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Research article

Effects of exercise therapy on Huntington's Disease motor symptoms – A meta-analysis

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Abstract

Background: Huntington's disease is an incurable neurodegenerative disorder. In addition to drug therapy, attempts are being made to improve the symptoms of this disease with exercise therapy. This meta-analysis therefore investigates these effects on individual symptom areas.
Methods: Search of the online databases PEDro, PubMed, Web of Science, and Scopus, keywords exercise OR exercise therapy OR physical therapy OR rehabilitation AND Huntington's Disease, published between 1990 and 2024. The PEDro score is used to check the methodological quality, and standardized mean differences (SMD) and their 95% confidence intervals (CI) are presented in forest plots for quantitative analysis.
Results: A total of 4833 publications were found. After excluding duplicates and studies that examined other topics, 12 studies remained, which were subjected to a qualitative analysis. Only seven studies achieved an average quality of at least five points, which were then examined quantitatively. SMD values between 4.34 and -3.03 were found, but almost all of them were favouring the control group.
Discussion: The widely varying and sometimes inconclusive values could have been caused by sample sizes that were too small, different interventions, disease status, unequal groups at baseline, and active control groups.
Conclusions: Therefore, more high-quality studies with clear intervention concepts and larger sample sizes are needed.

1. Introduction

Huntington's Disease (HD) is an incurable autosomal-dominantly inherited neurodegenerative brain disorder characterized by involuntary, uncoordinated movements and flaccid muscle tone. It is one of the most common hereditary brain disorders with an average prevalence of 2.71:100,000. Here, a progressive destruction of the striatum (important brain area for muscle control and basic mental functions) takes place. First symptoms usually appear in the 4th decade of life as disorders of body movements and emotions. It usually begins with hyperkinesia (involuntary movements) with reduced muscle tone. Later, hypokinesia (lack of movement) and an increase in muscle tone are more common. The further course is characterized by an increasing loss of muscle control, including facial expressions, and finally of brain function as a whole [1–3].

There is no known therapy that cures the disease itself or stops it permanently. Some vitamins and dietary supplements are used with varying degrees of success to protect the cells from oxidative stress, and to slow down the progression of the disease. A pallidal deep brain stimulation (DBS) appears to have positive effects, particularly on motor symptoms. The progression of the disease cannot be halted by this stimulation, but an increase in quality of life is shown.Tetrabenazine and dopamine antagonists are also used to treat hyperkinesia. But the

use of tetrabenazine could lead to a worsening of depression and suicidal tendencies and to increased extrapyramidal syndromes in some patients [4–6].

In pre-manifest HD, aerobic walking or cycling exercise with moderate intensity are investigated, in mid-stage/moderate HD, a task-specific training (walking, sit to stand), combined aerobic (cycling), stretching and strengthening exercises, and respiratory muscle training with increasing resistance are investigated. Here, improvements in VO2max, inspiratory and exspiratory pressure are visible [7–12].

Hypothesis

Exercise therapy has an effect on motor symptoms in Huntington's Disease.

2. Methods

2.1. Systematic Literature Review

In this meta-analysis, the PRISMA guidelines are followed as defined by [13].

Electronic databases including PEDro, PubMed, Web of Science, and Scopus were searched to identify studies that used exercise therapy in Huntington's Disease patients. As search terms, the following combinations are used: exercise OR exercise therapy OR physical therapy OR rehabilitation AND Huntington's Disease. All publications between 1990 and 2024 were included. Reference lists of relevant articles were also hand-searched for additional studies.

2.2. Study Selection

All relevant studies identified by the systematic literature review were screened. Studies were included in the qualitative analysis if they satisfied all of the following criteria:

1. Appropriate experimental design
2. Used exercise therapy
3. Included human patients with Huntington's Disease, no limitations in age, stage of disease, or medication status
4. Used single or multiple exercise sessions
5. Analyzed short- or long-term intervention
6. Outcomes measured motor symptoms
7. Publication between 1990 and 2024. Review articles and articles not written in English, German, French, or Spanish were excluded.

2.3. Data extraction

Data were extracted from the full-text version of the publications. Key data included number of participants, severity/stage of disease, study design, type of exercise, duration of the study, number of treatment sessions, number of trials per session, outcomes, and presentation of results.

2.4. Methodological quality

To evaluate the methodological quality of all studies found, the PEDro score [14] is used. Criteria:

1. Specified eligibility criteria
2. Random allocation
3. Concealed allocation
4. Similar groups at baseline
5. Blinded test persons
6. Blinded therapists
7. Blinded assessors
8. $>$ 85% of at least one key outcome obtained
9. All test persons received treatment or control condition, if not, data analysis by intention to treat
10. Results of between-group comparisons are reported,
11. Point measures and measures of variability are reported [14].

All studies with a score of$\geq$ 5 (medium methodological quality) are included into meta-analysis.

2.5. Data synthesis for meta-analysis

To evaluate the effects of exercise therapy, standardized Mean Differences (SMD) and 95 % Confidence Intervals (CI) for continuous outcomes are calculated and depicted in forest plots. A differentiation is made between small (SMD $>$ 0.3), medium (SMD $>$ 0.5), and strong effect SMD $>$ 0.8) [15]. The risk of bias was assessed by use of funnel plots/Egger test [16]. It was decided to use a random-effects model, as the effects varied across the studies. Heterogeneity of studies and subgroups is evaluated by I² test. A differentiation is made between low heterogeneity (I^2 = 25%), moderate (I^2 = 50%), and high (I^2 = 75%) [17, 18]. For these analyses, RevMan 5.4 software is used [19].

The following Figure 1 shows the flow of the study.

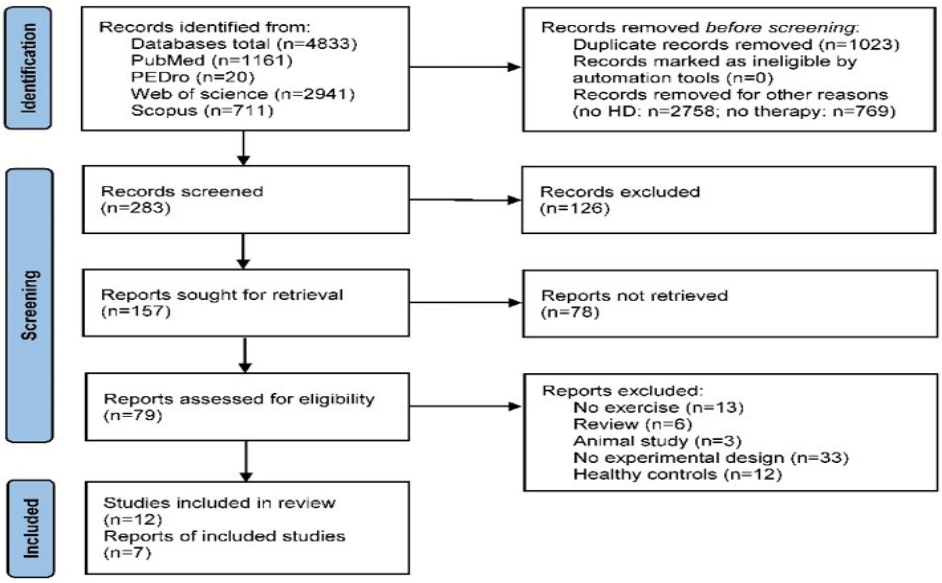

Figure 1: Flow of the study

3. Results

3.1. Study population

In total, 4833 papers were found in the databases PEDro, PubMed, Web of Science, and Scopus. Before screening, 4550 records were removed (duplicates, no HD or no therapy). After screening, 157 left and were sought for retrieval, where 79 of them could be assessed for eligibility. Here, 67 reports had to be excluded (no exercise, review, animal study, no experimental design or healthy controls. So 12 studies could be included into review, after assessing the methodological quality, seven studies were included into the meta-analysis.

The following Table 1 shows all characteristics of the studies included into review and qualitative assessment.

Publication	Design	N	Participants	Intervention type	Sets/reps	Duration	Outcomes	Results
Aldine et al 2021 [7]	EG/CG	40 EG 34 CG 6	Pre-manifest HD 15 m, 25 f 20 to 60 years	Home based EG: Moderate to vigorous intensity walking CG: stretching, toning, core-strength, balance exercises	3 x per week Advanced from 15 to 50 minutes over the first six weeks	24 weeks	UHDRS	About 70% of participants completed the study No significant differences in posttest Improvement in UHDRS motor score in both groups
Andrews et al 2023 [8]	EG/CG	20 EG 10 CG 10	Pre-manifest and early HD 9 m, 11 f 27 to 70 years	EG: Moderate intensity cycling CG: rest	Single bout 20 minutes	Single bout	SVIPT	No signifcant differences Higher accuracy in EG Higher speed in both groups Higher improvement in skill acquisition across blocks in EG
Busse et al 2013 [20]	RCT	31 EG 16 CG 15	HD Mean 50 years 15 m, 16 f	EG: aerobic cycling, Self-directed walking, strengthening CG: no intervention	2 x per week Advanced from 20 to 30 minutes 2 set/ 10 rep	12 weeks	UHDRS Gait speed 6-minute-walk	No significant differences Improvement in UHDRS for CG Improvement in 6-minute-walk in both groups
Kegelmeyer et al 2010 [21]	CO	20 EG 12 CG 8	Early and mid-stage HD	EG: video game based dancing exercise CG: no intervention	2 x per week 45 minutes	6 weeks	Tinetti test 4-square step	Greater improvement in Tinetti test in mid-stage Greater improvement in UHDRS in early-stage Improvement in 4-square step test in EG
Khalil et al 2012 [22]	EG/CG	25 EG 13 CG 12	HD	Home based EG: exercise (not described) CG: no intervention	3 x per week	8 weeks	Gait Balance Function	Significant differences in posttest Improvement in gait speed in EG Improvement in balance in EG Improvement in function in EG
Khalil et al 2013 [9]	RCT	25 EG 13 CG 12	Early and mid-stage HD Mean 52 years	Home based EG: flexibility, balance, strengthening, resistance and relaxation exercises + light intensity walking CG: no intervention	3 x per week/ 1 x per week	8 weeks	UHDRS Gait speed Step time BBS 30 sec chair rise PPT	Significant changes in EG Improvement in UHDRS in EG Improvement in gait speed in EG Improvement in step time in EG Improvement in BBS in EG Improvement in 30 sec chair rise
Quinn et al 2014 [10]	RCT	28 EG 15 CG 13	Mid-stage HD 13 m, 115 f Mean 57 years	EG: Task-specific mobility training CG: no intervention	60 minutes 2 x per week	8 weeks	PPT UHDRS BBS Gait speed 30 sec chair rise TUG	Improvement in UHDRS in EG Improvement in 30 sec chair rise in EG
Quinn et al 2016a [11]	RCT	32 EG 17 CG 15	16 m, 16 f Age 19-76 years	EG: strengthening, aerobic, stretching exercises CG: no intervention	50 minutes 3 x per week	12 weeks	UHDRS 3-min-walk 15 rep chair rise Finger tapping	Improvement in UHDRS in EG Improvement in 15 rep chair rise in CG Improvement in 3-min-walk in CG Improvement in finger tapping in EG
Quinn et al 2016b	RCT	29 EG 14 CG 15	Early to mid-stage HD,	EG: aerobic, strengthening exercises CG: no intervention	3 x per week	12 weeks	VO2max UHDRS	Significant differences in posttest Improvement in VO2max in EG Improvement in UHDRS in EG
Reyes et al 2014	RCT	18 EG 9	Manifest HD 11 m, 7 f	EG: respiratory muscle training with increasing	6 x per week	16 weeks	6 min-walk	Small change in both groups

		CG 9	Mean 53 years	resistance CG: respiratory muscle training at minimum resistance				
Reyes et al 2015 [12]	RCT	18 EG 9 CG 9	Manifest HD 11 m, 7 f Age 32-70 years	Home based exercise EG: respiratory muscle training CG: respiratory muscle training at minimum load	10 sets/ 10 reps 6 x per week	16 weeks	6-min-walk	Improvement in 6-min-walk in EG
Trinkler et al 2019 [23]	RCT	19 EG 8 CG 11	HD	EG: contemporary dance practice CG: no intervention	120 minutes 1-3 x per week	20 weeks	UHDRS	Improvement in UHDRS

Table 1: Study characteristics of the studies included in systematic review (EG = experimental group, CG = control group, RCT = randomized controlled trial, CO = cross-over design, N = number of participants, HD = Huntington's Disease, m = male, f = female, UHDRS = Unified Huntington's Disease Rating Scale, SVIPT, BBS = Berg Balance Scale, PPT = physical performance test, TUG = Timed Up and Go test

3.2. Methodological quality

The mean PEDro score for all studies was 4.33 ± 2.25 (M ± SD). Studies with ≥ 5 points were included in the quantitative analysis. So the final sample consists of seven studies with a PEDro score of 5.86 ± 1.12 (M ± SD).
The following Table 2 shows the complete results for the methodological quality, measured by PEDro-score.

Table 2: Complete results for methodological quality by PEDro score (1 = reported criterion, 0 = not reported)

Publication	1	2	3	4	5	6	7	8	9	10	11	PEDro total
Aldine et al 2021 [7]	1	0	0	1	0	0	1	0	0	1	1	5
Andrews et al 2023 [8]	1	0	0	1	0	0	0	1	0	1	1	5
Busse et al 2013 [20]	1	1	0	0	0	0	0	0	0	1	1	4
Kegelmeyer et al 2010 [21]	0	1	0	0	0	0	0	0	0	1	0	2
Khalil et al 2012 [22]	0	0	0	0	0	0	0	0	0	0	0	0
Khalil et al 2013 [9]	1	1	0	1	0	0	0	0	0	1	1	5
Quinn et al 2014 [10]	1	1	1	0	0	0	1	1	0	1	1	7
Quinn et al 2016a [11]	1	1	0	0	0	0	1	1	0	1	1	6
Quinn et al 2016b	0	1	0	0	0	0	1	1	0	0	1	4
Reyes et al 2014	0	1	0	0	0	0	0	0	0	0	0	1
Reyes et al 2015 [12]	1	1	1	1	1	0	0	1	0	1	1	8
Trinkler et al 2019 [23]	1	1	0	0	0	0	1	0	0	1	1	5

Footnote: (1) specified eligibility criteria, (2) random allocation, (3) concealed allocation, (4), similar groups at baseline, (5) blinded test persons, (6) blinded therapists, (7) blinded assessors, (8) > 85% of at least one key outcome obtained, (9) all test persons received treatment or control condition, if not, data analysis by intention to treat, (10) results of between-group comparisons are reported, (11) point measures and measures of variability are reported [14].

The total scores range from zero (Khalil et al., 2012) to eight [12], where only seven studies reach at least five points and can be included into quantitative analysis [7–12] Trinkler et al., 2019). Only two studies fulfill the third criterion [10, 12], one fulfills the fifth [12], none the sixth and ninth.

3.3. Quality of outcomes

All coefficients for interrater reliability range from 0.78 (6 min walk) to 0.99 (BBS, PPT, TUG). For intrarater reliability, coefficients range from 0.74 (6 min walk) to 0.98 (BBS). Test-retest coefficients range from 0.64 (finger tapping) to 0.99 (6 min walk, TUG). A reported Cronbach α shows values from 0.83 (UHDRS) to 0.99 (3 min walk). The most investigated validity aspect is the concurrent validity.

Coefficients range here from to -0.32 (finger tapping) to 0.99 (6 min walk, GAITRite measures). Construct validity is only reported for BBS with $Chi^2 = 35.68$. In SVIPT, the psychometric properties are partly investigated, but there are no concrete values reported. For the 15 rep chair rise, there are no psychometric properties reported.

3.4. Risk of bias (funnel plots)

The following Figures 2 and 3 show the results for funnel plots, divided into assessments with score minimization and assessments with score maximization.

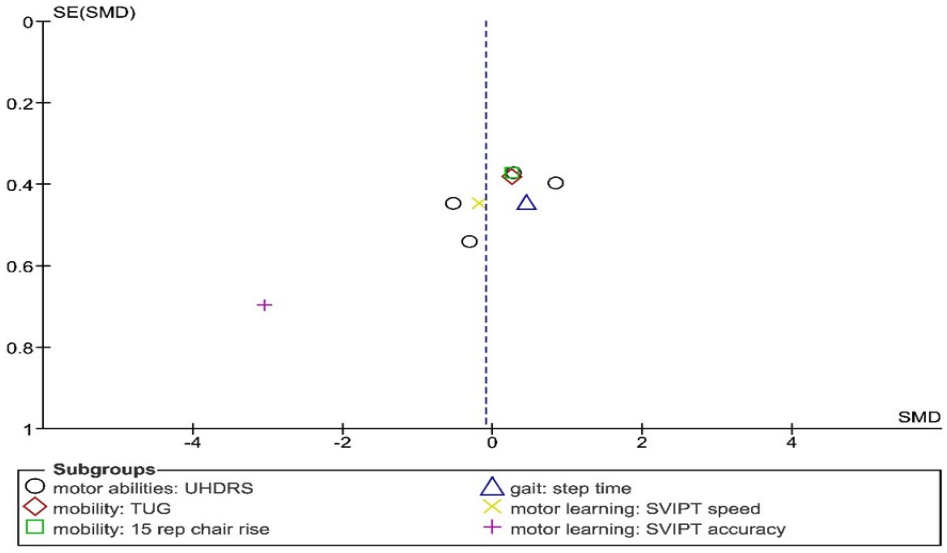

Figure 2: Risk of bias as funnel plot for variables with score minimization (motor abilities: UHDRS, mobility: TUG, 15 rep chair rise, gait: step time, motor learning: SVIP speed and accuracy)

Table 3: Overview of all outcomes used showing their values for psychometric properties

Outcome	Reliability	Validity	References
BBS (Berg Balance Scale)	Interrater ICC = 0.71-0.99 Intrarater ICC = 0.98 Cronbach α = 0.96	Construct Chi^2 = 35.68	Berg et al [24] La Porta et al [25]
TUG (Timed Up and Go)	Interrater r= 0.91-0.99 Test-retest r = 0.91-0.99	Concurrent -BBS r = -0.81 -Gait speed r = -0.61 -Barthel Index r = -0.78	Podsiadlo, & Richardson [26] Rydwick et al [27]
PPT (Physical Performance Test)	Interrater r = 0.99 Cronbach α = 0.87	Concurrent - POMA r = 0.50-0.80	Reuben, & Siu [28]
SVIPT (Sequential visual isometric pinch task)	No concrete values	No concrete values	
UHDRS (Unified Huntington's Disease Rating Scale)	Interrater ICC = 0.62-0.94 Cronbach α = 0.83-0.95	Concurrent - SARA r = -0.89	Huntington Study Group [29]
Finger tapping	Test-retest r = 0.86-0.94 Test-retest stability r = 0.64-0.87	Concurrent -MCS r = -0.32—0.63 -Pegboard r = 0.31-0.72	Pal et al [30] Schatz [31]
GAITrite	Test-retest ICC = 0.82-0.92	Concurrent -Vicon ICC = 0.92-0.99	Benz et al [32] Webster et al [33]
15 rep chair rise	Not reported	Not reported	
30 sec chair rise	Test-retest ICC = 0.84-0.92	Concurrent -Leg press r = 0.71-0.78	Jones et al [34]
3 min walk	Test-retest ICC = 0.99 Cronbach α = 0.99	Concurrent -6 min walk r = 0.94	Ibikunle et al [35]
6 min walk	Interrater ICC = 0.78 Intrarater ICC = 0.74 Test-retest ICC = 0.99	Concurrent -VO2max r = 0.66 -12 min walk r = 0.99	Eng et al [36] Kosak, & Smith [37]

Here, only one outlier is visible (result for motor learning variable accuracy from [8]. The other studies are all in nearly the same range and evenly distributed.

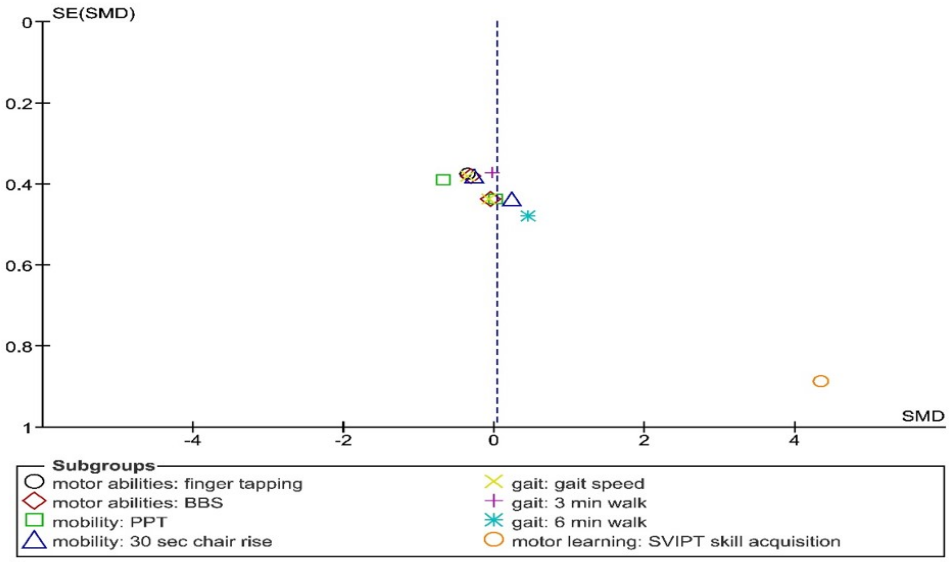

Figure 3: Risk of bias as funnel plot for variables with score maximization (motor abilities: finger tapping and BBS, mobility: PPT and 30 sec chair rise, gait: speed, 3min walk and 6 min walk, motor learning: SVIPT skill acquisition)

Here, only one outlier is visible (result for motor learning variable skill acquisition from [8]. The other studies are all in nearly the same range and evenly distributed.

3.5. Effect sizes

The following Figures 4 and 5 show the results for effect sizes as forest plots, divided into assessments with score minimization and score maximization.

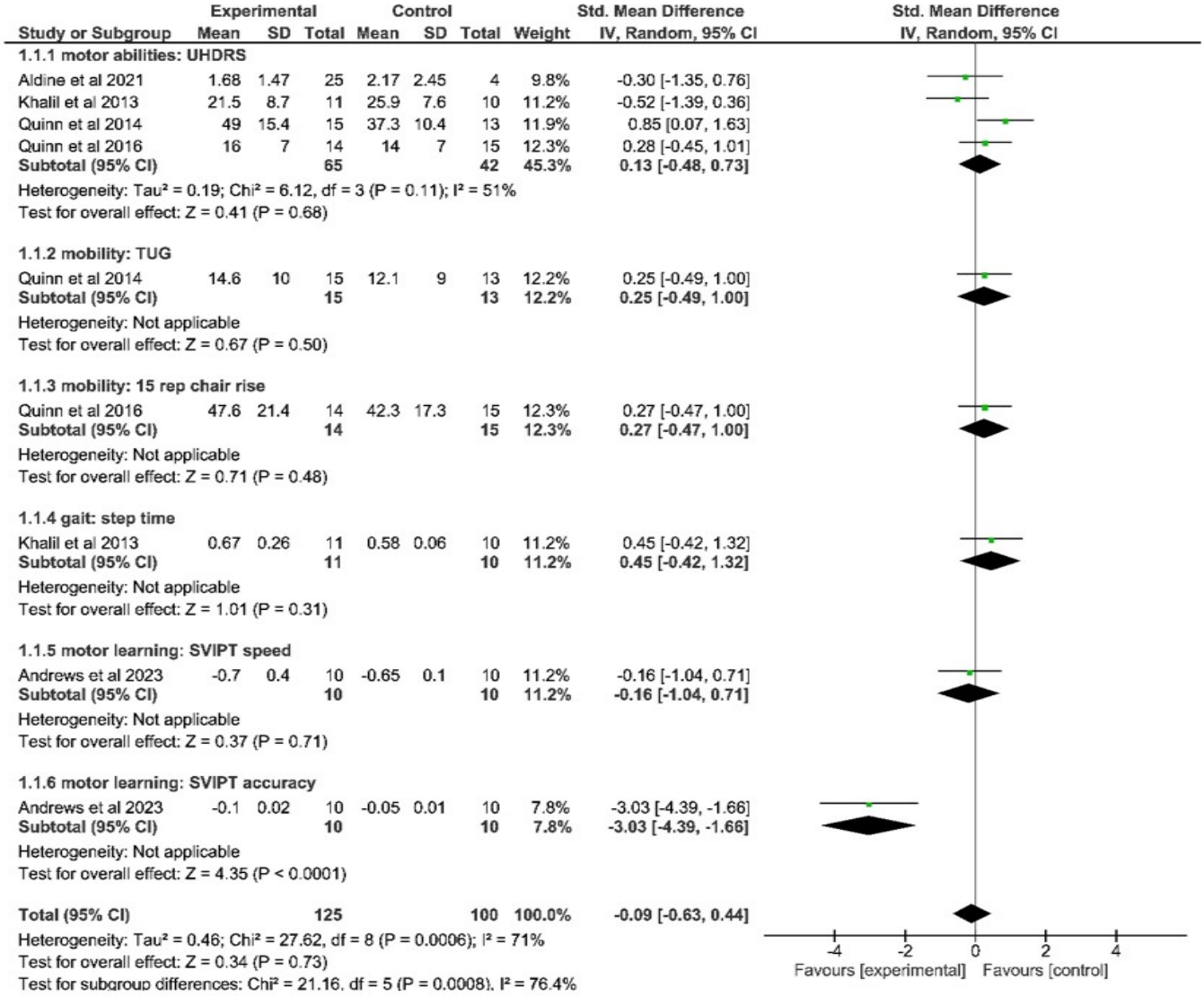

Figure 4: Effect sizes SMD and 95% CI as forest plot for variables with score minimization (motor abilities: UHDRS, mobility: TUG, 15 rep chair rise, gait: step time, motor learning: SVIP speed and accuracy) and heterogeneity of subgroups (I^2)

Here, motor abilities are assessed by UHDRS scale, mobility by TUG and 15 rep chair rise, gait by step time, motor learning by the SVIPT variables speed and accuracy.

The heterogeneity of studies and groups is very high and significant (see $Chi^2 = 27.62$*** and $I^2 = 71\%$ as well as $Chi^2 = 21.16$*** and $I^2 = 76\%$). For this, the random model to calculate effect sizes is used.

Effect sizes between the studies range from -3.03 for SVIPT variable accuracy [8] to 0.85 for UHDRS motor score [10]. Effect sizes between subgroups (areas motor abilities, mobility, gait and motor learning) range from -3.03 (motor learning accuracy) to 0.45 (gait).

Here, negative SMD values favour the experimental group, positive values favour the control group. Thus, effects for motor abilities, mobility, and gait are in favour to the control group, and the effect for motor learning is in favour to the experimental group. All effects are predominantly in the low to medium range and not significant, excepting the effect for the motor learning variable accuracy, which is strong and very significant. The total effect for all assessments combined is in a medium range and not significant.

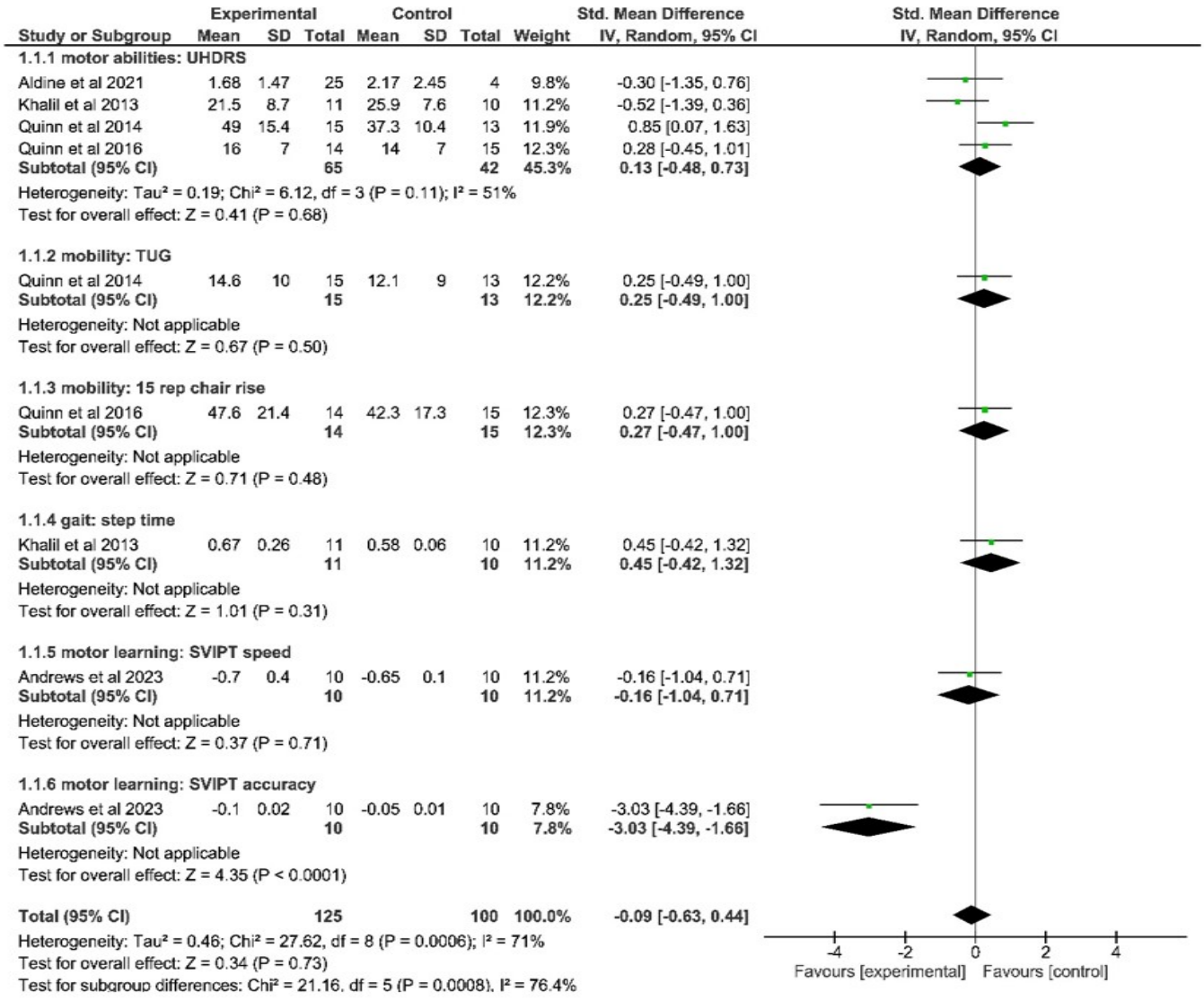

Figure 5: Effect sizes SMD and 95% CI as forest plot for variables with score maximization (motor abilities: finger tapping and BBS, mobility: PPT and 30 sec chair rise, gait: speed, 3min walk and 6 min walk, motor learning: SVIPT skill acquisition) and heterogeneity of subgroups (I^2)

Here, heterogeneity of the studies/subgroups is very high and significant (see Chi² = 30.47 and $(I^2) = 65\%$ as well as $Chi^2 = 27.60$ and $(I^2) = 75\%$). For this, the random model to calculate the effect sizes is used.

Effect sizes between the studies range from 4.34 for motor learning variable skill acquisition [8] to -0.67 for PPT [10]. Effect sizes between the subgroups range from 4.34 for motor learning to -0.35 for mobility (PPT).

Here, negative SMD values describe an effect favouring the control group, positive values describe an effect favouring the experimental group. Thus, effects for motor abilities, mobility, gait (speed and 3 min walk) favour the control group, the effects for gait (6 min walk) and motor learning favour the experimental group.

All effects are predominantly in the low to medium range and not significant, excepting the effect for the motor learning variable skill acquisition.

4. Discussion and Limitations

In this paper, the effects of exercise therapy on motor symptoms in Huntington's Disease are investigated.

In total, only seven studies reached at least a medium methodological quality (≥ 5) and could therefore be analysed quantitatively.

Nearly all effect sizes are in a low to medium range and in favour to the control group, but not significant.

Only for motor learning variables, a strong and significant effect is visible, favouring the experimental group.

All studies had small sample sizes. In addition, the exercise interventions are very different (type, duration, intensity, etc.). Here, the duration ranges from a single bout [8] to 24 weeks [7].

The participants in the studies analysed are pre-manifest [7, 8] or mid-stage HD patients [9–12]. The effects of special exercise programs in later-stage patients have apparently only just been investigated in one study, although the results have not yet been officially published [38].

Groups often were not similar at baseline. For this, an improvement in the intervention group is not visible in the effect size. Thus, [9] do not make it clear that the EG improved by 0.29 m/s and the CG maintained its value from the pretest. Since both groups therefore have almost identical values in the posttest, hardly any effect size is visible. This is also evident in this study in terms of step time. In some cases,

the groups differed greatly in terms of demographic characteristics, albeit not significantly, as was the case with [7] (EG: n = 34; 32% male CG: n = 6; 67% male).

Some of the studies investigated home-based exercises [7, 9, 12], but did the test persons implement the training plan exactly? [10, 11] investigated home-based exercise too, but with supervision by a therapist. A lack of supervision may have led to poor technical execution of movements, even when watching a DVD with correct execution, for example. There is evidence that supervised training has greater effects on various motor skills (e.g. strength, balance) compared to unsupervised training in healthy older adults [39]. For this reason, it seems obvious that the effect size is not as high in these studies.

In some cases, the completion rate is only about 70% [7]. Such a study cannot therefore be considered representative. However, this study is negligible due to its achieved effect size of 0.3.

The control group partly had an alternative program instead of no intervention, so it was an active control condition [7, 12]. This raises the question of the extent to which a placebo effect could have reduced the effect in favour of the experimental group, which has also been shown in drug studies [40], among other things.

The psychometric properties of the assessments play a role, too. If a test instrument is not reliable or valid, it is difficult to interpret or judge these results. The psychometric properties known from classical test theory are used to determine how objective, reliable, and accurate a test is. Compliance with these criteria (intra- and interrater reliability and validity) is regarded as indispensable for test construction. The validity is the central quality criterion, because a high degree of validity also guarantees a high degree of objectivity, consistency, and reliability. For this purpose, the quality of outcomes was assessed using reliability (inter- and intrarater reliability), and validity scores. The criteria for reliability were classified into low (< 0.60), acceptable (0.60-0.70), moderate (0.70-0.80), good (0.80-0.90), and high (> 0.90) [41], for validity into low (< 0.40), moderate (0.40-0.60), and high (> 0.60) [42]. All test procedures demonstrate good to high reliability, with the exception of the SVIPT and the 15 rep chair rise, for which no specific information is available. This also applies to the validity values. However, it was the SVIPT that achieved by far the highest effect size. Due to the lack of psychometric properties, this should be treated with particular caution.

There is a strong heterogeneity between the individual subgroups. This is due to the different assessment methods with their different scales. This is partly due to the fact that the study does not provide specific data on pre- or post-testing, but only changes between the two test dates, as in [8]. However, it still made sense to summarize all studies despite differing assessments, as this allowed categories to be formed, thereby reducing the number of graphs.

In total, the hypothesis can only be confirmed for the motor learning variables.

Prospects

To evaluate the effects of exercise therapy, more high quality studies must follow with larger sample sizes, comparable groups, interventions with precise descriptions and longer intervention periods with interim evaluations and follow-ups.

Article Information

Conflicts of interest: There is nothing to declare.

Author's contributions: Design, data acquisition, analysis and interpretation, draft, final approval: AD. Data acquisition and analysis, revision: LMT.

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Disclaimer (Artificial Intelligence): The author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.), and text-to-image generators have been used during writing or editing of manuscripts.

Competing Interests: Authors have declared that no competing interests exist.

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