Does physical activity improve motor function and gait in huntington disease? A systematic review and meta-analysis

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Introduction. Huntington's disease (HD) is a degeneration of the brain.

Objective. To assess the evidence of the physical activity (PA) to improve motor function, gait speed, and walking endurance in individuals with HD.

Materials and methods. Two reviewers independently screened references and selected relevant studies to identify randomized controlled trials (RCT), from MEDLINE/PubMed, CENTRAL, PEDro, Scopus, CINAHL, Web of Science databases from inception to September 2021. Two reviewers evaluated risk of bias by the PEDro scale. The primary outcome was assessed motor function, gait speed and walking endurance as a secondary outcome was evaluated activities of daily living (ADL), lower limb functionality strenght, balance, mobility and cognition function in HD.

Results. Eight RCT were finally included (231 individuals). Forest plots showed a positive effect for gait endurance, the mean difference (MD) was 17.40 (95% CI from 5.40 to 29.35; p = 0.004), the MD lower limb functionality strength was 1.76 (95% CI from 0.18 to 3.33; p = 0.03) favoring PA group and the MD cognition function was 1.83 (95% CI from 0.50 to 3.16; p = 0.007). No benefits were found for motor function, gait speed, ADL, balance and mobility.

Conclusions. Positive effects of programs PA were observed for walking endurance lower limb functionality strenght and cognition function in low and moderate stage of HD. However, no benefits were found for motor function, gait speed, ADL, balance and mobility. All authors included aerobic exercises in their programs but is unclear if vigorous and intensive PA is optimal for individuals with HD.

Key words. Chorea. Exercise. Gait. Huntington's disease. Motor function. Physical activity.

Introduction

Huntington's disease (HD) is a neurodegenerative syndrome characterized by selective regional degeneration of the central nervous system [1]. HD includes motor impairments such as involuntary movements (chorea), that affect ambulation [2], cognitive/behavioral symptoms [3] and neuropsychiatric disorders [4] that progress over 15-20 years and culminate in death [3]. These deficiencies cause a greater risk of falling, which affects the activities of daily living (ADL) and decreases quality of life (QoL) [5]. For this reason, it is important to investigate treatments to alleviate and reduce these alterations [6].

Physical activity (PA) has been shown to have highly beneficial effect on the brain [7]. PA is defined as 'any movement produced by skeletal muscles resulting in energy expenditure' [8]. PA includes sports, physical exercise and activities carried out in ADL, leisure and displacement [9]when appropriately evaluated and advised by a health professional. Physical exercise is a subcategory of PA, which is planned, structured, and repetitive [8].

Some articles have been published regarding PA in HD individuals [10-14]. However, to the best of our knowledge no meta-analysis of randomized controlled trials (RCT) have been found. Thus, the objective of this meta-analysis was to identify and analyze RCT in HD adults who undergo PA as a treatment to improve motor function and gait.

Materials and methods

The primary outcome was motor function, gait speed and endurance. Secondary outcomes were ADL, lower limb functional strength and mobility,

balance, and cognitive function. Motor function is the capacity to learn or to show the skillful and efficient assumption, modification, maintenance and control of voluntary movement patterns and postures. Gait is defined as the manner in which an individual walks, considered by speed, cadence, rhythm, and step and stride length [15]. Gait endurance is related to the ability to perform walking over an extended period.

This study followed the recommendations of the PRISMA 2020 [16] and the PICOS criteria. A computerized search strategy was carried out in the following databases CENTRAL, MEDLINE/PubMed, Web of Science, PEDro database, CINAHL, TripDatabase, Scopus and manual search in Google Scholar. The PubMed search strategy was used and adapted it for to other databases (Appendix). Inclusion criteria were RCTs published in English, Spanish, Portuguese, French, Italian and Chinese from inception to September 2021; studies involving HD adults; PA alone or combined with another rehabilitation approach or dual task (motor-cognitive function training) as intervention group; usual care or another physical therapy as control group; studies that assessed the main variables. Exclusion criteria were studies with animal models.

Two authors (LLL/RC) with a third author (AP) in the event of disagreement conducted searches for eligible articles and data extraction independently. Duplicate articles were rejected, and the remaining studies were analyzed for their relevance. Screening of the articles was initially based on the title and secondly by the abstract and the full text. The following data were extracted by two authors independently (LLL and RC): first author, country, year of publication, setting; gender, mean age and sample size by groups; PA interventions; usual care or control group interventions; intervention duration; outcome measures; follow up; main results and adverse events.

Study risk of bias assessment

It was evaluated by two independent researches (SS and LLL) by the PEDro scale score [17], if there were discrepancies was performed by another researcher (RC). There were the following cut-off points: 9-10: excellent; 6-8: good; 4-5: fair; <4: poor.

Synthesis methods

A mean difference (MD) was used if all studies used the same tool to measure an outcome, and a standard mean difference (SMD) if the tool varied between studies. p values lower than 0.05 were used for the determine statistical significance. The generic inverse variance method was used of adjusted effect estimates and its standard error. Each study estimate of the relative treatment was given a weight that is equal to the inverse of the variance of the effect estimate. The effect size was classified as 0.2, 0.5, 0.8, and 1.3, which were considered small, medium, large, and very large, respectively [18]. All effect size measures were expressed with a 95% confidence interval. Heterogeneity was expressed and visually assessed by forest plots and using the I^2 statistic. It was classified high if I^2 was >75%. Missing data of studies was requested by email from the corresponding author. Narrative review and tables were used when there was insufficient data for quantitative analysis. Funnel plots were used to show the risk of publication bias.

Figure 1. PRISMA diagram of the process used to identify studies. RCT: randomized controlled trials.

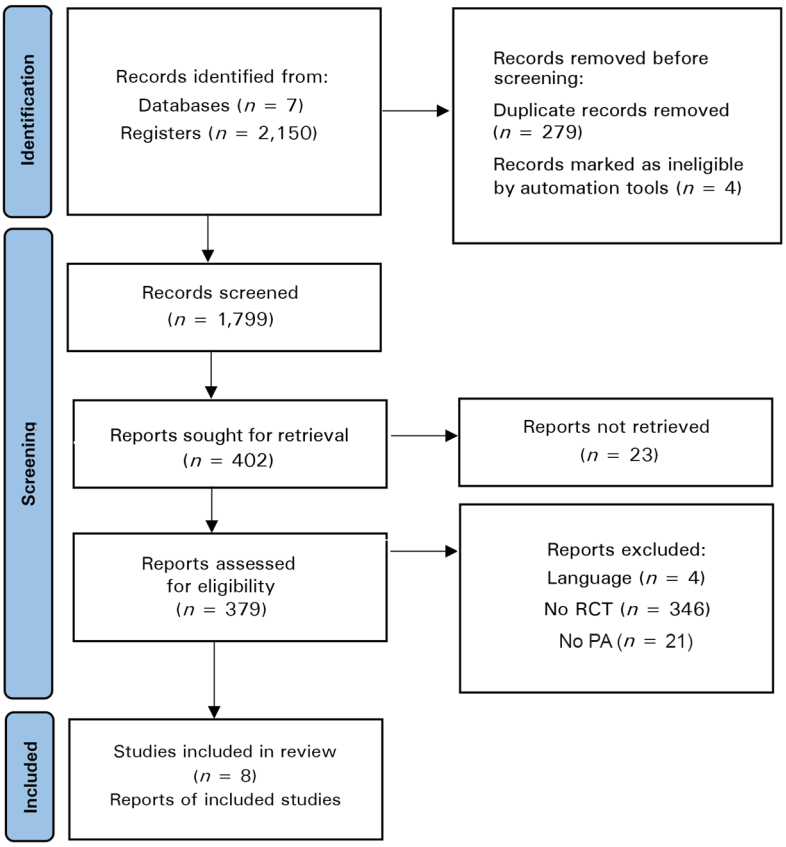

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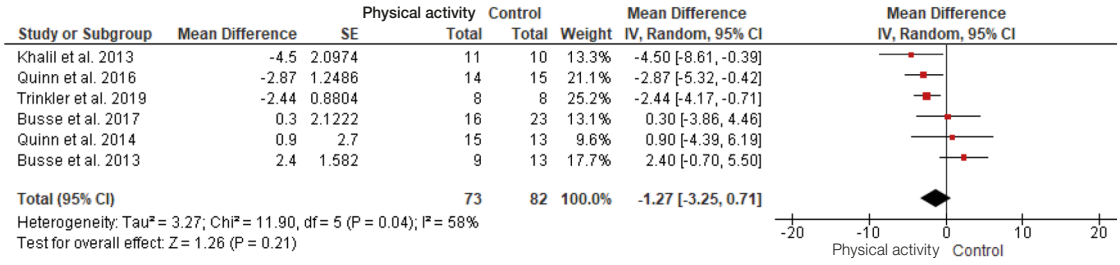
Figure 2. Meta-analysis for the comparison of physical activity group and control group for motor function by Unified Huntington Disease Rating Scale Total Motor Score and their subscales. Performed by Revman version 5.4. https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman.



Results

Study selection

The figure 1 shows the PRISMA flow chart. Finally, 8 RCT were included [19-26]. Inter-rater agreement by Cohen's Kappa index showed an almost perfect agreement (κ = 81).

Study characteristics

Table I summarize the characteristics of the studies selected. It included 231 HD individuals. The programs of the PA group differ across studies. Aerobic exercise such as static cycling or walking, stretching and resistance training were the most common activities. However, Trinkler et al intervention [19] consisted of contemporary dance, whereas Cruickshank et al [20] included a cognitive therapy in addition to PA. All control groups continue with their usual care, except Busse et al [25] that included a social interaction intervention. Most of the study intervention programs were performed at home, and some of them in combination with gym or studio in-group sessions. The intervention period ranged from 8 to 36 weeks.

Motor function was measured in seven studies by the Unified Huntington Disease Rating Scale total Motor Score (UHDRS-TMS) [27] and Total Functional Capacity (TFC), which evaluates capacity to work, self-care tasks, perform domestic chores, live independently and handle finances. The scale has 31 items with the highest score as inability to execute the motor task. Gait speed was measured in four studies by the 10 Meter Walk Test and gait endurance was assessed in four studies by 6-Minute Walk Test.

Regarding the ADL was also measured in five studies. The most common tool used was the Physical Performance Test (PPT) [28]. Lower limb functional strength was assessed using 10/15 repetitions or a 30-second sit-stand test. Cognitive function was measured in five studies by the UHDRS part-II or their subscales. Higher scores indicate better cognitive performance. Balance was evaluated in five studies and the most common tool was the Berg Balance Scale (BBS) [29]. The Activities-specific Balance Confidence Scale (ABC) [30] was used in two studies and the Romberg test. Finally, mobility was evaluated in two studies by the Timed Up and Go Test (TUG) [31].

Risk of bias in included studies

Table II summarize the mean PEDro scale score of included studies. It was 6.5 points (range 5-8) out of 10-point criteria, indicating a good score. No study with 9-10 points was found, because it is difficult to blind the individuals and therapist. In addition, a funnel plot was performed for each meta-analysis, and no publication bias was found.

Syntesis of results

One comparison performed between control group (CG) and PA group. The age of participant and UHDRS-TMS were included as covariates in all models. Adjusted estimates were calculated for adjusting for baseline measures of outcome scores. This approach was taken in order to provide the most valid effect size estimates for this individuals.

Motor function

A meta-analysis was performed for six studies (Fig. 2). A pooled MD -1.27 (95% CI from -3.25 to 0.71, p = 0.21) was found in the endpoint showed non-sig-

Table I. Study characteristics, outcome measures, setting and results.

	Sample size; mean age SD; male/female	Intervention physical activity group	Intervention control group	Outcome measures	Setting	Results
Thompson et al 2012. Australia [23]	PAG: *n* = 9; 53.8±2.9 CG: *n* = 11; 52.3±2.6 Early-to-middle stage HD	The gym exercise comprised supervised group sessions 5 m. warm-up,10 m. aerobic exercise, 40 m. resistance exercise, 5 m. cool-down, once/week for 36 weeks; A tailored, self-monitored home-based exercise 3 times /week for 24 weeks and OT 1h Usual care medication	Usual care medication anti-psychotics, anti-depressants, anxiolytics, anti-dyskinetics	Motor function: UHDRS-TMS Balance: ABC-UK, SOT Body composition: X-ray Lower/upper limb muscle strength: Dynamometry Neurocognitive/psychological: SDMT, HVLT-R, D-KEFS, TMT and BDI-II. Patient-derived goals: GAS QoL: SF-36v2, Health Questionnaire, Huntington's Disease-Quality-of-Life-Battery-for-Careers. Assessment: T0: baseline: T1: 36 weeks	Gym and home	Better PAG for motor function, balance, upper/lower muscle strength, cognitive, walking-up-and-down stairs and walking around the house (ABC-UK) and fat-free mass D-KEFS, HVLT-R, BDI-II, QOL and postural stability and GAS ND. No adverse events Adherence: 85% in gym and 56% in home
Busse et al 2013 United Kingdom [21]	PAG: *n* = 16; 53.3±12.5; 8/9 CG: *n* = 15; 47.4±9.5; 8/7 Early to middle stages HD	The gym exercise comprised supervised group sesions. 20-30 m. of aerobic exercise (cycle ergometer) 55%-75%<age-predicted maximal heart rate and moderate to hard levels of exertion on modified Borg scale (4-6), resistance exercises 10 repetitions (leg press, leg extension, lateral pull down, hamstring curl, calf raises). Followed by self-directed walking sessions twice weekly for the duration of the intervention.2 times/week home-based walking program for 10 m./day twice per week increasing time progressively up to a 30 m, maximum (3-4 Borg scale). once/week for 12 weeks. Usual care medication	Usual care medication: analgesic, anti-choreic, anti-depressant, antihypertensive, diabetes and other	Motor function: UHDRS mMS Cognitive function: UHDRS cognitive subscales Capacity to work: UHDRS-TFC ADL: PPT Functional lower limb strength: 30-s sit-to-stand test Standing balance: Romberg test Gait speed: 10-MWT Walking endurance: 6-M walking test. QoL: SF-36 Falls: diary data Retention/adherence rates Assessment: T0: baseline, T1: 12 weeks, T2: 24 weeks	Gym and home	Better PAG for 6-M walking test and SF-36 MCS No falls Adverse events: in 4 individuals (fatigue, back pain) Adherence: 82%
Khalil et al 2013 United Kingdom [26]	PAG: *n* = 13; 54.2±9.9; NR CG: *n* = 12; 51.3±16.9; NR Early to middle stages HD	Exercise at home using DVD based on the patients' specific abilities: 1 section) warm up and flexibility activities, 2-4 section) strength, flexibility, balance and coordination and endurance exercises, sit-to-stand, stepping up onto stairs, and getting on and off the floor, 5 section) relaxation, stretching and breathing techniques. 3 times/week for 8 weeks in addition 30 minutes of walking once/week at a light intensity for 8 weeks. Total 32 sessions Usual care medication	Usual care medication	Motor function: UHDRS mMS. Gait: speed (m/s), step time (s), step time (CV%) Balance: BBS ADL: PPT Functional lower limb strength: 30-seconds sit to stand test Health –related quality of life: PF, RP, RE, SF-36, MH, VT, BP, GH, PCS, MCS	Home	Better PAG for motor function, gait speed, balance, lower limb strength and ADL Quality of life as measured by the No adverse events Adherence: 29.4 SD 1.8
Quinn et al 2014 United Kingdom, Netherlands, Germany, Norway [22]	PAG: *n* = 15; 55 ±10; 7/8 CG: *n* = 13; 59.4±10; 6/7 Middle stage	Task-specific home 3-based training by physiotherapist focusing on walking 20 m., sit-to-stand (10-15 m.) and standing (15-20 m.) one hour per 2 times /week for 8 weeks Maximum and average heart rate using a heart rate monitor Usual care medication	Usual care medication	Motor function: UHDRS-TMS Cognitive function: UHDRS cognitive score ADL: PPT, IPAQ, MET minutes Lower limb strength: 30-s sit to stand test Gait speed: 10-MWT Balance: BBS Mobility: TUG Vitality: 7-item Vitality Scale Depression: HADS global score QoL: EuroQoL-5D, HDQoL. Assessment: T0: baseline, T1: 8 weeks, T2: 16 weeks follow up	Home	Effect sizes on all measures were small. ND between groups Adverse events: 5 PAG (3 falls, 2 slips), 1 CG (behavior change) Retention: 15 (SD) 96,9% Adherence: 14.5 (SD) 1.3

Table I. Study characteristics, outcome measures, setting and results *(cont.)*.

	Sample size; mean age SD; male/female	Intervention physical activity group	Intervention control group	Outcome measures	Setting	Results
Quinn et al 2016 United Kingdom, Netherlands, Germany, Norway [24]	PAG: *n* = 17; 53±11; 9/8 CG: *n* = 15; 51±17; 7/8 Middle-late stage	Aerobic exercise (cycle ergometer) 5-25min warm up intensity increasing, last 3-min decreasing intensity, 10-15 m. resistance exercises (lower limb, sit to stand by chair, seated weighted wood chop, plank by wall, chair lunge) and 2.3-m. stretching (chair stretches – calf, hamstrings, quads, neck, triceps, upper back 15-20 seconds each) Total 50 m./session for 3 times/week for 12 weeks Usual care medication	Usual care medication	Motor function: UHDRS mMS ADL: IPAQ Cognition: UHDRS cognitive subscales (word reading, stroop interference, SDMT) and TMT Functional lower limb strength:15 repetitions sit-to-stand test Physical fitness: predicted VO2 maximum. Gait speed: 3-m walk test. Dual tasking: simple dual task complex dual task Depression: HADS QoL: EQ-5D-3L Falls: diary data Assessment: T0 baseline, T1: 13 weeks, T2: 26 weeks follow up	Hospital-based gym, or home	Better PAG for motor function, physical fitness, QoL, falls ratio. Adherence: 13 participants the trial completed >75%, one 61% Adverse events: 2 EG, 1 CG
Busse et al 2017 United Kingdom [25]	PAG: *n* = 22 (16 analyzed); 56.1±10.3; 12/10 CG: *n* = 24 (22 analyzed); 53.7±9.9; 13/11	Physical activity self-management intervention was grounded within the framework of self-determination theory: 1 section: warm up and flexibility activities, 2-4 section: balance, strength, flexibility, and coordination and exercise aerobic (walking), stepping up onto stairs, functional tasks sit-to-stand, and getting on and off the floor, 5 section: relaxation, stretching and breathing techniques. Patients developed up to 3 realistic physical activity goals and were assisted with individual physical activity progression through goal discussion. 14-week Usual care medication	Usual care medication and social intervention (conversational interaction) 6 social interactions	Motor function: UHDRS mMS, UHDRS TMS Cognitive function: SDMT, verbal fluency ADL: PPT, IPAQ-short form Mobility: TUG Home and community mobility: Life Space Space Assessment Self-efficacy: Lorig scale Generic health: EQ-5D, ICECAP-A Coaching satisfaction: PAS Healthcare Climate Questionnaire Walking endurance: 6-M walking test Assessment: T0: baseline, T1: 16 weeks, T2: 26 weeks follow up Falls: diary data	Home Assessments conducted in the clinic 8 sites	Motor function: ND A program physical activity self-management and coaching intervention is feasible and worthy of further investigation. No adverse events were related to the intervention Retention: PAG: 77%, CG: 92% Adherence: PAG: 82%, CG: 100% Falls: EG: 14, CG: 24
Cruickshank et al 2018 Australia [20]	PAG: *n* = 9; 53.8±2; 4/5 CG: *n* = 9; 51.2±2.7; 5/4	Supervised exercise aerobic (cycle ergometer) and resistance (machines) strengthening exercises, walking, balance and fine motor exercises. Cognitive therapy (paper and pencil and cognitive exercises) and ADL. Gym: 60 m. once/week followed by home:60 m. session per 3 times/week for 36 weeks. Usual care medication	Usual care medication	Gait speed: 10-MWT Balance: BBS Functional lower limb strength: 10 repetitions sit-to-stand test Upper/Lower limb strength: dynamometry Manual dexterity: Timed Nut and Bolt Test Walking endurance: 6-M walking test Adherence: diary data Assessment: T0: baseline, T1 36 weeks end of treatment	Gym and home	Better PAG manual dexterity and lower limb muscle strength. Gait, balance, walking endurance and upper No adverse events were related to the intervention
Trinkler et al 2019 France [19]	PAG : *n* = 19; 8/11 CG: *n* = 12; 4/8 The patients' ages ranged from 43 to 78 years with a median of 53 years	Contemporary dance: Each session consisted of four parts:1) a warm-up session, including body consciousness and exercises relaxation techniques, 2) the individuals explored their personal way of moving to a particular music theme, 3) patients improvised dance movements together, 4) with auto- and one to one massage exercises on the floor closed each workshop Once/week	Usual care medication and everyday life habits	Motor function: UHDRS-TMS Cognitive function: UHDRS cognitive score and subscales (verbal fluency, stroop interference, SDMT) and MDRS TMT A/B Depression PBA Irritability Lack of enthusiasm Lack of social activities Lack of initiative Apathy: LARS	Studio	Better PAG motor function and cognition end of treatment Neuropsychiatric variables ND No adverse events

Table I. Study characteristics, outcome measures, setting and results *(cont.)*.

	Sample size; mean age SD; male/female	Intervention physical activity group	Intervention control group	Outcome measures	Setting	Results
Trinkler et al 2019 France [19] *(cont.)*		ifor 20 weeks 2h per session	Usual care medication	QoL T0: baseline, T1: 20 weeks end of treatment and T2: 20 weeks follow up		

ADL: Activities of daily living; ABC-UK: Activities-Specific Balance Confidence United Kingdom version; BBS: Berg Balance Scale; BDI-II: Beck Depression Inventory-II; BP: bodily pain; D-KEFS: Delis-Kaplan Executive Function System; EQ-5D-3L: EuroQol quality of life; FAS: functional assessment scale; GAS: Goal Attainment Scale; GH: general health perception; HADS: Hospital Anxiety and Depression Scale; HD: Huntington's Disease; HDQoL: Huntington's Disease Health-related quality of life; HVLT-R: Hopkins Verbal Learning Test-Revised; IPAQ: International Physical Activity Questionnaire MCS: mental component summary; LARS: Lille Apathy Rating Scale; MCS: Mental Component Summary; MDRS: Mattis Dementia Rating Scale; MH: mental health; mMS: modified Unified Huntington's Disease Rating Scale-motor score; m: minutes; 10-MWT: 10 meters walking test; NBT: Timed Nut and Bolt test; ND: no difference between groups; OT: occupational therapist; PAG: physical activity group; PBA: Problem Behavior Assessment; PCS; physical component summary; PPT: Physical Performance Test; QoL: quality of life; RF: role limited owing to physical problems; RP: role limited owing to emotional problems; SD: standard deviation; SDMT: Symbol Digit Modalities Test; SF-36: 36 Short Form Health Survey; SF: social functioning; SOT: Sensory Organization Test; SWAL QoL: swallow quality of life questionnaire; TMS: total motor score; TFC: total functional capacity of Unified Huntington's Disease Rating Scale; TMT: Trail Making Test; TUG: Timed Up and Go; UHDRS::Unified Huntington's Disease Rating Scale; VT: vitality; (m): minutes, (s): second.

nificant differences between PA and CG. Thompson et al [23] measured motor control but no data available was obtained for meta-analysis, and no benefits were described for the PA group.

Gait speed and endurance

Four studies evaluated gait endurance (Fig. 3 a-b). A pooled MD 17.40 (95% CI from 5.40 to 29.35; p = 0.004). Positive effects were found for PA group. Heterogeneity by I^2 statistic showed a 0%. Four studies assessed gait speed by meters per second. No significant effects were found for PA group with a pooled MD –0.03 (95% CI from –0.31 to 0.26; p = 0.84).

Lower limb functional strength and mobility

Three studies assessed lower limb functional strength by 30-second sit-to-stand test (Fig. 4 a-b). A pooled MD 1.76 (95% CI from 0.18 to 3.33; p = 0.03) was found favoring the PA group. Heterogeneity by I_2 statistic showed a 41%. Cruickshank et al [20] assessed this outcome by 10-repetition sit-to-stand test. In addition, they used isometric and isokinetic strength testing protocols with a positive effect for the PA group. Quinn et al [24]and participants were randomized into either exercise or control (usual care assessed this variable by a 15-repetition sit-to-stand test, but no differences between groups was found. Two studies analyzed mobility by the TUG test the MD was -0.47 (95% CI from -0.94 to 0.01; p = 0.06). No differences were found between groups.

Activities of daily living, balance and cognitive function

Four studies evaluated ADL (Fig. 5 a-c) by the PPT. A pooled MD 1.87 (95% CI from -0.10 to 3.83, p = 0.06) showing no between-group differences. Four studies analyzed balance, a pooled SMD 1.96 (95% CI of -0.50 to 4.43; p = 0.12) was performed. No positive effect was found for the PA group. Four studies assessed cognitive function by the UHDRS score and Trail Making Test B. The SMD was 1.83 (95% CI from 0.50 to 3.16; p = 0.007) favoring the PA group.

Falls

Falls were measured by Busse et al [21,25], Quinn et al [22,24] and Khalil et al [26] during the intervention period but a meta-analysis was not possible. Busse et al [25] reported 14 falls for the PA group and 24 falls for the CG. Quinn et al [22] reported 3 falls in the PA group. Busse et al [21] and Khalil et al [26] did not report any fall. Finally, Quinn et al [24] reported a fall incidence of 1.12 for the CG and 0.82 for the PA group. Therefore, there was a reduction of fall incidence.

Treatment adherence

Trinkler et al [19], Thompson et al [23], Quinn et al [24], Khalil et al [26], Busse et al [21], Quinn et al [22], Cruickshank et al [20] found a good adherence during the intervention period. However, it decreased in the home-based PA program. Busse et al [25] did not assess adherence treatment.

Figure 3. Meta-analysis for the comparison of physical activity group and control group (a) walking endurance by 6 Minute Walk test and (b) gait speed by meters per seconds. Performed by Revman version 5.4. https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman.

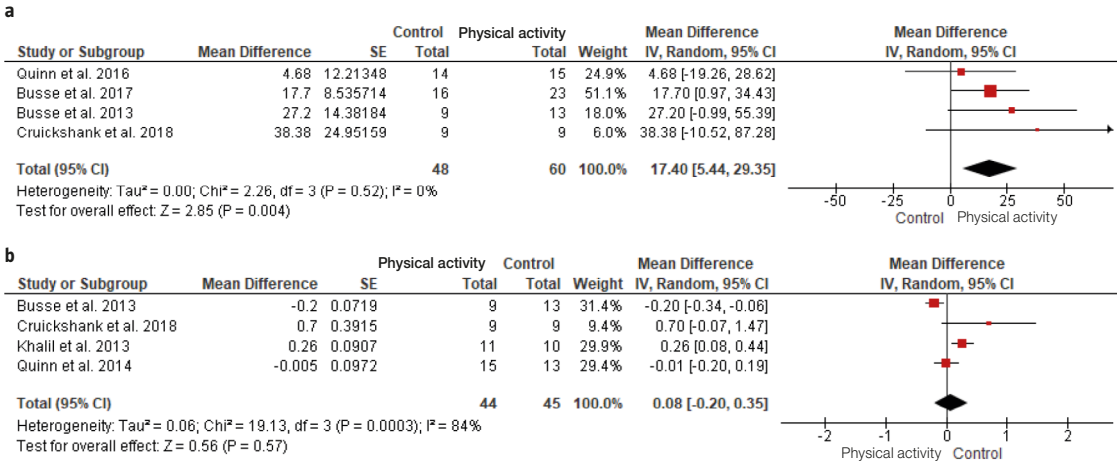
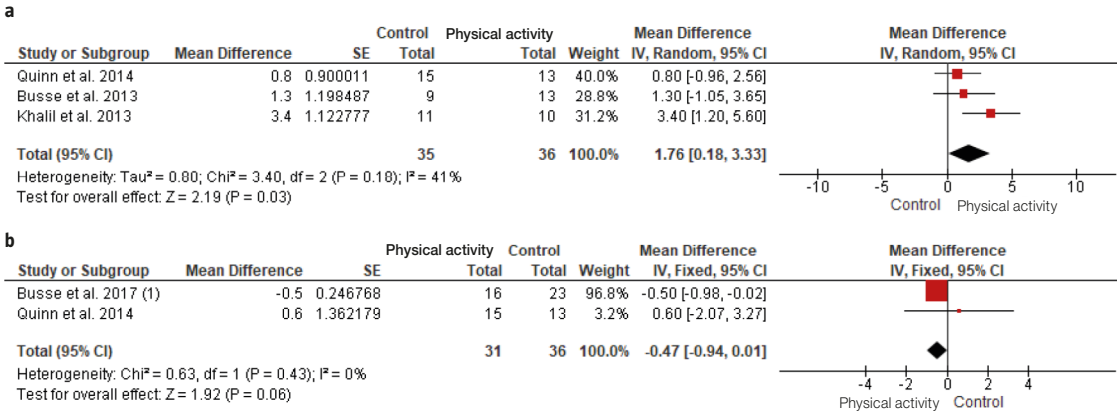


Figure 4. Meta-analysis for the comparison of physical activity group and control group (a) lower limb functional strength by sit to stand test; (b) and mobility by Timed Up and Go test. Performed by Revman version 5.4. https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman.



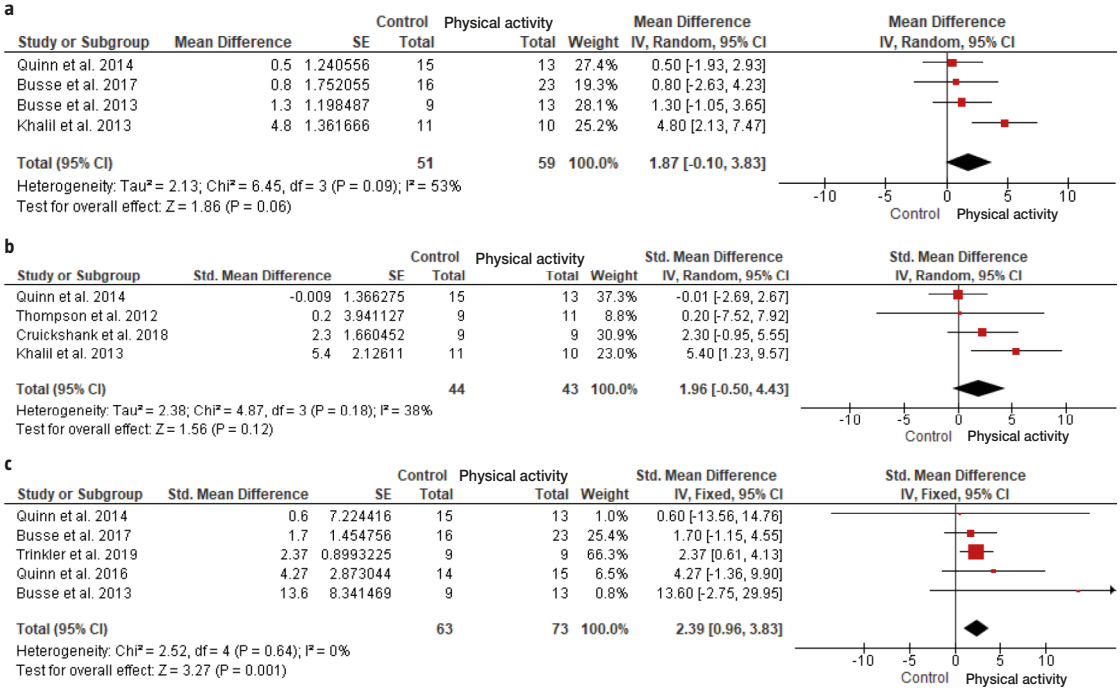
Adverse events

Cruickshank et al [20] described no adverse events associated to the intervention. Busse et al [25] reported seven adverse events but were consequence of concurrent illness. Quinn et al [22] informed one serious adverse event in the PA group due to a fall at night. Quinn et al [24] reported that two individuals of the PA group had symptoms of concomitant conditions that were aggravated during the intervention. Busse et al [21] related four individuals with fatigue and back pain. Khalil et al [26] and Thompson et al [23] no described adverse events. Trinkler et al [19] did not measure this outcome.

Discussion

A PA-based program shows benefits in terms of increased gait endurance, lower limb functionality strenght, and cognitive function in HD individuals. However, no positive effects were observed for mo-

Figure 5. Meta-analysis for the comparison of physical activity group and control group (a) activities of daily living by Physical Performance test (b), balance by Berg Balance scale and Activities and Specific Balance Confidence United Kingdom version; (c) and cognition by Unified Huntington Disease Rating Scale Cognitive Function part II and Trail Making Test. Performed by Revman version 5.4. https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman.



tor function, ADL, gait speed, mobility, and balance. All authors agreed to use the UHDRS-TMS to assess motor function, following the recommendations of Mestre et al[32]. Additionally, PA seems to decrease the incidence of falls. Adherence to treatment was considerable when it was carried out face-to-face and decreased when it became self-administered at home.

The results of this meta-analysis are somewhat confusing, leading to apparent contradictions, such as significant improvements in walking endurance but no effect on motor function, balance, gait speed, and mobility. This fact is also found in the study of Warburton et al [33] who reports health benefits of PA, including improvements in cardiopulmonary function and endurance, but it does not translate into improved performance of motor tasks. The PA increases aerobic capacity and muscle strength and therefore physical well-being [34]. Taking into account that many authors included aerobic exercise in their intervention.

Our analysis suggests that a PA program has positive effects on cognition. This finding is in the line described by Kemoun et al [35]equilibrium and endurance on cognitive function and walking efficiency in patients with dementia [36] and in the chronic phases of acquired brain injury [37]. Aerobic exercise influences neurophysiological pathways that promote enhanced post-exercise cognitive functioning, such as working memory, processing speed, and executive function [38]. Low-to-moderate intensity coupled with high-intensity exercise sessions appear to improve the performance on several cognitive concepts in healthy people [39]. It can be confirmed that movement facilitates cognition throughout life [40].

It has been observed that falls and cognition are closely related [41]. It is important to consider that incidence of falls is a factor of making individuals dependent on a caregiver. It has been revealed that performing PA leads to a growth of the hippocampal volume and also increases the serum in the brain-derived neurotrophic factor (BDNF) [42], which is known to cross the blood-brain barrier [43]. In last term, the fact of BDNF signaling at synapses improves long-term potentiation, a proce-

Tabla II. PEDro scale.

	Eligibility criteria[a]	Random allocation	Concealed allocation	Baseline comparability	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up[b]	Intention-to treat analysis	Between groups comparisons	Point estimates and variability	Score
Thompson et al, 2012	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6
Busse et al, 2013	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	7
Khalil et al, 2013	Yes	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	5
Quinn et al, 2014	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	7
Quinn et al, 2016	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Busse et al, 2017	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	7
Cruickshank et al, 2018	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7
Trinkler et al, 2019	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	5

[a] This criterion not influences internal validity of the study. This item is not used to calculate the PEDro score. [b] Defined an adequate follow-up as less than 15% drop-outs.

dure of synaptic strengthening associated with memory and learning.

PA programs for physical and strength training, as well as balance and coordination, must be adapted to the individual with HD and depend on the stage of the disease. The PA programs included multimodal training interventions and it might be convenient to analyze and evaluate the various types of interventions in isolation to observe their effectiveness. For example, it has been shown that trunk movement in individuals with HD is affected during walking with an increase in the amplitude and speed of the medio-lateral sway [44]. It could be that core stability exercises improve gait and balance, as it has been shown in other neurological diseases [45,46].

An issue that needs further investigation is PA intensity, as vigorous exercise has been shown in animal models to worsen HD [47]. Therefore, the PA program should be necessary to carefully adapt to each HD individual by a qualified personnel. It is recommended that all PA training interventions should be accompanied by frequent assessments for any accelerated worsening of symptoms [12].

The development and definition of methods to enable PA behavior change is of great interest to neurological practice. This could be due in part to better recognition of the pivotal role of PA as a potential disease-modifying intervention [48]. Implementing secondary preventive strategies is crucial need for the large numbers of individuals living with chronic diseases [49]. HD is a neurodegenerative disease with a slow progression, that presents different questions for any clinical trial design, and a better understanding of the characteristics of illness progression is essential for researchers [50].

Limitations

The results of this meta-analysis are mainly based on small studies with few individuals. Most of them were at the early or middle stages of the disease. The control group of the studies did not perform any physical intervention. The included studies were heterogeneous in terms of intensity, diversity of PA program, time, and had limited use of intention-to-treat analysis, follow-up, and implementation of allocation concealment to account for losses due to follow-up dropouts.

Conclusions

A program of PA including of aerobic and anaerobic exercises improves walking endurance, lower limb functional strength and cognitive function in early or middle stages of HD. Aerobic PA can be recommended because is safe and reports some benefits. However, many questions related to the role of the intensity of strength exercises, as part of a PA pro-

gram in HD are still unclear. High-quality studies are needed to address these questions.

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Appendix. MEDLINE/PubMed search.

('human s'[All Fields] OR 'humans'[MeSH Terms] OR 'humans'[All Fields] OR 'human'[All Fields]) OR ('huntington'[All Fields] OR 'huntington s'[All Fields] OR 'huntingtons'[All Fields] OR 'Huntington's disease'[All Fields] OR ('chorea'[MeSH Terms] OR 'chorea'[All Fields] OR 'choreas'[All Fields])) AND ('physical activity' '[All Fields] OR 'therapeutic exercise'[All Fields] OR ('exercise'[MeSH Terms] OR 'exercise'[All Fields] OR ('training'[All Fields] AND 'exercise'[All Fields]) OR 'training exercise'[All Fields]) OR ('exercise'[MeSH Terms] OR 'exercise'[All Fields] OR ('physical'[All Fields] AND 'activity'[All Fields]) OR activity).

¿La actividad física mejora la función motora y la marcha en la enfermedad de Huntington? Una revisión sistemática y metaanálisis

Introducción. La enfermedad de Huntington (EH) es una degeneración del cerebro.

Objetivos. Evaluar la evidencia de la actividad física (AF) para mejorar la función motora y la marcha en las personas con EH.

Materiales y métodos. Dos revisores examinaron de forma independiente las referencias y seleccionaron ensayos controlados aleatorizados en Medline/PubMed, CENTRAL, PEDro, Scopus, CINAHL y Web of Science desde el inicio hasta septiembre de 2021 y evaluaron el riesgo de sesgo mediante la escala PEDro. Las variables principales fueron la función motora y la marcha, y las secundarias, las actividades de la vida diaria (AVD), la funcionalidad (extremidades inferiores), el equilibrio, la movilidad y la función cognitiva en la EH.

Resultados. Se incluyeron ocho ensayos controlados aleatorizados (231 individuos). Se observó un efecto positivo para la resistencia en la marcha, la diferencia de medias fue de 17,4 (intervalo de confianza al 95%: 5,4-29,35; p = 0,004), la diferencia de medias para la funcionalidad (extremidades inferiores) fue de 1,76 (intervalo de confianza al 95%: 0,18-3,33; p = 0,03) y la diferencia de medias para la función cognitiva fue de 1,83 (intervalo de confianza al 95%: 0,5-3,16; p = 0,007) a favor del grupo de AF. No se encontraron beneficios para la función motora, la velocidad de marcha, las AVD, el equilibrio y la movilidad.

Conclusiones. Los programas de AF mejoran la resistencia en la marcha, la función cognitiva y la funcionalidad (extremidades inferiores) en la EH. Sin embargo, no se observaron efectos positivos para la función motora, la velocidad de la marcha, las AVD, el equilibrio y la movilidad. Todos los autores incluyeron ejercicios aeróbicos en sus programas, pero no está claro si la AF vigorosa e intensiva es óptima para las personas con EH.

Palabras clave. Actividad física. Corea. Ejercicio. Enfermedad de Huntington. Función motora. Marcha.