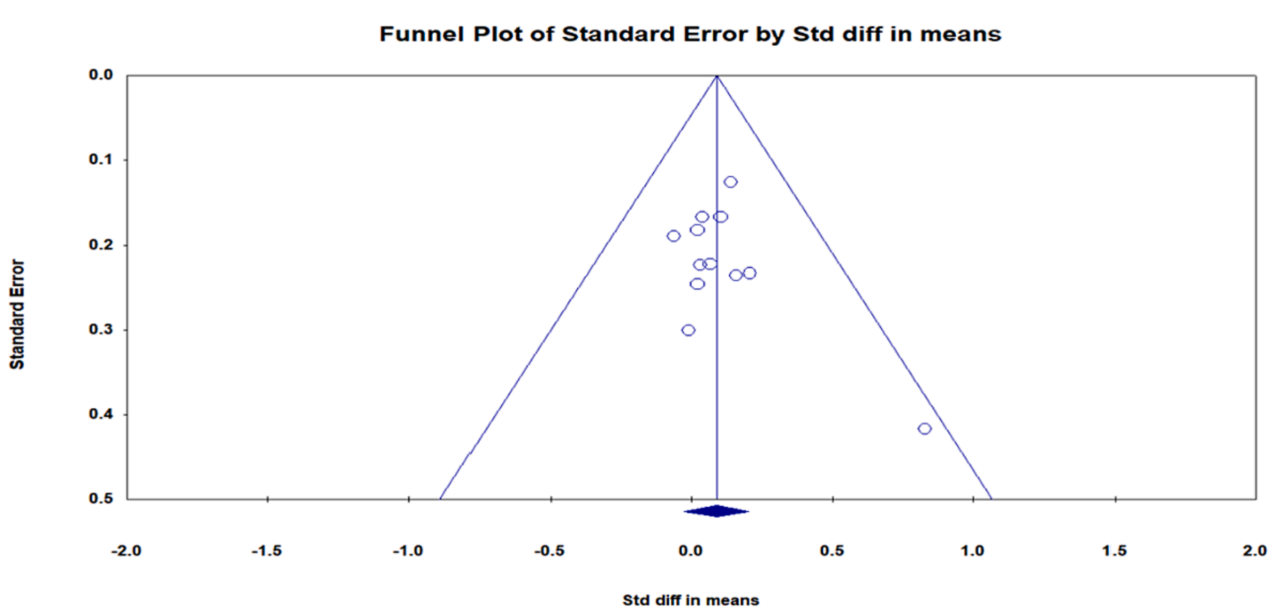
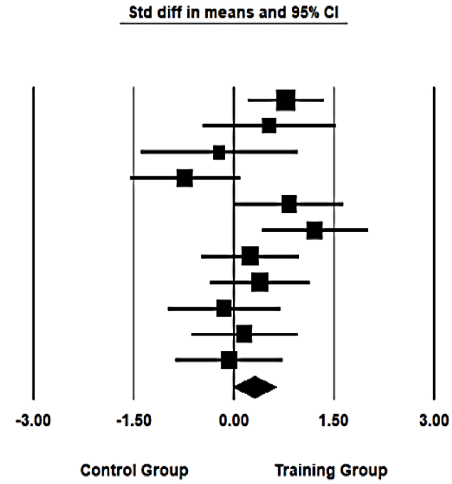


Fig. 2. Funnel plot analysis. Std diff in means.

Study name	Subgroup within study	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Rimmer et al (2004)	Peak heart rate(beat/min-1)	0.78	0.29	0.21	1.35	2.67	0.01	12.65
Varela et al (2001)	Peak heart rate(beat/min-1)	0.53	0.51	-0.47	1.52	1.03	0.30	7.10
Millar et al(1993)	Peak heart rate(beat/min-1)	-0.21	0.60	-1.40	0.97	-0.36	0.72	5.62
Tsimaras et al(2003)	Peak heart rate(beat/min-1)	-0.74	0.42	-1.56	0.09	-1.75	0.08	8.92
Mendonca et al (2013)	Peak heart rate(beat/min-1)	0.83	0.42	0.01	1.65	1.99	0.05	9.02
Boer et al (2016)/IT	Peak heart rate(beat/min-1)	1.21	0.41	0.42	2.01	2.99	0.00	9.30
Boer et al (2016)/CAT	Peak heart rate(beat/min-1)	0.24	0.37	-0.49	0.98	0.64	0.52	10.11
Cowley et al (2011)	Peak heart rate(beat/min-1)	0.39	0.38	-0.36	1.14	1.03	0.30	9.91
Alicja Naczk(2021)	Peak heart rate(beat/min-1)	-0.14	0.43	-0.98	0.69	-0.34	0.74	8.79
Seron et al(2017)/ATG	Peak heart rate(beat/min-1)	0.16	0.40	-0.63	0.95	0.39	0.69	9.35
Seron et al(2017)/RTG	Peak heart rate(beat/min-1)	-0.07	0.41	-0.87	0.73	-0.17	0.87	9.24
		0.30	0.17	-0.02	0.63	1.82	0.07	



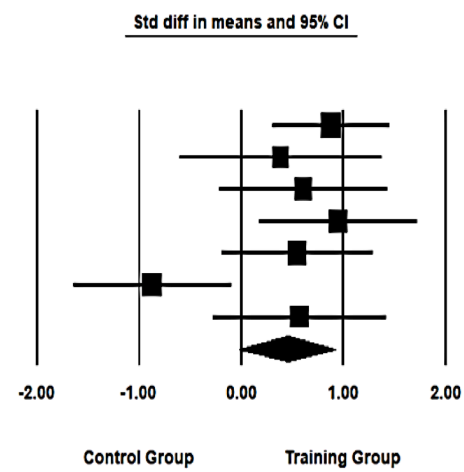
Heterogeneity: Q=18.34, df= 10 (p=0.05), I^2=45.49

Tau^2=0.14

Note: **IT:** interval training**; CAT:** continuous aerobic training**; ATG:** Aerobic Training Group**; RTG:** Resistance Training Group

Fig. 3. Forest plot of the effects of exercise programs on peak heart rate of individuals with DS.

Study name	Subgroup within study	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Rimmer et al (2004)	Peak VO2 (ml·min-1)	0.88	0.29	0.30	1.45	2.99	0.00	17.57
Varela et al (2001)	Peak VO2 (ml·min-1)	0.39	0.50	-0.60	1.38	0.77	0.44	11.53
Tsimaras et al(2003)	Peak VO2 (ml·min-1)	0.61	0.42	-0.21	1.42	1.45	0.15	13.80
Boer et al (2016)/IT	Peak VO2 (ml·min-1)	0.95	0.39	0.18	1.72	2.41	0.02	14.48
Boer et al (2016)/CAT	Peak VO2 (ml·min-1)	0.55	0.38	-0.20	1.29	1.44	0.15	14.87
Cowley et al (2011)	Peak VO2 (ml·min-1)	-0.87	0.40	-1.65	-0.10	-2.21	0.03	14.43
Alicja Naczk(2021)	Peak VO2 (ml·min-1)	0.57	0.43	-0.29	1.42	1.30	0.19	13.31
		0.45	0.24	-0.01	0.92	1.90	0.06	

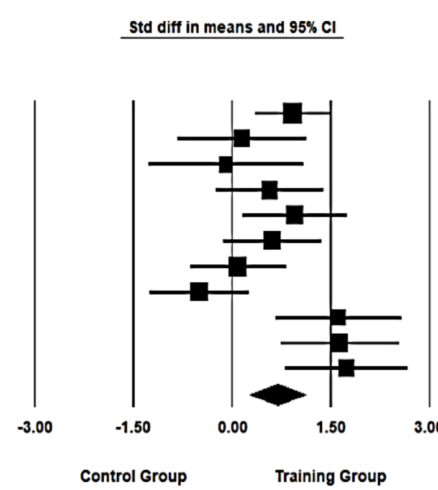


Heterogeneity: Q=15.19, df= 6 (p=0.02), I^2=60.49

Tau^2=0.24

Fig. 4. Forest plot of the effects of exercise programs on peak oxygen consumption (ml.min^{-1}) of individuals with DS.

Study name	Subgroup within study	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Rimmer et al (2004)	Peak VO2(ml·kg-1·min-1)	0.92	0.29	0.34	1.50	3.12	0.00	11.28
Varela et al (2001)	Peak VO2(ml·kg-1·min-1)	0.15	0.50	-0.83	1.13	0.30	0.77	8.09
Millar et al(1993)	Peak VO2(ml·kg-1·min-1)	-0.09	0.60	-1.27	1.08	-0.16	0.88	6.79
Tsimaras et al(2003)	Peak VO2(ml·kg-1·min-1)	0.57	0.42	-0.25	1.38	1.37	0.17	9.34
González-Agüero et al (2014)	Peak VO2(ml·kg-1·min-1)	0.95	0.41	0.16	1.75	2.35	0.02	9.49
Boer et al (2016)/IT	Peak VO2(ml·kg-1·min-1)	0.61	0.38	-0.14	1.36	1.60	0.11	9.88
Boer et al (2016)/CAT	Peak VO2(ml·kg-1·min-1)	0.09	0.37	-0.65	0.82	0.23	0.82	10.01
Cowley et al (2011)	Peak VO2(ml·kg-1·min-1)	-0.50	0.38	-1.26	0.25	-1.31	0.19	9.84
Alicja Naczk(2021)	Peak VO2(ml·kg-1·min-1)	1.61	0.49	0.65	2.57	3.28	0.00	8.23
Seron et al(2017)/ATG	Peak VO2(ml·kg-1·min-1)	1.64	0.46	0.73	2.55	3.54	0.00	8.63
Seron et al(2017)/RTG	Peak VO2(ml·kg-1·min-1)	1.73	0.48	0.80	2.67	3.64	0.00	8.44
		0.69	0.22	0.27	1.12	3.20	0.00	



Heterogeneity: Q=28.81, df= 10 (p=0.00), I^2=65.29

Tau^2=0.33

Fig. 5. Forest plot of the effects of exercise programs on peak oxygen consumption (ml.kg^{-1}min^{-1}) of individuals with DS.

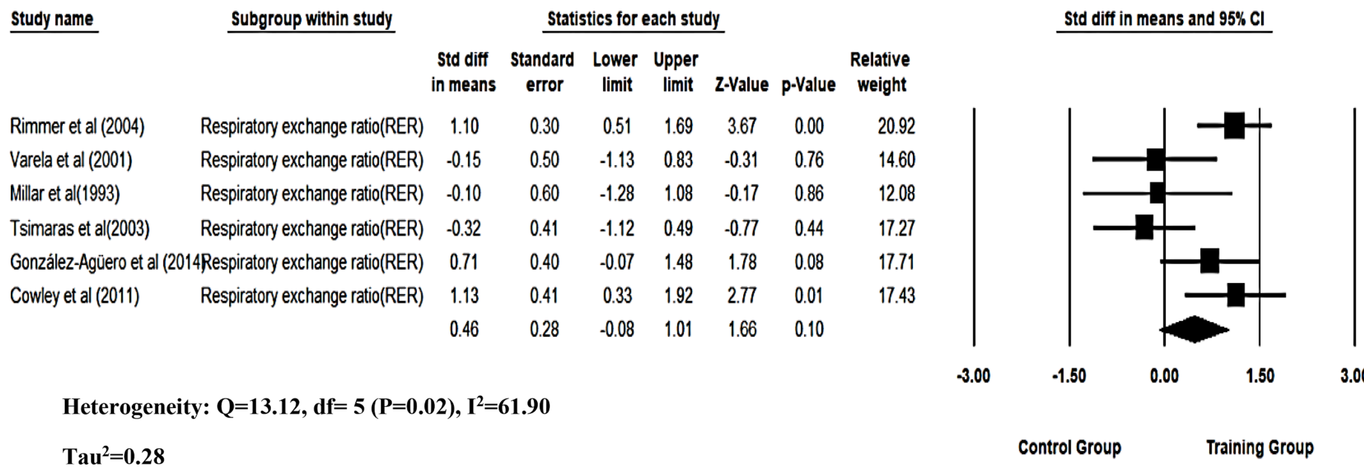


Fig. 6. Forest plot of the effects of exercise programs on respiratory exchange ratio of individuals with DS.

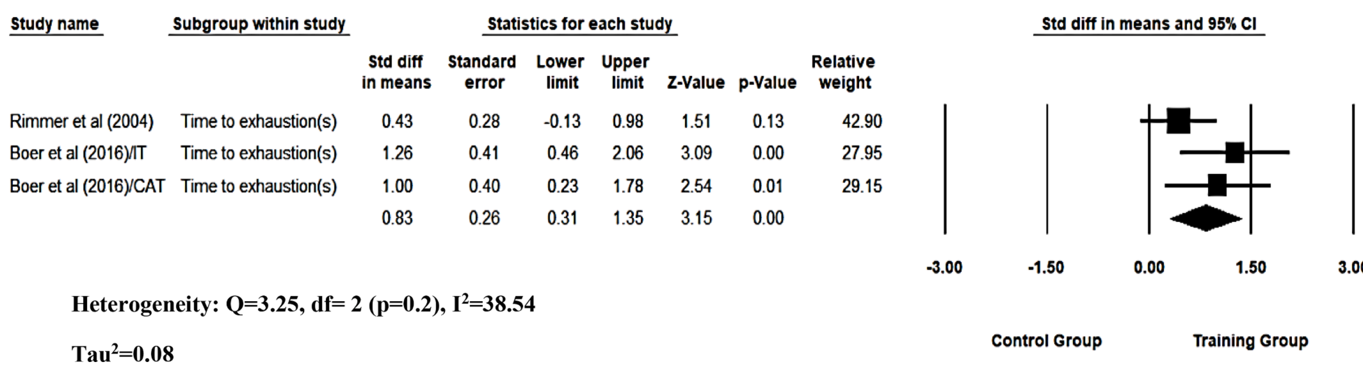


Fig. 7. Forest plot of the effects of exercise programs on time to exhaustion(s) of individuals with DS.

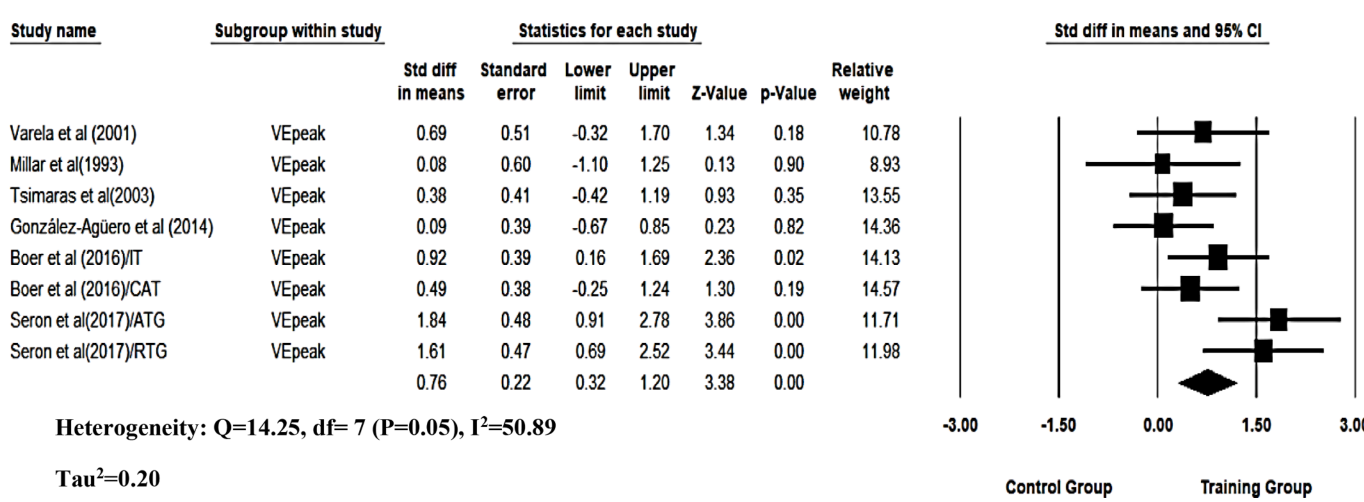


Fig. 8. Forest plot of the effects of exercise programs on peak minute ventilation of individuals with DS.

4. Discussion

Reduced exercise capacity in individuals with DS poses a significant challenge, as low levels of fitness and physical activity have been linked to reduced survival rates within this population. While other factors may also contribute to this issue, physiological differences such as chronotropic incompetence, low levels of muscle strength, and muscle hypotonicity are recognized as major contributors (Saeid Bahiraei et al., 2023; Mendonca, Pereira, & Fernhall, 2010; Pitetti et al., 2013).

Meta-analyses found programs were effective in increasing the maximum workload achieved peak oxygen consumption (ml. kg −1min-1) (d: 0.69; 95 % confidence interval [CI], 0.27–1.12; P: 0.001), time to exhaustion (d: 0.83; CI, 0.31–1.35, P: 0.001), and peak minute ventilation (d: 0.76; CI, 0.32–1.20; P: 0.001) in people with DS. Finding of this review suggested an intervention of about 12 weeks which cardiovascular benefits may be observed beginning at this time with an intensity of 50 % to 70 % of VO_{2peak}. Positive changes in fitness were achieved using activities such as swimming, cycling, or aerobics. The absence of unexplained withdrawals or negative effects in any of the studies indicates that cardiovascular exercise programs are safe for individuals with DS. This finding can be considered significant evidence, suggesting that individuals with DS can safely engage in cardiovascular exercise programs without any adverse outcomes.

As we have indicated, the data regarding HR has shown an increase in various types of protocols, but in other studies, it does not appear to have changed significantly (Boer & Moss, 2016; Mendonca, Pereira, & Fernhall, 2013; Rimmer et al., 2004). According to these articles, a 30-minute aerobic machine-based exercise on a treadmill and stationary bicycle for 12 weeks, 30-minute combined aerobic and resistance training for 12 weeks, and interval training for 12 weeks can improve peak heart rate. Patients with DS produce less significant hormonal responses, including catecholamine, in response to the same workload as healthy persons. This reduced hormonal response may explain why individuals with DS have difficulty engaging in high-intensity and prolonged physical activities. (Fernhall & Otterstetter, 2003). The absence of a rise in catecholamine during exercise is associated with reduced heart rate change in these individuals when performing the same activities as healthy individuals. (Fernhall et al., 2009). The findings of the current study, which suggest that exercise may not significantly impact heart rate in individuals with DS, are consistent with previous research. However, it is important to note that the desired effect of exercise on heart rate in this population may require longer and more intense training sessions to compensate for the reduced catecholamine response to physical activity. Therefore, designing appropriate exercise programs that take into account the unique physiological characteristics of individuals with DS is crucial in promoting cardiovascular health in this population.

$VO_{2\ max}$ is regarded as the gold standard for measuring cardiorespiratory fitness(Boer & Moss, 2016). Since this variable improves with exercise, its measurement is appropriate for measuring cardiorespiratory fitness. In the study of disabled people and/or those with sedentary lifestyles, $VO_{2\ peak}$ is the criterion for measuring cardiorespiratory fitness. In most patients, a steady increase in workload to exhaustion provides a $VO_{2\ peak}$ close to $VO_{2\ max}$ during cardiovascular fitness testing. Researchers calculate $VO_{2\ max}$ according to the following criteria: (a) plateau or decline in oxygen absorption in the last minute. b) attaining maximal heart rate (220-age), and c) a respiratory exchange of at least 1.1 (Varela et al., 2001).

The $VO_{2\ peak}$ significantly improved in the rowing group, the swim group, and both the interval and continuous aerobic exercise groups when compared to the control group.(Boer & Moss, 2016) plyometric exercise training González-Agüero et al (2014) $VO_{2\ peak}$ with IT improved more significantly when compared with the CAT group (Boer & Moss, 2016). Rest periods between work intervals allow individuals to work at higher intensities when compared with continuous exercise. Concerning peripheral adaptations, mitochondrial capacity, and CA2 + cycling has been shown to improve to a larger extent with IT compared with CAT. Trapp et al. (2008) demonstrated that mitochondrial oxidative capacity improved by as much as 31 % after 15 weeks of IT. Fernhall et al. (2013) postulate that autonomic dysfunction is the principal contributor to the poor aerobic capacity and maximal oxygen consumption of PWDS, which may lead to their poor cardiometabolic risk profiles.

Some studies on the effect of different interventions on aerobic capacity, particularly $VO_{2\ peak}$ in patients with DS, have revealed increased $VO_{2\ peak}$ levels (Lewis & Fragala-Pinkham, 2005; Parab et al., 2019; Savucu, 2010; Silva et al., 2017), but others have not identified a response to exercise concerning this variable(Millar et al., 1993; Seron et al., 2017; Varela et al., 2001).

In the present study, exercise did not significantly increase $VO_{2\ peak}$ among patients with DS. The lack of progress or change in $VO_{2\ peak}$ may be due to the intensity or low training volume since this intensity and volume of stimulation did not produce sufficient stimulation for $VO_{2\ peak}$ alterations. Studies with longer workout courses (28 weeks) and higher intensity (60–85 % of $VO_{2\ peak}$) found a significant increase in aerobic capacity(Boer & Moss, 2016; Varela et al., 2001).

Research has shown that during prolonged muscular exercises, there is a reaction in the body's adrenal hormones such as cortisol, catecholamines, and sex hormones like testosterone. In healthy individuals, this increase in hormones is well documented during maximal activities. However, in individuals with DS, these hormonal responses may not occur as effectively, which may explain their limited ability to sustain high-intensity activities for longer periods (Fernhall & Otterstetter, 2003). On the other hand, individuals with DS often lack the motivation and drive to engage in repetitive and long-term physical activities, leading to a sedentary lifestyle that exacerbates their risk factors for cardiovascular diseases. Therefore, it is crucial to design exercise programs that are diverse, engaging, and tailored to the specific needs and preferences of individuals with DS.

It appears that assessments, such as labor capacity, and motor economy among others, are as relevant as $VO_{2\ peak}$ and other cardiovascular variables when assessing the exercise achievements of individuals with DS. Thus, it is likely that $VO_{2\ peak}$ does not improve in some cardiovascular variables. That is, gains in endurance, maximum work capacity, strength, or motor economy as a "secondary" reaction to exercise training can have a favorable effect on work, recreation, and other activities of daily life, as well as reducing the risk of cardiovascular disease (Varela et al., 2001).

The improvement of VE_{peak} in the current study demonstrates the importance of designing appropriate exercise programs in facilitating the breathing process during exercise. The reason for this improvement is probably due to several factors. One possibility is that exercise training increases the strength and endurance of respiratory muscles, such as the diaphragm and intercostal muscles, which can lead to an increase in VE_{peak}. Another possibility is that exercise training improves overall cardiovascular fitness, which can increase oxygen delivery to the body and improve the efficiency of gas exchange in the lungs. Additionally, regular exercise may lead to changes in breathing patterns and increased lung capacity, which can also contribute to improvements in VE_{peak}.

It's worth noting that the exact mechanisms responsible for the improvement in VE_{peak} in people with DS after exercise training may differ based on factors such as the individual and the type of exercise utilized. Therefore, more research is necessary to fully comprehend the reasons behind and potential advantages of exercise training on respiratory function in this group.

This study revealed a significant increase in fatigue duration, quantified in other studies as job performance or distance to tiredness. This improvement is likely attributable to lifestyle changes and exercise program participation. Similarly, such adaptive adjustments can majorly impact an individual's capacity to carry out everyday tasks and integrate into society, hence delivering general advantages for daily life (Mendonca, Pereira, & Fernhall, 2011). The precise mechanisms underlying these improvements are not yet fully understood. However, it is thought that exercise training can enhance cardiovascular function and increase the efficiency of oxygen utilization, leading to improvements in aerobic capacity and delay in the onset of fatigue.

CRediT authorship contribution statement

Saeid Bahiraei: Writing – review & editing, Writing – original draft, Software, Methodology. **Mahbanou Ghaderi:** Validation, Conceptualization. **Esmail Sharifian:** Supervision, Project administration. **Sheida Shourabadi Takabi:** Software, Data curation. **Sara Sepehri Far:** Writing – original draft, Methodology. **Guillermo R. Oviedo:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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