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Effects of community exercise therapy on metabolic, brain, physical and cognitive function following stroke: *A randomised controlled pilot trial*.

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ABSTRACT

Background: Exercise therapy could potentially modify metabolic risk factors and brain physiology alongside improving function post stroke

Objective: To explore the short term metabolic, brain, cognitive and functional effects of exercise following stroke

Methods: 40 participants (>50years, >6months post-stroke, independently mobile) were recruited to a single-blind, parallel, randomised controlled trial of community based exercise (19 weeks, 3×week, "exercise" group) or stretching ("control" group). Primary outcome measures: glucose control and cerebral blood flow. Secondary outcome measures: cardiorespiratory fitness; blood pressure; lipid profile; body composition; cerebral tissue atrophy and regional brain metabolism; physical and cognitive function.

Results: Exercise did not change glucose control (Homeostasis model assessment 1·5 ± 0·8 to 1·5 ± 0·7 vs. 1·6 ± 0·8 to 1·7 ± 0·7, p=0·97, CI -0·5 to 0·49). Medial temporal lobe tissue blood flow increased with exercise (38 ± 8 to 42 ± 10ml/100g/min, p<0.05, CI 9.0 to 0.1) without any change in grey matter tissue volume. There was no change in medial temporal lobe tissue blood flow in the control group (41 ± 8 to 40 ± 7ml/100g/min, p=0.13, CI -3.6 to 6.7) but significant grey matter atrophy. Cardiorespiratory fitness, diastolic blood pressure, high-density lipoprotein cholesterol, physical function and cognition also improved with exercise.

Conclusion: Exercise therapy improves short-term metabolic, brain, physical and cognitive function, without changes in glucose control following stroke. The long-term impact of exercise on stroke recurrence, cardiovascular health and disability should now be explored. Clinical trial registration: URL: http://www.controlled-trials.com/ISRCTN41026907 Trial identifier: ISRCTN41026907

Key words: Stroke, exercise, metabolic risk factors, cerebral blood flow, physical function, cognition.

Introduction

Stroke affects 152,000 individuals in the UK per year [1] and is the leading cause of adult disability. [2] Approximately a third of individuals with stroke will have another stroke [3] and 75% present with cardiac disease. [4] There is a need to develop practical interventions that reduce disability levels and prevent stroke recurrence and cardiovascular disease.

Stroke recurrence is influenced by a number of modifiable metabolic risk factors, including impaired glucose control, dyslipidaemia, hypertension, obesity, and low cardiorespiratory fitness. [5] Metabolic abnormalities promote cellular changes that result in the alteration of the structure and function of blood vessels and this damage can, in turn, lead to stroke and other vascular dysfunctions such as reduced cerebral blood flow. [6-8] In the healthy population increasing physical activity has been shown to be an inexpensive, safe, and effective method of improving metabolic risk factors and vascular control with minimal side effects.[9, 10] Prospective observational studies in healthy individuals also indicate that a physically active lifestyle may be neuroprotective: preventing age-related decline in cerebral blood flow, brain atrophy, and cognitive function. [11, 12] Whether exercise can be used for similar benefit following stroke, where low levels of physical activity are a particular problem, [13] has yet to be fully defined. [14]

Strong evidence demonstrates structured exercise leads to short and long term functional benefits post stroke. [14] What has not been determined is whether exercise therapy can be used to improve function, but also to modify metabolic and cerebrovascular control in the short term leading to long-term reduction in stroke recurrence and improved cardiovascular health. The limited translation of current exercise and stroke research findings

into clinical care [15] also highlights a need for the development of feasible exercise interventions that can be incorporated into the stroke pathway.

This pilot randomised controlled trial aims to explore the effects of structured community exercise on metabolic risk factors, brain, physical and cognitive function post stroke. The primary hypothesis was that structured exercise would improve glucose control and brain blood flow. Secondary hypotheses were that structured exercise would improve cerebral atrophy/metabolism, cardiorespiratory fitness, blood pressure, lipid profile, body composition and clinical outcomes (walking ability, balance, cognition, and quality of life) and that exercise would be more effective than a home stretching programme in improving metabolic risk factors, cerebral blood flow/atrophy/metabolism and clinical outcomes.

Methods

Study design: Single centre, single-blind, parallel, randomised controlled trial of community exercise therapy compared with a stretching control group. The study was approved by the County Durham and Tees Valley Research and Ethics Committee. All subjects gave informed written consent for the study according to the Declaration of Helsinki. The study was conducted from May 2011 to February 2012.

Participants: Eligible subjects were >50 years; had a stroke (>six months previously); able to complete six minute walk test (with/without stick); living at home; completed all NHS physiotherapy; and were not already undertaking regular exercise (≥3 x week, moderate intensity). Exclusion criteria were: absolute and relative contraindications to exercise testing (American Heart Association guidelines);[16] insulin dependent diabetes; neurological disorders other than stroke; pain on walking (>5 on visual analogue scale); inability to follow two stage commands; cognitive problems (mini mental scale examination <24); untreated major depression; contraindications to magnetic resonance imaging.

Setting: Participants were recruited from stroke services in the North East via referral from stroke health professionals or local newspaper advert.

Structured Exercise Intervention: The intervention was adapted from the Fitness and Mobility Exercise programme, [17] (Appendix A) a 'mixed' exercise intervention incorporating functional movement and previously demonstrated to be effective and feasible following stroke. [18, 19] Briefly, community leisure centre classes were run by a physiotherapist and physical activity instructor for 19 weeks (3 x week, 45-60 minutes). This duration was selected as interventions of a similar length have improved both function [20] and glucose control post stroke. [21] To progress the cardiovascular element of the exercise programme a heart rate training zone was calculated for participants using the Karvonen

formula ((Heart rate reserve *training %)+resting heart rate). [22] Initially participants trained at 40-50% of their maximum heart rate measured by a heart rate monitor (Polar, Finland), with increasing increments of 10% every four weeks up to 70-80%, as tolerated. Strength/balance exercises were progressed by increasing repetitions and loading.

Control Intervention: The control group completed a matched duration home stretching programme. Stretching was chosen as other potential control interventions such as yoga or Tai chi can improve metabolic risk factors [23] whereas these benefits have not been demonstrated with stretching. Participants were given an instruction booklet and diary to record stretches and changes in medication/diet/physical activity and contacted fortnightly to check progress.

Outcomes

Outcomes were assessed at baseline and within one week post intervention by assessors blinded to the study hypotheses and group assignment.

Glucose control: After a 12 hour fast, glucose and insulin were measured before and after a 75g glucose load, as described previously. [24] The Homeostasis Model Assessment of Insulin Sensitivity (HOMA) was used to calculate insulin sensitivity at baseline ((fasting insulin U/ml *fasting glucose mmol/L)/22.5).[25]

Grey matter atrophy, cerebral blood flow, and regional metabolism: Magnetic resonance imaging was undertaken pre and post intervention to measure cerebral tissue atrophy, blood flow, and regional metabolism. This protocol was selected as exercise can increase global cerebral blood flow [26] and volume [27] and specifically increase blood flow in the dentate gyrus. [28] Imaging was performed using a whole body 3.0T magnetic resonance (MR) scanner (Achieva, Philips Medical Systems, Best, Netherlands).

Anatomical T_1 weighted images were collected (FOV 240 × 180 × 216 mm^3; TR 8.3 ms; TE 4.6 ms) and were segmented in SPM8 to produce grey and white matter masks from which longitudinal changes in brain structure over time were examined using voxel based morphometry (VBM).

Cerebral blood flow (CBF) was measured using arterial spin labelling (FAIR method, TE 23 ms, TR 4s, 4×4×6mm^3 resolution; FOV 256 × 256 × 84 mm^2) with inflow times from 900ms to 2400ms (300ms steps). The imaging volume was positioned parallel to the anterior commissure-posterior commissure line with lower slices covering the hippocampus. Perfusion weighted and magnitude images were computed for each inflow time from which T_1 and proton density maps were derived. The inflow transit delay was computed by fitting the perfusion signal versus inflow time to a general kinetic model. CBF was then quantified based on perfusion signal, proton density images and transit delay, assuming T_1 of the blood to be 1550ms and blood brain partition coefficient to be 0.9. Global CBF was measured using the grey and white matter masks. Medial temporal lobe grey matter blood flow was assessed as it was defined as a region of interest from the volumetric scans.

Metabolite data (N-acetylaspartate (NAA)/total creatine ratio) were collected from a single voxel of 40 × 15 ×10 mm^3 covering the dentate gyrus using MR spectroscopy (PRESS; TE of 38 ms, TR of 3 s, 128 averages). Spectra were analysed in jMRUI software, using the QUEST algorithm. [29]

Cardiorespiratory fitness: A maximal progressive recumbent bicycle exercise test was undertaken following a previously devised protocol. [30] Briefly, expired gases were analysed at rest (five minutes) and continuously during the test using a mixing chamber methodology (Metalyzer 3B Cortex, Leipzig, Germany). A three minute warm up (20 watts)

was followed by 10-watt increments every minute until the patient was unable to pedal at 50 revolutions per minute or voluntarily terminated the test.

Resting blood pressure: Resting diastolic (DBP) and systolic blood pressure (SBP) was recorded twice using a semi-automated sphygmomanometer after ten minutes sitting.

Lipid profile: Fasted total cholesterol, triacylglyceride, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) were determined pre and post intervention. Calculation of LDL was obtained using the Friedewald formula. [31]

Body composition: Height and weight were measured using a standard rigid stadiometer to the nearest 0.1cm and calibrated scales to the nearest 0.2kg (Seca medical 769 column scale, USA). Body mass index was calculated as kg/m^2. Body composition was measured using air displacement plethysmography (BodPod, Life Measurement Inc., CA, USA). [32]

Physical and cognitive outcomes: Pre and post intervention assessments were made of 1) physical performance: six minute walk test; [33] ten metre walk test [34] and Berg Balance Scale, [35] 2) cognitive function: Addenbrooke's Cognitive Examination Revised (ACE-R), [36] and 3) quality of life: Stroke Impact Scale Version 2.0 (SIS). [37]

Feasibility assessment: Protocol feasibility criteria were: compliance to the study protocol (≥90%); attrition rate (≤10%); clinical safety (100%) and effective data processing (100%). Ratings used to define study feasibility were: (1) protocol feasible (all success criteria achieved); (2) protocol feasible with minor modifications (≥75% success criteria achieved); (3) protocol feasible with major modifications (≥50% success criteria achieved) and (4) protocol not feasible (none of success criteria achieved). [38]

Safety outcomes: Exercise testing followed ACSM safety guidelines. [39] Trial safety reporting was undertaken in line with national guidelines. [40]

Sample size: For cerebral blood flow (CBF) sample size calculation was based on our previous CBF measurements which showed intra-subject reproducibility of 8.5%. Effect size was postulated at 10%, which is a conservative estimate compared to animal data showing the effect of exercise in the mouse. [28] This data indicate that the method has >95% power to detect a 10% change in CBF at significance of p=0.01 using pairwise measurements in a group of 16 subjects. [41, 42] Sample size was increased to 20 subjects to allow for 20% dropout. The sample size for metabolic control was determined from the published data on the effect of aerobic exercise upon metabolic control following stroke. [21] Based on changes in basal insulin (delta 23 ± 35 vs. -9 ± 42) and 5% confidence level, a sample size of 20 gives >80% power. To provide sufficient power to explore both primary outcomes we recruited 20 patients into the intervention and 20 into the control group.

Randomisation: A computerised random number generator was used to allocate treatment by an independent administrator after screening. After establishing participant eligibility and consent the administrator was telephoned for the next number in the sequence to enable participant randomisation.

Statistical methods: Data were inspected for outliers and assessed for normality of distribution. Groups were compared at baseline using an independent sample t-test if data conformed to the assumptions of normality; if not the independent samples Mann Whitney-U test was applied. Between and within group differences were assessed from change scores compared using independent sample t-tests. Pre- and post-intervention within group analyses were performed using a paired t-test if data conformed to the assumptions of normality, if not

the Wilcoxon signed rank test was applied. Statistical significance was indicated if $p<0{\cdot}05$. Data are presented as means ± SD unless otherwise indicated.

Results

Participant flow: Participants were recruited from two local stroke services over a six-month period. Four hundred possible participants were screened (see Figure 1 for participant flow) to recruit forty participants.

Participant characteristics: Of the 40 participants 34 were male and 37 had an ischaemic stroke. Impairment levels were mild to moderate (National Institute for Health Stroke Scale range 0-8) with 55% of participants not achieving age and gender related distances on the six minute walk test. There were no significant differences in baseline measures between the exercise and control group (Table 1).

To test the primary and secondary hypotheses within and between group differences were investigated for all outcomes:

Primary outcomes

The effects of structured exercise on glucose control

Glucose control: Baseline fasted glucose levels in both groups were normal (<7·8mmol/l) (Table 2). At baseline six individuals (3 exercise/3 control) had impaired glucose tolerance (IGT) (>7·8 - <11·1mmol/l), and three (1 exercise/2 control) had newly diagnosed Type 2 diabetes (T2DM) (>11·1mmol/l). Neither a within or between group difference was demonstrated post intervention in two-hour glucose or baseline insulin sensitivity (HOMA) (Table 2). Two of the three exercisers starting with IGT changed to within normal limits and the individual with T2DM changed to IGT. One of the three controls with IGT changed to within normal limits and the two with T2DM changed to IGT.

The effects of exercise on cerebral blood flow

Cerebral Blood Flow: There was no change in global grey matter CBF post intervention (Table 2). Regional analysis of medial temporal lobe CBF in the areas seen to suffer structural change (Figure 3: clusters 1 and 2) revealed a paired group increase in flow following exercise (38± 8 vs. 42 ± 10 ml/min/100g, p=0·05), but not in controls (41 ± 8 vs. 40 ± 7 ml/min/100g, p=0·27). A between group difference in regional CBF was not observed.

Secondary outcomes

Cerebral tissue volume: Paired regional analysis revealed a significant bilateral atrophy of the medial temporal lobe in the control group that was not observed in the exercise group (Figure 3). A between group difference was not observed in cerebral tissue volume.

Cerebral metabolism: Good quality MR Spectroscopy data were available in 16 exercisers and 15 controls due to the technical challenges of acquiring spectroscopy in the dentate gyrus. Analysis of the spectra of the ratio of *N*-Acetylaspartate to creatine (NAA/Cre) demonstrated no change following the intervention (Table 2).

Cardiorespiratory fitness: Significant within group changes were demonstrated with exercise in peak oxygen consumption (increased by 17%) and work rate (Table 2, Figure 2, Panel A). There were significant between group differences in peak oxygen consumption and peak work rate in favour of the exercise group (Table 2).

Blood pressure: A significant within group increase was demonstrated in diastolic BP in the control group (Table 2). There was a significant between group difference in resting diastolic but not systolic BP in favour of exercise (Table 2, Figure 2, Panel B).

Lipid profile: A significant within group improvement in high density lipoprotein cholesterol (HDL-C) was observed with exerciser. (Table 2) HDL-C levels increased significantly in the exercise group compared to controls (Table 2, Figure 2, Panel C). Total

cholesterol and low density lipoprotein cholesterol (LDL-C) levels were unchanged in both groups following the intervention (Table 2).

Body composition: Body mass index and composition were unchanged in both groups following the intervention (Table 2).

The effects of exercise on clinical outcomes

Significant within group improvements were observed in both groups in measures of walking and balance. Significant within group improvements were only made in the exercise group in cognition and stroke recovery, mood, strength and overall physical activity. Significant between group differences were demonstrated in favour of the exercise intervention in walking ability, balance, cognition, mood and overall stroke recovery (Table 3).

Protocol feasibility

The trial protocol was deemed feasible as all the criteria defined for success were achieved. 100% (20/20) of the participants in the exercise group completed the intervention undertaking >90% of the outcome assessments and exercise sessions. No serious adverse events or adverse events were reported over the course of the trial, indicating interventions were safe and the exercise protocol was delivered at the right intensity. Participants randomised to the exercise intervention group completed an average of 53 hours out of a possible 57 hours exercise.

Discussion

This pilot study demonstrated for the first time that community based exercise therapy is a feasible short-term method of modifying metabolic risk factors and maintaining cerebral tissue volume in the medial temporal lobe, alongside improving physical function, cognition and some aspects of quality of life, independent of changes in glucose control.

In contrast to our original hypothesis and data published previously by another group, [21] exercise did not have a significant effect on glucose control at a group level. It should be noted, however, that only 23% were defined as having Type 2 diabetes or Impaired Glucose Tolerance following an oral glucose tolerance test in the present group, compared with 50% in the previous study. [21] It is possible that the apparent stability in glucose control following exercise reflects the number of study participants who already had adequate glucose control, rather than a lack of effect of exercise therapy on glucose regulation. Indeed, of the four with impaired glucose control in the exercise group, three made clinically significant changes in glucose control. Independent of glucose control, however, there remains significant benefits of structured exercise to people living with stroke, which will now be discussed.

Analysis of the brain imaging data revealed significant atrophy of the medial temporal lobe in the control group over the 19 week study. In comparison, medial temporal lobe tissue structure was maintained and regional blood flow was increased following exercise. Memory loss and brain atrophy occur with age. [27] Age related losses in brain volume are, however, not uniform and interestingly the medial temporal lobe is one of the areas where significant age related loss occurs. [43] and it is also an area that plays a vital role in cognition.[44] The fact volume was maintained in this area with exercise and regional blood flow increased, and the changes in cognition observed may indicate exercise is a possible means of ameliorating

age-related atrophy post stroke and improving long term cognition. The only other study to observe the effect of exercise on cerebral blood flow after stroke reports the impact of treadmill training upon cerebral blood flow assessed by transcranial Doppler and noted improvements in vasomotor reactivity. [45] Our findings extend this work by using a quantitative direct measure of cerebral blood flow with regional analysis. Our results demonstrate promising exercise related changes in blood flow and cerebral atrophy, and although differences noted were within group rather than between group, these novel promising findings warrant further exploration in larger better powered studies.

Exercise produced significant short-term improvements in cardiorespiratory fitness, lipid profile and blood pressure. Cardiorespiratory fitness increased by 17% (3ml/kg/min) following exercise. Although this improvement may appear small, increasing cardiorespiratory fitness by 3ml/kg/min could potentially enable individuals with stroke to sustain light activities of daily living (requiring approximately 10.5ml/kg/min) and undertake more vigorous activities like fast walking/jogging (requiring approximately 21 ml/kg/min). [46]

Exercise resulted in a 23% increase (0.3mmol/L) in HDL-C. A 0.06mmol/L increase has been linked to a 6% reduction in coronary heart disease [47] and as 75% of stroke survivors present with cardiac disease [48] this is a finding worthy of further long term exploration. Previous stroke studies have demonstrated no change in lipid profile [49] or changes in cholesterol and LDL-C, but not HDL-C, with exercise [50]. Our study is unique in demonstrating exercise can improve HDL-C post stroke, this improvement may have been due to the length of the intervention and warrants further investigation.

Exercise reduced diastolic blood pressure by 3mmHg, which again could have led to reduction in stroke recurrence as a reduction of DBP of 4 mmHg has been shown to reduce

the relative risk of recurrent stroke by 28%.[51] Only a small number of previous studies have observed the effect of exercise on blood pressure post stroke with variable findings. [50, 52] A recent systematic review of lifestyle interventions for secondary stroke prevention demonstrated lifestyle interventions could potentially reduce blood pressure when combined with medication and medical guidelines. [53] The effect on blood pressure should be further explored in a larger study as blood pressure is the main driver of vascular risk following stroke. [5]

Exercise led to clinically significant improvements in both walking speed (0·3 ± 0·14 m/s) and endurance (85 ± 47m), supporting recent findings. [14] Overall cognition, as measured by the ACE-R, improved with exercise and this finding was in line with previous interventional studies in healthy individuals.[54] Quality of life also increased in terms of mood and recovery with promising within group improvements in physical function and strength. At present the impact of exercise on quality of life post stroke has yet to be determined [55] but the few trials that have explored this area demonstrate exercise can potentially improve quality of life particularly in terms of mood and physical functioning. [56-58]

Reviewing all the results it was encouraging to find significant between group differences in so many outcomes given the size and the pilot nature of the study. This highlights the potential positive impact of this type of exercise intervention post stroke.

No participants left the exercise intervention or experienced any adverse events and participants attended over 90% of the sessions over the 19 weeks. One of the most commonly reported barriers to exercise post stroke is transport. [59] Although transport was not provided to the intervention, and not all participants had access to a car, the high attendance

rates indicate in this instance travel was not a barrier to adherence. Adherence to an exercise intervention is a key determinant of its success, so these findings are very encouraging.

Our study has some limitations. The groups were not matched for contact time with the research team, meaning that quality of life measures may have improved due to socialisation rather than exercise. As the primary outcome of the trial was based on physiological measures not quality of life, an attention matched control group was not deemed a primary objective The decision not to have an attention matched control group was made to optimise retention, as a matched control group with a similar stretching protocol to our own experienced high dropout rates (>40%).[21] The high dropout rates could have confounded results so it was decided that adherence with the intervention was more important than an attention matched control programme. Although the exercise intervention resulted in multiple short-term effects, our sample was relatively small and larger multi-centre studies are needed to establish if these changes can be maintained over time and influence stroke recurrence and comorbidities. The cohort was predominantly male. The fact women have higher pre-stroke disability, are more likely to live alone or in care, and have worse post-stroke functional [60] may have led to low female recruitment and have implications for translating research findings for women into clinical care. Finally, the participants were self-selected and only had mild-moderate deficit (Median NIHSS 3, range 0-8) which may limit extension of these findings to people with more severe deficit.

Conclusions/Implications

In conclusion, this randomised controlled pilot trial demonstrates that structured community delivered exercise therapy after stroke results in short term improvements in metabolism, physical function, cognition and quality of life and promising changes in cerebral atrophy/blood flow, independent of changes in glucose control. The study protocol

was deemed feasible and larger studies should now be conducted exploring the long term effects of structured exercise on stroke recurrence, cardiovascular health and disability.

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Table 1 Baseline demographics and clinical characteristics. Data are mean ± SD or mean unless otherwise stated

Variables	Exercise group (n=20)	Control group (n=20)	P value
Demographics			
Gender M/F	18/2	16/4	0·39
Age (years)	68 ± 8	70 ± 11	0·49
Body mass index (kg/m²)	26 ± 4	26 ± 4	0·96
Smoker/non smoker	1/19	3/17	0·30
Mini-mental state examination	28 ± 2	29 ± 1	0·52
Months since stroke(range)	21 ± 34 (6-144)	16 ± 12 (6-43)	0·41
Stroke Characteristics (No. /%)			
Cerebral hemisphere			
Right	10 (50%)	11 (55%)	0·76
Left	9 (45%)	7 (35%)	0·53
Bilateral	1 (5%)	2 (10%)	0·56
Haemorrhagic stroke	1	2	0·56
Vascular location of lesion			
Cortical	5 (25%)	3 (15%)	0·44
Subcortical			
Basal ganglia	4 (20%)	3 (15%)	0·67
Cerebellar	2 (10%)	3 (15%)	0·64
Brain stem	0 (0%)	1 (5%)	0·32
Thalamus	0 (0%)	1 (5%)	0·32
Internal capsule	0 (0%)	1 (5%)	0·32
Subcortical other	7 (35%)	6 (30%)	0·74
Unknown	2 (10%)	2 (10%)	1·0
Functional Characteristics			
NIHSS score	3 ± 3 (0-8)	2 ± 2 (0-7)	0·58
Walking speed m/s	1·2 ± 0·4	1·2 ± 0·3	0·96
6 minute walk distance (m)	428 ± 131	419 ± 127	0·84
Medication (No. /%)			
Beta blocker	3 (15%)	6 (30%)	0·27
ACE inhibitor	7 (35%)	11 (55%)	0·21
Diuretic	5 (25%)	3 (15%)	0·44
Anti-arrhythmic	7 (35%)	3 (15%)	0·15
Calcium channel blocker	2 (10%)	4 (20%)	0·39
Statin	18 (90%)	17 (85%)	0·64

Table 2 Metabolic risk factors and cerebral blood flow and spectroscopy outcomes. *Data are mean ± SD unless otherwise stated*

Variable	Exercise				Control				Group x Time
	Baseline	19 weeks	Δ	P value	Baseline	19 weeks	Δ	P value	(95% CI)
Metabolic Risk Factors									
Peak oxygen consumption (ml/kg/min)	18 ± 5	21 ± 5	3	<·01*	18 ± 5	18 ± 5	0	0·62	<·01* (1·3 to 5·2)
Peak work rate (Watts)	112 ± 36	121 ± 37	9	<·01*	105 ± 34	101 ± 35	-4	0·13	<·01* (0·1 to 0·3)
Systolic blood pressure (mmHg)	137 ± 27	143 ± 19	6	0·33	135 ± 13	137 ± 11	2	0·50	0·64 (-10 to 16)
Diastolic blood pressure (mmHg)	84 ± 10	81 ± 11	-3	0·32	83 ± 11	88 ± 10	5	0·04†	0·04† (-14 to 0·4)
Total cholesterol (mmol/l)	4·5 ± 1·2	4·7 ± 1·2	0.2	0·47	4·4 ± 0·8	4·2 ± 0·8	-0·2	0·36	0·33 (-0·3 to 0·9)
LDL-C (mmol/l)	2.5 ± 0·9	2·5 ± 0·9	0	0·75	2·5 ± 0·7	2·4 ± 0·7	-0·1	0·96	0·79 (-0·5 to 0·6)
HDL-C (mmol/l)	1·3 ± 0·4	1·6 ± 0·6	0.3	<·01*	1·4 ± 0·4	1·4 ± 0·3	0	0·76	0·01† (0·05 to 0·4)
HOMA index	1·5 ± 0·8	1·5 ± 0·7	0	0·99	1·6 ± 0.8	1·7 ± 0.7	0·1	1·0	0·97 (-0·5 to 0·49)
Two hour glucose (mmol/l)	7 ± 2·7	6·4 ± 1·7	-0.6	0·17	6·8 ± 2·6	6·5 ± 2·2	-0·3	0·53	0·63 (-1·7 to 1·1)
Body mass index (kg/m²)	26 ± 4	26 ± 4	0	0·06	26 ± 3	26 ± 4	0	0·45	0·25 (-0·7 to 0·2)
Fat mass (%)	29 ± 9	28 ± 8	-1	0·07	32 ± 7	32 ± 9	0	0·89	0·22 (-3·8 to 0·9)
Brain Physiology									
Grey matter CBF (ml/100g/min)	34 ± 5	36 ± 14	2	0·39	35 ± 7	33 ± 6	-2	0·32	0·21 (-2·4 to 10·4)
Medial temporal lobe region CBF (ml/100g/min)	37·6 ± 8	42·2 ± 9·6	4·6	0·05†	41 ± 7·7	39·5 ± 7·2	-1·5	0·27	0·13 (-1·4 to 10·3)
Dentate gyrus spectroscopy (NAA/Cr)	0·95 ± 0·34	1·01 ± 0·23	0·06	0·67	0·93 ± 0·28	0·98 ± 0·23	0·05	0·55	0·64 (-0·23 to 0·38)

Figure legend *p<0·01, †p<0·05; LDL-C-low density lipoprotein cholesterol; HDL-C-high density lipoprotein cholesterol; HOMA-homeostasis model of insulin sensitivity; CBF-cerebral blood flow; NAA/Cr-N-acetlyaspartate/creatine; Group x Time- between group difference, CI-confidence interval.

Table 3 Clinical outcomes-walking ability, balance, cognition, and quality of life. *Data are mean ± SD unless otherwise stated.*

Variable	Exercise				Control				Group x Time
	Baseline	19 weeks	Δ	P-value	Baseline	19 weeks	Δ	P-value	(95% CI)
Physical Function									
Six minute walk test (m)	428 ± 131	513 ± 131	85	<·01*	419 ± 127	441 ± 126	22	0·02†	<0·01* (42 to 86)
Walking speed (m/s)	1·2 ± 0·4	1·5 ± 0·3	0·3	<·01*	1·2 ± 0·3	1·3 ± 0·3	0·1	0·04†	<0·01* (0·1 to 0·3)
Berg Balance Scale	50 ± 4	55 ± 2	5	<·01*	50 ± 5·6	52 ± 5	2	0·04†	<0·01* (0·9 to 5)
Cognition									
ACE-R	86 ± 8	92 ± 5	6	<·01*	89 ± 6	91 ± 8	2	0·19	0·04† (0·29 to 7·8)
Quality of Life Stroke Impact Scale									
Stroke recovery	66 ± 28	79 ± 22	13	<·01*	79 ± 22	82 ± 17	3	0·1	0.05† (0·3 to 21)
Mood	77 ± 24	87 ± 12	10	0·02†	85 ± 19	84 ± 18	-1	0·60	0·02† (2·2 to 20)
Strength	74 ± 27	79 ± 23	5	0·04†	78 ± 21	83 ± 18	5	0·23	0·77 (-8 to 10)
Memory	85 ± 19	85 ± 18	0	0·81	87 ± 19	90 ± 13	3	0·52	0·64 (-9·9 to 6)
Communication	87 ± 21	88 ± 19	1	0·70	96 ± 6	95 ± 6	-1	0·76	0·62 (-6 to 9)
Activities of daily living	82 ± 19	85 ± 25	3	0·42	90 ± 17	90 ± 15	0	0·75	0·39 (-3 to 8)
Community mobility	86 ± 25	91 ± 19	5	0·08	90 ± 16	91 ± 12	1	0·40	0·26 (-3 to 10)
Hand	66 ± 42	69 ± 42	3	0·13	78 ± 31	85 ± 28	7	0·07	0·42 (-11 to 4·9)
Participation	72 ± 29	76 ± 28	4	0·53	89 ± 18	89 ± 18	0	0·17	0·31 (-7 to 21)
Physical total	308 ± 92	324 ± 96	16	0·03†	336 ± 78	348 ± 64	12	0·10	0·67 (-15 to 24)

Figure legend- *P<0·01, †p<0·05, ACE-R-Addenbrooke's Cognitive Examination-Revised; Group x Time-between group difference, CI-confidence interval

Appendix A Exercise intervention

Component	Description	Duration/Repetitions/Intensity
Warm up	• Slow marching • Slow marching with arm swing • Knee circle • Ankle circles	Five minutes/Low intensity
Stretching	• Trunk side stretch and rotation • Gastrocnemius • Quadriceps • Gluteus maximus • Hamstring.	Five minutes/ Three stretches on each side
Functional strengthening	• Heel-toe raises • Chair push-ups • Sit-to-stand • Sit-to-stand and walking around chair • Wall push-ups • Squat with a gym ball	15 minutes/ Start with two sets of five increase to three sets of ten, variable speed
Balance	• Forward reach • Heel to toe standing and walking • Walking and change direction • Standing on one leg • Hip flexion, abduction and extension	15 minutes
Agility and fitness	• Forward, side and box step onto a step • Walking forwards (if able progress to gentle jogging) • Walking backwards • Side stepping • Fast marching • Step touch • Box step • Hamstring curl	15 minutes/Start with five minutes of exercise gradually increase to 15 minutes/Perceived exertion should be 4-5 out of 10 on Borg scale (fairly light to somewhat hard)/ To increase intensity add hand weights, increase the height of the step.
Cool down	• Combination of warm up and stretches	Five minutes/Low intensity

Figure 3 SPM glass brain view and co-ordinates of specific grey matter atrophy in the control group after the intervention

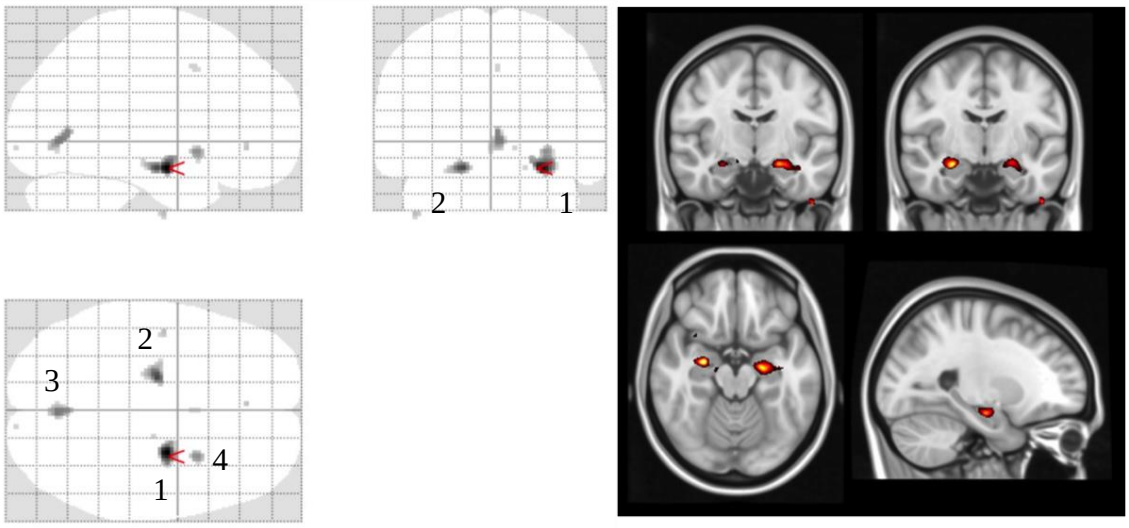
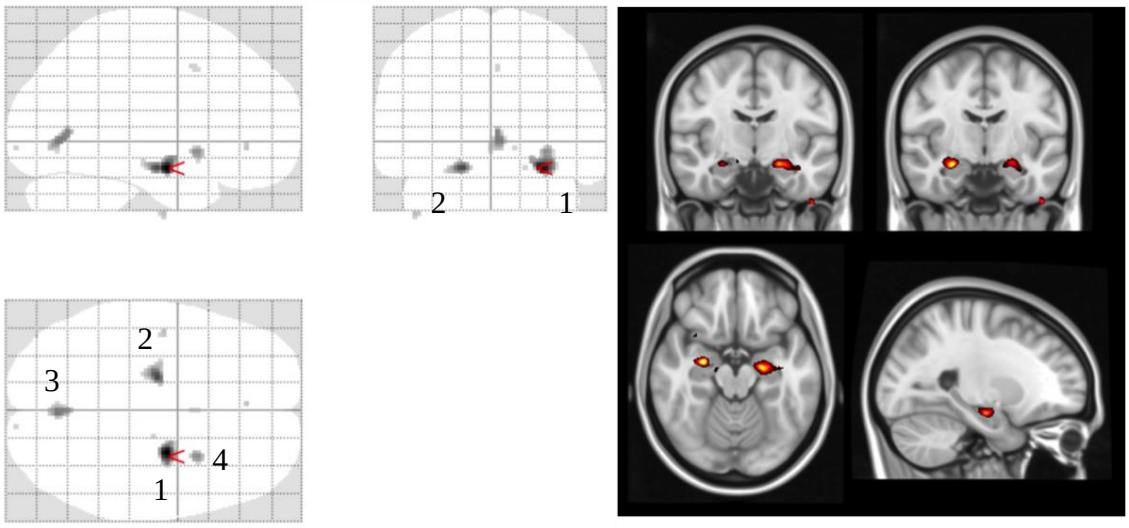


Figure legend: Within group comparison showed significant bilateral atrophy of medial temporal lobe in the control group ($p<0·05$) while the exercise group showed no significant changes. Data are thresholded at $p<0·001$ (uncorrected) and applying a minimum cluster size ($k>10$). Coordinates of the significant differences are:

Region Number			x	y	z	Cluster T	Voxels
1	Parahippocampal gyrus	Right	28	-8	-18	5·90	85
2	Parahippocampal gyrus	Left	-18	-14	-18	4·91	56
3	Lingual gyrus	Right	2	-72	-2	4·42	42
4	Inferior putamen	Right	30	10	-8	4·23	26

Figure 3 SPM glass brain view and co-ordinates of specific grey matter atrophy in the control group after the intervention



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3	Lingual gyrus	Right	2	-72	-2	4·42	42
4	Inferior putamen	Right	30	10	-8	4·23	26