Aerobic exercise interventions reduce blood pressure in patients after stroke or transient ischaemic attack: a systematic review and meta-analysis

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ABSTRACT

Objective Secondary vascular risk reduction is critical to preventing recurrent stroke. We aimed to evaluate the effect of exercise interventions on vascular risk factors and recurrent ischaemic events after stroke or transient ischaemic attack (TIA).

Design Intervention systematic review and meta-analysis.

Data sources OVID MEDLINE, PubMed, The Cochrane Library, Web of Science, The National Institute for Health and Care Excellence, TRIP Database, CINAHL, PsycINFO, SCOPUS, UK Clinical Trials Gateway and the China National Knowledge Infrastructure were searched from 1966 to October 2017.

Eligibility criteria Randomised controlled trials evaluating aerobic or resistance exercise interventions on vascular risk factors and recurrent ischaemic events among patients with stroke or TIA, compared with control.

Results Twenty studies (n=1031) were included. Exercise interventions resulted in significant reductions in systolic blood pressure (SBP) −4.30 mm Hg (95% CI −6.77 to −1.83) and diastolic blood pressure −2.58 mm Hg (95% CI −4.7 to −0.46) compared with control. Reduction in SBP was most pronounced among studies initiating exercise within 6 months of stroke or TIA (−8.46 mm Hg, 95% CI −12.18 to −4.75 vs −2.33 mm Hg, 95% CI −3.94 to −0.72), and in those incorporating an educational component (−7.81 mm Hg, 95% CI −14.34 to −1.28 vs −2.78 mm Hg, 95% CI −4.33 to −1.23). Exercise was also associated with reductions in total cholesterol (−0.27 mmol/L, 95% CI −0.54 to 0.00), but not fasting glucose or body mass index. One trial reported reductions in secondary vascular events with exercise, but was insufficiently powered.

Summary Exercise interventions can result in clinically meaningful blood pressure reductions, particularly if initiated early and alongside education.

INTRODUCTION

Stroke is the second leading cause of death and adult disability worldwide, affecting approximately 15 million individuals annually.[1] One in five people who suffer a stroke die within the first 30 days[2], and over 40% of the remainder are left functionally dependent at 6 months.[3] Annual direct and indirect costs to the UK are estimated at £9 billion[4], with costs of €38 billion across Europe.[5] These patients typically have atherosclerotic disease and classical vascular risk factors such as hypertension, diabetes, dyslipidemia, obesity and physical inactivity; that are also seen in patients with coronary heart disease (CHD). One in four strokes are recurrent,[6] associated with greater morbidity, mortality and economic consequences[7] than primary stroke. Therefore, secondary stroke prevention is paramount.

Evidence relating to the secondary prevention of stroke has evolved concentrating on pharmacological (antithrombotics,[8] antihypertensives,[9] lipid-lowering[10] and surgical (carotid endarterectomy, stenting)[11] interventions. The evidence base for non-pharmacological interventions, particularly exercise, is less clear. Physical inactivity is an independent predictor of primary stroke.[12] Despite this, only around a half of adults over the age of 65 years in the UK meet nationally recommended levels of weekly physical activity (150 min of moderate intensity activity, eg, brisk walking),[13] and this declines further after stroke or transient ischaemic attack (TIA).[14] There is overwhelming evidence that aerobic exercise and health education delivered as cardiac rehabilitation, reduces blood pressure, re-infarction rates, cardiovascular and overall mortality among patients with CHD.[15] Cardiac rehabilitation is now an established part of CHD management, with the US and UK registry data showing sustained improvements in physical activity 1 year after cardiac rehabilitation.[16 17] Due to the similarities between coronary and cerebrovascular disease, risk factor management after stroke or TIA could benefit from aligning to a similar structure to that of CHD.

Physical fitness training after stroke is safe and improves walking speed and balance.[18] However, less attention has been paid to whether exercise can reduce secondary vascular risk. A Cochrane review conducted in 2013[19] and systematic review in 2014[20] only included two randomised controlled trials (RCTs), the results of which were inconclusive regarding the impact of exercise on secondary vascular risk. Since then, interest in this area has increased. This systematic review aims to evaluate the effect of exercise interventions on secondary vascular risk factors (blood pressure, lipid profile, plasma fasting glucose and body mass index (BMI)) and risk of recurrent stroke.

METHODS

This study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.[21] Operational definitions were detailed prior to search initiation based

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on recommendations from the Cochrane Handbook of Systematic Reviews on Interventions.[22]

Selection criteria

We included studies evaluating adults (aged >18 years) who had suffered a stroke (ischaemic or haemorrhagic) or TIA according to the WHO definition.[23] Only RCTs assessing the effects of exercise or physical fitness interventions compared with usual care or sham were included. Exercise therapy included cardiorespiratory (aimed at improving fitness), resistance (aimed at improving muscle strength or endurance) or mixed components. Interventions termed 'aerobic' involved a clear aim to enhance physical fitness by stimulating heart rate and respiratory rate, for example, running, walking, circuits, cycling. Studies of physical therapy (therapies used to promote, maintain or restore physical function, eg, walking, balance, etc), were only included if they involved cardiorespiratory or resistance components. Only studies reporting on systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting glucose (FG), BMI or secondary cerebrovascular events and cardiovascular death were included.

Search strategy

Electronic databases search included OVID MEDLINE, PubMed, Web of Science, The Cochrane Library, The National Institute for Health and Care Excellence, TRIP Database, CINAHL, PsycINFO, SCOPUS, UK Clinical Trials Gateway and the China National Knowledge Infrastructure, from 1966 to October 2017. Selected medical subject headings were combined with free text terms relating to stroke (eg, cerebrovascular accident, cerebral infarction), TIA (eg, transient ischaemic attack, mini-stroke), exercise (eg, physical activity, aerobic exercise) and secondary prevention (eg, outcomes, vascular events, death, BP, lipid profiles, glucose, weight or BMI), to create a search strategy finalised for MEDLINE (see online supplementary material). This was adjusted for use in other databases using appropriate Boolean operators and search symbols. Chinese translations were used for Chinese databases (see online supplementary material). Reference lists of all relevant studies and systematic reviews were scanned for additional potentially relevant studies. Our search did not extend to grey literature.

Study selection and data extraction

Two review authors (CW and ANA) independently eliminated duplicate and irrelevant studies from title and abstract. Full texts of the remaining studies were obtained and critically reviewed by both authors independently for inclusion. Both reviewers independently extracted data into a prepiloted spreadsheet. Data included participant demographics, study setting and timeframe, intervention arms and their descriptors and outcome measures. The Consensus on Exercise Reporting Template (CERT)[24] was used to characterise the reporting of exercise specifics (eg, equipment required, group vs individual, level of supervision, etc) (see online supplementary material). Data required for meta-analysis were collected, including mean differences and associated SD between baseline and postintervention outcome assessments. Basic unit conversions for lipid and glycaemic profiles were undertaken to ensure international system of units for analysis (see online supplementary material). Discrepancies in study selection or data extraction were discussed by both reviewers and adjudicated by a third reviewer (MS).

Quality appraisal

All studies meeting inclusion criteria for the review were assessed independently by both reviewers (CW and ANA) for risk of bias using a checklist developed by the Cochrane Collaboration establishing bias attributable to patient selection, randomisation, blinding, attrition and reporting.[25] Studies at high risk of bias in one or more domains were classed as high risk overall, while those with unclear information in any domain were classed as moderate risk. Low-risk studies met low-risk criteria for each domain. Quality assessment of evidence for each outcome measure that pooled data (SBP, DBP, TC, LDL-C, HDL-C, FG and BMI) was also undertaken using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach.[26] An initial grading of 'high quality' for RCTs was downgraded by one level for serious concerns (or by two levels for very serious concerns) about the risk of bias, inconsistency, indirectness, imprecision or publication bias relating to combined evidence for each outcome (see online supplementary material).

Data analysis

A qualitative synthesis of study characteristics was undertaken. Statistical analyses of outcome data were performed using RevMan 5 (V.5.3 from the Cochrane Collaboration). Meta-analyses for continuous variables (SBP, DBP, TC, LDL-C, HDL-C, FG and BMI) used the mean difference and the SD of the mean difference, between intervention and control groups. Not all trials reported changes in the SDs preintervention and postintervention. In these instances, trial authors were contacted directly to request missing data, and where this was not possible, we used indirect methods to estimate missing values.[27] We calculated the I^2 statistic to assess statistical heterogeneity.[28] A random effects model was applied due to anticipated heterogeneity in population (stroke severity, TIA) and exercise interventions. For meta-analysis of outcomes reported by 10 trials or more, we assessed publication bias using tests by Egger *et al*[29] and Begg and Mazumdar[30] in STATA statistical software (V.14.0, StataCorp), although we acknowledge that funnel plot asymmetry can be due to reasons other than publication bias. Prespecified subgroup analyses were undertaken to estimate the effects of variables such as inclusion of studies at high risk of bias, the effect of early (within 6 months) versus late (after 6 months) exercise initiation, incorporation of health education and participant type (TIA/non-disabling stroke vs severe stroke). Further details on the complete statistical tests used are available in the online supplementary material.

RESULTS

Following removal of duplicates, 11 899 citations were identified; from which 39 full-ext articles were retrieved (figure 1). After exclusions were applied, 20 RCTs were retained for review and meta-analysis involving 1031 patients.[31–50]

Quality appraisal

Ten studies were at low risk of bias,[33 34 37 39 43–46 48 50] seven were at moderate risk of bias[31] and three were at high risk of bias[35 38 42] (table 1). GRADE assessment of the quality of evidence for each meta-analysed outcome ranged from moderate to very low (see online supplementary material).

Study characteristics

Twenty selected RCTs recruited 1031 patients from 10 countries, details of which are summarised in table 2. Average ages of study participants ranged from 52 to 69 years. Sixteen trials involved only patients who had suffered

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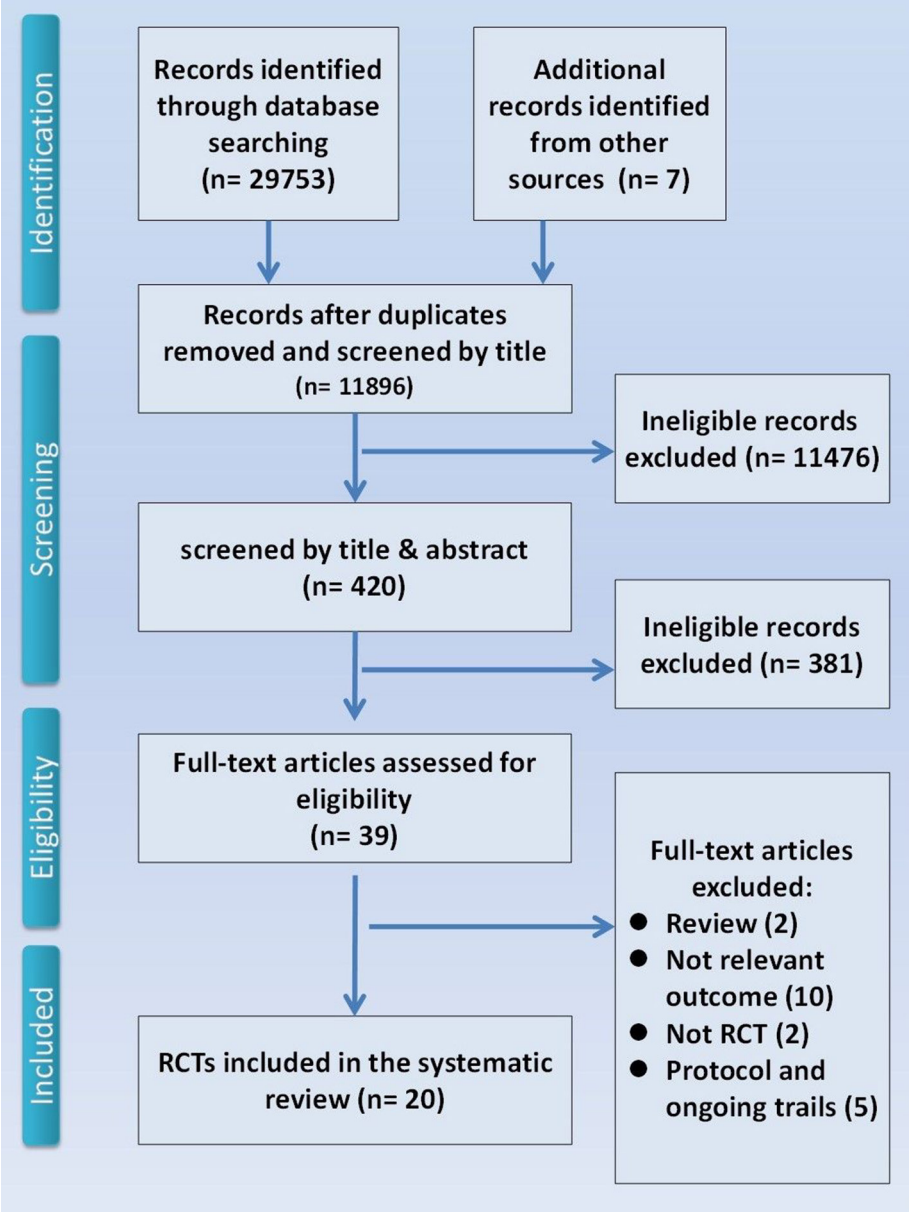

Figure 1 Flow diagram for study selection process. RCT, randomised controlled trial.

stroke,[31–36 38–40 42 44–46 48–50] two included only patients with TIA[37 47] and two included both stroke and TIA.[41 43] Eleven trials recruited patients to interventions within 6 months[32 36–39 41–45 47] and nine trials after 6 months[31 33–35 40 46 48–50] of the index event. The majority of studies recruited only ambulant participants (with or without walking aids), while five studies recruited patients with more severe stroke.[31–33 44 45] Five studies excluded patients on the basis of cognitive impairment.[35 38 40 43 48] Exercise interventions were compared with *usual care* in 12 studies,[32 34 36–38 40–42 47–49] *therapeutic activities* in 4 studies (eg, standing and balance training),[35 44–46] *stretching* in 3 studies[31 33 50] and an *education programme* in 1 study.[39] Exercise interventions varied considerably as reported according to the CERT (see online supplementary material). Overall programme duration ranged from 6 weeks to 6 months and weekly frequency of sessions from 1 to 5, with each session ranging in duration from 30 to 90 min. Most exercise interventions involved 3×1 hourly sessions per week (mean weekly minutes=175, median=180), but minutes of weekly programmed exercise activity ranged from 60 to 350 min. Eleven studies involved graded increases in exercise duration or intensity[31 32 35 37 39 40 46–50]; only three did not include target heart rate changes.[39 41 49] Four interventions included health educational,[34 37 38 43] and only two involved any home programme content.[37 39] Studies reported poorly on qualifications of supervising health professionals, intervention fidelity and whether exercise was delivered individually or in groups. All studies reported outcome measures relevant to secondary vascular risk, most commonly blood pressure (13 studies), with lipid profile, fasting glucose and BMI reported in at least eight studies. One study reported on vascular events rates.[37] Two studies referred to the same intervention and group of patients, but reported on different outcome measures,[44 45] thus were viewed as one study for statistical purposes.

QUANTITATIVE SYNTHESIS (META-ANALYSIS)

Blood pressure

Data on SBP and DBP were pooled from 12 studies including 606 patients (intervention n=305).[31 32 34–37 39 40 43 47 48 50] Blood pressure data from one study[40] did not include measures of

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Table 1 Risk of bias assessed using Cochrane risk of bias tool (high, low, unclear)

Study	Sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data addressed	Free of selective outcome reporting	Other bias	Risk of bias
Potempa *et al*[31]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
Katz-Leurer *et al*[32]	Low	Unclear	Low	Unclear	Low	Low	Low	Moderate
Ivey *et al*[33]	Low	Low	Low	Low	Low	Low	Low	Low
Lennon *et al*[34]	Low	Low	Low	Low	Low	Low	Low	Low
Rimmer *et al*[35]	High	Unclear	Low	Unclear	Low	Low	Low	High
Toledano-Zarhi *et al*[36]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
Faulkner *et al*[37]	Low	Low	Low	Low	Low	Low	Low	Low
Liu and Yan[38]	High	Unclear	Low	Low	Unclear	Unclear	Unclear	High
Kono *et al*[39]	Low	Low	Low	Low	Low	Low	Low	Low
Jin *et al*[40]	Low	Low	Low	Unclear	Unclear	Low	Low	Moderate
Boss *et al*[41]	Unclear	Unclear	Yes	Yes	Low	Low	Low	Moderate
Xinzhou[42]	High	Unclear	Low	Low	Unclear	Unclear	Unclear	High
Kirk *et al*[43]	Low	Low	Low	Low	Low	Low	Low	Low
Wang *et al*[44]	Low	Low	Low	Low	Low	Low	Low	Low
Wang *et al*[44]	Low	Low	Low	Low	Low	Low	Low	Low
Tang *et al*[46]	Low	Low	Low	Low	Low	Low	Low	Low
Woolley *et al*[47]	Unclear	Low	Low	Low	Unclear	Low	Low	Moderate
Lee *et al*[48]	Low	Low	Low	Low	Low	Low	Low	Low
Zou *et al*[49]	Low	Low	Low	Low	Unclear	Low	Low	Moderate
Moore *et al*[50]	Low	Low	Low	Low	Low	Low	Low	Low

variability and was excluded from meta-analysis. There were significantly greater reductions in SBP with exercise interventions compared with controls (−4.30 mm Hg, 95% CI −6.77 to −1.83 mm Hg, I^2=33%; GRADE of evidence: moderate level) (figure 2). Both tests by Begg and Mazumdar (Pr>|z|=0.373) and Egger *et al* (P>|t|=0.226) suggested low risk for publication bias.

There were significantly greater reductions in DBP with exercise interventions compared with controls (−3.12 mm Hg, 95% CI −4.89 to −1.34 mm Hg; GRADE of evidence: low level) (figure 3). There was significant heterogeneity (I^2=68%) and evidence of publication bias (test by Begg and Mazumdar Pr>|z|=0.047, test by Egger *et al* P>|t|=0.033, 95% CI −8.87 to −0.47).

Exercise interventions initiated within 6 months[32 36 37 39 43 47] of index stroke or TIA appeared to have a larger effect on SBP (−8.46 mm Hg, 95% CI −12.18 to −4.75, I^2=0%) than those initiated after 6 months (−2.33 mm Hg, 95% CI −3.94 to −0.72, I^2=0%).[31 34 35 40 48 50] The benefits for DBP became non-significant with exercise initiated after 6 months (−2.08 mm Hg, 95% CI −4.82 to 0.66, I^2=70%). Exercise interventions involving an education component[34 37 39 43] also appeared to have greater effects on SBP (−7.81 mm Hg, 95% CI −14.34 to −1.28, I^2=40%) compared with those with no education component (−2.78 mm Hg, 95% CI −4.33 to −1.23, I^2=0%).[31 32 35 36 47 48 50] Exclusion of one study at high risk of bias[3535] did not significantly effect overall results (see online supplementary material).

Lipid profiles

Nine RCTs reported on total cholesterol (n=370 patients; intervention n = 185)[33–35 42 43 45 46 49 50] (figure 4A). Pooled analysis showed significant overall reductions in total cholesterol with exercise compared with control (−0.27 mmol/L, 95% CI −0.54 to 0.00 mmol/L, I^2=70%, p=0.05; GRADE of evidence: low). This beneficial effect however disappeared with the exclusion of two studies that were at high risk of bias[35 42] (−0.13 mmol/L, 95% CI −0.40 to 0.14, online supplementary material).

Levels of LDL-C have stronger correlations with risk of future stroke and are the main target of lipid-lowering interventions.[51] Seven RCTs reported on LDL-C (n=303 patients; intervention n=151)[35 39 42 44 46 49 50] (figure 4B). There was no effect of exercise compared with control (−0.28 mmol/L, 95% CI −0.63 to 0.07 mmol/L, I^2=85%; GRADE of evidence: very low), except among interventions involving health education.

Higher levels of HDL-C have been associated with reduced risk of stroke among diverse populations.[52] Nine RCTs reported on HDL-C (n=394 patients; intervention n=197)[33 35 39 42 43 45 46 49 50] (figure 4C). There was no effect of exercise compared with control (+0.08 mmol/L, 95% CI −0.02 to 0.17 mmol/L, I^2=77%; GRADE of evidence: very low).

Fasting blood glucose

Seven RCTs measured fasting glucose changes (n=364 patients; intervention n=135).[33 37 38 43 44 46 49] There was no effect of exercise on fasting glucose compared with control (−0.14 mmol/L, 95% CI −0.29 to 0.01, moderate heterogeneity I^2=42%; GRADE of evidence: moderate; figure 4D). Subgroup analyses did not alter these findings.

Body mass index

EIght RCTs (n=446 patients; intervention n=225) measured BMI at baseline and follow-up.[34 35 37 39 43 49 50] There was no effect of exercise on BMI compared with control (−0.0 kg/m^2, 95% CI –0.26 to 0.25 kg/m^2, I^2=32%; GRADE of evidence: moderate; figure 4E), nor any effects from subgroups.

Secondary vascular events

One study randomised 70 patients with non-cardioembolic stroke to a 24-week programme of exercise including salt reduction and dietary education or to usual care with health education.[39] It was

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Table 2 Summary characteristics of studies included in the review

Study	Participant characteristics (N, diagnosis, average age, % male)	Setting	Intervention initiation (poststroke/TIA)	Intervention and control description	Frequency and duration	Outcome measures
Potempa *et al*[31] USA	n=42 (19 intervention) Hemiplegic stroke Age range 21–77 years Male 54.8%	Exercise laboratory	>6 months	Intervention: aerobic exercise training programme using leg cycle ergometer aiming for 30%–50% HRR. Control: passive range of motion protocol.	Frequency: 3×per week Session length: 30 min Duration: 10 weeks	Baseline and at 10 weeks: ► BP
Katz-Leurer *et al*[32] Israel	n=92 (46 intervention) Moderate severity stroke (SSS) Age 63 years Male 54.3%	Outpatient clinic	<48 hours	Intervention: aerobic programme of leg cycle ergometry increasing from 10 min 5 times per week to 30 min 3×a week, aiming for 60% HRR. Control: passive stretching.	Frequency: 3–5×per week Session length: 10–30 min Duration: 8 weeks	Baseline and at 8 weeks: ► BP
Ivey *et al*[33] USA	n=46 (26 intervention) Hemiplegic stroke Age 63.1 years Male—unclear	Unclear	>6 months	Intervention: progressive treadmill exercise training (T-AEX) aiming for 40%–50% HRR. Control: passive stretching.	Frequency: 3×per week Session length: 40 min Duration: 6 months	Baseline and at 10 weeks: ► FG ► Body weight
Lennon *et al*[34] Ireland	n=46 (23 intervention) All stroke severities (~75% ambulant) Age 60 years Male 60.9%	Outpatient cardiac rehabilitation programme	>1 year	Intervention: upper or lower limb cycle ergometry aiming for 50%–60% HRR, along with 2×life skills sessions (stress and relaxation). Control: usual care (functional activities, balance and gait).	Frequency: 2×per week Session length: 30 min Duration: 10 weeks	Baseline and at 10 weeks: ► Cardiac risk score ► BP ► BMI ► Lipids
Rimmer *et al*[35] USA	n=41 (14 MISD, 14 LILD, 13 TE) Hemiplegic stroke Age 59.6 years Male 40%	University-based medical centre	>6 months	Intervention: MISD—increasing target HR every 4 weeks (40%–49% HRR, 50%–59% HRR, 60%–69% HRR). LILD aimed to increase exercise time each 4 weeks (30, 45, 60 min). Control: balance and gait activities (TE).	Frequency: 3×per week Session length: 30–60 min Duration: 14 weeks	Baseline and at 14 weeks: ► BP ► Lipid profile ► BMI
Toledano-Zarhi *et al*[36] Israel	n=28 (14 intervention) Minor stroke Age 65 years Male 75%	Outpatient clinic	1–3 weeks	Intervention: 2×weekly sessions of treadmill, arm and leg cycle ergometry aiming for target 50%–70% HRR and 1 session of strength, flexibility and coordination training. Control: usual care (stretching and functional activities).	Frequency: 3×per week Session length: 35–55 min Duration: 6 weeks	Baseline and 3 months: ► BP
Faulkner *et al*[37] New Zealand	n=60 (30 intervention) TIA Age 69 years Male 52%	Outpatient cardiac rehabilitation clinic	<2 weeks	Intervention: 2× weekly 90 min sessions of walking and cycling exercise aiming for 50%–85% HRR, increasing incrementally each week. Also 1× weekly 30 min health education session (vascular risk, stroke prevention, nutrition, BP, medication compliance, stress). Control: routine care and secondary prevention advice	Frequency: 3×per week Session length: 30–90 min Duration: 8 weeks	Baseline, 8 weeks and 3 months: ► BP ► Lipid profile ► FG ► BMI
Liu and Yan[38] China	n=98 (50 intervention) Moderate to severe stroke Age 55 years Male 49%	Hospital clinic	>2 weeks	Intervention: treadmill exercise programme aiming for target HR (170-age)/min. Control: standard rehabilitation programme not involving aerobic exercise	Frequency: 5×per week Session length: 30–40 min Duration: 6 weeks	Baseline and at 6 weeks: ► FG
Kono *et al*[39] Japan	n=70 (35 intervention) Mild stroke (non-cardioembolic) Age 63.5 years Male 68.6%	Hospital clinic or home based	>1 month	Intervention: clinic based—5 min warm up, 20–30 min cycle ergometry, 20 min resistance exercises, 5 min cool down. Alternatively, home based—6000 steps daily, 30–60 min walking 3–5×per week. Lifestyle modification education (diet, smoking, alcohol). Control: lifestyle modification education only.	Frequency: 1–2×per week clinic based or 3–5×per week home based Session length: 60 min Duration: 24 weeks	Baseline and 3 months and 6 months: ► CV death or hospitalisation ► BP ► Lipids ► BMI
Jin *et al*[40] China	n=128 (65 intervention) Mild stroke (ambulant) Age 57 years Male 71.2%	Outpatient rehabilitation clinic	>6 months	Intervention: aerobic cycling training aiming for 50%–70% HRR. Control: passive stretching and walking (20%–30% HRR)	Frequency: 5×per week Session length: 40 min Duration: 12 weeks	Baseline and 12 weeks: ► BP ► BMI
Boss *et al*[41] The Netherlands	n=20 (10 intervention) Mild stroke or TIA Age 63 years Male 70%	Outpatient stroke clinic	<1 week	Intervention: aerobic exercise and strength training, with incremental intensity. Control: usual care.	Frequency: 3×per week Session length: 60 min Duration: 8 weeks	Baseline and at 6 and 12 months: ► BP ► LDL-C
Xinzhou[42] , China	n=45 (15 aerobic exercise, 15 aerobic and resistance, 15 control) Mild stroke Age range 39–68 years Male—unclear	Hospital clinic	<6 months	Intervention: 5× weekly sessions of aerobic treadmill training aiming for 50%–80% HRR, with or without elastic band resistance training. Control: usual care.	Frequency: 5×per week Session length: 40–60 min Duration: 8 weeks	Baseline and at 6 weeks: ► Lipid profile

Continued

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Table 2 Continued

Study	Participant characteristics (N, diagnosis, average age, % male)	Setting	Intervention initiation (poststroke/TIA)	Intervention and control description	Frequency and duration	Outcome measures
Kirk *et al*[43] UK	n=24 (12 intervention) Mild stroke or TIA Age 67 years Male 79.2%	Outpatient cardiac rehabilitation clinic	<1 month	Intervention: circuit training (walking, running, press-ups, squats, shoulder press, bicep curls, step ups, arm raises) aiming for 50%–70% HRR. Health education (exercise, alcohol, diet, medications). Control: usual care.	Frequency: 1–2×per week Session length: 60 min Duration: 18 weeks	Baseline and at 6 months: ► CVD risk score ► Lipid profile ► FG ► BP ► BMI
Wang *et al*[44] China	n=48 (24 intervention) Severe stroke Age 56 years Male 73%	Outpatient rehabilitation clinic	2–6 weeks	Intervention: leg cycle ergomtery aiming for 50%–70% HRR. Control: usual care (physiotherapy, occupational therapy, Chinese manipulation).	Frequency: 3×per week Session length: 40 min Duration: 6 weeks	Baseline and 6 weeks: ► FG ► Lipid profiles
Wang *et al*[45] China	n=54 (27 intervention) Severe stroke Age 53 years Male 70.4%	Outpatient rehabilitation clinic	1–6 months	Intervention: leg cycle ergomtery aiming for 50%–70% HRR. Control: usual care (physiotherapy, occupational therapy, Chinese manipulation).	Frequency: 3×per week Session length: 40 min Duration: 6 weeks	Baseline and 6 weeks: ► FG ► Lipid profiles ► Weight
Tang *et al*[46] Canada	n=50 (25 intervention) Mild stroke Age 66 years Male 58%	Outpatient research facility	>1 year	Intervention: progressive intensity exercises involving incline walking, cycle ergometry, sit to stands, step ups. Intensity increase from 40% to 70%–80% HRR every 4 weeks. Control: balance, flexibility, stretching (<40% HRR).	Frequency: 3×per week Session length: 60 min Duration: 6 months	Baseline and 6 months: ► Lipid profiles ► FG
Woolley *et al*[47] New Zealand	n=25 (13 intervention) TIA Age 66 years Male 84%	Outpatient rehabilitation clinic	<2 weeks	Intervention: 30 min session of aerobic exercise (cycling and treadmill walking) aiming for 50%–85% HRR. Followed by 60 min session of upper and lower body resistance, balance and core-stability exercises. Control: usual care.	Frequency: 2×per week Session length: 90 min Duration: 8 weeks	Baseline and at 8 weeks ► BP
Lee *et al*[48] Korea	n=26 (14 intervention) Hemiplegic stroke Age 64 years Male— unclear	Community rehabilitation clinic	>1 year	Intervention: combined aerobic (20 min incline walk, steps) and resistance (20 min squats, lunges, flexion/extension shoulders, hips, knees) exercise aiming for 50%–60% HRR, along with stretching. Control: walking, playing Korean chess.	Frequency: 3×per week Session length: 90 min Duration: 16 weeks	Baseline and 6 months: ► BP (peripheral and central) ► BMI
Zou *et al*[49] China	n=56 (28 intervention) Mild stroke Age 52 years Male 39.3%	Outpatient rehabilitation clinics	>6 months	Intervention: resistance leg training (leg press, extension, curls) aiming for muscle failure between 10 and 12 repetitions. Control: active and passive stretching.	Frequency: 3×per week Session length: 40 min Duration: 8 weeks	Baseline and at 19 weeks: ► BMI ► FG ► Lipids
Moore *et al*[50] UK	n=40 (20 intervention) Mild stroke Age 69 years Male 85%	Community leisure centres	>6 months	Intervention: mixed balance and strength training (40%–50% HRR increasing to 70%–80% HRR by week 4) Control: matched-duration home stretching programme.	Frequency: 3×per week Session length: 45–60 min Duration: 19 weeks	Baseline and at 19 weeks: ► Lipid profile ► BMI ► BP

HRR, heart rate reserve; BP, blood pressure; HR, heart rate; FG, fasting glucose; BMI, body mass index; LILD, low intensity longer duration; MISD, moderate intensity short duration; SSS, Scandinavian Stroke Scaler; TC, total cholesterol; TE, therapeutic exercise; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

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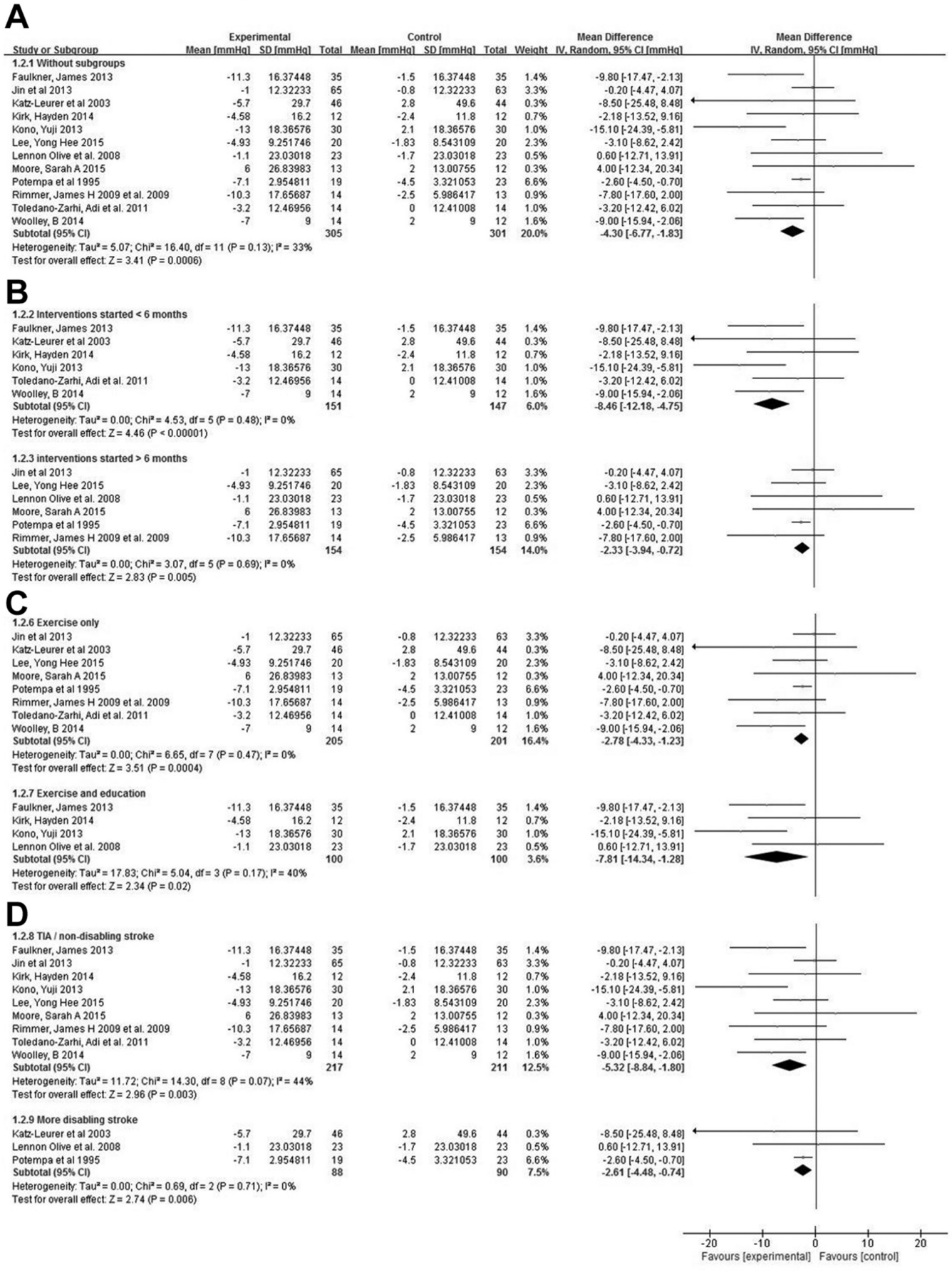

Figure 2 Forest plots of the effects of exercise vs control interventions on (A) systolic blood pressure, including effects of (B) early (<6 months) vs late initiation (>6 months), (C) inclusion of an educational component and (D) population condition (stroke vs transient ischaemic attack).

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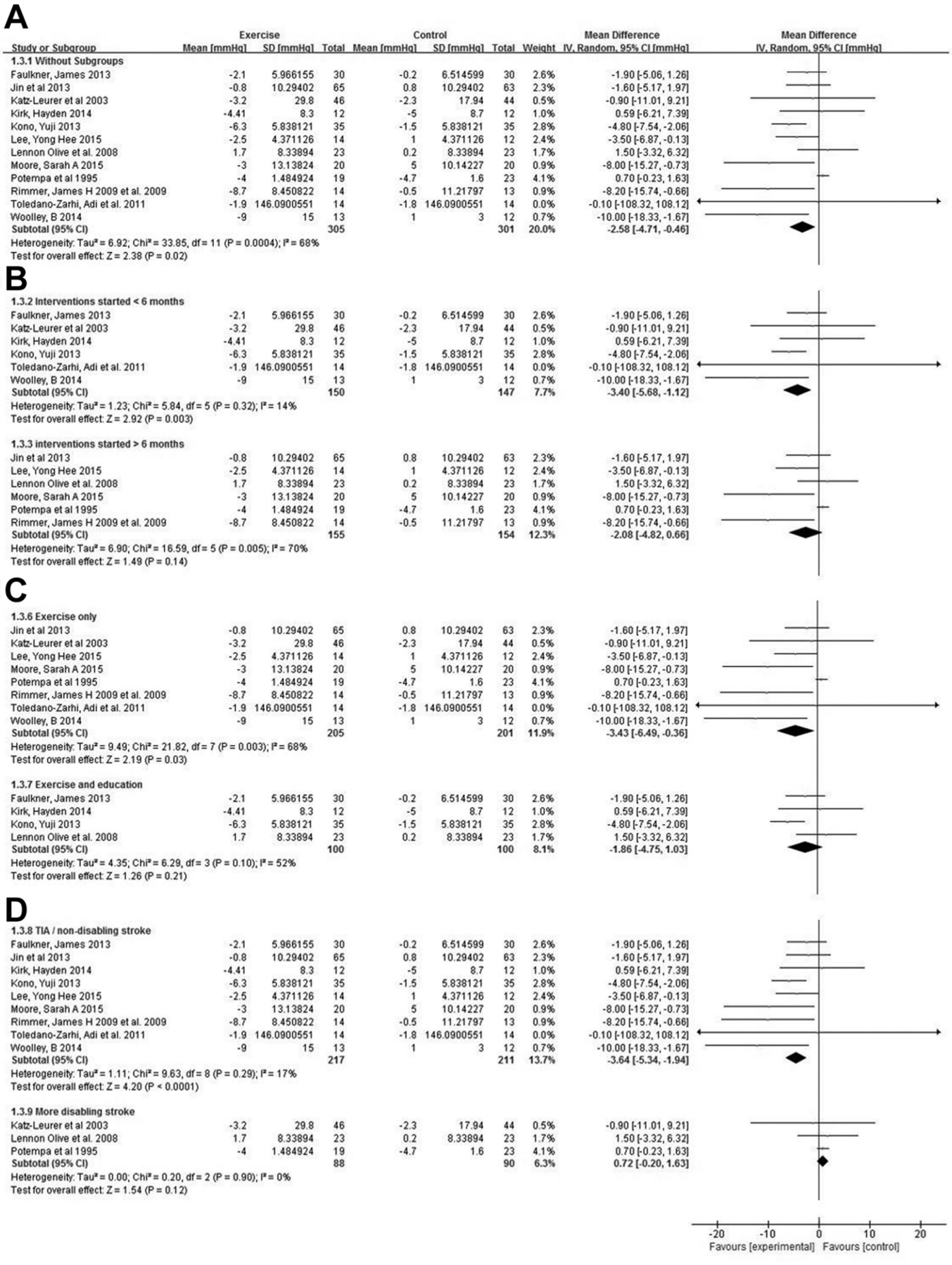

Figure 3 Forest plots of the effects of exercise vs control interventions on (A) diastolic blood pressure, including effects of (B) early (<6 months) vs late initiation (>6 months), (C) inclusion of an educational component, and (D) population condition (stroke vs transient ischaemic attack).

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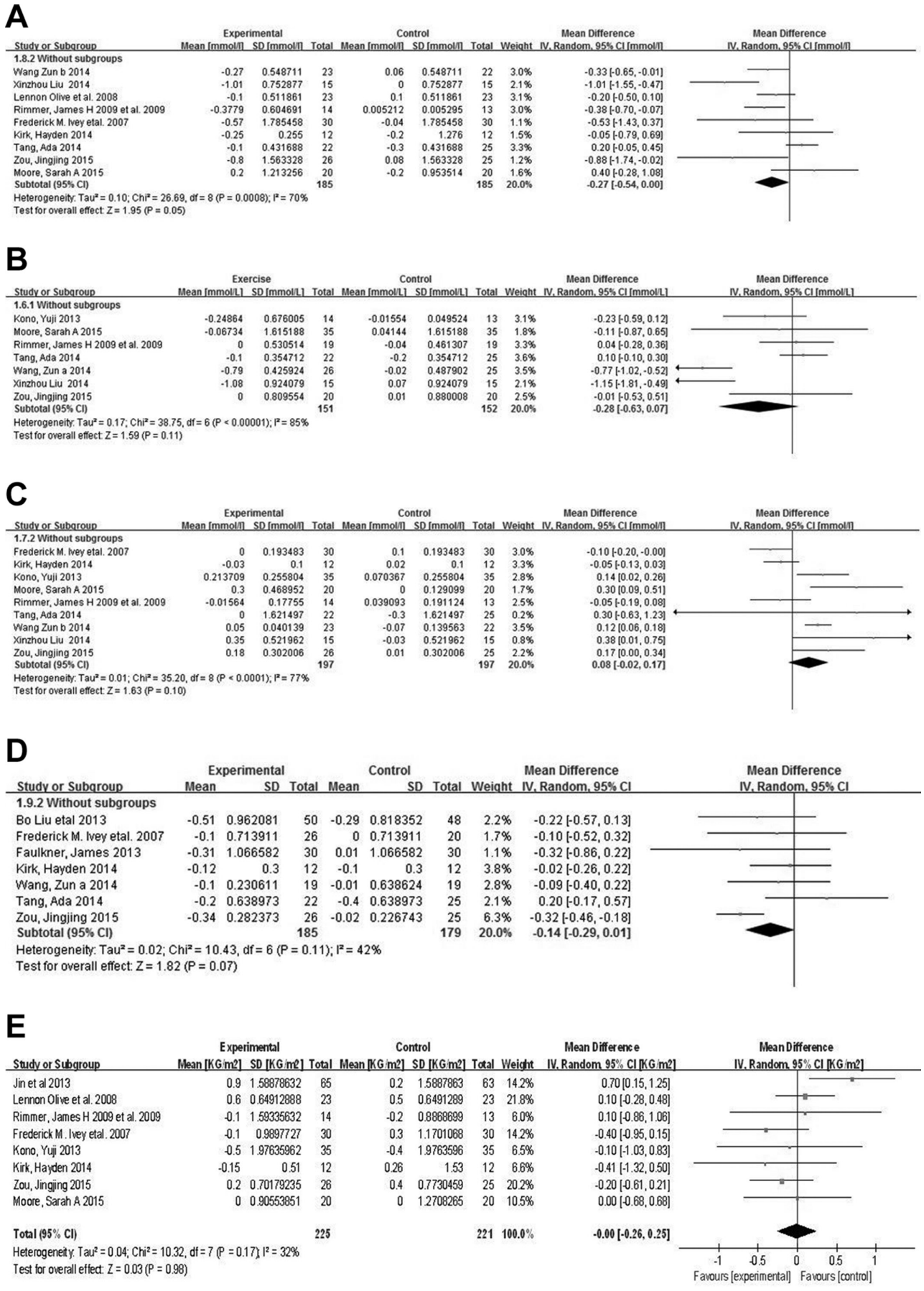

Figure 4 Forest plots of the effects of exercise vs control interventions on (A) total cholesterol, (B) low-density lipoprotein cholesterol, (C) high-density lipoprotein cholesterol, (D) fasting glucose and (E) body mass index.

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terminated early after results showed significantly fewer hospitalisations or deaths secondary to stroke, myocardial infarction or peripheral arterial disease in the intervention group (adjusted HR 0.194, 95% CI 0.121 to 0.737, p=0.005). The intervention in this trial also resulted in greater reductions in SBP, DBP and increased levels of HDL-C.

Adverse events

Three patients from the 20 RCTs suffered adverse events. All adverse events were unrelated to the exercise interventions (see online supplementary material). One trial[41] reported benign ECG abnormalities on exercise testing prior to exercise interventions, and one patient went on to have percutaneous coronary intervention for underlying CHD.

DISCUSSION

Effect of exercise on vascular risk factors

Exercise interventions can lead to clinically meaningful reductions in SBP and DBP after stroke or TIA. This is important because SBP and DBP may be equally important predictors of secondary stroke risk.[53] While exercise causes immediate elevations in heart rate, cardiac output and peripheral vasodilatation through nitric oxide release,[54] the long-lasting effects that may mediate blood pressure reduction include enhanced endothelial sensitivity to nitric oxide, a reduction in sympathetic tone and salt load, all ultimately reducing systemic vascular resistance.[55]

Antihypertensive therapy reduces the risk of secondary stroke by 24% and myocardial infarction by 21% when compared with placebo.[56] A recent meta-analysis of 10 RCTs evaluating antihypertensive therapy after stroke showed that these effects occurred with reductions in SBP of 5.1 mm Hg and DBP of 2.5 mm Hg across a range of antihypertensive classes.[57] Thus, the blood pressure reductions associated with exercise interventions in our meta-analysis (SBP 4.3 mm Hg, DBP 2.5 mm Hg) compare favourably with pharmacological approaches. The effects of exercise may be additive to pharmacological intervention. For example, a trial evaluating the effects of an exercise programme in patients with drug-resistant hypertension (patients already taking three antihypertensives) revealed mean SBP and DBP reductions of 6 (±12) mm Hg and 3 (±7) mm Hg, respectively in the exercise group compared with controls (p=0.03).[58]

Exercise is associated with increased calorific expenditure, peripheral insulin sensitivity[59] and enhanced muscle metabolism of cholesterol.[60] Our analysis suggested that exercise may have beneficial effects on lipid profiles in patients after stroke, although heterogeneity in these data means the results should be interpreted cautiously.

Exercise programmes initiated within 6 months after stroke or TIA had greater blood pressure reductions compared with programmes initiated after 6 months. This may be because individuals are more likely to engage with behaviour modification soon after illness compared with later, often referred to as the 'sentinel event effect' as is evidenced for smoking cessation interventions following myocardial infarction.[61] Early intervention may be of increased benefit after stroke and TIA as the risks of recurrence are highest within the first few months.[62] However, significant reductions in SBP were still observed when interventions were started later. Therefore, promoting exercise, even in the chronic phase after stroke, may still lead to clinically important benefits. The inclusion of a health education component alongside exercise interventions also appeared beneficial. Indeed, meta-analyses of education interventions targeting diet result in clinically meaningful in blood pressure and lipids,[63 64] and may be an important part of a holistic secondary stroke prevention programme.

Secondary vascular events

One study reported on vascular outcomes, reporting that exercise participants were approximately 80% less likely to suffer a vascular death or hospitalisation over a median follow-up of 2.9 years. The early initiation (1 month postevent), long intervention duration (24 weeks), inclusion of salt reduction education and the use of activity monitors (which may themselves improve overall levels of physical activity[65]) may have contributed to the observed effectiveness and the large reductions in SBP (13.0 mm Hg) and DBP (6.3 mm Hg). In addition, by including patients with non-cardioembolic ischaemic stroke only, the investigators may have selected a group of patients standing to benefit most from classical vascular risk reduction. Nevertheless, this was a small, single-centre study and further research to establish the link between exercise and reduced secondary vascular events remains a priority.

Future research

Another priority area for research relates to enhancing the uptake of exercise as an intervention. In the UK, despite the strong evidence base for cardiovascular mortality reduction with exercise-based cardiac rehabilitation, and its provision freely within the National Health Service, fewer than half of eligible patients take up the intervention.[66 67] This may be due to a number of factors such as multimorbidity, problems with transport and poor social support.[68] To extend the potential benefits of exercise, future research should evaluate facilitators and barriers to participation in exercise interventions among patients with stroke, and the role of emerging assistive technologies in enhancing intervention delivery, for example, smartphones, fitbits, tablet PCs. Future trials should also include full descriptions of intervention characteristics (ie, following the CERT) so clinicians know which types and intensities of exercise should be prescribed in clinical practice.

Safety of exercise

Patients and clinicians may have concerns about engaging in physical activity soon after stroke or TIA. Our results suggest that exercise interventions are safe to undertake in patients with stroke or TIA, even in the very early phases. A Cochrane review of 58 trials of physical fitness training for functional recovery after stroke also reported excellent safety data with no reports of severe adverse events.[18]

Limitations

Owing to the significant variation in the type of exercise intervention, it is difficult to ascertain the ideal design for effectiveness. The relatively small number of studies and participants precluded investigating the effects of specific components of exercise interventions (eg, single vs group sessions). However, exercise interventions initiated early rather than late, and those combined with health education appeared more effective for reducing SBP. It is still uncertain if the effects of the interventions relate to behaviour change outside of the exercise sessions. Only one study used activity monitors to link exercise with increased overall step counts.[39]

Since vascular risk factors were measured at the end of the study interventions, we do not know if the beneficial effects of exercise extend beyond the intervention duration. Studies of exercise in other patient cohorts have suggested a decline in

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beneficial effects soon after intervention termination,[69] although data from cardiac rehabilitation studies demonstrate reductions in cardiovascular mortality and hospitalisation that persist at 12 months follow-up.[70 71] The majority of participants in included trials were relatively young (average age 69 years) with mildly disabling stroke or TIA who were ambulant. This may limit the generalisability of our findings to older, more disabled patients with stroke. Our analysis suggested only modest SBP reductions among exercise studies that included more disabled patients with stroke, with no changes in DBP. These patients, who often experience greater fatigue, functional and cognitive impairment, may find it more difficult to comply with the frequency, duration and target heart rates of prescribed exercise that lead to beneficial effects.

The quality of evidence (GRADE) for the outcomes ranged from moderate to very low, primarily due to inconsistency and imprecision of results. All of the included studies were small pilot trials, none powered independently to detect significant differences in any of the vascular risk factors measured. These small studies may also be subject to inherent exaggeration of effect sizes due to variations in methodological quality and heterogeneity of patient cohorts. Although we performed funnel plots for publication bias, we did not search grey literature nor included manuscripts outside of the English and Chinese language. Therefore, there is a risk of publication and language bias.

Our results suggest that clinicians managing patients with stroke or TIA should recommend aerobic exercise (eg, brisk walking, cycling, stepping), aiming for target heart rate reserves of between 50% and 70%, for around 150–180 min per week (divided over 2–3 sessions). Exercise sessions should be prioritised to start early (ie, within 6 months) after stroke or TIA. One way to deliver the suggested aerobic exercise interventions in combination with health education, may be to refer to existing local phase III/IV cardiac rehabilitation services, some of which across the UK are already accepting stroke referrals.[43] However, in order for this to become an established service, high-quality RCTs, recruiting larger, less selected groups of stroke survivors, and incorporating longer follow-up, are desperately needed to investigate the effects of exercise on cardiovascular events and mortality.

CONCLUSION

Exercise interventions poststroke and TIA are safe and contributed to clinically meaningful reductions in blood pressure, the strongest modifiable predictor of secondary stroke. This was most pronounced among interventions initiated within 6 months of the index event and those incorporating health education. There were also beneficial effects of exercise for lipid profiles.

What is already known

- Exercise after stroke has been shown to improve walking speed and balance, but its effect on secondary vascular risk factors is less well studied.

What this study adds

- Exercise programmes after stroke or TIA are safe and result in clinically meaningful reductions in systolic and diastolic blood pressure.
- The beneficial effects of exercise programmes are enhanced if started within 6 months of stroke or TIA and incorporate health education.

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