BMJ Open Sport & Exercise Medicine

Elucidating the role of physical exercises in alleviating stroke-associated homeostatic dysregulation: a systematic review and meta-analysis

Vanina Myuriel Villagra Moran,[1,2] Irin Sultana Nila,[2,3] Rajesh Madhuvilakku,[2,4] Dewan Md Sumsuzzman,[2,4] Zeeshan Ahmad Khan,[2,4] Yonggeun Hong [1,2,3,4,5]

To cite: Villagra Moran VM, Nila IS, Madhuvilakku R, *et al*. Elucidating the role of physical exercises in alleviating stroke-associated homeostatic dysregulation: a systematic review and meta-analysis. *BMJ Open Sport & Exercise Medicine* 2024;**10**:e001906. doi:10.1136/bmjsem-2024-001906

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjsem-2024-001906).

Accepted 10 October 2024

For numbered affiliations see end of article.

Correspondence to
Professor Yonggeun Hong; yonghong@inje.ac.kr

ABSTRACT

Background This study aimed to investigate the role of physical exercises as a non-pharmacological intervention for ameliorating post-stroke dysregulated homeostatic parameters.

Methods Embase, PubMed, PEDro, ISI Web of Science and CENTRAL were searched until April 2024. Parallel randomised controlled trials (RCTs) analysing the effect of post-stroke physical exercises (PSPE) on homeostatic parameters such as blood glucose, oxygen consumption (VO_2), high-density lipoprotein (HDL), low-density lipoprotein (LDL), systolic (SBP) and diastolic blood pressure (DBP) in individuals with stroke were selected.

Results Sixteen RCTs (n=698) were included. PSPE reduced fasting glucose levels (MD=−0.22; 95% CI −0.22 to −0.02; p=0.00) and increased the VO_2 (MD=2.51; 95% CI 1.65 to 3.37; p=0.00) and blood HDL levels (MD=0.07; 95% CI 0.00 to 0.13; p=0.00). However, we did not observe beneficial effects on LDL, SBP and DBP parameters. Further analyses demonstrated that both low and moderate exercises are more suitable for improving blood glucose and VO_2 in this population.

Discussion PSPE have the potential to improve dysregulated post-stroke parameters by reducing blood glucose levels and increasing VO_2 and HDL levels. However, the small size and limited number of included studies limited the precision of our results. Further research is needed to comprehensively analyse the effects of PSPE, particularly on LDL levels and blood pressure.

PROSPERO registration number CRD42023395715.

WHAT IS ALREADY KNOWN

⇒ Physical exercises have demonstrated their therapeutic efficacy in restoring early post-stroke mobility, enhancing cardiorespiratory fitness and improving walking ability.

⇒ However, our understanding of how these exercises influence post-stroke homeostasis regulation remained limited.

WHAT THIS STUDY ADDS

⇒ Physical exercises have the potential to improve post-stroke dysregulated homeostasis, by positively influencing blood glucose, VO_2 and high-density lipoprotein.

⇒ Selecting the appropriate exercise intensity is crucial, as both low and moderate-intensity exercises have proven to be more effective in enhancing post-stroke homeostasis parameters, such as blood glucose and VO_2.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may facilitate the development of personalised exercise programmes that target specific physiological outcomes, enhancing the effectiveness of stroke recovery.

INTRODUCTION

Stroke is a cerebrovascular pathological condition characterised by the abrupt onset of neurological and motor deficits that endure for more than 24 hours and may lead to death.[1 2] With a global incidence of 12.2 million cases per year, stroke stands as the second most prevalent cause of mortality and the third leading cause of complex functional disability in adults.[3 4] Post-stroke clinical implications not only involve motor system dysfunction but also the disruption of internal homeostasis.[5 6]

Homeostasis ensures the internal equilibrium within an organism, allowing the regular functioning of physiological processes despite variations in the external environment.[7 8] This state of balance within the body involves the constant adjustment of parameters such as blood pressure, acid levels, blood sugar, energy, oxygen and proteins.[9 10] In the acute stage of stroke (1–7 days),[11] homeostasis is disrupted by inflammatory and metabolic reactions to brain infarction. This results in the dysregulation of blood glucose, blood pressure and oxygen saturation, which worsens the patient's condition.[5] In subacute (>7 days–6 months) and chronic phases (>6 months),[11] due to the histological changes in the paretic skeletal muscles and the

significant inactivity,[12] the prevalence of abnormally high blood glucose and insulin resistance may increase to 80%.[13 14] Chronically, individuals who had a stroke also experience low cardiorespiratory fitness (CRF).[15] Stroke survivors exhibit a mean peak oxygen consumption (VO_2 peak) of 15.6 mL/min/kg, which is significantly lower than the minimum level (20 mL/min/kg) required for independent living.[15] This suggests that even the performance of the simplest activities of daily living (ADL) can push them close to their maximum aerobic capacity.[16] Oxygen consumption (VO_2) is considered a homeostatic parameter because it reflects the body's dynamic regulation of oxygen intake and utilisation to maintain internal balance and ensure cellular function.[17 18] Additionally, VO_2 is intrinsically associated with glucose metabolism, as elevated VO_2 indicates optimal glucose oxidation for energy production.[19]

Furthermore, stroke-associated motor impairment also contributes to risk factors such as dyslipidaemia, where elevated levels of low-density lipoprotein (LDL) or reduced levels of high-density lipoprotein (HDL) (≤35 mg/dL) are associated with increased stroke severity.[20] Therefore, the proper management of these homeostatic parameters has emerged as a critical factor in the clinical evolution post-stroke.

Exercise involves planned, structured and repetitive physical activities aimed at improving or maintaining physical fitness.[21] There is strong evidence supporting the effectiveness of exercises on CRF,[22 23] walking ability[24] and as a preventive measure for patients who had a stroke.[25] Traditionally, the primary goal of incorporating exercises into a physiotherapeutic rehabilitation plan is to restore early post-stroke mobility.[26] Consequently, the limited studies addressing physiological variables involved in homeostasis as targeted rehabilitation objectives highlight the need for further research to better understand the effects and mechanisms by which exercises can benefit these parameters in patients who had a stroke.[26–29] Moreover, despite the positive evidence supporting the use of exercises in stroke rehabilitation, ongoing discussions persist regarding the optimal intensity and effectiveness of different types of exercises for post-stroke individuals.[27 30]

Therefore, this study aimed to provide a more comprehensive understanding of the impact of exercises as a non-pharmacological intervention on homeostatic parameters in stroke. We conducted a systematic review and meta-analysis to assess the role of exercises on blood glucose, VO_2, lipid profile and blood pressure (BP). Also, we compared the effectiveness of exercises based on the intensity of maximum heart rate (HRmax), as low-intensity (30–50% HRmax),[31] moderate-intensity (60–70% HRmax) and high-intensity (≥80% HRmax),[32] and type of exercise. This work will help to develop tailored exercise programmes that target specific physiological variables for stroke survivors, enhancing the outcomes of rehabilitation interventions.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[33] and the ethical issues in preparing and publishing systematic reviews by Wager *et al*.[34] The study protocol was registered in 2023 at the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42023395715. Additional information about the registration can be found on the PROSPERO website (https://www.crd.york.ac.uk/prospero/). PRISMA checklist for Abstract and manuscript are found as supplemental material.

Eligibility criteria

Parallel randomised control trials (RCTs) meeting the following criteria based on the formula PICO (population, intervention, comparator, outcomes) were selected:

a. Population: Adult patients (≥18 years old) diagnosed with ischaemic or haemorrhagic stroke.
b. Intervention: Aerobic exercise (AE) or resistance training (RT) that reported intensity and frequency.
c. Comparator: Conventional care for stroke survivors involving passive or active range of motion exercises, stretching, balance training or unstructured on-ground walking.
d. Outcomes: Primary outcomes included homeostatic model assessment (HOMA) for insulin resistance, fasting glucose, VO_2, lipid parameters measured by HDL, LDL, systolic blood pressure (SBP) and diastolic blood pressure (DBP). Secondary outcomes included heart rate (HR), total triglycerides, Fugl Meyer Assessment (FMA) as a sensorimotor impairment index post-stroke,[35] body mass index (BMI) and 2-hour blood glucose. The 2-hour blood glucose test, along with fasting glucose values, strengthens the recognition of misdiagnosed diabetes mellitus (DM), which is strongly associated with a high mortality rate in acute stroke.[36]

Records were excluded if they were non-randomised controlled trials (non-RCTs), reviews or conference abstracts, if they involved conditions other than stroke or included transient ischaemic attack (TIA) and subarachnoid haemorrhage (SAH), if they did not specify AE or RT as intervention or included weight-supported treadmill and in-bed exercises, if they had an incompatible control group such as AE and RT or an absence of it, and finally, if they used different outcome measures.

Literature search strategy

The present systematic review and meta-analysis encompassed original articles reporting data on homeostatic parameters in post-stroke individuals with physical exercises as intervention. The literature search was performed in Embase, MEDLINE (via PubMed), ISI Web of Science (WoS) and Physiotherapy evidence base (PEDro) until April 2024, using the combination of keywords such as (Homeostasis) AND (Stroke) AND (Physical exercises), along with their respective synonyms. There were no

restrictions on language or publication year, and no filters were applied.

To locate registered protocols or unpublished reports, we accessed to clinical trials registries, including Cochrane Central Register of Controlled Trials (CENTRAL) and the National Institutes of Health Clinical Trials Registry (ClinicalTrials.gov) (online supplemental tables S1-S5).

To further identify related reports, an extensive snowball search was conducted. This involved backward citation retrieval by manually searching the reference lists of eligible articles and forward citation searching through Google Scholar. Additionally, to ensure comprehensive coverage and minimise the chance of missing relevant studies, we thoroughly examined systematic reviews and meta-analyses that employed similar keywords (online supplemental table S6).

Selection process

The collected citations from the search strategy were imported into the EndNote V.20 references manager (EndNote; Philadelphia, USA) by the first author (VMVM) to eliminate duplicates. Subsequently, reports were randomly allocated using the Rayyan Systematic Reviews Web tool.[37]

The references database was then shared with a second author (ISN) for independent dual screening. Both authors (VMVM and ISN) began the screening process by manually excluding records containing keywords such as (RAT), (MICE) and (ANIMAL), followed by a review of titles and abstracts. Finally, the full texts were comprehensively examined.

Prior to the final selection of reports, Kappa statistics (κ) were calculated to verify the qualitative assessment and level of agreement between reviewers when applying the selection criteria for this systematic review and meta-analysis.[38] The κ values <0.40 indicate poor agreement, κ values between 0.40 and 0.75 represent good agreement, while values >0.75 reflect excellent agreement in the selection of reports. Disagreements were resolved through consensus, and in cases where accordance could not be achieved, a third independent author (ZAK) was consulted for a final recommendation.

To assess and identify multiple reports from the same study, we extracted and compared key information including authors' names, sample sizes, baseline data and intervention characteristics. This approach ensured that each unique study was represented accurately in our final dataset. No automation tool was used during the screening process.

Data collection process

Two independent authors (VMVM, ISN) conducted data extraction from each report. Initially, a pilot data extraction was performed on 30% of the included articles, aiming to identify potential issues, ensure consistency and establish accuracy before proceeding with full-scale data extraction.[39] Any discrepancies encountered during the extraction process were resolved through consensus or by consulting a third author (DMS).

Data items

The following information was recorded: study characteristics (first author, year of publication, research location, study model and design), study population characteristics (sample size, age), characteristics of stroke (type, side, site and stage), description of interventions and their intensities from both experimental and control groups, and outcomes (HOMA, fasting glucose, VO_2, HDL, LDL, SBP, DBP, HR, total triglycerides, BMI, FMA and 2-hour blood glucose).

Numerical data presented solely in graphical form were extracted using the GetData Graph Digitizer (http://getdata-graph-digitizer.com).

Study risk of bias assessment

The Risk of bias (Rob) in the selected articles has been conducted by two independent authors (VMVM, ISN) throughout the PEDro scale for rating the quality of RCTs. This scale contains 11 items, divided between external validity (item 1, not included in the calculation of the score), internal validity (items 2–9) and statistical reporting (items 10–11) related to eligibility criteria, random allocation, concealed allocation, baseline comparability, blinding of participants, blinding of therapists, blinding of assessors, adequate follow-up (85%), intention-to-treat analysis, between-group statistical comparisons, reporting of point measures and measures of variability. Items are rated 'Yes' or 'No' (1 or 0) between items 2 and 11, with a total score of 10.

The inter-rater reliability of PEDro score ranges from 'poor' to 'excellent', categorised as follows: score <4 are considered 'poor', 4–5 are considered 'fair', 6–8 are considered 'good' and 9–10 are considered 'excellent'.[40] Conflicts concerning risk of bias assessment were settled by consensus. The level of agreement between the two reviewers regarding the assessment of inter-rater reliability was evaluated through κ calculation,[38] and any disagreements were resolved by consensus.

Calculation of effect size

For effect size analysis, we calculated the mean difference (MD) with a 95% CI when the same measurement scale was used for each outcome.[39] If the data were given differently of 'Mean and SD', the following formulas were applied to convert them: mean and SE to SD, (SD=SE*√sample size); mean and SEM to SD (SD=SEM*√sample size).[41] When only the median was given, we converted it to mean and SD by an automatic calculator of the Hozo *et al*[42] method. The MD was computed by selecting only the final mean values from both the intervention and the control groups.[43]

Effect size pooling

The meta-analysis was done through StataSE V.16 software (StataCorp LP; College Station, Texas, USA), when at least two RCTs were comparable in terms of population,

study design, interventions, comparison and outcomes. When five or more reports were included in the analysis and demonstrated statistical homogeneity ($I^2 \leq 50\%$), we applied fixed-effect inverse variance method.[39] Conversely, in the presence of substantial heterogeneity ($I^2 > 50\%$), we used random-effect DerSimonian-Laird method.[39 44–46] For analyses involving fewer than five reports, we employed the random-effects Hartung-Knapp-Sidik method to ensure the highest level of result certainty.[47 48]

Furthermore, in cases where conducting a meta-analysis is not feasible due to a limited number of reports, visual data presentation becomes crucial for transparent reporting.[49] Organising the data into tables that convey detailed information proves to be more efficient than relying on textual formats.[49 50] Therefore, we synthesised the data regarding the effect of resistance training on homeostatic parameters, categorising by outcomes.

Heterogeneity and inconsistency assessment

To determine statistical consistency (heterogeneity) among included reports, the I^2 test with a 95% CI was estimated.[51 52] Heterogeneity levels were categorised as non-significant, low, moderated and high when I^2 value fell within the ranges of 0–25%, 26–50%, 51–75% and 75–100%, respectively.[39 53] Leave-one-out sensitivity analysis was performed when three or more reports were included. This involved repetitively removing one study at a time to confirm that our results were not influenced by any single study and to identify potential sources of heterogeneity.[54] Subgroup analyses were performed only when each subgroup contained at least two comparable reports.

Meta-biases

Publication bias was evaluated via Egger's test, visual inspection of funnel plots when at least five observations were included, using StataSE software ($p<0.05$).[55 56] If the publication bias was detected, the trim-and-fill method was used to calculate the corrected effect size by estimating the number of missing studies.[57] To evaluate reporting bias arising from unpublished studies, thorough search was conducted in clinical trial registries.[58]

Strength of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence by to reviewers independently. The GRADE system classifies evidence certainty into four levels: very low, low, moderate and high level.[59] Downgrading criteria involve risk of bias, inconsistency, indirectness, imprecision and publication bias, while upgrading criteria include large effect, plausible confounding and dose-response.[60] Discrepancies in the assessment of evidence certainty were resolved through consensus, with a third author consulted if required.

Changes from PROSPERO protocol

We adjusted the original registered protocol to enhance the quality and relevance of this systematic review and meta-analysis. The modifications were implemented as follows:

a. We refined the scope of included interventions to encompass solely AE and RT to facilitate separate analyses based on the type of exercises, thereby increasing statistical homogeneity.
b. The outcomes measures were reorganised to prioritise the most relevant outcomes related to body homeostasis. This reorganisation elevated HOMA, fasting glucose, VO_2, lipid profile and BP to primary outcomes, while secondary outcomes included HR, total triglycerides, BMI, FMA and 2-hour blood glucose.
c. The risk of bias assessment tool was done by the PEDro scale.
d. We adjusted the statistical analysis approach by applying fixed-effect inverse variance method for datasets with five or more reports demonstrating statistical homogeneity. In cases of substantial heterogeneity, the random-effect DerSimonian-Laird method was applied. Additionally, when a small number of studies were involved, the random-effects Hartung-Knapp-Sidik method was used.
e. Subgroup analyses will be conducted when at least two reports are comparable in each group.

Patient and public involvement

This study did not involve direct participation from patients and/or the public in its design, conduct or dissemination. The research questions and outcome measures were developed through a comprehensive review of existing literature and expert consensus. Consequently, patient recruitment and the analysis of intervention burden were not applicable. Results were primarily disseminated through publication in peer-reviewed journals and presentations at academic conferences.

RESULTS

Study selection

The search strategy initially retrieved a total of 1978 records, comprising 1156 from Embase, 619 from PubMed, 151 found WoS, 48 from CENTRAL and 3 in PEDro. After removing duplicates and excluding studies using semiautomatic tools, the titles and abstracts of 1123 records were screened, leading to the examination of 25 reports in full text. Among them, 11 RCTs met the eligibility criteria. Moreover, 12 reports were identified through backward and forward citation tracking, with 5 satisfying the inclusion criteria. Accordingly, 16 reports were eligible for inclusion in this systematic review and meta-analysis, as illustrated in figure 1. The calculated κ confidence was 0.832, suggesting an excellent level of agreement among reviewers during the selection process. The completed list of excluded studies after thorough full-text screening is provided in online supplemental table S7.

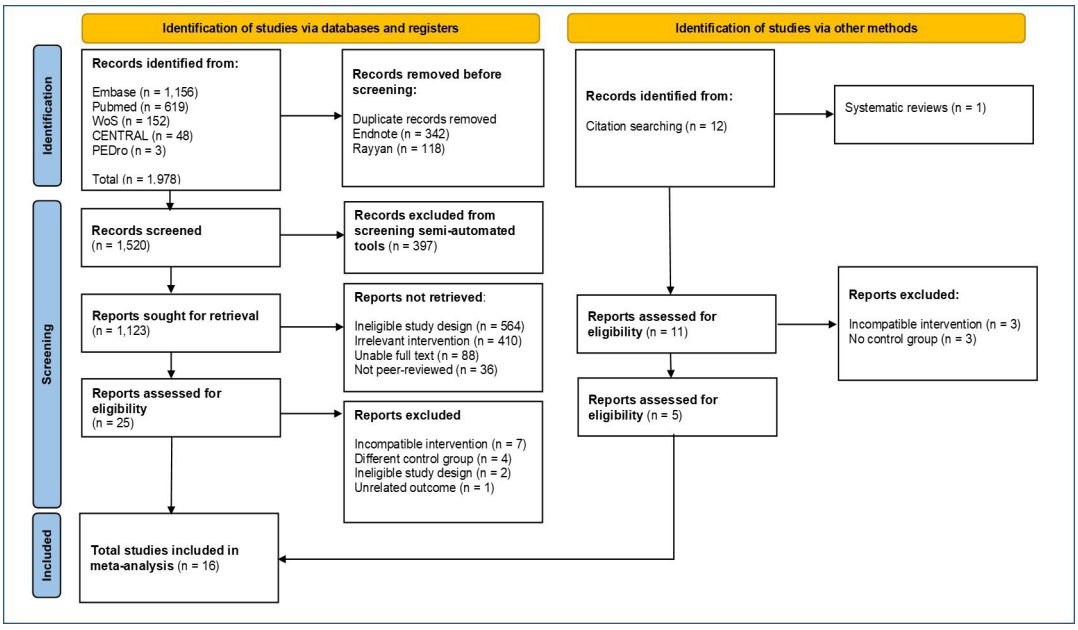

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the studies selection process.

Study characteristics

The characteristics of the eligible reports are delineated in table 1. The included studies conducted between 1995 and 2022 consist of RCTs, involving a total of 698 stroke survivors across diverse regions including Brazil, Canada, China, Ireland, Israel, Switzerland and the USA.

a. Population: The age range of individuals varies from 52.3±6.9 to 68.7±6.1, with 75% of participants observed in the chronic stroke stage,[22 24 27 29 32 61–68] while 25% were in subacute stage.[31 64 67 69 70]
b. Intervention: AE was performed in 13 of the 16 reports,[22 27 31 32 62 64–66 68–71] while RT was implemented in the remaining 3.[29 61 63] AEs were further classified based on type and intensity. Type of exercise classification included treadmill training (TreT) and ergometer-based training (ET), while intensities were categorised as low, moderate, high-intensity exercises.
c. Comparison: Exercise interventions were compared with conventional care and stretching/balance programme.
d. Outcomes: VO_2 were reported in 10 articles[22 24 27 32 63–66 68]; heart rate in 7 articles[22 29 31 64 67–69]; fasting glucose,[27 27 29 29 31 31 63 64 66 68 70 70] BP (SBP, DBP)[22 29 64 67–69] in 6 articles; HOMA[27 29 31 65 70] and BMI[22 29 32 64 65] in 5 articles; HDL, LDL, total triglycerides[29 31 66 70] and FMA[29 31 68 70] in 4 articles; and finally, and 2-hour blood glucose in 3 articles.[29 31 32 70]

Detailed description of interventions in experimental and control groups are displayed in detail in online supplemental table S8.

Study risk of bias assessment

Among the 16 included studies, 2 of them received inter-rater reliability of 'excellent' (scores 9–10), 9 articles 'good' (scores 6–8), and 5 articles rated as 'fair' (score 4–5), determined by the PEDro scale for physiotherapy clinical trials.[34] No studies received a score lower than 4 (score<4='poor') (online supplemental table S9). The agreement among authors concerning inter-rater reliability was outstanding, with a κ coefficient of 0.987.

Results of synthesis

AE reduced blood glucose levels

As demonstrated in figure 2, by using the random-effects Hartung-Knapp-Sidik method, a meta-analysis of HOMA indicated that AE may lead to the reduction of insulin resistance (MD=−0.47; 95% CI −1.14 to 019; I^2=65.97% (95% CI 0% to 84%); p=0.16), although the CI showed some uncertainty in the precise magnitude of the effect (figure 2A). In fasting glucose analysis, we applied a fixed-effects inverse-variance model and found that AE can potentially decrease the fasting blood glucose levels (MD=−0.22; 95% CI −0.22 to −0.02; I^2=0.00% (95% CI 0% to 79%) p=0.02) (figure 2B).

Post-stroke individuals can potentially increase their VO_2 through AE

The meta-analysis conducted using the random-effects DerSimonian-Laird method demonstrated a substantial increase in VO_2 among post-stroke survivors following AE (MD=2.51; 95% CI 1.65 to 3.37; I^2=66.86% (CI 33% to 84%); p=0.00) (figure 3).

AE can elevate HDL levels after stroke

The random-effects Hartung-Knapp-Sidik method indicated that engaging in AE after a stroke may lead to a notable improvement in HDL levels (MD=0.07; 95% CI 0.00 to 0.13; I^2=0.43% (95% CI 0% to 90%); p=0.04) (figure 4A). However, we did not find a valuable effect of

Table 1 Characteristics of the studies

Study (year)	Country	Study design	Participants (n)		Age Mean (SD)		Stage of stroke	Intervention		Intensity	Outcomes
			E	C	E	C		E	C		
Macko *et al* (2005)	USA	RCT	32	29	63 (10)	64 (8)	Chronic (>6 months)	Treadmill exercise (TreT)	Conventional care	Moderate intensity	VO_2 peak (mL/kg/min)
Wang *et al* (2014)	China	RCT	23	22	54 (7.2)	52 (12.1)	Subacute (1–6 months)	Low intensity ergometer aerobic training (ET)	Conventional rehabilitation programme	Low intensity	HOMA Fasting glucose (mmol/L) HDL, LDL (mmol/L) 2-hour blood glucose (mmol/L) Total triglycerides (mmol/L) HR (bmp) FMA
Wang *et al* (2014)	China	RCT	21	22	57 (6.8)	55 (11.5)	Subacute (2–6 weeks)	Low intensity ergometer aerobic training (ET)	Conventional rehabilitation programme	Low intensity	HOMA Fasting glucose (mmol/L) HDL, LDL (mmol/L) 2-hour blood glucose Total triglycerides (mmol/L) FMA
Serra *et al* (2022)	USA	RCT	20	19	68 (2)	63 (1)	Chronic (>6 months)	TreT	Stretching/balance programme	Moderate intensity	HOMA Fasting glucose (mmol/L) VO_2 peak (mL/kg/min) BMI ($kg{\cdot}m^2$)
Zou *et al* (2015)	China	RCT	26	25	52.3 (6.9)	51.4 (7.2)	Chronic (>6 months)	RT	Stretching	High intensity	HOMA Fasting glucose (mmol/L) HDL, LDL (mmol/L) 2-hour blood glucose (mmol/L) Total triglycerides BMI ($kg{\cdot}m^2$) FMA
Ofori *et al* (2019)	USA	RCT	10	10	58.8 (8.3)	62.4 (8.8)	Subacute	Ergometer cycling (ET)	Conventional care	Low intensity	SBP (mm Hg) DBP (mm Hg) HR (bpm)
Globas et al. (2012)	Switzerland	RCT	18	18	68.6 (6.7)	68.7 (6.1)	Chronic (>6 months)	High-intensity aerobic treadmill exercise (TreT)	Conventional care	High intensity	VO_2 peak (mL/kg/min)
Tang *et al* (2014)	Canada	RCT	22	25	65.9 (6.4)	66.9 (7.8)	Chronic (>1 year)	High-intensity aerobic exercise cycle ergometer (ET)	Low-intensity non-aerobic balance/ flexibility (BF)	High intensity	Fasting glucose (mmol/L) VO_2 peak (mL/kg/min) HDL, LDL (mmol/L) Total triglycerides (mmol/L)

Continued

Table 1 Continued

Study (year)	Country	Study design	Participants (n)		Age Mean (SD)		Stage of stroke	Intervention		Intensity	Outcomes
			E	C	E	C		E	C		
Jin *et al* (2013)	China	RCT	65	63	57.6 (6.6)	56.3 (6.5)	Chronic (>6 months)	Cycling training (ET)	Conventional care	Moderate intensity	VO_2 peak (mL/kg/min)
Gambassi *et al* (2019)	Brazil	RCT	11	11	66.4 (10.1)	60.5 (13.2)	Chronic	RT	Conventional care	Moderate intensity	SBP, DBP (mm Hg) HR (bmp)
Ivey et al. (2007)	USA	RCT	26	20	63 (45.89118)	62 (44.72135955)	Chronic (>6 months)	TreT	Conventional care	Moderate intensity	HOMA Fasting glucose (mmol/L) VO_2 peak (mL/kg/min)
Potempa *et al* (1995)	USA	RCT	19	13	NA	NA	Chronic (>6 months)	Cycle ergometer training (ET)	Passive range-of-motion exercise	High intensity	VO_2 peak (mL/kg/min) SBP, DBP (mm Hg) HR (bmp) FMA
Serra *et al* (2019)	USA	RCT	17	8	58.1 (4.947726751)	61.5 (3.676955262)	Chronic (>6 months)	TreT	Stretching/balance programme	Moderate intensity	VO_2 peak (mL/kg/min) BMI ($kg{\cdot}m^2$)
Lennon *et al* (2008)	Ireland	RCT	23	23	59.0 (10.3)	60.5 (10.0)	Chronic (>1 year)	Cycle ergometer training (ET)	Conventional care	Moderate intensity	VO_2 (mL/kg/min) BMI ($kg{\cdot}m^2$) SBP, DBP (mm Hg)
Ivey *et al* (2017)	USA	RCT	14	15	57 (14)	55 (9)	Chronic (>6 months)	Strength training (RT)	Conventional care	High-intensity	VO_2 peak (mL/kg/min)
Toledano-Zarhi *et al* (2011)	Israel	RCT	14	14	65 (10)	65 (12)	Subacute (1–3 weeks)	(AE) Treadmill, hand-bike machine and stationary bike	Strength, flexibility and coordination exercises	Moderate intensity	HR (bpm) SBP, DBP (mm Hg) rest

AE, aerobic exercise; DBP, diastolic blood pressure; ET, ergometer-based training; HR, heart rate; RCT, randomised controlled trial; RT, resistance training; SBP, systolic blood pressure; TreT, treadmill training.

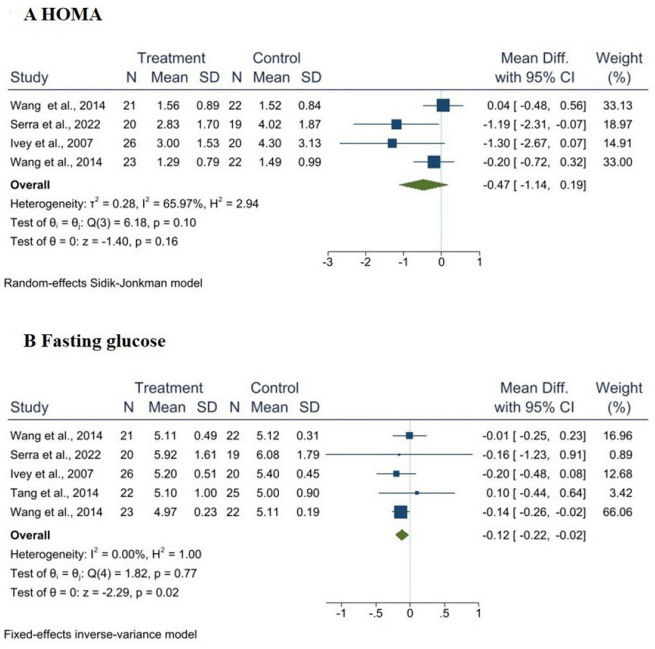

Figure 2 Forest plot showing effect sizes (MD) and 95% CI from included studies, comparing the effect of post-stroke aerobic exercises (intervention group) and alternative interventions (control group) on (A) homeostatic model assessment (HOMA), (B) fasting glucose. MD, mean difference; N, sample size.

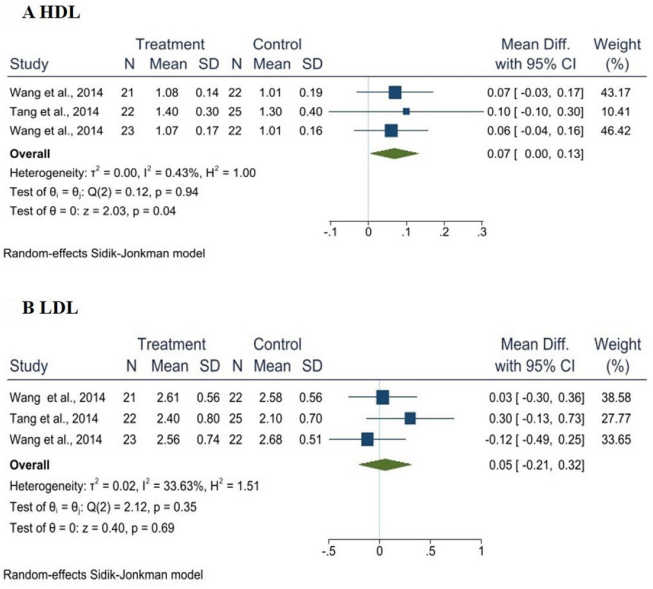

Figure 4 Forest plot showing effect sizes (MD) and 95% CI from included studies, comparing the effect of post-stroke aerobic exercises (intervention group) and alternative interventions (control group) on (A) high-density lipoprotein (HDL), (B) low-density lipoprotein (LDL). MD, mean difference; N, sample size.

AE on LDL (MD=0.05; 95% CI (-0.21 to 0.32); I^2=33.63% (CI 0% to 90%); p=0.69) (figure 4B).

AE on haemodynamic parameters

After performing fixed-effects inverse-variance model (online supplemental figure S1), we observed a mean decrease of 3.1% in SBP (MD=−2.33; 95% CI −5.96 to 1.29; I^2=47.72% (95% CI 0% to 81%); p=0.21) (online supplemental figure S1A) and 1.7% in DBP (MD=−0.51; 95% CI −2.66 to 1.65); I^2=24.19% (95% CI 0% to 69%); p=0.65) (online supplemental figure S1B) after AE. However, the wide CIs suggest uncertainties in the precise magnitude of the effects. Further studies are needed to validate the effects of AE on BP.

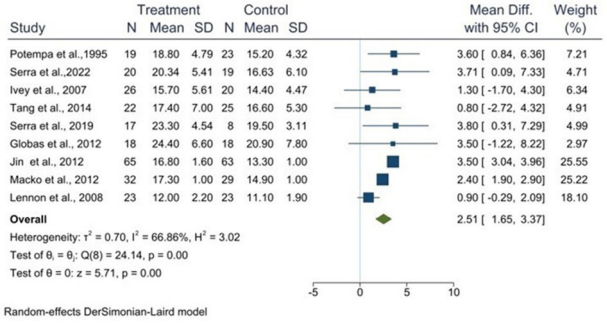

Figure 3 Forest plot showing effect sizes (MD) and 95% CI from included studies, comparing the effect of post-stroke aerobic exercises (intervention group) and alternative interventions (control group) on oxygen consumption (VO_2). MD, mean difference; N, sample size.

Effect of AE on secondary outcomes

Applying the fixed-effects inverse-variance model revealed a favourable reduction of HR after AE (MD=−2.95; 95% CI −5.19 to −071; I^2=37.41% (95% CI 0 to 75%); p=0.01) (online supplemental figure S2). Moreover, the results of the random-effects Hartung-Knapp-Sidik method indicated that AE may not have beneficial implication on BMI (MD=1.36; 95% CI −1.07 to 3.80; I^2=65.89% (95% CI 0% to 81%); p=0.27) (online supplemental figure S3), total triglycerides (MD=−0.10; 95% CI −0.40 to 0.20; I^2=95.00% (95% CI 91% to 98%); p=0.51) (online supplemental figure S4), FMA (MD=8.08; 95% CI −4.04 to 20.20; I^2=79.55% (95% CI 0% to 84%); p=0.19) (online supplemental figure S5) and on 2-hour blood glucose (MD=−1.05; 95% CI −2.82 to 0.71; I^2=92.10%; p=0.24) (online supplemental figure S6). The reported CIs suggest a level of uncertainty regarding the precise extent of the effects. Therefore, further investigation is warranted to confirm the impact of exercises on BMI, total triglycerides, FMA and 2-hour blood glucose secondary outcomes.

Subgroup analysis

Subgroup analysis was executed to compare the effectiveness of different types of exercises on the significant key outcomes. Our findings indicated that TreT (MD=−1.23; 95% CI −2.10 to −0.36; I^2=6.51%; p=0.90) may be more effective than ET (MD=−0.08; 95% CI −0.46 to 0.30; I^2=0.01%; p=0.52) in reducing insulin resistance among

stroke survivors (online supplemental figure S7). However, when analysing the effect on fasting glucose based on type of exercise, both TreT (MD=−0.20; 95% CI −0.47 to 0.08; I^2=0.00; p=0.94) and ET (MD=−0.10; 95% CI −0.21 to 0.00; I^2=0.00; p=0.49) did not demonstrate favourable changes within-group analysis (online supplemental figure S8). Moreover, concerning the enhancement of VO_2, both TreT (MD=2.43; 95% CI 1.95 to 2.92; I^2=0.00; p=0.77) and ET (MD=2.31; 95% CI 0.50 to 4.12; I^2=83.12%; p=0.00) demonstrated effectiveness in improving VO_2 among stroke survivors (online supplemental figure S9).

The observed heterogeneity in HOMA and VO_2 can be attributed to the inclusion of these two AE types, TreT and ET. Similarly, we assessed the high heterogeneity in BMI through post hoc subgroup analysis, revealing a substantial decrease in I^2 from 65.89% to 27.83% in the ET group (online supplemental figure S10). This finding offers a potential explanation for the varying levels of heterogeneity in this analysis.

Influence of AE intensity

A second subgroup analysis was performed to test the hypothesis of whether the effect of AE on our significant key outcomes varied depending on the intensity. We found that moderate intensity of AE (MD=−1.23; 95% CI −2.10 to −0.36; I^2=6.51%; p=0.90) exhibited better performance on HOMA compared with low-intensity of AE (MD=−0.08; 95% CI −0.46 to 0.30; I^2=0.00%; p=0.52) (online supplemental file 11). In fasting glucose analysis, low intensity of AE (MD = −011; 95% CI −0.22 to −0.00; I^2=0.00%; p=0.35) demonstrated greater effectiveness in reducing blood glucose levels than moderate intensity of AE (MD=−0.20; 95% CI −0.47 to 0.08; I^2=0.01%, p=0.94) (online supplemental figure S12). In the VO_2 case, moderate intensity of AE (MD=2.48; 95% CI 1.49 to 3.46; I^2=77.76%; p=0.01) appeared to be more effective in increasing VO_2 compared with high AE intensity (MD=2.71; 95% CI 0.73 to 4.66; I^2=0.00%; p=0.44) (online supplemental figure S13). Furthermore, no changes were observed when assessing the effect of different intensities of AE on SBP (online supplemental figure S14A) and DBP (online supplemental figure S14B).

Sensitivity analysis

We conducted a leave-one-out analysis to explore the potential sources of heterogeneity in outcomes that could not be adequately explained by the subgroup analysis and to ensure that our findings were not driven by any single study. In the total triglyceride's analysis, removing the report of Wang *et al*[70] reduced the I^2 value from 95.00% to 2.76% (online supplemental table S10). Similarly, in the FMA analysis, by excluding the report of Potempa *et al*,[68] the I^2 value (79.55%) decreased to 27.13% and the p value turned significant (online supplemental table S11).

These results suggest that the heterogeneity observed may stem from the mix of intensities, while Potempa *et al*[68] performed high-intense cycle ergometer training and Wang *et al*[70] performed low-intensity of cycle ergometer training. Additionally, the significant change in the FMA p value indicated that the previous main results may have been influenced by this single study. Sensitivity analysis of 2-hour blood glucose could not be done due to the limited number of studies.

Publication and reporting bias

We estimated the publication bias on fasting glucose analysis (Egger's test, p=0.6053) (online supplemental figure S18A), VO_2 analysis (Egger's test, p=0.9701) (online supplemental figure S18B), SBP analysis (Egger's test; p=0.6754) (online supplemental figure S18C) and HR analysis (Egger's test; p=0.1225) (online supplemental figure S18D). However, none of the data suggested an evident risk of publication bias. Moreover, we did not find any relevant registered protocols or unpublished studies that might influence our study results.

Certainty of evidence

The GRADE approach attributed a 'moderate level of certainty of evidence' to the analysis of fasting glucose, HDL, LDL, SBP and BP. This rating was downgraded by one level due to the limited sample size, which was considered insufficient to calculate a precise effect estimate.

A 'low level of certainty of evidence' was estimated for HOMA, VO_2, HR, total triglycerides and FMA, with a downgrade of two levels primarily attributed to inconsistency arising from high heterogeneity, although it was explained, and the small sample size, which compromised the precision of effect size estimation. Furthermore, BMI and received a 'very low level of certainty', downgrading by three levels, due risk of bias, inconsistency and imprecision. Detailed GRADE assessments can be found in online supplemental table S12. The footnotes provide clarification on the reasons for the downregulation of the certainty for each outcome.

RT on post-stroke homeostatic parameters

Three RCTs analysing the effects of RT on homeostatic parameters were included. The individual study effect size with 95% CI suggests that RT might potentially impact blood glucose lipid parameters. Significant improvements were observed in HOMA, HDL, LDL and 2-hour blood glucose levels. Ivey *et al*[63] evaluated the impact of RT on VO_2 and reported no considerable changes in this parameter among stroke survivors. Similarly, Gambassi *et al*[61] found that RT may improve HR but did not affect SBP or DBP.

Additional research is needed to better understand the feasibility and true effects of RT on homeostatic parameters in this population. Data from studies analysing the effects of post-stroke homeostatic parameters are shown in table 2.

Type of stroke prevalence

Identification of stroke characteristics holds significant importance as it can help tailor interventions for specific

Table 2 RT on post-stroke homeostatic parameters

Outcome	Stroke stage	N(E)	N(C)	Mean difference	95% CI
HOMA					
Zou *et al*, 2015	Chronic	26	25	−0.520	(−0.730 to 0.310)
Fasting glucose					
Zou *et al*, 2015	Chronic	24	26	−0.240	(−0.427 to 0.053)
VO_2					
Ivey *et al*, 2017	Chronic	14	15	2.500	(−1.261 to 6.261)
HDL					
Zou *et al*, 2015	Chronic	26	25	0.140	(0.096 to 0.184)
LDL					
Zou *et al*, 2015	Chronic	26	25	−0.740	(−0.990 to 0.490)
SBP					
Gambassi *et al*, 2019	Chronic	11	11	−5.750	(−15.929 to 4.429)
DPB					
Gambassi *et al*, 2019	Chronic	11	11	−8.200	(−17.956 to 1.556)
2-hour blood glucose					
Zou *et al*, 2015	Chronic	26	25	−1.480	(−1.933 to 1.027)
Total triglycerides					
Zou *et al*, 2015	Chronic	26	25	−0.010	(−0.241 to 0.221)
HR					
Gambassi *et al*, 2019	Chronic	11	11	−11.400	(−20.079 to 2.721)
BMI					
Zou *et al*, 2015	Chronic	26	25	0.300	(−1.429 to 2.029)
FMA					
Zou *et al*, 2015	Chronic	26	25	0.900	(−1.904 to 3.704)

BMI, body mass index; DBP, diastolic blood pressure; FMA, Fugl Meyer Assessment; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein.

populations. Among the 16 included reports in this meta-analysis, 10 of them contributed to the systematic review describing the characteristics of stroke found in a total of 984 participants (from both experimental and control groups). We classified the characteristics into three categories: type, side and site of stroke (online supplemental figure S19). The ischaemic stroke group constituted 56% of the total stroke survivors, followed by haemorrhagic stroke (37%) (online supplemental figure S19A). In terms of stroke side, the right hemisphere was observed to be predominantly affected (53%), followed closely by the left hemisphere (47%) (online supplemental figure S19B). Finally, the site of the stroke group was subclassified according to the location of the brain lesion: cortex, subcortical, brainstem, unknown and mixed (more than one location). Interestingly, the data revealed a prevalence of 50% in subcortical stroke locations, followed by cortical locations at 29% (online supplemental figure S19C). Previous literature indicated that lacunar infarcts are likely to occur most often in subcortical regions,[6] including motor and sensory deficits and a less favourable prognosis compared with cortical strokes.[71]

DISCUSSION

This study represents the first attempt to evaluate the impact of post-stroke physical exercises (PSPE), such as AE and RT, on homeostasis parameters after stroke. Stroke triggers physiological responses that reflect the body's adaptive homeostatic mechanisms.[72 73] One such response is hyperglycaemia, which is often a stress consequence triggered by the activation of the hypothalamic-pituitary-adrenal axis[74] or related to pre-existing undiagnosed diabetes mellitus (DM).[61] Notably, 61% of non-diabetic stroke individuals experience late-onset hyperglycaemia.[72] Although these physiological changes aim to restore balance, they can be life-threatening under vulnerable conditions, as elevated glucose levels are strongly associated with increased cerebral oedema, neuronal death, larger infarct volumes[75] and a heightened risk of recurrent stroke.[75]

Our meta-analysis demonstrated that moderate intensity of TreT might be a promising approach to reduce blood glucose levels and insulin resistance in the stroke population. These results align with findings by Ivey

et al,[27] who reported improvements in insulin resistance following TreT exercises at 60% to 70% of HR in hemiparetic stroke survivors. Additionally, Wang *et al*[70] showed that even low-intensity of ET effectively improved glucose tolerance among extremely weak non-diabetic stroke patients. These enhancements may be attributed to exercise-induced muscle glycogen synthesis[76] and the reduction of tumour necrosis factor-α levels, which modulate skeletal muscle metabolism and systemic insulin resistance.[77] The effectiveness and adaptability of exercises, regardless of functional level, highlight their role as a preventive measure in reducing cardiovascular events and mortality rates.[28 78]

After stroke, muscle atrophy on the hemiparetic side becomes the primary factor affecting VO_2 levels.[79] This atrophy, combined with impaired haemodynamic responses and physical deconditioning,[80] often leads patients who had a stroke into a detrimental cycle characterised by insufficient oxygen intake and greater energy demands.[81] Consequently, this imbalance results in metabolic strain, persistent fatigue and a decline in motor function,[80 82] critically impacting the clinical evolution of these individuals.

The current study revealed that moderate intensity of both ET and TreT are more effective for optimising VO_2 in stroke survivors than high intensity AE. These findings broadly support the study of Potempa *et al*[68] that indicated that training workload is a key predictor of treatment response on aerobic capacity. Especially, moderate intensity cycling ET effectively reduces submaximal effort and increases maximal VO_2 levels, overpassing the benefits of passive range-of-motion exercises in disabled post-stroke individuals.[68] Improved VO_2 levels may enhance motor performance and energy management,[68] contributing to greater independence and better functional outcomes. Although this study did not analyse the specific physiological changes responsible for the exercise benefits on VO_2, existing literature suggests potential adaptations, such as improved blood flow in the non-paretic lower limb,[83] better arterial-venous oxygen differences and increased minute ventilation.[84] Moreover, due to its lower balance requirements, ET is often regarded as the optimal form of aerobic exercise after stroke.[22]

The inverse relationships between HDL and LDL levels, known for their potent atherogenic effects, are key players in the pathophysiology of ischaemic strokes.[15] Consequently, the beneficial impacts of exercises on HDL are clinically pertinent, especially considering the observed 36% reduction in stroke risk for every 1 mmol/L increase in HDL.[81]

Consistent with our results, Moore *et al*[85] demonstrated an increase of 0.3 mmol/L in HDL levels after AE. However, we did not observe favourable changes in LDL levels. Zou *et al*[29] suggested that RT may positively influence both HDL and LDL levels. This potential effect could be due to an increased percentage of type I muscle fibres and upregulated activity of lipid-protein transformation pathways.[29] Additionally, existing literature indicates that lifestyle modifications (such as a low-fat diet) and pharmacological therapies like Midodrine, combined with exercise, may be necessary to effectively reduce LDL and total triglyceride levels.[24 53] Based on these outcomes, incorporating both types of exercises into training may provide a comprehensive approach to managing lipid parameters in the stroke population. We considered that investigating the combined effects of these exercise types, rather than their independent effects, offers a promising direction for future research.

In the acute phase of stroke, elevated BP often serves as a compensatory mechanism to increase cerebral perfusion to ischaemic brain tissue, typically decreasing spontaneously over time.[86] However, research suggests that individuals who initially normalise their BP post-stroke may experience hypertension again after a few months.[87] Our study aligns with the findings of Zou *et al*,[29] which indicated no significant impact of exercise on BP. Conversely, Ofori *et al*[69] reported that in subacute stage of stroke, 8 weeks of ergonomic cycling training effectively reduced BP. Similarly, Sandberg *et al*[23] demonstrated that daily in-bed cycle exercise normalised BP during the acute phase of moderate-to-severe stroke. These findings highlight the potential of adapted exercises in managing BP during early stroke rehabilitation. Regulating BP through non-pharmacological interventions may be pivotal for stroke prognosis, as spontaneous drop in BP during the acute phase can worsen ischaemic damage,[86] while sustained high BP in the chronic phase significantly increases the risk of stroke recurrence.[87] Given the mixed results regarding the effects of RT and AE on BP, further research is needed to confirm the feasibility and efficacy of exercise interventions for BP management, especially in different phases of stroke recovery.

This study faced limitations due to the scarcity of reports on both AE and RT, which prevented meta-analysis for this last-mentioned type of intervention. The limited number of studies allowed subgroup analyses based on AE type and intensity to be performed only for outcomes such as fasting glucose, HOMA and HDL. This restriction hindered a comprehensive understanding of how training variability affects other parameters such as LDL and BP.

Additionally, the small number of studies in certain outcome analyses avoid the possibility of publication bias assessment through visual funnel-plot asymmetry.[88] Further clinical trials are needed to thoroughly investigate the impact of both aerobic and anaerobic exercises on the physiological parameters crucial for stroke population to enhance the robustness and reliability of future meta-analytic findings.

Moreover, this meta-analysis was conducted using the final values of both control and experimental groups, in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.[39] This guidance suggests that MD computed from final values effectively reflect intervention effects, similar to analyses based on changes from baseline to final measurements. Consequently, we

assumed a linear relationship between baseline and final values. However, the absence of a direct calculation of the correlation coefficient (r) might introduce certain limitations in our study. Therefore, we recommend interpreting our findings with appropriate caution.

Despite the previously mentioned limitations, our study offers a comprehensive understanding of the physiological effects of exercise following the disruption of homeostasis post-stroke. Additionally, evaluating the impact of exercise intensity on effectiveness contributes to the safe and customised inclusion of physical activity in stroke rehabilitation.

Taken together, the integration of exercise emerges as a promising non-pharmacological strategy for managing homeostatic parameters among stroke survivors, including blood glucose, VO_2 and HDL levels. While the effects of exercises on BP and LDL remain uncertain, the results of this systematic review and meta-analysis offer valuable insights for refining rehabilitation programmes. These findings can help reduce risk factors for recurrent stroke and allow for the customisation of exercise programmes to target specific physiological outcomes, potentially leading to more effective recovery from stroke.

Author affiliations
[1]Department of Physical Therapy, Graduate School of Inje University, Gimhae, Gyeongsangnam-do, Republic of Korea
[2]Biohealth Products Research Center (BPRC), Inje University, Gimhae, Gyeongsangnam-do, Republic of Korea
[3]Department of Digital Anti-aging Healthcare, Graduate School of Inje University, Gimhae, Gyeongsangnam-do, Republic of Korea
[4]Department of Physical Therapy, College of Healthcare Medical Science & Engineering, Gimhae, Gyeongsangnam-do, Republic of Korea
[5]Department of Rehabilitation Science, Graduate School of Inje University, Gimhae, Gyeongsangnam-do, Republic of Korea

Acknowledgements The authors would like to acknowledge the invaluable support and critical comments of members in 'Biological Clock and Aging Control' laboratory. This study was completed as part of the dissertation for the Master of Science by VMVM.

Contributors Conceptualisation: YH. Investigation: VMVM. Formal analysis: VMVM, ZAK, ISN and DMS. Data curation: VMVM, ISN. Visualisation: VMVM, ISN and MR. Writing—original draft preparation: YH and VMVM. Writing—review and editing: YH and VMVM. Supervision: YH. Funding acquisition: YH. Guarantor: YH. All authors read and approved the final version of the manuscript.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iD
Yonggeun Hong http://orcid.org/0000-0003-1288-0546

REFERENCES

1 Alharbi AS, Alhayan MS, Alnami SK, *et al*. Epidemiology and risk factors of stroke. *Arch Pharm Pract* 2019.
2 Feske SK. Ischemic Stroke. *Am J Med* 2021;134:1457–64.
3 Feigin VL, Brainin M, Norrving B, *et al*. World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. *Int J Stroke* 2022;17:18–29.
4 Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. *Circ Res* 2017;120:439–48.
5 Díez-Tejedor E, Fuentes B. Homeostasis as basis of acute stroke treatment: stroke units are the key. *Cerebrovasc Dis* 2005;20 Suppl 2:129–34.
6 Robert Teasell M, Hussein N. Clinical consequences of stroke. *Evid based rev of stroke rehab* 2016;2016:1–30.
7 Davies KJA. Adaptive homeostasis. *Mol Aspects Med* 2016;49:1–7.
8 Kotas ME, Medzhitov R. Homeostasis, inflammation, and disease susceptibility. *Cell* 2015;160:816–27.
9 Fuentes B, Díez-Tejedor E. General care in stroke: relevance of glycemia and blood pressure levels. *Cerebrovasc Dis* 2007;24 Suppl 1:134–42.
10 Modell H, Cliff W, Michael J, *et al*. A physiologist's view of homeostasis. *Adv Physiol Educ* 2015;39:259–66.
11 Bernhardt J, Hayward KS, Kwakkel G, *et al*. Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. *Int J Stroke* 2017;12:444–50.
12 Hafer-Macko CE, Yu S, Ryan AS, *et al*. Elevated Tumor Necrosis Factor-α in Skeletal Muscle After Stroke. *Stroke* 2005;36:2021–3.
13 Ivey FM, Hafer-Macko CE, Macko RF. Exercise training for cardiometabolic adaptation after stroke. *J Cardiopulm Rehabil Prev* 2008;28:2–11.
14 Ryan AS, Dobrovolny CL, Smith GV, *et al*. Hemiparetic muscle atrophy and increased intramuscular fat in stroke patients. *Arch Phys Med Rehabil* 2002;83:1703–7.
15 Han S-C, Fu T-C, Hsu C-C, *et al*. The validation of oxygen uptake efficiency slope in patients with stroke. *Medicine (Baltimore)* 2021;100:e27384.
16 Macko RF, DeSouza CA, Tretter LD, *et al*. Treadmill aerobic exercise training reduces the energy expenditure and cardiovascular demands of hemiparetic gait in chronic stroke patients. A preliminary report. *Stroke* 1997;28:326–30.
17 Levine BD. : what do we know, and what do we still need to know? *J Physiol (Lond)* 2008;586:25–34.
18 Rosado-Pérez J, Mendoza-Núñez VM. Relationship Between Aerobic Capacity With Oxidative Stress and Inflammation Biomarkers in the Blood of Older Mexican Urban-Dwelling Population. *Dose Resp* 2018;16.
19 Pruett ED, Oseid S. Effect of exercise on glucose and insulin response to glucose infusion. *Scand J Clin Lab Invest* 1970;26:277–85.
20 Yeh P-S, Yang C-M, Lin S-H, *et al*. Low levels of high-density lipoprotein cholesterol in patients with atherosclerotic stroke: a prospective cohort study. *Atherosclerosis* 2013;228:472–7.
21 Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985;100:126:126–31:.
22 Jin H, Jiang Y, Wei Q, *et al*. Effects of aerobic cycling training on cardiovascular fitness and heart rate recovery in patients with chronic stroke. *NRE* 2013;32:327–35.
23 Sandberg K, Kleist M, Enthoven P, *et al*. Hemodynamic responses to In-Bed Cycle Exercise in the acute phase after moderate to severe stroke: A randomized controlled trial. *J of Clinical Hypertension* 2021;23:1077–84.
24 Macko RF, Ivey FM, Forrester LW, *et al*. Treadmill Exercise Rehabilitation Improves Ambulatory Function and Cardiovascular Fitness in Patients With Chronic Stroke. *Stroke* 2005;36:2206–11.
25 Pin-Barre C, Laurin J. Physical Exercise as a Diagnostic, Rehabilitation, and Preventive Tool: Influence on Neuroplasticity and Motor Recovery after Stroke. *Neural Plast* 2015;2015:608581.
26 Craig LE, Wu O, Bernhardt J, *et al*. Predictors of poststroke mobility: systematic review. *Int J Stroke* 2011;6:321–7.

27 Ivey FM, Ryan AS, Hafer-Macko CE, *et al*. Treadmill aerobic training improves glucose tolerance and indices of insulin sensitivity in disabled stroke survivors: a preliminary report. *Stroke* 2007;38:2752–8.
28 Ivey FM, Stookey AD, Hafer-Macko CE, *et al*. Higher Treadmill Training Intensity to Address Functional Aerobic Impairment after Stroke. *J Stroke Cerebrovasc Dis* 2015;24:2539–46.
29 Zou J, Wang Z, Qu Q, *et al*. Resistance training improves hyperglycemia and dyslipidemia, highly prevalent among nonelderly, nondiabetic, chronically disabled stroke patients. *Arch Phys Med Rehabil* 2015;96:1291–6.
30 Billinger SA, Arena R, Bernhardt J, *et al*. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:2532–53.
31 Wang Z, Wang L, Fan H, *et al*. Adapted low intensity ergometer aerobic training for early and severely impaired stroke survivors: a pilot randomized controlled trial to explore its feasibility and efficacy. *J Phys Ther Sci* 2014;26:1449–54.
32 Serra MC, Accardi CJ, Ma C, *et al*. Metabolomics of Aerobic Exercise in Chronic Stroke Survivors: A Pilot Study. *J Stroke Cerebrovasc Dis* 2019;28:104453.
33 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010;8:336–41.
34 Wager E, Wiffen PJ. Ethical issues in preparing and publishing systematic reviews. *J Evid Based Med* 2011;4:130–4.
35 Kim H, Her J, Ko J, *et al*. Reliability, Concurrent Validity, and Responsiveness of the Fugl-Meyer Assessment (FMA) for Hemiplegic Patients. *J Phys Ther Sci* 2012;24:893–9.
36 Kelly JO, Kilbreath SL, Davis GM, *et al*. Cardiorespiratory fitness and walking ability in subacute stroke patients11No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the author(s) or upon any organization with which the author(s) is/are associated. *Arch Phys Med Rehabil* 2003;84:1780–5.
37 Ouzzani M, Hammady H, Fedorowicz Z, *et al*. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5:210.
38 McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)* 2012;22:276–82.
39 Higgins J, The Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1. 0 [Updated March 2011]*. 5.2011.Available: https://handbook-5-1.cochrane.org/
40 Cashin AG, McAuley JH. Clinimetrics: Physiotherapy Evidence Database (PEDro) Scale. *J Physiother* 2020;66:59.
41 Zhang Y-H, Wang D-W, Xu S-F, *et al*. α-Lipoic acid improves abnormal behavior by mitigation of oxidative stress, inflammation, ferroptosis, and tauopathy in P301S Tau transgenic mice. *Redox Biol* 2018;14:535–48.
42 Wan X, Wang W, Liu J, *et al*. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
43 Deeks JJ, Higgins JP, Altman DG, *et al*. Analysing data and undertaking meta-analyses. In: *Cochrane handbook for syst rev of interventions*. . 2019: 2019. 241–84.
44 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
45 Nila IS, Sumsuzzman DM, Khan ZA, *et al*. Identification of exosomal biomarkers and its optimal isolation and detection method for the diagnosis of Parkinson's disease: A systematic review and meta-analysis. *Ageing Res Rev* 2022;82:101764.
46 Sumsuzzman DMd, Choi J, Jin Y, *et al*. Neurocognitive effects of melatonin treatment in healthy adults and individuals with Alzheimer's disease and insomnia: A systematic review and meta-analysis of randomized controlled trials. *Neuroscience & Biobehavioral Reviews* 2021;127:459–73.
47 Bender R, Friede T, Koch A, *et al*. Methods for evidence synthesis in the case of very few studies. *Res Synth Methods* 2018;9:382–92.
48 Kontopantelis E, Reeves D. Performance of statistical methods for meta-analysis when true study effects are non-normally distributed: A simulation study. *Stat Methods Med Res* 2012;21:409–26.
49 McKenzie JE, Brennan SE. Synthesizing and presenting findings using other methods. In: *Cochrane Handbook for Syst Rev of Interventions*. . 2019: 2019. 321–47.
50 Sumsuzzman DM, Khan ZA, Choi J, *et al*. Assessment of functional roles and therapeutic potential of integrin receptors in osteoarthritis: A systematic review and meta-analysis of preclinical studies. *Ageing Res Rev* 2022;81:101729.
51 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
52 von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. *BMC Med Res Methodol* 2015;15:35:35:.
53 Veerbeek JM, van Wegen E, van Peppen R, *et al*. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. *PLoS One* 2014;9:e87987.
54 Patsopoulos NA, Evangelou E, Ioannidis JPA. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. *Int J Epidemiol* 2008;37:1148–57.
55 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
56 Sterne JAC, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001;323:101–5.
57 Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455–63.
58 Guyatt GH, Oxman AD, Montori V, *et al*. GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol* 2011;64:1277–82.
59 Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
60 Hj S, Jp H, Ge V. Chapter 14: completing 'summary of findings' tables and grading the certainty of the evidence. In: *Cochrane handbook for systematic reviews of interventions: version*. 2022.
61 Gambassi BB, Coelho-Junior HJ, Paixão Dos Santos C, *et al*. Dynamic Resistance Training Improves Cardiac Autonomic Modulation and Oxidative Stress Parameters in Chronic Stroke Survivors: A Randomized Controlled Trial. *Oxid Med Cell Longev* 2019;2019:5382843.
62 Globas C, Becker C, Cerny J, *et al*. Chronic stroke survivors benefit from high-intensity aerobic treadmill exercise: a randomized control trial. *Neurorehabil Neural Repair* 2012;26:85–95.
63 Ivey FM, Prior SJ, Hafer-Macko CE, *et al*. Strength Training for Skeletal Muscle Endurance after Stroke. *J Stroke Cerebrovasc Dis* 2017;26:787–94.
64 Lennon O, Carey A, Gaffney N, *et al*. A pilot randomized controlled trial to evaluate the benefit of the cardiac rehabilitation paradigm for the non-acute ischaemic stroke population. *Clin Rehabil* 2008;22:125–33.
65 Serra MC, Hafer-Macko CE, Robbins R, *et al*. Randomization to Treadmill Training Improves Physical and Metabolic Health in Association With Declines in Oxidative Stress in Stroke. *Arch Phys Med Rehabil* 2022;103:2077–84.
66 Tang A, Eng JJ, Krassioukov AV, *et al*. Exercise-induced changes in cardiovascular function after stroke: a randomized controlled trial. *Int J Stroke* 2014;9:883–9.
67 Toledano-Zarhi A, Tanne D, Carmeli E, *et al*. Feasibility, safety and efficacy of an early aerobic rehabilitation program for patients after minor ischemic stroke: A pilot randomized controlled trial. *NeuroRehabilitation* 2011;28:85–90.
68 Potempa K, Lopez M, Braun LT, *et al*. Physiological outcomes of aerobic exercise training in hemiparetic stroke patients. *Stroke* 1995;26:101–5.
69 Ofori EK, Frimpong E, Ademiluyi A, *et al*. Ergometer cycling improves the ambulatory function and cardiovascular fitness of stroke patients-a randomized controlled trial. *J Phys Ther Sci* 2019;31:211–6.
70 Wang Z, Wang L, Fan H, *et al*. Effect of low-intensity ergometer aerobic training on glucose tolerance in severely impaired nondiabetic stroke patients. *J Stroke Cerebrovasc Dis* 2014;23:e187–93.
71 MacKay-Lyons MJ, Makrides L. Cardiovascular stress during a contemporary stroke rehabilitation program: Is the intensity adequate to induce a training effect? *Arch Phys Med Rehabil* 2002;83:1378–83.
72 Rinomhota AS, Cooper K. Homeostasis: restoring the internal wellbeing in patients/clients. *Br J Nurs* 1996;5:1100–8.
73 Kernan WN, Viscoli CM, Inzucchi SE, *et al*. Prevalence of abnormal glucose tolerance following a transient ischemic attack or ischemic stroke. *Arch Intern Med* 2005;165:227–33.
74 Kruyt ND, Biessels GJ, DeVries JH, *et al*. Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. *Nat Rev Neurol* 2010;6:145–55.
75 Li WA, Moore-Langston S, Chakraborty T, *et al*. Hyperglycemia in stroke and possible treatments. *Neurol Res* 2013;35:479–91.
76 Hafer-Macko CE, Ryan AS, Ivey FM, *et al*. Skeletal muscle changes after hemiparetic stroke and potential beneficial effects of exercise intervention strategies. *J Rehabil Res Dev* 2008;45:261–72.

77 Rosenthal M, Haskell WL, Solomon R, *et al*. Demonstration of a relationship between level of physical training and insulin-stimulated glucose utilization in normal humans. *Diabetes* 1983;32:408–11.
78 Gentile NT, Seftchick MW, Huynh T, *et al*. Decreased mortality by normalizing blood glucose after acute ischemic stroke. *Acad Emerg Med* 2006;13:174–80.
79 Qureshi AI, Huang W, Lobanova I, *et al*. Effect of Moderate and Severe Persistent Hyperglycemia on Outcomes in Patients With Intracerebral Hemorrhage. *Stroke* 2022;53:1226–34.
80 Billinger SA, Coughenour E, Mackay-Lyons MJ, *et al*. Reduced cardiorespiratory fitness after stroke: biological consequences and exercise-induced adaptations. *Stroke Res Treat* 2012;2012:959120.
81 Compagnat M, Daviet J-C, Batcho C, *et al*. Oxygen Cost During Walking in Individuals With Stroke: Hemiparesis Versus Cerebellar Ataxia. *Neurorehabil Neural Repair* 2020;34:289–98.
82 Ryan AS, Dobrovolny CL, Silver KH, *et al*. Cardiovascular fitness after stroke: Role of muscle mass and gait deficit severity. *J Stroke Cerebrovasc Dis* 2000;9:185–91.
83 Ivey FM, Ryan AS, Hafer-Macko CE, *et al*. Improved Cerebral Vasomotor Reactivity After Exercise Training in Hemiparetic Stroke Survivors. *Stroke* 2011;42:1994–2000.
84 Oyake K, Baba Y, Ito N, *et al*. Cardiorespiratory factors related to the increase in oxygen consumption during exercise in individuals with stroke. *PLoS One* 2019;14:e0217453.
85 Moore SA, Hallsworth K, Jakovljevic DG, *et al*. Effects of Community Exercise Therapy on Metabolic, Brain, Physical, and Cognitive Function Following Stroke. *Neurorehabil Neural Repair* 2015;29:623–35.
86 Jansen PAF, Schulte BPM, Poels EFJ, *et al*. Course of blood pressure after cerebral infarction and transient ischemic attack. *Clin Neurol Neurosurg* 1987;89:243–6.
87 Rodgers A, MacMahon S, Gamble G, *et al*. Blood pressure and risk of stroke in patients with cerebrovascular disease. *BMJ* 1996;313:147.
88 Song F, Hooper L, Loke YK. Publication bias: what is it? How do we measure it? How do we avoid it? *OAJCT* 2013;2013:71.