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TITLE

Effect of exercise interventions on health-related quality of life after stroke and transient ischaemic attack: a systematic review and meta-analysis.

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Effect of exercise interventions on health-related quality of life after stroke and transient ischaemic attack: a systematic review and meta-analysis.

Unstructured abstract

Exercise interventions have been shown to help physical fitness, walking and balance after stroke, but data is lacking on whether such interventions lead to improvements in health-related quality of life (HRQoL). In this systematic review and meta-analysis, thirty randomised controlled trials (n=1,836 patients) were found from PubMed, OVID MEDLINE, Web of Science, CINAHL, SCOPUS, The Cochrane Library and TRIP databases when searched from 1966 to Feb 2020, that examine the effects of exercise interventions on HRQoL after strokem or transient ischaemic attack (TIA). Exercise interventions resulted in small to moderate beneficial effects on HRQoL at intervention end (standardised mean difference (SMD) -0.23; 95% CI -0.40 to -0.07) that appeared to diminish at longer term follow up (SMD -0.11; 95%CI -0.26 to 0.04). Exercise was associated with moderate improvements in physical health (SMD -0.33; 95% CI -0.61 to -0.04) and mental health (SMD -0.29; 95% CI -0.49 to -0.09) domains of HRQoL while effects on social or cognitive composites showed little difference. Interventions that were initiated within 6 months, lasted at least 12 weeks in duration, involved at least 150 minutes per week, and included resistance training appeared most effective. Exercise can lead to moderate beneficial effects on HRQoL and should be considered an integral part of stroke rehabilitation.

Word Count 201

Non-standard Abbreviations and Acronyms:

HRQoL - Health Related Quality of Life; RCT -Randomised controlled trial, TIA – Transient Ischaemic attack; CERT - Consensus on Exercise Reporting Template; GRADE - Grading of Recommendations, Assessment, Development and Evaluations;

1. Introduction

There are now more than a staggering 80 million stroke survivors worldwide[1], approximately 40% of whom remain functionally dependent at 6 months[2] due to persistent motor, sensory, cognitive or psychological impairment. Not only does this lead to significant societal economic costs[3], but people with stroke report significantly poorer health-related quality of life (HRQoL) compared to age and sex matched controls[4,5]. Tools to assess HRQoL are multidimensional and often include physical, mental, and participatory composites, however, they are a valid measure of overall health status[6]. Stroke related reductions in HRQoL may be related to disability and neurological impairments, but also due to the increased risk of stroke recurrence. A quarter of all stroke is recurrent[7] and associated with greater morbidity and economic consequences than primary stroke[8]. With modifiable risk factors accounting for nearly 90% of the incidence burden of stroke[9], interventions that aim to improve functional recovery and reduce risk of recurrence may have the biggest impact on improving longer term HRQoL in this population.

Exercise interventions, delivered to increase cardiorespiratory fitness, strength or endurance may be an attractive approach to improving HRQoL among stroke survivors. Varying levels of evidence exists to support the benefit of exercise on physical[10], emotional[11], and participatory[12] function after stroke, as well as its impact on future vascular risk[13]. Despite this, structured exercise-based rehabilitation programmes are not routine aspects of care for most stroke services across Europe, unlike services for coronary artery disease, heart failure and pulmonary disease, where such programmes are commissioned to reduce mortality, morbidity, hospitalisation, symptom burden, and improve HRQoL[14-16]. A recent Cochrane review from 2016 synthesised data from 58 randomised controlled trials (RCT) of physical fitness programmes after stroke, demonstrating they improved walking speed, walking distances and balance[10]. However, only a few trials reported quality of life measures, with inconsistent results, limiting the conclusions that could be drawn on the effects of exercise on HRQoL. Interest in the role of exercise after stroke has recently however gained significant momentum. Given the importance of HRQoL as a primary outcome stroke rehabilitation, this systemic review and meta-analysis aimed to evaluate the effectiveness of structured exercise programmes on improving HRQoL after stroke or transient ischaemic attack (TIA). Further, we looked to explore potential intervention determinants of effectiveness.

2. Methods

This review followed the processes set out according to the Preferred Reporting of Items for Systematic Reviews and Meta-analyses (PRISMA) guideline[17], with operational definitions detailed *a priori* based on the recommendations from the Cochrane Handbook of Systematic Reviews on Interventions[18]. A priori aims and methodology were registered with PROSPERO (CRD42020156992).

2.1. Inclusion criteria

Studies were included if they evaluated adults (aged > 18 years) who had suffered a stroke (ischaemic or haemorrhagic) or TIA according to the World Health Organisation definitions[19]. Only RCTs of structured exercise interventions were included. Interventions could have a cardiorespiratory focus (aiming to increase cardiorespiratory fitness by stimulating heart rate and respiratory rate e.g. walking, running, cycling), a resistance focus (aiming to increase muscle strength or endurance through movements of incrementing loads e.g. weight training) or contain mixed components. Interventions focusing on therapeutic exercise (aiming to restore physical function e.g. walking, standing, balance) were excluded unless they specifically included a cardiorespiratory or resistance component. Only studies reporting HRQoL as primary or secondary outcome measures were included.

2.2. Search strategy

The following electronic databases were searched from 1966 to February 2020: PubMed, OVID MEDLINE, Web of Science, CINAHL, SCOPUS, The Cochrane Library and TRIP database. Subject heading and free text terms relating to stroke (e.g. cerebrovascular accident, ischaemic stroke, haemorrhagic stroke), TIA (e.g. mini-stroke, transient ischaemic attack), exercise (e.g. aerobic, resistance, physical activity) and HRQoL (e.g. quality of life, health related quality of life) were used to produce a search strategy for OVID MEDLINE (supplementary material). This was adjusted using Boolean operators for the other databases. Reference lists of included studies and reviews were scanned for additional relevant articles. Grey literature was not searched.

2.3. Study selection and data extraction

The initial list of articles was reviewed independently by two review authors (DT and ANA) who removed duplicate and irrelevant articles from screening title and abstract. Full texts of the remaining studies were critically analysed by both authors for final inclusion, and data was extracted into a predesigned spreadsheet. Extracted data included participant demographics, study design, intervention and control details (timeframe, descriptors, setting, frequency, duration), information on recruitment and retention, and outcome measures. Specifics of the exercise interventions were recorded using The Consensus on Exercise Reporting Template (CERT)[20] to establish adequacy of intervention reporting. Data for quantitative meta-analysis including mean differences (MD) between treatment groups and associated standard deviations (SD) from baseline and follow up assessments were recorded. Any disagreements in study selection of data extraction were discussed collectively by both reviewers and adjudicated by a third reviewer (BM).

2.4. Study quality assessment

Both review authors (DT and ANA) independently reviewed each study meeting the inclusion criteria using the Risk of Bias 2 (RoB 2) checklist developed by the Cochrane Collaboration[21]. This tool evaluates study bias attributable to the randomisation process, deviation from the assigned treatment arm, adherence, missing outcome data, outcome measurements and reporting of results. Studies that are deemed high risk in any one of these domains or some risk in more than one domain are classed as high risk overall, those are deemed to exhibit some risk in any one of the domains are classed as intermediate risk, while those at low risk in all domains are classed as low risk overall. A quality assessment at the level of the outcome measure (HRQoL) was also undertaken using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach[22]. This system depicts the level of certainty related to study findings based on risk of bias, imprecision, inconsistency, indirectness, publication bias, magnitude of effect, dose responsiveness and adjustment for confounders.

2.5. Data analysis

Study characteristics and outcomes were synthesised qualitatively and summarised in tabular form. Quantitative meta-analyses were undertaken using the MD and SD of the HRQoL measures between intervention and control groups in RevMan v5.3. Trial authors were contacted directly for raw data when the MD and SD were not available from the published articles, however where this was not possible, indirect methods for estimating these values were employed[23]. Due to the variation in HRQoL outcomes used amongst studies, we calculated the standardised mean differences (SMD) to report effect sizes, along with 95% confidence intervals (CI). For the primary outcome (overall HRQoL) 95% prediction intervals (PI) have also been calculated to estimate where the true effect size lies for 95% of similar studies that may be conducted going forward. Furthermore, for HRQoL measures where lower scores indicate better health (e.g. Nottingham Health Profile, Stroke Adapted Sickness Impact Profile), outcome scores were multiplied by -1 to ensure that score effect changes aligned with measures where higher scores indicated better health (e.g. EQ-5D, SF-36). For studies with more than 1 effect size e.g. multiple HRQoL outcomes, an average was calculated that represented the overall general effect[24]. Where studies included more than 1 exercise treatment which varied due to duration, the longest was compared against control. If multiple arms involved differing modes of exercise e.g. aerobic vs resistant vs combination, the combination was compared to control for the main analysis and the modes were compared in subgroup analyses. In addition to the main meta-analysis concentrating on the effect on overall HRQoL score, further analyses were performed to evaluate the effects on the physical, emotional, cognitive and social or participatory score composites. Further, prespecified sub-group analyses were conducted to evaluate the effect sizes of interventions depending on the timing of exercise initiation (< 6 months vs ≥ 6 months), the type of exercise (aerobic vs resistance vs mixed), the duration of programme (< 3 months vs ≥ 3 months), whether interventions meet UK exercise guidelines[25] (< 150 minutes per week vs ≥ 150 minutes per week), and the setting (home vs centre based). Effect sizes magnitude was classified as small (SMD less than or equal to 0.20), medium (SMD 0.21-0.79) or large (SMD equal to or greater than 0.80)[26]. Statistical heterogeneity was estimated by calculating the I^2 statistic which represents the percentage of total variation in effect size estimates across studies that is attributable to between study variability. Random effect models were used for estimating treatment effects due to heterogeneity in target populations and exercise interventions across studies, as well as substantial statistical heterogeneity indicated by I^2 [13]. Funnel plots were used to assess for publication bias.

3. Results

After removal of duplicate manuscripts and identifying additional citations a total of 2,275 articles were screened for title and abstract, from which 37 full texts were reviewed leading to the final inclusion of 30 RCTs[27-56] (**figure 1**).

3.1. Quality assessment

Of the 30 studies included, nine were considered low risk[34-36,40,45,46,48,51,55] fourteen were considered to exhibit some risk[29-31,33,37,39,42,43,48,49,50,52,54,56] and seven were considered high risk of bias[27,28,32,38,41,44,53,] (supplementary material). The GRADE assessment for the outcome of overall HRQoL determined moderate quality (supplementary material).

3.2. Study characteristics

The 30 RCTs involved 1,841 participants from 14 countries (supplementary material). Average age of participants ranged from 52 to 75 years, two studies included participants with TIA in addition to stroke[45,48] and 16 studies included only those who were independently ambulant[27-31,33,34,37-39,43,44,46,48, 50,51,53]. Nine studies excluded participants on the basis of cognitive impairment (e.g. MMSE minimum cut off range 16-24)[27,31,38-40,43,44,46,50,54] and 4 only recruited participants who had hemiparesis[36,40,47,51]. Only 4 studies reported on the presence of specific neurological deficits such as sensory impairment, hemianopia, or neglect for example[33,43,54,56]. Most studies included patients with mild neurological or functional impairments (supplementary material). One study included only patients with persistent fatigue[42], and another only those with depression[37]. Eleven studies specified recruitment into exercise interventions within 6 months[27,31,36,45,48,49,51,53-56] and 13 studies after 6 months[28-30,34,35,37,38,40,43,44,46,47,50] of index stroke or TIA.

Interventions involved aerobic exercises only in 10 studies[29,40,41,43,44,48,49,52,53,55], resistance exercises only in 4 studies[30,34,3747] and a combination of the two in 14 studies[27,28,31-33,35,36,38,39,42,45,46,50,51,54,56]. The most common duration and frequency of exercise was *45-60 minutes*, *3 times weekly* for *12 weeks*, although the weekly exercise minutes ranged from 90 to 270 minutes, and the overall intervention duration ranged from 4 to 40 weeks. Nineteen exercise interventions prescribed exercise intensity according to targets (heart rate reserve, 1 repetition max, Borg's perceived exertion)[28,33-37,40-42,44-46,48,50-53,55,56], eight were home based[27,31,32,39,44,49,54,56] but only 1 was unsupervised and caregiver delivered[54]. Control interventions were varied and included stretching, relaxation, education, balance training, repetitive task training, lifestyle advice, massage, strength training and very light aerobic interventions in addition to usual care. Exercise intervention reporting according to the CERT criteria varied considerably (supplementary material VI). Aspects that were well reported (> 75% of studies) included the exercise equipment required, whether it was supervised or not, and details of the type of exercise to enable replication. However, aspects that were poorly reported (<25% of studies) included the qualification of the instructors and the incorporation of motivation or other non-exercise components. Only 3 studies involving a total of 81 intervention participants actually reported on whether participants met the exercise targets (e.g. intensity) set[33,46,48].

In total, 8 different HRQoL rating scales were used. Nine studies used the Short Form-36[27,30-33,36,44,45,47,51], three studies used the Short Form-12[37,39,40], Seven studies used the Stroke Impact Scale[31,32,34,37,41,46,53], five used EQ-5D[43, 48,49,50,55], three used the Nottingham Health Profile[28,35,52], two studies used the Stroke Adapted Sickness Impact Profile[29,42], 1 study used the Stroke Specific Quality of Life Score[38], and one the World Health Organisation-5 Wellbeing Index[56]. All studies evaluated outcomes at end of intervention and 12 studies included longer term follow up which ranged 1 to 9 months [31-35,37,42,43,48,50,54,55].

3.3. Quantitative meta-analysis

3.3.1. Overall HRQoL

Data on overall HRQoL scores were pooled from 24 studies that included 1,451 participants (intervention n=711).[27-29,31-35,38-51,53-55] **figure 2a** highlights a small to moderate beneficial effect of exercise interventions over control groups on overall HRQoL, albeit with significant heterogeneity (SMD -0.23; 95% CI -0.40 to -0.07; p=0.006; I^2 56%). The 95% PI's however ranged from -0.53 to 0.06 indicating some uncertainty with this primary outcome finding (supplementary material VII). Eleven studies (n = 792, intervention n=405) reported on longer term (3-9 months post intervention) effects of exercise interventions on overall HRQoL.[31-35,42,43,48, 50,54,55] Pooled data in **figure 2b** shows a non-significant benefit with exercise interventions (SMD -0.11; 95%CI -0.26 to 0.04; p=0.16; I^2 14%). There was no funnel plot asymmetry to suggest publication bias for either of the above analyses, and sensitivity analysis removing studies at high risk of bias did not significantly affect the treatment effect (supplementary material).

3.3.2. Composite HRQoL

The effects of exercise interventions on the physical, mental, social and cognitive subdomains of HRQoL are highlighted in **table 1**. Exercise interventions were associated with significant and moderate improvements in physical health composites (SMD -0.33; 95% CI -0.61 to -0.04; p=0.03; I^2 73%)[27,31,33,35,38,39-41,44-47,54] and mental health composites (SMD -0.29; 95% CI -0.53 to -0.11; p=0.004; I^2 53%)[31-33,35,38-41,44-47,53,54,56] while effects on social or cognitive composites were non-significant. Further, the effects of exercise interventions on composite HRQoL outcomes at longer term follow up were also non-significant, with smaller effect sizes and wide confidence intervals.

3.3.3. Effect of intervention characteristics

Figure 3 highlights the effect of various intervention characteristics on overall HRQoL scores. Exercise programmes that combined both aerobic and resistance modes of exercise appeared to have greater beneficial effects on HRQoL (SMD -0.21; 95% CI -0.39 to -0.03; p=0.02; I^2 38%) compared to programmes involving aerobic exercise only (SMD -0.18; 95% CI -0.40 to 0.05; p=0.12; I^2 33%). Programmes lasting at least 12 weeks (SMD -0.27; 95% CI -0.49 to -0.05; p=0.01; I^2 66%) also appeared more effective than programmes of shorter duration (SMD -0.09; 95% CI -0.30 to 0.13; p 0.43; I^2 0%). Exercise interventions initiated within 6 months of index event (SMD -0.21; 95% CI -0.39 to -0.03; p=0.02; I^2 12%) appeared to result in more consistent benefits than those recruiting after 6 months (SMD -0.29; 95% CI -0.67 to 0.09; p=0.14; I^2 75%), and those involving ≥ 150 minutes per week (SMD -0.36; 95% CI -0.71 to -0.02; p=0.04; I^2 66%) appeared more effective than less intensive programmes (< 150 minutes per week; SMD -0.14; 95% CI -0.33 to 0.04; p=0.13; I^2 40%). Both home and centre delivered exercise interventions resulted in benefits to HRQoL (Centre based SMD -0.25; 95% CI -0.49 to -0.02; p=0.03; I^2 64% vs home based SMD -0.25; 95% CI -0.45 to -0.06; p=0.009; I^2 16%).

3.3.4. Adverse events

Only 7 studies[33,35,39,40,46,48,56] reported adverse events among 447 participants. There were no serious adverse events, and only 2 adverse events related to exercise, 1 patient who suffered a fall and 1 who experienced hip pain during exercise.

4. Discussion

4.1. Exercise and HRQoL

This meta-analysis has shown that exercise interventions can lead to small to moderate beneficial effects on HRQoL measures among people suffering stroke and TIA. These findings are consistent with a prior systematic review from 2011, however, this review only included 9 RCTs[57]. A more recent Cochrane review of physical fitness training after stroke from 2016 also suggested that interventions may result in inconsistent effects on HRQoL, however there was insufficient evidence to draw reliable conclusions with only 9 RCTs (n=583) included in the analysis[10]. These inconsistencies may have been due to the relatively small number of studies included. The current analysis has benefited from a comprehensive search strategy resulting in the inclusion of 30 studies, data from 26 of which have been used in meta-analyses (n=1,721), facilitating a greater level of confidence in the analysis and results.

Exercise may lead to improvements in HRQoL for numerous reasons. In the short term, exercise is known to modulate neurotransmitter pathways involving dopamine, noradrenaline and serotonin in ways that enhance alertness, cognitive function and overall wellbeing[58]. Animal models also demonstrate that longer term modulation of such pathways through exercise may result in improvements to learning and memory[59], neuronal adaptation to harmful stress responses[60] as well as stabilisation of mood[61]. In addition, evidence from both animal and human studies suggests that exercise interventions reduce inflammatory processes[62] as well as apoptotic gene marker expression[63], promotes vascular angiogenesis and expression of vascular growth factors[64] and neuroplastic markers such as brain derived neurotropic factor[65], and improves the activation of affected muscles following stroke[66]. Indeed such effects are the cornerstone of neuroplastic recovery, and accordingly, research is now focusing on the effects of very early exercise to help neurological recovery after stroke[67]. A recent clinical review of the biological effects of exercise after stroke by Kramer et al suggested these effects may lead to structural changes on functional MRI scanning of the brain that indicated neuroplastic change[68]. Thus, it is understandable to see why the aforementioned 2016 Cochrane review[10] of 58 RCTs (n=2,797) found that exercise interventions resulted in improved walking speed, walking capacity, balance scores and global indices of disability after stroke. Further, they reported significant improvements in cardiorespiratory fitness (peak oxygen consumption) which is a key determinant of mobility status and independent living[69]. These effects are likely to help lead to physical and mental benefits to patient's quality of life, and ultimately their active participation in daily life.

Most participants in the trials included in this review had minimal disability. However, their age and comorbidities match closely those of cardiac populations studies in trials of cardiac rehabilitation. A recent meta-analysis of 41 RCTs of exercise based cardiac rehabilitation in patients with coronary artery disease also demonstrated moderate improvements in overall HRQoL (SMD 0.28; 95% CI 0.05-0.5)[70], similar in magnitude to that seen in this review.

The current review found the greatest beneficial effects in the physical and mental domains of HRQoL, however, the non-significant trend in improvement for the social or participatory domain may have been due to a smaller number of studies and participants. Importantly, exercise participants have often reported the benefits from socialisation at exercise classes that may have meaningful effects on HRQoL[71]. It is unclear from this review whether exercise improves the cognitive domain of HRQoL. However, exercise interventions have been shown to improve vascular risk factors after stroke[13], which are key predictors of vascular cognitive impairment longer term. It may be that the duration of follow up in the present studies (< 12 months) was not long enough to pick up changes in cognitive function afforded by vascular risk reduction through exercise. The currently recruiting RCT MoveIT study will help determine the effectiveness of a 12-week mixed exercise programme to prevent cognitive decline after stroke or TIA[72].

The beneficial changes to HRQoL seen with exercise appears to diminish on longer term follow up (3-9 months post intervention. This raises concern about the ability of currently investigated programmes to result in longer term lifestyle behaviour change. What is still unknown is whether patients continue to exhibit higher levels of physical activity after the structured programmes are complete, or whether physical activity levels decline. Qualitative studies on the facilitators and barriers to exercise after stroke have highlighted both individual level (ill health, neurological impairment, transport, costs) as well as system level (staff apprehension about exercise, difficult referral pathways) barriers to exercise[71,73]. Further research is needed to understand behaviour patterns after exercise intervention completion, as well as how programmes and service pathways can be optimised to ensure patients have the capability, opportunity and motivation to participate in exercise and continue it long term[74], as well as ensure longer term follow up of outcome measures.

4.2. Exercise intervention characteristics

Analysis of specific exercise intervention characteristics has shown that programmes that are at least 12 weeks long appear to have greater effects on HRQoL than shorter programmes. A programme duration of 12 weeks was the most common in this review and is a common duration for many cardiac rehabilitation programmes[75]. It may be that this duration provides enough structure and supervision to support behaviour change and overcome barriers to exercise, or that it simply may be a duration of time required for the longer-term effects of exercise on cerebral and muscle physiology to take place.

In addition, exercise interventions involving at least 150 minutes per week also appeared to result in greater benefits to HRQoL. This cut-off was chosen as it represents the UK department of health recommendations for weekly level of physical activity and exercise[25]. Again, this may relate to an overall dose effect. A prospective populational cohort study of more than 1.1 million people in Korea demonstrated significant reductions in cardiovascular event rates as the frequency of physical activity episodes per week increased incrementally from 1 to > 5 times[76].

The mode of exercise delivery may also be important. In this analysis, programmes that incorporated both resistance and aerobic exercises appeared to result in greater benefits to HRQoL than aerobic interventions alone. While aerobic exercise may lead primarily to improved fitness, endurance and vascular risk factor profiles, incremental loading forces with resistance training should result in improved bone mineral density and muscle anabolism that aids resilience and functional movements such sit to stand and climbing stairs. Further, a recent systematic review of 16 RCTs in older adults showed that resistance training resulted in significant improvements in both upper and lower limb strength and functional capacity that formed an effective treatment against the frailty phenotype[77]. Too few interventions evaluating resistance training alone were available for meaningful comparative analysis, however, the evidence suggests that effective programmes should look to combine both types of exercise.

Both homed based and centre based exercise interventions appeared beneficial for HRQoL, although studies of home-based interventions exhibited more consistent effects. This is encouraging in that it provides breadth in how effective exercise programmes can be delivered. Such enhancement in patient preference options may lead to increased programme uptake and adherence and suggests that high-tech expensive equipment is not necessary for improved outcomes. Most home-based programmes were however still supervised by exercise or physical therapists. The only study that was unsupervised and caregiver delivered by Vloothius et al (2019) did not demonstrate improvements in HRQoL[54]. A recent Cochrane Review of 6 RCTs (n=333) showed no effect of care-giver mediated exercises on basic or extended daily functional ability[78]. One study in the review indicated a possible beneficial effect of care-giver mediated exercise on the physical composite of HRQoL, but the effect was small and the evidence low quality[79]. Remote supervision of exercise using technology such as telehealth has been shown to extend the benefits of exercise-based rehabilitation in cardiac populations[80] and may be a useful avenue of research to bridge this potential gap in stroke.

Exercise interventions initiated within 6 months may also result in more consistent effects on HRQoL compared to those started later. This may be due to a greater susceptibility to behaviour change soon after acute illness, otherwise termed a 'sentinel event effect', and this appeared to exist when evaluating the effects of exercise on vascular risk factors[13].

4.3. Adverse events

While adverse event reporting was relatively low among studies, the overall events reported were reassuringly low. Although most participants among these RCTs were mildly impaired or ambulant, several studies (n=5) only recruited patients who had hemiparesis or moderate impairment of daily activities. Despite this and the safety reports from Cochrane reviews of physical activity programmes after stroke[10], one must be cautious when translating this to stroke populations with greater severities of impairment.

4.4. Limitations

This review had several limitations. First, there was significant heterogeneity in population characteristics (diagnosis, impairment, time post stroke etc) that may limit the generalisability of findings to all survivors of stroke or TIA, in particular those who are more severely disabled, as well as heterogeneity in the exercise interventions (frequency, intensity, mode, duration etc) that may limit generalisability of findings to existing delivered exercise programmes. High levels of statistical heterogeneity (inconsistencies in treatment effects, I^2, broad prediction intervals) when analysing the primary outcome and certain subgroups of exercise intervention e.g. resistance programmes, mean that we are still uncertain of the effects such programmes have on HRQoL. While we attempted to understand the effects of key intervention characteristics on HRQoL, questions remain about whether individual or group-based activities are more effective, and whether measurable biomarkers can predict responses to exercise and help tailor more effective interventions. Furthermore, there is a paucity of data on what proportion of participants actually reach the intended exercise intensities of the programmes, and whether achieving these targets has an effect on the outcomes from the interventions. Second, there were significant variations in the type of HRQoL measure used. Differences in how they are scored, the composites they involve their responsiveness to change and whether they are generalised or stroke specific may mean that aggregating differences as standardised means may over or underestimate some of the differences seen. Third, multiple sub-group comparisons of the effects of intervention characteristics involve fewer participants and generally produce larger 95% CIs meaning that there is less certainty with regards to the effects seen. Fourth, few studies included longer term follow up, and even though this analysis did not find statistically significant benefits at this timepoint, it could have been due to underpowered sample. Fifth, most of the studies included were small pilot or feasibility trials of exercise, whose primary outcome was something other than HRQoL. Such studies may overestimate effect sizes due to methodological quality. However, excluding studies at high risk of bias did not alter the overall outcomes greatly in this study. Sixth, many of the interventions studied prescribed exercise according to target heart rates or perceived effort. What we do not know is whether such targets were achieved during the programmes and whether this would influence the effectiveness of the interventions. The recent CARE-CR study showed that participants of an exercise based cardiac rehabilitation programme achieve target heart rates less than 50% of the time during the exercises classes[81]. Seventh, the control interventions varied significantly, from lower forms of exercise (e.g. voluntary[53]) to advice. Limited data on the amount of physical activity and exercise undertaken in the control groups limits our interpretation of the true potential effect size exercise exerts on HRQoL. Eighth, exercise interventions are difficult to blind, which introduces the potential of a placebo effect on a subjective outcome measure such as HRQoL. Ninth, we did not search the grey literature or include trials published in languages other than English, which may have led to language and publication bias. However, funnel plot analysis of the studies included was reassuringly symmetrical. Furthermore, exclusion of eligible trials may have occurred due to excluding clinical trial registries from the search databases initially used. However a subsequent search on ClinicalTrials.gov for eligible studies did not identify any missing from the review.

5. Conclusions

Exercise programmes that combine aerobic and resistance training appear to result in moderate improvements in HRQoL. In addition to the mounting evidence for its beneficial effects on cardiorespiratory fitness, walking, balance and vascular risk profile, health policy decision makers need to consider its integration into existing rehabilitation pathways following stroke and TIA. The limitations of small, underpowered studies (e.g.

overestimation of effect sizes) may pave the way for a definitive, multi-centre, high quality RCT evaluating both the effectiveness and cost effectiveness of exercise on HRQoL. This should aim to recruit more severely affected participants and aim to define the most effective intervention designs and service provision pathways, considering the most important facilitators and barriers to participation. Further, work should also strive to understand the most effective means of creating long lasting beneficial health behaviour change with the ultimate aim of improving the lives of people who have suffered stroke and TIA.

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Supplementary materials:

Expanded materials and methods – I & II

Tables – I – V

Online figures – I & II

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Figure Legends:

Figure 1. CONSORT diagram of study selection process.

Figure 2. Forrest plots comparing the effect of exercise interventions on overall HRQoL compared to control arms at end of intervention (a), and at follow up between 3 and 9 months post intervention (b).

Figure 3. Effect of intervention characteristics on overall HRQoL after stroke and TIA

Table 1. Effects of exercise interventions on separate subdomains of HRQoL

Effect at post intervention assessment			
HRQoL Subdomain	Number of RCTs	Participants (intervention)	Effect estimate SMD (95% CI); P value
Physical	14	802 (398)	-0.33 (-0.04 to -0.61); p=0.03
Mental health	15	935 (460)	-0.29 (-0.09 to -0.49); p=0.004
Social / participatory	10	443 (224)	-0.20 (0.09 to -0.49); p=0.17
Cognitive	6	308 (154)	-0.05 (0.35 to -0.45); p=0.82
Effect at longer term follow up assessment (3-9 months)			
HRQoL Subdomain	Number of RCTs	Participants (intervention)	Effect estimate SMD (95% CI); P value
Physical	5	294 (152)	-0.12 (0.37 to -0.60); p=0.64
Mental health	6	374 (192)	-0.07 (0.25 to -0.38); p=0.69
Social / participatory	5	243 (135)	-0.19 (0.07 to -0.45); p=0.16
Cognitive	2	141 (72)	0.01 (0.51 to -0.49); p=0.96

Negative SMDs favour exercise groups.

Figure 1. CONSORT diagram of study selection process.

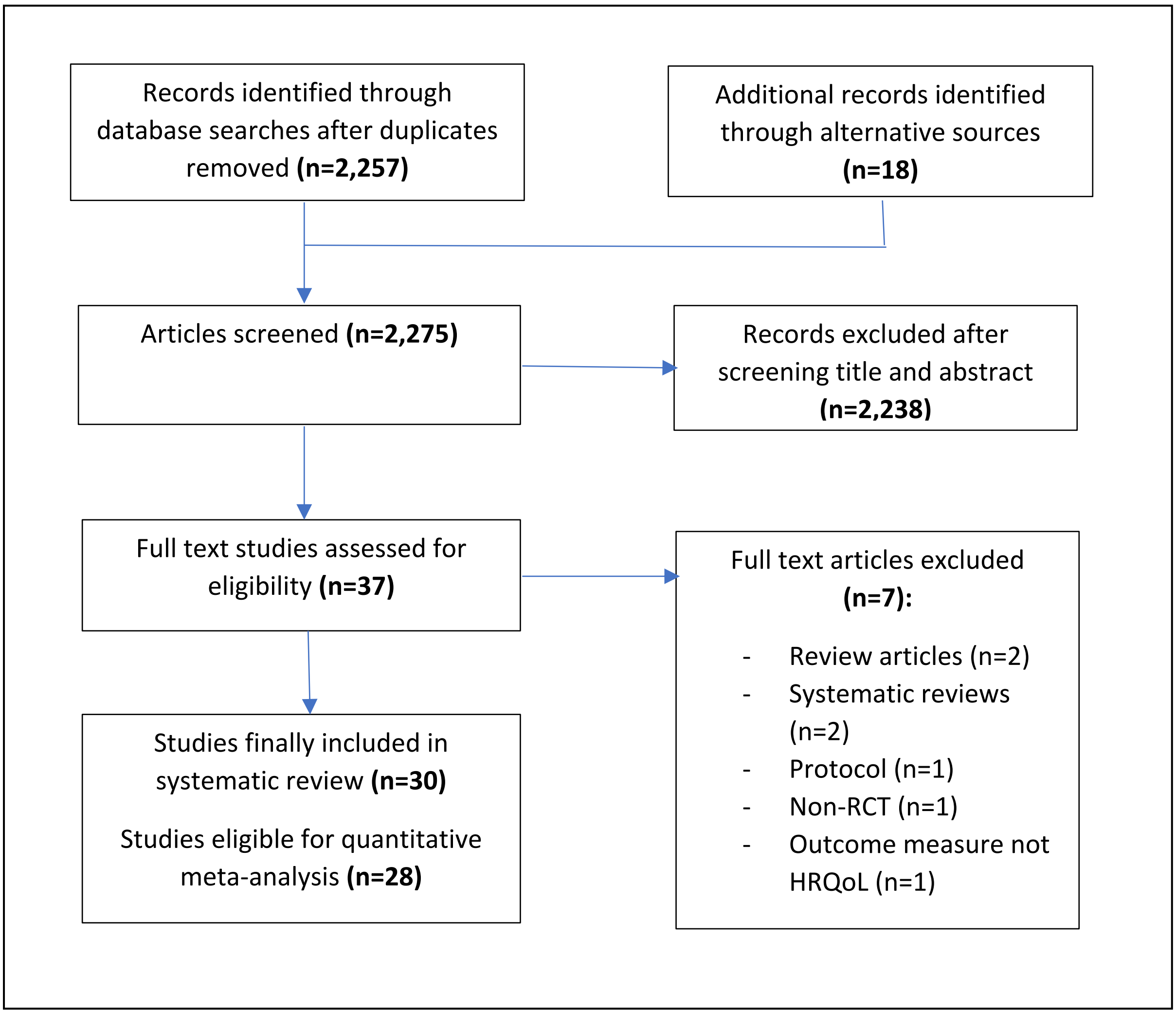
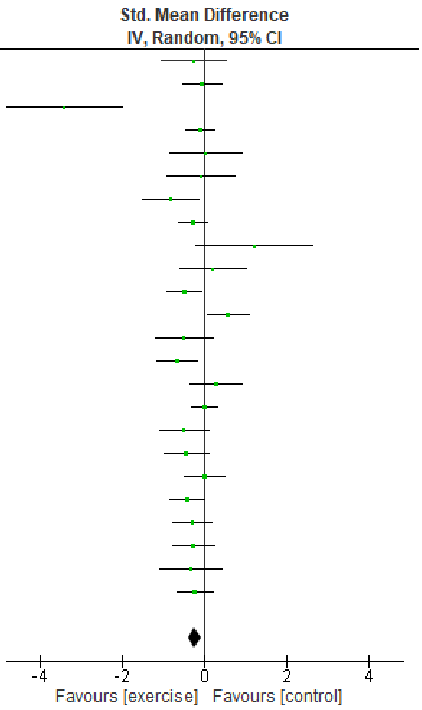


Figure 2. Forrest plots comparing the effect of exercise interventions on overall HRQoL compared to control arms at end of intervention (a), and at follow up between 3 and 9 months post intervention (b).

(a)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ada 2003	12	6.2	11	13.6	6.1	14	2.9%	-0.25 [-1.05, 0.54]
Ada 2013	-70	17	34	-69	18	34	5.0%	-0.06 [-0.53, 0.42]
Aidar 2016	-66.2	6	11	-42.2	7.5	11	1.2%	-3.40 [-4.79, -2.01]
Dean 2012	-43.5	9.5	65	-42.5	10.5	68	6.2%	-0.10 [-0.44, 0.24]
Duncan 1998	-44	16.7	10	-44.5	16.7	10	2.5%	0.03 [-0.85, 0.91]
Flansbjer 2008	-58.8	19.5	15	-57.3	19.3	9	2.8%	-0.07 [-0.90, 0.75]
Globas 2012	-52.28	6	18	-46.2	8.3	18	3.5%	-0.82 [-1.50, -0.14]
Gordon 2012	-43.15	12.5	64	-39.6	12.2	64	6.1%	-0.29 [-0.63, 0.06]
Heron 2017	-53	29.7	5	-85.8	17.6	5	1.2%	1.21 [-0.20, 2.63]
Kirk 2014	-61.5	13.7	12	-64.6	14.8	12	2.9%	0.21 [-0.59, 1.01]
Lai 2006	-93	22.5	44	-77.5	37.9	49	5.5%	-0.49 [-0.90, -0.07]
Langhammer 2008	28.6	25.1	32	16.2	16.1	31	4.7%	0.58 [0.07, 1.08]
Lee 2018	-0.79	0.15	18	-0.72	0.12	14	3.3%	-0.50 [-1.21, 0.22]
Mead 2007	-85.6	7.4	32	-79	11.8	34	4.8%	-0.66 [-1.15, -0.16]
Moore 2015	-81.7	22	20	-87.3	16.1	20	3.9%	0.28 [-0.34, 0.91]
Nave et al 2019	-0.7	0.3	84	-0.7	0.3	82	6.5%	0.00 [-0.30, 0.30]
Rosenfeldt 2019	-79.3	12.7	16	-73.5	11	34	4.0%	-0.49 [-1.10, 0.11]
Sandberg 2016	-87.2	9.1	29	-81.1	17.5	27	4.5%	-0.44 [-0.97, 0.09]
Shaughnessy 2012	-577	102	29	-577	83	34	4.8%	0.00 [-0.50, 0.50]
Sudentski 2005	-81.3	14.2	44	-75.3	14.5	49	5.5%	-0.41 [-0.83, -0.00]
Vahlberg 2017	-0.745	0.27	34	-0.667	0.26	33	4.9%	-0.29 [-0.77, 0.19]
Vloothuis 2019	-59.3	9.8	32	-56.6	10.6	29	4.7%	-0.26 [-0.77, 0.24]
Yoo 2011	-3.32	0.75	14	-3.07	0.71	14	3.1%	-0.33 [-1.08, 0.41]
Zedlitz 2012	15.4	12.1	38	18.1	11.5	45	5.3%	-0.23 [-0.66, 0.21]
Total (95% CI)			**711**			**740**	**100.0%**	**-0.23 [-0.40, -0.07]**

Heterogeneity: Tau² = 0.09; Chi² = 52.21, df = 23 (P = 0.0005); I² = 56%
Test for overall effect: Z = 2.73 (P = 0.006)



(b)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ada 2013	-67	19	34	-72	19	34	8.6%	0.26 [-0.22, 0.74]
Flansbjer 2008	-54.8	17.9	15	-49.3	20.1	9	2.8%	-0.28 [-1.11, 0.55]
Lai 2006	-95.8	13.5	40	-85.8	31.9	40	10.0%	-0.40 [-0.85, 0.04]
Langhammer 2008	23.7	29.25	32	17.4	22.05	31	8.0%	0.24 [-0.26, 0.74]
Mead 2007	-80.75	7.4	32	-75.8	11.8	34	8.2%	-0.49 [-0.98, -0.00]
Nave et al 2019	-0.7	0.3	79	-0.7	0.3	65	18.3%	0.00 [-0.33, 0.33]
Sandberg 2016	-89.6	11.3	29	-84.7	18.3	27	7.1%	-0.32 [-0.85, 0.21]
Sudentski 2005	-80.9	13.7	40	-75.9	15.7	40	10.1%	-0.34 [-0.78, 0.11]
Vahlberg 2017	-0.714	0.3	34	-0.75	0.2	33	8.6%	0.14 [-0.34, 0.62]
Vloothuis 2019	-72.69	18.25	32	-70.49	17.6	29	7.8%	-0.12 [-0.62, 0.38]
Zedlitz 2012	15.7	13.9	38	16.4	11	45	10.5%	-0.06 [-0.49, 0.38]
Total (95% CI)			**405**			**387**	**100.0%**	**-0.11 [-0.25, 0.03]**

Heterogeneity: Chi² = 11.58, df = 10 (P = 0.31); I² = 14%
Test for overall effect: Z = 1.50 (P = 0.13)

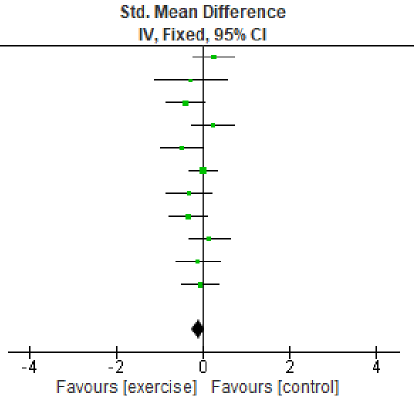


Figure 3. Effect of intervention characteristics on overall HRQoL after stroke and TIA

Intervention characteristic	Criteria	No. RCTs	Participants (intervention)	SMD	95% CI Lower limit	95% CI Upper limit	SMD and 95% CI's	P value	I^2
Exercise initiation	< 6 months	10	595 (288)	-0.21	-0.03	-0.39		**0.02**	12%
	> 6 months	10	501 (253)	-0.29	0.09	-0.67		0.14	75%
Exercise type	Aerobic	8	552 (274)	-0.18	0.05	-0.40		0.12	33%
	Resistance	2	46 (26)	-1.69	1.57	-4.95		0.31	94%
	Mixed	14	853 (411)	-0.21	-0.03	-0.39		**0.02**	38%
Programme duration	< 12 weeks	7	338 (175)	-0.09	0.13	-0.30		0.43	0%
	≥ 12 weeks	16	1,063 (520)	-0.27	-0.05	-0.49		**0.01**	66%
Weekly minutes	< 150	11	851 (420)	-0.14	0.04	-0.33		0.13	40%
	≥ 150	10	447 (226)	-0.36	-0.02	-0.71		**0.04**	66%
Setting	Centre based	17	913 (447)	-0.25	-0.02	-0.49		**0.03**	64%
	Home based	7	538 (264)	-0.25	-0.06	-0.45		**0.009**	16%