Rehabilitation through high-intensity exercise in the early stages of stroke: systematic review and meta-analysis

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Summary

Introduction: High intensity training (HIT) has been shown to be safe and feasible, and to report many health related benefits to stroke patients. The objective of this review was to examine the effects of high intensity exercise on functional recovery and health related quality of life in the acute and subacute phases of stroke.
Material and method: Six databases were searched up to october 2023, looking for studies that compared the effect of HIT to other exercise interventions in the first six months after having a stroke.
Results: Seven papers were identified 163 patients were studied with a mean age of 65 years. Statistically significant differences were found for the variables of quality of life and health (average standardized mean difference [SMD] 1.07, with a 95% Confidence Interval [95%CI] of 0.94-1.33; P <0.001), and balance (SMD 0.86, 95%CI 0.41-1.30; P = 0.0002); while for the variable mental health (SMD 0.05, 95%CI -0.33-0.44; P = 0.79) and cardiorespiratory fitness (SMD 0.56, 95%CI -0.01-1.14; P = 0.055) the results of the meta-analysis were not significant.
Conclusions: These results suggest that the implementation of HIT protocol has positive results on quality of life and health of stroke patients, and is safe during the acute and subacute stages of stroke.

Key words:
Physical Condition. Therapeutic exercise. Quality of life. Health.

Rehabilitación mediante ejercicio de alta intensidad en las fases tempranas del ictus: revisión sistemática y metaanálisis

Resumen

Introducción: El ejercicio de alta intensidad (HIT) ha demostrado ser un modelo seguro y factible que ofrece beneficios en la salud de los pacientes con ictus. El objetivo de este metaanálisis fue examinar los efectos del ejercicio de alta intensidad sobre la recuperación funcional y la calidad de vida relacionada con la salud en las fases aguda y subaguda del ictus.
Material y método: Se realizó una búsqueda en seis bases de datos de hasta octubre de 2023 de ensayos clínicos que investigaron los efectos de HIT comparado con otras intervenciones de ejercicio en los primeros seis meses tras haber sufrido un accidente cerebrovascular.
Resultados: Se identificaron siete artículos en los que se estudió a 163 pacientes con una media de edad de 65 años. Se hallaron diferencias estadísticamente significativas para las variables de calidad de vida y salud (diferencia de medias estandarizadas [DME] promedio 1,07, con un intervalo de confianza del 95% [IC95%] de 0,94-1,33; p <0,001), y para el equilibrio (DME 0.86, IC95% 0,41-1,30; p = 0,0002); mientras que para la variable salud mental (DME 0,05, IC95% -0,33-0,44; p = 0,79) y capacidad cardiorrespiratoria (DME 0.56, IC95% -0,01-1,14; p = 0,055) los resultados del metaanálisis fueron no significativos.
Conclusiones: Estos resultados sugieren que la implementación de un protocolo HIT es beneficioso para la mejora de la calidad de vida y la salud, así como mostrarse como una estrategia segura en pacientes en fases aguda y subaguda del ictus.

Palabras clave:
Condición física. Ejercicio terapéutico. Calidad de vida. Salud.

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Introduction

In recent decades, Western populations have aged gradually and significantly. This has led to an increase in the incidence of age-related ailments, with stroke being the third most relevant disease within the relevant group in 2019[1]. That year, there were more than 12 million new cases of stroke worldwide and almost 7 million deaths[2]. Not just in Spain but throughout Europe, stroke is the second cause of dementia after Alzheimer's disease and the first cause of disability[3].

The main sequelae in patients who have suffered a stroke are reduced motor control and changes in sensation[4]. Their cardiorespiratory capacity is also reduced by 50%[5], which leads to greater physical inactivity[6], increasing the risk of stroke recurrence[7].

High-intensity exercise includes any exercise model in which at least 70% of the reserve heart rate (HRR) or maximal oxygen consumption (VO_{2max}), 75% of the maximum heart rate (HR_{max}) or a score of 14 on the Borg Rating Of Perceived Exertion (RPE) scale[8] is reached. It can be applied continuously or at intervals through short bursts of vigorous activity followed by periods of low activity[9].

Currently, rehabilitation programmes for stroke patients have a limited impact on the recovery of aerobic capacity[10]. However, in view of the benefits and degree of safety reported by HIT protocols in healthy individuals and patients with other chronic diseases[11,12], the application of this exercise model has been proposed with the aim of reducing morbidity in stroke patients[10]. There is also evidence that it would be safe and beneficial for the cardiopulmonary health of these patients[13–15] although what the best exercise protocol might be is still a subject of debate[10,16].

The potential for functional recovery has been shown to be greatest in the first months after the onset of stroke[4], but the bulk of the existing evidence looks at the impact of high-intensity exercise on rehabilitation from the disease, including either all its phases or just the chronic phase. So, the aim of this review was to study the effect of HIT interventions in the acute and subacute phases of stroke.

Materials and methods

This systematic review with meta-analysis was conducted according to the PRISMA guidelines (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*)[17].

Search strategy

All clinical trials that studied the effects of HIT on patients in the acute and subacute phases were included. The studies were considered for inclusion regardless of size provided that they included a control group to compare outcomes.

We searched the *Medline database via PubMed, Cochrane Library (Willey), Web of Science (Clarivate),* and the *Embase database via embase.com (Elsevier), SportDiscus (EBSCOhost)* and *BVSalud (Literatura Latino Americana e do Caribe em Ciências da Saúde-LILACs)* up to October 2023. Controlled vocabulary (MeSH terms) was used, employing keywords and synonyms to refine the search. The references in the articles included in systematic reviews were checked to identify other potentially eligible studies.

The study was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42023432785). Study titles and summaries which could be relevant to this review were obtained. Two authors verified the inclusion criteria of the studies found. In the event of disagreement in this regard, consensus was reached through common agreement. The full texts of the articles were then assessed applying the inclusion and exclusion criteria.

Selection of the studies and eligibility criteria

The following inclusion criteria were established: 1) clinical trials, 2) with described intervention including high intensity exercise according to ESC criteria, and 3) stroke in acute or subacute phase.

The following exclusion criteria were chosen: 1) stroke in chronic phase, 2) measurement of intensity which was a variable other than VO_{2max}, HR or RPE, and 3) interventions that did not include aerobic exercise, defined as any activity that uses large muscle groups, can be maintained continuously and is of a rhythmic nature[18].

Data extraction and bias and quality risk analysis

The following information was collected from the original studies selected: authors, year of publication, characteristics of the patients (age and mean time elapsed after the onset of stroke), characteristics of the intervention (duration and intensity of the sessions) and outcome measures with their statistical significance.

The quality of the studies was assessed using the PEDro scale[19] and the level of evidence with the appraisal sheet provided by the University of Oxford's Centre for Evidence-Based Medicine (OCEBM)[20].

Statistical analysis

Jamovi v2.3.21 was used for this meta-analysis. For all the studies which presented continuous data variables, the standardised mean difference (SMD) between pre and post-intervention values was chosen with a 95% confidence interval as outcome measure (Table 1). For a variable present in more than two studies, the random effects model was used as a statistical approach. Regarding the other variables, when only comparing two studies, the fixed effects model was used for analysis[21].

Secondary studies on the same trial were included in this meta-analysis, so, despite the existence of comparable variables between them, these could not be analysed, thereby limiting the size of this study. This was an impediment when performing the analysis because having taken them into account would have magnified the effect, since they are variables measured in the same patients.

Table 1. Standardised measures for the meta-analysis variables.

Variables	Title of the article	Outcome measured	No. of subjects	Intervention			Control		
				Ni	SMDi	SD SMDi	Nc	SMDc	SD SMDc
Capacidad cardio-rrespiratoria	Sandberg 2016	6MWT (m)	56	29	105.1	76.2	27	35.9	93.2
	Hornby 2016	6MWT (m)	32	15	116.0	101.4	17	29.0	77.5
	Krawcyk 2019	GCT-TT (Watts)	63	31	7.7	31.7	32	6.7	32.7
Calidad de vida y salud	Sandberg 2016	EQSD VAS	56	29	14.9	16.6	27	0.7	12.9
	Hornby 2016	Physical SF36	32	15	9.0	4.9	17	2.0	5.3
Mental health	Krawcyk 2019	WHOS (mental well being)	63	31	4.0	15.3	32	5.0	12.4
	Hornby 2022	Subdominio Mental Health	44	27	3.0	13.1	17	0.0	10.6
Balance	Sandberg 2016	SLS (Single Leg Stand)	56	29	10.4	7.4	27	0.9	7.6
	Hornby 2016	Escala Berg	32	15	8.0	10.6	17	5.0	10.8

Variables	Title of the article	Outcome measured	Intervention						
			Ni	PREi value	SD PREi	POSTi value	POSTi SD	SMDi	SD SMDi
Cardiorespiratory capacity	Sandberg 2016	6MWT (m)	29	394.7	114.7	499.8	93.1	105.1	76.2
	Hornby 2016	6MWT (m)	15	116.0	88.0	232.0	149.0	116.0	101.4
	Krawcyk 2019	GCT-TT (Watts)	31	118.5	43.1	126.2	46.3	7.7	31.7
Quality of life and health	Sandberg 2016	EQSD VAS	29	72.3	22.3	87.2	9.1	14.9	16.6
	Hornby 2016	Physical SF36	15	35.0	7.3	44.0	6.1	9.0	4.9
Mental health	Krawcyk 2019	WHOS (mental well being)	31	65.0	23.0	69.0	16.0	4.0	15.3
	Hornby 2022	Subdominio Mental Health	27	51.0	19.0	54.0	18.0	3.0	13.1
Balance	Sandberg 2016	SLS (Single Leg Stand)	29	9.6	10.3	20.0	10.6	10.4	7.4
	Hornby 2016	Escala Berg	15	32.0	16.0	40.0	11.0	8.0	10.6

Variables	Title of the article	Outcome measured	Control						
			Nc	PREc value	SD PREc	POSTc value	POSTc SD	SMDc	SD SMDc
Cardiorespiratory capacity	Sandberg 2016	6MWT (m)	27	384.3	131.9	420.2	131.6	35.9	93.2
	Hornby 2016	6MWT (m)	17	131.0	108.0	160.0	111.0	29.0	77.5
	Krawcyk 2019	GCT-TT (Watts)	32	119.5	44.0	126.2	47.9	6.7	32.7
Quality of life and health	Sandberg 2016	EQSD VAS	27	80.4	18.9	81.1	17.5	0.7	12.9
	Hornby 2016	Physical SF36	17	36.0	7.5	38.0	7.4	2.0	5.3
Mental health	Krawcyk 2019	WHOS (mental well being)	32	64.0	18.0	69.0	17.0	5.0	12.4
	Hornby 2022	Subdominio Mental Health	17	63.0	12.0	63.0	16.0	0.0	10.6
Balance	Sandberg 2016	SLS (Single Leg Stand)	27	11.8	10.8	12.7	10.7	0.9	7.6
	Hornby 2016	Escala Berg	17	33.0	16.0	38.0	14.0	5.0	10.8

Ni: sample size of intervention group; SMDi: Standardised mean difference in intervention group; SD SMDi: Standard deviation of standardised mean difference in intervention group; Nc: sample size of control group; SMDc: Standardised mean difference in control group; SD SMDc: Standard deviation of the standardised mean difference in control group: PREi value: Pre-intervention mean in experimental group: SD PREi: Pre-intervention standard deviation in experimental group: PREc value: Pre-intervention mean in control group: SD PREc: Pre-intervention standard deviation in control group.

Results

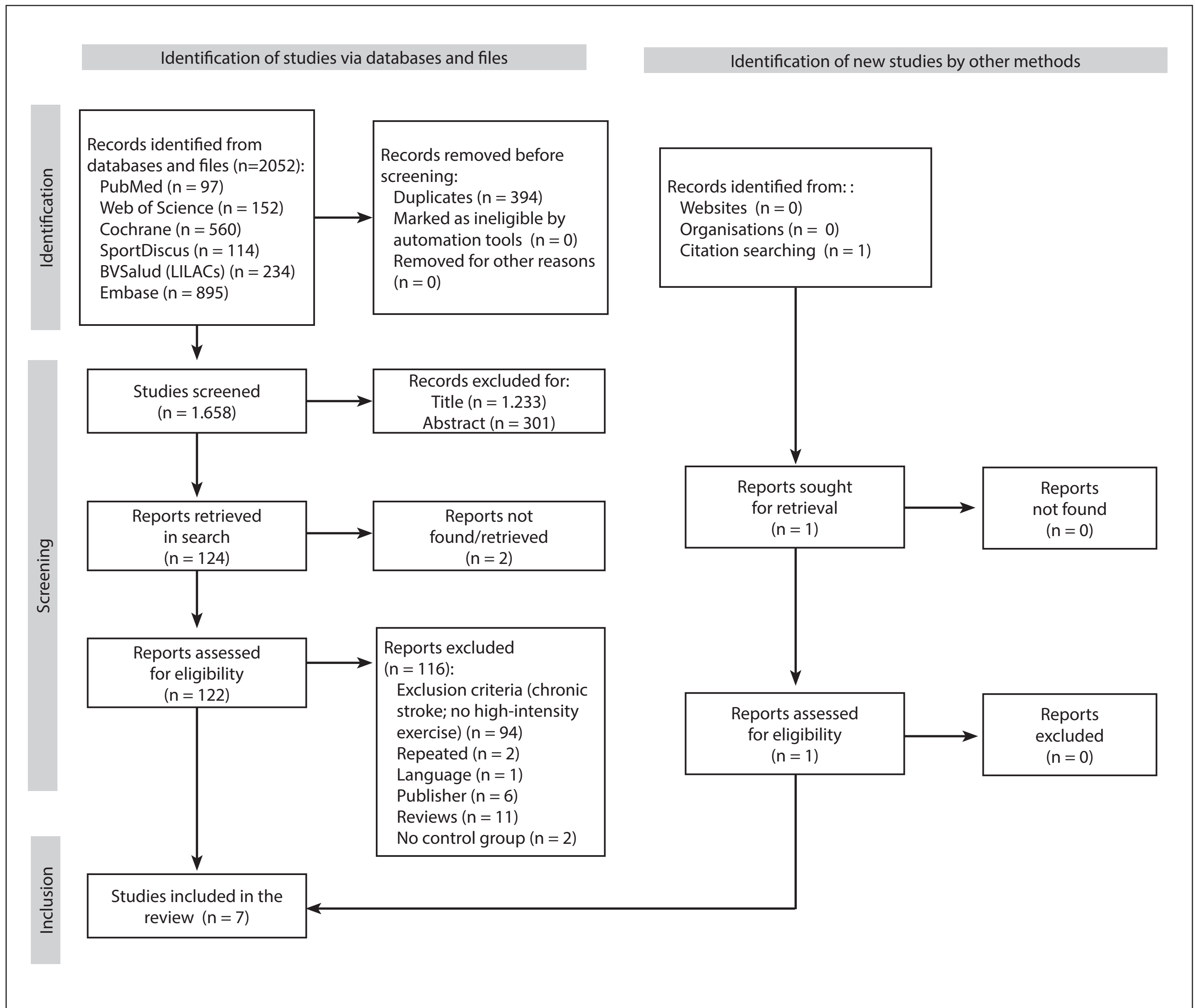
Systematic review

2052 studies were identified initially, of which 122 were considered potentially eligible. Finally, 7 articles met the inclusion criteria and were selected for the review (Figure 1).

Characteristics of the studies included

Of the 7 articles included, 3 are randomised controlled trials (RCTs) (Krawcyk, *et al.*[22], Hornby, *et al.* 2016[23] and Sandberg, *et al.*[24]). Of those remaining, Wijkman, *et al.*[25] is a secondary analysis of Sandberg, *et al.*[24], and Leddy, *et al.*[26], Mahtani, *et al.*[27] and Hornby, *et al.* 2022[28] are secondary analyses of Hornby, *et al.* 2016[23].

Figure 1. PRISMA flow diagram.



The studies were published between 2016 and 2022. They were carried out in different countries, namely Denmark, Sweden and the United States.

Characteristics of the participants

The participants in the studies analysed were aged between 18 and 75. They were required to have the minimal degree of stability and mobility to do the exercise in question (ability to walk five metres with minimal or moderate assistance) and the ability to understand written and spoken instructions, including the ability to give informed consent[22–28].

Characteristics of the interventions and conditions of the control groups

Table 2 shows the information collected on the interventions in the studies reviewed here, including RCTs and secondary analyses. Three studies[22,24,25] focussed on interval-based exercise interventions, while the other four used continuous exercise. Different instruments were used for rehabilitation: a treadmill was used in four of the studies[23,26-28], an ergometer in three[22,24,25] and steps or walking on flat ground were used in the other three[23,26,27].

Different parameters were used to measure the intensity of the exercise, most studies using more than one: VO_{2max} and HR_{max} were

Table 2. Comparison of the interventions

Intervention	Sub-type	RCTs & secondary analyses	Participants
Type	HIT HIIT	4 3	86 (+12) 98
Method	Treadmill Cycle ergometer Floor/steps	4 3 3	86 (+12) 98 63 (+12)
Intensity measure	VO_{2max} HR_{max} HRR RPE (Borg)	2 2 5 5	58 85 99 (+12) 128 (+12)
Time	< 40 min ≥ 40 min	1 6	40 144 (+12)
Frequency	<4 days/week 4-5 days/week	2 5	58 126 (+12)
Duration of the programme	8-12 weeks	7	184 (+12)
Training environment	Hospital Outpatients	1 6	29 155 (+12)

RCTs Randomised controlled trials; HIT: High intensity training; HIIT: High intensity interval training. "(+12)" refers to patients in the Holleran, *et al.* protocol[29].

used in two studies[24,25], HRR in five[23,26-29] and RPE in the other five[22,23,25-27].

The interventions lasted between eight and twelve weeks. Turning to session frequency, there were sessions two days a week in two publications[24,25] and sessions four-to-five days a week in the rest. The sessions in only one study lasted less than 40 minutes[22]. Finally, six studies were conducted in an outpatient setting and only one in a hospital setting[25].

A "(+12)" is added in parentheses in some sections. This refers to patients who completed the protocol described by Holleran *et al.*[29], a pilot study which was conducted to gauge the feasibility of the trial described by Hornby *et al.*[23], and which, therefore, followed the same intervention but did not involve a control group, meaning that the participants were not included in the tables.

Quality assessment

The PEDro (Physiotherapy Evidence Database) scale was used to evaluate the methodological quality of the studies included in this review (Table 3). Of the seven articles included, five scored 6-8 points out of 10, meaning that their methodological quality can be considered good. Of the remaining two articles, one obtained a score of 5 and the other, 4, indicating an acceptable degree of quality.

The selection criteria were specified in all the studies and they all started with groups of patients who shared similar baseline characteristics.

In all but one case[26], subject allocation was randomised and concealed. The assessors were blinded in some cases[22-24,26]. Bar two exceptions[26,27], results were presented for all the participants assigned to the intervention or the control group. When this was not possible, the data were analysed by "intention to treat". Finally, in no case were the measures of the outcomes obtained in more than 85% of the participants. This was because they did not attain that percentage or because no explicit mention was made of it.

All the trials met the requirements of a randomised clinical trial, classified as level 1b.

Meta-analysis

Cardiorespiratory capacity

Three studies reported pre- and post-intervention cardiorespiratory capacity data. The SMDs ranged from 0.03 to 0.95, all estimates being positive. The estimated mean SMD was 0.56, with a 95% confidence interval (95% CI) of between -0.01 and 1.14, using the random effects model. The mean result showed no significant differences ($z = 1.92$, $P = 0.055$). Cochran's Q test was not significant, but a mean heterogeneity was observed in the results ($Q(2) = 5.83$, $P = 0.05$, $T^2 = 0.16$, $I^2 = 64.8\%$). The 95% prediction interval for the results ranged from -0.42 to 1.54 (Figure 2).

Quality of life and health

A total of two studies reported pre- and post-intervention quality of life and health data. The SMDs ranged from 0.94 to 1.33, all estimates

Table 3. PEDro (*Physiotherapy Evidence Database*).

STUDIES	1	2	3	4	5	6	7	8	9	10	11	PEDro scale score
Hornby, *et al.* 2022	X	X	X	X					X	X	X	6/10
Leddy, *et al.* 2016	X			X			X			X	X	4/10
Krawcyk, *et al.* 2019	X	X	X	X			X		X	X	X	7/10
Sandberg, *et al.* 2016	X	X	X	X			X		X	X	X	7/10
Mahtani, *et al.* 2017	X	X	X	X						X	X	5/10
Wijkman, *et al.* 2018	X	X	X	X					X	X	X	6/10
Hornby, *et al.* 2016	X	X	X	X			X		X	X	X	7/10

1: eligibility criteria; 2: random allocation; 3: allocation concealed; 4: baseline similarity; 5: blinded subjects; 6: blinded therapists; 7: blinded assessors; 8: key outcome measures in >85% subjects; 9: monitoring and analysis by "intention to treat"; 10: between-group comparisons; 11: point measures and measures of variability. "X" indicates "yes" and blank means "no".

Figure 2. Forest plot for cardiorespiratory capacity

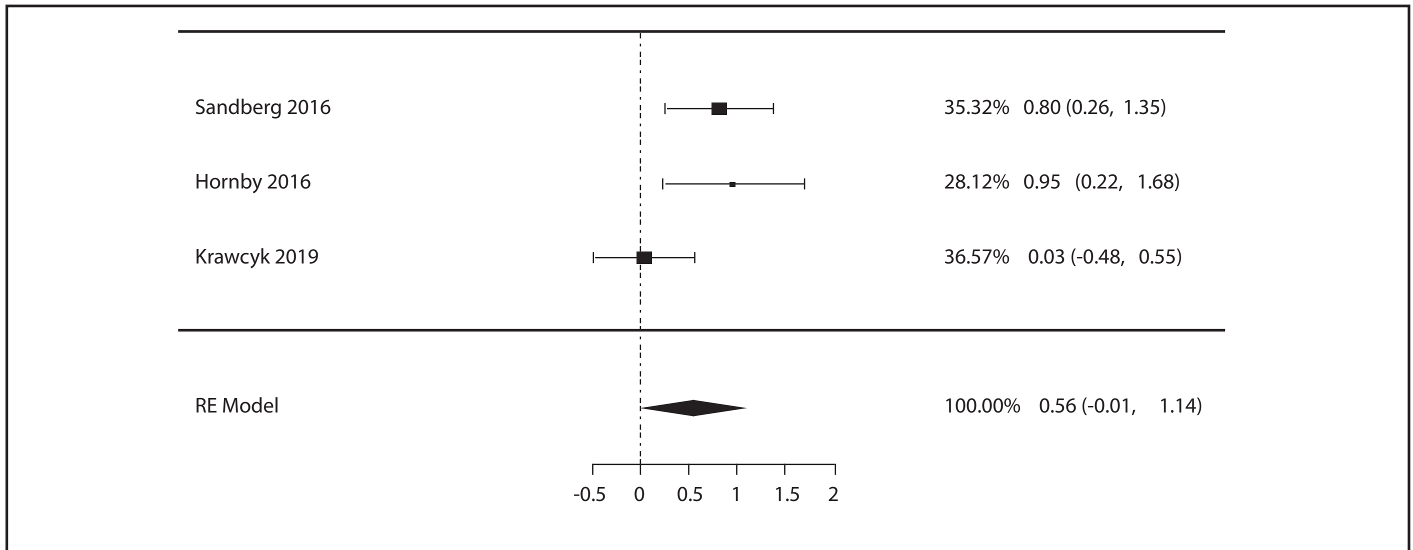
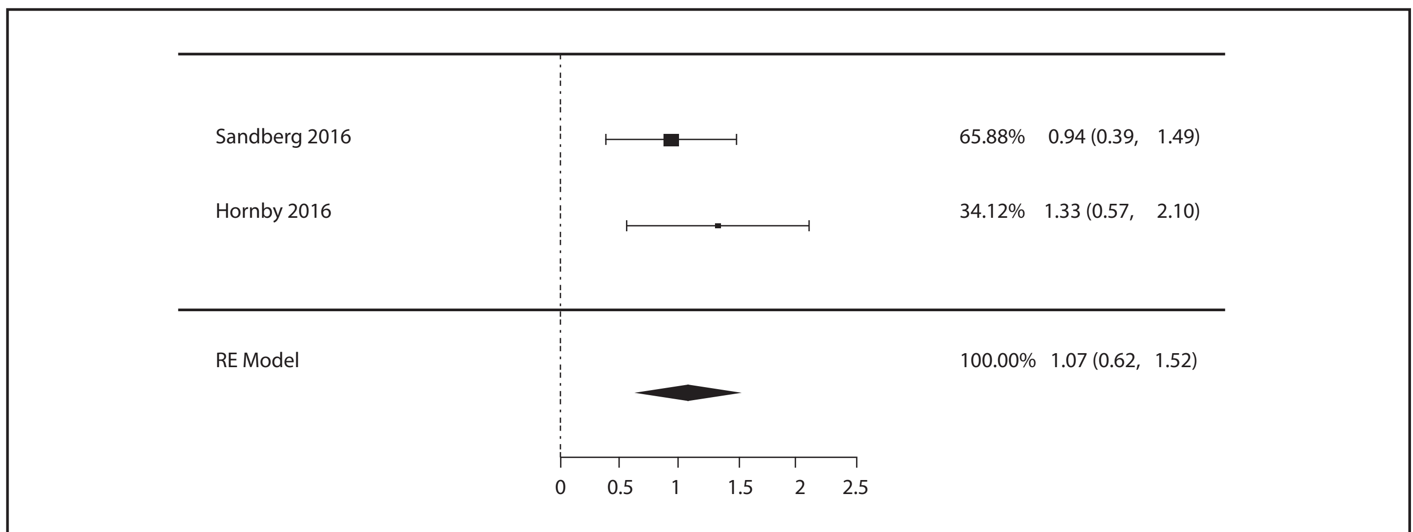


Figure 3. Forest plot for quality of life and health.



being positive. The estimated mean SMD was 1.07, with a 95% CI of between 0.62 and 1.52, using the random effects model. The mean result showed significant differences (z = 4.69, P = 0.0001). According to Cochran's Q test, there was no significant heterogeneity in the true results (Q(1) = 0.67, P = 0.41, I^2 = 0.00%) (Figure 3).

Mental health

Two studies reported pre- and post-intervention mental health data. The SMDs ranged from -0.07 to 0.24, half of the estimates being negative. The estimated mean SMD was 0.05, with a 95% CI of between -0.33 and 0.44, using the random effects model. The mean result showed no significant differences (z = 0.27, P = 0.79). According to Cochran's Q test, there was no significant heterogeneity in the true results (Q(1) = 0.61, P = 0.44, I^2 = 0.00%) (Figure 4).

Balance

A total of two studies reported pre- and post-intervention balance data. The SMDs ranged from 0.27 to 1.25, all estimates being positive. The estimated mean SMD was 0.86, with a 95% CI of between 0.41 and 1.30, using the random effects model. The mean result showed significant differences (z = 3.79, P = 0.0002). According to Cochran's Q test, the true results were apparently heterogeneous (Q(1) = 4.49, P = 0.03, I^2 = 77.75%) (Figure 5).

Publication bias

Egger's test only produced evidence of publication bias for the balance variable (P = 0.03).

Figure 4. Forest plot for mental health.

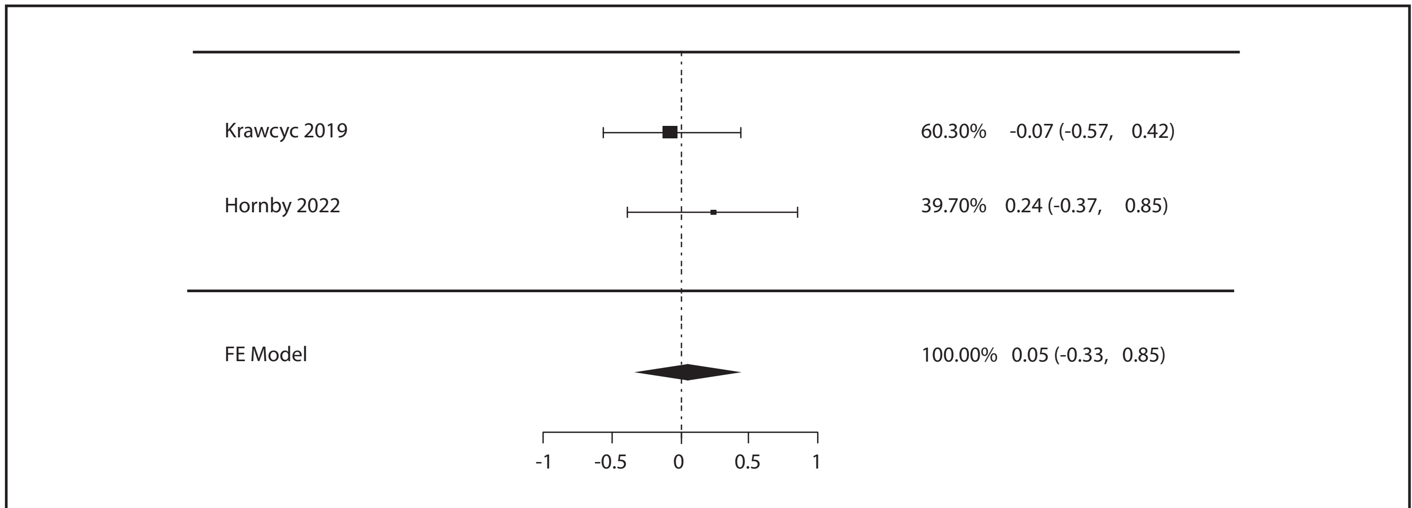
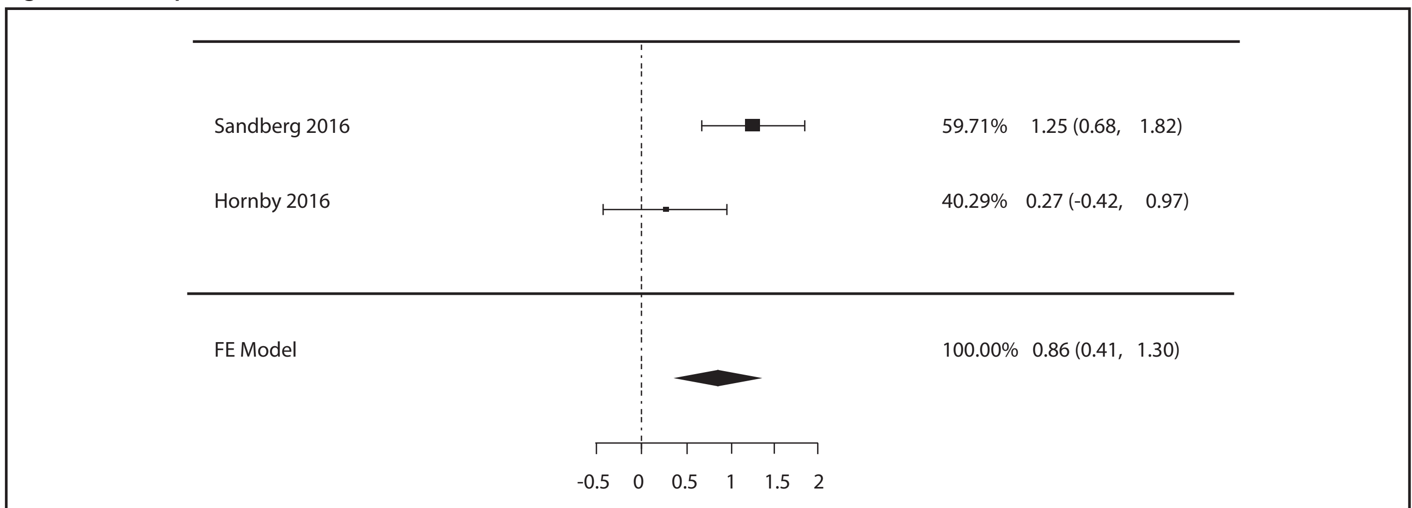


Figure 5. Forest plot for balance.



Adverse events

The adverse events found were analysed in depth without observing significant differences between groups, these being similar in terms of number of events. Such events involved fractures, wounds, falls without injury and joint and muscle pain, along with cardiorespiratory events (high blood pressure, angina and pulmonary aspiration) requiring hospitalisation[23,26]. Two articles did not report this information at all[27,28], one article recorded an absence of intervention-related adverse events[22] and two reported that there had been no serious adverse events at any point in their trials[24,25].

Discussion

From the data presented in this meta-analysis, we suggest that a high-intensity exercise protocol has beneficial effects on quality of life and health, and balance in the early phases of stroke patients compared to conventional interventions, but no significant effects in terms of mental health or cardiorespiratory capacity. It was possible to include four of the seven articles in the quantitative analysis section with a good quality of evidence..

Cardiorespiratory capacity and haemodynamic variables

We found positive but not significant results for cardiorespiratory capacity in the intervention group. A previous meta-analysis including chronic patients reported significant beneficial effects on cardiorespiratory fitness from HIT[13]. This could be because patients in this phase of recovery usually start with reduced cardiovascular capacity, so the margin for improvement is greater. In the early stages of stroke, the potential for recovery of capacity to pre-stroke values is greater because

the patients have not been suffering the consequences of the disease for so long, and therefore have not suffered deterioration through inactivity for such a long time. Furthermore, greater aerobic capacity has been associated with a reduction in cardiovascular risk factors and stroke recurrence, in part due to the lower blood pressure and serum cholesterol levels it causes[30]. Our analysis did not study haemodynamic variables, but, in their original articles, Krawcyk, *et al.*[22] and Wijkman, *et al.*[25] observed a significant drop in heart rate, indicating a favourable outcome of intervention.

Quality of life and health

Previous studies have confirmed, with a strong level of evidence, that aerobic exercise improves not only cardiorespiratory fitness and disability but also mobility and balance in all stages of recovery[7,16], directly affecting quality of life. In our study, we were able to confirm that HIT significantly improved quality of life and health in the intervention groups compared to the control groups. However, this is not consistent with outcomes described previously by other authors[31]. This discrepancy could be explained by the lower intensity to which the intervention group in said study was subjected (60-80% HRR).

Mental health and cognition

Our study did not observe any benefits from HIT above those registered with traditional rehabilitation protocols. So the results concerning any impact that aerobic exercise may have on current degree of depression and mental well-being are inconclusive[16]. This could be due to the limited number of patients recruited, so we can only say that the results provided may not be definitive.

Balance

Our quantitative analysis agrees with the conclusions of the review by Saunders, *et al.*[16] ,which establishes with a strong level of evidence that aerobic exercise produces a greater improvement in terms of balance than conventional rehabilitation interventions in all stages of recovery.

Kinematics

Changes in kinematics have been studied from different perspectives. Holleran, *et al.*[29] reported a significant improvement in stride speed, cadence and length. This suggests that high-intensity exercise may be a factor which can improve the prognosis when recovering the ability to walk efficiently, although the evidence to date is limited by the number of studies found.

Adverse events

No serious adverse events were observed in any of the studies included in this review. However, it should be noted that, of the seven articles, only two analysed these in depth. They did not show any clear relationship with the intervention[23,26]. Two studies observed an absence of serious adverse events during their trials[24,25]; Krawcyk, *et al.*[22] saw no type of adverse event at all and the other two did not touch on the subject[27,28].

Other reviews back up the safety of HIT in stroke patients in all stages of recovery, such as Luo, *et al.*[13], Anjos, *et al.*[15] and Fahey, *et al.*[33] where no significant differences were found between high-intensity exercise and control groups, and no increase was observed in the rate of adverse events compared to conventional rehabilitation.

The evidence available suggests that this model is safe and well tolerated. However, despite the safe nature of the protocols, Wijkman *et al.*[25] observed a significant rise in systolic blood pressure in response to exercise. For this reason, we consider it essential that this exercise model be prescribed and supervised by trained professionals, and carefully adapted to the individual needs of each subject, and that the physiological variables of each patient be rigorously monitored during the intervention.

Strengths and limitations

It should be noted that different definitions can be used to describe intensities of effort. We chose to follow the indications of the European Society of Cardiology (ESC), so some studies were ruled out, mainly because the intensity levels they proposed were less demanding than those sought. On the other hand, the search was carried out in the leading databases, so we believe that we managed to group together the most relevant studies on the subject.

Because this is a relatively new line of research (first study found in 2016), there is not much literature available. This is a limitation and we must be cautious about the contributions presented here. However, the methodological quality analysis confirms that five trials were of good quality and the other two presented an acceptable level of evidence.

Conclusions

Our meta-analysis suggests that the implementation of an HIT protocol may be beneficial in terms of improving quality of life and health, and that it is a safe strategy in patients in the acute and subacute phases of stroke.

Conflict of interest

The authors declare no conflict of interest.

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