Exercise Interventions in Huntington's disease: An Individual Patient Data Meta-Analysis

Rebecca Playle PhD[1], Polyxeni Dimitropoulou PhD[1], Mark Kelson PhD[2], Lori Quinn EdD[3], Monica Busse PhD[1]

Affiliations
1. Centre for Trials Research, Cardiff University, Wales, United Kingdom
2. University of Exeter, United Kingdom
3. Teachers College, Columbia University, New York, New York

Corresponding author
Dr Rebecca Playle
Head of Health Services Research Statistics
Centre for Trials Research
College of Biomedical and Life Sciences
Cardiff University
4th Floor, Neuadd Meirionnydd, Heath Park
Cardiff. CF14 4YS
United Kingdom
Tel: +44(0)29 20687516
Email: playlera@cf.ac.uk

Word count. 3685
Running title. Exercise Interventions in Huntington's disease
Key words. Huntington's Disease, Exercise, Physical Activity, Individual patient data meta-analyses

~~**Funding sources and conflicts of interest:** Funding was provided by Health and Care Research Wales. The Centre for Trials Research, Cardiff University, is funded by the Wales Assembly Government through Health and Care Research Wales. The authors declare no competing interests.~~
~~Financial disclosure for previous 12 months:~~
~~RP: Grants and Research: European Framework funding, Health and Care Research Wales (HCRW), Gossweiler Foundation; Salary: Cardiff University~~
~~PD: Grants and Research: Health and Care Research Wales (HCRW), Gossweiler Foundation; Salary: Cardiff University~~
~~MK: Salary: University of Exeter~~

~~LQ: Grants and Research: Huntington Study Group; Jacques and Gloria Gossweiller Foundation; Royalties: Elsevier Publishers for textbook Documentation for Rehabilitation: A guide to clinical decision making in physical therapy; Salary: Columbia University, Cardiff University~~

Abstract

Background: Physical activity may be beneficial in Huntington's disease, however studies to date have been underpowered to detect change. We combined data from five randomized controlled feasibility trials using individual patient data meta-analyses.

Methods/Design: All trial interventions comprised a combination of supervised and self-directed physical activity, with varied emphasis on aerobic, strength, endurance, flexibility, and task training. Duration ranged from eight to 16 weeks. The primary outcome was the modified Unified Huntington's Disease Rating Motor Score. Secondary outcomes included the Symbol Digit Modality Test, Berg Balance Scale, 30-second Chair stand, Timed Up and Go, Gait speed, Physical Performance Test, six-minute Walk, International Physical Activity Questionnaire, Hospital Anxiety and Depression Scale, EuroQol Health Utility Index, Short-Form 36 Health Related Quality of Life Scale. The primary analysis employed a two-stage approach. A one-stage approach was explored as a sensitivity analysis using a cross-classified (by study site) linear mixed effects model.

Results. 121 participants provided complete data. Risk of bias was moderate; however primary outcomes were blind assessed. Primary pooled effect estimates adjusted for baseline modified motor score (95% CI) were 0.2 (-2.1 to 2.6) favoring control. There was considerable heterogeneity between the studies.

Conclusions. There was no evidence of an exercise effect on the modified motor score in these relatively short duration interventions. Longer duration trials incorporating supervised components meeting frequency, intensity, time and type principles are required. Lack of common outcomes limited the analysis and highlight the importance of a core outcome set for evaluating exercise in Huntington's disease.

Introduction.

Huntington's disease (HD) is a neurodegenerative disease which results in impairment of cognition, motor function, and behavior[1]. These impairments decrease independence in activities of daily living and quality of life[2] even from relatively early in the disease. At present, pharmacological interventions focus on symptom management, including decreasing chorea and minimizing depression and anxiety, however none have been effective in producing a disease-modifying effect. The evaluation of non-pharmacological interventions, such as exercise and physical activity, as both stand-alone and adjunctive therapies, has therefore never been more relevant.

A recently published mixed methods systematic review[3] suggests that there is preliminary support for the benefits of exercise and physical activity in HD in terms of motor function, gait speed, and fitness, as well as a range of physical and social benefits identified through patient-reported outcomes, however large sample randomized controlled trials are still unavailable. Interventions that incorporated aerobic and strengthening programs in people with early-mid stage HD were recommended. This finding has been further supported by positive findings in a more recent study of high intensity exercise in people with HD[4]. There is equivocal evidence in support of multi-disciplinary rehabilitation interventions, which incorporate physical and occupational as well as a range of other functional training activities. While several studies[5-11] report beneficial effects on a range of cognitive and motor outcomes, the strength of this evidence is relatively weak due to a lack of randomized controlled studies.

Our group have conducted a series of randomized controlled trials (RCTs) focused on aerobic conditioning, strength training, flexibility and balance exercises, task-specific training and promotion of physical activity, and have demonstrated the feasibility, acceptability and safety of these interventions in people with early-mid stage HD[12-16]. Although these studies have evaluated relatively short term (8-16 weeks) interventions, individually they have provided some indication that changes in motor function, mobility, endurance, fitness and quality of life can be achieved through regular exercise and physical activity.

Large scale, long-term clinical trials, both pharmacological and non-pharmacological interventions, are limited in individuals with HD for several reasons, most notably because HD is rare and most clinics have wide geographical catchment areas. This latter issue is further compounded in exercise trials, where in-person visits are essential to ensure intervention fidelity. In order for exercise interventions in HD to progress, researchers must utilize statistical analysis, such as meta-analysis, that can combine datasets making the best use of well-designed studies.

Recently, with the advent of increased data sharing, meta-analyses utilizing the individual patient data (IPD) from each study have become more common. A key advantage of IPD meta-analysis is that analyses across studies can be standardised and additional statistical power may be available when baseline prognostic factors can be adjusted for consistently[17]. They are also more flexible when the effects of patient level treatment interactions are of interest[18].

The purpose of this paper is to present results from an individual patient data meta-analysis

conducted across five feasibility RCTs of exercise intervention in patients with HD[12-16].

Methods.

Inclusion and exclusion criteria. All trials (n=5) included in this meta-analysis were small feasibility randomised controlled trials (RCTs) published by the same primary authors[12-16]. The trials examined supervised and self-directed exercise and physical activity interventions in patients with HD, used similar comparators and outcomes, and measured the isolated effects of exercise. Details of individual trial interventions, comparators, outcomes and analyses are shown in Table 1.

Participants in the trials had to satisfy the following common inclusion criteria (1) diagnosis of HD, confirmed by genetic testing and neurological examination (2) over 18 years' old and (3) on stable medication regimen for 4 weeks prior to initiation of trial and able to maintain a stable regime for the course of trial. Participants in ENGAGE-HD[14], Move to Exercise[15] and TRAIN-HD[16] had difficulties with walking and/or balance whilst participants in COMMET-HD[12] had the ability to walk independently as a primary means of mobility. Participants in ExeRT-HD[13] were able to use an exercise bike independently. Common exclusion criteria were (1) any physical or psychiatric condition prohibiting the completion of the intervention or assessments, (2) or history of additional prior major neurological condition such as stroke or orthopaedic condition limiting mobility.

Combined dataset. The data from each separate study were combined into one dataset for the individual patient data meta-analysis. Any outcomes that were recorded in two or more of the individual trials were included in the individual meta-analyses. Appropriate time-points were selected in the separate trials to consider as pre- and post- intervention time points in the meta-analysis. Repeat data from the same patient (identified by their unique ID) were removed from the primary dataset such that only the first occurrence in a trial for a participant was retained.

Primary outcome. The Unified Huntington's disease rating scale (UHDRS) modified motor score (mMS) was the primary outcome, calculated as the sum of scorings for the items: dysarthria, tongue protrusion, finger taps left and right hand, pronate/supinate left and right hand, luria, gait, tandem walking and retropulsion pull. A higher score indicates a worse outcome.

Secondary outcomes. Secondary outcomes included the Symbol Digit Modality Test (SDMT), Berg Balance Scale (BBS), 30-sec chair stand test (30sCST), Timed Up and Go test (TUG), Gait speed (derived from 10-metre walk test), Physical Performance Test (PPT), Six-minute walk test (6MWT), International Physical Activity Questionnaire (IPAQ), Hospital Anxiety and Depression Scale (HADS), EuroQol Health Utility Index (EQ5D), Short-Form 36 Health Related Quality of Life Scale (SF-36). The PPT scoring method was slightly different between trials; the original PPT was used in initial trials and the modified PPT in later trials). We used the available PPT component scores for all analyses. In ExeRT-HD, the 2-minute walk was utilized as an outcome; we imputed 6MWT data from 2-minute walk data. For all secondary outcomes except HADS and EQ5D a higher score denotes an improved outcome.

Risk of bias assessment. The risk of bias for each trial was assessed in accordance with the Cochrane Collaboration Guidelines[19]. Details of randomization; allocation concealment; blinding of intervention supervisors; blinding of participants; blinding of outcome assessors; handling of incomplete data; and reporting of results were considered.

Power calculations, sample size and expected treatment effects. A retrospective power calculation was carried out in order to estimate the achieved power of the combined study as an aid only for interpretation and discussion rather than prospective design. A final combined sample size of 121 patients was available for this individual patient data meta-analysis. Based on a two-sided t-test, this provides 87% power at a 5% level of significance to detect a standardised effect size 0.4 equivalent to a decrease from a mean of 15 to 12.2 (with a common SD of 7) for the primary outcome measure of the UHDRS modified motor score (mMS).

Meta-analysis. Individual participant meta-analysis was carried out via a random effects linear regression two stage approach. A random effects model was used to account for study heterogeneity and allowed for a calculation of the contribution of each study to the overall treatment effect estimate. Heterogeneity was assessed using the I^2 statistic as well as a visual inspection of the forest plot.

Baseline values for outcomes were included where available as a covariate. Variables used to balance the randomization in all studies (age and gender) were also included in all models. Covariates considered for inclusion in the primary outcome model were: Total Functional Capacity (TFC) and Symbol Digit Modality Test (SDMT), where they were available in at least four of the studies. In two studies SDMT were derived from the UHDRS total cognitive scores. Analysis included participants who completed all assessments with available data. Only those outcomes where data were available for least 3 out of the 5 studies were included in the meta-analysis.

Sensitivity analyses.
Analyses of the primary outcome was also carried out via a one-stage individual participant data meta-analysis. Here a two-level mixed effects model was used to account for clustering within study. This also allowed for the addition of a cross-classified term to adjust for any additional possible correlation of four sites that were common to individual feasibility trials. Intra-cluster correlation coefficients (ICCs) were calculated from the cross-classified models[20] and are presented as ICC_{site} (the ICC for participants in the same site but different studies), ICC_{study} (the ICC for participants in the same study but different sites) and $ICC_{combined}$ (the ICC for participants in the same site and study). A one stage sensitivity analysis including minimisation variables not present across all studies was also carried out. This resulted in some studies being excluded due to the complete case nature of the analysis. Numbers of participants included in each analysis are given in individual results tables.

Subgroup analyses. Subgroup analyses of key baseline participant-level characteristics (age, gender, function at baseline (Total Functional Capacity (TFC)) and mMS at baseline. were performed on the primary outcome via the inclusion of subgroup*intervention interaction terms. Subgroup variables were centered to ensure separation of within and across study interactions, within study interaction terms are

given in results[18]. The statistical analysis was conducted in Stata version v13.1 (StataCorp LP, USA).

Ethical considerations including data ownership and confidentiality. Participants in the individual trials previously consented to their data being used for relevant research purposes. Each trial has published its main results prior to this meta-analysis.

Results.

Study characteristics. Five studies were included in this individual patient data meta-analysis[3–7]. Data for 158 participants were included in the combined dataset. Twelve participants took part in more than one trial and hence only the first occurrence was retained. Both age and gender were well balanced, as expected, since these variables were used in the minimization algorithms for all studies. The average age of patients across all studies was 53.2 years (SD 11.4) with little variation between studies. The proportion of males overall was 50.4% (61/121) with 48.4% in the control and 52.6% in the intervention across studies.

Risk of Bias. Each study was carried out by the same lead investigators and followed similar protocols. Allocation concealment was achieved in each study via the implementation of a randomization process independent of recruitment to remove selection bias. The study publications did not describe the process of sequence generation but personal communication with the study authors indicated that computer generated minimization algorithms were used in each study. Due to the nature of the intervention it was not possible to blind the participants and therapists, however in four out of five studies outcome assessors were blinded to minimize bias. In Move to Exercise, only the primary outcome assessment (UHDRS Total Motor Score (TMS), from which mMS is derived) and one further secondary outcome (BBS) were assessed blinded (using independent video rating). In common with most physiotherapy rehabilitation trials, each study was open so the risk of bias is therefore moderate. A key risk of bias assessment compares baseline outcomes measures in completers versus non-completers. These data are given in *Supplemental Table 1* and provide evidence that there is little drop-out bias present in the complete data set.

Results of Published Studies. The original between-group intervention effects (95% confidence intervals) on mMS for four of five studies included (namely MtoE, COMMET-HD, EXERT-HD and ENGAGE-HD), were –4.5 [–8.8; –0.2] (n=21, favouring intervention); 2.4 [−0.9; 5.7] (n=21, favouring control); -2.87 [-5.42; -0.32] (n= 29), favouring intervention and 0.3 [-2.1; 3.40] (n=39, favouring control), respectively. Results for mMS were not reported in TRAIN-HD (only TMS was included as a motor outcome).

Results of Individual Studies. Summary data for the primary outcome, the UHDRS modified motor score (mMS) for participants included in this individual patient data meta-analysis are given in Table 2. The total sample size of the complete data set is n=121. Participants who appeared in more than one trial (n=12) and participants who had missing

mMS score at either baseline or follow-up (n=25) were excluded. Overall the scores are slightly higher in the intervention arm than the control arm at baseline and remain higher in the intervention arm at follow-up.

Results of Synthesis. Figure 1 shows the forest plot of the individual and combined study effects adjusted for mMS at baseline, age and gender. There is considerable heterogeneity in the results of the five feasibility RCTs. Moreover the confidence intervals for each individual study are wide and cross the line of no effect. The main overall treatment effect is 0.23 (95% CI) (-2.10 to 2.56). The pooled effect demonstrated a small negative treatment effect for the intervention (higher mMS scores indicate worse motor impairment) that was not statistically significant (see Table 3). Additional covariates (TFC and SDMT) were included in the primary model. TFC was measured in all five studies but the sample size was reduced slightly due to missing data, while the model with SDMT only included the four studies it was measured in. The inclusion of TFC, functional capacity at baseline, reversed the pooled effect to favour the intervention. SDMT itself was significantly predictive of outcome (higher baseline covariate levels were associated with improved outcome). However, including SDMT did not alter the main pooled treatment effect.

Subgroup analysis. There were four pre-specified subgroup analyses for the primary outcome. The results of these analyses are shown in *Supplemental Table 2*. None of the analyses suggested that there were any clinically relevant subgroup effects.

Secondary outcomes. Only those secondary outcome present in at least 3 studies were included in the meta-analysis. (Table 4). None of outcomes demonstrated evidence of effect. Neither the ordinal or binary models for PPT converged and results are not presented. This was most likely due to small numbers.

Sensitivity analyses. Unadjusted effects and effects adjusted for baseline mMS and minimization variables (age and gender) are given for the cross-classified models in *Supplemental Table 3*. The treatment effect is slightly larger than the estimate obtained in the primary analysis with narrower confidence intervals. This reflects the differing modeling estimation methods and assumptions of the two stage pooled and one stage mixed model but does not alter the conclusions. The ICCs estimated from the mixed cross-classified models were mainly low but showed there was some variation in the outcome due to participants in the same study but different sites (ICC_{study}) as well as participants from the same study and site ($ICC_{combined}$). These moderate ICCs reduced to close to zero when the model was adjusted for baseline mMS, suggesting that the clustering effect was mainly due to individual variation in baseline mMS. Leaving the cross-classification by site out of the one stage model gives an adjusted combined treatment effect and 95% CI of 0.4 (-0.9 to 1.6), the conclusions are therefore unchanged. The second sensitivity analysis included those participants who took part in more than one of the studies included in this meta-analysis in a mixed repeated measures model. Twelve participants contributed additional results to this analysis however the estimates did not differ to the primary analysis (main effect and 95% CI 0.04 (-0.8 to 1.6), p=0.473).

Discussion.

The majority of published exercise and physical activity trials and studies in HD to date have

been non-randomized interventions in small populations over relatively short durations with low study power. In five previous feasibility RCTs, we have shown that exercise interventions are feasible and acceptable in HD. Two of the studies also showed promising benefits in a range of physical and social patient reported outcomes. Here we have conducted the first ever individual patient data meta-analysis of randomized feasibility trials of exercise in people with HD where individual studies were not powered to test treatment effects.

We did not find any clear evidence of an overall intervention effect on the primary motor outcome. Although adjusting for baseline functional capacity (TFC) reversed the pooled treatment effect in favour of the intervention there was no evidence of a differential effect for function in subgroup analyses suggesting variation between studies in baseline capacity. Although the study populations in these five trials were very similar with respect to age and gender, there was a large amount of heterogeneity in the primary outcome. This heterogeneity is likely from two sources, namely the interventions and the HD status of the included participants. The severity of HD as indicated by Disease Burden Score (DBS) was comparable in the two studies it was measured in, as was IPAQ and TFC therefore we surmise that variation in the patient populations can be discounted as the main source of heterogeneity.

While all the interventions utilized some form of supervised and self-directed exercise and/or physical activity, the components, duration, intensity and frequency varied, hence the interventions and how participants responded varied considerably. Moreover, some were conducted in a single or only two sites whilst others were larger multi-site trials. The intervention heterogeneity can be explained by the developmental stage of the evaluations that were included in this individual patient data meta-analyses. The UK Medical Research Council Framework for Development and Evaluation of Complex Interventions was followed. In this, an iterative process of feasibility and acceptability evaluations is conducted before moving to full scale efficacy evaluation. Detailed mixed methods evaluations were included in each of the five feasibility trials and each subsequent trial incorporated a slightly different intervention focus based on the previous findings.

The first trial, Move to Exercise, reported highly significant results. This is not unusual in small, single site studies, conducted by highly motivated investigators and where estimates can therefore be inflated. Whilst extremely encouraging, the importance of continuing to develop the evidence base for exercise in HD was recognized. The subsequent trial, COMMET-HD, did not provide any signs of positive intervention effects. The process evaluation indicated that the intervention participants had not achieved a sufficiently intense exercise dose and had not engaged in self-directed exercise, although there was no indication why the control group had improved over and above the intervention group. TRAIN-HD was a home-based physiotherapist delivered task-specific training intervention however did not incorporate any clear aerobic focus. In the TRAIN-HD process evaluation, whilst participants reported benefits these were not borne out in the study data. These findings led to the design of ExeRT-HD, a multi-center, highly supervised aerobic and task-specific training intervention conducted over a 12-week duration and ENGAGE-HD, a physical activity behavior change intervention which focused on encouraging individuals to set physical activity goals and engage in ongoing life-style physical activity. The greatest positive effects of all trials in this study were noted in ExeRT-HD and Move to Exercise. In ExeRT-HD the

intervention had been specifically designed based on knowledge gained from preceding feasibility trials to involve frequent and intensive supervised exercise. This was not quite enough to overcome the negative effects observed in COMMET-HD resulting in a pooled effect which did not favour the intervention. Heterogeneity in the primary results may indicate they are measuring different aspects of the intervention and pooled results should be interpreted with caution.

Adequately powered large RCTs are difficult to achieve in rare conditions[21], therefore alternatives are being sought. Although randomised trials are the gold standard for obtaining unbiased treatment effect estimates, cohort non randomised interventional studies may be able to provide treatment effects that can be adjusted to account for the lack of randomisation. Methods used to adjust the estimates are the subject of current research by this group and others. Statistical methods such as Propensity Score weighting allow researchers and analysts to provide approximations of treatment effects when randomised effects cannot be obtained.

In our initial studies, and as part of the feasibility evaluations, we considered a range of outcomes, minimization variables and covariates. Some of these outcomes were not feasible to collect and some were modified in subsequent trials. This meant that there was some missing data either at baseline or follow up for a range of the outcomes. One of the conclusions from this individual patient data meta-analysis is that a core outcome set for exercise interventions in HD patients would help standardize trial outcomes and aid further meta-analysis. If assessing outcomes of a short term intervention, it is critical that the primary outcome is selected based on the anticipated targets of that intervention that are along the causal pathway. Although the UHDRS TMS (from which the modified motor score is derived) is the current gold standard for assessing motor impairment in HD, it is subject to rater bias and inherent variability particularly in the short term. A composite outcome may also better reflect the objectives of exercise studies in this population given that HD results in a triad of symptoms[22].

Our findings highlight the importance of including a measure of motor impairment as a baseline covariate in future trials. Furthermore, there should be consideration of disease severity (including cognition and apathy) in exercise prescription. In-depth exploration of relevant aspects of disease severity that limit exercise participation is urgently required to inform the development of interventions for later stage HD[21]. We conclude from the analyses reported here that future interventions must be delivered for longer durations and should consider frequency and intensity of exercise. Furthermore, supervision and support to exercise appear to be critical factors in facilitating adherence and optimizing outcome.

Funding sources and conflicts of interest: Funding was provided by Health and Care Research Wales. The Centre for Trials Research, Cardiff University, is funded by the Wales Assembly Government through Health and Care Research Wales. The authors declare no competing interests.
Financial disclosure for previous 12 months:
RP: Grants and Research: European Framework funding, Health and Care Research Wales (HCRW), Gossweiler Foundation; Salary: Cardiff University
PD: Grants and Research: Health and Care Research Wales (HCRW), Gossweiler Foundation; Salary: Cardiff University
MK: Salary: University of Exeter
LQ: Grants and Research: Huntington Study Group; Jacques and Gloria Gossweiller Foundation; Royalties: Elsevier Publishers for textbook Documentation for Rehabilitation: A guide to clinical decision making in physical therapy; Salary: Columbia University, Cardiff University
MB: Grants and Research: European Framework funding, Health and Care Research Wales (HCRW), Wellcome Trust, Medical Research Council UK, Gossweiler Foundation, National Institute of Health Research (NIHR); Salary: Cardiff University

~~**Funding**. Funding was provided by Health and Care Research Wales. The Centre for Trials Research, Cardiff University, is funded by the Wales Assembly Government through Health and Care Research Wales.~~

Acknowledgements. The authors gratefully acknowledge all the participants (and their family members and caregivers) who participated in the individual trials that has made this individual patient data meta-analyses possible. All participants also gave their permission for their coded data to be accessed by researchers conducting other Huntington's disease-related research.

Author Roless' contributions

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

RP: 1B, 1C, 2A, 2B, 3A, 3B
PD: 1C, 2B, 2C, 3A 3B
MK: 1A, 1B, 2A, 3B
LQ: 1A, 3B
MB 1A, 1B, 2C, 3A, 3B

Ethical Compliance Statement:

The authors confirm that the approval of an institutional review board and patient consent were not required for this secondary analysis of previously collated anonymized data. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

References

1. Walker FO. Huntington's disease. *Lancet*. 2007;369(9557):218-228.
2. Helder DI, Kaptein AA, Van Kempen GM, Van Houwelingen JC, Roos RA. Impact of Huntington's disease on quality of life. *Mov Disord*. 2001;16(2):325-330.
3. Fritz NE, Rao AK, Kegelmeyer D, Kloos A, Busse M, Hartel L, Carrier J, Quinn L. Physical therapy and exercise interventions in Huntington's disease: a mixed methods systematic review. *Journal of Huntington's Disease.* 6 (2017) 217–235. doi: 10.3233/JHD-170260
4. Frese S, Petersen JA, Ligon-Auer M et al. Exercise effects in Huntington disease. *J Neurol.* 2017 Jan;264(1):32-39. doi: 10.1007/s00415-016-8310-1
5. Zinzi P, Salmaso D, De Grandis R et al. Effects of an intensive rehabilitation programme on patients with Huntington's disease: A pilot study. *Clin Rehabil.* 2007;21(7):603-13.
6. Piira A, van Walsem MR, Mikalsen G, Nilsen KH, Knutsen S, Frich JC. Effects of a one year intensive multidisciplinary rehabilitation program for patients with Huntington's disease: A prospective intervention study. *PLoS Curr.* 2013, Sep 20;5. doi: 10.1371/currents.hd.9504af71e0d1f87830c25c394be47027.
7. Thompson JA, Cruickshank TM, Penailillo LE et al. The effects of multidisciplinary rehabilitation in patients with early-to-middle-stage Huntington's disease: A pilot study. *Eur J Neurol.* 2013;20(9):1325-9. doi: 10.1111/ene.12053.
8. Piira A, vanWalsem MR, Mikalsen G, Øie L, Frich JC, KnutsencS. Effects of a two-year intensive multidisciplinary rehabilitation program for patients with Huntington's disease: A prospective intervention study. *PLOS Curr Huntingt Dis.* 2014 Nov 25.

doi:10.1371/currents.hd.2c56ceef7f9f8e239a59ecf2d94cddac.

9. Cruickshank TM, Thompson JA, Dom´ınguez DJF et al. The effect of multidisciplinary rehabilitation on brain structure and cognition in Huntington's disease: An exploratory study. *Brain Behav.* 2015;5(2).

10. Ciancarelli I, Tozzi Ciancarelli MG, Carolei A. Effectiveness of intensive neurorehabilitation in patients with Huntington's disease. *Eur J Phys Rehabil Med.* 2013;49(2): 189-95.

11. Frich JC, Røthing M, Berge AR. Participants', caregivers', and professionals' experiences with a group-based rehabilitation program for Huntington's disease: A qualitative study. *BMC Health Serv Res.* 2014 Sep 17;14:395. doi: 10.1186/1472-6963-14-395.

12. Busse M, Quinn L, DeBono K et al. A randomized feasibility study of a 12-week community-based exercise program for people with Huntington's disease. *J Neurol Phys Ther*. 2013;37(4):149-158. doi:10.1097/NPT.0000000000000016.

13. Quinn L, Hamana K, Kelson M et al. A randomized, controlled trial of a multi-modal exercise intervention in Huntington's disease. *Parkinsonism Relat Disord*. 2016 Oct; 31:46-52. doi: 10.1016/j.parkreldis.2016.06.023

14. Busse M, Quinn L, Drew C et al. Physical Activity Self-Management and Coaching Compared to Social Interaction in Huntington Disease: Results From the ENGAGE-HD Randomized, Controlled, Pilot Feasibility Trial. *Phys Ther.* 2017 Jun 1;97(6):625-639. doi: 10.1093/ptj/pzx031.

15. Khalil H, Quinn L, Van Deursen R et al. What effect does a structured home-based exercise programme have on people with Huntington's disease? A randomized, controlled pilot study. *Clin Rehabil*. 2013;27(7):646-658.

doi:10.1177/0269215512473762.

16. Quinn L, DeBono K, Dawes H et al. Task-Specific Training in Huntington Disease: A Randomized Controlled Feasibility Trial. *Phys Ther.* 2014;94(11):1555-68. doi:10.2522/ptj.20140123.

17. Riley RD, Lambert PC, Abo-Zaid G. Mata-analysis of individual participant data: rationale, conduct and reporting. *BMJ* 2010; 340:c221. doi: 10.1136/bmj.c221.

18. Hua H, Burke DL, Crowther MJ, Ensor J, Tudur Smith C, Riley RD. One stage individual participant data meta-analysis models: estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and across-trial information. *Stat Med.* 2017; 36(5):772-789. doi: 10.1002/sim.7171

19. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.

20. Cafri G, Hedeker D and Aarons GA. An introduction and interaction of cross-classified, multiple membership, and dynamic group random-effects models. *Psychol Methods* 2015; 20(4):407-421. doi: 10.1037/met0000043.

21. Mueller SM, Petersen JA and Jung HH. Exercise in Huntington's Disease: Current State and Clinical Significance. *Tremor and Other Hyperkinetic Movements* 2019; 1-9:601. doi: 10.7916/tm9j-f874.

22. Scholbel SA, Palermo G, Auinger P et al. Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. Neurology 2017; Dec 12; 89(24): 2495-2502. doi: 10.1212/WNL.0000000000004743

List of Table Legends

Table 1: Details of individual trial interventions, comparators, outcomes and analyses

Table 2. Primary outcome summary data from each individual trial

Table 3. Primary outcome for IPD meta-analysis

Table 4. Secondary outcomes for IPD meta-analysis

List of Figure Legends

Figure 1. Forest plot of the individual and combined treatment effects from the IPD meta-analysis

Supplementary Tables (online only)

Supplemental Table 1. Baseline summary data for completers vs non-completers across studies

Supplemental Table 2. Interaction effects for the primary outcome

Supplemental Table 3. IPD meta-analysis one stage cross-classified 2-level modelling (sensitivity analysis)

Table 1: Details of individual trial interventions, comparators, outcomes and analyses

Trial	Frequency and setting	Exercise Mode	Comparator	Outcomes	Blinding and analyses	Minimization variables *(in addition to baseline scores)*
COMMET-HD[12] (ISRCTN 59910670); n=31 at 2 sites	12 structured, gym-based, sessions plus home-based, independent 2/week, 12 weeks	Aerobic training (cycle ergometer), functional strength training, regular walking programme	Usual care	UHDRS modified motor score UHDRS cognitive scales 6-minute walk test (6mWT) 10 metre walk test 30-s chair stand test (30sCST) Romberg test Daily step counts % of sedentary time % time in moderate/ high physical activity Self-reported 7-day physical activity recall (IPAQ) SF-36 health related quality of life Submaximal exercise test (HR/ perceived exertion at minute 9)	Assessor blind for all outcomes; complete case intention-to-treat	Gender, Disease Burden Score (DBS), physical activity
ExeRT-HD[13] (ISRCTN11392629); n=32 at 6 sites	Structured exercises 3/week (21/36 supervised), 12 weeks	Aerobic training (cycle ergometer), functional strength training	Usual care	UHDRS modified motor score Symbol Digit Modality Test Word fluency Simple and complex dual task Trail making A & B Stroop 3-minute walk test Finger tapping Self-reported 7-day physical activity recall (IPAQ) HADS EQ5D Health Index Weight (in kg) VO2 max	Assessor blind for all outcomes; Complete case intention-to-treat	Age, UHDRS TMS, Gender; Site
Move to Exercise (MtoE)[15]; n=21 at 1 site	Home-based, DVD 3/week; 8 weeks	Functional strength training, flexibility and balance	Usual care	UHDRS modified motor score Berg Balance Scale Gait analysis measures using Gait Rite including gait speed and spatiotemporal measures of gait SF-36 health related quality of life	Assessor blind for 2 outcomes; (Berg Balance Scale; UHDRS modified motor scale);	Age, TFC

		training (using exercise DVD)			Complete case intention-to-treat	
TRAIN-HD[16](ISCTRN94284668); n=28 at 6 sites	Supervised Home-based; twice/week; 8 weeks	Functional strength training, regular walking programme, task specific training	Usual care	UHDRS-Total Motor Score UHDRS cognitive scales Physical Performance Test Berg Balance Scale Gait Speed Fast Gait Speed 30-s chair stand test (30sCST) Timed Up and Go test Goal Attainment Scale Vitality Score HADS HD QoL scale EQ5D Health Index	Assessor blind for all outcomes; Complete case intention-to-treat	Gender, Site, DBS
Engage-HD[14] (ISRCTN 65378754); n=46 at 8 sites	Supervised 1-hour long home visits (6 visits) home-based, self-directed;14 weeks	Regular walking programme, Functional strength training, flexibility and balance training (using exercise DVD)	Social contact (inactive control)	UHDRS modified motor score Symbol Digit Modality Test Category fluency Physical Performance Test 6-minute walk test (6mWT) Timed Up and Go test Self-reported 7-day physical activity recall (IPAQ) Life Space Assessment Lorig Self-Efficacy Scale EQ5D Health Index ICE-CAP Health Utility Assessment	Assessor blind for all outcomes	Age, UHDRS TMS, Gender; Site

Table 2. Primary outcome summary data from each individual trial

	Control			Intervention		
	n	Baseline Mean (SD)	Follow-up Mean (SD)	n	Baseline Mean (SD)	Follow-up Mean (SD)
MtoE	7	18.7 (5.7)	21.1 (5.9)	8	19.1 (8.3)	17.5 (6.9)
COMMET-HD	11	14.5 (7.9)	13.2 (7.0)	9	11.0 (6.4)	15.4 (5.1)
TRAIN-HD	11	13.1 (6.8)	13.8 (5.6)	12	18.8 (6.5)	18.3 (6.0)
ExeRT-HD	12	11.3 (5.4)	11.1 (5.3)	11	13.3 (6.1)	11.5 (6.4)
ENGAGE-HD	23	14.6 (6.1)	14.1 (5.0)	17	14.5 (5.8)	14.7 (5.2)

Table 3. Primary outcome for IPD meta-analysis

	n	Treatment Effect (95% confidence interval)	P-value
mMS adjusted for baseline mMS, age and gender (primary model)	121	0.2 (-2.1 to 2.6)	0.848
mMS adjusted for baseline mMS, age, gender and TFC	114	-0.7 (-2.0 to 0.7)	0.336
mMS adjusted for baseline mMS, age, gender and SDMT	104	0.3 (-1.8 to 2.5)	0.754

Table 4. Secondary outcomes for IPD meta-analysis

Secondary outcomes adjusted for respective baseline scores, age and gender	Number of studies	n	Treatment Effect 95% confidence interval	P-value
Symbol Digit Modality Test	4	107	0.81 (-1.17 to 2.79)	0.422
EQ5D	4	108	0 (-0.06 to 0.05)	0.900
Timed Up and Go test	3	84	-1.64 (-3.59 to 0.31)	0.100
6-minute walk test (6mWT)	3	85	18.77 (-6.02 to 43.56)	0.138